

The influence of dopaminergic medication on balance automaticity in Parkinson's disease

Craig D. Workman^{a,b,*}, T. Adam Thrasher^{a,b}

^a Department of Health and Human Performance, University of Houston, 3855 Holman Street, 104 Garrison Gym, Houston, TX, 77204, USA

^b Center for Neuromotor and Biomechanics Research, 4733 Wheeler Ave, Houston, TX, 77204 USA

ARTICLE INFO

Keywords:

Parkinson's disease
Balance
Dual-task
Medication
Posturography

ABSTRACT

Background: Studies have shown that dual-task standing balance in Parkinson's disease (PD) is significantly diminished. Additionally, it is well accepted that dopaminergic medication improves dynamic balance (Berg Balance Scale, mini-BESTest), but standing balance (force platform posturography) may suffer. What remains unknown is how dopaminergic medication influences standing balance automaticity in PD.

Research question: Does dopaminergic medication improve standing balance automaticity during a phoneme monitoring dual-task in PD?

Methods: This was a cross-sectional study. Sixteen subjects with PD completed single- and dual-task standing with eyes open and eyes closed for 3 min each in off and on medication states. 95% confidence ellipse area, anterior-posterior sway velocity, medial-lateral sway velocity, and integrated time to boundary were calculated. Data were analyzed with a repeated measures ANOVA.

Results: Dopaminergic medication significantly increased ellipse area ($p = 0.002$) and decreased the performance on the secondary task ($p = 0.004$). Different eyes conditions (open vs. closed) significantly increased both sway velocities (anterior-posterior = $p < 0.001$, medial-lateral = $p < 0.001$), and increased integrated time to boundary ($p < 0.001$). There were also task by eyes condition interaction effects for anterior-posterior velocity and integrated time to boundary ($p = 0.015$ and $p = 0.009$, respectively). Increases in sway velocity and integrated time to boundary seen in the eyes condition and interaction effects are traditionally interpreted as poorer balance performance. However, in the context of stability/maneuverability tradeoff, the changes may indicate an increase in freedom of movement instead of a decrease in stability.

Significance: The data did not support a medication-induced improvement in automaticity, as measured by significant medication by task interactions. An alternate interpretation for medication-induced balance changes in PD includes an increase in maneuverability without sacrificing stability after taking dopaminergic medication.

1. Introduction

Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder, affecting approximately 1 million people in the US [1]. The impetus for the brain changes that cause PD are not well understood and most cases are idiopathic [2,3]. However, the motor symptoms, the most cardinal of which are rest tremor, rigidity, bradykinesia, postural instability, and gait impairment, are well documented [2–4]. These are usually treated with dopaminergic medications like dopamine replacement, dopamine agonists, and inhibitors [2–5]. These medication-induced improvements are limited and may not impact all motor deficits [6]. In addition to the cardinal symptoms, PD subjects also experience decreased motor automaticity [7], which is achieved when a given motor task is performed without attentional control [8].

Dual-tasking involves performing a primary motor task (e.g., standing) and a secondary task (e.g., conversing) simultaneously and is the primary means of assessing the automaticity of a given motor task. Conceptually, if the primary task is automatic, then the simultaneous performance of a secondary task would have little to no effect on the primary task. Nevertheless, dual-tasking often results in deteriorations, i.e. dual-task interference [9], of one or both tasks [10]. Dual-task interference [7,11–16] and the impact of various PD treatments on postural performance in PD balance with the eyes open and the eyes closed [17–19] have been previously investigated, but it is still unclear how dopaminergic medication influences motor automaticity in PD, and the subsequent impact on dual-task interference.

Investigations on the effects of medication on dual-task balance are scarce; for example, McNeely et al. [16] researched the effect of

* Corresponding author. Present address: Department of Health and Human Physiology, University of Iowa, N418 Field House, Iowa City, IA, 52242, USA.

