The utility of an instrumented pull test to evaluate postural instability in Parkinson's disease

Joy Lynn Tan

ORCID identifier: 0000-0002-1312-1325

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Department of Medical Bionics
Faculty of Medicine, Dentistry and Health Sciences
The University of Melbourne

Abstract

Postural instability is one of the cardinal symptoms of Parkinson's disease (PD). Postural instability can present on diagnosis, and commonly becomes more prominent with disease progression, resulting in subsequent falls and diminished quality of life. The treatment of postural instability is challenging, as it is often refractory to management with levodopa and deep brain stimulation of conventional targets such as the subthalamic nucleus. To assess postural instability, the most commonly used measure in the clinical setting is the pull test according to item 30 of the Unified Parkinson's disease rating scale (UPDRS), where an examiner performs a brisk backward tug at the patient's shoulder level and grades the corrective response. While easy to administer, outcomes can vary due to variability in test administration and interpretation.

A comprehensive literature review revealed laboratory based assessments provided a more objective method to measure postural responses compared to clinical assessments in people with PD. These techniques were conventionally employed in people with PD in later disease stages who already demonstrate postural instability. Laboratory based assessments presented a method to identify abnormalities before postural instability is clinically evident and effects of therapies. The recent development of instrumentation of clinical balance tests offered an alternative technique to precisely quantify postural responses. Here, we developed an instrumented version of the pull test and investigate its utility to quantify postural instability in people with PD ranging from mild to moderate disease severity.

In Study 1, the sensitivity of the instrumented pull test was investigated in healthy young participants. Postural responses were modified by presenting a startling auditory stimulus concurrent with the backwards pull. Such stimuli evoke StartReact effects and are known to speed reaction times. The instrumented pull test could detect small 10 ms decreases in postural reaction time evoked by the startling stimulus. The ability to detect such changes in healthy individuals highlights the utility of instrumented techniques and justifies further investigation in people where changes to balance is of interest.

Subsequently, the instrumented pull test was used to characterise postural responses in eighteen people with mild PD (Hoehn and Yahr ≤ 2) in Study 2. Subclinical abnormalities in trunk and step responses were detected in participants with mild PD compared to healthy

controls. Furthermore, levodopa did not restore postural responses in participants with PD to that of healthy controls (Study 3). These findings demonstrate changes to postural stability can occur in mild disease. Abnormalities of postural responses which remain refractory to levodopa also suggest non-dopaminergic pathways may be implicated in the pathophysiology of postural instability in mild PD.

Pedunculopontine deep brain stimulation (PPN DBS) is a therapy developed specifically to alleviate axial symptoms of gait and postural abnormalities unresponsive to conventional therapies such as levodopa. In Study 4, the instrumented pull test was used to quantify postural responses in five people with PD and moderate to severe postural instability receiving PPN DBS. Off and on stimulation, the instrumented pull test was able to detect postural responses with greater resolution compared to clinical assessments (axial items 27 to 30 of the motor subsection of the Unified Parkinson's disease rating scale (UPDRS) and the Mini-BESTest. However, the use of the instrumented pull test, and interpretation of findings was limited by the small sample size and highly variable postural responses in participants with moderate to severe postural instability. On stimulation, improvement in overall balance scores was demonstrated across all participants with the Mini-BESTest but not axial items of the UPDRS.

This thesis demonstrated the utility of the instrumented pull test as a potential assessment tool to evaluate postural instability in PD. Identification of postural abnormalities provides valuable insights in the assessment and management of postural instability in people with PD. Clinicians should consider that subclinical postural abnormalities can be present in people with mild PD, even when patients are on levodopa. Findings from this thesis strongly support the need for further studies to explore variables of postural responses that may be useful to detect people with PD at risk of falls and for clinicians to deliver targeted interventions earlier in disease course.

Declaration

This is to certify that:

i. This thesis comprises only my original work towards the PhD doctoral degree

ii. Due acknowledgement has been made in the text to all other material used

iii. This thesis is less than 100,000 words length, exclusive of tables, references and appendices

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Joy Tan

September, 2019

Preface

This thesis with publication is comprised of eight chapters, two of which are peer-reviewed publications in Chapter 3 and 4. No part of this thesis has been submitted for other qualifications or was carried out prior to enrolment in the PhD. No third-party editorial assistance was provided in preparation of the thesis. The publication status, contributions of each author and funding sources regarding each of these chapters are described below.

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Contributors: J.L.T., T.P., P.B. and W.T conceived and designed research; J.L.T. and T.P. performed experiments; J.L.T. and T.P. analysed data; J.L.T. and T.P. interpreted results of experiments; J.L.T. and T.P. prepared figures and video; J.L.T., and T.P., drafted the manuscript; all authors edited and revised manuscript, and approved the final version of manuscript. J.L.T. contributed at least 60% of the work towards this study (see Appendix 4 for co-author authorisation forms).

