Advancing the Assessment and Treatment of Signs and Symptoms of Parkinson Disease

David Scott May

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Advancing the Assessment and Treatment of Signs and Symptoms of Parkinson Disease
by
David Scott May

A dissertation presented to
The Graduate School
of Washington University in
partial fulfillment of the
requirements for the degree
of Doctor of Philosophy

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List of Abbreviations

%ATSF = percent of active time spent freezing
BBS = Berg Balance Scale
BESTest = Balance Evaluation Systems Test
DBS = deep brain stimulation
FOG = freezing of gait
GOT = Go Outside and Turn
GPi = globus pallidus internus
IADL = instrumental activity of daily living
IMU = inertial measurement unit
LEDD = levodopa equivalent daily dose
MCID = minimum clinically important difference
MDS-UPDRS = Movement Disorder Society-Sponsored Revision of the Unified Parkinson Disease Rating Scale
MMSE = Mini Mental State Examination
NFOG-Q = New Freezing of Gait Questionnaire
PD = Parkinson disease
PDQ-39 = Parkinson Disease Questionnaire-39
PDQ-39-SI = Parkinson Disease Questionnaire-39 Summary Index
PDSS = Parkinson Disease Sleep Scale
pFOG = probability of freezing of gait
PIGD = postural instability and gait difficulty
PSQI = Pittsburgh Sleep Quality Index
STN-DBS = subthalamic nucleus deep brain stimulation
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David Scott May

*Washington University in St. Louis*

*June 2022*
Dedicated to my family and friends for their unwavering support and encouragement.
ABSTRACT OF THE DISSERTATION

Advancing the Assessment and Treatment of Signs and Symptoms of Parkinson Disease

by

David Scott May

Doctor of Philosophy in Movement Science

Washington University in St. Louis, 2022

Professor Gammon M. Earhart, Chair

People with PD often report signs and symptoms that negatively impact quality of life. Among these are balance difficulties, impaired gait, and FOG. New treatment and assessment strategies for these signs and symptoms are needed, as current techniques are limited. While new treatment and assessment strategies continue to emerge, gaps in knowledge persist. Deep brain stimulation (DBS) has been utilized in many people with PD throughout the 21st century, but it is unknown specifically how subthalamic nucleus deep brain stimulation (STN-DBS) affects balance. Alternative treatment strategies, such as a dental mouthpiece, have also been proposed. While dental mouthpieces have shown promise in improving PD-related signs and symptoms in a small number of people with PD, it is unknown whether this treatment will show any benefit in a larger group of people with PD. Wearable sensors can be used in the laboratory setting to assess FOG, but it is unclear whether they can be successfully utilized to assess FOG in the real world. The primary purposes of this dissertation were to determine: 1) the specific effects of STN-DBS and levodopa on balance, 2) the effects of a dental mouthpiece on motor signs and symptoms and quality of life in people with PD, and 3) the feasibility of our sensor-based FOG assessment method for use in the real world.
In Chapter 2, we used a comprehensive balance assessment to determine the effects of STN-DBS and levodopa on overall balance and on components of balance. We noted that the combination of STN-DBS and levodopa improves overall balance and four of six components of balance. This work is a critical first step toward more thorough understanding of the effects of STN-DBS and levodopa on balance in people with PD and can inform clinical care for this population.

In Chapter 3, we examined whether a dental mouthpiece has acute benefits on motor signs and symptoms of PD or quality of life benefits in people with PD after one month of use. We observed no significant benefits of mouthpiece use in people with PD after correcting for multiple comparisons. Our results directly contradict prior literature on the effects of a dental mouthpiece in people with PD, as we found no benefits of mouthpiece use in a larger sample of people with PD. Future studies are necessary to determine whether other treatment strategies can provide benefits for people with PD by acting on a similar mechanism.

In Chapter 4, we assessed the performance of our sensor-based FOG assessment method during traditional laboratory-based gait and turning tasks, simulated real world activities performed in the laboratory, and during real world use. We determined that our sensor-based method is feasible for assessing FOG in the real world.

Our results indicate that a larger real world validation study of our sensor-based FOG assessment method is warranted. The success of our sensor-based method suggests that wearable sensors may eventually be useful for assessment and even treatment of various signs and symptoms of PD in the real world.
Chapter 1: Background and Specific Aims
1.1 Introduction

People with Parkinson disease (PD) often report disturbances in activities of daily living, gait, balance, and quality of life. Some people with PD also experience a debilitating phenomenon called freezing of gait (FOG), which is described as an inability to step when attempting to do so. Current treatment and assessment options for many of these signs and symptoms are limited. While dopaminergic medication (levodopa) effectively reduces the severity of tremors, bradykinesia, and rigidity, it lacks the same efficacy for reducing balance dysfunction, sleep disorders, and FOG. Furthermore, FOG is difficult to assess accurately and reliably, due to its context-dependent and episodic nature. As such, current assessment techniques are of limited utility for determining any potential treatment effect on FOG. New treatment strategies and assessment techniques for these issues continue to emerge, but gaps in knowledge persist. The studies of this dissertation aim to provide insights into emerging treatment and assessment techniques for the signs and symptoms of PD.

1.2 The Effects of STN-DBS and Levodopa on Balance

In the 21st century, deep brain stimulation (DBS) has emerged as a treatment option for the signs and symptoms of PD. DBS is often placed to target the subthalamic nucleus (STN) in people with PD. People with STN-DBS show improved overall balance when ON-stimulation, compared to when OFF-stimulation in one small study. Some reports suggest short-term or no significant improvement in balance following STN-DBS surgery. Others show a significant decline in automatic postural responses and an increase in falls six months after receiving STN-DBS. A reference group of people with PD that did not have STN-DBS did not demonstrate these changes. It remains unclear how subthalamic nucleus deep brain stimulation (STN-
DBS) affects balance when utilized in conjunction with levodopa. Levodopa is generally considered less effective for treating balance than for treating tremors, bradykinesia, or rigidity,\textsuperscript{1–4} though one study suggests an association with improved balance.\textsuperscript{18} The ambiguities in existing literature regarding DBS, levodopa and balance may reflect the variability and inadequacy of many balance assessment strategies used. Automatic postural responses to external perturbations, for example, are known to be impaired in people with PD,\textsuperscript{19} but many balance assessment tools do not incorporate this component of balance. Therefore, there is a need to assess balance more comprehensively in this population.

The Balance Evaluation Systems Test (BESTest) provides a comprehensive assessment of balance and is reliable and valid for use in people with PD.\textsuperscript{20,21} The BESTest includes an overall balance score, as well scores for six balance systems: (I) Biomechanical Constraints, (II) Stability Limits/Verticality, (III) Anticipatory Postural Adjustments, (IV) Postural Responses, (V) Sensory Orientation, and (VI) Stability in Gait. By using the BESTest to compare balance in the most optimal treated state (i.e., combination of medication and STN-DBS) to balance in the least optimal state (i.e., no medication and no DBS), we can determine whether available strategies effectively treat balance when used in conjunction, or whether balance deficits remain. Moreover, use of the BESTest could provide insight about which specific components of balance are affected by these treatments.

### 1.3 Dental Mouthpieces and Parkinson Disease

Several case studies and reports have shown assorted motor and quality of life benefits for people with PD with use of a dental mouthpiece. These studies examined different types of mouthpieces that are typically modeled after those used for temporomandibular joint disorder. In
three such studies, participants reported improvements in quality of life metrics, relative to
baseline, with use of a dental mouthpiece. Specifically, one of these reports describes
improvements in a participant’s ability to perform activities of daily living independently.
Another describes improvements in sleep quality and fatigue levels, and a third describes
improvements in general quality of life as measured by the Parkinson Disease Questionnaire-39
(PDQ-39). Of these three studies, two also describe improvements in motor function with use
of a mouthpiece, relative to baseline. One participant showed improvement in grip strength,
and the other showed improvements in the Four Square Step Test, gait mechanics, and grip
strength in the non-dominant hand. However, current knowledge is limited by variance in
mouthpiece design across studies, limited collection of standardized outcome measures, and the
small number of participants studied thus far. An exploratory study is needed to examine
whether a mouthpiece can affect motor symptoms and quality of life in a larger sample of people
with PD.

1.4 Real World Assessment of FOG

1.4.1 The Difficulties of Assessing FOG

FOG is episodic in nature, and is difficult to reliably elicit. FOG often disappears when
people with FOG consciously focus on walking, like when being observed by a clinician.
Anxiety may elicit FOG for many people, though anxiety is difficult to safely reproduce
while walking in a clinic setting. FOG occurs more often when “OFF” dopaminergic medication,
but patients are typically “ON” dopaminergic medication when visiting a clinician.
Additionally, many clinic settings and corridors are broad and free of obstacles, though FOG
often occurs when navigating narrow spaces and turning. Currently, clinicians and researchers
primarily rely on the New Freezing of Gait Questionnaire (NFOG-Q) to assess FOG. The
NFOG-Q is a useful screening tool to differentiate between freezers and non-freezers, and shows a high reliability of scores between people with PD and their caregivers. However, as a self-report measure, it is inherently subject to issues of recall bias. It does not correlate with observed FOG severity in lab settings. Additionally, the NFOG-Q has only modest test-retest reliability and is not responsive to small changes in FOG. New methods are needed to assess FOG, as clinical trials and clinicians rely on accurate and responsive outcome measures to assess potential responses to treatment.

1.4.2 Wearable Sensors and FOG

Several inertial sensor-based methods for assessing FOG have been developed in attempts to meet the need for new means of assessment. However, it is unclear whether such methods are capable of accurately assessing FOG during unstructured spontaneous movements of daily life. In one recent study, a sensor-based FOG assessment method detected significantly more presumed FOG events during unsupervised home use in people with known FOG compared to people without known FOG. Little else is known about the performance of sensor-based FOG assessment methods in the real world. It is important to determine whether such methods can be used to detect FOG during activities of daily living outside the laboratory, however, as some people with FOG do not reliably demonstrate FOG in a lab or clinic setting, and some only freeze when “OFF” medication.

In recent years, researchers in our lab have worked with engineering colleagues to develop one such method of detecting FOG using inertial sensors. This method uses a two-stage detector for determining the zero-velocity and trembling events in gait, and then utilizes a point-process filter to calculate the probability of FOG. This method was validated in a number of participants in a laboratory setting, adapts to individual gait patterns, and automatically detects
FOG in real time.\textsuperscript{36–38} However, this approach has not yet been tested outside of structured gait and turning tasks in a laboratory setting. It is unknown whether our sensor-based FOG assessment method can accurately assess FOG when working with data from unstructured, spontaneous real-world movements. For example, side stepping while putting items away in the kitchen, stepping forward and backward while vacuuming, or fidgeting while sitting could confound our sensor-based method. Comparing sensor-based measures of FOG severity in the home/community to measures of FOG severity in the lab will allow us to determine the feasibility of our sensor-based method for assessing FOG in this type of environment. If feasible, researchers and clinicians with access to wearable sensors could more comprehensively and objectively assess FOG in the future. Wearable sensors could theoretically be used in this manner as the “gold standard” method for determining FOG severity.

1.5 Summary and Critical Next Steps

Additional treatment strategies are needed for people with PD, as many signs and symptoms of the disease continue to impair quality of life significantly, despite advancements in care. Emerging treatment and assessment techniques for signs and symptoms of PD offer promise for addressing many of these factors, such as balance deficits. However, knowledge of emerging treatment strategies is limited by a lack of rigorous outcome measures. Studies utilizing more comprehensive and standardized outcome measures are needed to provide insight. Additionally, real world assessments of signs and symptoms of PD, such as FOG, are needed to provide more accurate information about mobility in people with PD.

In Aim 1, we will, for the first time, use a comprehensive, standardized measure (i.e., the BESTest) to compare balance in the optimally treated state (ON-Medication/ON-stimulation) to
balance in the untreated state in people with PD and STN-DBS. This will allow us to understand, in detail, how balance is affected by these treatments, providing information about overall balance and components of balance. Aim 2 is the first attempt to study systematically the effects of a dental mouthpiece using standardized, comprehensive outcome measures in a group of people with PD rather than in single individuals. This work will allow us to determine if this line of treatment has benefit to people with PD and if it should be explored further. Aim 3 will, for the first time, determine if our method for detecting FOG using wearable sensors is suitable for use in the home/community. If found to be suitable, this method would provide researchers and clinicians with a valuable technique for assessing real-world FOG severity.

1.6 Specific Aims

1.6.1 Specific Aim 1

Determine the effects of STN-DBS and levodopa on balance in people with PD.

Hypothesis 1: Participants will show significantly improved balance when on stimulation and on levodopa compared to off stimulation and off levodopa.

1.6.2 Specific Aim 2

Determine the effects of a dental mouthpiece on motor signs and symptoms and quality of life in people with PD.

Hypothesis 2a: With a dental mouthpiece, participants will show significant improvement compared to baseline in motor signs and symptoms.
Hypothesis 2b: With a dental mouthpiece, participants will show significant improvement compared to baseline in quality of life.

1.6.3 Specific Aim 3

Determine if our wearable sensor-based FOG assessment method is feasible for assessing real world FOG severity in people with PD and FOG.

Aim 3a: Compare the performance of our sensor-based FOG assessment method to existing FOG assessment methods during 1) laboratory-based gait tasks designed to maximally elicit FOG; 2) tasks designed to mimic real world activities of daily life in a simulated home setting within the laboratory, and 3) unsupervised home use.

Hypothesis 3a: Observed correlation patterns will elucidate the feasibility of our approach for unsupervised use in the real world.

Aim 3b: Determine the accuracy of our sensor-based FOG assessment method, relative to the gold standard of expert video review, while performing tasks designed to mimic real world activities of daily life in a simulated home setting within the laboratory.

Hypothesis 3b: Our sensor-based method will detect FOG with an accuracy above 80% during tasks designed to mimic real world activities of daily life in a simulated home setting within the laboratory.
1.7 References


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Chapter 2: STN-DBS and Levodopa Improve Balance in People with PD

This chapter has been published:

2.1 Introduction

Balance dysfunction, a risk factor for falls, impairs quality of life for people with Parkinson’s disease (PD). Dopaminergic medication and deep brain stimulation of the subthalamic nucleus (STN-DBS) are common treatment strategies for the cardinal motor signs and symptoms of PD. Levodopa effectively reduces the severity of tremors, bradykinesia, and rigidity, but lacks the same efficacy for reducing balance dysfunction, though one study suggests an association with improved balance. The effect of STN-DBS on balance remains unclear. People with STN-DBS show improved overall balance when ON-stimulation, compared to when OFF-stimulation in one small study. The effects of STN-DBS on balance over time are also not known. Some reports suggest short-term or no significant improvement in balance following STN-DBS surgery, whereas others show a significant decline in automatic postural responses and an increase in falls six months after receiving STN-DBS. A reference group of people with PD that did not have STN-DBS did not demonstrate these changes.