E-mail addresses: craig-workman@uiowa.edu (C.D. Workman), athrashe@central.uh.edu (T.A. Thrasher).

medication on dual-task gait and balance in PD using clinical balance scales (i.e., Berg Balance Scale and mini-BESTest) and dual-task Timed Up and Go. Their results indicated significant medication effects on the balance scales, but not dual-task Timed Up and Go. Although there is great utility and reliability in these clinical balance scales and clinical tests, they are subjective and susceptible to administrator biases. Force platform posturography, on the other hand, is a more objective measure and is useful for determining the more subtle characteristics of standing balance. Additionally, the choice of a secondary task is also important, because aspects necessary in some secondary tasks, such as articulation (e.g., n-back, serial subtraction), may affect posturographic measures independently [20] and may mask or muddle dual-task effects.

The aim of this study was to assess how dopaminergic medication affected long-duration (3 min) standing balance with the eyes open and the eyes closed while dual-tasking in PD. It was hypothesized that PD medication would improve balance automaticity by respectively decreasing and increasing primary and secondary task performance in dual-task conditions on-medication over single-task off-medication conditions.

2. Methods

2.1. Subjects

Sixteen subjects (4 female) with mild to moderate PD (i.e., Hoehn and Yahr I – III [21]) were recruited from PD-specific activity groups in the greater Houston area. Inclusion criteria were a diagnosis of PD, on an unchanged regimen of dopaminergic medication for ≤ 3 months, and able to stand unassisted for ≥ 3 min. Subjects were excluded if they had injuries or surgeries that caused unusual stance, respectively scored < 24 or < 17 on the Montreal Cognitive Assessment (MoCA) [22] or telephone MoCA [23], experienced freezing of gait, had deep brain stimulation, or a diagnosis of dementia or other neurodegenerative diseases. This study was approved by the University of Houston's Institutional Review Board, and all subjects provided written informed consent.

2.2. Equipment and tasks

Center of Pressure (COP) data were collected using a NeuroCom Balance Master force platform (NeuroCom International Inc., Clackamas, OR, USA). Variables of interest were the 95% confidence ellipse area, anterior-posterior (AP) and medial-lateral (ML) COP sway velocity, and integrated time to boundary (iTTB) estimates (an integral of the curve of the instantaneous time it would take for the center of pressure to exceed the base of support boundary at a given speed and direction). Because COP 95% confidence ellipse area is representative the behavior of the COP in both AP and ML directions [24], this variable was used as the primary variable of interest in the assessment of balance automaticity. PD motor symptoms were assessed using the motor section of the Movement Disorder Society Unified Parkinson's Disease Rating Scale [25] (MDS-UPDRS III).

The primary task was quiet stance, which was performed with eyes open (EO) and eyes closed (EC). To guard against the possibility of a fall, the subjects donned a safety harness, which was attached to the overhead harness-beam of the NeuroCom apparatus such that the harness would “catch” the subject immediately after a fall. In the event of a fall, the trial was aborted and restarted; if the fall occurred during a DT trial, a novel story/phoneme was played (see below). Each trial lasted 3 min. The secondary task was a phoneme monitoring task, which has previously been shown to elicit dual-task interference in PD [26], during which the subjects listened to pre-recorded speech (i.e., an unfamiliar fairytale) through headphones and counted the number of times a specific word occurred. The subjects were instructed to count mentally (i.e., not tally with fingers) and to listen to the details of the story in order to answer questions at the end of the trial. This secondary

task provided two outcomes: proportion of correct number of words counted (PM-Tally) and proportion of questions correctly answered (PM-Score). Tally reports greater than the correct tally were scored according to the following example. A report of ‘10’ when the correct tally was ‘8’ was scored as $(8 - |10 - 8|) / 8 = 6 / 8 = 75\%$.

This secondary task was selected because it has face validity with real-life situations, like attending to a conversation while standing [26]. In addition, phoneme monitoring allowed for the performance of long-duration balance tasks, which mimic real-life situations that the subjects experience on a daily basis. Several recordings of ~195 s duration were prepared by study personnel such that across all combinations of medication, task, and eyes conditions, each trial had a novel recording and phoneme to tally. Each phoneme consisted of a noun (e.g., house, bell, snail) with 6–12 occurrences within the recording time. A relatively broad range of occurrences was desirable to help ensure the subjects were constantly listening for the new phoneme and not relying on a tally from a previous trial.

