# THE INFLUENCE OF DOPAMINERGIC MEDICATION ON GAIT AND BALANCE AUTOMATICITY AND NONLINEAR REGULARITY IN PARKINSON'S DISEASE

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A Dissertation presented to

The Faculty of the Department

of Health & Human Performance

University of Houston

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In Partial Fulfillment

of the Requirements of the Degree:

Doctor of Philosophy

in Kinesiology

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By

Craig D. Workman

Fall 2018

THE INFLUENCE OF DOPAMINERGIC MEDICATION ON GAIT AND BALANCE

AUTOMATICITY AND NONLINEAR REGULARITY IN PARKINSON'S DISEASE

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ABSTRACT

Dual-tasking studies have shown that gait and balance automaticity in Parkinson's disease (PD) is significantly diminished. It is also well accepted that dopaminergic medication improves single-task gait and some aspects of balance. Yet, how dopaminergic medication influences gait and balance automaticity in PD is not well understood. Additionally, gait and balance automaticity studies in PD have almost exclusively employed linear measures to describe outcomes. Unlike linear measures, nonlinear analyses like Approximate Entropy and Recurrence Quantification Analysis account for the regularity of the entire signal and can help determine the automaticity of the intended movement pattern. Therefore, this study aimed to determine how dopaminergic medication influenced the automaticity of gait and balance via linear and nonlinear analyses of joint angle and center of pressure (COP) path signals while single- and dual-tasking in PD. Sixteen subjects with PD completed single- and dual-task walking and standing (eyes open and eyes closed) for 3 minutes off and on medication. Gait velocity, cadence, and stride length were measured, as well as kinematic variables (mean, maximum, and SD angles of bilateral hip, knee, and shoulder joint) were calculated to describe gait performance. For balance, 95% confidence ellipse area, anterior-posterior sway velocity, medial-lateral sway velocity, and integrated time to boundary were calculated. For the nonlinear analyses, approximate entropy and percent determinism were calculated for bilateral hip, knee, and shoulder joints, as well as the COP path. Data were statistically analyzed with a series of repeated measures ANOVAs and linear mixed effects models controlling for gait velocity for the linear and nonlinear

analyses of joint angle data. For gait, the analysis indicated that dopaminergic medication significantly improved gait velocity ($p$ = 0.007) and several kinematic variables. Dual-tasking significantly interfered with cadence ($p$ = 0.042), stride length ($p$ < 0.001), and some kinematic measures, despite medication state. Dopaminergic medication mostly impacted the less PD-affected hip and knee joints, while dual-tasking primarily affected the less-PD affected hip joints. For balance, dopaminergic medication significantly increased ellipse area ($p$ = 0.002) and decreased the performance on the secondary task ($p$ = 0.004), while dual-tasking significantly increased sway velocity in both directions (anterior-posterior = $p$ < 0.001, medial-lateral = $p$ < 0.004) and integrated time to boundary ($p$ < 0.001). There were also several medication*task interactions among the balance variables. Overall, both dopaminergic medication and dual-tasking seemed to hinder balance performance, when analyzed using traditional interpretations. However, because medication only increased sway area, we propose that PD medication improved balance maneuverability without a decrease in stability. For the nonlinear analyses, there were significant medication effects on the Approximate Entropy of the more-PD affected knee while dual-tasking ($p$ = 0.014) and the less-PD affected knee while dual-tasking ($p$ = 0.004), both of which indicated that off-medication dual-tasking was more regular than on-medication dual-tasking. The analysis also revealed that balance task complexity, specifically eyes open vs. eyes closed, was reflected in the analysis of the COP path, with more complex tasks eliciting significantly less regular/deterministic results. Overall, the significant gait differences in dual-tasking between off- and on-medication states indicated motor improvements from taking dopaminergic medication improved dual-tasking. However, the lack of significant interactions and secondary task effects did not

support a medication-induced improvement in gait automaticity. Lastly, the nonlinear characteristics of gait and balance in PD seemed to be differently affected by medication and task complexity. The medication-induced decreases in regularity, coupled with accepted improvements in gait performance with medication, may indicate that PD patients are too regular in their joint movements off medication.

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# *III. Introduction*

Parkinson's disease (PD) is a neurological movement disorder that progressively disables those living with the disease. PD is the second most prevalent neurodegenerative disorder, affecting approximately 1 million people in the US. Those most commonly afflicted are the elderly, among whom the prevalence of PD is higher than young adults, with an increase in incidence with age. The mechanism for the symptoms associated with PD, i.e., the systematic cell death of the dopamine (DA) producing substantia nigra and the subsequent dysfunction of the other basal ganglia and the neuromuscular system, are well established and have been recognized for centuries. The motor and non-motor symptoms associated with PD are also well established. These include the cardinal motor symptoms of resting tremor, rigidity, bradykinesia, postural instability, and gait impairment, which are common to most patients with PD. DA-ergic medications, like levodopa, ameliorate some of the more disabling motor complications. Nevertheless, despite the aid of medication, the cardinal impairments, and their combinations, have direct and sometimes complex impacts on daily life and independence of PD patients.

**III.I Statement of the Problem**

An important aspect of PD, with respect to daily living, is a reduced ability to automatically perform a task – that is, to perform a task outside of attentional control. This reduced automaticity, and the very real impact it has on PD patients, has been well established in PD research. However, little is known about how DA-ergic medications, like levodopa, affect automaticity in PD. This effect is important to understand, because performing tasks automatically is vital in an environment where patients are often required

to direct attention to various secondary tasks, such as carrying on a conversation, while performing an automatic primary task, like walking. Additionally, what little research that has been performed to address this topic has only consisted of simple temporo-spatial measures of gait (e.g., mean velocity and cadence) and balance (e.g., center of pressure [COP] sway area), which may not be sufficiently intricate to understand the complex effects of DA on automaticity.

### III.II Purpose of the Study

The purpose of this study was to investigate the effects DA-ergic medications on the automaticity of gait and standing balance in PD. An additional purpose was to extend the scope of gait and balance assessment in automaticity research beyond simple linear analyses, like velocity and COP sway area which analyze the signal in piecemeal or as an average of occurrences, to nonlinear analyses that determine the variability (i.e., predictability) of entire signals, such as Approximate Entropy (ApEn) and Recurrence Quantification Analysis (RQA).

### III.III Research Aims and Hypotheses

The following aims and hypotheses are intended to address the gaps of knowledge discussed in the statement of the problem:

**Aim 1: To investigate the effect of levodopa on the automaticity of overground gait in PD.** To measure gait automaticity, a dual-task (DT) paradigm, in which subjects perform a primary task (i.e., walking) at the same time as a secondary cognitive task, was employed. DT paradigms are employed in automaticity research because the more automatic a task, the less dual-task interference (DTi) is evident. For example, if gait is a perfectly automatic task, it will not be affected by the performance of a

secondary cognitive task. In other words, the gait pattern of someone walking without talking would look the same as when that person walks while talking. Because changes to any of the individual characteristics of gait, i.e., step length and stride length, affect the velocity of movement, gait velocity served as the primary surrogate of gait automaticity.

**H1:** Dual-task gait velocity in the on-medication state (ON) will significantly improve from the single-task gait velocity in the off-medication state (OFF).

**Aim 2: To investigate the effect of levodopa on the automaticity of standing balance in PD.** To measure standing balance, a DT paradigm like that used in Aim 1 was employed. Standing balance is also considered an automatic task, and the same standard of automaticity suggested in Aim 1 also applies to balance. The primary variables of interest involved the behavior of the COP during eyes open (EO) and eyes closed (EC) standing conditions. Common COP characteristics of interest include COP 95% ellipse area ($COP_{area}$; the area of an ellipse that contains 95% of the COP path), anterior-posterior (AP) and medial-lateral (ML) COP sway velocity ($vCOP_{AP}$ and $vCOP_{ML}$, respectively), and time to boundary estimates (TTB; the time it would take for the center of pressure to exceed the base of support boundary at a given speed and direction). Because $COP_{area}$ represents the behavior of the COP in both AP and ML directions, $COP_{area}$ was used as the primary variable of interest in the assessment of balance automaticity.

**H2:** $COP_{area}$ in the dual-task on-medication state (ON) will significantly improve from the single-task off-medication state (OFF) for both EO and EC conditions.

**Aim 3: To determine the influence of levodopa on the regularity of nonlinear, whole-signal predictability characteristics of joint angles and COP path during DT gait and balance**. Specifically, this study investigates the predictability of these signals by quantifying the ApEn and percentage of determinism (%DET), as determined via RQA, of joint angles (gait) and the COP path (balance). The predictability of the joint angles during walking provides an indication of the overall stability of walking. It is already well accepted that PD gait is not only unstable, but also more variable. That is, as PD patients walk, their step-to-step or stride-to-stride variability is significantly larger than would be expected for their age and increased step/stride variability is a marker of gait instability. This phenomenon is sufficiently common in PD that gait instability is one of the cardinal symptoms; and variability in steps/strides necessarily stems from variability in joint angles. Additionally, the predictability of the COP path informs the aggregate stability of standing balance, which is known to be impaired in PD. Posturography in PD patients indicates instability via larger than expected $COP_{area}$, $vCOP_{AP}$, and $vCOP_{ML}$.

However, because the impact of medication state on DT-ing in PD is still novel, it is unclear if step and stride variability or COP path variability are improved while performing a DT when ON. Additionally, because the coordination of the joints may vary substantially without a significant impact on stride length or step length means and the size of the COP path (i.e. $COP_{area}$) does not provide an indication of predictability, measures that are sensitive to changes in variability/predictability, like

ApEn and %DET, are important to understanding the gait and balance instability that is typically seen in DT-ing conditions in PD.

**H3:** The ApEn will significantly decrease (i.e., more predictable) and %DET will be significantly increase (i.e., more regular/deterministic) in DT-ON compared with ST-OFF.

### III.IV Significance of the Problem

It is important to understand how DA-ergic medication mitigates the loss of automaticity in PD, because it is the most popular approach to treating the cardinal symptoms of PD. It is well accepted that DA-ergic medications improve PD gait in single task (ST) conditions, but the impact of such medications on PD patients' ability to DT is still unclear. As previously stated, the linear measures of mean and SD may not be sufficiently sensitive to address the complexities of PD walking and balance during a DT. Furthermore, DT-ing is an integral part of daily living. In fact, an argument could be made that appropriate execution of many activities of daily living necessarily requires efficient DT-ing capabilities. And with many *de novo* patients opting out of DA-ergic medications until symptoms become sufficiently disabling, it is possible that their ability to DT is also impaired and negatively impacting their ADLs. Thus, not understanding the effect of DA on DT gait and balance in PD, and to some extent DT ability in general, may lead to some patients attempting unsafe DT activities in an impaired state (i.e., when OFF). Additionally, better understanding the linear and nonlinear characteristics of DT gait and balance, both ON and OFF, may help researchers better understand the occurrences of higher risks of falling PD patients experience. Understanding these characteristics may

also eventually help therapists create or integrate DT aspects into current PD therapies to retrain lost DT ability.

## *IV. Manuscripts Introduction*

Below are three manuscripts, each addressing one of the aims discussed above, which have been prepared and formatted for submission to different refereed journals. As such, minor differences in abstracts and headings/subheadings may be found. However, in order to comply with college guidelines, and to provide continuity to the entire document, tables, figures, and headings/subheadings will be consecutively numbered and referencing will be combined in both style and numbering so that only one reference list at the end of the entire dissertation document will be shown. Additionally, figure captions will accompany the figures at the end of each manuscript.

# *V. Manuscript 1, Gait Automaticity*

**V.I Title Page**

Title: The Influence of Dopaminergic Medication on Gait Automaticity in Parkinson's Disease.

