Title

Relationships Between Sensorimotor Inhibition and Mobility in Older Adults With and Without Parkinson's Disease.

Journal

The Journals of Gerontology Series A, 76(4)

ISSN

1079-5006

Authors

Martini, Douglas N
Morris, Rosie
Madhyastha, Tara M
et al.

Publication Date

2021-03-31

DOI

10.1093/gerona/glaa300

Peer reviewed

THE GERONTOLOGICAL SOCIETY OF AMERICA®

Journals of Gerontology: Medical Sciences
cite as: *J Gerontol A Biol Sci Med Sci*, 2021, Vol. 76, No. 4, 630–637
doi:10.1093/gerona/glaa300
Advance Access publication November 30, 2020

OXFORD

Research Article

Relationships Between Sensorimotor Inhibition and Mobility in Older Adults With and Without Parkinson's Disease

Douglas N. Martini, PhD,[1,2,*] Rosie Morris, PhD,[1] Tara M. Madhyastha, PhD,[3] Thomas J. Grabowski, MD,[3] John Oakley, MD, PhD,[4] Shu-Ching Hu, MD, PhD,[4,5] Cyrus P. Zabetian, MD, MS,[4,5] Karen L. Edwards, PhD,[6] Amie Hiller, MD,[1,7] Kathryn Chung, MD,[1,7] Katrina Ramsey, MPH,[8] Jodi A. Lapidus, PhD,[8,9] Brenna Cholerton, PhD,[10] Thomas J. Montine, MD, PhD,[10] Joseph F. Quinn, MD,[1,7] and Fay B. Horak, PhD, PT[1,7]

[1]Department of Neurology, Oregon Health and Science University, Portland. [2]Department of Kinesiology, University of Massachusetts Amherst. [3]Department of Radiology, University of Washington School of Medicine, Seattle. [4]Department of Neurology, University of Washington School of Medicine, Seattle. [5]Veterans Affairs Puget Sound Health Care System, Seattle, Washington. [6]Department of Epidemiology, University of California, Irvine. [7]Portland Veterans Affairs Health Care System, Oregon. [8]Biostatistics & Design Program, Oregon Health and Science University, Portland. [9]School of Public Health, Oregon Health and Science University, Portland. [10]Department of Pathology, Stanford University School of Medicine, Palo Alto, California.

*Address correspondence to: Douglas N. Martini, PhD, Department of Kinesiology, University of Massachusetts, Amherst 30 Eastman Lane, Amherst, MA 01003. E-mail: dmartini@umass.edu

Received: February 4, 2020; Editorial Decision Date: November 22, 2020

Decision Editor: Jay Magaziner, PhD, MSHyg

Abstract

Background: Reduced cortical sensorimotor inhibition is associated with mobility and cognitive impairments in people with Parkinson's disease (PD) and older adults (OAs). However, there is a lack of clarity regarding the relationships among sensorimotor, cognitive, and mobility impairments. The purpose of this study was to determine how cortical sensorimotor inhibition relates to impairments in mobility and cognition in people with PD and OAs.

Method: Cortical sensorimotor inhibition was characterized with short-latency afferent inhibition (SAI) in 81 people with PD and 69 OAs. Six inertial sensors recorded single- and dual-task gait and postural sway characteristics during a 2-minute walk and a 1-minute quiet stance. Cognition was assessed across the memory, visuospatial, executive function, attention, and language domains.

Results: SAI was significantly impaired in the PD compared to the OA group. The PD group preformed significantly worse across all gait and postural sway tasks. In PD, SAI significantly correlated with single-task foot strike angle and stride length variability, sway area, and jerkiness of sway in the coronal and sagittal planes. In OAs, SAI significantly related to single-task gait speed and stride length, dual-task stride length, and immediate recall (memory domain). No relationship among mobility, cognition, and SAI was observed.

Conclusions: Impaired SAI related to slower gait in OA and to increased gait variability and postural sway in people with PD, all of which have been shown to be related to increased fall risk.

Keywords: Cognition, Gait, Short-latency afferent inhibition, Transcranial magnetic stimulation

Age-related sensorimotor and cognitive declines negatively affect everyday motor activities such as walking and fall risk. Gait, balance, and cognitive dysfunction are hallmarks of Parkinson's disease (PD), a disease specific to older populations. Dopaminergic drug therapies alleviate some of the motor dysfunction associated with PD, but do not improve all aspects of gait or balance (1).

For example, postural sway becomes more variable and postural responses remain bradykinetic despite faster gait speed with levodopa (2). Falls are the leading cause of fatal and nonfatal injuries in older adults (OAs) (3) with nearly 6 times the risk of falling in people with PD (4). In fact, 50% of people with PD will fall within 3 months while on dopaminergic therapy, and falls are twice as common in PD than any other neurological disease (5). Since dopaminergic supplementation does not improve balance or prevent falls, there may be other neurotransmitter deficits that affect mobility in people with PD (6–8).

Within the past decade, evidence suggests that cortical cholinergic activity is reduced in early PD and is related to gait and balance impairments (6,9–11). Positron emission tomography revealed relationships between reduced cortical cholinergic activity and decreased gait speed (9), as well as reduced pedunculopontine nucleus cholinergic activity and increased sway area in people with PD (10). Further, γ-aminobutyric acid (GABA) signaling dysfunction is observed throughout the central nervous system in PD, which may be related to both dopaminergic and cholinergic system dysfunction (7,8). Altered communication among these neurotransmitter systems could have negative widespread effects across motor and cognitive performance.

Traditionally viewed as a surrogate for cortical cholinergic activity, reduced short-latency afferent inhibition (SAI), assessed with transcranial magnetic stimulation (TMS), is related to slower gait speed, shorter stride length, and an increased dual-task cost (DTC) on gait speed in people with moderate–severe PD and OA fallers (12,13). SAI assesses the inhibition of corticomotoneuronal activation immediately following electrical, peripheral somatosensory stimulation (12–14). The connection between SAI and cholinergic activity began with impaired SAI observed in people with Alzheimer's disease compared to healthy elderly, but not in individuals with frontotemporal dementia (no cholinergic dysfunction) (15). SAI is also impaired by an anticholinergic drug that affects cognition (16). However, GABA activity and dopaminergic replacement therapy have also recently been shown to suppress SAI (17,18). What is clear is that SAI is a measure of inhibition, driven by a peripheral stimulation prior to cortical activation, regardless of which neurotransmitter(s) are responsible for the inhibition. Thus, for this study, SAI was used as an assessment of cortical sensorimotor inhibition with an unknown, complex relationship to neurotransmitter activity.