2.3. Procedures

All testing was performed in one session and began with the off-medication state (OFF). To achieve this, subjects underwent a minimum 12-hour overnight medication withdrawal. Sessions always commenced with the administration of the UPDRS III, followed by measuring their foot length (i.e., distance between toes and heels). The latter was necessary for the iTTB calculation (see below). Subjects then performed the following tasks in random order: 1) phoneme monitoring while seated comfortably in a quiet room, 2) single-task (ST) standing eyes open (STEO), 3) single-task standing eyes closed (STEC), 4) dual-task (DT) standing eyes open (DTEO), and 5) dual-task standing eyes closed (DTEC). The dual-task conditions were a combination of the standing and phoneme monitoring tasks. As mentioned above, each condition was performed one time for 3 min. Sufficient rest (≥ 1 min) between conditions was provided when necessary by having the subjects sit in a chair. Whenever the subjects performed the phoneme monitoring task, they were told the new word they were to tally and that they were going to be asked questions about the content of the story. No other explicit instructions for directing attention were provided.

After the OFF trials were completed, the subjects took their dopaminergic medication as prescribed for their first/morning dose and waited until they achieved a stable “on” feeling (minimum of 45 min) before commencing the on-medication testing (ON). Subject demographic information (i.e., weight, time since diagnosis, PD medication and dosages) were collected during this transition. Aside from a new set of randomized conditions, ON testing was the same as OFF. This study was part of a larger study, which included other testing conditions. Overall, a complete visit for one subject lasted approximately 4 h. Subjects were encouraged to rest and eat snacks during the waiting period between OFF and ON testing.

2.4. Data processing

COP data were exported using the NeuroCom software and imported into MATLAB (The MathWorks, Natick, MA) for analysis. Data were filtered using a second-order Butterworth low-pass filter with a 10 Hz cutoff [27]. COP_{area} was calculated by plotting the COP path on a coordinate plane and calculating the area of an ellipse that contained 95% of the path data points. The velocity of COP movement in AP and ML directions (AP-Velocity and ML-Velocity, respectively) were calculated by determining the instantaneous speed and direction of the COP path at a given time point. iTTB was calculated using the COP AP velocities to determine the time it would take the COP to reach the theoretical AP stability boundaries (i.e., the toes and the heels) from its current position at its current velocity and cause a loss of stability sufficient to warrant a corrective step. This calculation generates a time to boundary series that creates a curve. Integrating this series, and

looking only below an arbitrarily selected 10 s threshold, iTTB then provides a number that represents relative instability for the entire trial; this variable is expressed as a percentage of the entire area beneath the threshold (i.e., 10 s x total duration) [28]. Traditional interpretations of these variables are that larger COP_{area}, faster COP velocities, and larger iTTB indicate instability [24].

Additionally, to investigate the association between the primary and secondary tasks, dual-task effect (DTE) [9] was calculated as follows:

$$\text{Task DTE (\%)} = \frac{(\text{DT Task} - \text{ST Task})}{\text{ST Task}} \times 100\%$$

Where “ST/DT Task” respectively represent the single- and dual-task performance for a given variable. Furthermore, to visually characterize the relationship between the tasks and provide another indication of medication-induced automaticity, DTE ON was subtracted from DTE OFF (i.e., Task Δ DTE = ON Task DTE – OFF Task DTE), where “Task” is a primary or secondary task. Δ DTE was calculated for COP_{area} and the phoneme tally. Then, the DTE relationship between COP_{area} and phoneme tally were plotted on a coordinate plane as (x,y) = (Δ DTE_{area}, Δ DTE_{tally}), with the x-axis as change in balance effect and y-axis as change in phoneme monitoring effect.