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**V.II Abstract**

**Background:** Dual-tasking studies have shown that gait automaticity in Parkinson's disease (PD) is significantly diminished. Additionally, it's well accepted that dopaminergic medication improves single-task gait. But, how dopaminergic medication influences gait automaticity in PD has not been sufficiently understood. **Research Question:** Does dopaminergic medication improve gait automaticity and dual-tasking in PD? **Methods:** This study was a cross-sectional design, where sixteen subjects with PD completed single- and dual-task walking for 3 minutes off and on medication. Gait velocity, cadence, and stride length were measured. Kinematic variables included mean, maximum, and SD angles of bilateral hip, knee, and shoulder joints. Data were analyzed with a repeated measures ANOVA and a linear mixed effects repeated measures model. **Results:** Dopaminergic medication significantly increased gait velocity ($p = 0.007$), stride length ($p = 0.046$). After controlling for gait velocity, several kinematic variables were also improved with medication. Despite medication state, dual-tasking significantly interfered with cadence ($p = 0.042$), stride length ($p < 0.001$), and some kinematic measures, Dopaminergic medication mostly increased the hip and knee joint angles, while dual-tasking primarily decreased the hip joint angles on the less PD-affected side. There was no significant interaction between medication status and task condition. **Significance:** The significant differences in dual-tasking between off- and on-medication states indicates that motor improvements from taking medications improved dual-tasking. However, the lack of significant interactions and secondary task effects does not support a medication-induced improvement in automaticity.

Keywords: Parkinson's disease, gait, dual-task, medication, kinematics

## V.III Introduction

Parkinson's disease (PD) is a degenerative neurological movement disorder. It is the second most prevalent neurodegenerative disorder, affecting approximately 1 million people in the US [1]. The causes of PD are not well understood; most cases are classified as idiopathic [2,3]. The cardinal PD motor symptoms include rest tremor, rigidity, bradykinesia, postural instability, and gait impairment [2–4]. The most common treatments are dopaminergic medications like dopamine replacement, dopamine agonists, and inhibitors, which help alleviate motor complications [2–6].

How dopaminergic medication impacts other known aspects of PD life, specifically the effect on diminished motor automaticity, is still unclear. In fact, it has been suggested that some PD symptoms, like those related to bradykinesia, are indicative of a general loss of motor automaticity [7].Motor automaticity is achieved when a given motor task is performed without attentional control, and with enough practice, even complex motor tasks can be performed with relatively little attentional demand [8]. As a skill evolves from novelty to automaticity, several changes in brain activation patterns or the strength of connectivity between involved areas have been observed [8–10].

Motor automaticity can be assessed using dual-task paradigms. Dual-tasking involves performing a primary motor task (e.g., walking) concurrent with a secondary, cognitive task (e.g., conversing). Dual-tasking often results in performance detriments of one or both of the simultaneously performed tasks. These decreases in performance are called dual-task cost or dual-task interference [11]. Dual-task paradigms are

employed in automaticity research because the more automatic a task, the less dual-task interference is evident. Dual-task interference in PD gait has been well documented (see Wu et al. [7] for a review), but what remains unknown is how dopaminergic medication influences motor automaticity in PD, and the subsequent impact on dual-task interference.

Current reports in this area are scarce and still relatively novel. Those who have explored this question have reported mixed results. One study found limited effects on straight walking and turning [12] and another found significant effects on more complex gait tasks and clinical balance measures [13]. These discrepancies are likely a consequence of the different primary and secondary tasks that were used in those studies. Specifically, the secondary tasks of these studies varied in difficulty, had different attentional demands, and were performed over short durations (i.e., ≤ 1 min).

The aim of this study was to determine the effect of medication on gait automaticity in PD. Our approach is to assess the impact of dopaminergic medication on self-selected gait speed while dual-tasking during a long-duration (3 min) forward walk. Additionally, objective kinematic measures and a constant-attention secondary task were employed to ensure consistent measurements and dual-task interferences. It was hypothesized that medication would improve gait automaticity in terms of gait velocity, stride length, joint angles, and secondary task performance.

## V.IV Methods

### *V.IV.I Subjects*

Table 1 displays the subjects' demographic information. Sixteen subjects (female = 4) with mild – moderate PD (i.e., Hoehn and Yahr [14] I – III) were recruited from PD-specific activity groups in the greater Houston area. Inclusion criteria were: 1) a diagnosis of PD from a movement disorder specialist, 2) an unchanged regimen of dopaminergic medication for at least 3 months, and 3) the ability to walk unassisted for at least 3 min. Subjects were excluded if they: 1) had injuries or surgeries that caused unusual gait, 2) respectively scored < 24 or < 17 on the MoCA [15] or telephone MoCA [16], 3) experienced freezing of gait, 4) had deep brain stimulation, or 5) 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.

### *V.IV.II Equipment and Tasks*

Kinematic data were collected using the Xsens MVN Biomech Awinda wireless system (Xsens Technologies B.V., Enschede, The Netherlands). This system includes 17 inertial motion trackers (triaxial accelerometers, gyroscopes, and magnetometers) placed on the locations shown in Figure 1. Movement information was collected at 60 Hz by each tracker and was integrated into a full-body kinematic model by the accompanying software. Variables of interest were bilateral hip, knee, and shoulder angles in the sagittal plane. Gait velocity, cadence, and stride length were calculated using a stopwatch and counting steps by direct observation over a known distance of 7.3 m in the middle of the

3-min gait trial. PD motor symptoms were assessed using the motor section of the Movement Disorder Society Unified Parkinson's Disease Rating Scale [17] (UPDRS III).

The primary task was overground walking at a self-selected speed for 3 min. Walking was performed unassisted and in the forward direction in a hallway sufficiently long to accommodate the long-duration trials. The secondary task was a phoneme monitoring task, during which the subjects listened to pre-recorded text through headphones worn over the ears. Subjects were given a specific word and instructed to count the number of times that it occurred in the recording. The subjects were informed that they had to perform the counting in their minds (i.e., not with the fingers). Furthermore, they were instructed to listen to the details of the text in order to answer questions at the end of the trial. There were two outcomes measured for the phoneme monitoring task: 1) percent of correct number of words counted (PM-Tally), and 2) percent 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%.

Phoneme monitoring was chosen as the secondary task because it has face validity with real-life situations such as when one converses while walking and maintains constant attention to the conversation [18]. In addition, the secondary phoneme monitoring task accommodated the long-duration gait task within the dual-task paradigm implemented in this study. A long-duration primary task was desired to assess how dual-tasking affects real-life situations the subjects experience on a daily basis and to increase the robustness of the objective variables. Several auditory recordings of ~195 s were

prepared so that each condition had a different recording and phoneme to tally. No practice or familiarization trials were performed.

*V.IV.III Procedures*

All testing was performed in one session, which began with the off-medication state (OFF). To achieve this, the night before and the morning of their visit, subjects adjusted the time they took their medication and/or skipped doses to coincide with a ≥ 12-hour overnight medication withdrawal. Upon arrival, subjects were outfitted with the Xsens sensors and the anthropometric measurements were determined and implemented in the software's kinematic model. Outfitting immediately before performing the other tests provided consistent conditions for the UPDRS III and single-task phoneme monitoring measures, during both OFF and on-medication states (ON), because once donned, the subjects did not remove the equipment. This ensured that any changes in UPDRS III and single task phoneme monitoring were not a result of different physical conditions.

Once equipped, testing commenced with the administration of the UPDRS III. The subjects then performed the following tasks in randomized order: 1) phoneme monitoring while seated comfortably in a quiet room, 2) single-task gait, and 3) dual-task gait, which was a combination of gait and phoneme monitoring. Each condition was performed for 3 min. Rest (≥ 1 min) between walking conditions was provided when necessary by having the subjects sit in a wheelchair at the end of each trial. Before all phoneme monitoring trials, the subjects were reminded that they would be asked questions about the content of the text and the phoneme tally at the end of the walk. No other explicit instructions for directing attention were provided.

After all trials were completed, the subjects took their medications as normally prescribed for their first/morning dose. The ON testing commenced 45 – 60 min later (or longer if the subject needed more time to achieve a stable 'on' state). Subject demographic information (i.e., age, weight, time since diagnosis, PD medication and dosages) were collected and recorded during this transition time. ON testing was completed in the same manner as OFF testing, with the same instructions and a new set of randomized conditions.

*V.IV.IV Data Processing*

Joint angle data relative to body segments (i.e., 0º in the standing, neutral position) were exported from the Xsens software and imported into MATLAB (The MathWorks, Natick, MA) for analysis. Data were filtered using a second-order Butterworth low-pass filter with 2.5 Hz (hip and shoulder angles) and 5 Hz (knee angles) cutoff frequencies, as determined by spectral analysis. Joint excursion was described as the absolute value of the difference between a local maximum and the subsequent local minimum, as shown in Figure 2. An absolute angle for each step was calculated in the same fashion for each joint, which provided a series of angles for that joint. The mean, maximum, and standard deviation of the bilateral hip, knee, and shoulder angles were calculated to provide a representation of segment movement and variability over the gait trial.

Additionally, in order to better understand the relationship between the primary and secondary tasks, dual-task effect (DTE) [11] was calculated as follows:

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

Where '*ST/DT Task*' respectively represents the single- and dual-task performance for a given variable. Furthermore, to visually characterize the relationship between the tasks and provide an indication of medication-induced automaticity, DTE ON was subtracted from DTE OFF (i.e., Task ΔDTE = ON Task DTE – OFF Task DTE), where 'Task' is a primary or secondary task. ΔDTE was calculated for gait velocity and the phoneme tally. Then, the DTE relationship between gait velocity and phoneme tally were plotted on a coordinate plane with (x,y) = ($\Delta DTE_{velocity}$, $\Delta DTE_{tally}$) for each subject with the x-axis as change in gait effect and y-axis as change in phoneme monitoring effect (see Figure 3 below).

*V.IV.V Statistical Analysis*

A 2-factor repeated-measures ANOVA, medication (OFF vs. ON) by task (ST vs. DT), was employed to test the hypotheses for the temporo-spatial gait variables (velocity, cadence, and stride length) and the phoneme monitoring variables. For the kinematic variables (mean, maximum, and SD bilateral hip, knee, and shoulder angles), a linear mixed effects model for repeated measures was performed, with medication (OFF vs. ON) and task (ST vs. DT) and the medication*task interaction as fixed effects, gait velocity as a repeated measure covariate, and maximum likelihood as the estimation method. This model was chosen to account for the correlation of each subject's data (i.e., each pairing of medication and task was highly correlated within a subject) and to use the available data fully. The covariate was included to control for the well-accepted

medication-induced improvements in gait velocity [2]. In addition, because PD symptoms are either unilaterally present or more severe [2], hip, knee, and shoulder angles were stratified into more-affected and less-affected sides instead of left and right sides. The assumptions for a repeated-measures ANOVA and linear mixed effects were reviewed or tested. The normality assumption of each variable was checked via histograms, skewness, and kurtosis statistics of the residuals of outcome variables. Pairwise comparisons (i.e., paired *t*-tests) were performed to clarify any significant differences. Significance was accepted at $p < 0.05$. Statistical analysis was performed using SPSS 23 (IBM Corp., Armonk, NY, USA).

## V.V Results

All subjects completed all of the trials according to study protocol. The assumptions for the statistical tests were sufficiently met by all of the variables and no adjustments were made. Table 2 contains the results of the analysis, stratified by medication and task. All significant differences are symbolically indicated. Major findings are summarized below.

### *V.V.I Temporo-Spatial Variables*

There was a significant main effect of medication on gait velocity ($p = 0.007$), but no main effect of task or interaction effect ($p = 0.123$ and $p = 0.371$, respectively). Post-hoc comparisons indicated that single-task gait velocity was faster ON than OFF ($p = 0.01$) and that dual-task gait was faster ON than OFF ($p = 0.043$).

There was a significant main effect of task on cadence ($p = 0.042$), but no medication or interaction effects ($p = 0.592$ and $p = 0.174$, respectively). Pairwise

comparison of the task effect indicated that cadence was lower during single-task walking OFF than dual-task walking OFF ($p = 0.029$).

There was a significant main effect of task on stride length ($p < 0.001$), but no medication or interaction effects were found ($p = 0.073$ and $p = 0.562$, respectively). Pairwise analysis of the task effect indicated significant differences across both medication states. While OFF, stride length was larger during single-task walking than dual-task walking ($p = 0.007$). While ON, stride length was also larger during single-task walking than dual-task walking ($p = 0.007$).

