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4 **Exploring the Effects of Dopamine on Sensorimotor Inhibition and Mobility in**
5 **Older Adults**
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4 **Abstract**

5 Background: Dopaminergic activity decreases in older adults (OAs) with normal aging and is
6 further reduced in Parkinson's disease (PD), affecting cortical motor and sensorimotor
7 pathways. Levodopa is the prevailing therapy to counter dopamine loss in PD, though not all PD
8 motor signs improve with levodopa. The purpose of this preliminary study was to explore the
9 effects of levodopa on sensorimotor inhibition, gait and quiet standing in OAs and to investigate
10 the relationships between sensorimotor inhibition and both gait and standing balance both OFF-
11 and ON-levodopa.
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21 Methods: Fifteen OA males completed a gait, balance and sensorimotor assessments before
22 and one hour after they were given a 100mg dose of levodopa. Short-latency afferent inhibition
23 quantified sensorimotor inhibition. Wearable sensors characterized gait (two-minute walk) and
24 standing balance (one-minute stance).
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30 Results: No sensorimotor inhibition, gait, or standing balance measures changed from OFF- to
31 ON-levodopa. When OFF-levodopa, worse inhibition significantly related to
32 increased double stance ($r=0.62$; $p=0.01$), increased jerkiness of sway ($r=0.57$; $p=0.03$) and
33 sway area ($r=0.58$; $p=0.02$). While ON-levodopa, worse inhibition related to increased arm
34 swing range of motion ($r=0.63$; $p=0.01$) and jerkiness of sway ($r=0.53$; $p=0.04$). The relationship
35 between SAI and arm swing excursion significantly changed from OFF- to ON-levodopa ($z = -$
36 3.05 ; $p = 0.002$; 95% confidence interval = $-0.95 - -0.21$).
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46 Conclusion: Sensorimotor inhibition relationships to both gait and balance may be affected by
47 dopamine in OAs. Cortical restructuring due to the loss of dopamine may be responsible for the
48 heterogeneity of levodopa effect in people with PD and OAs.
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53 **Key words:** Gait; Balance; Short-Latency Afferent Inhibition; Drug Related
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1. Introduction

Dopaminergic activity decreases in normal aging, with an exacerbated decrease observed in Parkinson's disease (PD).[1] In PD, dopaminergic denervation may result in cortical restructuring that alters the roles of neurotransmitters in motor pathways.[2] Evidence from rodent stroke indicate that dopamine has a role in sensorimotor integration in the somatosensory cortex.[3] Altered motor and sensory pathways following a decrease in dopaminergic activity manifests as gait and balance impairments in people with PD. Levodopa, a dopamine replacement medication, is the prevailing therapy to treat motor signs and symptoms of PD. However, not all PD motor signs and symptoms improve with levodopa. Some components of gait and standing balance deteriorate from OFF- to ON-levodopa states in people with PD,(Curtze and others 2015; Wilson and others 2020) but the reasons that levodopa negatively impacts some motor functions remain unclear.

Short-latency afferent inhibition (SAI), a surrogate for sensorimotor inhibition, was initially linked to cholinergic activity because the cortical inhibition quantified by SAI improved with a cholinergic agonist.[6] Other studies subsequently observed effects of gamma aminobutyric acid agonists and levodopa on SAI.(Di Lazzaro and others 2005; Di Lazzaro and others 2002; Sailer and others 2003) SAI worsens in the ON-levodopa state in people with PD.[9] Cumulatively, the implication is that SAI results from complex neurophysiological interactions controlling inhibition in the sensorimotor pathway. The reduction of sensorimotor inhibition in the ON-levodopa state may contribute to the observed heterogenous effects of levodopa on gait and balance in PD.