In addition to mobility impairments, people exhibit cognitive decline as they age. PD exacerbates these cognitive impairments, particularly as the disease progresses. Each of the neurotransmitters that influences SAI are also associated with cognitive impairment in aging and PD (7,8). The relationship between mobility dysfunction and SAI, as well as between cognition and mobility suggests that the relationship between SAI and mobility disability may be mediated by cognitive dysfunction. However, this mediation effect remains speculative, because no investigation to date has assessed the relationships among mobility, SAI, and cognition in the same group of people with PD or OA.

The aim of this investigation was to determine the relationships between SAI and mobility (objective gait and balance characteristics) in people with PD and OAs. We hypothesized that SAI, gait, postural sway, and cognition will all be worse in people with mild PD compared to healthy OAs. Additionally, we hypothesize that SAI significantly relates to different gait and balance characteristics in people with PD compared to OAs. Further, we hypothesized that cognition mediates, or directly influences, the relationship between SAI and mobility.

Method

Both University of Washington and Oregon Health & Science University Institutional Review Boards approved this study, where the subjects were recruited and tested. All participants provided written informed consent.

Subjects and Clinical Assessments

Eighty-one participants with idiopathic PD and 69 healthy OAs were recruited from an ongoing Pacific Udall Center project. Participants were screened for TMS eligibility before enrollment. Inclusion criteria included diagnosis of idiopathic PD using the United Kingdom Parkinson's Disease Society Brain Bank criteria (19), being on a dopaminergic therapy, and ability to stand unsupported for 30 seconds. Exclusion criteria included: inability to walk for 2 minutes without an assistive device, any TMS contraindication, any musculoskeletal injury/abnormality that would affect mobility, or any neurological disorder aside from PD. All participants with PD were tested ON their normal dopaminergic therapy due to the interaction with SAI (18).

The Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III, and the modified Hoehn & Yahr (HY) score were used by a movement disorders neurologist to assess motor and disease severity (20). Additionally, each participant was assigned a cognitive diagnosis of no cognitive impairment, mild cognitive impairment, or PD dementia at a diagnostic consensus conference (20).

The PD group was slightly younger (67.4 years [7.7] vs 69.9 [6.6]; $p = .04$), had fewer years of education (16.1 [2.3] vs 17.0 [2.0]; $p = .02$), and a higher MDS-UPDRS III score (25.0 [12.9] vs 2.2 [3.8]; $p < .01$) than the OA group. A chi-squared test indicated that the proportion of males was higher in the PD group (69% vs 49%; $p < .05$). The PD group had 46 participants designated as having mild cognitive impairment and 7 with PD dementia, while the OA group had 23 participants designated with mild cognitive impairment and 1 with dementia. Lastly, the PD group had a median H&Y score of 2.0 (minimum: 1; maximum: 4), a disease duration of 7.9 (4.8) years, and an average calculated (21) levodopa equivalent daily dose (LEDD) of 701.6 mg/d (519.8).

Transcranial Magnetic Stimulation

TMS of the motor cortex was performed with a Magstim 200 (Magstim Co.). A figure-of-eight coil (external loop diameter of 9 or 7 cm, site specific) was positioned over the hemisphere associated with the most affected hand in PD participants and the dominant hand in control participants. Motor-evoked potentials (MEPs) were recorded from the first dorsal interosseous muscle through disposable, Ag/AgCl surface electrodes. Samples were amplified (gain: 2000) and bandpass filtered (100–5 kHz) using BIOPAC MP150 system (BIOPAC Systems, Inc.) or amplified (CED 1902 isolated preamplifier, Cambridge Electronics), converted from analog to digital (sampling rate 40 KHz, PowerLab, ADInstruments), and recorded for offline analysis (LabChart, ADInstruments). Resting motor threshold was determined as the percentage of the minimum stimulator output to elicit an MEP of 50 μV in 5 out of 10 trials.

Short-Latency Afferent Inhibition

SAI was performed using a modified version of a protocol previously described (14). A peripheral, electric conditioning stimulus was applied over the median nerve followed by the central test stimulus,

TMS. The intensity of the conditioning stimulus was set at the amplitude required to elicit a visible twitch of the first dorsal interosseous muscle. For the purpose of this investigation, we used 20 ms as the N20 latency across all participants. The interstimulus intervals (ISIs) were randomly applied from N20 + 0 ms to N20 + 5 ms, in 1-ms increments. A total of 10 trials were collected and the conditioned peak-to-peak MEP magnitudes averaged for each ISI. A grand mean of the ISIs is expressed as the percentage of the unconditioned MEP magnitudes. Participants were instructed to remain at rest, while sitting as still as possible, and refrain from keeping their eyes closed.

Cognition

The cognitive assessments included the following domains: (i) learning and memory (Hopkins Verbal Learning Test-Revised [HVLT-R], immediate and delayed recall trials and Logical Memory I and II); (ii) visuospatial processing (Judgment of Line Orientation [JLO]); and (iii) executive function/working memory/attention (phonemic verbal fluency, Stroop test, Trail Making Test, parts A and B [TMT A and B], Letter–Number Sequencing Test [LNST]), language (Boston Naming Test, semantic verbal fluency), and global cognition (Montreal Cognitive Assessment [MoCA]). For analyses including the TMT, part A was subtracted from part B to minimize the effect of motor disability, as previously described (20).