*V.V.II Kinematic Variables*

All significant differences in the kinematic variables below were attained after controlling for velocity. On the more-affected side, mean hip angle had a significant main effect of medication ($p = 0.007$), but no medication or interaction effects ($p = 0.069$ and $p = 0.735$, respectively). Pairwise comparisons indicated that single-task hip angle was smaller OFF than ON ($p = 0.027$). There was also a significant medication effect for mean knee angle ($p = 0.034$), but not a main effect of task or an interaction effect ($p = 0.192$ and $p = 0.346$, respectively). Pairwise comparisons found that the dual-task joint angle was smaller OFF than ON ($p = 0.023$). Furthermore, there was a significant main effect of task for the mean shoulder angle ($p = 0.01$), but not a significant medication or interaction effect ($p = 0.202$ and $p = 0.999$, respectively). Pairwise analysis indicated that while ON, the single-task shoulder angle was larger than the dual-task shoulder angle ($p = 0.29$).

On the less-affected side, the mean hip angle had significant main effects of medication and task ($p < 0.001$ and $p = 0.005$, respectively), but not a significant interaction effect ($p = 0.986$). For the medication effect, pairwise comparisons indicated that both single-task and dual-task hip joint excursions OFF were smaller than ON ($p = 0.001$ and $p = 0.001$, respectively). The task main effect followed a similar pattern with single-task OFF larger than dual-task OFF and single-task ON larger than dual-task ON ($p = 0.01$ and $p = 0.011$, respectively). Mean knee angle had a significant main effect of medication ($p = 0.008$), but no significant task or interaction effects ($p = 0.351$ and $p = 0.485$, respectively). Pairwise comparison found that single-task OFF was less than ON ($p = 0.015$). There were also significant main effects of medication and task for mean shoulder angle ($p = 0.014$ and $p = 0.044$, respectively), but not an interaction effect ($p = 0.221$). Pairwise comparisons indicated that dual-task shoulder joint excursion OFF was smaller than ON ($p = 0.009$) and that when OFF the single-task joint angle was larger than the dual-task joint angle ($p = 0.026$).

*V.V.III Phoneme Monitoring*

There were no significant main effects on PM-Tally or PM-Score.

*V.V.IV Change in Dual-task Effect*

The effect the primary and secondary tasks had on one another during dual-tasking OFF and ON are presented in Figure 3. Visual inspection indicates that, after taking dopaminergic medication, most subjects either experienced no change in dual-task effect (values arbitrarily close to zero) or changed to a cognitive-priority strategy.

**V.VI Discussion**

The primary hypothesis for the study was that dopaminergic medication would improve dual-task walking such that ON dual-task would be significantly improved over OFF single-task. The results of the study do not support this hypothesis. However, PD gait, which is characterized by short, shuffling steps [3], was significantly improved in dual-tasking after taking dopaminergic medication. Our findings also indicated several other medication and task effects. This means that medication was effective at improving gait velocity and joint angles, particularly on the less-affected side (see Table 2), and that the secondary task was sufficient to interfere with gait, despite medication state.

The results of this study indicate that improved dual-tasking ON is most likely the result of improved motor function and not improved automaticity. The lack of significant interactions and effects on the phoneme monitoring task challenge the concept of an improvement in automaticity after taking dopaminergic medication. Rather, these findings supports to the idea that motor automaticity is centrally controlled, especially considering that PD medication has variable effects on executive functions [19].

There are several dual-tasking models that have been suggested to describe dual-task interference. The two most popular of these are the capacity sharing model and the bottleneck model. Briefly, the capacity sharing model suggests that all tasks are performed within a finite capacity and exceeding the limits of capacity causes interference with one or both concurrently performed tasks [11,20]. The bottleneck theory, on the other hand, divides the mechanisms into motor and cognitive sections,

and interference occurs only when one attempts to perform two concurrent tasks using the same mechanism [11,21]. Our data fits well with the capacity sharing model, which suggests that all tasks are performed within a finite capacity and exceeding the limits of capacity causes interference with one or both concurrently performed tasks [11,20]. Because phoneme monitoring is performed without any motor demands, and forward walking requires little or no cognitive demand, we assume that the tasks of this study operated with different mechanisms and the interference was the result of an exceeded capacity.

The change in dual-task effect presented in Figure 3 implies that, while ON, some PD subjects may have adopted the so-called 'posture-second' dual-task strategy, which is in agreement with previous findings [22]. This strategy postulates that PD subjects wrongly prioritize secondary, cognitive tasks at the expense of postural stability. This undesirable prioritization may partly explain why PD subjects are more prone to loss of balance and falls than their neurologically healthy peers [23].

**V.VII Conclusions**

Dopaminergic medication improved some aspects of dual-tasking in the mild-moderate PD subjects, but this was likely a result of improved motor function, especially on the less-affected side. Our findings do not support a medication-induced improvement in automaticity, but they do support the 'capacity sharing model' of dual-task interference, because the purely cognitive secondary task was sufficient to interfere with gait performance.

## Tables

Table 1. Subject demographic information.

| Demographics | Mean ± SD |
|---|---|
| Sex | 12 male, 4 female |
| Age | 67.13 ± 7.54 yrs. |
| Height | 171.16 ± 9.53 cm |
| Mass | 80.93 ± 14.28 kg |
| UPDRS III (OFF) | 44.44 ± 13.34 |
| UPDRS III (ON) | 24.44 ± 8.17 |
| More-affected side | Right = 9, Left = 7 |
| Time since diagnosis | 6.72 ± 5.79 yrs. |
| Levodopa Equivalent Dose | 669.53 ± 230.57 |

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

Table 2. The results of the data analysis, stratified by task and medication. Data are presented as mean ± SD.

| Variable Name | Condition | | | |
|---|---|---|---|---|
| | ST-OFF | DT-OFF | ST-ON | DT-ON |
| Velocity (m/s) | 1.23 ± 0.18 | 1.20 ± 0.21 | 1.31 ± 0.14* | 1.26 ± 0.16* |
| Cadence (steps/min) | 114.46 ± 10.05 | 119.54 ± 11.84† | 117.74 ± 8.44 | 118.74 ± 9.65 |
| Stride Length (m/stride) | 1.29 ± 0.16 | 1.21 ± 0.15† | 1.33 ± 0.13 | 1.27 ± 0.12*† |
| More-affected (degrees) | | | | |
| Hip | | | | |
| Mean | 37.09 ± 5.45 | 36.12 ± 5.16 | 39.10 ± 6.08* | 37.71 ± 5.46 |
| Max | 40.43 ± 5.33 | 39.46 ± 5.11 | 42.83 ± 6.53* | 41.63 ± 5.96* |
| SD | 1.74 ± 2.15 | 1.43 ± 0.91 | 1.75 ± 1.03 | 1.52 ± 0.83 |
| Knee | | | | |
| Mean | 60.55 ± 4.55 | 59.38 ± 5.45 | 61.46 ± 6.16 | 61.27 ± 5.80* |
| Max | 64.61 ± 3.98 | 63.59 ± 4.01† | 65.38 ± 5.20 | 64.9 ± 5.19* |
| SD | 1.68 ± 0.80 | 1.74 ± 0.75 | 1.80 ± 0.81 | 1.71 ± 0.75 |
| Shoulder | | | | |
| Mean | 13.08 ± 11.71 | 10.14 ± 8.34 | 14.26 ± 10.23 | 11.32 ± 9.59† |
| Max | 18.89 ± 13.56 | 17.13 ± 12.29 | 22.85 ± 13.65 | 18.99 ± 12.88 |
| SD | 2.27 ± 0.97 | 2.21 ± 1.53 | 3.36 ± 2.95 | 3.11 ± 3.04 |
| Less-affected (degrees) | | | | |
| Hip | | | | |
| Mean | 37.21 ± 5.65 | 36.05 ± 5.32† | 39.34 ± 5.40* | 38.20 ± 5.17*† |
| Max | 40.82 ± 6.54 | 39.37 ± 5.62† | 43.34 ± 6.07* | 41.53 ± 5.20*† |
| SD | 1.47 ± 0.94 | 1.25 ± 0.39 | 1.66 ± 0.80 | 1.33 ± 0.66† |
| Knee | | | | |
| Mean | 61.57 ± 4.41 | 61.43 ± 3.84 | 63.21 ± 4.96* | 62.45 ± 4.35 |
| Max | 65.29 ± 4.67 | 65.43 ± 4.25 | 67.25 ± 4.75* | 66.59 ± 4.83 |
| SD | 1.68 ± 0.80 | 1.54 ± 0.72 | 1.70 ± 0.71 | 1.74 ± 0.96 |
| Shoulder | | | | |
| Mean | 18.02 ± 11.23 | 14.35 ± 10.74† | 19.48 ± 9.49 | 18.58 ± 9.72* |
| Max | 24.29 ± 12.53 | 20.57 ± 12.28 | 29.29 ± 13.03 | 27.62 ± 11.53* |
| SD | 2.50 ± 0.90 | 2.16 ± 0.95 | 4.73 ± 5.69 | 4.10 ± 4.55 |
| Phoneme Monitoring (%) | | | | |
| Tally | 87.30 ± 9.98 | 79.11 ± 17.29 | 88.23 ± 14.91 | 87.39 ± 13.36 |
| Score | 62.66 ± 26.20 | 50.94 ± 29.00 | 50.21 ± 25.57 | 53.75 ± 25.62 |

Note: ST = single-task, DT = dual-task, OFF = off-medication state, ON = on-medication state. * = ON significantly different than OFF within the same task. † = DT significantly different than ST within the same medication state.

Figure 1. Xsens sensor locations (17 total) on the head, sternum, posterior pelvis (i.e., L5/Sacrum), and bilaterally on the shoulders, upper arms, forearms, hands, thighs, lower legs, and feet. Sensors are shown on top of straps for clear visualization.

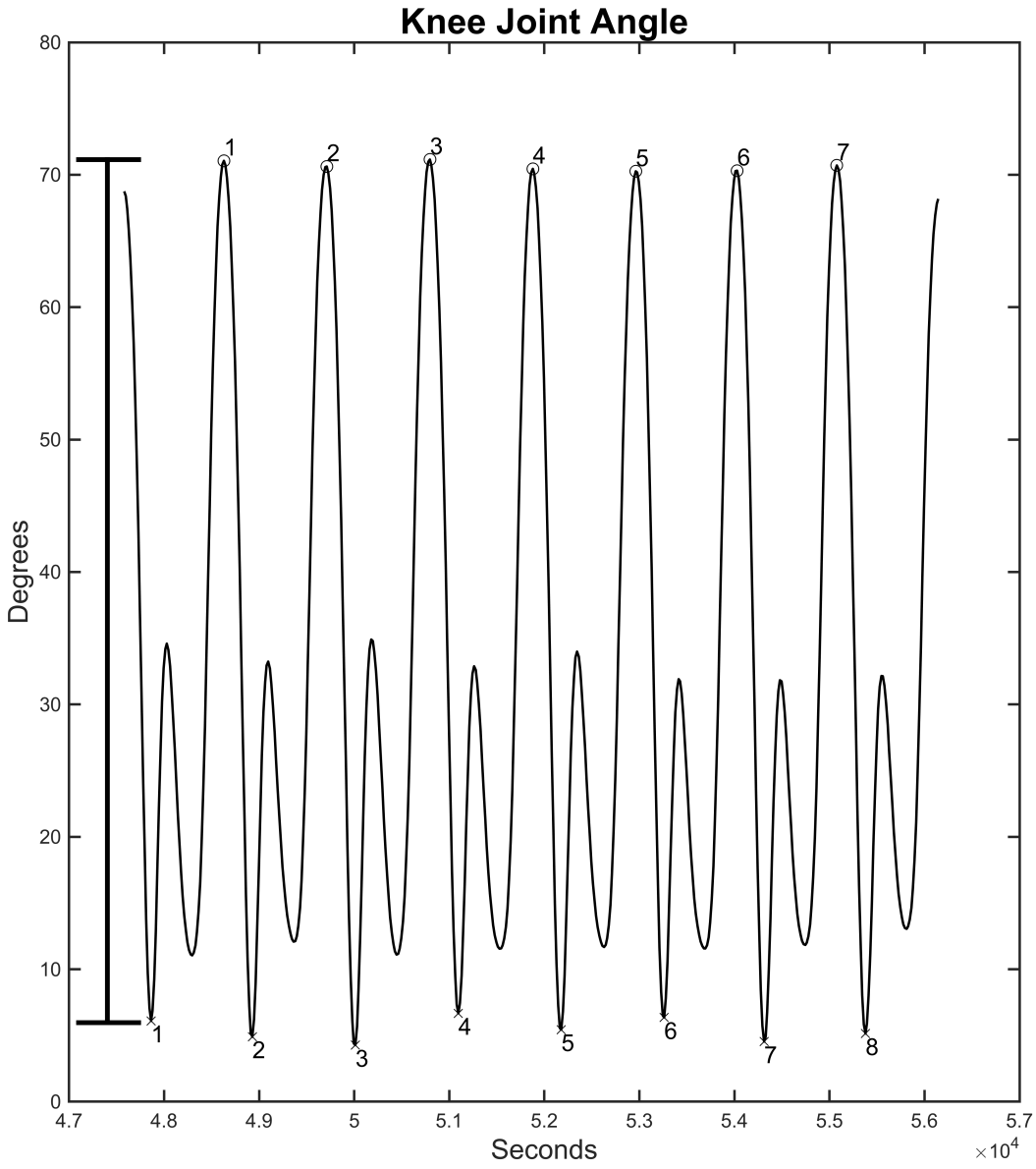


Figure 2. Example of a knee joint signal. The vertical line on the left of the figure represents the absolute change in joint angle measured and collected during data analysis. Note how the secondary peaks are ignored and not included in the joint angle measurements.