Although gait speed improves with dopamine in PD, postural stability during walking (double support time) and standing balance (sway area, frequency, smoothness) are unaffected or worsen with dopaminergic medication in PD.(Curtze and others 2015; Wilson and others 2020)

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4 Both gait and standing balance relate to the amount of sensorimotor inhibition quantified by SAI
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6 in people with PD, older adults (OA), and OA fallers.(Martini and others 2020; Martini and others
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8 2021; Pelosin and others 2016; Rochester and others 2012) Specifically, abnormal postural
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10 sway or slower gait are associated with worse SAI is in these populations.(Martini and others
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12 2020; Martini and others 2021; Pelosin and others 2016; Rochester and others 2012) Despite
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14 established dopaminergic decreases with aging, the effect of levodopa on these relationships is
15
16 not known.[1] Establishing the relationships among levodopa, sensorimotor inhibition, and
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18 mobility in OAs could provide greater insight into the heterogeneous effects of levodopa on
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20 mobility in PD.
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27 The purpose of this exploratory investigation was to examine the effects of levodopa on
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29 sensorimotor inhibition and mobility in OAs. Specifically, we aimed to investigate the effects of
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31 levodopa on sensorimotor inhibition, gait, and quiet standing balance in OAs. Further, we aimed
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33 to explore the relationships between sensorimotor inhibition and both gait and standing balance
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35 in OAs OFF- and ON-levodopa. We hypothesized that sensorimotor inhibition, gait stability and
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37 standing balance will be worse, while other characteristics of gait will remain unchanged from
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39 the OFF- to ON-levodopa state, consistent with the aforementioned heterogeneous effect of
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41 levodopa on gait in the PD literature. Finally, we hypothesize that worse gait stability and
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43 standing balance measures will correlate to worse sensorimotor inhibition.
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50 **2. Methods**

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52 The Oregon Health & Science University Institutional Review Board approved this study. All
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54 participants reviewed the study purpose and procedures involved before signing the informed
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56 consent.
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2.1 Participants

Fifteen healthy OA males were recruited from an ongoing Pacific Udal Center project at Oregon Health & Science University. Participants were screened for TMS eligibility before enrollment. Inclusion criteria included the ability to stand unsupported for 30 seconds. Exclusion criteria included: inability to walk for two minutes without an assistive device, any TMS contraindication, any musculoskeletal injury that would affect mobility, any neurological disorder, a failed medical screen (completed by JGN) for taking levodopa, or any cholinergic medication. A single 100/25 mg dose of levodopa/carbidopa was given to each participant after completing the “OFF-levodopa medication state” assessment. No participant reported an adverse event as a result of ingesting a single 100/25 mg dose of levodopa/carbidopa.

Each participant completed the following clinical assessments: Montreal Cognitive Assessment (MoCA; range=0-30), Activities Balance Confidence (ABC; range=0-100) scale, and the Falls Efficacy Scale (FES; range=0-100). The participants completed the MoCA prior to the OFF-levodopa state sensorimotor inhibition and mobility assessments. Upon completing the OFF-levodopa state assessments, participants were given their single 100/25 mg tablet (levodopa/carbidopa) with carbonated water and an option of fruit. Participants waited an hour before starting the “ON-levodopa state” assessments. During the wait, participants completed the ABC and FES scales. After one hour, participants completed the ON-levodopa state sensorimotor inhibition and mobility assessment in the same order as the OFF-levodopa state assessment.

2.2 Transcranial Magnetic Stimulation (TMS)

TMS of the motor cortex was performed with a Magstim 200 (Magstim Co.). A figure-of-eight coil (external loop diameter of 9cm) was positioned over the hemisphere associated with the

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4 dominant hand. Motor-evoked potentials (MEPs) were recorded from the first dorsal
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6 interosseous muscle through disposable, Ag/AgCl surface electrodes. Samples were amplified
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8 (gain: 2000) and bandpass filtered (100Hz-5kHz) using BIOPAC MP150 system (BIOPAC
9
10 Systems, Inc). Resting motor threshold was determined as the percentage of the minimum
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12 stimulator output to elicit an MEP of 50 μ V in five out of ten trials.
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18 2.3 Short-Latency Afferent Inhibition