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Other publications and conference presentations during candidature

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Other publications

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Lee, W.L., Sinclair, N.C., Jones, M., **Tan, J.L.**, Proud, E.L., Peppard, R., McDermott, H.J., Perera, T., 2019. Objective evaluation of bradykinesia in Parkinson's disease using an inexpensive marker-less motion tracking system. Physiol. Meas. 40, 014004. https://doi.org/10.1088/1361-6579/aafef2

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My patients who inspire me to be the best clinician I can be.

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Abbreviations

APS	American Physiological Society
CI	95% confidence interval
DBS	Deep brain stimulation
EMG	Electromyography
FOG	Freezing of gait
FOGQ	Freezing of gait questionnaire
GFQ	Gait and falls questionnaire
GPi	Globus pallidus pars interna
HY	Hoehn and Yahr
LED	Levodopa equivalent dose
LMM	Linear mixed models
MDS	Movement Disorders Society
Mini-BESTest	Mini-Balance Evaluations Systems Test
MMSE	Mini-Mental State Examination
ms	milliseconds
NA	Not available
PD	Parkinson's disease
PPN	Pedunculopontine nucleus
SD	Standard deviation
STN	Subthalamic nucleus
UPDRS	Unified Parkinson’s disease Rating Scale
Zi	Zona incerta

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CHAPTER 1. INTRODUCTION

1.1 Background

Parkinson's disease (PD) is the second most common neurodegenerative condition after Alzheimer's disease (Nussbaum and Ellis, 2009), affecting over 6.2 million people worldwide (GBD 2015 Neurological Disorders Collaborator Group, 2017). In 2014, there was an estimated 65,000 people with PD living in Australia ("Deloitte Economic Access report," 2015). As the incidence of PD increases with age (Lees et al., 2009), the prevalence of PD is expected to double in developed countries from 2005 to 2030 due to the world's ageing population (Dorsey et al., 2007). The typical age of onset ranges between 65 to 70 years (Tysnes & Storstein, 2017).

Postural instability is considered one of the cardinal symptoms of PD, together with tremor, akinesia, and rigidity (Jankovic, 2008). Dopamine depletion underlies the pathogenesis of motor impairments in PD, with non-dopaminergic lesions further suggested to contribute to postural instability (Kalia and Lang, 2015; Rodriguez-Oroz et al., 2009) (detailed in Chapter 2 literature review). These symptoms are associated with the loss of neurons in the subcortical and cortical brain regions, resulting in an ascending progression of neurodegeneration, characterised by six Braak stages (Braak et al., 2003) and the presence of Lewy bodies (Chase et al., 1998; Lewy, 1912).

Postural instability is the impairment in balance that compromises the ability to maintain or change posture during tasks of static or dynamic activities (Kim et al., 2013). It is a major contributor to falls with associated morbidity and mortality in PD (Allen et al., 2013; Giladi et al., 2005; Kerr et al., 2010; Kim et al., 2013; Latt et al., 2009; Robinson et al., 2005). Falls and recurrent falls occur at a significantly higher rate in people with PD compared to the older healthy population (Allen et al., 2013; Parashos et al., 2013; Rudzińska et al., 2013; Wood et al., 2002) with falls occurring three times more frequently in people with PD compared to age matched healthy controls in the community (Rudzińska et al., 2013). The risk of fractures from falls in people with PD is up to three times higher than age and sex matched controls (Sleeman et al., 2016; van den Bos et al., 2013). Hip fractures frequently occur, resulting in longer hospital admissions and decreased mobility on discharge in people with PD compared to age matched controls (Malochet-Guinamand et al., 2015; Walker et al., 2013). Postural instability typically manifests as unsteadiness during walking, falls and even

the inability to stand. Mild postural instability is known to occur in early stages in people with PD, and become more prominent with disease progression (Kim et al., 2013). In people with PD, postural instability is identified as a risk factor for falls (Kerr et al., 2010; Latt et al., 2009).

In clinical practice in people with PD, postural instability is typically assessed with the pull test, where an examiner briskly pulls the patient backwards at the shoulders and visually grades the response (Fahn et al., 1987; Hunt and Sethi, 2006). Postural instability is usually scored using the Unified Parkinson's Disease Rating Scale (UPDRS) (0 - normal to 4 - severe), as published by the International Movement Disorder Society (Fahn et al., 1987). This method has been used extensively in the assessment of individuals with PD, but suffers poor reliability and very limited scaling (score/4) (Hunt and Sethi, 2006; Nonnekes et al., 2013; Visser et al., 2008b). Pull test scores often do not correlate with important clinical endpoints such as falls and the integer-based rating lacks sensitivity to detect fine postural changes (Bloem et al., 1998; Ebersbach and Gunkel, 2011).

In contrast, laboratory based techniques commonly employing platform perturbations offer precise information about the nature of balance responses. Platform perturbations employ motorised platforms that slide or rotate under the feet, resulting in a standardised balance perturbation across multiple participants. Kinetic (e.g. centre of pressure), kinematic (e.g. joint goniometry/limb displacement), and neurophysiological (e.g., muscle recruitment) endpoints (Visser et al., 2008b) are subsequently quantified. These studies of platform perturbation suggest subclinical changes in postural responses may present in mild PD (HY $\leq$ 2). Use of platform perturbations has also been used to elucidate the effects of therapy on postural instability in people with PD (Bloem et al., 1996; Horak et al., 1996; Kam et al., 2014).