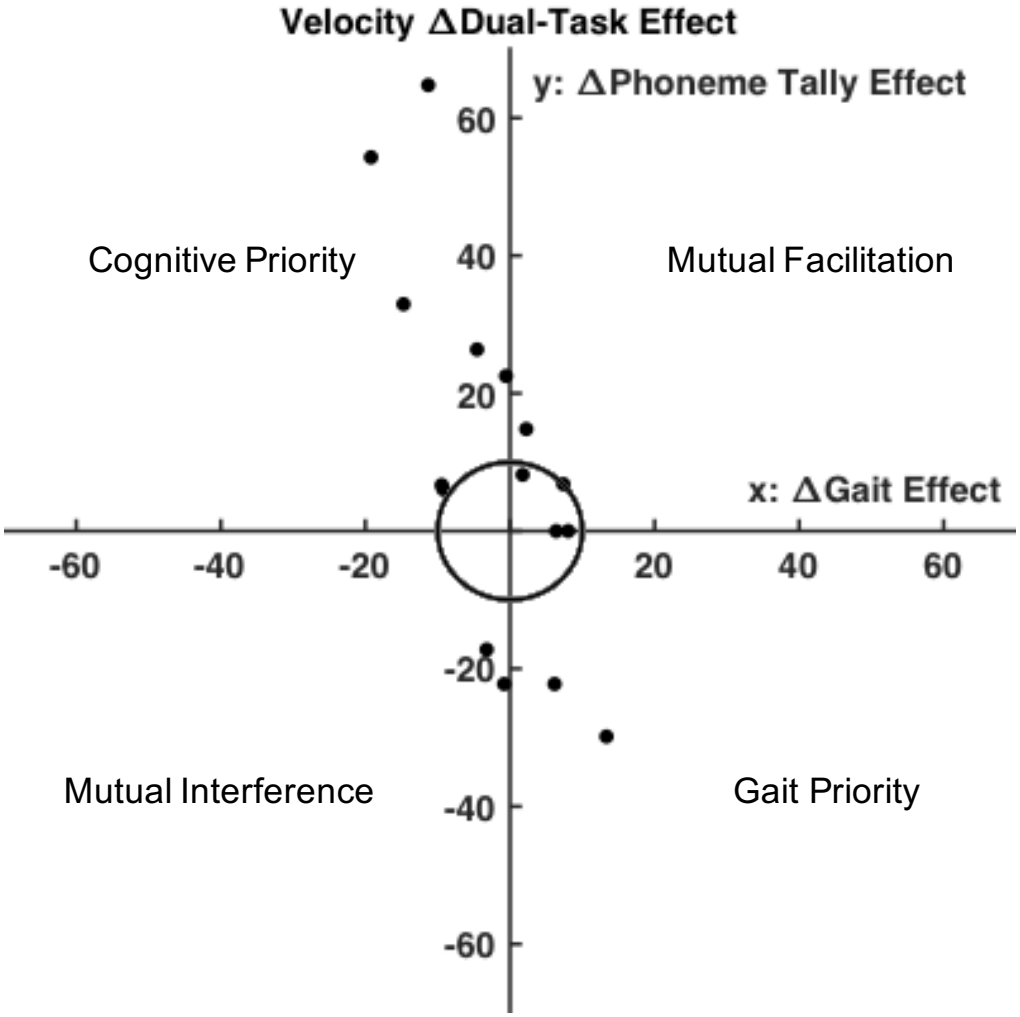


Figure 3. Plot of the change in dual-task effect for velocity. Each point represents the change in dual-task effect for a subject from OFF to ON and is plotted with the change in dual-task effect for gait velocity as ‘x’ and the change in dual-task effect for phoneme tally as ‘y’. The quadrants are labeled to indicate the relationship between the primary and secondary tasks. Points arbitrarily within a circle of radius 10 (minimal clinically meaningful differences are unknown) about the origin are interpreted as ‘no effect’. Note that several subjects experienced either ‘no effect’ or shifted to a ‘cognitive priority’ dual-task strategy when ON.

# *VI. Manuscript 2, Balance Automaticity*

## VI.I Title Page

Title: The Influence of Dopaminergic Medication on Balance Automaticity in Parkinson's Disease.

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**VI.II Abstract**

**Background:** Dual-tasking studies have shown that balance automaticity in Parkinson's disease (PD) is significantly reduced. Additionally, it is well accepted that dopaminergic medication improves dynamic balance, but standing balance may suffer. What remains unknown is how dopaminergic medication influences standing balance automaticity in PD. **Research Question:** Does dopaminergic medication improve standing balance automaticity and dual-tasking 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 minutes 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 interaction effects for anterior-posterior velocity and integrated time to boundary ($p = 0.015$ and $p = 0.009$, respectively). These eyes condition and interaction effect increases in sway velocity and integrated time to boundary 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.

Keywords: Parkinson’s disease, balance, dual-task, medication, posturography

## VI.III 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]. The motor symptoms, however, are well documented, the most cardinal of which are rest tremor, rigidity, bradykinesia, postural instability, and gait impairment [2–4]. These are usually treated with dopaminergic medications like dopamine replacement, dopamine agonists, and inhibitors [2–6]. However, these medication-induced improvements are limited and may not impact all motor deficits [24]. In addition to the cardinal symptoms, PD subjects also experience decreased motor automaticity [25]. Motor automaticity is achieved when a given motor task is performed without attentional control [7].

Dual-tasking involves performing a primary motor task (e.g., standing) and a secondary task (e.g., conversing) simultaneously. Automaticity is commonly assessed using dual-task paradigms. If the primary task is automatic, then the simultaneous performance of a secondary task would have little to no effect on the primary task. However, dual-tasking often results in deteriorations, i.e. dual-task interference [11], of one or both tasks [8]. Dual-task interference [13,25–30] and the impact of various PD treatments on postural performance in PD balance with the eyes open and the eyes closed [31–33] 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.

Only a few have investigated the effects of medication on dual-task balance. McNeely et al. [13] researched the effect of medication on dual-task gait and balance in PD using clinical balance scales (i.e., Berg Balance Scale and mini-BESTest). Their results indicated significant medication effects on the balance scales, but not dual-task Timed Up and Go. Although there is great utility in clinical balance scales, especially in assessing changes over time and in different balance domains, more objective laboratory measures like those obtained with force platform posturography are useful for determining 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 [34] 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. The different eyes conditions were desirable to increase task complexity in a graded way (i.e., single-task eyes open < single-task eyes closed < dual-task eyes open < dual-task eyes closed) and to aid in comparisons with other posturographic studies that have employed either or both conditions. Additionally, objective posturographic measures and a constant-attention secondary task that did not require motor activity were employed to strengthen the robustness of the results and the dual-task interference interpretations. It was hypothesized that the medications would improve balance automaticity such that objective measures of the primary and

secondary task performance in the dual-task conditions on-medication would be significantly decreased compared to single-task off-medication conditions.

## VI.IV Methods

### *VI.IV.I Subjects*

Sixteen subjects (4 female) with mild to moderate PD (i.e., Hoehn and Yahr [14] I – III) were recruited from PD-specific activity groups in the greater Houston area (see Table 3 for demographic information). Inclusion criteria were a diagnosis of PD from a movement disorder specialist, 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 MoCA [15] or telephone MoCA [16], 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.

### *VI.IV.II Equipment and Tasks*

Center of Pressure (COP) data were collected using the 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 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 [35], 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 [17] (MDS-UPDRS III).

The primary task was quiet stance, which was performed with eyes open (EO) and eyes closed (EC). Each trial lasted for 3 min. The secondary task was a phoneme monitoring task, 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% (see Manuscript 1).

This secondary task was selected because it has face validity with real-life situations, like attending to a conversation while standing [18]. 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 so that each trial had a novel recording and phoneme to tally. No familiarization trials were performed.

*VI.IV.III 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 calculation of integrated time to boundary (iTTB; 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 at the end of a trial. Whenever the subjects performed the phoneme monitoring task, they were reminded of the 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 45 – 60 min later (or longer if the subject needed more time to achieve a stable ‘on’ state) 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.

*VI.IV.IV 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 [36]. $COP_{area}$ was calculated by plotting the COP path on a coordinate plane and calculating the area of an ellipse that contains 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 10s 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., 10s x total duration) [37]. Traditional interpretations of these variables are that larger $COP_{area}$, faster COP velocities, and larger iTTB indicate instability [35].

Additionally, in order to better understand the relationship between the primary and secondary tasks, dual-task effect (DTE) [11] was calculated as follows:

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

Where '*ST/DT Task*' respectively represent the single- and dual-task performance for a given variable. For measures where a larger value indicates a poorer performance (e.g., $COP_{area}$), a negative sign is inserted at the beginning of the formula [11]. Furthermore, to visually characterize the relationship between the tasks and provide an indication of medication-induced automaticity, DTE ON was subtracted from DTE OFF (i.e., Task ΔDTE = ON Task DTE – OFF Task DTE), where 'Task' is a primary or secondary task. ΔDTE 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 with (x,y) = ($\Delta DTE_{area}$, $\Delta DTE_{tally}$) with the x-axis as change in balance effect and y-axis as change in phoneme monitoring effect (see Figure 5 below).

*VI.IV.V 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. For 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. *Post-hoc* pairwise comparisons (i.e., paired *t*-tests) were performed to clarify any significant differences. Significance was accepted at $p < 0.05$. Statistical analysis was performed using SPSS 23 (IBM Corp., Armonk, NY, USA).

**VI.V Results**

All subjects completed all of the testing conditions according to the study protocol. Table 3 displays the subject demographic information. The assumptions for a repeated measures ANOVA were sufficiently met by all of the variables and there were no violations of the sphericity assumption. Table 4 contains the results of the analysis, stratified by medication state. Figure 4 displays the same data in graphical form and indicates the significant differences with lines and tick marks. Significant findings are summarized below.

*VI.V.I Center of Pressure 95% Confidence Ellipse Area*

For $COP_{area}$, there were significant medication ($p = 0.002$) and task ($p = 0.034$) main effects, but not a significant effect of eyes condition (p=0.629). Further analysis indicated that OFF-STEC was less than ON-STEC (p = 0.041), OFF-DTEC was less than ON-DTEC (p = 0.023), and ON-STEC was greater than ON-DTEC ($p = 0.021$). This means the subjects utilized a larger area to maintain their balance for the same task and eyes conditions after taking medication and that performing the secondary task ON reverted area measurements toward OFF values. Figure 4 displays several other significant differences that were found in the pairwise comparisons.