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20 SAI was performed using a modified version of a protocol previously described.(Martini and
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22 others 2020; Martini and others 2021) Participants were instructed to remain at rest, sitting as
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24 still as possible, and refrain from keeping their eyes closed. A peripheral, electric conditioning
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26 stimulus was applied over the median nerve followed by the central test stimulus, TMS. The
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28 intensity of the conditioning stimulus was set at the amplitude required to elicit a visible twitch of
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30 the first dorsal interosseous muscle. For the purpose of this investigation, we used 20ms as the
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32 N20 latency across all participants.(Martini and others 2020; Martini and others 2021) The
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34 interstimulus intervals (ISI) were randomly applied from N20+0ms to N20+5ms, in 1ms
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36 increments. Ten trials were collected and the conditioned peak-to-peak MEP magnitudes were
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38 averaged for each ISI. The grand mean of the ISIs is expressed as the percentage of the
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40 unconditioned MEP magnitudes. A SAI grand mean around 100% indicates minimal or no
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42 sensorimotor inhibition (worse), as this indicates that the peripheral nerve stimulation ascending
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44 signal provides limited inhibition of the descending motor signal.
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52 2.4 Mobility Assessment

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54 Inertial sensors (Opals, APDM Inc.) were placed on each wrist and foot, around the waist, and
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56 over the sternum to characterize gait and standing balance using Mobility Lab software (APDM,
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58 Inc).[14] Gait was characterized during a two-minute walk, back-and-forth over a seven-meter
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4 path, requiring 180 degree turns at the ends of the marked path. Participants were instructed to
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6 walk at a comfortable, self-selected pace. Gait variables of interest were double limb support (%
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8 of gait cycle), speed (meters/second [m/s]), stride time (s), stride length (m), arm swing
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10 excursion (degrees [d]), and turn velocity (d/s). Standing balance was characterized while
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12 participants stood quietly for one minute looking straight ahead with foot position standardized
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14 by a template. The balance variables of interest were jerkiness of sway, root mean square
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16 (RMS) relative to the mean sway, sway velocity, and sway area.
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22 2.5 Statistical Analyses

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24 Data were inspected for normality using histograms and the Kolmogorov-Smirnov test. Balance
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26 variables were not normally distributed, so they were natural log transformed to improve
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28 normality. Paired samples t-tests were used to compare medication state differences in SAI, gait
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30 and balance variables. Pearson's correlations assessed the relationships between SAI and
31
32 mobility variables. For significant relationships between SAI and mobility variables, the
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34 magnitude of Pearson's correlations were statistically compared using the R statistics package
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36 cocor and Fisher's z transformation of overlapping variables (e.g. OFF and ON-levodopa).[15,
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38 16] Cohen's *d* effect sizes were calculated to characterize the magnitude of the medication
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40 effect and were interpreted as weak (<0.50), moderate (0.50-0.79) or strong (≥ 0.80).[17] Alpha
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42 was set *a priori* to $p < 0.05$. IBM SPSS version 27 was used for statistical analyses. Data are
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44 presented as mean(standard deviation), unless otherwise indicated.
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51 3. Results

52 3.1 Participants

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4 The 15 OA males that participated in this study were 65.8(6.5) years-old, with an average height
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6 of 175.1(9.4) cm and mass of 81.1(7.8) kg. The average MoCA score was 27.8(1.5), indicating
7
8 no cognitive impairment. The average FES was 10.3(0.7) and the ABC was 98.3(1.9), indicating
9
10 no fear of falling.
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15 3.2 SAI in the OFF- versus ON-levodopa states 16

17 There was no significant difference in SAI between the OFF- and ON-medication states ($t=0.56$;
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19 $p=0.59$; Cohen's $d=0.14$). The average OFF-levodopa state SAI was 66.5(17.3)% and the
20
21 average ON-levodopa state SAI was 64.4(16.3)% (**Figure 1**). Average SAI values in both OFF-
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23 and ON-levodopa states for these OAs are similar to previously reported values in OAs.(Martini
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25 and others 2020; Martini and others 2021; Pelosin and others 2016; Rochester and others
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27 2012)
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33 3.3 Gait and Standing Balance Differences Between Medication States 34

35 Levodopa had no significant effect on gait or postural sway variables (**Table 1**). Though not
36
37 significant, arm swing excursion had a moderate effect size (Cohen's $d=0.50$), with less arm
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39 swing excursion in the ON-levodopa compared to the OFF-levodopa state.
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44 3.4 Correlations Between SAI and Mobility 45