These ambiguities regarding the effects of STN-DBS on balance may reflect variability of assessment and underscore the need for more comprehensive and consistent balance assessment in this population. Balance is often assessed following STN-DBS through the postural instability and gait difficulty (PIGD) items of the Unified Parkinson’s Disease Rating Scale (UPDRS) or the Movement Disorders Society-Sponsored Revision of the UPDRS (MDS-UPDRS). Others applied a more detailed balance assessment, such as the Berg Balance Scale (BBS), to investigate the effects of DBS. However, all these ratings provide limited insight into the specific components that contribute to balance, such as verticality, reactive postural responses, or stability in gait with or without cognitive influences. Therefore, a more
comprehensive clinical assessment will improve our understanding of how levodopa and STN-DBS affect balance.\textsuperscript{14}

The Balance Evaluation Systems Test (BESTest) provides a comprehensive assessment of balance, covering six balance systems: (I) Biomechanical Constraints, (II) Stability Limits/Verticality, (III) Anticipatory Postural Adjustments, (IV) Postural Responses, (V) Sensory Orientation, and (VI) Stability in Gait. This test is reliable, valid, and accurately predicts prospective fall risk in people with PD.\textsuperscript{15,16} Using the BESTest in this population will help determine if and how specific balance systems respond to both levodopa and STN-DBS. The combination of levodopa (ON-medication) and STN-DBS (ON-stimulation) represents a common treated state and is perhaps the most optimal treated state in this population. By comparing balance performance in the most optimal treated state to balance in the least optimal treated state, we can determine whether these strategies effectively treat balance and its components when used in conjunction, or whether balance deficits remain. This knowledge could assist clinicians in tailoring intervention strategies for people with PD following STN-DBS. Therefore, the primary aim of this study was to determine whether total BESTest balance scores differ while ON-medication/ON-stimulation compared to OFF-medication/OFF-stimulation. We hypothesized that total BESTest scores would be higher, indicating better balance performance, in the ON-medication/ON-stimulation condition relative to the OFF-medication/OFF-stimulation condition.

As an exploratory aim, we also examined if certain sections of the BESTest showed significant changes between the ON-medication/ON-stimulation condition and the OFF-medication/OFF-stimulation condition. Little is known regarding the responsiveness of specific
domains of balance to these treatment strategies, but such findings could provide a rationale for therapeutically targeting specific deficits and then testing such strategies in future studies. We speculated that sections (III) Anticipatory Postural Adjustments, (IV) Postural Responses, and (VI) Stability in Gait would show improvement when ON-medication/ON-stimulation compared to OFF-medication/OFF-stimulation as: (1) previous studies report medication improves scores on the BBS, a measure which largely focuses on anticipatory postural adjustments;\textsuperscript{6} (2) STN-DBS improves scores on a similar postural response measure;\textsuperscript{11} and (3) a combination of STN-DBS and medication improved gait performance during the Dual Task Timed Up and Go.\textsuperscript{7} We did not speculate on the sections for (I) Biomechanical Constraints, (II) Stability Limits/Verticality, or (V) Sensory Orientation due to a lack of existing literature.

2.2 Materials and Methods

2.2.1 Participants

This study used cross-sectional participant data from baseline assessments of a pilot randomized clinical trial examining the feasibility and efficacy of physical therapy following STN-DBS surgery.\textsuperscript{17} The randomized clinical trial was registered on clinicaltrials.gov (NCT: 03181282). Participants were at least 30 years of age and met the following inclusion criteria: (1) neurologist diagnosed idiopathic PD between Hoehn & Yahr (H&Y) stages II-IV; (2) at least one year post-bilateral STN-DBS; (3) able to attend assessment sessions; and (4) able to provide informed consent. Exclusion criteria included: (1) diagnosis of atypical parkinsonism; (2) evidence of dementia (i.e., Mini-Mental Status Exam (MMSE) score ≤24/30);\textsuperscript{18} or (3) inability to walk ten meters with or without an assistive device. Only participants who were at least one year
after DBS surgery were included in this study to ensure that DBS settings were optimized. Written informed consent was obtained from each participant in accordance with the Declaration of Helsinki and the policies and procedures of the Human Research Protection Office at Washington University in St. Louis. This study was approved by the Institutional Review Board at Washington University in St. Louis (201609148).

### 2.2.2 Assessments

Balance was assessed by the Balance Evaluation Systems Test (BESTest). The 27-item BESTest is a clinical assessment of balance, with a total possible score of 108 points.\(^1\) Higher scores indicate better balance. The BESTest is highly reliable in people with PD\(^1\) and features six sections corresponding to six components of balance. The total BESTest raw score for each participant was divided by the total possible amount of points (108) to calculate a total percentage score. The raw score for each of the six balance system sections was converted to a percentage score by dividing the raw score by the total possible points for each section.

The BESTest was performed for each participant while in the following conditions: (1) ON-medication/ON-stimulation and (2) OFF medication/OFF-stimulation. These conditions were tested on separate days within one week of each other. The order of testing conditions was randomized. For the ON-medication/ON-stimulation day, ON medication was determined by a participant report of feeling ON during testing and occurred 45–90 min following levodopa intake. The participants’ stimulators remained ON throughout this session. The stimulation parameters were unchanged from those that were optimized clinically by a movement disorders neurologist. For the OFF-medication/OFF-stimulation day, OFF medication was defined as greater than or equal to 12 h since the last intake of anti-PD medication. Participants’ stimulators
were turned OFF upon arrival to the laboratory, and testing commenced 45 min later. Stimulators were turned back on upon completion of the testing session. The rater was blinded to the testing condition.

Total levodopa equivalent daily dose (LEDD) was calculated by documenting the amount of each antiparkinsonian drug taken daily by each participant and using a formula to determine the total daily dose of antiparkinsonian medication. The mean and standard deviation of participants’ LEDD values were calculated to characterize the sample. The Movement Disorders Society-sponsored revision of Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) is a valid and reliable clinical assessment for people with Parkinson’s disease. MDS-UPDRS-II and MDS-UPDRS-III were administered to characterize the severity of general parkinsonian motor symptoms in the sample. The MDS-UPDRS-II is a questionnaire pertaining to motor experiences of daily living, with questions regarding activities within the past week. As participants were OFF-medication/OFF-stimulation for a brief time, the MDS-UPDRS-II was only administered once in the ON-medication/ON-stimulation condition. The MDS-UPDRS-III is a general motor examination performed by a clinician or rater. The MDS-UPDRS-III was performed both ON-medication/ON-stimulation and OFF-medication/OFF-stimulation to show motor performance in the optimal treated state and the least optimal treated state.

2.2.3 Statistical Analysis

Means and standard deviations were calculated for participant characteristics, such as age, MDS-UPDRS-III scores, years since PD diagnosis, and months since DBS surgery. A formal power analysis was not conducted specifically for this analysis since these data were taken from baseline measures from a study to assess physical therapy strategies in people with
PD and STN-DBS. The alpha level of significance was set at 0.05. Statistical analysis was performed in R software version 3.6.0, R Foundation for Statistical Computing, Vienna, Austria. R code used for data analysis is available at https://github.com/dsmay11/R-Code-STN-DBS-Balance/blob/master/DBS%20Balance%20Code%20Final.Rmd. The scoring distributions for the total BESTest, each of its six sections, and for the MDS-UPDRS-III were checked for normality with Shapiro-Wilk tests, both in the ON-medication/ON-stimulation condition and OFF-medication/OFF-stimulation condition. Scores from the ON-medication/ON-stimulation condition and the OFF-medication/OFF-stimulation condition were then compared for the total BESTest to assess our primary aim, for each of its six sections to assess our exploratory aim, and for the MDS-UPDRS-III to characterize the effects of the treatments on motor performance. A paired t-test was used for each of these comparisons if the normality assumption was not violated for either treatment condition. Otherwise, a Wilcoxon signed-rank test was used. For our exploratory aim, a multiple comparisons correction was applied to the resulting probability values for each of the six sections of the BESTest using the Holm–Bonferroni method and the “p.adjust” function from the “stats” package in R. Cohen’s d was calculated for total BESTest score, each of the six sub-sections, and for the MDS-UPDRS-III, to show effect size between the ON-medication/ON-stimulation and OFF-medication/OFF-stimulation conditions.

### 2.3 Results

Participant characteristics are listed in Table 2.1. The ON-medication/ON-stimulation condition is represented in Table 2.1 as “ON,” and the OFF-medication/OFF-stimulation condition is represented as “OFF.” Participants ranged from 12 months to 101 months since STN-DBS implantation.
Table 2.1. Participant Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years (mean ± SD)</td>
<td>65.0 ± 6.9</td>
</tr>
<tr>
<td>Sex (males, females)</td>
<td>M= 21, F= 8</td>
</tr>
<tr>
<td>ON MDS-UPDRS-III score (mean ± SD)</td>
<td>33.0 ± 11.2</td>
</tr>
<tr>
<td>OFF MDS-UPDRS-III score (mean ± SD)</td>
<td>49.3 ± 12.4</td>
</tr>
<tr>
<td>Years since PD diagnosis (mean ± SD)</td>
<td>11.9 ± 4.7</td>
</tr>
<tr>
<td>Months since DBS implantation (mean ± SD)</td>
<td>40.5 ± 30.0</td>
</tr>
<tr>
<td>Mini Mental State Examination score (median, [Q1 - Q3])</td>
<td>29.0, [28.0–30.0]</td>
</tr>
<tr>
<td>MDS-UPDRS II Score (mean ± SD) ^A</td>
<td>16.2 ± 7.1</td>
</tr>
<tr>
<td>Total levodopa equivalent daily dose (mean ± SD) ^A</td>
<td>1,020.4 ± 615.4</td>
</tr>
<tr>
<td>DBS voltage (left mean/right mean ± left SD/right SD) ^B</td>
<td>2.7/2.7 ± 0.8/0.8</td>
</tr>
<tr>
<td>DBS pulse width (μs) (left mean/right mean ± left SD/right SD) ^B</td>
<td>61.2/61.2 ± 5.9/5.9</td>
</tr>
<tr>
<td>DBS frequency (hz) (left mean/right mean ± left SD/right SD) ^B</td>
<td>168.1/170.2 ± 25.9/24.9</td>
</tr>
</tbody>
</table>

DBS, deep brain stimulation; MDS-UPDRS, Movement Disorders Society-sponsored revision of Unified Parkinson’s Disease Rating Scale; PD, Parkinson’s disease; Q1, quartile 1; Q3, quartile 3; SD, standard deviation. ^A-MDS-UPDRS-II and total levodopa equivalent daily dose are derived from n = 28 due to missing data. ^B-DBS voltage, pulse width, and frequency are derived from n = 26 due to missing data. “Left” refers to left side stimulation and “right” refers to right side stimulation.

Mean total BESTest percentage scores and BESTest sub-section percentage scores with standard deviations for the ON-medication/ON-stimulation (ON) and OFF-medication/OFF stimulation (OFF) conditions are presented in Table 2.2. Probability values from paired t-tests or Wilcoxon signed-rank tests comparing BESTest scores in the ON and OFF conditions are shown in Table 2.2 in addition to effect sizes.
Table 2.2 BESTest Scores by Section

<table>
<thead>
<tr>
<th>Section</th>
<th>OFF (mean ± SD)</th>
<th>ON (mean ± SD)</th>
<th>p-Value</th>
<th>Cohen’s d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total BESTest score</td>
<td>59.2 ± 16.5</td>
<td>67.6 ± 10.9</td>
<td>&lt;.0001 *</td>
<td>0.77</td>
</tr>
<tr>
<td>I. Biomechanical Constraints</td>
<td>48.1 ± 24.9</td>
<td>51.7 ± 23.3</td>
<td>0.3543 *</td>
<td>0.22</td>
</tr>
<tr>
<td>II. Stability Limits/Verticality</td>
<td>79.2 ± 10.6</td>
<td>86.0 ± 8.6</td>
<td>0.0320 *</td>
<td>0.54</td>
</tr>
<tr>
<td>III. Anticipatory Postural Adjustments</td>
<td>57.9 ± 20.1</td>
<td>67.4 ± 10.5</td>
<td>0.0160 *</td>
<td>0.55</td>
</tr>
<tr>
<td>IV. Postural Responses</td>
<td>55.0 ± 25.9</td>
<td>63.4 ± 23.4</td>
<td>0.1018</td>
<td>0.38</td>
</tr>
<tr>
<td>V. Sensory Orientation</td>
<td>52.2 ± 21.2</td>
<td>60.5 ± 14.8</td>
<td>0.0320 *</td>
<td>0.62</td>
</tr>
<tr>
<td>VI. Stability in Gait</td>
<td>57.1 ± 21.1</td>
<td>69.1 ± 16.5</td>
<td>0.0132</td>
<td>0.63</td>
</tr>
</tbody>
</table>

*p-values for each of the six sub-sections have been adjusted using the Holm–Bonferroni method.
* Indicates Wilcoxon signed-rank test. p-values are otherwise derived from paired t-test.

Total BESTest percentage scores were significantly better in the ON-medication/ON-stimulation condition, compared to the OFF-medication/OFF-stimulation condition. Mean percentage scores for sections (II) Stability Limits/Verticality, (III) Anticipatory Postural Adjustments, (V) Sensory Orientation, and (VI) Stability in Gait were significantly better in the ON-medication/ON-stimulation condition, compared to the OFF-medication/OFF-stimulation condition. Mean percentage scores for sections (I) Biomechanical Constraints and (IV) Postural Responses did not significantly differ between conditions. MDS-UPDRS-III scores were significantly improved in the ON-medication/ON-stimulation condition relative to the OFF-medication/OFF-stimulation condition, as determined by Wilcoxon signed-rank test (p < 0.0001, d = 1.46).

2.4 Discussion

Levodopa and STN-DBS improves overall balance in people with PD, compared to the untreated state (OFF-medication/OFF-stimulation). Levodopa and stimulation, when used in tandem, may affect balance through improved performance in stability limits/verticality.
anticipatory postural adjustments, sensory orientation, and stability in gait. Levodopa and stimulation do not appear to change biomechanical constraints or reactive postural responses, at least in the present sample.

The difference in total BESTest scores between conditions represents improvement in overall balance when ON-medication/ON-stimulation was compared to OFF-medication/OFF-stimulation. This indicates that either medication or stimulation, or the combination of the two, improves balance. These findings support our primary hypothesis, and support results from other balance assessments showing that either levodopa or levodopa with STN-DBS improves overall balance. However, our study does not distinguish whether medication or STN-DBS alone accounts for the difference in total BESTest scores.