2.5. Statistical analysis

A 3-factor repeated-measures ANOVA, medication (OFF vs. ON) by task (ST vs. DT) by eyes condition (EO vs. EC), was employed to investigate the hypotheses. COP_{area}, mean AP-Velocity and ML-Velocity, and iTTB were input into this statistical model. Because the phoneme monitoring task did not have two ST performances (i.e., performed once while seated comfortably), a 2-factor repeated measures ANOVA, medication (OFF vs. ON) by task (ST vs DTEO vs. DTEC) was performed for analysis of this task. The assumptions for a repeated measures ANOVA were reviewed or tested. The normality assumption of each variable was checked via histograms, skewness, and kurtosis statistics. Because task had three levels in the phoneme monitoring repeated measures ANOVA, sphericity (i.e., Mauchly’s Test of Sphericity) was also assessed, and where violations occurred, Greenhouse-Geisser corrected statistics were used. Uncorrected *post-hoc* pairwise comparisons and effect sizes (i.e., paired *t*-tests, Cohen’s *d*) were performed to clarify any significant differences. A paired *t*-test was also performed on the UPDRS III scores to confirm the effectiveness of the medication. Significance was accepted at $p < 0.05$. Statistical analysis was performed using SPSS 23 (IBM Corp., Armonk, NY, USA). Data are reported as mean \pm SD.

3. Results

All subjects completed safely all of the testing conditions and no subject reported tiredness or fatigue, which may have influenced the results. All but one of the subjects reported feeling completely “ON” after the minimum 45 min waiting time; the other subject required 60 min before feeling completely “ON”. Medication also had a positive impact on UPDRS III scores with ON testing less than OFF ($p < 0.001$, $d = 2.46$). Table 1 displays the subject demographic information. It is noted that all subjects completed the telephone MoCA during recruitment and scored above the mild cognitive impairment cutoff (i.e., < 17) [23]. Table 2 contains the mean \pm SD of the analyzed data.

3.1. Center of pressure 95% confidence ellipse area

For COP_{area}, there were significant medication ($F = 14.004$, $p = 0.002$) and task ($F = 5.466$, $p = 0.034$) main effects, but not a significant effect of eyes condition ($F = 0.243$, $p = 0.629$; Table 3).

Table 1

Subject demographic information. Data are mean \pm SD, where appropriate.

Demographics	
Sex	12 male, 4 female
Age	67.1 \pm 7.5 yrs.
Height	171.2 \pm 9.5 cm
Weight	80.9 \pm 14.3 kg
Telephone MoCA	19.6 \pm 1.7
UPDRS III (OFF)	44.4 \pm 13.3
UPDRS III (ON)	24.4 \pm 8.2
Time since diagnosis	6.7 \pm 5.8 yrs.
Levodopa Equivalent Dose	669.5 \pm 230.6

Note: MoCA = Montreal Cognitive Assessment, UPDRS III = part III of the MSD-UPDRS, OFF = off-medication state, ON = on-medication state.

Table 2

The mean \pm SD of the analyzed data, stratified by medication state, task, and condition.

Variable	Medication State	
	OFF	ON
COP _{area} (cm ²)		
STEO	1.73 \pm 1.00	4.29 \pm 5.05
STEC	2.54 \pm 2.04	4.34 \pm 2.56
DTEO	2.03 \pm 1.72	2.75 \pm 1.85
DTEC	1.89 \pm 0.79	2.89 \pm 1.76
AP-Velocity (cm/s)		
STEO	1.27 \pm 0.27	1.35 \pm 0.49
STEC	1.89 \pm 0.55	1.98 \pm 0.70
DTEO	1.25 \pm 0.35	1.43 \pm 0.49
DTEC	1.67 \pm 0.44	1.73 \pm 0.50
ML-Velocity (cm/s)		
STEO	0.64 \pm 0.30	0.58 \pm 0.23
STEC	0.76 \pm 0.35	0.72 \pm 0.30
DTEO	0.71 \pm 0.41	0.64 \pm 0.24
DTEC	0.72 \pm 0.32	0.66 \pm 0.22
iTTB (% total area)		
STEO	5.33 \pm 3.87	5.86 \pm 3.89
STEC	11.90 \pm 5.88	12.55 \pm 5.79
DTEO	5.38 \pm 4.42	6.98 \pm 4.33
DTEC	9.48 \pm 5.50	10.09 \pm 4.65
Phoneme Monitoring (%)		
Tally		
ST	87.30 \pm 9.98	88.23 \pm 14.91
DTEO	87.03 \pm 11.72	82.29 \pm 13.56
DTEC	91.38 \pm 10.60	85.42 \pm 12.31
Score		
ST	62.66 \pm 26.20	50.20 \pm 25.57
DTEO	63.28 \pm 26.44	63.96 \pm 31.93
DTEC	73.28 \pm 24.54	45.21 \pm 24.22