46 Worse SAI in the OFF-levodopa state significantly related to increased double limb support,
47
48 jerkiness of sway, and sway area (**Figure 2**). SAI OFF was not significantly related to OFF: gait
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50 speed ($r = -0.34$), stride time ($r = 0.24$), stride length ($r = -0.19$), arm swing excursion ($r = 0.16$),
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52 turn velocity ($r = -0.23$), RMS Sway ($r = 0.38$), or sway velocity ($r = 0.19$). Worse SAI in the ON-
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54 levodopa state significantly related to increased arm swing excursion and jerkiness of sway
55
56 (**Figure 2**). SAI ON was not significantly related to ON: double limb support ($r = 0.45$), gait
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58 speed ($r = -0.12$), stride time ($r = 0.19$), stride length ($r = -0.01$), turn velocity ($r = 0.04$), RMS
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4 Sway ($r = 0.14$), sway velocity ($r = -0.27$), or sway area ($r = 0.23$). There were no significant
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6 relationships between the change in SAI and the change in gait or balance measures from OFF-
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8 to ON-levodopa states. The relationship between SAI and arm swing excursion significantly
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10 changed from OFF- to ON-levodopa ($z = -3.05$; $p = 0.002$; 95% confidence interval for the
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12 difference in Person's $r = -0.95 - -0.21$).
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17 **4. Discussion**

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19 The aim of this study was to quantify gait, standing balance, and sensorimotor inhibition in OAs
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21 in OFF- and ON-levodopa states. We aimed to explore the impact of levodopa on mobility and
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23 SAI in healthy OAs to gain more insight into the impact of dopamine on mobility and
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25 sensorimotor inhibition in people with PD. Unlike findings in PD cohorts, our preliminary findings
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27 suggest that levodopa has no effect on either mobility or SAI in OAs. However, levodopa-
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29 dependent relationships were observed between mobility and SAI. In the OFF-levodopa state,
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31 worse SAI significantly correlated with worse performance for specific aspects of gait and
32
33 balance. Since increased double limb support reflects a decreased ability to balance on one
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35 foot, the OFF-levodopa state SAI-mobility relationships reflect a role for sensorimotor inhibition
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37 in gait stability of OAs. This early observation is mirrored for OFF-levodopa state balance, with
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39 worse stability (e.g. increased jerkiness of sway and sway area) related to worse sensorimotor
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41 inhibition. Unlike the OFF-levodopa state, the ON-levodopa state resulted in significant
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43 relationships between worse SAI and increased arm swing excursion (gait) and worse jerkiness
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45 of sway (balance). The increased arm excursion with worse SAI is interesting, as the worse
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47 sensorimotor inhibition indicated by higher SAI may result in larger arm excursion while walking,
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49 but only when ON-levodopa. Further, the relationship between SAI and arm swing excursion
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51 significantly changed from OFF- to ON-levodopa and a moderate effect (Cohen's $d = 0.50$). This
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53 observation is particularly interesting because levodopa can result in large, dyskinetic arm
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55 excursion while walking in patients with PD.(Curtze and others 2015)
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6 There were no changes in gait or balance performance after taking a 100mg dose of levodopa.