To our knowledge, no existing literature specifically addresses how biomechanical constraints, stability limits/verticality, and sensory orientation respond to levodopa and STN-DBS in people with PD. Our results show that biomechanical constraints do not respond to this combined treatment. This is, perhaps, not surprising as the biomechanical constraints section of the BESTest focuses on standing alignment and lower extremity strength. Additionally, underlying orthopedic issues could limit treatment effects in the biomechanical constraints section. We did find, however, that scores for stability limits/verticality significantly improved when ON-medication/ON-stimulation, compared to OFF-medication/OFF-stimulation, suggesting these treatment strategies improve participants’ abilities to reach and lean to the limits of stability. We also found participants better integrated and responded to sensory feedback from multiple systems when treated with levodopa and STN-DBS, as the scores for the sensory
orientation section significantly improved ON-medication/ON-stimulation compared to OFF-medication/OFF-stimulation.

Our results support some previous studies examining the effects of levodopa or STN-DBS on some balance components in people with PD. For example, our results align with a previous report where levodopa improved BBS scores, which largely reflects anticipatory postural adjustments. Our gait stability results from the BESTest also agree with previous reports where levodopa improves gait balance, and that levodopa combined with STN-DBS improves Dual Task Timed Up and Go performance. Additionally, a previous report showed that STN-DBS improves automatic postural reaction stability, which is similar to the postural reactions section of the BESTest. However, our results from this section suggest levodopa and STN-DBS do not improve postural responses, as we did not find levodopa and STN-DBS significantly improved scores for this section. This discrepancy could be due to differences in testing procedure, as previous findings were derived from translations delivered by a servo-driven platform, whereas the BESTest relies on manual perturbations by a rater.

It is important to note that even in the optimally treated state (ON-medication/ON-stimulation), balance deficits persist in people with PD with STN-DBS. Leddy et al. proposed a 69% total BESTest cutoff score for identifying fallers in people with PD, with scores below 69% indicating an increased fall risk. Though this cutoff score was not determined specifically for people with STN-DBS, the mean total BESTest score in the current study of 67.6% (SD = 10.9%) in the ON-medication/ON-stimulation condition does fall below this 69% cutoff score. While more work is needed to determine an accurate BESTest cutoff score for identifying fallers specifically in people with STN-DBS, the mean total BESTest score in the current study does
appear to reflect balance deficits even in the optimally treated condition. No established normative values for each section of the BESTest exist for this population, but scores from some sections of the BESTest in the current study appear low, even in the optimally treated state. For example, participants had scores lower than 70% in five of the six BESTest sections in the ON-medication/ON-stimulation condition. Though these results require replication on larger samples, these initial results suggest that balance interventions targeting several components of balance may be important for this population.

Several limitations should be noted when interpreting our results. The sample size was relatively small ($n = 29$), participants were highly variable regarding time since DBS surgery, and all participants had stimulation electrodes implanted in the STN. No participants in this study had DBS at other sites, such as the globus pallidus internus (GPI), so no conclusions can be drawn from these results regarding how stimulation at other brain sites may affect balance. Moreover, our aim here was to study people in their most optimal and least optimal states, thus the two treatments were either both OFF or both ON. Therefore, we are not able to determine how medication alone or stimulation alone affects each component of balance. Of note, these findings may be influenced by volunteer bias from two perspectives. Firstly, people with PD and DBS may be reluctant to go OFF-medication/OFF-stimulation, so these results reflect only those willing to withhold treatment for this study. Secondly, participants for this study were recruited to participate in a randomized controlled trial, which would require them to consent to participating in physical therapy twice weekly for eight weeks. As such, the balance performance of those unwilling to participate in a physical therapy program may not be represented in these findings.
Despite the limitations, our results provide novel insight into which specific domains of balance are affected by the current treatment techniques (concurrent STN-DBS and medication) for people with PD. The random order of testing the ON-medication/ON-stimulation and OFF-medication/OFF-stimulation conditions may have helped to avoid the effects of fatigue and learning. Additionally, the rater was blinded to participants’ treatment conditions, minimizing rater bias, although occasionally there was a readily apparent difference in balance performance between conditions. These results represent a crucial first step to more accurately understanding the effects of levodopa and STN-DBS on balance among people with PD. Future work should isolate the effects of each treatment (i.e., medication, stimulation) on individual balance systems, as measured by the BESTest. Further, investigators should longitudinally examine how pre-surgical demographic factors and specific stimulation parameters affect balance over time in people with DBS.

2.5 Conclusions

Levodopa combined with STN-DBS improves overall balance in people with PD. Stability limits/verticality, anticipatory postural adjustments, sensory orientation, and gait stability also significantly improved ON-medication/ON-stimulation compared to OFF-medication/OFF-stimulation. Biomechanical constraints and postural responses did not change significantly between conditions. These results provide the first step to understanding the effects of current treatment strategies on domains of balance in people with PD and STN-DBS.
2.6 Acknowledgements

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2.7 References


Chapter 3: Our Dental Mouthpiece did not Improve Signs and Symptoms of PD

This chapter has been published:

3.1 Introduction

For people with Parkinson disease (PD), advances in medical treatments have increased lifespans but have not effectively mitigated the decline in function and the characteristic signs and symptoms of the disease.\textsuperscript{1,2} People with PD often report disturbances in sleep, activities of daily living, gait, and balance. Gait and balance dysfunction are known to negatively affect quality of life among people with PD and are considered risk factors for falls.\textsuperscript{3} Walking ability appears to be particularly important in this population, as impairments in ambulation precede impairments in other gait-dependent activities.\textsuperscript{4}

Standard treatment approaches for PD include pharmacologic and surgical interventions, but these are only partially effective in addressing PD signs and symptoms. As such, adjunct therapies are needed. The use of a dental mouthpiece is one such adjunct therapy that has to date only been explored in a small number of people with PD. Previous work has examined different types of mouthpieces that are typically modelled after those used for temporomandibular joint disorder. One clinical report described a woman with PD who showed improvements in grip strength along with improvements in motor function and quality of life while wearing a mouthpiece.\textsuperscript{5} This report relied on subjective observation for determining improvements in motor function and did not provide a formal quality of life measure or questionnaire. In another case report, a participant indicated use of a bruxism splint improved their sleep quality and fatigue levels.\textsuperscript{6} However, this was also based on subjective report rather than any formal assessment tool.

A more recent case study found some objective improvements in selected gait and balance measures in a participant with PD while wearing a dental mouthpiece.\textsuperscript{7} The Four-Square Step Test and grip strength in the non-dominant hand showed significant improvements with the
mouthpiece compared to the patient’s baseline condition without the mouthpiece. Additionally, this participant reported significant increases in quality of life while wearing the mouthpiece, as evidenced by scores on the Parkinson Disease Questionnaire-39 (PDQ-39) and Global Rate of Change Scale. The researchers reported the participant’s gait mechanics differed with use of the mouthpiece, with the participant holding his arms closer to midline.\(^7\)

Doctor Donald Moeller, an author of this publication, has produced similar mouthpieces for people with PD in his dental practice for several years, and, anecdotally, has noticed various acute improvements in motor function and received patient self-reports of improved sleep and quality of life with mouthpiece use. Similar results have also been reported in the media.\(^8\) However, these reports were based on clinical observations and spontaneous self-reports of improvement rather than standardized assessment techniques in the context of a systematic research study.

Present knowledge regarding the effects of a mouthpiece on motor function and quality of life in people with PD is limited by a lack of standardized outcome measures, variance in mouthpiece design across studies, and the small number of participants studied thus far. Our current understanding of the topic is based on a small handful of clinical reports, case studies, and clinical observations. Furthermore, the mechanism(s) underlying the effects of a mouthpiece on gait and motor function is not well understood. It is possible that because afferent inputs from the trigeminal nerve project to the nucleus raphe of the reticular formation, abnormal input from the mandibular branch of the trigeminal nerve may affect rhythmic motor function such as gait, as well as balance.\(^9\) Stimulation of the nucleus raphe can produce rhythmic contractions of muscle groups which could potentially affect gait and posture.\(^9\) A mouthpiece may function to promote a more optimal maxillomandibular vertical interrelationship and reduce irritation or
abnormal feedback from the mandibular branch of the trigeminal nerve, or more specifically the auriculotemporal nerve, to the nucleus raphe.\textsuperscript{10} Future exploration of mechanisms may be warranted, but not before studies are conducted to determine the potential effects and feasibility of a mouthpiece in a larger sample of participants.

Thereby, in this exploratory pilot study, the primary objective was to examine whether a larger group of people with PD demonstrate any acute improvement in motor symptoms and gait with mouthpiece use. A broad range of motor outcomes was chosen due to the varying types of motor effects seen in previous reports. The secondary objectives were to: 1) examine whether people with PD perceive any long-term improvement in PD-related symptoms and quality of life after one month of mouthpiece use and 2) determine the feasibility of the mouthpiece as a treatment strategy for people with PD as they perform their activities of daily living.

### 3.2 Materials and Methods

This was a single group, pilot study. For inclusion in the study, all participants were required to: 1) have a diagnosis of idiopathic, typical Parkinson disease according to the UK Brain Bank Criteria, Hoehn & Yahr stages I-III; 2) have stable PD medications for the two weeks prior to the in-person visit; 3) be able to walk at least 10 meters at baseline with or without an assistive device; 4) have their own teeth and/or dentures; 5) be willing to try to wear a mouthpiece for one month; 6) be over the age of 30; and 7) provide written or verbal informed consent. Participants were excluded from participation if they had: 1) any pre-existing medical conditions that would inhibit full participation in the study tasks; 2) absence of any dentition; 3) cognitive impairments indicated by a Mini-Mental Status Exam (MMSE) score of <24;\textsuperscript{11,12} 4) freezing of gait which moderately or severely impacted walking; or 5) current use of an oral appliance (e.g., a dental mouthpiece, retainer, or braces). No formal power analysis was
conducted due to the exploratory nature of this pilot study and lack of existing efficacy data. Written informed consent was obtained from each participant in accordance with the Declaration of Helsinki and the policies and procedures of the Human Research Protection Office at Washington University in St. Louis. This study was approved by the Institutional Review Board at Washington University in St. Louis (201904098) and was registered on clinicaltrials.gov (NCT: 04082663).

All participants arrived at Washington University in St. Louis for an in-person visit. During this in-person visit, baseline (WITHOUT-mouthpiece) motor performance and a variety of questionnaires pertaining to sleep and quality of life were completed. All participants were then fitted with a custom mouthpiece and asked to wear the mouthpiece while resting quietly for at least 25 minutes. Motor performance was then reassessed with the mouthpiece in place for each participant (WITH-mouthpiece). All participants were then asked to take the mouthpiece home and wear it as much as possible during sleep and daily activities for one month. After one month, participants were asked to fill out the same questionnaires pertaining to their quality of life and new questionnaires regarding experiences with the mouthpiece and mail these back to the research team (one-month follow-up).

Participants were recruited through the Greater St. Louis Chapter of the American Parkinson Disease Association, advertisements posted on social media sites, and flyers posted on campus. Recruitment began in August 2019. In-person visits took place from September 20, 2019 to September 27, 2019, and the follow-up period lasted one month from the in-person visit.
3.2.1 In-Person Motor and Gait Assessments

At the in-person visit, motor performance was assessed using a variety of clinical tools under two conditions: WITHOUT-mouthpiece and WITH-mouthpiece. We hypothesized that, during mouthpiece use, participants would show improvement on motor outcomes.

Participants were instructed to walk at a normal pace over an electronic walkway (GAITRite, CIR Systems Inc., Franklin, NJ) to assess spatiotemporal gait parameters including gait velocity, cadence, and stride length during ambulation. Participants completed at least three trials of walking both WITHOUT-mouthpiece and WITH-mouthpiece, and the parameters from each trial were averaged for both conditions (WITHOUT-mouthpiece and WITH-mouthpiece). Grip strength was also assessed for both conditions, using a handheld dynamometer. Participants completed two grip strength trials for the dominant hand and two trials for the non-dominant hand WITH and WITHOUT the mouthpiece, and the results were averaged for each hand.

The Mini-BESTest, a 14-item assessment of dynamic balance, was administered WITH and WITHOUT the mouthpiece. Each of these 14 items were rated on a 3-level ordinal scale (0-2) and added together to produce a minimum possible score of 0, indicating poor balance, and a maximum possible score of 28, indicating good balance. The Movement Disorders Society Unified Parkinson Disease Rating Scale motor subsection (MDS-UPDRS-III) was administered to assess disease severity. This portion of the MDS-UPDRS assesses various motor signs and symptoms often seen in people with PD and produces scores ranging from a minimum possible score of 0, indicating no signs and symptoms of PD, to a maximum possible score of 132, indicating severe signs and symptoms of PD. The Mini-BESTest and MDS-UPDRS-III were video recorded, and the videos were subsequently scored by a blind rater to reduce bias. (Note
that scores for the rigidity section of the MDS-UPDRS-III, which cannot be determined from videos, were provided by the original unblinded assessor.)

To evaluate fine motor control, various handwriting metrics were assessed. In accordance with procedures utilized by Bajaj et al., participants were asked to write the standard sentence “A little dog ran down the road” five times.\textsuperscript{15} A blind rater then measured the mean sentence length, the mean height of the letter “d” as measured from baseline to top of the letter, and the 3D Index for each participant across each of the five attempts. The 3D Index, a measure of progressive micrographia, quantifies any decline in height of the letter “d” over the course of a sentence, where “d\textsubscript{1}” represents the height of the first letter “d” \[ (d_{1}−d_{2}) + (d_{1}−d_{3}) + (d_{2}−d_{3}) ] .\textsuperscript{15}

3.2.2 One-Month Follow-Up Questionnaires and Assessments

Questionnaires were used to assess a variety of domains at two time-points: WITHOUT-mouthpiece (baseline) and after one month of mouthpiece use (one-month follow up). We hypothesized that, with mouthpiece use, participants would show improvement in each questionnaire and quality of life metric. To assess freezing of gait, the New Freezing of Gait Questionnaire (nFOG-Q), a nine-item questionnaire about frequency and severity of freezing symptoms during activities of daily living within the past month, was administered.\textsuperscript{16} Scores on the nFOG-Q can range from 0-29, with a score of 0 corresponding to no freezing and a score of 29 representing severe and frequent freezing. To assess sleep quality, the Parkinson’s Disease Sleep Scale (PDSS) and the Pittsburgh Sleep Quality Index (PSQI) were administered. The PDSS contains 15 items which are each rated using a visual analogue scale.\textsuperscript{17} Low scores on the PDSS represent poor sleep quality, while high scores represent good sleep quality. The PSQI contains 19 items divided into seven components, and total scores can range from 0 (representing
good sleep quality) to 21 (representing poor sleep quality). To assess general quality of life, the Parkinson’s Disease Questionnaire-39 (PDQ-39), a 39-item health status questionnaire with eight dimensions, was administered. The sum of the eight dimension scores was divided by eight to produce a Parkinson’s Disease Questionnaire-39 Summary Index (PDQ-39 SI) score, which can range from 0, indicating no PD-related reduction in quality of life, to 100, indicating significant PD-related reduction in quality of life. Participants completed these questionnaires WITHOUT-mouthpiece and at one-month follow-up.