Gait and Postural Sway

Inertial sensors (Opals, APDM Inc.) were placed on each wrist and foot, around the waist, and over the sternum to characterize gait and standing postural sway using Mobility Lab software (APDM, Inc.) (22). Gait was characterized over a 2-minute, single- (ST) and dual-task (DT) walk back and forth over a 7-m path, requiring 180 degree turns at the ends of the marked path. The secondary task was a modified AX-continuous performance task (23). Participants listened to a series of letters through headphones while walking and were instructed to depress a hand-held button as quickly as possible when the letter sequence "A-X" was presented. Participants were instructed to walk at a comfortable, self-selected pace. Gait variables of interest were gait speed, stride length, stride length variability, foot strike angle, foot strike angle variability, turn duration, peak turn velocity, and number of steps in a turn. Postural sway was characterized while participants stood quietly for 1 minute looking straight ahead with feet width standardized by a template (24). The postural sway variables of interest were jerk in the sagittal and coronal planes, root mean square relative to the mean (RMS) in the sagittal and coronal planes, and sway area (25). Each of the gait and postural sway variables were selected due to their importance to gait and postural sway in people with PD (26).

Statistical Analyses

Data were inspected for normality using histograms and the Kolmogorov–Smirnov test. Gait variability and postural sway variables were not normally distributed, and were log base-10 transformed to improve normality. Dual-task cost (DTC; %) was calculated ([DT – ST]/ST × 100) for each gait and sway characteristic. Independent samples *t* tests were used to compare group differences across demographic and SAI variables. Multivariate general linear models compared group differences for cognitive, gait, and postural sway performance. Four multivariate general linear models were used for ST and DT gait and postural sway variables, and one multivariate general linear model was used for all of the cognitive variables. Age, education history, sex, and site were used as covariates. Pillai's Trace *F* statistic was used to test the significance of each variable in the multivariate general linear model analyses. We did not apply a statistical correction for multiple comparisons because no post hoc analyses were required as there are only 2 groups (PD and OAs). The between-subject effects reported are a continuation of the cognition, gait, and postural sway variables entered in the omnibus GLM. Because we were testing a prespecified set of hypotheses involving correlated variables, we did not adjust *p*-values for multiple comparisons (27). Partial correlations and a series of linear regression models with mobility as the dependent variable and SAI, cognition, and covariates as independent variables assessed the mediation of the relationships. To determine whether cognition was a mediator in the causal pathway between SAI and mobility, we first tested the effect of SAI on gait and sway outcomes, while controlling for covariates. The cognitive variable was then introduced to the regression models with mobility outcomes to determine if cognition was directly associated with the outcome. Observation of at least a 10% change in the standardized β coefficient for SAI would provide evidence of mediation by cognition (28). Alpha was set a priori to $p < .05$. IBM SPSS version 25 was used for statistical analyses.

Results

Short-Latency Afferent Inhibition

The PD group exhibited worse SAI than the OA group (77.0 [18.9] versus 69.9 [21.7], respectively; $F_{(1,148)}$: 4.47; $p = .04$) as seen in Figure 1. Although there was quite a bit of overlap, 48/81 PD subjects showed 20% or less inhibition whereas 28/69 OA showed 20% or less inhibition.

Cognitive Assessments

The PD group named significantly fewer animals, had a significantly worse immediate memory score for the Logical Memory test, fewer words read for Stroop reading, and significantly slower times-to-complete the TMT A test than the OA group. A multivariate general linear model test yielded significant effects for age ($F_{(14,127)}$: 2.79; $p < .01$), education history ($F_{(14,127)}$: 2.39; $p = .01$), sex ($F_{(14,127)}$: 5.06; $p < .01$), site ($F_{(14,127)}$: 4.39; $p < .01$), and PD status ($F_{(14,127)}$: 2.18; $p = .01$). Table 1 provides the results for cognitive results.

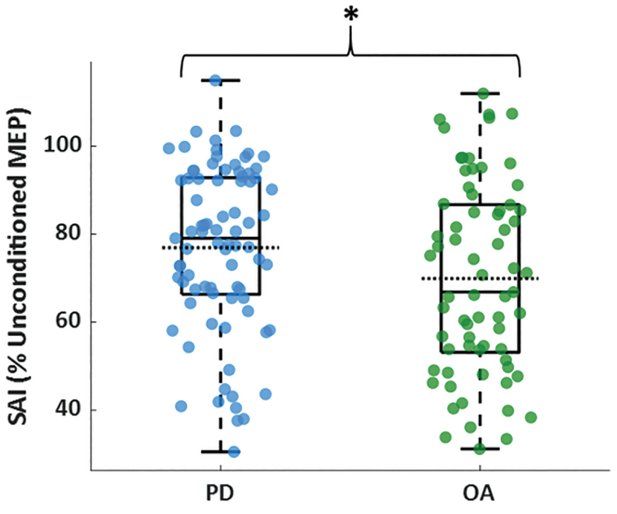

Figure 1. Group box-and-scatter plots for short-latency afferent inhibition (SAI). Dashed line represents the group mean. *$p < .05$. Full color version is available within the online issue.

Gait and Postural Sway Characteristics

The PD group walked with a reduced gait speed and foot strike angle, shorter stride length, increased foot strike angle variability and increased stride length variability, more steps in a turn, slower peak turn velocity, and longer turn durations than the OA group in both the ST and DT gait conditions. For ST gait, the multivariate general linear model test yielded significant effects for age ($F_{(8,137)}$: 3.02; $p < .01$), sex ($F_{(8,137)}$: 8.34; $p < .01$), and PD status ($F_{(8,137)}$: 5.98; $p < .01$). For DT gait, the multivariate general linear model test yielded significant effects for age ($F_{(8,136)}$: 2.99; $p < .01$), sex ($F_{(8,136)}$: 5.41; $p < .01$), site ($F_{(8,136)}$: 2.10; $p = .04$), and PD status ($F_{(8,136)}$: 8.38; $p < .01$). There were no significant effects of group for the DTC of gait. Table 2 provides the results for the gait assessment.