Note: OFF = off-medication state, ON = on-medication state, COP = center of pressure, ST = single-task, DT = dual-task, EO = eyes open, EC = eyes closed, AP = anterior-posterior, ML = medio-lateral, iTTB = integrated time to boundary.

3.2. Integrated time to boundary

For iTTB, there was a significant main effect of eyes ($F = 54.649$, $p < 0.001$) but not significant medication or task main effects ($F = 1.055$, $p = 0.321$ and $F = 1.739$, $p = 0.207$, respectively). However, there was a significant task by eyes interaction effect ($F = 8.884$, $p = 0.009$; Table 3).

Table 3
Significant pairwise comparisons and effect sizes.

COP _{area} Condition	<i>p</i> - value	Cohen's <i>d</i>
OFF-STE _C vs. ON-STE _C	0.041	0.56
OFF-DTE _C vs. ON-DTE _C	0.023	0.64
OFF-DTE _C vs. ON-DTE _C	0.021	0.64

iTTB		
Condition	<i>p</i> - value	Cohen's <i>d</i>
OFF-STE _O vs. OFF-STE _C	< 0.001	1.80
OFF-STE _O vs. OFF-DTE _C	0.003	0.90
OFF-DTE _O vs. OFF-DTE _C	0.005	0.82
OFF-STE _C vs. OFF-DTE _O	< 0.001	1.49
ON-STE _O vs. ON-STE _C	< 0.001	1.62
ON-STE _O vs. ON-DTE _C	< 0.001	1.15
ON-DTE _O vs. ON-DTE _C	< 0.001	1.09
ON-STE _C vs. ON-DTE _O	< 0.001	1.14
ON-STE _C vs. ON-DTE _C	0.018	0.66

AP-Velocity		
Condition	<i>p</i> - value	Cohen's <i>d</i>
OFF-STE _O vs. OFF-STE _C	< 0.001	1.62
OFF-STE _O vs. OFF-DTE _C	< 0.001	1.12
OFF-DTE _O vs. OFF-DTE _C	< 0.001	1.09
OFF-STE _C vs. OFF-DTE _O	< 0.001	1.45
ON-STE _O vs. ON-STE _C	< 0.001	1.65
ON-STE _O vs. ON-DTE _C	< 0.001	1.33
ON-DTE _O vs. ON-DTE _C	< 0.001	1.12
ON-STE _C vs. ON-DTE _O	< 0.001	1.19

ML-Velocity		
Condition	<i>p</i> - value	Cohen's <i>d</i>
OFF-STE _O vs. OFF-STE _C	0.002	0.94
ON-STE _O vs. ON-STE _C	0.007	0.79
OFF-DTE _O vs. OFF-DTE _C	< 0.001	1.09
ON-STE _C vs. ON-DTE _O	< 0.001	1.19

PM-Score		
Condition	<i>p</i> - value	Cohen's <i>d</i>
OFF-DTE _C vs. ON-DTE _C	0.002	0.94
OFF-DTE _C vs. ON-ST	0.009	0.75

Note: OFF = off-medication state, ON = on-medication state, COP = center of pressure, ST = single-task, DT = dual-task, EO = eyes open, EC = eyes closed, AP = anterior-posterior, ML = medio-lateral, iTTB = integrated time to boundary.