Additionally, after one month of mouthpiece use, five Global Rate of Change scales were used to determine whether participants perceived improvement in each of five domains: overall PD symptoms, sleep, walking, balance, and quality of life. Participants were asked to rate the overall status of each of these compared to before using the mouthpiece. These Global Rate of Change scales provide participants with 15 possible responses, ranging from “a very great deal worse” to “a very great deal better.” Each of the 15 possible responses is shown in Figure 1, and each possible response corresponds with a numeric value ranging from 1 to 15. A response of “about the same” corresponds with a value of 8, while responses of “a very great deal worse” and “a very great deal better” correspond with values of 1 and 15 respectively. Mean responses were calculated using these numeric values for each domain (overall PD symptoms, sleep, walking, balance, and quality of life).

### 3.2.3 Feasibility Assessment

Upon study completion or withdrawal, participants were given an exit questionnaire, in which they were asked to report any discomfort while wearing the mouthpiece and whether they would be likely to continue wearing it in the future if allowed to keep it. The exit questionnaire
also included an open-ended question for participants to report any thoughts or concerns regarding use of the mouthpiece. To determine feasibility of the mouthpiece as a treatment option, the overall dropout rate of the study and the percentage of participants reporting they would be likely to continue wearing the mouthpiece in the future, were assessed. Participants were also asked to record the number of hours they wore the mouthpiece each day in a journal to assess adherence to treatment.

### 3.2.4 Mouthpiece

A licensed maxillofacial surgeon (author DM) fabricated the mouthpieces for this study and customized the fit of each participant’s mouthpiece on-site at Washington University in St. Louis. Alginate impressions were obtained of the mandibular arch. A dental stone model was then created and used to fabricate a thermoplastic soft vinyl flat planed non-anterior repositioning removable splint fitted to rest on the lower teeth, giving the mouthpiece the general appearance of a “horseshoe” shape. No articulators or opposing models were used. The appropriate occlusal vertical thickness was established by correlation to participant height using metrics described by Giddon et al. Discomfort caused by excessive vertical dimension, premature occlusal contacts, or interferences in protrusion or lateral movements was addressed by modifying the mouthpiece to participant satisfaction. Once fitted and provided with the mouthpiece, participants were asked to rest quietly with the mouthpiece in place for at least 25 minutes before completing WITH-mouthpiece motor testing.

### 3.2.5 Statistical Analysis and Software
Study data were managed using REDCap electronic data capture tools hosted at Washington University in St. Louis.\textsuperscript{22,23} Scores from each condition for each variable were examined for skewness and outliers (mean score ± 3 SD). WITHOUT-mouthpiece and WITH-mouthpiece motor assessment data (n=20) were compared, and WITHOUT-mouthpiece and one-month follow-up questionnaire data (n=13, Table 3.3) were compared. Two tailed Wilcoxon signed-rank tests were used for each of these comparisons. The alpha level of significance was set at .05. Statistical analysis was performed in R software version 3.6.0, R Foundation for Statistical Computing, Vienna, Austria.\textsuperscript{24} For each Wilcoxon signed-rank test resulting in a significant p-value <.05, an adjusted p-value was also calculated using the Holm-Bonferroni method and the “p.adjust” function from the “stats” package in R.\textsuperscript{24} The “readxl” package was used to import data to R.\textsuperscript{25} The “ggplot” function from the package “ggplot2” was used to create Figure 1.\textsuperscript{26} For more information regarding statistical analysis, the R code used for data analysis is freely available at https://github.com/dsmay11/DAPD.

### 3.3 Results

Twenty participants completed all parts of the in-person visit. Six participants withdrew from the study during the one-month period due to discomfort with the mouthpiece and completed the exit questionnaire. One participant was lost to follow-up. Thirteen participants completed the study and returned the one-month follow-up questionnaires. Participant demographics are listed in Table 3.1.
Motor assessment results, both WITHOUT-mouthpiece and WITH-mouthpiece are shown in Table 3.2. WITH-mouthpiece, gait velocity and cadence increased significantly compared to WITHOUT-mouthpiece. Stride length showed a trend toward significant improvement WITH-mouthpiece compared to WITHOUT-mouthpiece (p=.053). However, any significant differences in these outcomes did not persist after correction for multiple comparisons. No other motor assessments showed significant differences between the two conditions.
Table 3.2. Motor Assessment Results

<table>
<thead>
<tr>
<th></th>
<th>Baseline WITHOUT Mouthpiece (Mean ± SD), n=20</th>
<th>WITH Mouthpiece (Mean ± SD), n=20</th>
<th>WITH vs. WITHOUT Mouthpiece Comparison p value, n=20</th>
<th>WITH vs. WITHOUT Mouthpiece Mean Difference [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dominant Hand Grip Strength (kg)</td>
<td>30.63 ± 13.35</td>
<td>30.9 ± 13.74</td>
<td>.88</td>
<td>0.28 [-1.42, 1.97]</td>
</tr>
<tr>
<td>Non-Dominant Hand Grip Strength (kg)</td>
<td>29.65 ± 14.18</td>
<td>29.15 ± 14.45</td>
<td>.53</td>
<td>-0.50 [-1.92, 0.92]</td>
</tr>
<tr>
<td>Average Sentence Length (cm)</td>
<td>12.37 ± 3.13</td>
<td>12.05 ± 3.34</td>
<td>.44</td>
<td>-0.32 [-0.95, 0.31]</td>
</tr>
<tr>
<td>Average Sentence Height (cm)</td>
<td>0.70 ± 0.20</td>
<td>0.68 ± 0.20</td>
<td>.09</td>
<td>-0.03 [-0.06, 0.002]</td>
</tr>
<tr>
<td>Average Sentence 3D Index (cm)</td>
<td>0.10 ± 0.31</td>
<td>0.11 ± 0.26</td>
<td>.96 (^{A})</td>
<td>0.02 [-0.12, 0.15]</td>
</tr>
<tr>
<td>MDS-UPDRS III (Blinded)</td>
<td>37.25 ± 8.67</td>
<td>37.35 ± 7.39</td>
<td>.67</td>
<td>0.1 [-2.27, 2.47]</td>
</tr>
<tr>
<td>Mini-BESTest (Blinded)</td>
<td>19.44 ± 3.58</td>
<td>19.28 ± 4.06</td>
<td>.72</td>
<td>-0.17 [-1.29, 0.96]</td>
</tr>
<tr>
<td>Gait Velocity (m/s)</td>
<td>1.10 ± 0.24</td>
<td>1.15 ± 0.22</td>
<td>.04(^{*}) (.36)</td>
<td>0.05 [0.01, 0.09]</td>
</tr>
<tr>
<td>Cadence (steps/min)</td>
<td>105.66 ± 12.88</td>
<td>107.75 ± 11.97</td>
<td>.02(^{*}) (.20)</td>
<td>2.09 [0.64, 3.54]</td>
</tr>
<tr>
<td>Stride Length (cm)</td>
<td>125.33 ± 24.27</td>
<td>128.53 ± 22.74</td>
<td>.05 (.40)</td>
<td>3.20 [0.51, 5.88]</td>
</tr>
</tbody>
</table>

*Indicates p value < .05. Adjusted p values from Holm-Bonferroni multiple comparisons correction are shown in parentheses.

Questionnaire results for the participants who returned questionnaire data after one month (n=13) are shown in Table 3.3. No questionnaire data showed significant differences between time points.
Of the 13 participants who completed the study, the most common response for each of the Global Rate of Change scales was “about the same” with 46.2%, 53.8%, 69.2%, 69.2%, and 61.5% of participants choosing this response for their overall PD symptoms, sleep, walking, balance, and quality of life, respectively. On average, participants indicated their overall PD symptoms, sleep, walking, balance, and quality of life were somewhere between “about the same” or “a tiny bit better” after one month of mouthpiece use, as mean responses for each of these were between 8 and 9. Figure 3.1 shows the mean responses for each domain, as well as individual participant response values for each of the 13 participants who completed the study.

Table 3.3. Questionnaire Results

<table>
<thead>
<tr>
<th></th>
<th>Baseline WITHOUT Mouthpiece (Mean ± SD), n=13</th>
<th>One-Month Follow-Up (Mean ± SD), n=13</th>
<th>One-Month Follow-Up vs. WITHOUT Mouthpiece Comparison p value, n=13</th>
<th>One-Month Follow-Up vs. WITHOUT Mouthpiece Mean Difference [95% CI], n=13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parkinson’s Disease Sleep Scale (PDSS)</td>
<td>89.3 ± 29.5A</td>
<td>91.7 ± 29.9A</td>
<td>.89</td>
<td>2.4 [-7.8, 12.5]</td>
</tr>
<tr>
<td>Pittsburgh Sleep Quality Index (PSQI)</td>
<td>7.7 ± 3.5</td>
<td>7.6 ± 3.5</td>
<td>.99</td>
<td>-0.1 [-1.5, 1.4]</td>
</tr>
<tr>
<td>Parkinson’s Disease Questionnaire 39 Summary Index (PDQ-39 SI)</td>
<td>18.2 ± 9.2</td>
<td>17.3 ± 11.1</td>
<td>.22</td>
<td>-0.8 [-4.7, 3.1]</td>
</tr>
<tr>
<td>New Freezing of Gait Questionnaire (nFOG-Q)</td>
<td>4.9 ± 7.6</td>
<td>4.3 ± 7.5</td>
<td>.83</td>
<td>-0.5 [-2.7, 1.6]</td>
</tr>
</tbody>
</table>

A Indicates n=11 due to missing data
In the exit questionnaire, 13 of 19 participants reported discomfort while wearing the mouthpiece, and 13 of 18 participants reported they would be unlikely or very unlikely to continue wearing the mouthpiece if allowed to keep it (one participant did not answer this question). In the open-ended item of the exit questionnaire, 9 of 19 participants reported that they thought the mouthpiece was too “large” or “bulky,” and 8 of 19 participants reported that the mouthpiece was “too rough” or “has rough spot(s).” Thirty percent of participants (6 of 20) formally withdrew from the study due to discomfort with the mouthpiece. Thirteen participants, including two who withdrew from the study due to discomfort, reported the number of hours the mouthpiece was worn each day while participating in the study. Days for which no information was reported, or for which the participant had withdrawn from the study, were excluded from analysis. For this group of participants, the mean ± SD number of hours the mouthpiece was worn each day was 15.41 ± 5.56.
3.4 Discussion

The results of this study do not provide sufficient evidence to show that dental mouthpieces improve motor performance, sleep, or quality of life acutely or with long-term use in people with PD. While there were significant acute changes in two gait parameters relative to baseline and a trend toward a significant change in another, these could be due to the problem of multiple comparisons. Indeed, none of these changes were statistically significant after correcting for multiple comparisons. With long-term use of the mouthpiece, no questionnaires showed significant changes, and, as a group, participants perceived little to no change in symptoms and quality of life metrics associated with PD on the Global Rate of Change scales. Participants reported various types of discomfort with the mouthpiece, and most indicated they would not be likely to continue to use the mouthpiece.

To determine if the acute changes seen in gait parameters were clinically important despite the lack of statistical significance after correcting for multiple comparisons, we compared these changes to existing minimum clinically important difference (MCID) values when available. The difference in gait velocity between WITHOUT-mouthpiece and WITH-mouthpiece time points was significant (p=.03), but it represents a 0.04 m/s increase, which is lower than the MCID of 0.05m/s.\(^{27}\) To our knowledge, no MCID values have been proposed for cadence or stride length in people with PD.

Prior knowledge of the effects of mouthpieces on motor function and quality of life in people with PD has exclusively been derived from clinical reports, case studies, and clinical observations. One of these reports of mouthpiece use in people with PD showed changes in gait mechanics and balance while wearing the mouthpiece. Two of these reports indicate that grip strength, as assessed by handheld dynamometry, improves while wearing a mouthpiece, and
three of these reports showed various improvements in quality of life while wearing a mouthpiece relative to baseline. However, two of these reports showing improvements in quality of life relied on subjective report and lacked a formal quality of life assessment tool. The results of the current study do not agree with any of these prior findings when corrected for multiple comparisons. While certain individuals may benefit from the use of a mouthpiece, this benefit may not extend to the broader population of people with PD. Additionally, some of these previous studies relied on subjective strategies to assess factors such as quality of life, and the more rigorous techniques in the current study may contribute to the discrepancy with previous findings.

The current study has several limitations. The sample size was relatively small for assessment of acute motor effects (n=20), and even smaller for quality of life effects (n=13). Thus, we may not have had adequate power to detect these effects if present. Participants were not blinded to treatment condition, and therefore any improvements in motor outcomes could have resulted from performance bias while wearing the mouthpiece. The order of testing (WITHOUT-mouthpiece vs. WITH-mouthpiece) was kept consistent across all participants, meaning order effects could have been present. For example, participants may have become increasingly fatigued as the session progressed, leading to worse performance in WITH-mouthpiece motor testing relative to WITHOUT-mouthpiece motor testing. However, participants were given a 25-minute rest session with the mouthpiece in place prior to WITH-mouthpiece motor testing to reduce the likelihood of this type of fatigue.

While several case studies regarding the use of a mouthpiece for treatment of PD-related motor signs and symptoms have been published, this pilot study does not support the use of a mouthpiece as a treatment strategy in people with PD. Further, a mouthpiece, in the form
described in this study, does not appear to be feasible on a large scale as a treatment for people with PD. The overall dropout rate was high (30%), and over half of all participants indicated they were unlikely to continue wearing it. Future research could explore whether a thinner, smoother, less obtrusive mouthpiece is feasible as a treatment option, as many participants stated the mouthpiece was too large, bulky, and/or rough in the current study. Future work could also assess the effects of the mouthpiece at additional time intervals of hours, days, and weeks to determine time course of effects, if any.

3.5 Conclusions

Gait velocity and cadence improved slightly but significantly while wearing a mouthpiece compared to baseline. However, these changes were not statistically significant after correcting for multiple comparisons. Additionally, these changes were likely not clinically meaningful when interpreted in context of existing literature. We did not find significant differences in any other motor or quality of life variables. A mouthpiece, in the form used here, may not be a feasible or appropriate treatment option for people with PD as indicated by various reports of discomfort. Therefore, the current study does not provide adequate evidence to further pursue this type of mouthpiece as a treatment strategy for motor signs and symptoms or quality of life in people with PD.