The PD group exhibited greater sway across all the sway characteristics and sway conditions (ST and DT) than the OA group. The multivariate general linear model for ST postural sway only yielded a significant effect for PD status ($F_{(5,140)}$: 7.83; $p < .01$). While the multivariate general linear model for DT postural sway yielded a

Table 1. Cognitive Performance

		PD	OA	*p*
Learning and memory	HVLT immediate	24.1 (6.3)	24.2 (4.6)	>.05
	Logical Memory immediate	**12.9 (3.9)**	**14.7 (3.8)**	**.04**
	HVLT delayed	8.4 (2.9)	8.5 (2.3)	>.05
	Logical Memory delayed	11.8 (4.2)	13.3 (4.1)	>.05
Visuospatial	JLO	12.4 (1.9)	12.6 (2.1)	>.05
Executive function/working memory/attention	Phonemic fluency	45 (14.3)	48.8 (11.6)	>.05
	Stroop interference	35.8 (9.9)	37.0 (8.5)	>.05
	TMT B-A (s)	53.3 (44.6)	42.3 (23.9)	>.05
	LNST	10.0 (2.3)	10.0 (2.1)	>.05
	Stroop reading	**86.2 (17.8)**	**95.7 (14.8)**	**.01**
	TMT A (s)	**35.1 (13.8)**	**29.3 (8.3)**	**<.01**
Language	**Semantic fluency**	**19 (6.4)**	**21.7 (4.8)**	**.01**
	Boston Naming Test	28.7 (1.4)	28.9 (4.8)	>.05
Global cognition	MoCA	25.9 (3.0)	26.3 (3.0)	>.05

Note: HVLT = Hopkins Verbal Learning Test; JLO = Judgment of Line Orientation; LNST = Letter–Number Sequencing Test; MoCA = Montreal Cognitive Assessment; OA = older adult; PD = Parkinson's disease; TMT A and B = Trail Making Test, parts A and B. The bolded variables are significantly different between groups. Values are mean (*SD*).

Table 2. Gait and Sway Variables

			PD	OA	*p*
Gait	ST	Gait speed (m/s)	1.06 (0.18)	1.12 (0.17)	>.05
		Foot strike angle (°)	19.62 (6.27)	23.27 (4.23)	<.01
		Foot strike angle variability	2.36 (0.88)	2.09 (0.67)	.04
		Stride length (m)	1.16 (0.18)	1.20 (0.14)	>.05
		Stride length variability	0.05 (0.03)	0.04 (0.02)	.04
		Turn duration (s)	2.37 (0.39)	2.15 (0.33)	<.01
		Peak turn velocity (°/s)	159.84 (36.18)	184.50 (35.72)	<.01
		# Steps in a turn	4.09 (0.75)	3.67 (0.55)	<.01
	DT	Gait speed (m/s)	1.01 (0.20)	1.09 (0.18)	.04
		Foot strike angle (°)	18.31 (6.60)	22.38 (4.24)	<.01
		Foot strike angle variability	2.51 (1.03)	2.15 (0.81)	.04
		Stride length (m)	1.11 (0.20)	1.18 (0.14)	.03
		Stride length variability	0.06 (0.03)	0.05 (0.04)	.02
		Turn duration (s)	2.44 (0.41)	2.17 (0.33)	<.01
		Peak turn velocity (°/s)	156.77 (34.22)	183.54 (33.00)	<.01
		# Steps in a turn	4.24 (0.86)	3.77 (0.60)	<.01
Sway	ST	Jerk AP (cm/s^3)	0.004 (0.005)	0.002 (0.002)	.02
		Jerk ML (cm/s^3)	0.003 (0.011)	0.001 (0.0003)	<.01
		RMS AP (cm/s^2)	0.101 (0.058)	0.070 (0.025)	<.01
		RMS ML (cm/s^2)	0.042 (0.038)	0.021 (0.010)	<.01
		Sway area (cm^2)	0.008 (0.010)	0.003 (0.002)	<.01
	DT	Jerk AP (cm/s^3)	0.005 (0.007)	0.003 (0.002)	.01
		Jerk ML (cm/s^3)	0.008 (0.045)	0.001 (0.002)	<.01
		RMS AP (cm/s^2)	0.100 (0.056)	0.067 (0.029)	<.01
		RMS ML (cm/s^2)	0.045 (0.045)	0.021 (0.011)	<.01
		Sway area (cm^2)	0.011 (0.019)	0.003 (0.002)	<.01

Note: AP = anterior-Posterior; DT = dual task; ML = medial-lateral; OA = older adult; PD = Parkinson's disease; RMS = root mean square; ST = single task. The gait variability and all sway measures were log transformed for analyses. Values are mean (*SD*).

significant effect for PD status ($F_{(5,140)}$: 6.50; $p < .01$) and sex ($F_{(5,140)}$: 2.84; $p = .02$). The PD and OA groups did not differ for the DTC of sway. Table 2 provides the results for the sway assessment.

Correlations With SAI

In the PD group, SAI significantly correlated with foot strike angle variability, stride length variability, jerkiness of sway in the medio-lateral and antero-posterior directions, as well as sway area during ST gait and ST postural sway. The positive correlations indicate that worse (less inhibition) SAI related to worse (increased) gait and sway variability in the PD group. SAI did not relate to any cognitive variable in the PD group. See Figure 2A–E for the significant correlations between SAI and gait/sway for the PD group.

In the OA group, SAI was significantly related to ST gait speed, as well as stride length under ST and DT conditions. The negative correlations indicate that worse (less inhibition) SAI related to slower gait and reduced stride length in the OA group. Further, SAI was significantly correlated with the memory test outcome, HVLT immediate recall. The negative correlations indicate that worse (less inhibition) SAI related to fewer recalled words in the OA group. See Figure 2F–I for the significant correlations between the SAI and gait/cognition for the OA group. Supplementary Figures 1–3 provide the relationships between SAI and every cognitive, gait, and postural sway variable.