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8 In contrast, fine motor skill speed has been reported to improve in healthy OAs with three,
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10 100mg doses of levodopa over a 24-hour period.[18] The observed improvement in fine motor
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12 skill was not observed in healthy young adults, suggesting that exposure to levodopa can
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14 improve fine motor performance in healthy OAs.[18] The dosage used to improve fine motor skill
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16 was selected based on the minimum levodopa dose to induce cognitive change in the
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18 subjects.[18] However, more recent studies established that a single, 100mg dose of levodopa
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20 induced cognitive deficits in young and older adults.[19, 20] The difference in effects of brief
21
22 levodopa exposure on cognitive versus motor performance could be related to the different
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24 dopaminergic pathways involved in cognition and mobility. While the nigrostriatal pathway
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26 (substantia nigra to striatum) plays a role in motor function, the mesolimbic/cortical
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28 dopaminergic pathway (ventral tegmental area to amygdala/hippocampal and frontal cortex)
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30 likely plays a role in cognition. Additional research is needed to determine why a single dose of
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32 levodopa appears to differentially affect the two dopaminergic pathways.
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40 Contrary to the PD-SAI literature,[9] there appears to be no effect of levodopa on SAI in OAs
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42 without PD. The nigrostriatal dopaminergic pathway in OAs is largely intact and therefore may
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44 be unaffected by a single or multiple doses of levodopa. Deficiency in the dopaminergic
45
46 nigrostriatal pathway is related to the motor impairments in people with PD. The motor changes
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48 observed from the OFF- to ON-levodopa in PD is attributed to the conversion of levodopa to
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50 dopamine. The increased dopaminergic activity could positively and negatively affect
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52 compensatory mechanisms adopted for sensorimotor inhibition deficiencies in people with PD.
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54 A possible compensatory mechanism for nigrostriatal dopamine deficiency in people with PD
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56 proposes an upregulation of cholinergic activity,[2] which may partially explain why a single
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58 dose of cholinergic drugs can improve SAI.[6] However, this effect of cholinergic drugs on SAI is
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4 complicated since prolonged exposure (six weeks) to an acetylcholinesterase inhibitor results in
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6 no change in SAI in people with PD.[21]
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10 To date, only gait characteristics in the pace domain significantly related to sensorimotor
11 inhibition in OAs.(Martini and others 2021; Pelosin and others 2016) Specifically, gait speed and
12 stride length were slower and shorter, respectively, with worse SAI.[13] The results herein
13 expand on these findings with the observations that SAI was significantly related to
14 spatiotemporal gait characteristics and postural sway characteristics, both in the OFF- and ON-
15 levodopa states in healthy OAs. While no gait pace domain variable significantly related to SAI
16 in this OA cohort, dynamic (gait) and quasi-static (quiet standing) stability variables were
17 significantly related to SAI, such that worse SAI related to worse stability during gait and
18 standing balance. The different relationships between mobility and SAI from OFF- to ON-
19 levodopa states of the OAs herein could portend different relationships between SAI and
20 mobility in the OFF-levodopa state for people with PD. To date, the relationships between SAI
21 and mobility in people with PD are reported in the ON-levodopa state, limiting the ability to
22 differentiate the effects of disease and drug on the relationships between SAI and mobility in
23 people with PD. The identification of these different relationships could explain some of the
24 heterogeneity in gait and balance responsiveness to levodopa in PD.
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46 Limitations to this study include the small sample size and the dosing of levodopa. A single,
47 100/25 mg dose of levodopa/carbidopa may not have been strong enough to induce
48 neurophysiological changes in some OAs without a known nigrostriatal dopaminergic deficit.
49 However, this design was previously used with success in establishing changes in cognitive
50 performance in both young and older adult populations.[19, 20] Another limitation is the limited
51 characterization of cognition. A comprehensive cognitive assessment could determine if
52 levodopa has similar effects on cognition as shown previously. The lack of a placebo might limit
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4 the interpretation of the relationship between SAI and gait OFF- and ON-levodopa. Additionally,
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6 there were no females in this study, limiting the generalizability of these findings. Finally, using
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8 neuronavigation for the TMS procedure could reduce MEP variability, resulting in greater
9
10 consistency between TMS sessions (OFF- and ON- levodopa).[22]
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15 **5. Conclusion**

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17 A single dose of levodopa does not appear to affect cortical sensorimotor inhibition or mobility in
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19 OAs. However, sensorimotor cortical inhibition is related to balance and gait performance in
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21 OAs, and these relationships appear to be affected by levodopa. Combined with the established
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23 effects of levodopa on mobility and SAI in people with PD, our preliminary results suggest that
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25 an underlying cortical restructuring due to the loss of dopamine activity and levodopa, a
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27 disease-drug interaction, is responsible for the heterogeneous effects of levodopa in PD. Future
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29 investigations that implement a double-blind, crossover design with a placebo, in a larger
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31 population of OAs and young adults is the clear next step to explain the heterogeneity of
32
33 balance and gait performance in OAs and the heterogeneous effect levodopa has on gait and
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35 balance in PD.
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42 **Financial Disclosures:** OHSU and Dr Horak have a significant financial interest in APDM