*VI.V.II Integrated Time to Boundary*

For iTTB, there was a significant main effect of eyes ($p < 0.001$) but not significant medication or task main effects ($p = 0.321$ and $p = 0.207$, respectively). However, there was a significant task by eyes interaction effect ($p = 0.009$). Pairwise comparisons further clarified these effects. During OFF, the effect of eyes was that STEO was less than both STEC ($p < 0.001$) and DTEC ($p = 0.003$), and DTEO was less than DTEC ($p = 0.005$). For the OFF interaction effect, STEC was greater than DTEO ($p < 0.001$). The effect of eyes while ON was similar to OFF, with STEO was less than both STEC ($p < 0.001$) and DTEC ($p < 0.001$), and DTEO less than DTEC ($p < 0.001$). For the ON interaction effect, STEC was greater than both DTEO ($p < 0.001$) and DTEC ($p < 0.018$). Thus, the subjects' iTTB values worsened after closing their eyes (i.e., eyes open less than eyes closed), and taking dopaminergic medication or performing a secondary task did not influence this pattern. Indeed, as can be seen in Table 4, iTTB values for the same balance conditions were very similar across medication states. Figure 4 displays the other significant differences that were found in the pairwise comparisons.

*VI.V.III COP Velocity, Anterior-Posterior*

AP-Velocity also had a significant main effect of eyes ($p < 0.001$) but not significant medication or task main effects ($p = 0.237$ and $p = 0.125$, respectively). Additionally, there was a significant task by eyes interaction effect ($p = 0.015$). Pairwise comparisons for AP-Velocity closely mirrored iTTB results, with the eyes closed conditions significantly faster (i.e., worse) than the eyes open conditions, despite

medication state. Specifically, during OFF, STEO was slower than both STEC and DTEC ($p < 0.001$ and $p < 0.001$, respectively), while DTEO was slower than DTEC ($p = 0.001$). The OFF interaction effect maintained this theme and indicated that STEC was faster than DTEO ($p < 0.001$). During ON, STEO was slower than both STEC and DTEC ($p < 0.001$ and $p < 0.001$, respectively), and DTEO was slower than DTEC ($p < 0.001$). The ON interaction effect also indicated that STEC was faster than DTEO ($p < 0.001$). Thus, as was seen in the iTTB results, AP-Velocity was worsened after the subjects closed their eyes and was not affected by medication state or the secondary task. The remaining significant differences are shown in Figure 4.

*VI.V.IV COP Velocity, Medial-Lateral*

There was a significant eyes condition main effect for ML-Velocity ($p < 0.001$), but not significant medication or task main effects ($p = 0.268$ and $p = 0.802$, respectively). Pairwise comparisons further indicated that OFF-STEO was slower than OFF-STEC ($p = 0.002$) and that ON-STEO was slower than ON-STEC ($p = 0.007$). See Figure 4 for other significant, pairwise findings.

*VI.V.V Phoneme Monitoring*

There was a significant medication effect of for PM-Score ($p = 0.004$), with OFF-DTEC greater than ON-DTEC ($p = 0.002$), but not a significant task main effect ($p = 0.567$). There was also a significant interaction effect for PM-Score ($p = 0.044$). Pairwise comparisons indicated that OFF-DTEC was greater than ON-ST ($p = 0.009$).

*VI.V.VI Dual-Task Effect*

Figure 5 shows the ΔDTE for (x,y) = ($\Delta DTE_{area}$, $\Delta DTE_{tally}$) 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.

**VI.VI 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 [35], and our results agree with previous findings that PD medication increases $COP_{area}$ and functional limits of stability [31–33], but not necessarily clinical balance scales [13].

These apparent discrepancies can be reconciled with alternate interpretations of the gestalt of these variables in PD. For example, consider the stability/maneuverability tradeoff [38], 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 [33] for an example). Furthermore, because dopaminergic medication causes well-accepted improvements in these stability-simulating symptoms [2–6], 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 not necessarily a decrease in stability.

The effects on the phoneme monitoring task, especially the significant negative medication effect while dual-tasking, do not support the concept of a medication-induced 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 [19].

Lastly, several dual-tasking models have been suggested to describe how dual-tasking is controlled, with two models as 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 [11]. 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 [11]. 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.

## VI.VII 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.

Table 3. Subject demographic information. Data are mean ± SD, where appropriate.

| **Demographics** | |
|---|---|
| Sex | 12 male, 4 female |
| Age | 67.13 ± 7.54 yrs. |
| Height | 171.16 ± 9.53 cm |
| Mass | 80.93 ± 14.28 kg |
| UPDRS III (OFF) | 44.44 ± 13.34 |
| UPDRS III (ON) | 24.44 ± 8.17 |
| Time since diagnosis | 6.72 ± 5.79 yrs. |
| Levodopa Equivalent Dose | 669.53 ± 230.57 |

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

Table 4. The results of the data analysis stratified by medication state, task, and condition. Data are presented as mean ± SD.

| Variable | Medication State | |
|---|---|---|
| | OFF | ON |
| $COP_{area}$ ($cm^2$) | | |
| STEO | 1.73 ± 1.00 | 4.29 ± 5.05 |
| STEC | 2.54 ± 2.04 | 4.34 ± 2.56 |
| DTEO | 2.03 ± 1.72 | 2.75 ± 1.85 |
| DTEC | 1.89 ± 0.79 | 2.89 ± 1.76 |
| AP-Velocity (cm/s) | | |
| STEO | 1.27 ± 0.27 | 1.35 ± 0.49 |
| STEC | 1.89 ± 0.55 | 1.98 ± 0.70 |
| DTEO | 1.25 ± 0.35 | 1.43 ± 0.49 |
| DTEC | 1.67 ± 0.44 | 1.73 ± 0.50 |
| ML-Velocity (cm/s) | | |
| STEO | 0.64 ± 0.30 | 0.58 ± 0.23 |
| STEC | 0.76 ± 0.35 | 0.72 ± 0.30 |
| DTEO | 0.71 ± 0.41 | 0.64 ± 0.24 |
| DTEC | 0.72 ± 0.32 | 0.66 ± 0.22 |
| iTTB (% total area) | | |
| STEO | 5.33 ± 3.87 | 5.86 ± 3.89 |
| STEC | 11.90 ± 5.88 | 12.55 ± 5.79 |
| DTEO | 5.38 ± 4.42 | 6.98 ± 4.33 |
| DTEC | 9.48 ± 5.50 | 10.09 ± 4.65 |
| Phoneme Monitoring (%) | | |
| Tally | | |
| ST | 87.30 ± 9.98 | 88.23 ± 14.91 |
| DTEO | 87.03 ± 11.72 | 82.29 ± 13.56‡ |
| DTEC | 91.38 ± 10.60‡ | 85.42 ± 12.31 |
| Score | | |
| ST | 62.66 ± 26.20 | 50.20 ± 25.57† |
| DTEO | 63.28 ± 26.44 | 63.96 ± 31.93 |
| DTEC | 73.28 ± 24.54*† | 45.21 ± 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, v = velocity, AP = anterior-posterior, ML = medio-lateral, iTTB = integrated time to boundary. *, †, and ‡ = significantly different from its pair. See Figure 4 for other significant differences.

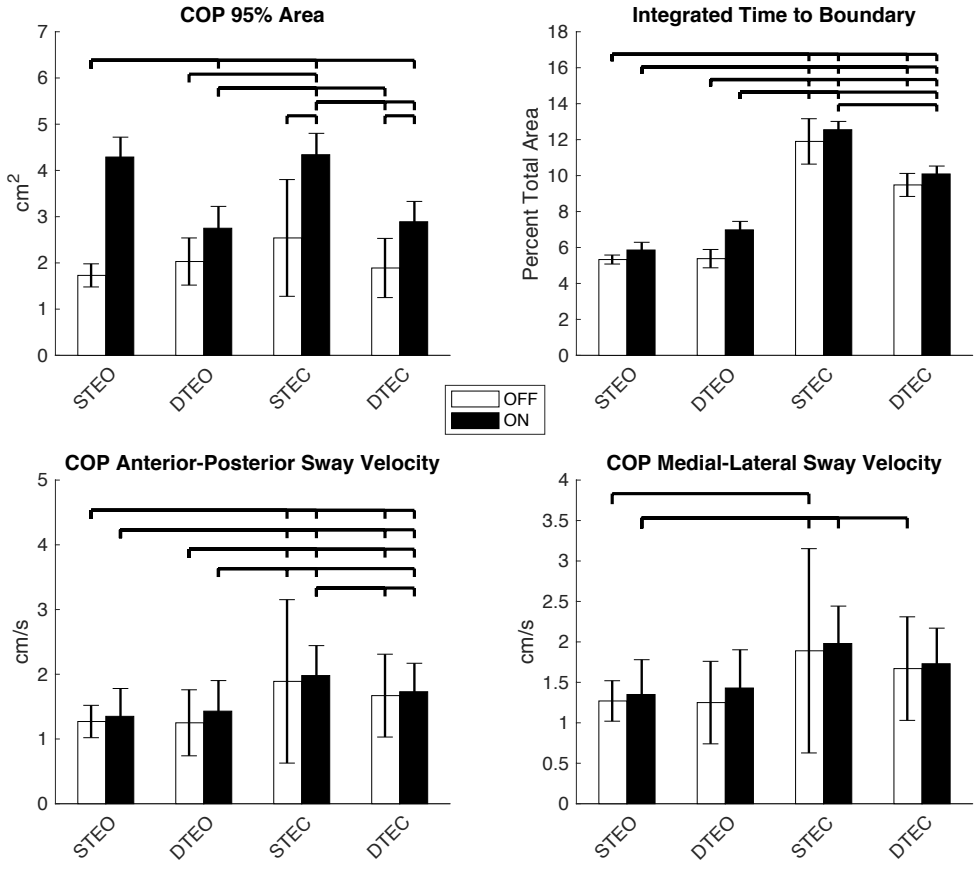


Figure 4. Bar graphs depicting the mean ± SEM data for COP 95% area (top-left), integrated time to boundary (top-right), velocity of the COP in the anterior-posterior direction (bottom-left), and velocity of the COP in the medial-lateral direction. Significant differences ($p < 0.05$) are indicated by the lines and tick marks, with the left-most bar being significant from the others indicated. COP = center of pressure, ST = single-task, DT = dual-task, EO = eyes open, EC = eyes closed, OFF = off-medication state, ON = on-medication state.