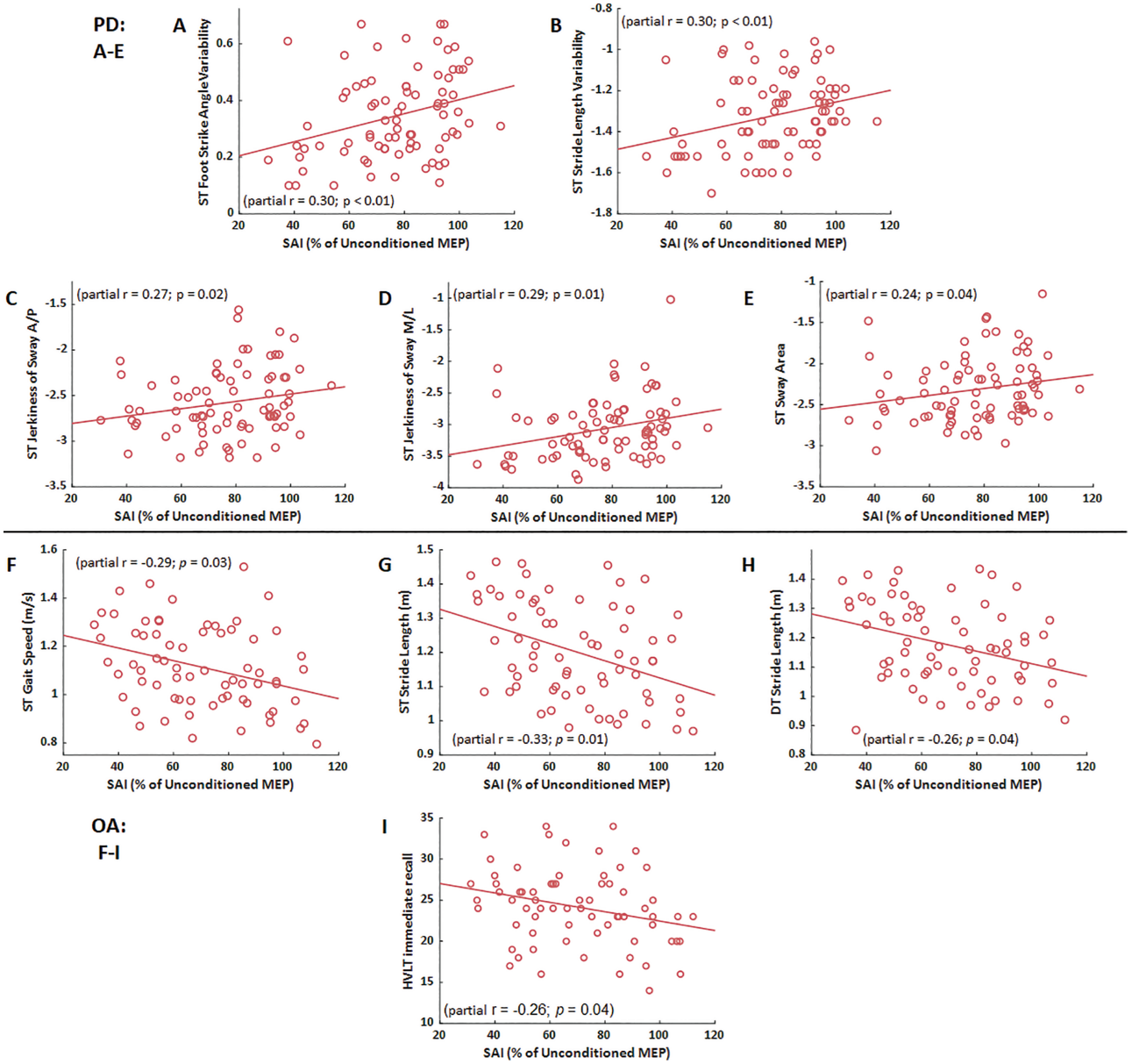

Figure 2. (**A–E**) Scatter plots only include the Parkinson's disease (PD) group. The plots highlight the significant relationships between short-latency afferent inhibition (SAI) and variability-related gait metrics; SAI and jerkiness of sway; as well as SAI and sway area. (**F–I**). Scatter plots only include the older adult (OA) group. The plots highlight the significant relationships between SAI and pace-related gait metrics, as well as SAI and memory (Hopkins Verbal Learning Test [HVLT] immediate recall). Lines represent the best-fit line. All correlations are significant ($p < .05$). Full color version is available within the online issue.

Regression Analyses

Since SAI was not related to cognition in the PD group, cognition cannot be a mediator in the relationship between SAI and mobility in this sample of people with PD. A mediation requires a relationship across all factors in the proposed mediation. However, SAI was related to verbal learning (HVLT immediate recall) and gait (speed and stride length) in the OA group. Mediation analysis was performed in the OA group only for the gait characteristics significantly correlated with SAI. The following regression analyses characterize how much memory may directly influence the relationship between SAI and mobility in OAs. Age, education history, sex, and site were included as covariates, as previously discussed. None of the variables in any of the regression models had a variance inflation factor greater than 1.4, establishing that multicollinearity was not an issue.

We found little or no evidence that cognition mediated the relationship between SAI and gait characteristics. The adjusted (age, education history, sex, and site) SAI significantly related to ST gait speed (β = −0.27; *SE* = 0.13; *p* = .04) and ST stride length (β = −0.27; *SE* = 0.11; *p* = .02) in the OA group. However, the adjusted SAI was not a significant predictor of DT stride length. When the HVLT immediate recall variable was included in the model for ST gait speed, the standardized β for SAI decreased by 16% to −0.23 (*SE* = 0.13) and was no longer a significant predictor of gait speed. Although the standardized β for SAI decreased by more than the suggested 10% minimum (28) with memory test scores in the model, the effect was very small. When the HVLT total recall variable was included in the model for stride length, the standardized β for SAI decreased only 5% to −0.26 (*SE* = 0.11; *p* = .04). HVLT immediate recall was never a significant predictor of either gait characteristic in the regression models. See Figure 3 for the conceptualization of the model.

Discussion

This is the first investigation to assess SAI, cognition, gait, and postural sway in the same participants with and without PD. Our results show that people with PD have impaired SAI, cognition, gait, and postural sway compared to OAs. Impaired SAI either related to increased gait variability (in the PD group) or to decreased gait pace (in the OA group). Interestingly, we observed a relationship between SAI and postural sway in the PD group, which is the first report of this relationship. We also observed a relationship between SAI and memory in the OA cohort.