43
44 Wearable Technologies, a Clario company, that may have a commercial interest in the results of
45
46 this research and technology. This potential conflict has been reviewed and managed by OHSU.
47
48 No other author has a financial disclosure to claim.
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54
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References

- Bohnen, N.I.; Kanel, P.; Müller, M.L. Molecular imaging of the cholinergic system in Parkinson's disease. *International review of neurobiology*. 141:211-250; 2018
- Cohen, J. *Statistical power analysis for the behavioral sciences* (rev: Lawrence Erlbaum Associates, Inc; 1977
- Curtze, C.; Nutt, J.G.; Carlson-Kuhta, P.; Mancini, M.; Horak, F.B. Levodopa Is a Double-Edged Sword for Balance and Gait in People With Parkinson's Disease. *Mov Disord*. 30:1361-1370; 2015
- Di Lazzaro, V.; Oliviero, A.; Profice, P.; Pennisi, M.; Di Giovanni, S.; Zito, G.; Tonali, P.; Rothwell, J. Muscarinic receptor blockade has differential effects on the excitability of intracortical circuits in the human motor cortex. *Experimental brain research*. 135:455-461; 2000
- Di Lazzaro, V.; Oliviero, A.; Saturno, E.; Dileone, M.; Pilato, F.; Nardone, R.; Ranieri, F.; Musumeci, G.; Fiorilla, T.; Tonali, P. Effects of lorazepam on short latency afferent inhibition and short latency intracortical inhibition in humans. *J Physiol*. 564:661-668; 2005
- Di Lazzaro, V.; Oliviero, A.; Tonali, P.A.; Marra, C.; Daniele, A.; Profice, P.; Saturno, E.; Pilato, F.; Masullo, C.; Rothwell, J.C. Noninvasive in vivo assessment of cholinergic cortical circuits in AD using transcranial magnetic stimulation. *Neurology*. 59:392-397; 2002
- Diedenhofen, B.; Musch, J. cocor: A comprehensive solution for the statistical comparison of correlations. *PloS one*. 10:e0121945; 2015
- Floel, A.; Vomhof, P.; Lorenzen, A.; Roesser, N.; Breitenstein, C.; Knecht, S. Levodopa improves skilled hand functions in the elderly. *European Journal of Neuroscience*. 27:1301-1307; 2008
- Julkunen, P.; Säisänen, L.; Danner, N.; Niskanen, E.; Hukkanen, T.; Mervaala, E.; Könönen, M. Comparison of navigated and non-navigated transcranial magnetic stimulation for motor cortex mapping, motor threshold and motor evoked potentials. *Neuroimage*. 44:790-795; 2009
- Linssen, A.; Sambeth, A.; Vuurman, E.; Riedel, W. Cognitive effects of methylphenidate and levodopa in healthy volunteers. *European Neuropsychopharmacology*. 24:200-206; 2014
- Luo, Y.; Roth, G.S. The roles of dopamine oxidative stress and dopamine receptor signaling in aging and age-related neurodegeneration. *Antioxidants and Redox Signaling*. 2:449-460; 2000
- Mancini, M.; Chung, K.; Zajack, A.; Martini, D.N.; Ramsey, K.; Lapidus, J.; Horak, F.B.; Nutt, J.G. Effects of augmenting cholinergic neurotransmission on balance in Parkinson's disease. *Parkinsonism & related disorders*. 69:40-47; 2019
- Mancini, M.; King, L.; Salarian, A.; Holmstrom, L.; McNames, J.; Horak, F.B. Mobility Lab to Assess Balance and Gait with Synchronized Body-worn Sensors. *J Bioeng Biomed Sci. Suppl* 1:007; 2011
- Martini, D.N.; Morris, R.; Kelly, V.E.; Hiller, A.; Chung, K.A.; Hu, S.-C.; Zabetian, C.P.; Oakley, J.; Poston, K.; Mata, I.F. Sensorimotor Inhibition and Mobility in Genetic Subgroups of Parkinson's Disease. *Frontiers in Neurology*. 11:893; 2020
- Martini, D.N.; Morris, R.; Madhyastha, T.M.; Grabowski, T.J.; Oakley, J.; Hu, S.-C.; Zabetian, C.P.; Edwards, K.L.; Hiller, A.; Chung, K. Relationship between Sensorimotor Inhibition and Mobility in Older Adults with and without Parkinson's Disease. *The Journals of Gerontology: Series A*. 76:630-637; 2021
- Meng, X.-L.; Rosenthal, R.; Rubin, D.B. Comparing correlated correlation coefficients. *Psychological bulletin*. 111:172; 1992