3.3. COP velocity, anterior-posterior

AP-Velocity also had a significant main effect of eyes ($F = 62.728, p < 0.001$) but not significant medication or task main effects ($F = 1.52, p = 0.237$ and $F = 2.635, p = 0.125$, respectively). Additionally, there was a significant task by eyes interaction effect ($F = 7.482, p = 0.015$; Table 3).

3.4. COP velocity, medial-lateral

There was a significant eyes condition main effect for ML-Velocity ($F = 25.975, p < 0.001$), but not significant medication or task main effects ($F = 1.323, p = 0.268$ and $F = 0.065, p = 0.802$, respectively; Table 3).

3.5. Phoneme monitoring

There was a significant medication effect of for PM-Score ($F =$

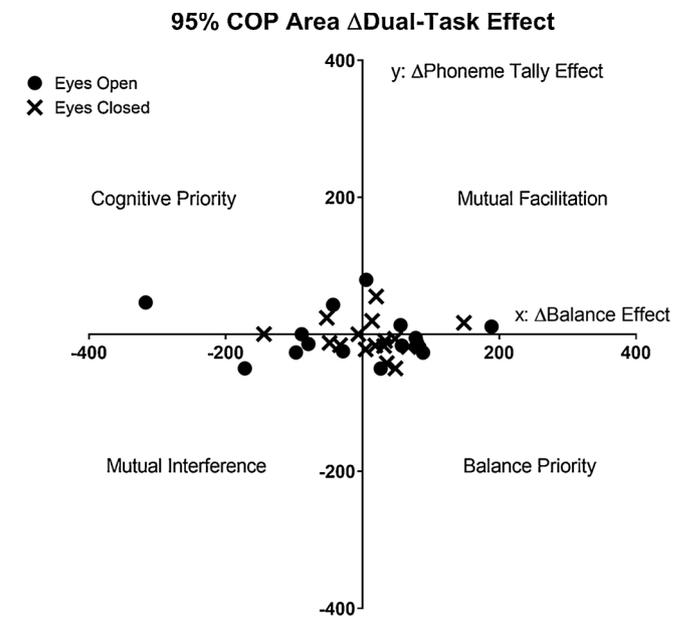


Fig. 1. Scatterplot of the change in dual-task effect for COP_{area}. Each point represents the change in dual-task effect for a subject from OFF to ON and are plotted as (x,y) = (Δ DTE_{area}, Δ DTE_{tally}) for eyes open and eyes closed conditions. The quadrants are labeled to indicate the relationship between the primary and secondary tasks.

11.867, $p = 0.004$), but not a significant task main effect ($p = 0.567$). There was also a significant interaction effect for PM-Score ($F = 3.462, p = 0.044$; Table 3).

3.6. Dual-task effect

Fig. 1 shows the Δ DTE for (x,y) = (Δ DTE_{area}, Δ DTE_{tally}) with the x-axis as change in balance effect and y-axis as change in phoneme monitoring effect. Visual inspection of this figure does not indicate any noteworthy patterns.

4. Discussion

The goal of this study was to determine to what extent the medications would improve balance automaticity such that ON dual-task conditions would be significantly improved over OFF single-task conditions. Given that the only significant medication changes occurred with COP_{area} and there were not any significant interactions, the results do not support this hypothesis. Additionally, larger COP_{area}, COP velocities, and iTTB values indicate instability when traditionally interpreted [24], and our results agree with previous findings that PD medication increases COP_{area} and functional limits of stability [17–19], but not necessarily clinical balance scales [16].