SAI, a measure of cortical sensorimotor inhibition, is worse in people with PD than OAs as observed herein and in previous reports (12,13,18). SAI is a neurophysiological assessment of sensorimotor inhibition generated by observing inhibition of a digit muscle twitch in response to motor cortex stimulation immediately following sensor stimulation from the same arm. To date, the exact pathway responsible for SAI remains unknown. However, the neurotransmitters active in the pathway have been identified through drug and disease studies, which implicate GABA (17) and acetylcholine (15,16), as well as dopamine (18). This observed influence by dopamine is specific to the PD population such that SAI is impaired only when people are ON their dopamine replacement therapy.

Similar to previous studies (12,13,29–32), the PD group exhibited slower gait pace and turning characteristics, with increased gait variability compared to the OA group. Emerging evidence highlights the importance of the gait variability for fall risk in both PD and OA groups (32,33). Similarly, impaired turning relates to falls (4). The number of turns that occur daily in the real world, exceeds 700 (34), presenting multiple scenarios for a fall to occur in a day. Compounding this gait dysfunction, the PD group also had greater postural sway area and jerkiness of sway during quiet stance compared to the OAs, which also mimics previous observations (35–37). All of these gait and postural sway differences were observed in the presence of the PD group ON their dopaminergic medication, suggesting that simply increasing the available dopamine does not improve all mobility dysfunction inherent to PD, even in this relatively mild group. Other neurotransmitter networks, perhaps reliant on modulation of dopamine, are likely to be a factor in mobility dysfunction in PD.

SAI significantly related to multiple characteristics of gait, including the pace and variability gait domains (26). We showed that worse sensorimotor inhibition related to increased gait variability in people with PD, but related to decreased gait speed and stride length in OAs. These results conflict and expand previous studies that observed relationships between SAI and pace-related variables in people with PD (12,13). However, one of these investigations observed a relationship between SAI and the percent change (ie, DTC) in gait speed under a dual-task gait condition in a group of PD fallers, OA fallers, and OA nonfallers (12). Conversely, we observed no relationships between SAI and DTC on gait in either group, perhaps because our PD group was more mild and we did not recruit fallers. In our cohort, only 8 (2 OAs) reported 1 or 2 falls within the previous 3 months of participation.

Increased gait variability is associated with a loss of gait automaticity and to increased fall risk (32). If increased gait variability reflects lack of gait automaticity, impaired sensorimotor inhibition (SAI) may reflect inability to control gait automatically and an increased reliance on cortical attentional networks, which also play a significant role in overall cognition. The PD group exhibited worse executive function and working memory, which suggests an impaired cognitive reserve. Combined with impaired gait automaticity, people with PD may be over-taxing their cognitive reserve in order to perform activities of daily living without falling. Similar to increased gait variability, increased DTC also reflects loss of gait automaticity (32). The lack of group differences for DTC on

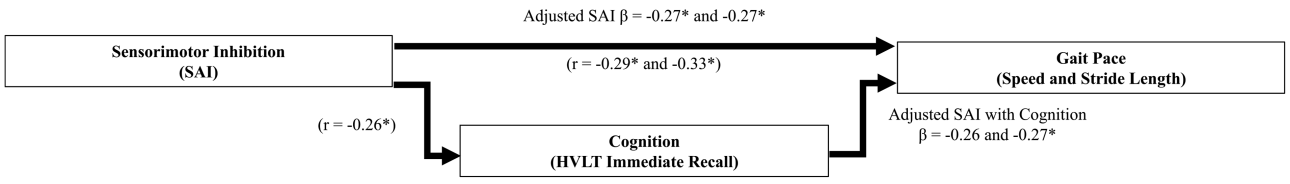

Figure 3. Mediation hypothesis: The regression-based mediation analyses do not support this hypothesis. In older adults (OAs), sensorimotor inhibition (SAI) correlated with gait pace (speed and stride length) and with cognition (Hopkins Verbal Learning Test [HVLT] immediate recall). However, there is no effect on the adjusted SAI β when cognition is entered into the regression model has with gait pace. *r* = partial correlation coefficient; Adjusted = age, education history, sex, and site variables in regression model; **p* < .05.

gait and sway, as well as no observed relationship between SAI and DTC, may reflect a lack of difficulty of the secondary task chosen for this investigation. Additionally, a difference in severity of PD may account for different results across these studies. The MDS-UPDRS III scores for the previous investigations were 29 (13) and 30 (12), whereas the people with PD in this investigation had a MDS-UPDRS III score of 25, suggesting more mild PD. Further, Pelosin et al. (12) recruited PD fallers exclusively, while this study did not limit recruitment to PD fallers. However, regardless of disease duration or motor dysfunction severity, SAI is consistently worse in people with PD compared to OAs.

We report the first observed relationship between worse SAI and increased jerkiness of sway and sway area in people with PD. This relationship, only observed in the PD group, could be influenced by dopaminergic therapy. While in the ON dopaminergic medication state, people with PD have worse SAI then during their OFF state (18). Further, while in the ON state, people with PD do not exhibit improved postural sway compared to the OFF state (2,35). Our PD group was tested in the ON dopaminergic medication state, which would cause worse inhibition (SAI) and worse postural sway. A dysfunctional pathway between the basal ganglia and sensorimotor cortex could be responsible for the relationship between SAI and postural sway observed in our ON dopaminergic medication state PD group. Indeed, a recent imaging investigation observed a change in functional connectivity pathways between the basal ganglia and sensorimotor cortex in people with PD from the OFF to ON medication states (38).

The importance of cognition in gait control is supported by the effect of cognitive impairment on gait variability (39,40). SAI did not relate to cognition in this group of people with PD, but related to memory in OAs. A recent review of the literature suggests that SAI has a stronger relationship with memory and, while the relationship between SAI and attention was the weakest among the 4 cognitive domains (eg, visuospatial, memory, executive function, and attention) included (41). Similarly, we observed that impaired memory was significantly related to impaired SAI and attention was not. An important distinction is that we observed these relationships in our OA group, while the review specifically described the relationship between cognition and SAI in people with PD (41).