3.6 Acknowledgements

The authors would like to thank Martha Hessler, Elinor Harrison, Adam Horin, Peter Myers, and Ryan Duncan for their assistance with participant recruitment and data collection. This project was supported by research pilot funds from the Program in Physical Therapy, Washington University in St. Louis School of Medicine.
3.7 References


9. Torvik A. Afferent connections to the sensory trigeminal nuclei, the nucleus of the solitary tract and adjacent structures; an experimental study in the rat. J Comp Neurol. 1956;106(1):51-141. doi:10.1002/cne.901060104


Chapter 4: Our Wearable Sensor-Based Approach is Feasible for Real World Use

This chapter is currently under review:

4.1 Introduction

It is estimated that over 80% of people with Parkinson disease (PD) eventually experience a phenomenon called freezing of gait (FOG), which is a “brief episodic absence or marked reduction of forward progression of the feet despite the intention to walk.”\textsuperscript{1,2} FOG causes falls and is often resistant to levodopa,\textsuperscript{3,4} the most commonly prescribed medication to treat the symptoms of PD. FOG is episodic in nature,\textsuperscript{5} and is difficult to reliably elicit and assess. FOG can be directly observed in a clinical or laboratory setting and can be quantified through video review by a movement disorders expert. However, FOG often disappears when people with FOG consciously focus on walking, like when being observed by a clinician.\textsuperscript{6–8} Factors that trigger FOG, such as anxiety,\textsuperscript{9,10} are difficult to safely reproduce while walking in a clinic setting. Many clinic settings and hallways are broad and free of obstacles, whereas FOG often occurs when navigating narrow spaces and turning.\textsuperscript{6} Therefore, FOG severity, as observed in a clinical or laboratory setting, is unlikely to reflect FOG severity in the real world. Video review is also onerous, time-consuming, and is not practical in a clinical setting. There is therefore a need for an adequate approach to assess FOG severity.

Clinicians and researchers currently rely primarily on the New Freezing of Gait Questionnaire (NFOG-Q) to assess FOG severity. The NFOG-Q is a useful screening tool to differentiate between freezers and non-freezers and shows a high reliability of scores between people with PD and their caregivers.\textsuperscript{11,12} However, as a questionnaire, it is inherently subject to the problem of recall bias. It does not correlate with observed FOG severity in lab settings.\textsuperscript{13} Additionally, the NFOG-Q has only modest test-retest reliability and is not responsive to small
changes in FOG.\textsuperscript{14} New methods are needed to assess FOG, as clinical trials and clinicians rely on accurate and responsive outcome measures to assess potential responses to treatment.

In recent years, wearable inertial measurement units (wearable sensors) and associated algorithms have been proposed as methods for assessing real-world FOG severity. Researchers in our laboratory have worked with engineering colleagues to develop one such method.\textsuperscript{15,16} Our method uses a two-stage detector for determining the zero-velocity and trembling events in gait, and then utilizes a point-process filter to calculate the probability of FOG during these events. Our method was validated in a laboratory setting, can be adapted for individual gait patterns, and can automatically detect FOG in real time.\textsuperscript{15–17} However, this algorithm has not yet been tested outside of structured gait and turning tasks.

It is important to determine whether wearable sensor methods like ours can be used to detect FOG during real-world activities outside the laboratory or clinic, as some people with FOG do not reliably demonstrate FOG in a laboratory or clinical setting. Wearable sensors could theoretically be used in the future as the “gold standard” method for assessing FOG severity. While several sensor-based methods for assessing FOG have been developed, it is unclear whether such methods are capable of accurately assessing FOG during unstructured spontaneous movements of daily life. In one recent study, a sensor-based FOG assessment method was shown to detect significantly more presumed FOG events during unsupervised home use in people with known FOG compared to people without known FOG.\textsuperscript{18} Little else is yet known about the performance of sensor-based FOG assessment methods in the real world. An important first step to determine if further studies are warranted is to test the sensors while performing activities designed to mimic instrumental activities of daily life (IADLs) in a simulated home setting within the laboratory and compare the performance of our sensor-based measures in the home to
measures of FOG severity in the laboratory. This would allow us to determine whether our sensor-based FOG assessment method is feasible in a home environment.

Therefore, the primary objective of this study was to compare the performance of our sensor-based FOG assessment method to existing FOG assessment methods during 1) laboratory-based gait tasks designed to maximally elicit FOG, 2) tasks designed to mimic IADLs in a simulated home setting within the laboratory, and 3) unsupervised home use. Our rationale was that observed correlation patterns would elucidate the feasibility of our approach for unsupervised use in the real world. The secondary objective was to determine the accuracy of our sensor-based FOG assessment method while performing tasks designed to mimic IADLs in a simulated home setting within the laboratory.

4.2 Materials and Methods

4.2.1 Participants

Participants were recruited from the Movement Disorders Clinic at Washington University in St. Louis. For inclusion in this study, all participants were required to: 1) be age 30 or older; 2) have a diagnosis of “clinically definite PD” ; 3) have a history of FOG in the past 2 months according to the treating movement disorders neurologist; 3) be able to walk for at least 100 feet with or without an assistive device. Participants were excluded from the study if they had: 1) any pre-existing medical conditions that would inhibit full participation in the study tasks or 2) cognitive impairments indicated by a Mini-Mental Status Exam (MMSE) score of <24. Written informed consent was obtained from each participant in accordance with the Declaration of Helsinki and the policies and procedures of the Human Research Protection Office at
Washington University in St. Louis. This study was approved by the Institutional Review Board at Washington University in St. Louis (protocol 202004254).

We recruited and tested 20 participants. One participant's data was excluded from analysis because she was unable to complete the gait tasks (described below) without prolonged pauses in walking for resting in the middle of the tasks. The research team determined at the time of testing that this participant's data would be excluded because their pauses would preclude the human expert's assessment of FOG.

4.2.2 Procedure

All participants arrived at Washington University for one in-person visit. Participants were instructed to take their regular doses of levodopa at their usual times on the day of the in-person visit. Disease severity was measured at the in-person visit with the Movement Disorders Society Unified Parkinson’s Disease Rating Scale (MDS-UPDRS).20 The MDS-UPDRS Part III was administered by a certified examiner. At the beginning of the in-person visit, each participant also completed the NFOG-Q.

At the in-person visit, participants completed a series of walking and turning tasks designed to elicit FOG in a clinical setting (clinic FOG tasks) and a series of tasks in a simulated apartment room designed to mimic activities that participants might perform in the home and community in daily life (simulated IADL tasks), while wearing inertial measurement units (sensors) to detect FOG. All clinic FOG tasks and simulated IADL tasks were video recorded for review. After the in-person visit, participants took the sensors home and wore them during their daily activities for three days (home portion) before returning them to the study team. No video recording occurred during the home portion of the study. Three sensors were worn by
participants throughout all components of the study, with one sensor placed on the dorsum of each foot (in pouches strapped onto the participant's shoes) and one sensor placed over the left hip (in a pouch clipped to a belt). Participants completed three clinic FOG tasks and four simulated IADL tasks during the in-person visit. Instructions for each clinic FOG task and each simulated IADL task were highly standardized to avoid differences in instruction between participants. The same two research team members tested all participants, with one always giving instructions and the other never speaking during the tasks and simply walking behind the participant at all times for safety. The highly disciplined protocol was intended to balance the number of left and right turns in each task, and to avoid positive or negative emotional cues during testing, as it was clear during pilot testing that these factors influenced the probability of FOG occurrence. Detailed information about each of these tasks is provided in the Appendix.

The three clinic FOG tasks were designed to incorporate multiple triggers of FOG drawn from previous studies\textsuperscript{13,21} and our own pilot testing. The clinic FOG tasks were labelled: 1) Hallway Pivot, 2) Go Outside and Turn (GOT), and 3) 360-Degree Turn. The Hallway Pivot task consisted of walking in a straight line down a hallway, turning 180 degrees toward the left or right when instructed and then continuing to walk in the opposite direction. The GOT task consisted of walking out of a clinical examination room through an open door into a hallway, making a 180 degree turn within an open box marked on the floor in the middle of the hallway, and then walking around the perimeter of the box before walking back into the clinical examination room. The 360 Degrees Turn task was performed by standing in place and turning 360 degrees when instructed. Each clinic FOG task was performed as a single task and in a dual-task format with a concurrent cognitive task (counting down in steps of three, starting from a 3-digit number randomly chosen for each trial). Each participant completed each clinic FOG task
at least once per direction (i.e. turning once toward the right and once toward the left) as a single task and once per direction as a dual task.

The simulated IADL tasks consisted of 1) vacuuming the floors of the simulated apartment room (vacuum task), 2) emptying a dishwasher and putting dishes away in clearly marked cabinets and drawers positioned around the simulated apartment room (dish task), 3) sitting in a recliner with a footstool for at least ten minutes (sitting task), and 4) walking through the hallways, doorways, and elevators of the clinic building to a given destination to simulate navigating a public building such as a clinician’s office or store (community task). Each participant completed each simulated IADL task once.

After the in-person visit, participants wore the sensors at home for three days. Participants were instructed to remove the sensors from the pouches each night for charging while sleeping and were instructed not to remove the pouches from the shoes until the study was complete. Participants were asked to wear these shoes with the sensors donned as much as possible while awake but were given permission to temporarily remove these shoes if desired for aesthetic purposes (e.g. while wearing more formal clothing for dinner at a restaurant) or to protect the devices (e.g. bathing). Each participant and any individuals present who resided with the participant were educated in how to charge the sensors each night and how to don them in the correct positions the next morning after charging. Home instructions are detailed in the Appendix.

4.2.3 Equipment

Foot and left hip motion were recorded by inertial measurement units (IMUs) that included tri-axial gyroscopes and accelerometers housed in wearable sensors. These consisted of
Physilog 6 sensors (Gait up SA, Lausanne, Switzerland) sampled at 128 Hz for the first 6 participants, and ActiGraph GT9X Link (ActiGraph, Pensacola, Florida) sampled at 100 Hz for the remaining participants. The change of sensors was necessitated by breakage of one sensor that could not be replaced due to pandemic-related semiconductor chip shortages. Data were downloaded for offline analysis after the in-person visit and again after home use.

4.2.4 Data Analysis

We detected FOG events in sensor data by first calculating probability of FOG using the Probability of Freezing of Gait (pFOG) algorithm developed by Prateek et al. FOG events were the times when pFOG for either foot was above a threshold of 0.7. The Python programming language was used for cleaning, processing, and analysis of data. The pandas, NumPy, SciPy, and tkinter packages were used throughout various steps of this work. Matplotlib and Seaborn were used to generate Figures 4.1 and 4.2. Events separated by less than 2 seconds were merged into single FOG events.

Foot sensor data was analyzed only for segments when the participant was non-sedentary, as indicated by hip sensor data. We considered sedentary all time segments with total hip angular velocity (sum of absolute value of hip angular velocity in each of the three axes) less than 1 deg/s, and excluded these from analysis. An example is a participant sitting in a chair and bouncing his or her leg up and down. Non-sedentary (active) times were calculated as times when total hip angular velocity (filtered through a centered 20s moving average window) in any plane was above 1 deg/s. For all portions of the study, including the in-person visit and the home portion of the study, sedentary times were removed from analysis.
For the in-person visit, only data from during the clinic FOG tasks and the simulated IADL tasks were analyzed. For both the in-person visit and the home portion of the study, the sensor-based percent of active time spent freezing (Sensor-Based %ATSF) was calculated by dividing the total amount of time spent freezing by the total amount of active time and multiplying the result by 100. For the in-person visit, Sensor-Based %ATSF was calculated for the whole visit (clinic FOG tasks plus simulated IADL tasks) and separately for the simulated IADL tasks only.

A licensed physical therapist with experience in assessment and treatment of people with PD analyzed the video recordings to determine when FOG occurred during the clinic FOG tasks and the simulated IADL tasks. In accordance with past work, the beginning of a FOG episode was defined as the moment when the gait pattern appeared arrested or it appeared as if the participant was trying unsuccessfully to initiate or continue locomotion or turning. The end of a FOG episode was defined as the moment when an effective step had been performed and was followed by at least one more effective step. For each participant, the rater summed up the total amount of time spent freezing and the total amount of time spent performing each task. The remaining data were used to calculate the video-based percent of active time spent freezing (Video-Based %ATSF) for the whole in-person visit (clinic FOG tasks plus simulated IADL tasks) and separately for the simulated IADL tasks only.

Video review was considered the “gold standard” for detecting FOG during the in-person visit. Any times for which the sensors and video review both detected FOG were labelled as true positives, and any times for which neither method detected FOG were labelled as true negatives. Accuracy was determined by calculating the ratio of the true positives plus true negatives to the total length (in samples) of the dataset. Accuracy was calculated for the whole in-person visit...
(clinic FOG tasks and simulated IADL tasks) as well as for each simulated IADL task individually, to determine if certain IADL tasks were associated with greater or lesser detection accuracy.

Without video recording in the home, it is impossible to calculate the accuracy of our sensor-based FOG detection method during home use. Therefore, we examined the correlations between Video-Based %ATSF measures from the in-person visit and Sensor-Based %ATSF at home to determine whether the amount of FOG detected for each person during the in-person visit correlates with the amount of FOG detected for each person at home. We also examined the correlations between Video-Based %ATSF measures and the Sensor-Based %ATSF measures from the in-person visit to provide additional information about performance of the sensor-based FOG detection during clinic FOG tasks and simulated IADL tasks. Additionally, we examined the correlation between the NFOG-Q and all %ATSF measures to determine how the NFOG-Q relates to observed measures of FOG severity. All %ATSF scores, as well as NFOG-Q scores, were checked for normality using Shapiro-Wilk tests. Because each set of %ATSF scores was found to have a non-normal distribution, Spearman’s rank correlations (Spearman’s $\rho$) were used throughout.

## 4.3 Results

Nineteen participants completed the study. Participant demographics are provided in Table 4.1.
Correlations between the NFOG-Q, measures from the entirety of the in-person visit, and Sensor-Based %ATSF from the home (n=19) are shown in Figure 4.1. The Sensor-Based %ATSF from the in-person visit correlated strongly with the Video-Based %ATSF from the in-person visit ($\rho= 0.77$). The Sensor-Based %ATSF from the home also correlated strongly with the Sensor-Based %ATSF from the in-person visit ($\rho= 0.72$). The Sensor-Based %ATSF from the home showed a weak correlation with the Video-Based %ATSF from the in-person visit ($\rho= 0.25$). The NFOG-Q showed no strong correlation with any objective measures of %ATSF from the entirety of the in-person visit or from the home.

<table>
<thead>
<tr>
<th>Table 4.1. Participant Demographics, n=19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years (mean ± SD)</td>
</tr>
<tr>
<td>Sex (males, females)</td>
</tr>
<tr>
<td>MDS-UPDRS-III score (mean ± SD)</td>
</tr>
<tr>
<td>Hoehn &amp; Yahr Stages (Stage 2, 3, 4)</td>
</tr>
<tr>
<td>New Freezing of Gait Questionnaire score</td>
</tr>
</tbody>
</table>
Figure 4.1: In-Person Visit Correlations. n=19. Values represent Spearman’s Rho values. “In-Person Visit” refers to Clinic FOG Tasks + Simulated IADL tasks. “Sensor %ATSF” refers to sensor-based percent active time spent freezing, and “Video %ATSF” refers to video-based percent of active time spent freezing, as determined by an expert rater upon video review.