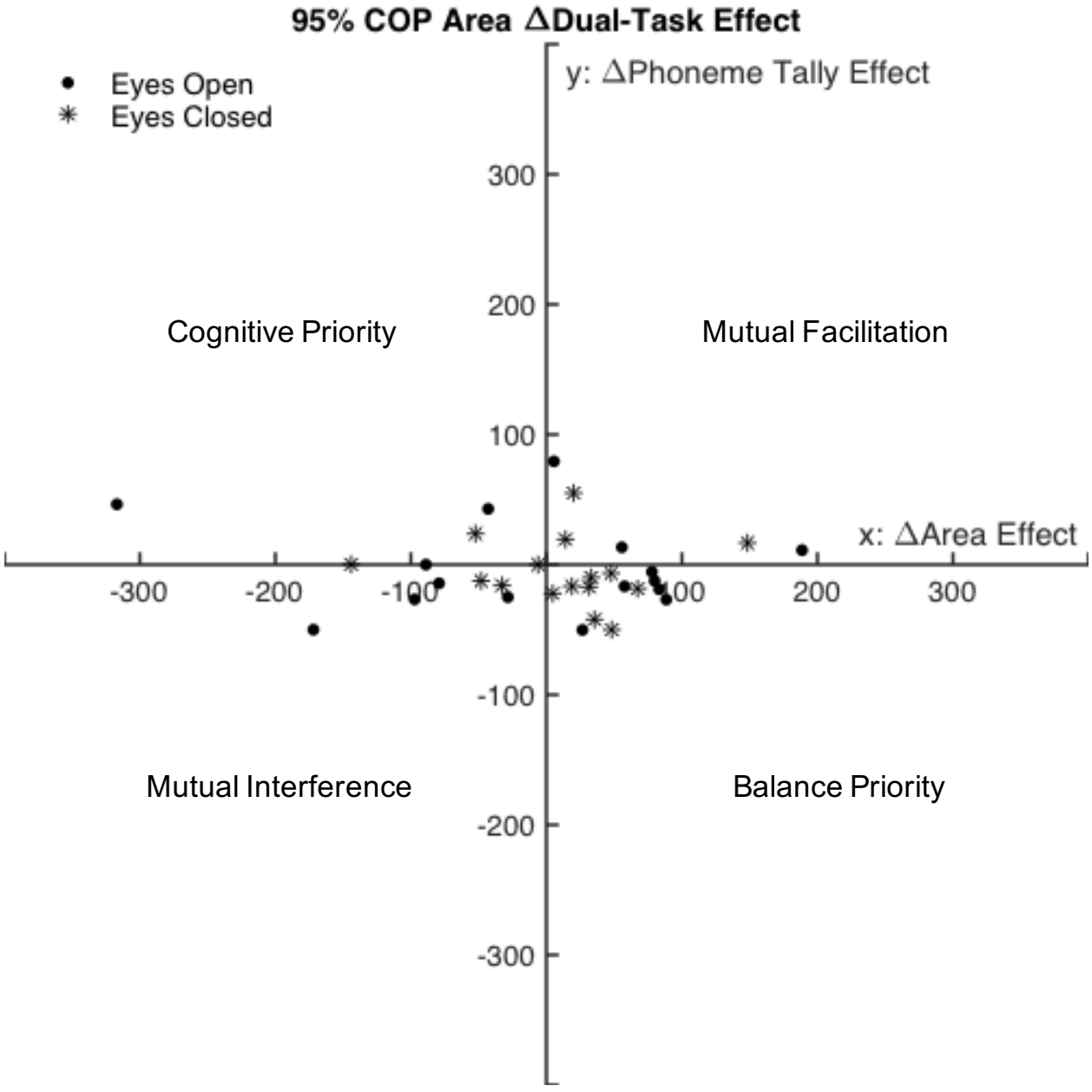


Figure 5. Scatterplot of the change in dual-task effect for $COP_{area}$. Each point represents the change in dual-task effect for a subject from OFF to ON and are plotted as (x,y) = ($\Delta DTE_{area}$, $\Delta DTE_{tally}$) for eyes open and eyes closed conditions. The quadrants are labeled to indicate the relationship between the primary and secondary tasks.

# *VII. Manuscript 3, Nonlinear Analyses*

**VII.I Title Page**

Title: The Influence of Dopaminergic Medication on Nonlinear Analyses of Gait and Balance in Parkinson's Disease

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**VII.II Abstract**

An understanding of how dual-tasking and Parkinson's disease (PD) medication effect gait and balance regularity informs patients, caregivers, and clinicians about frailty and fall risk. However, dual-task gait and balance studies in PD have almost exclusively employed linear measures to describe regularity outcomes. Nonlinear analyses, which take into account the regularity of entire signals, are less prevalent. Some have used nonlinear techniques to analyze PD balance, but only in the on-medication state. It is still unclear how the nonlinear aspects of joint angles or standing posture are affected by PD medication. This study aimed to determine how dopaminergic medication influenced the regularity/determinism of joint angle and center of pressure (COP) path signals while single- and dual-tasking in PD. Sixteen subjects with PD completed single- and dual-task gait and standing balance trials for 3 minutes off and on dopaminergic medication. Approximate entropy and percent determinism were calculated for bilateral hip, knee, and shoulder joints, as well as the COP path. There were significant medication effects on the approximate entropy of the more-PD affected knee while dual-tasking ($p$ = 0.014), the less-PD affected knee while dual-tasking ($p$ = 0.008), both of which indicated that medication decreased the regularity of the signal. The analysis also revealed that balance task complexity was reflected in the evaluation of the COP path, with more complex tasks (i.e., eyes closed) eliciting significantly less regular/deterministic signals. The medication-induced decreases in regularity, coupled with accepted improvements in gait performance with medication, may indicate that PD patients are too regular in their joint movements, especially off medication.

Keywords: Parkinson's disease, gait, balance, dual-task, medication, nonlinear

**VII.III Introduction**

Parkinson's disease (PD) affects approximately 1 million people in the US and is the second most prevalent degenerative neurological movement disorder [1]. The cardinal PD motor symptoms are rest tremor, rigidity, bradykinesia, postural instability, and gait impairment [2–4], which are often treated pharmacologically with dopamine replacement, dopamine agonists, and inhibitors [2–6], but sometimes with limited effects [24]. Additionally, a decrease in automaticity, when a given motor task is performed without attentional control [7], is also common in PD [25]. Automaticity is assessed via performance in dual-task paradigms, during which subjects perform a primary task (e.g., walking) concurrent with a secondary task (e.g., phoneme monitoring). Any detriments to the performance of the primary and/or secondary tasks in dual-task paradigms can be interpreted as dual-task interference [8,11]. Dual-task interference in PD gait and balance has been well documented [7,13,25,26,28,30] and the impact of dopaminergic medication on gait and balance in PD has been previously investigated [31–33].

However, most researchers in this area have almost exclusively employed traditional temporal-spatial measures of gait (e.g., velocity, stride length) and descriptive statistics (e.g., mean and SD) of the center of pressure, both sets of which are linear. Although these linear analyses and statistics are informative, they do not consider the features of the entire signal and they do not provide information about the regularity of gait or balance signals. To determine some of the more complex traits of these signals, e.g., movement regularity, nonlinear analyses (e.g., Approximate Entropy and Recurrence Quantification Analysis) are required. A few have applied nonlinear analyses in describing hand tremor [39,40] and standing postural variables [39,41] in

PD, but no research has been conducted that has used nonlinear techniques to describe PD gait and those describing balance were always performed while subjects were in the on-medication state [39,41].

It is important to understand movement regularity in PD because the regularity of gait and balance signals is associated with frailty and fall risk in older adults [42,43]. It is also worthwhile to appreciate how task complexity, i.e., dual-tasking, affects regularity, especially because most activities of daily living involve performing multiple tasks at once. In addition, many PD subjects experience periods of being off-medication, the so-called wearing-off effect [2], while performing these dual-task activities of daily living; therefore, a dual-task paradigm is also helpful in understanding how medication affects movement regularity in real-life situations. Thus, understanding how both dual-tasking and PD medication together affect regularity will provide useful information to clinicians and caregivers to ensure that PD subjects are operating within their capabilities.

Therefore, the aim of this study was to assess the influence of dopaminergic medication on the nonlinear characteristics of gait and balance while dual-tasking for long-durations (3 min). It was hypothesized that medication would improve the nonlinear aspects of the gait and balance signals such that dual-task conditions on-medication would be significantly more regular (i.e., smaller ApEn, larger %DET) compared with single-task off-medication conditions. These two techniques were chosen from the various other nonlinear tools because of their analogous and relatively simple interpretations.

## VII.IV Material and Methods

### *VII.IV.I Subjects*

Sixteen subjects (female = 4) with mild to moderate PD (i.e., Hoehn and Yahr [14] I – III) were recruited from PD-specific activity groups in the greater Houston area. Inclusion criteria were: 1) a diagnosis of PD from a movement disorder specialist, 2) on an unchanged regimen of dopaminergic medication for ≥ 3 months, and 3) able to stand and walk unassisted for ≥ 3 min. Subjects were excluded if they had injuries or surgeries that caused unusual gait or stances, respectively scored < 24 or < 17 on the Montreal Cognitive Assessment (MoCA) [15] or telephone MoCA [16], 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.

### *VII.IV.II Equipment and Tasks*

Kinematic data were collected using the Xsens MVN Biomech Awinda wireless system (Xsens Technologies B.V., Enschede, The Netherlands), which includes 17 inertial motion trackers (triaxial accelerometers, gyroscopes, and magnetometers) placed at the body segments shown in Figure 6. Movement data were collected at a 60 Hz sampling rate by each tracker, which were integrated into a full-body kinematic model by the Xsens software. Bilateral hip, knee, and shoulder angles in the sagittal plane were extracted. Balance data were collected using the NeuroCom Balance Master force platform (NeuroCom International Inc., Clackamas, OR, USA) operating at 100 Hz. The path of the center of pressure (COP) was determined. PD motor symptoms

were assessed using the motor section of the Movement Disorder Society Unified Parkinson's Disease Rating Scale [17] (UPDRS III).

The two primary tasks were: 1) overground gait at a self-selected speed, and 2) standing balance with eyes open and eyes closed. Each primary task was performed one time for 3 min. The secondary task was a phoneme monitoring task, during which the subjects listened to audio text (i.e., an unfamiliar fairytale) through on-ear headphones and counted the number of times a pre-determined word occurred. The subjects were instructed to perform the counting mentally (i.e., not tally with fingers) while attending to the details of the story and answer questions at the end of the trial. Phoneme monitoring provided two outcomes; the proportion of words correctly tallied (PM-Tally) and the 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%).

Phoneme monitoring was ideal for the desired long-duration collection time, because it has face validity with real-life situations like conversing while walking or standing. A long-duration data collection time provided sufficient data for the nonlinear analyses and also mirrors real-life situations the subjects experience on a daily basis. Several auditory recordings of ~195 s long were prepared so that each condition had a novel story and phoneme to tally. No practice or familiarization trials were performed.

*VII.IV.III Procedures*

Testing always began with the off-medication state (OFF). All trials were completed in one session. To ensure the subjects were in a stable off state, they were instructed to undertake a minimum 12-hour overnight medication withdrawal. First, the subjects' anthropometric measurements were determined and input into Xsens software kinematic model and they were outfitted with the Xsens sensors. This provided consistent conditions for the non-gait trials (i.e., UPDRS III, single-task phoneme monitoring, balance trials), during both OFF and on-medication (ON) states. This was necessary because once the sensors were donned, the subjects did not remove them.

After the sensors were placed, testing always commenced with the UPDRS III. The subjects then performed trials in blocks, organized by gait tasks and balance tasks. These blocks were randomly ordered. For the gait block, the subjects performed, in random order: single task (ST) phoneme monitoring while seated comfortably in a quiet room (ST-PM; if not completed in a previous balance block), ST gait, and dual-task (DT) gait, which was a combination of gait and phoneme monitoring. For the balance block, the following tasks were performed in random order: (ST-PM; if not completed in previous gait block), single-task standing eyes open (STEO), single-task standing eyes closed (STEC), dual-task standing eyes open (DTEO), and dual-task standing eyes closed (DTEC). As before, the dual-task conditions were a combination of the ST standing and phoneme monitoring tasks. Each condition was performed one time for 3 min. When needed, the subjects sat in a chair for at least one minute between conditions or blocks to rest. Before all phoneme monitoring conditions, the subjects

were reminded to attend to the story to answer the questions and report the phoneme tally at the end of the trial. No other explicit instructions for directing attention were provided.

Once all OFF trials were completed, the subjects took their medication as normally prescribed for their first/morning dose. ON testing commenced ~ 45 – 60 min later, with more time allowed to achieve a subjective 'on' state when needed. During this transition time, subject demographic information (i.e., weight, time since diagnosis, PD medication and dosages) were collected. ON testing proceeded with the same condition instructions as OFF, but a new set of randomized blocks and conditions were provided.

*VII.IV.IV Data Processing*

Segment-relative joint angles (i.e., 0º in the standing, neutral position) were exported using the Xsens software and COP paths were exported using the NeuroCom software. All data were imported into MATLAB (The MathWorks, Natick, MA) for analysis. Joint angle data were filtered using a second-order Butterworth low-pass filter with 2.5 Hz (hip and shoulder angles) and 5 Hz (knee angles) cutoff frequencies, as determined by spectral analysis, while COP data were filtered using a second-order Butterworth low-pass filter with a 10 Hz cutoff frequency [36].