1
2
3
4 Obi, K.; Amano, I.; Takatsuru, Y. Role of dopamine on functional recovery in the contralateral
5 hemisphere after focal stroke in the somatosensory cortex. *Brain research*. 1678:146-
6 152; 2018
7
8 Pelosin, E.; Ogliaastro, C.; Lagravinese, G.; Bonassi, G.; Mirelman, A.; Hausdorff, J.M.;
9 Abbruzzese, G.; Avanzino, L. Attentional Control of Gait and Falls: Is Cholinergic
10 Dysfunction a Common Substrate in the Elderly and Parkinson's Disease? *Front Aging*
11 *Neurosci*. 8:104; 2016
12
13 Rochester, L.; Yarnall, A.J.; Baker, M.R.; David, R.V.; Lord, S.; Galna, B.; Burn, D.J. Cholinergic
14 dysfunction contributes to gait disturbance in early Parkinson's disease. *Brain*. 135:2779-
15 2788; 2012
16
17 Sailer, A.; Molnar, G.F.; Paradiso, G.; Gunraj, C.A.; Lang, A.E.; Chen, R. Short and long latency
18 afferent inhibition in Parkinson's disease. *Brain*. 126:1883-1894; 2003
19
20 Vo, A.; Seergobin, K.N.; MacDonald, P.A. Independent effects of age and levodopa on reversal
21 learning in healthy volunteers. *Neurobiology of aging*. 69:129-139; 2018
22
23 Wilson, J.; Alcock, L.; Yarnall, A.J.; Lord, S.; Lawson, R.A.; Morris, R.; Taylor, J.-P.; Burn, D.J.;
24 Rochester, L.; Galna, B. Gait progression over 6 years in Parkinson's disease: Effects of
25 age, medication, and pathology. *Frontiers in aging neuroscience*. 12; 2020
26

27 **Figure Legends**

28 **Figure 1:** Levodopa Effects on SAI. Box and scatter plot of SAI during OFF and ON levodopa
29 states. Grey dashed lines indicate the direction of change in SAI for individual. Black dashed
30 line indicates group mean.
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37 **Figure 2:** Top Row: Scatter plots highlighting the Pearson correlations between SAI and gait
38 during the OFF (blue) and ON (red) levodopa states. Bottom Row: Scatter plots highlighting the
39 Pearson correlations between SAI and standing posture during the OFF (blue) and ON (red)
40 levodopa states. Sway data presented as natural log transformed data. Solid gray line
41 represents the best fit line.
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Table 1: Mobility

		OFF	ON	Cohen's <i>d</i>
Gait	Double Support (%)	19.1(2.6)	19.1(2.7)	0.03
	Stride Time (s)	1.1(0.1)	1.1(0.1)	0.34
	Gait Speed (m/s)	1.2(0.1)	1.2(0.1)	-0.12
	Stride Length (m)	1.3(0.1)	1.3(0.1)	0.09
	Arm Swing (d)	48.6(9.0)	45.8(10.1)	0.50
	Turn Velocity (d/s)	184.8(33.6)	179.2(31.0)	0.22
Postural Sway	Jerk	-2.3(0.8)	-2.2(0.7)	-0.11
	RMS	-2.6(0.5)	-2.6(0.4)	-0.01
	Velocity	-1.4(0.6)	-1.4(0.7)	-0.002
	Sway Area	-6.0(0.8)	-5.9(0.8)	-0.19

Mean(standard deviation). Postural sway variables are natural log transformed.