Correlations between the NFOG-Q, measures from the simulated IADL task portion of the in-person visit, and Sensor-Based %ATSF from the home (n=19) are shown in Figure 4.2. The Sensor-Based %ATSF from the simulated IADL tasks and the Video-Based %ATSF from the simulated IADL tasks correlated especially strongly (ρ= 0.87). The Sensor-Based %ATSF from the simulated IADL tasks also correlated strongly with the Sensor-Based %ATSF from the home (ρ= 0.73). The Sensor-Based %ATSF from the home showed a moderate correlation with
the Video-Based %ATSF from the simulated IADL tasks ($\rho = 0.50$). The NFOG-Q showed little to no correlation with the Video-Based %ATSF from the simulated IADL tasks or the Sensor-Based %ATSF from the simulated IADL tasks.

Figure 4.2: Simulated IADL Task Correlations. n=19. Values represent Spearman’s Rho values. Simulated IADL tasks refer to the Vacuum, Dish, Sitting, and Community tasks, which all occurred during the in-person visit. “Sensor %ATSF” refers to sensor-based percent of active time spent freezing, and “Video %ATSF” refers to video-based percent of active time spent freezing, as determined by an expert rater upon video review.
The mean accuracy across participants (n=19) for the entire in-person visit, i.e., clinic FOG tasks plus simulated IADL tasks, is shown in Table 4.2. The mean accuracy across participants (n=19) for each simulated IADL task is also displayed in Table 4.2. The mean accuracy for the entire in-person visit, as well as for each simulated IADL task, was above 90%. Mean accuracy correlated negatively with Video-Based %ATSF for the in-person visit ($\rho=-0.93$) so that accuracy was higher for participants with lower Video-Based %ATSF values.

<table>
<thead>
<tr>
<th>Table 4.2. Sensor-Based FOG Detection Accuracy, n=19</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-Person Visit (Clinic FOG Tasks + Simulated IADL Tasks)</td>
</tr>
<tr>
<td>Vacuum Task</td>
</tr>
<tr>
<td>Dish Task</td>
</tr>
<tr>
<td>Sitting Task</td>
</tr>
<tr>
<td>Community Task</td>
</tr>
<tr>
<td>Values are mean accuracy (percentage) ± SD</td>
</tr>
</tbody>
</table>

Following Mancini et al., we included a third sensor at the waist to filter out sedentary time from analysis. Our method succeeded in excluding only the times which were very likely to be sedentary. During the in-person visit, this modification only made a difference for two out of 19 participants, and it only filtered out time during the sitting task for both participants. The addition of this modification improved accuracy during the sitting task for these two participants. No times during other tasks were filtered out as sedentary for any participants.

Out of 19 participants, two did not have any observed FOG during the in-person visit. Five did not have any observed FOG during the simulated IADL tasks. All participants with observed FOG during the simulated IADL tasks also had observed FOG during the clinic FOG tasks. Across participants with observed FOG, the average duration of FOG episodes was 5 seconds for the entire in-person visit. For the 14 participants with observed FOG during the
simulated IADL portion of the in-person visit, the average duration of FOG episodes was also 5 seconds. Overall, participants spent less time with FOG during the simulated IADL tasks compared to the in-person visit as a whole (clinic FOG tasks plus simulated IADL tasks). The mean %ATSF across all 19 participants is shown in Table 4.3 for each sensor and video-based measure.

Table 4.3. Percent of Active Time Spent Freezing (%ATSF), n=19

<table>
<thead>
<tr>
<th>Measure</th>
<th>Mean %ATSF ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensors: In-Person Visit (Clinic FOG Tasks + Simulated IADL Tasks)</td>
<td>6.36 ± 7.31</td>
</tr>
<tr>
<td>Sensors: Simulated IADL Tasks</td>
<td>1.84 ± 3.25</td>
</tr>
<tr>
<td>Sensors: Home</td>
<td>1.94 ± 3.06</td>
</tr>
<tr>
<td>Video Review: In-Person Visit (Clinic FOG Tasks + Simulated IADL Tasks)</td>
<td>11.22 ± 11.08</td>
</tr>
<tr>
<td>Video Review: Simulated IADL Tasks</td>
<td>1.90 ± 2.68</td>
</tr>
</tbody>
</table>

Values are mean %ATSF ± SD

4.4 Discussion

We examined the performance of our sensor-based FOG assessment during structured laboratory gait tasks, simulated real world activities, and three days of unsupervised home use. Our sensor-based method was successfully utilized in the home, for the first time, by 19 participants. Correlations between our sensor-based approach and expert video review, correlations between home and laboratory measures of FOG, and high accuracy values during simulated real-world activities suggest that our sensor-based FOG assessment method is feasible for unsupervised use in the real world and is capable of accurately assessing FOG during real world activities.
The Sensor-Based %ATSF from the in-person visit correlated strongly ($\rho= 0.77$) with the Video-Based %ATSF from the in-person visit. Therefore, during the in-person visit, participants with greater amounts of FOG according to expert review tended to show greater amounts of FOG according to our sensor-based method. This relationship was even stronger for the simulated IADL task portion of the in-person visit ($\rho= 0.87$). These results suggest that our sensor-based method is capable of accurately assessing FOG during structured clinic FOG tasks and during simulated IADL tasks.

Correlations between Sensor-Based %ATSF in the home and other measures of FOG severity require more careful interpretation, as we did not have video recordings of participants in their homes and therefore lack a gold standard for comparison. Nonetheless, results suggest our sensor-based method can assess FOG in the home. Sensor-Based %ATSF in the home correlated strongly with Sensor-Based %ATSF from the in-person visit and the simulated IADL task portion of the in-person visit. These relationships suggest our sensor-based FOG assessment method was capable of accurately assessing FOG in the real world, and that the addition of unsupervised, unstructured movement patterns did not significantly confound our detection method. Correlations between Sensor-Based %ATSF in the home and Video-Based %ATSF from the in-person visit were not as strong, though the correlation was stronger for the simulated IADL task portion of the visit (0.50) than for the in-person visit as a whole (0.25). It is, perhaps, not surprising that FOG in the home might more closely resemble FOG during the simulated IADL tasks than FOG during the clinic FOG tasks. The clinic FOG tasks were designed to maximize the chance to elicit FOG. Some participants may have experienced FOG during these tasks but not during typical household activities. It is also not particularly surprising that Sensor-Based %ATSF in the home correlates more strongly with sensor-based measures from the lab.
than with video-based measures from the lab. Some differences are expected between video review and sensor measures when assessed at the same time.\textsuperscript{15} Likewise, some differences are expected between sensor measures when taken at two different time points, as FOG severity may vary throughout the day. By comparing sensor-based measures in the home and video-based measures from the in-person visit, we are compounding these differences, and any correlation is therefore expected to be lower.

The NFOG-Q showed very little correlation with objective measures of FOG throughout the study. This supports previous work showing that the NFOG-Q does not correlate with observed FOG in lab settings.\textsuperscript{13} Our sensor-based measurements, both in-person and at home, were much more closely related to the gold standard of expert video review during the in-person visit and the simulated-IADL task portion of the visit than the NFOG-Q. Our results suggest the NFOG-Q is insufficient as an assessment of real world FOG.

The simulated IADL tasks introduced in this study required participants to move and walk in ways that our sensor-based FOG assessment method had not yet encountered, such as side-stepping, repeatedly stepping forward and backward (during the vacuum and dish tasks), and sitting in a recliner for at least ten minutes, a task which typically involves occasional movement and adjustment of the lower extremities. Prior to this study, it was unclear how our sensor-based FOG assessment method would perform during such activities. However, the accuracy of our sensor-based method was above 90\% across the entire in-person visit and during each of the simulated IADL tasks, further demonstrating the ability of our sensor-based method to assess FOG during real world activities.
Interestingly, accuracy values were even higher for the simulated IADL tasks than for the in-person visit as a whole. One potential explanation for this could be that participants spent less time freezing during the simulated IADL tasks compared to the in-person visit as a whole. Even though we merged any FOG episodes detected by our sensor-based method that occurred within two seconds of each other, our sensor-based method appears to still be detecting long FOG episodes as shorter, successive bursts of FOG episodes and therefore undercounting the %ATSF relative to the human rater. Indeed, Sensor-Based %ATSF was lower than Video-Based %ATSF for the in-person visit and the simulated IADL tasks, and overall accuracy decreased with increasing Video-Based %ATSF for the in-person visit. While the two second threshold for merging episodes was found to be optimal for the sensor-based FOG assessment method developed by Mancini et al., future work could examine whether this threshold is most optimal for our sensor-based method and whether other approaches could be used to modify the algorithm so that long FOG episodes are more accurately detected. However, the observed accuracy in this study is still quite high, and our approach already appears to be capable of assessing FOG severity during real-world settings for this sample of participants as a whole.

Several limitations of this study should be noted. The sample size was relatively small (n=19). With a larger sample of participants, we may have been able to detect more robust correlation patterns. The hardware used in this study was also not without limitations. The Gait Up sensors' ports became damaged after use by several participants. Both brands of sensors required overnight charging, as our detection algorithm required the devices' highest sampling rate. Participants had to be thoroughly educated to ensure they knew how to charge the devices each night (see Appendix). Devices with increased battery life and/or modifications to our approach to make it less energy intensive would allow for use of this method without overnight
charging and would make it easier to reliably implement. We had to modify commercially purchased pouches to affix the sensors to the participants' footwear. Products manufactured specifically for this purpose would also make our method easier to reliably implement. The detection algorithm does not yet include a user-friendly interface and required several hours of processing per participant (though processing was faster than real-time). Despite these limitations, the correlations and accuracy values observed in this study are promising and suggest that our sensor-based FOG assessment method is feasible for use in the real world. Larger validation studies of our sensor-based method appear to be warranted, possibly with video recording in the home, to assess the accuracy of our method more confidently during real world use.

4.5 Conclusions

Our sensor-based FOG assessment method was successfully utilized outside the laboratory for the first time. Correlation patterns between FOG assessment methods across settings, as well as high accuracy values during simulated real-world tasks, suggest our method is feasible for assessing FOG in the real world. The lack of correlation between the NFOG-Q and all objective measures of FOG further demonstrates the need for new FOG assessment methods in the real world.

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4.7 References


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Chapter 5: Conclusion
5.1 Summary

Overall, the studies of this dissertation sought to answer questions about emerging treatment strategies and assessment techniques for signs and symptoms of PD. This chapter will summarize the main findings and limitations of these studies, the significance of these results, and implications for future research.

The purpose of Chapter 2 was to determine the effects of STN-DBS and levodopa on balance. Past studies reported mixed results on the effects of STN-DBS and levodopa on balance,\(^1\)\(^-\)\(^{11}\) possibly due to the variability and inadequacy of balance assessments used. No work has yet utilized a comprehensive balance assessment, such as the BESTest,\(^{12}\) to study the combined effects of STN-DBS and levodopa on balance. This study used cross-sectional baseline data from a randomized clinical trial examining physical therapy after STN-DBS surgery.\(^{13}\) We compared total BESTest scores, as well as scores for each of its six sections, in the optimally treated state (i.e., combination of STN-DBS and levodopa) to those in the least optimal state (i.e., no medication and no DBS). We noted that total BESTest scores were significantly higher in the optimally treated state compared to the least treated state. We also noted that scores were significantly higher for Stability Limits/Verticality, Anticipatory Postural Adjustments, Sensory Orientation, and Stability in Gait in the optimally treated state vs. the least treated state, while Biomechanical Constraints and Postural Responses did not show a significant difference between conditions. Thus, our data suggest that STN-DBS and levodopa, when used together, improve overall balance and four of the six domains of balance, as described by the BESTest.

In Chapter 3, we examined the feasibility of a dental mouthpiece as a treatment strategy for PD-related signs and symptoms. Several case reports and studies have shown assorted benefits for signs and symptoms of PD with use of a dental mouthpiece.\(^{14\text{-}17}\) However,
knowledge of these potential benefits is limited by a lack of standardized outcome measures, variance in mouthpiece design across studies, and the small number of participants studied thus far. Using standardized outcome measures, we examined 1) whether a larger group of people with PD demonstrate any acute improvement in motor symptoms and gait with mouthpiece use, 2) whether people with PD experience any long-term improvement in PD-related symptoms and quality of life after 1 month of mouthpiece use, and 3) feasibility of a mouthpiece as a treatment strategy for people with PD as they perform their activities of daily living. We did not find significant acute or long-term improvements in any signs or symptoms of PD or quality of life measures with mouthpiece use, after correcting for multiple comparisons. Additionally, many participants described discomfort when wearing the mouthpiece, suggesting this treatment strategy, in its current form, may not be feasible for use in people with PD. Many participants indicated that the mouthpiece was too large and/or too rough.

The purpose of Chapter 4 was to determine whether wearable sensors, and our associated algorithm, can be used to assess FOG in the real world. Our sensor-based FOG assessment method accurately detects FOG during structured gait and turning tasks in the laboratory, but its real-world performance is unknown. The primary objective of this study was to compare the performance of our sensor-based FOG assessment method to existing FOG assessment methods during 1) laboratory-based gait tasks designed to maximally elicit FOG, 2) tasks designed to mimic IADLs in a simulated home setting within the laboratory, and 3) unsupervised home use to determine the feasibility of our approach for use in the real world. Our secondary objective was to determine the accuracy of our sensor-based FOG assessment method while performing tasks designed to mimic IADLs in a simulated home setting within the laboratory. Our sensor-based FOG assessment method was successfully utilized in the real world.
during three days of home use. Results from our sensor-based method correlated strongly with those from expert video review during simulated real world activities. Results from our sensor-based method during home use correlated strongly with results from our sensor-based method during simulated real world activities. Correlation patterns, as well as high accuracy values during simulated real world activities (above 90% relative to gold standard expert video review), suggest our method is feasible for real world use. The NFOG-Q, which is often used by clinicians and researchers to assess FOG severity, did not correlate with any objective measure of FOG.

5.2 Limitations

The studies of this dissertation are not without limitations. For Chapter 2, while all participants had their STN-DBS for at least one year at the time of the study, participants were still highly variable in time since DBS surgery. Additionally, the objective of Chapter 2 was to study people in their most optimal and least optimal states, so the effects of STN-DBS alone or levodopa alone on balance were not quantified in this study. Inclusion in the study described in Chapter 2 required participation in regular physical therapy and spending short periods of time without STN-DBS or levodopa treatment,\textsuperscript{13} which may be unpleasant. It is possible that our study of participants was especially eager for effective treatments for PD compared to the general population of people with PD. People who endured the difficulty of DBS surgery may be eager to know or show that the surgery had benefit to them. Thus, our participants could have consciously or unconsciously shown increased effort during balance testing while optimally treated (on STN-DBS and levodopa) compared to their least treated state. Increased effort likely would not dramatically alter scores from most sections of the BESTest. For example, the
Postural Reactions section tests a participant’s ability to recover from a sudden balance perturbation, and increased effort would likely not impact performance on such a measure. However, a participant’s amount of effort could affect performance on Biomechanical Constraints, which involves measures of strength, and Stability in Gait, which includes multiple items scored at least partly according to gait speed. Thus, it is possible that the significant difference between treatment conditions for the Stability in Gait section was partially due to increased effort during testing in the optimally treated state.