The regularity characteristics of the filtered bilateral hip, knee, and shoulder joint angle series and the filtered COP path series were determined using approximate entropy (ApEn) and Recurrence Quantification Analysis (RQA). ApEn is a family of statistics that determines the regularity of a given signal [44] and is computed by the

equation $ApEn(m,r,N) = \Phi^{m}(r) - \Phi^{(m+1)}(r)$. It is dependent on the length of compared runs (*m*) and the criterion for similarity between points within the series (*r*), and the number of data points within the series (*N*). ApEn estimates the probability that a series of patterns, which are similar for *m* observations, remains similar on the next iteration of comparisons (*m+1*). ApEn values range from 0-2, with smaller values indicating similarity between the *m* and *m+1* patterns; in other words, if $\Phi^{m}(r)$ and $\Phi^{m+1}(r)$ are similar, the difference between the two will be small, which indicates greater regularity of the series.

RQA considers the recurrent behavior of a dynamic signal using recurrence plots, which are graphical representations of recurrent patterns derived from a one-dimensional time series. RQA requires several inputs (i.e., embedding dimension, time delay, and threshold) to observe and interpret patterns to quantify the recurrent aspects of the recurrence plots [45]. For this study, the Cross Recurrence Plot (CRP) Toolbox [46] for MATLAB was used to perform the RQA analysis, and percent recurrence (%REC) and percent determinism (%DET) of the signal were chosen as the two outputs. %REC is the percentage of data points that fall within a specified radius. On the other hand, %DET is the percentage of recurrent points that form diagonal lines (≥ 2 points) in the recurrence plot, which are parallel to the central diagonal line. It serves as an estimation of the signal's regularity. Thus, %REC provides different information about the signal than ApEn, while %DET serves a complimentary role in estimating the regularity of the signal from a deterministic, as opposed to a probabilistic (ApEn), perspective.

It must be noted that choosing input parameters for RQA (i.e., embedding dimension, time delay, and threshold) and ApEn (i.e. embedding dimension and tolerance/radius; recall *m* and *r,* respectively) can be challenging and there are no concrete guidelines. The choice of input parameters has a noticeable effect on %REC, %DET, and ApEn. There are, however, some RQA input parameter selection guidelines offered by Pellechia and Shockley [45], one of which is choosing a threshold such that %REC is less than 5% but not too close to 0%. Thresholds were manually selected for each analysis so that %REC was in the range of 1%-5%. This is particularly important, because larger %REC values can inflate %DET values. The CRP Toolbox also includes codes to aid in calculating and selecting parameters based on the characteristics of the data series. As such, these codes were used to calculate embedding dimension and time delay for each series. Parameter selection for ApEn is less variable than RQA, but still lacks specific guidelines. Typically, the range of dimension (*m*) is 1-3, and tolerance (*r*) is 20% of the standard deviation of the data series. For this study, *m* was set to 2 and *r* was calculated as suggested above (i.e., $r = 0.2*SD$).

*VII.IV.V Statistical Analysis*

For the joint angles analysis, a linear mixed effects model for repeated measures was performed, with medication (OFF vs. ON) and task (ST vs. DT) and the medication by task interaction input as fixed effects, and gait velocity as a repeated measure covariate. Maximum likelihood was used as the estimation method. The covariate was included to control for anticipated improvements in gait velocity after taking dopaminergic medication [2]. Because PD often asymmetrically impacts patients, e.g.,

unilaterally present (mild) or unilaterally more severe (moderate), joint angles were stratified into more-affected and less-affected sides. Dependent variables included %DET and ApEn for the bilateral hip, knee, and shoulder joint angle series. For the COP path analysis, a 3-factor repeated-measures ANOVA, medication (OFF vs. ON) by task (ST vs. DT) by eyes condition (EO vs. EC), was employed with %DET and ApEn as dependent. The assumptions for a repeated measures ANOVA were reviewed and tested. The normality assumption of each variable was checked via histograms, skewness, and kurtosis statistics. *Post-hoc* comparisons (i.e., paired *t*-tests) were performed to determine pairwise differences. Significance was accepted at $p < 0.05$. Statistical analysis was performed using SPSS 23 (IBM Corp., Armonk, NY, USA).

**VII.V Results**

All subjects completed all of the testing conditions according to study protocol. Table 5 displays the subject demographic information. The assumptions for a repeated measures ANOVA were sufficiently met and no adjustments were made. Tables 6 and 7 contain the mean ± SD of %REC and the parameters calculated and input into the RQA analysis for the joint angle series and the COP path series, respectively. Figures 7 and 8 display the results of the statistical analyses and indicate significant pairwise differences with lines and tick marks.

*VII.V.I Joint Angles during Gait*

After controlling for gait velocity, there was a main effect of medication for ApEn at the more-affected knee ($p = 0.014$), but not a task or interaction effect ($p = 0.053$ and $p = 0.555$, respectively). Pairwise tests indicated that ApEn for the more-affected knee

was smaller (i.e., more regular) during OFF-ST than ON-ST ($p$ = 0.026). There was also a main effect of medication for ApEn at the less-affected knee ($p$ = 0.004), but not a task or interaction effect ($p$ = 0.380 and $p$ = 0.436, respectively). Paired comparisons further clarified that the OFF-DT ApEn of the less-affected knee angle was smaller/more regular than ON-DT of the same joint ($p$ = 0.010). There were no effects for %DET at any of the joints and no medication, task, or interaction effects for ApEn other than those detailed above.

*VII.V.II COP Path while Standing*

For ApEn, there was a significant main effect of the eyes condition ($p$ = 0.005) and a significant interaction effect between medication and eyes conditions ($p$ = 0.002). There were no main effects of medication or task ($p$ = 0.714 and $p$ = 0.505, respectively) and no other interaction effects ($p$-value range = 0.188 – 0.687). For the eyes condition main effect, paired analyses indicated that OFF-STEO was significantly smaller/more regular than OFF-STEC ($p$ = 0.005), OFF-DTEO was significantly smaller/more regular than OFF-DTEC ($p$ = 0.029), and ON-DTEO was significantly smaller/more regular than ON-DTEC ($p$ = 0.029). For the interaction effect, pairwise comparisons revealed that OFF-DTEO was smaller/more regular than ON-DTEC ($p$ = 0.016). Other significant paired effects are shown in Figure 8.

For %DET, there was a significant eyes condition main effect ($p$ = 0.046) but no medication or task main effects ($p$ = 0.900 and $p$ = 0.721, respectively) and no interaction effects ($p$-value range = 0.517 – 0.687). Pairwise analysis of the eyes

condition indicated that OFF-STEO was significantly larger (i.e., more regular) than OFF-DTEC ($p$ = 0.016). There were no other COP path findings for %DET.

**VII.VI Discussion**

The primary hypothesis for the study was that medication would improve the nonlinear aspects of the gait and balance signals such that dual-task conditions ON would be significantly more regular (smaller ApEn) and deterministic (larger %DET) compared to single-task OFF conditions. Because of a lack of significant medication by task interactions, the results of this study do not support the hypothesis. However, there were other noteworthy findings.

There were only two medication effects, reflected in the ApEn of the more-affected and less affected knee joint, during the gait trials and both ApEn measurements apparently increased (i.e., became less regular) during ON. This is particularly interesting, because temporal-spatial and joint angle analysis of these same subjects indicated significant improvements (see Manuscript 1). These studies, taken in combination with well accepted gait improvement after taking medication [47], suggest that PD subjects execute their movements with increased regularity when OFF medication and that medication-induced motor improvements may be accompanied by decreases in regularity. This is possible, since a certain degree of irregularity is accompanied by an increase in adaptability [48,49]. There were also several eyes condition balance effects on ApEn, but only one for %DET, with the EO conditions yielding more regular results than the EC conditions, despite task complexity (i.e., ST

vs. DT). These were as expected and denoted that an increase in balance difficulty (e.g., EC vs. EO) resulted in decreases in regularity, which agrees with previous understandings of balance regularity and stability [41].Furthermore, the lack of significant findings between EC conditions indicates that standing with EC alone is sufficient to affect balance signals so that performing a secondary task and/or taking PD medication were inadequate further challenge balance performance.

Overall, %DET and ApEn values for both gait and balance were respectively large and small across medication states and tasks. They were also exceptionally similar between tasks and conditions. This may indicate that both gait and balance control in PD subjects are very regular, despite medication state, task complexity, and visual condition. These similarities can be interpreted in a few ways. 1) a possible shift in the current interpretations of ‘stable gait’ and ‘stable balance’, which are currently based on linear regularity measures (i.e., SD, coefficient of variation [CV]), may be needed. These are traditionally interpreted as more regular findings being associated with increased stability. The similarity of our nonlinear data across medication states, tasks, and conditions challenges these interpretations, especially considering that these same subjects experienced significant gait and balance changes from different medication states, task complexities, and balance conditions (see Manuscript 1 and Manuscript 2); or 2), the similarity of these nonlinear findings in our data suggests that a novel interpretation of gait and balance stability exclusive to nonlinear measures, and separate from linear measures, may be necessary, especially with PD subjects. However, the application of these tools in PD movement, especially PD gait, is still

relatively novel, and further research comparing PD subjects with neurologically healthy age-matched and young control subjects is necessary. Future studies should include these and other nonlinear analyses when exploring automatic tasks to gain insights into impaired movement.

## VII.VII Conclusions

Dopaminergic medication caused significantly lower regularity of the knee joint angle signals during gait. When considered with improvements in motor function, PD patients may have undesirable increased regularity in their gait when OFF medication. Balance task complexity (i.e., eyes open vs. eyes closed) was detected by the nonlinear analyses and indicated improved balance signal regularity. Approximate Entropy and percent determinism findings were very similar, despite medication state, task complexity, and standing condition. These similarities may necessitate changes in our interpretation of gait and balance stability.

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Table 5. Subject demographic information. Data are mean ± SD, where appropriate.

| **Demographics** | |
|---|---|
| Sex | 12 male, 4 female |
| Age | 67.13 ± 7.54 yrs. |
| Height | 171.16 ± 9.53 cm |
| Mass | 80.93 ± 14.28 kg |
| UPDRS III (OFF) | 44.44 ± 13.34 |
| UPDRS III (ON) | 24.44 ± 8.17 |
| More-affected side | Right = 9, Left = 7 |
| Time since diagnosis | 6.72 ± 5.79 yrs. |
| Levodopa Equivalent Dose | 669.53 ± 230.57 |

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

Table 6. The %REC and parameters calculated and input into the RQA analysis for the joint angle series. Data are presented as mean ± SD.

| RQA Parameter | Condition | | | |
|---|---|---|---|---|
| | OFF-ST | OFF-DT | ON-ST | ON-DT |
| More-Affected | | | | |
| Hip | | | | |
| %REC | 2.40 ± 0.38 | 2.38 ± 0.31 | 2.47 ± 0.49 | 2.57 ± 0.52 |
| Dimension | 3.94 ± 0.57 | 3.94 ± 0.57 | 3.75 ± 0.45 | 3.75 ± 0.58 |
| Threshold | 0.13 ± 0.02 | 0.13 ± 0.01 | 0.14 ± 0.02 | 0.14 ± 0.01 |
| Knee | | | | |
| %REC | 2.64 ± 0.50 | 2.53 ± 0.53 | 2.35 ± 0.69 | 2.52 ± 0.43 |
| Dimension | 3.50 ± 0.73 | 3.63 ± 0.62 | 3.69 ± 0.48 | 3.69 ± 0.48 |
| Threshold | 0.13 ± 0.02 | 0.13 ± 0.03 | 0.13 ± 0.03 | 0.14 ± 0.03 |
| Shoulder | | | | |
| %REC | 2.31 ± 0.63 | 2.60 ± 0.68 | 2.39 ± 0.42 | 2.45 ± 0.47 |
| Dimension | 3.44 ± 0.63 | 3.38 ± 0.50 | 3.25 ± 0.45 | 3.31 ± 0.60 |
| Threshold | 0.15 ± 0.02 | 0.16 ± 0.05 | 0.15 ± 0.03 | 0.16 ± 0.03 |
| Less-Affected | | | | |
| Hip | | | | |
| %REC | 2.51 ± 0.37 | 2.40 ± 0.39 | 2.43 ± 0.38 | 2.51 ± 0.29 |
| Dimension | 3.88 ± 0.34 | 3.88 ± 0.62 | 3.88 ± 0.34 | 3.75 ± 0.45 |
| Threshold | 0.14 ± 0.03 | 0.13 ± 0.02 | 0.13 ± 0.02 | 0.13 ± 0.02 |
| Knee | | | | |
| %REC | 2.36 ± 0.66 | 2.49 ± 0.72 | 2.41 ± 0.47 | 2.29 ± 0.69 |
| Dimension | 3.88 ± 0.72 | 3.69 ± 0.79 | 3.63 ± 0.50 | 3.69 ± 0.60 |
| Threshold | 0.13 ± 0.03 | 0.12 ± 0.03 | 0.13 ± 0.03 | 0.14 ± 0.04 |
| Shoulder | | | | |
| %REC | 2.55 ± 0.72 | 2.24 ± 0.43 | 2.41 ± 0.56 | 2.60 ± 0.67 |
| Dimension | 3.38 ± 0.81 | 3.44 ± 0.51 | 3.25 ± 0.58 | 3.13 ± 0.62 |
| Threshold | 0.15 ± 0.03 | 0.14 ± 0.04 | 0.14 ± 0.03 | 0.14 ± 0.03 |

Note: RQA = Recurrence Quantification Analysis, %REC = percent recurrence, OFF = off-medication state, ON = on-medication state, ST = single-task, DT = dual-task. Time delay was fixed at 2 for all analyses.