There are potential limitations to the interpretation of the results of this investigation. First, TMS was collected at 2 different academic centers. However, the SAI grand mean is represented by a percentage of the participant's own MEPs, eliminating device influence. However, to be certain, there was no uncontrolled effect of site, we created a site variable and implemented it as a covariate throughout the analyses. Second, the effect of sex on SAI is unknown. Therefore, we statistically controlled for this limitation. Lastly, the participants with PD are more mild than moderate for severity, which may have led to differences in observations in this study compared to the literature and limit the generalizability of the results to mild PD.

This investigation confirmed that people with mild PD have worse cortical sensorimotor inhibition, cognition, gait, and sway than OAs. Further, worse cortical sensorimotor inhibition has different relationships to gait characteristics depending on Parkinson's status. Impaired inhibition related to slower gait in OA and to increased gait variability and postural sway in people with PD, all of which have been shown to be related to increased fall risk.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

Supplemental Figure 1. Dot and line graph presenting the magnitude of the relationships between SAI and each cognitive assessment outcomes for the PD (asterisks) and OA (circles) groups

Supplemental Figure 2. Dot and line graph presenting the magnitude of the relationships between SAI and each gait characteristic for the PD (asterisks) and OA (circles) groups.

Supplemental Figure 3. Dot and line graph presenting the magnitude of the relationships between SAI and each postural sway characteristic for the PD (asterisks) and OA (circles) groups.

Funding

This work was supported by the Pacific Udall Center (P50 NS062684) and the Department of Veterans Affairs Northwest Parkinson's Disease Research, Education and Clinical Center.

Conflict of Interest

Dr. Horak has a significant financial interest in APDM, a company that may have a commercial interest in the results of this research and technology for measuring mobility. This potential institutional and individual conflict has been reviewed and managed by OHSU. No other author has a financial disclosure to claim.

Acknowledgments

This publication was made possible with support from the Oregon Clinical and Translational Research Institute (UL1TR002369), from the National Center for Advancing Translational Sciences, and NIH Roadmap for Medical Research.

References

1. Smulders K, Dale ML, Carlson-Kuhta P, Nutt JG, Horak FB. Pharmacological treatment in Parkinson's disease: effects on gait. *Parkinsonism Relat Disord*. 2016;31:3–13. doi:10.1016/j.parkreldis.2016.07.006
2. Curtze C, Nutt JG, Carlson-Kuhta P, Mancini M, Horak FB. Levodopa is a double-edged sword for balance and gait in people with Parkinson's disease. *Mov Disord*. 2015;30:1361–1370. doi:10.1002/mds.26269
3. Stevens JA, Mack KA, Paulozzi LJ, Ballesteros MF. Self-reported falls and fall-related injuries among persons aged ≥ 65 years–United States, 2006. *J Safety Res*. 2008;39:345–349. doi:10.1016/j.jsr.2008.05.002
4. Bloem BR, Grimbergen YA, Cramer M, Willemsen M, Zwinderman AH. Prospective assessment of falls in Parkinson's disease. *J Neurol*. 2001;248:950–958. doi:10.1007/s004150170047
5. Stolze H, Klebe S, Baecker C, et al. Prevalence of gait disorders in hospitalized neurological patients. *Mov Disord*. 2005;20:89–94. doi:10.1002/mds.20266
6. Müller ML, Bohnen NI. Cholinergic dysfunction in Parkinson's disease. *Curr Neurol Neurosci Rep*. 2013;13:377. doi:10.1002/mds.20266
7. Barone P. Neurotransmission in Parkinson's disease: beyond dopamine. *Eur J Neurol*. 2010;17:364–376. doi:10.1111/j.1468-1331.2009.02900.x
8. Brichta L, Greengard P, Flajolet M. Advances in the pharmacological treatment of Parkinson's disease: targeting neurotransmitter systems. *Trends Neurosci*. 2013;36:543–554. doi:10.1016/j.tins.2013.06.003
9. Bohnen NI, Frey KA, Studenski S, et al. Gait speed in Parkinson disease correlates with cholinergic degeneration. *Neurology*. 2013;81:1611–1616. doi:10.1212/WNL.0b013e3182a9f558
10. Müller ML, Albin RL, Kotagal V, et al. Thalamic cholinergic innervation and postural sensory integration function in Parkinson's disease. *Brain*. 2013;136(Pt 11):3282–3289. doi:10.1093/brain/awt247