In Chapter 3, the people who volunteered for our study may have been more open to alternative treatments than others with PD and therefore more likely to show some benefit of mouthpiece use. Indeed, in casual conversations during study visits, participants were notably eager for some sort of benefit from any kind of alternative treatment. Participants were not blinded to their treatment condition (i.e., mouthpiece vs no mouthpiece), as such blinding would have been impossible, and therefore may have exerted more effort during motor testing with the mouthpiece in place. In addition, the order of testing was the same for all participants. Thus, it is possible that participants were more fatigued when performing motor assessments with the mouthpiece compared to when performing motor assessments without the mouthpiece at the beginning of the study visit. However, participants were given a 25-minute rest session after receiving the mouthpiece to mitigate this possibility. Despite limitations, the lack of any benefit from mouthpiece use in this sample of participants implies that such a treatment would be very unlikely to have any benefit for the general population of people with PD more broadly.

For Chapter 4, hardware and software used in our sensor-based method would benefit from modifications to make them more user-friendly, as described in detail in Chapter 4. More user-friendly software and hardware would make our method easier to implement reliably.
As volunteers drawn from a convenience sample, participants for Chapter 4 may have been more agreeable and eager to rigorously follow our directions and education for charging, donning, and doffing the sensors each day. The general population of people with PD may be less careful in the use of the sensors and more prone to using them incorrectly. Additionally, each study in this dissertation excluded participants with cognitive impairment. For Chapter 4, it is possible that our sensor-based method may not be appropriate for people with cognitive impairments or that close caregiver supervision and assistance may be necessary for our method to be utilized successfully in people with such impairments.

Finally, the sample size for each study was relatively small (n=29, n=20, and n=19 for Chapters 2, 3, and 4 respectively). It is possible that a larger sample size would have granted more statistical power to detect any benefit of a dental mouthpiece for people with PD in Chapter 3. A larger sample size may have also allowed for more robust statistical differences in Chapter 2 and more robust correlation patterns in Chapter 4.

5.3 Significance and Future Directions

5.3.1 Chapter 2

The results from Chapter 2 provide novel insight into which specific domains of balance are affected by STN-DBS and levodopa and are a critical first step toward more thorough understanding of the effects of STN-DBS and levodopa on balance in people with PD. These results can be used to inform care for people with PD by rehabilitation professionals. Even in the optimally treated state (i.e. combination of STN-DBS and levodopa), the overall BESTest score for participants in Chapter 2 was low. This low overall score suggests this group of participants may be at increased risk for falls, according to previous work which utilized the
BESTest in people with PD to determine a cutoff score for identifying fallers. While no BESTest cutoff score for identifying fallers has been proposed for people specifically with STN-DBS and PD, the overall score in this sample was below the proposed cutoff score for a broader sample of people with PD. Thus, balance interventions, education, and environmental modifications are warranted in this population. To determine which specific domains of balance should be targeted, we can examine the scores from each section.

Of all sections of the BESTest, participants in this sample had the lowest scores in Biomechanical Constraints, across both treatment conditions. This section, which assesses strength, range of motion, and quality of base of support, was also not significantly improved by STN-DBS and levodopa. These results suggest that people in this population may benefit from strength and flexibility interventions to improve balance and reduce fall risk. Postural Responses were also not significantly improved by current treatments. The Postural Responses section assesses a person’s ability to respond to a sudden external balance perturbation. This component of balance is more challenging than Biomechanical Constraints to directly target with rehabilitation interventions, but people with STN-DBS taking levodopa may benefit from education regarding their potentially impaired ability to respond to balance perturbations. People in this population may also benefit from environmental modifications, such as non-slip surfaces in bathrooms and showers, to mitigate the risk of a sudden balance perturbation, such as a slip.

Future studies should examine the benefits of perturbation training in people with PD and STN-DBS to determine whether rehabilitation interventions may be beneficial for fall risk reduction. Future research should examine the effects of STN-DBS alone on balance and of levodopa alone on balance, using the BESTest for each. This would allow for increased understanding of which specific components of balance are affected by these treatments.
individually. Future work could also examine how pre-surgical demographic factors and specific stimulation parameters affect balance over time in people with STN-DBS. This knowledge could allow clinicians to provide more individualized care in determining stimulation parameters and deciding which patients are optimal candidates for STN-DBS. Additionally, our study only included people with STN-DBS. DBS is often inserted at other sites, such as the globus pallidus internus (GPI). Future studies could examine the effects of DBS at other target sites, such as the GPI, on balance, as little is known about such effects.

### 5.3.2 Chapter 3

In Chapter 3, we did not find any benefit of dental mouthpiece use in our sample of people with PD. These results are significant, as they directly contradict prior literature. One reason for this discrepancy could be that our work utilized standardized outcome measures, which were largely lacking in many prior reports, to examine any potential benefits. Previous literature also consists entirely of case reports and case studies. It is possible that this treatment strategy was attempted in many other individuals as well, but only results indicating a benefit of mouthpiece use were published. Our results suggest that a dental mouthpiece, in its current form, is not an effective treatment strategy for people with PD, and clinicians and researchers should focus their time and resources on other strategies which may have more benefit.

However, some people with PD may truly have experienced benefits of mouthpiece use in prior small studies. The mechanism behind these benefits is unclear. There is a great need for additional treatment strategies in this population, and studies regarding the precise mechanism of benefit for these people may help researchers design a treatment which does have benefits in a larger sample of people with PD. It is possible that temporomandibular joint
exercises and related interventions could target this mechanism more directly and without the
difficulties of regular mouthpiece use. However, without understanding the precise mechanism
involved, any benefits of such interventions are mostly supported by speculation. Participants in
this study frequently indicated that the mouthpiece was too rough and large. Future research
could examine whether a thinner, smoother mouthpiece is of any benefit for people with PD.
Additionally, our work only examined acute and long-term (one month after receiving the
mouthpiece) effects of the mouthpiece. Future research could assess the effects of a mouthpiece
after different intervals of time to determine the time course of effects, if any. Future work could
examine the effects of a mouthpiece in a larger sample of people with PD. While we did not
perform a formal power analysis for our study due to its exploratory nature, our sample size was
small, and we were likely statistically underpowered to detect significant differences for many of
our outcome measures.

It should also be noted that while knowledge of the effects of a dental mouthpiece in
people with PD is limited and based on a handful of reports from a small number of participants,
similar mouthpieces have been used in a much larger number of people with post-traumatic
stress disorder (PTSD).\textsuperscript{22,23} In people with PTSD, the use of such a mouthpiece is associated with
significant reductions in PTSD-related symptoms such as headaches, nightmares, and sleep
disturbances.\textsuperscript{22,23} Future studies could assess whether a mouthpiece has any benefit for PD-
related signs and symptoms in people with PD and a history of PTSD, as people with PTSD have
an elevated risk of developing PD later in life.\textsuperscript{24,25}

5.3.3 Chapter 4

In Chapter 4, we found, for the first time, that our wearable sensor-based FOG
assessment method can be successfully utilized during real world activities. In accordance with
previous work, we also found a lack of correlation between the NFOG-Q and objective measures of FOG in our study. This further demonstrates the need for new assessment methods in the real world. Our findings have several other implications for clinical practice, as well. FOG is known to occur more often when off dopaminergic medication. Some people with PD experience a good effect from their medications all day, while others experience times of limited to no effect, despite taking their medications. One factor that makes FOG so challenging to reliably assess in the clinic is that some people may only freeze when their medications are not working well, but these times may not coincide with a scheduled clinic visit. Our sensor-based method, in combination with a patient log of medication administration times, would allow clinicians to determine whether patients freeze during such times of limited medication effect and how the wearing on and off of medications affects a specific patient’s FOG. This information could lead to more individualized care and optimization of medication regimens. Our sensor-based method could also be repeatedly utilized across a span of months or even years as a measure of FOG progression.

While our results from Chapter 4 are promising, a larger validation study of our sensor-based method in the real world is needed. We determined the accuracy of our method during simulated real world activities, but we did not use video cameras in participants’ homes and thus could not calculate accuracy of our method during actual home use. While video recording participants in the home presents unique challenges and privacy concerns, future studies could implement safeguards so that validation can occur. In addition to this validation work, further refinement of our algorithm is warranted. For example, in our study we decided to merge any FOG episodes detected by our sensor-based method within two seconds of each other, in accordance with recent literature regarding a similar sensor-based method. Future research
could examine whether the two-second threshold or a different threshold is optimal for FOG assessment during real world activities.

Clinicians can work with patients to determine triggers of FOG specific to each patient and can help patients identify strategies to either avoid these triggers, modify the environment to lessen the potency of these triggers, or minimize freezing during such triggering circumstances. Clinicians could currently do this in the real world by utilizing video recording in the home and marking FOG episodes during the video. However, this requires an expert reviewer to classify instances as FOG and is labor-intensive. Our method could be used, in conjunction with video in the home, to help clinicians determine specific FOG triggers in the real world, without the need for an expert reviewer. This would still require a human reviewer to determine which activities are occurring and triggering FOG but would significantly reduce the amount of labor and expertise required, as it would not be necessary for the reviewer to determine whether a patient is freezing or not.

When working with multiple hours of wearable sensor data, our method requires extensive processing time to determine the probability of FOG across the entire dataset. However, this processing does occur faster than real time. Thus, with some modifications, our method could be utilized to detect, and possibly even predict, FOG in real time. Future studies on this topic are warranted, as real time detection and prediction of FOG could have great benefits to people with FOG. For example, some people with FOG benefit from an external cue to end a freezing episode and resume normal ambulation. Our method could be used to deliver a cue such as a laser pointer, auditory cue, or tactile cue in real time as FOG is occurring or about to occur. In order to achieve this, our method would need to utilize wearable sensors with a wireless connection to a computer, rather than the sensors used in this study, which simply store data that
can later be downloaded to a computer. Prediction of FOG would also require modifications to the algorithm used in our study.\textsuperscript{18–20}\ Researchers would need to identify typical gait characteristics in the seconds preceding an FOG episode and modify the algorithm to detect these FOG precursors. Such work could be immensely helpful for many people with FOG and has the potential to greatly improve their quality of life.

Our method utilized inertial measurement units sampling at their maximum sampling rate (at least 100 Hz). Our algorithm requires raw accelerometry data and raw angular velocity data derived from the gyroscope in the units. Future work should determine whether such a high sampling rate is truly necessary, as a lower sampling rate would allow for faster processing and reduced file size. This would make our method more user-friendly. Additionally, if our method could be achieved using accelerometry data only, this would likely improve battery life in the sensors and could reduce the need for overnight charging, which introduces high potential for user error. Future work should also determine whether smart phones and smart watches could be utilized to provide sufficient data for our sensor-based method, as this would make it easier to implement.

5.3.4 Summary

Lessons learned from each of the studies in this dissertation can be used to optimize treatment and assessment strategies for people with PD in the future. Chapter 2 provides novel insight into the impacts of STN-DBS and levodopa on balance. Chapter 3 shows that a dental mouthpiece, in its current form, is not beneficial for people with PD, and Chapter 4 shows that our wearable sensor-based FOG assessment method is feasible for real world use. Wearable sensors hold great potential for future research opportunities and could even be used to comprehensively study balance and gait in the real world. Such advances could allow researchers
to gain an important real world understanding of balance in people with DBS, gait in people with PD while attempting novel treatment strategies, and patterns and severity of FOG in people with PD.
5.4 References


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Appendix: Supplementary Materials for Chapter 4
Task Instructions
Instructions to Participant before beginning:

“We are going to ask you to do some walking, some turning, and a few chores and activities like those you might do at home. This is to determine whether you experience a phenomenon called ‘freezing of gait’ during these tasks. I will be reading instructions from a script. I will not be telling you how you’re doing. This is not a test of how well you move or how fast you walk. You don't need to rush. For everything we ask you to do, we want you to do it at a comfortable pace. One of us will be near you at all times in case you need assistance with your balance. My instructions may sound robotic at times during these tasks. This is because we want to keep the instructions consistent for everyone. If you become dizzy or tired at any point and feel like you need to sit, let me know and I will pause the test and get a chair for you. Do you have any questions before we begin? [answer questions and ensure understanding.] Great.”

Notes for rater:

- For the dual task portion of each task, give the participant a number greater than 100.
- Read the directions slowly and clearly, giving plenty of time for participants to comprehend what is being said.
Go Outside and Turn:

Notes for rater: Start this task in the clinical exam room. Read instructions with participant sitting in chair facing door. Participants will start walking with toes at a marker 150 cm from door. If participant turns the wrong direction, do not tell them they made a mistake. Rather, for the subsequent trial, instead of simply saying “right” or “left,” say “to the right this time” or “to the left this time.” At end of each trial, once participant walks back into room (approximately halfway between door and starting position), say “stop.”

Instructions to participant:

[For Round 2, state “I will review the instructions for this task with you before we start it again.”]

1. “You can have a seat while I explain this task. When I say ‘ready, set, go,’ walk out the door into the open box marked on the floor in the middle of the hallway. You will turn around inside the box, walk out of the box, and walk all the way around the outside of the box, and then return to the room. When you walk through the door, I will tell you which direction to turn.
   If I say to turn left, you will turn around inside the box toward your left like this [demonstrate]. You will then walk out of the box and make another left turn to walk around the outside of the box like this [demonstrate] before returning to the room.
   If I say to turn right, you will turn around inside the box toward your right like this [demonstrate]. You will then walk out of the box and make another right turn to walk around the outside of the box like this [demonstrate] before returning to the room.

   Walk at a comfortable pace. Would you like me to demonstrate again? [Demonstrate if participant requests another demonstration.] Great, I will show you where to start. [Direct participant to assume starting position.]. Do you understand the instructions? [answer questions and ensure understanding before starting]. Great. When I want you to start, I will say "Ready, Set, Go." Please wait for me to give the cue.

2. “Please return to the starting position. [Direct participant.] I will tell you which direction to turn when you get to the door.”

3. Repeat above.

4. Repeat above.

-Sit and rest for at least 30 seconds-

5. “I will tell you which direction to turn when you get to the door. This time, I want you to count backward while you walk. I will give you a number to start with. You will count backward by three. Please count out loud. If you make a mistake with counting, continue counting down by three as if nothing happened. When I want you to start, I will say ‘ready, set, [and then your number.]’ So, for example, I might say ‘ready, set, 243.’ When I do this, you will start counting backward by three from the number I give you and start walking, like this: "243, 240, 237, and so on" [Demonstrate walking while counting down]. Walk at a comfortable pace. Do you have any questions? [answer questions and ensure understanding before starting] Great, please wait for me to give the cue.”
6. “Please return to the starting position. [Direct participant]. Start counting backward and walking when I give the cue.”
7. Repeat above.
8. Repeat above.
Hallway Walk:

Notes for rater: Start this task in the hallway. Read instructions with participant sitting in chair. Participants will walk to marker 6 m away from start, back to marker at 3 m away from start, and then return to marker 6 m away from start. Say “right and stop” or “left and stop” at end of task. If participant turns the wrong direction during a trial, do not tell them they made a mistake. Rather, wait until the end of that trial and then clarify instructions before beginning next trial. At the end of the trial, say “right and stop” or “left and stop.”