Table 7. The %REC and parameters calculated and input into the RQA analysis for the COP path series. Data are presented as mean ± SD.

| RQA Parameter | Condition | | | |
|---|---|---|---|---|
| | STEO | STEC | DTEO | DTEC |
| OFF | | | | |
| %REC | 2.91 ± 0.62 | 2.40 ± 0.52 | 2.50 ± 0.44 | 2.36 ± 0.56 |
| Dimension | 4.06 ± 0.57 | 4.06 ± 0.44 | 4.19 ± 0.40 | 4.06 ± 0.44 |
| Threshold | 0.11 ± 0.03 | 0.12 ± 0.04 | 0.12 ± 0.03 | 0.12 ± 0.04 |
| ON | | | | |
| %REC | 2.72 ± 0.77 | 2.50 ± 0.69 | 2.55 ± 0.69 | 2.32 ± 0.49 |
| Dimension | 4.00 ± 0.63 | 3.88 ± 0.50 | 4.06 ± 0.57 | 4.13 ± 0.50 |
| Threshold | 0.11 ± 0.03 | 0.11 ± 0.02 | 0.11 ± 0.04 | 0.12 ± 0.03 |

Note: RQA = Recurrence Quantification Analysis, %REC = percent recurrence, STEO = single-task, eyes open, STEC = single-task eyes closed, DTEO = dual-task eyes open, DTEC = dual-task eyes closed, OFF = off-medication state, ON = on-medication state. Time delay was fixed at 2 for all analyses.

Figure 6. Xsens sensor locations (17 total) on the head, sternum, posterior pelvis (i.e., L5/Sacrum), and bilaterally on the shoulders, upper arms, forearms, hands, thighs, lower legs, and feet. Sensors are shown on top of straps for visualization.

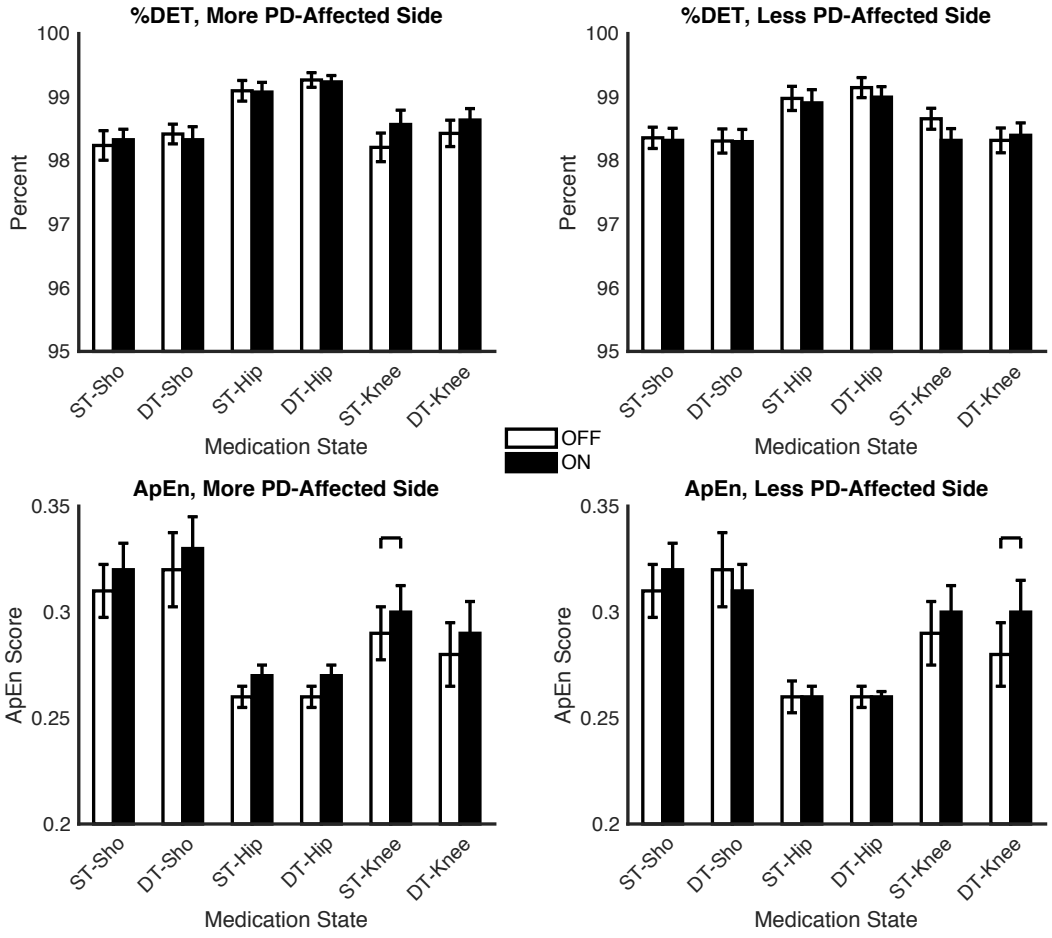


Figure 7. Bar graphs depicting the mean ± SEM joint angle data for percent determinism (%DET) on the more-affected (top-left) and less-affected (top-right) sides and approximate entropy (ApEn) on the more-affected (bottom-left) and less-affected (bottom-right) sides. Significance is indicated by the lines and tick marks. PD = Parkinson's disease, Sho = Shoulder, ST = single task, DT = dual-task, OFF = off-medication state, ON = on-medication state.

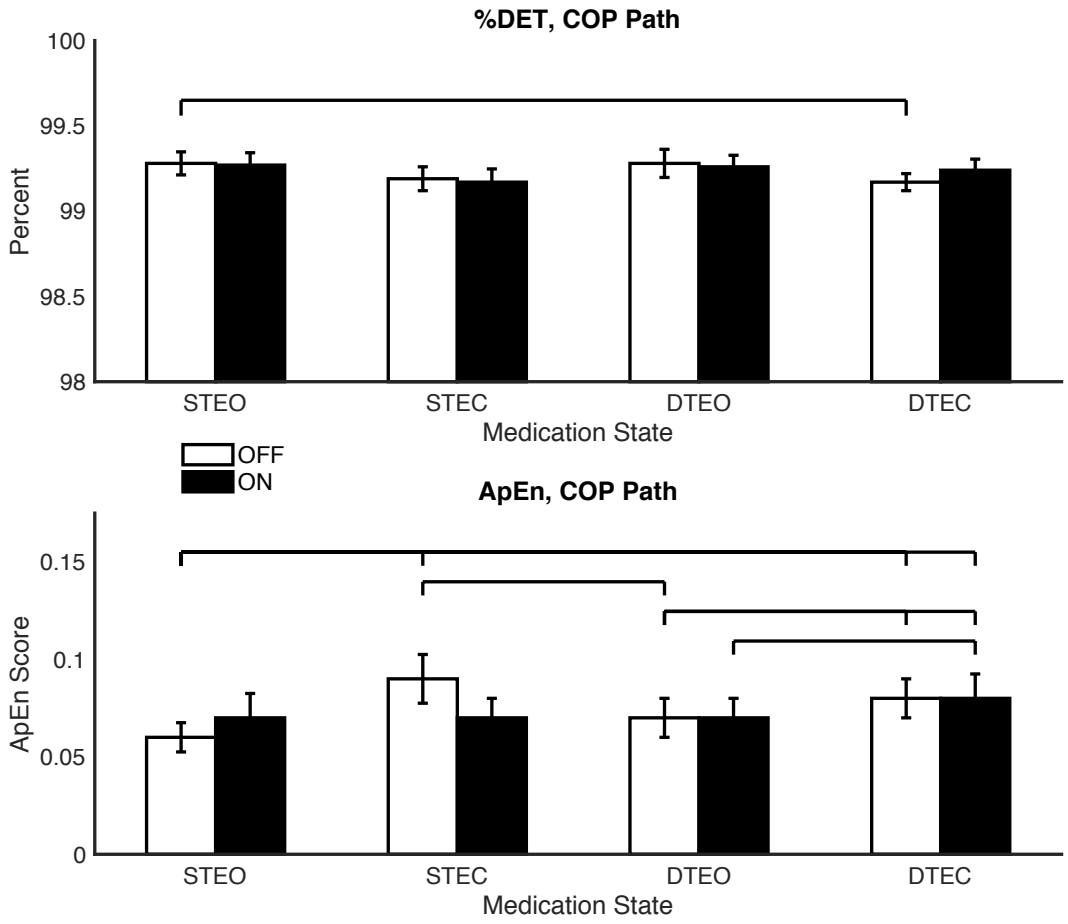


Figure 8. Bar graphs depicting the mean ± SEM center of pressure (COP) path data for percent determinism (%DET; top) and approximate entropy (ApEn; bottom). Significance is indicated by the lines and tick marks. STEO = single-task eyes open, STEC = single-task eyes closed, DTEO = dual-task eyes open, DTEC = dual-task eyes closed, OFF = off-medication state, ON = on-medication state.

## *VIII. Summary*

The aim of this dissertation was to determine how DA-ergic medication influenced the automaticity and nonlinear characteristics of gait and balance in PD. Three analyses were conducted to investigate the aims detailed above. The results of the gait analysis indicated that DA-ergic medication improved motor function and DT-ing negatively impacted performance, but the absence of significant interactions and secondary task improvements does not support an enhancement in gait automaticity. The balance analysis revealed that both DA-ergic medication and DT-ing negatively impacted posturographic balance measures, using traditional interpretations of these measures. However, a comprehensive look at the results may suggest that these PD subjects experienced more maneuverability and not instability. Nevertheless, these data do not provide evidence an improvement in balance automaticity. The nonlinear analyses, specifically the ApEn values, revealed that the motor improvements from DA-ergic medication typically found in gait are accompanied by decreases in regularity, suggesting that PD subjects may be undesirably regular in their joint excursions during gait.

Overall, the study yielded a few interesting conclusions. First, these results do not support a medication-induced improvement in either gait or balance automaticity; the significantly improved DT gait in the first manuscript is most likely an improvement in motor function and not automaticity. Second, even though both gait and balance control are considered automatic, these results indicate that DA-ergic medication has opposing effects on these processes. This suggests that gait automaticity and balance

automaticity are either differently controlled or differently affected by DA-ergic medication and DT-ing. Third, the co-occurrence of improved gait function and decreased signal regularity are suggestive of excessive uniformity of joint movements in PD and that DA-ergic medication decreases this uniformity, which may allow for more adaptable gait patterns. Finally, the appropriateness of nonlinear analyses in joint movement signals, and to some extent posturographic signals in PD, is novel to this study. The %DET and ApEn values were very similar among subjects and across conditions and alternate interpretations of ‘stability’ may need to be explored. Additionally, future study of other automatic movements (e.g., eye blinking) will provide a better understanding of automaticity in this population.

## *IX. References*


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