11. Morris R, Martini DN, Madhyastha T, et al. Overview of the cholinergic contribution to gait, balance and falls in Parkinson's disease. *Parkinsonism Relat Disord*. 2019;63:20–30. doi:10.1016/j.parkreldis.2019.02.017
12. Pelosin E, Ogliastro C, Lagravinese G, et al. Attentional control of gait and falls: is cholinergic dysfunction a common substrate in the elderly and Parkinson's disease? *Front Aging Neurosci*. 2016;8:104. doi:10.3389/fnagi.2016.00104
13. Rochester L, Yarnall AJ, Baker MR, et al. Cholinergic dysfunction contributes to gait disturbance in early Parkinson's disease. *Brain*. 2012;135(Pt 9):2779–2788. doi:10.1093/brain/aws207
14. Tokimura H, Di Lazzaro V, Tokimura Y, et al. Short latency inhibition of human hand motor cortex by somatosensory input from the hand. *J Physiol*. 2000;523 Pt 2:503–513. doi:10.1111/j.1469-7793.2000.t01-1-00503.x
15. Di Lazzaro V, Pilato F, Dileone M, et al. In vivo cholinergic circuit evaluation in frontotemporal and Alzheimer dementias. *Neurology*. 2006;66:1111–1113. doi:10.1212/01.wnl.0000204183.26231.23
16. Di Lazzaro V, Oliviero A, Profice P, et al. Muscarinic receptor blockade has differential effects on the excitability of intracortical circuits in the human motor cortex. *Exp Brain Res*. 2000;135:455–461. doi:10.1007/s002210000543
17. Di Lazzaro V, Oliviero A, Saturno E, et al. Effects of lorazepam on short latency afferent inhibition and short latency intracortical inhibition in humans. *J Physiol*. 2005;564(Pt 2):661–668. doi:10.1113/jphysiol.2004.061747
18. Sailer A, Molnar GF, Paradiso G, Gunraj CA, Lang AE, Chen R. Short and long latency afferent inhibition in Parkinson's disease. *Brain*. 2003;126(Pt 8):1883–1894. doi:10.1093/brain/awg183
19. Hughes AJ, Colosimo C, Kleedorfer B, Daniel SE, Lees AJ. The dopaminergic response in multiple system atrophy. *J Neurol Neurosurg Psychiatry*. 1992;55:1009–1013. doi:10.1136/jnnp.55.3.181
20. Cholerton BA, Zabetian CP, Quinn JF, et al. Pacific Northwest Udall Center of Excellence Clinical Consortium: study design and baseline cohort characteristics. *J Parkinsons Dis*. 2013;3:205–214. doi:10.3233/JPD-130189
21. Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. *Mov Disord*. 2010;25:2649–2653. doi:10.1002/mds.23429
22. Mancini M, King L, Salarian A, Holmstrom L, McNames J, Horak FB. Mobility lab to assess balance and gait with synchronized body-worn sensors. *J Bioeng Biomed Sci*. 2011;Suppl. 1:007. doi:10.4172/2155-9538.S1-007
23. Tekok-Kilic A, Shucard JL, Shucard DW. Stimulus modality and Go/NoGo effects on P3 during parallel visual and auditory continuous performance tasks. *Psychophysiology*. 2001;38:578–589. doi:10.1017/S0048577201991279
24. Maki BE, Holliday PJ, Fernie GR. Aging and postural control. A comparison of spontaneous- and induced-sway balance tests. *J Am Geriatr Soc*. 1990;38:1–9. doi:10.1111/j.1532-5415.1990.tb01588.x
25. Mancini M, Salarian A, Carlson-Kuhta P, et al. ISway: a sensitive, valid and reliable measure of postural control. *J Neuroeng Rehabil*. 2012;9:59. doi:10.1186/1743-0003-9-59
26. Morris R, Martini DN, Smulders K, et al. Cognitive associations with comprehensive gait and static balance measures in Parkinson's disease. *Parkinsonism Relat Disord*. 2019;69:104–110.
27. Rothman KJ. No adjustments are needed for multiple comparisons. *Epidemiology*. 1990;1:43–46.
28. Greenland S. Modeling and variable selection in epidemiologic analysis. *Am J Public Health*. 1989;79:340–349. doi:10.2105/ajph.79.3.340
29. Hausdorff JM. Gait dynamics in Parkinson's disease: common and distinct behavior among stride length, gait variability, and fractal-like scaling. *Chaos*. 2009;19:026113. doi:10.1063/1.3147408
30. Morris ME, Huxham F, McGinley J, Dodd K, Iansek R. The biomechanics and motor control of gait in Parkinson disease. *Clin Biomech (Bristol, Avon)*. 2001;16:459–470. doi:10.1016/s0268-0033(01)00035-3
31. Stack E, Ashburn A. Dysfunctional turning in Parkinson's disease. *Disabil Rehabil*. 2008;30:1222–1229. doi:10.1080/09638280701829938
32. Yogev G, Giladi N, Peretz C, Springer S, Simon ES, Hausdorff JM. Dual tasking, gait rhythmicity, and Parkinson's disease: which aspects of gait are attention demanding? *Eur J Neurosci*. 2005;22:1248–1256. doi:10.1111/j.1460-9568.2005.04298.x
33. Hausdorff JM, Balash J, Giladi N. Effects of cognitive challenge on gait variability in patients with Parkinson's disease. *J Geriatr Psychiatry Neurol*. 2003;16:53–58.
34. Mancini M, El-Gohary M, Pearson S, et al. Continuous monitoring of turning in Parkinson's disease: rehabilitation potential. *NeuroRehabilitation*. 2015;37:3–10.
35. Horak FB, Frank J, Nutt J. Effects of dopamine on postural control in parkinsonian subjects: scaling, set, and tone. *J Neurophysiol*. 1996;75:2380–2396. doi:10.1152/jn.1996.75.6.2380
36. Horak FB, Mancini M, Carlson-Kuhta P, Nutt JG, Salarian A. Balance and gait represent independent domains of mobility in Parkinson disease. *Phys Ther*. 2016;96:1364–1371. doi:10.2522/ptj.20150580
37. Mancini M, Horak FB, Zampieri C, Carlson-Kuhta P, Nutt JG, Chiari L. Trunk accelerometry reveals postural instability in untreated Parkinson's disease. *Parkinsonism Relat Disord*. 2011;17:557–562. doi:10.1016/j.parkreldis.2011.05.010
38. Gilat M, Bell PT, Ehgoetz Martens KA, et al. Dopamine depletion impairs gait automaticity by altering cortico-striatal and cerebellar processing in Parkinson's disease. *Neuroimage*. 2017;152:207–220. doi:10.1016/j.neuroimage.2017.02.073
39. Montero-Odasso M, Muir SW, Speechley M. Dual-task complexity affects gait in people with mild cognitive impairment: the interplay between gait variability, dual tasking, and risk of falls. *Arch Phys Med Rehabil*. 2012;93:293–299. doi:10.1016/j.apmr.2011.08.026
40. Muir SW, Speechley M, Wells J, Borrie M, Gopaul K, Montero-Odasso M. Gait assessment in mild cognitive impairment and Alzheimer's disease: the effect of dual-task challenges across the cognitive spectrum. *Gait Posture*. 2012;35:96–100. doi:10.1016/j.gaitpost.2011.08.014
41. Martin-Rodriguez JF, Mir P. Short-afferent inhibition and cognitive impairment in Parkinson's disease: a quantitative review and challenges. *Neurosci Lett*. 2020;719:133679. doi:10.1016/j.neulet.2018.06.048