Instructions to participant:

[For Round 2, state “I will review the instructions for this task with you before we start it again.”]

1. “You can have a seat while I explain this task. When I say ‘ready, set, go,’ you will walk down the hallway. At some point while you’re walking, I will say “left” or “right.” [Begin walking away from participant.] When I say “left,” you will turn around toward your left like this [demonstrate turn] and continue walking in the opposite direction. [Begin walking away from participant.] When I say “right,” you will turn around toward your right like this [demonstrate] and continue walking in the opposite direction. Do not stop walking until I say the word “stop.” Walk at a comfortable pace. Would you like me to demonstrate again? [Demonstrate if participant requests another demonstration.] Great, I will show you where to start. [Direct participant to starting position.] Do you understand the instructions? [answer questions and ensure understanding before starting]. Great, please wait for me to give the cue.”

2. “We will start from here this time. [Direct participant.] Great, please wait for me to give the cue.”

3. Repeat above.

4. Repeat above.

-Sit and rest for at least 30 seconds-

5. “This time, I want you to count backward while you walk. I will give you a number to start with. You will count backward by three. Please count out loud. If you make a mistake with counting, continue counting down by three as if nothing happened. When I want you to start, I will say ‘ready, set, [and then your number.]’ So, for example, I might say ‘ready, set, 243.’ When I do this, you will start counting backward by three from the number I give you and start walking, like this: "243, 240, 237, and so on" [Demonstrate walking while counting down]. Walk at a comfortable pace. Do you have any questions? [answer questions and ensure understanding before starting.] Great, please wait for me to give the cue.

6. “We will start from here this time. [Direct participant]. Start counting backward and walking when I give the cue.”

7. Repeat above.

8. Repeat above.
360 Degree Turns:

Notes for rater: Start this task in the clinical exam room. Read instructions with participant sitting in chair. Participant will start task facing door with backs of heels on the 150 cm from door mark. If participant turns the wrong direction during a trial, do not tell them they made a mistake. Rather wait until the end of that trial and then clarify instructions before beginning next trial.

Instructions to participant:

[For Round 2, state “I will review the instructions for this task with you before we start it again.”]

1. “You can have a seat while I explain this task. When I say ‘right,’ I want you to make a complete turn to the right, like this [demonstrate]. When I say ‘left,’ I want you to make a complete turn to the left, like this [demonstrate]. In other words, each time I say ‘right’ or ‘left’ you will make a complete turn in that direction. Turn at a comfortable pace. If you start to feel dizzy, let me know, and we can pause the test. Would you like me to demonstrate again? [Demonstrate if participant requests another demonstration.] Great, I will show you where to start. [Direct participant to starting position.] Do you understand the instructions? [answer questions and ensure understanding before starting]. Great, please wait for me to give the cue.” [Cue: “Ready, set, right/left.”]

2. “Right/left”
3. “Right/left”
4. “Right/left” [After participant completes turn: “Ok you can stop and take a step back now.”]

-Sit and rest for at least 30 seconds-

5. “This time, I want you to count backward while you turn. I will give you a number to start with. You will count backward by three. Please count out loud. If you make a mistake with counting, continue counting down by three as if nothing happened. When I want you to start counting, I will say ‘ready, set, [and then your number.]’ So, for example, I might say ‘ready, set, 243.’ When I do this, you will start counting backward by three from the number I give you, like this: “243, 240, 237, and so on”. While you are counting backward, I will say either ‘right’ or ‘left’ several times and you will make a complete turn in whichever direction I say. Turn at a comfortable pace. Do you have any questions? [answer questions and ensure understanding before starting.] Great, please wait for me to give your number. [Cue: “Ready, set, number.”] [After participant successfully subtracts by three twice, state “right/left.”]

6. “Right/left”
7. “Right/left”
8. “Right/left” [After participant completes turn: “Ok you can stop and take a seat now.”]
Activities of Daily Living (ADL) Tasks

Notes for rater: Take hard chair into simulated apartment room. Participant will sit in hard chair while rater reads the following instructions and the instructions for the first ADL task. After reading instructions for first ADL task, remove hard chair from room, and place it outside in the hallway. The hard chair can be brought back into the room at any point if participant wants to sit.

Instructions to participant: “We will go over to the room next door for the next few tasks.” [Direct participant to room.] “You can have a seat here.” [Direct participant to chair.] For these next few tasks, we will be doing activities and chores which you might do at home or in the community to see whether you experience freezing of gait. Again, this is not a test of how well you move or how fast you walk. You don't need to rush. If you get tired and need to sit at any point, let me know, and I will get the chair. Do you have any questions before we move on to the next task? [answer questions and ensure understanding.] Great.”

Vacuum Task:

Notes for rater: Start this task in the simulated apartment room. Place footstool far enough away from comfortable chair for participant to be able to vacuum between footstool and chair.

Instructions to participant: “For the next task, you will plug the vacuum in here. [Indicate the appropriate electrical outlet.] You will then vacuum this room. Try to vacuum every part of the room you can get to without moving furniture. Do not move any furniture for this task. When you finish, unplug the vacuum, and wrap the cord back up on the vacuum like it is now. The power button is here [indicate] and the foot release pedal is here [indicate]. Do you understand the instructions? [answer questions and ensure understanding before starting]. Great, you can begin.”

Dish Task:

Notes for rater: Place 4 plates, 4 bowls, 4 cups, 2 forks, 2 spoons, and 2 butter knives in the dishwasher, and then close the dishwasher before reading instructions. Have the cabinet spaces for each type of dish/silverware labelled (e.g. “plates here”) before beginning. Push footstool up against comfortable chair for this task. Start this task in the simulated apartment room.

Instructions to participant: “For the next task, you will unload the dishwasher and put the dishes away. Plates go over here and should be stacked on top of each other [indicate location.] Bowls go over here and should be stacked on top of each other on this shelf [indicate location.] Cups go over here on this shelf [indicate location.] Forks go here [indicate], spoons go here [indicate], and knives go here [indicate]. Only carry one dish or piece of silverware at a time. For example, don’t carry two forks at a time or two bowls at a time. Close the dishwasher when you finish. Do you understand the instructions? [answer questions and ensure understanding before starting]. Great, you can begin.”
Community Task:

Notes for rater: Start this task in the simulated apartment room.

Instructions to participant: “For the next task, you will walk to the elevator, take the elevator up to the first floor, get some hand sanitizer from the dispenser on the first floor, take the elevator back down to the basement, and then walk back to this room. I will walk with you. I won’t be giving you directions unless you ask me which way to turn. If you get lost and do not know which way to turn, you can ask me. Do you understand the instructions? [answer questions and ensure understanding before starting]. Great, you can begin.”

Sitting Task:

Notes for rater: Place 5 magazines and a bottle of hand sanitizer on small table or appliance near comfortable chair and set footrest in front of comfortable chair (approximately one foot from chair) before reading instructions. Start this task in the simulated apartment room.

Instructions to participant: “For this next part of the study, you will make yourself comfortable! You will sit in the rocking chair here and put your feet up on the footrest. Try to sit in whatever way is comfortable to you, like how you might sit at home. You can adjust the position of the footrest if you want, or you can ask us to adjust it for you. We want you to sit here for 10 minutes and read. Look through these magazines and find something to read for a few minutes. We will let you know when the 10 minutes have passed. Please use this hand sanitizer on your hands before and after touching the magazines. Do you understand the instructions? [answer questions and ensure understanding before starting]. Great, you can take a seat and begin.”
Gait Up Physilog Home Instructions
INSTRUCTIONS FOR SENSORS

For any questions, call at any time:

Pietro Mazzoni (phone number redacted) or David May (phone number redacted)

When you leave the lab today, you will be wearing 3 sensors: two clipped to your shoelaces, and one on your waist (left hip). Your sensor locations are:

LEFT FOOT: ________ RIGHT FOOT: ________ WAIST: ________

Please wear these sensors for the rest of today and each of the next 3 days. Please wear your sneakers with the sensors for as much of the day as you can, starting after you get up in the morning and until you go to bed at night.

You can wear your sensors inside and outside the house, even if it’s raining. The sensors will not be damaged by a few splashes of water. However, do not submerge the sensors in water.

Please wear the sensors for the following days:
- The rest of the day after you leave the lab (Day 0: ________)
- The first day after your lab testing day (Day 1: ________)
- The second day after your lab testing day (Day 2: ________)
- The third day after your lab testing day (Day 3: ________)
IN THE EVENING:

- I. TAKE THE SENSORS OFF.
  - Take the hip sensor pouch off your belt or pants. Leave the shoe sensor pouches on the shoes. Take the sensors out of the pouches to charge them.

- II. TURN THE SENSORS OFF
  - Press the button on one sensor (any sensor) and hold it pressed until the light changes from green to orange (about 1 second). If you hold the button down too long (over 5 seconds) this will cause the sensors to reset, and any data you’ve collected will be lost.

  Do not hold the button down for too long (over 5 seconds) when turning the sensors off.

  - Confirm the light is steadily off. If the light is flashing, repeat the above step or call Pietro or David (numbers above)
  - Repeat the above steps for the remaining 2 sensors

- III. CHARGE THE SENSORS
  - Plug a cable into each sensor and connect to a wall outlet
  - The sensors will flash purple for a few hours. They will change to steady green to indicate they have completed charging.

  Make sure to turn the sensors off before charging them.
IN THE MORNING:

- I. CONFIRM THE SENSORS ARE FULLY CHARGED.
  - If they are fully charged, the light on each sensor will be a steady green, and you can unplug the sensors.
  - If the lights are not steady green, let them keep charging and call Pietro or David (numbers above).

- II. TURN THE SENSORS ON
  - Press the button on one sensor (any sensor) and hold it pressed until the green light turns off (about 1 second)

  Do not hold the button down for too long (over 5 seconds) when turning the sensors on.

  - Confirm that the light is flashing green (about every second; each flash is very fast and faint; this is normal).
  - After a few seconds, the 3 sensors’ lights should be flashing green all at the same time.
  - If the 3 lights are not flashing green at the same time, turn each sensor off and repeat the above steps, or call Pietro Mazzoni (number above)
IN THE MORNING (Continued):

- III. WEAR THE SENSORS
  - Fasten the hip sensor pouch on your belt, near your left hip
  - Place each sensor in its pouch.
    - Be sure to put the left foot sensor on the participant’s left foot and the right foot sensor on the participant’s right foot.
    - Be sure to put each sensor in its pouch with the sticker facing away from the participant’s body. Do not put the sensors in the pouch upside down. See images

CORRECT

![Correct Hip Sensor Placement](image1)

![Correct Foot Sensor Placement](image2)

WRONG

![Incorrect Hip Sensor Placement](image3)

![Incorrect Foot Sensor Placement](image4)

Red Sensor= Left Foot
Blue Sensor= Right Foot
Green Sensor= Hip
AT THE END OF DAY 3:

- At the end of day 3: turn the sensors off and charge them. Let them stay plugged in and charging until a research team member is ready to pick them up.

- Take the pouches off your shoes and pants or belt. If you cannot get the pouches off the shoes, a research team member will be happy to do it for you when we pick the sensors up.

- Place the 3 sensors, the pouches, and the charging cables in the box provided.

- Wait for a phone call from Pietro or David who will provide instructions on how to return the sensors

Thank you for participating in our study!
Actigraph Link GT9X Home Instructions
INSTRUCTIONS FOR SENSORS

For any questions, call at any time:

Pietro Mazzoni (phone number redacted) or David May (phone number redacted)

When you leave the lab today, you will be wearing 3 sensors: two clipped to your shoelaces, and one on your waist (left hip). Your sensor locations are:

LEFT FOOT: ________ RIGHT FOOT: _______ WAIST: _________

Please wear these sensors for the rest of today and each of the next 3 days. Please wear your sneakers with the sensors for as much of the day as you can, starting after you get up in the morning and until you go to bed at night.

You can wear your sensors inside and outside the house, even if it’s raining. The sensors will not be damaged by a few splashes of water. However, do not submerge the sensors in water.

Please be sure to follow these directions when handling sensors.

Please wear the sensors for the following days:

- The rest of the day after you leave the lab (Day 0: _________)
- The first day after your lab testing day (Day 1: _________)
- The second day after your lab testing day (Day 2: _________)
- The third day after your lab testing day (Day 3: _________)
SENSOR ORIENTATION

This is the front side (screen side) of the sensors.

This is the back side (tape side) of the sensors.

Each sensor is labelled on the back with tape to show you where to place them on the study participant.

- The left foot sensor goes on the participant’s left foot.
- The right foot sensor goes on the participant’s right foot.
- The hip sensor goes on the participant’s left hip (clipped to belt).
IN THE EVENING:

- **I. TAKE THE SENSORS OFF.**
  - Take the hip sensor pouch off your belt or pants. Leave the shoe sensor pouches on the shoes. Take the sensors out of the pouches to charge them.

- **II. CHARGE THE SENSORS**
  - Plug each of the three charging docks in to a wall outlet
  - Place each sensor on a charging dock as shown below.
  - Charging dock should light up orange. This will change to green when they are fully charged.

![Charging dock](image)

When charging, back of sensor (tape) should face toward charging cable.

|⚠️|

If the charging dock does not show orange light during charging, remove the sensor, and make sure you have inserted it correctly into the charging dock.
IN THE MORNING:

- I. CONFIRM THE SENSORS ARE FULLY CHARGED.
  - If they are fully charged, the light on each charging dock will be a steady green, and you can unplug the sensors.
  - If the lights are not steady green, let them keep charging and call Pietro or David (numbers above).

- II. WEAR THE SENSORS
  - Fasten the hip sensor pouch on your belt, near your left hip
  - Place each sensor in its pouch.
    o Be sure to put the left foot sensor on the participant’s left foot and the right foot sensor on the participant’s right foot.
    o Be sure to put each sensor in its pouch with the front side (screen side) facing away from the participant’s body. Do not put the sensors in the pouch upside down. See images below.

CORRECT

WRONG

The battery icon on screen should be at the top and Actigraph logo should be at the bottom when inserting into pouch. If not, the sensor is upside down.
AT THE END OF DAY 3:

- At the end of day 3: place the sensors on the chargers. Let them stay plugged in and charging until a research team member is ready to pick them up.

- A research team member will assist you with taking the pouches off the shoes unless otherwise instructed.

- Place the 3 sensors, the pouches, the charging docks, and charging cables in the box provided.

- Wait for a phone call from Pietro or David who will provide instructions on how to return the sensors

Thank you for participating in our study!