These apparent discrepancies can be reconciled with alternate interpretations of the gestalt of these variables in PD. For example, consider the stability/maneuverability tradeoff [29], which postulates that an increase in stability (i.e., stiffness) is accompanied by a decrease in maneuverability (i.e., freedom of movement). However, some PD symptoms, e.g., stiffness and bradykinesia, might simulate stability in some posturographic measures. For example, PD subjects score in normal or above normal ranges on stable-platform sensory organization test (SOT) trials (i.e., SOT1 and SOT2; see Bronte-Stewart [17] for an example). Furthermore, because dopaminergic medication causes well-accepted improvements in these stability-simulating symptoms [2–5], it may not be appropriate to attribute the composite of the changes found in this study as an increase in maneuverability and a decrease in stability. Rather, because our subjects increased COP_{area} after taking dopaminergic medication without experiencing any other medication-induced balance

performance detriments, our data expand on the stability/maneuverability model and suggest that dopaminergic medication increased maneuverability in PD subjects, but did not necessarily decrease stability.

The effects on the phoneme monitoring task, especially the significant negative medication effect while dual-tasking, and the Δ DTE plot in Fig. 1 (few points shifting toward positive x) do not indicate any changes suggesting an improvement in automaticity. Rather, these findings add to the idea that motor automaticity is centrally controlled, especially considering that PD medication has variable effects on executive functions [30]. Another reason for the negative medication effect on PM-score could be that, because the subjects increased COP_{area} (i.e., explored more space), they adopted a “posture-first” strategy while dual-tasking, which is contrary to previous findings [31]. However, caution with this interpretation is suggested as only PM-Score, and not PM-Tally was affected; this could indicate that the questions asked at the end of phoneme trials were too challenging or too ambiguous. Such questions about the appropriateness of a given phoneme testing protocol will endure in future studies unless and until a standardized phoneme protocol is validated and made available.

Among the several dual-tasking models, two models are the most popular. The first is the capacity sharing model, which suggests a finite capacity for performing all tasks and concurrently performed tasks that exceed that capacity result in interference of one or both tasks [9]. The second is the bottleneck theory, which divides tasks into different mechanisms (e.g. motor and cognitive). In this model, interference occurs when two concurrent tasks try to use the same mechanism [9]. Because phoneme monitoring is purely cognitive, and standing balance requires little or no cognitive demand, the tasks of this study were assumed to operate using different mechanisms and our results are more consistent with the capacity sharing model.

Aside from the limitation of PM-Score discussed above, the most notable limitation in this study is the primary/secondary task pairing. Phoneme monitoring was chosen because it requires constant attention, is suitable for longer durations, and does not require motor performances (i.e., articulation) which have measurable impacts on posturographic measures [20]. Furthermore, it has previously elicited dual-task interferences in PD gait [26]. However, phoneme monitoring may not be sufficiently challenging to elicit large dual-task interference in standing balance, which is a less complex primary task than gait. One way to circumvent this limitation in the future would be to choose a more challenging secondary task that requires articulation (e.g., n-back, serial subtraction) and compare changes to a baseline performance of speaking nonsense words (e.g., “blah”) at a similar rate.

5. Conclusions

Using traditional interpretations of posturographic measures, dopaminergic medication hindered balance in the mild-moderate PD subjects in both single- and dual-task conditions. However, when considered in light of a stability/maneuverability tradeoff expanded for PD, subjects may experience only an increase in freedom of movement rather than instability. Secondary task performance was either not improved or significantly worsened with medication. These data do not support the idea of a medication-induced improvement in automaticity. This study adds evidence to the capacity sharing model of dual-task interference, because the purely cognitive secondary task was sufficient to interfere with balance performance.

Conflict of interest statement

None declared.

CRedit authorship contribution statement

Craig D. Workman: Conceptualization, Methodology, Software, Formal analysis, Investigation, Data curation, Writing - original draft, Visualization. **T. Adam Thrasher:** Conceptualization, Methodology, Validation, Writing - review & editing, Supervision.

Acknowledgements

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The authors would like to thank Ram Kinker Mishra, Raul Amador, and Hyder Jassim for their assistance during data collection. Also, Christopher J. Arellano, Beom-Chan Lee, and Mon Bryant for proofreading the manuscript. Lastly, the Kingwood, North Houston, and The Woodlands locations of Rock Steady Boxing chapters for their assistance with subject recruitment.

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