One of the main aims of medical therapy in people with PD is to improve symptomatic control (Lang and Lees, 2002). Dopamine replacement therapy comprising levodopa and dopamine agonists are the mainstay of treatment for PD (Lees et al., 2009; Salat and Tolosa, 2013). Of these, levodopa is well established as the most efficacious medications to manage the motor symptoms of PD, particularly tremor, akinesia, and rigidity (Lang and Lees, 2002). In contrast, postural instability typically shows minimal or no response to levodopa (Bloem et al., 1998; Di Giulio et al., 2016; Jacobs and Horak, 2006; Kam et al., 2014; King et al., 2010;

Rocchi et al., 2002). It is well acknowledged that PD is associated with pathology extending beyond the nigro-striatal dopaminergic system (Sethi, 2008). Accordingly, novel therapies that target non-dopaminergic systems such as cholinergic pathways may be beneficial for postural instability (Bohnen et al., 2009). Therapies such as deep brain stimulation (DBS) of the pedunculopontine nucleus (PPN), which comprise cholinergic neurons, have therefore been developed as an alternative treatment that may benefit symptoms of postural instability unresponsive to levodopa (Thevathasan et al., 2018).

While platform perturbations are sensitive to quantify small changes in postural responses to effects of therapy, correlations to clinical balance measures are poor (Bloem et al., 1998; Chastan et al., 2008; Schieppati and Nardone, 1991). Emerging evidence suggests truncal perturbations such as those elicited by the pull test yield different postural characteristics to those of moving platforms (Colebatch et al., 2016; Di Giulio et al., 2016; Govender et al., 2015). Postural responses of platform perturbations evoke a slip-like or tilting response which is fundamentally different from a truncal perturbation that is similar to being bumped in a crowd.

To overcome these shortcomings, complex laboratory setups have been attempted using motors, pendulums, and waist pulls to replicate truncal perturbations comparable to the clinical pull test (Azevedo et al., 2016; Di Giulio et al., 2016). These methods of measurement are often expensive and inaccessible, comprising video-based motion capture that requires dedicated space in specialised laboratories (Di Giulio et al., 2016; Foreman et al., 2011). Ideally, an objective method to characterise pull test responses should have excellent psychometric properties, be easy to administer, simple to operate, widely accessible, and portable. This is important to facilitate widespread adoption of the technique as an alternative assessment tool to assess postural responses within research and potentially, clinical settings.

The instrumented pull test in this thesis was developed to characterise the nature of elicited postural responses in people with PD. Like the clinical test, the perturbation was delivered manually by an examiner but with measurement of pull force. Both the trunk and step responses were assessed with motion tracking, akin to visual assessment by a clinician. This methodology may be useful to quantify abnormalities before postural instability is clinically

evident, track changes over time in people with PD and detect efficacy of therapies such as levodopa and deep brain simulation.

1.2 Aims

The overall aim of this thesis is to characterise postural instability in people with PD and explore the effects of therapies on postural responses using an instrumented version of the pull test. The thesis comprises four major components. Firstly, evidence related to the assessment and treatment of postural instability will be reviewed and synthesized with a focus on reactive postural responses and instrumented versions of clinical assessments. Secondly, instrumentation of the clinical pull test to quantify trunk and step responses using 3D motion tracking sensors is described. Thirdly, the instrumented pull test is used to characterise postural responses in healthy individuals and people with PD. Lastly, the instrumented pull test is used to determine the effects of therapies including levodopa and PPN DBS on postural responses in patients with PD.

Specifically, this thesis aims to:

1) Review and synthesize the evidence related to the assessment of postural instability in people with PD, with a focus on instrumented versions of clinical assessments.
2) Determine the capability of the instrumented pull test to detect small changes in postural responses in healthy young participants by using a loud auditory stimulus to modulate underlying motor preparation.
3) Investigate if the instrumented pull test can quantify abnormalities in postural responses in people with PD where the clinical pull test is unable to detect postural instability.
4) Determine if postural abnormalities identified in people with mild PD are levodopa responsive.
5) Evaluate the utility of the instrumented pull test to quantify postural responses in people with PD and moderate to severe postural instability receiving PPN DBS.

1.3 Thesis synopsis

To achieve the aims listed above, the following was undertaken. A narrative literature review was first conducted (Chapter 2). Subsequently, an instrumented pull test was developed (Chapter 3), and used to characterise postural responses in healthy young individuals (Study 1) and participants with mild PD (Study 2). The effects of therapies on postural responses to

the pull test were explored with levodopa (Study 3) and PPN DBS (Study 4) in people with PD.

Two publications have resulted from the work contained within this thesis (Publication 1 in Chapter 3 and Publication 2 in Chapter 4)

1) **Tan, J.L**., Thevathasan, W., McGinley, J., Brown, P., Perera, T., 2019. An Instrumented Pull Test to Characterize Postural Responses. JoVE J. Vis. Exp. e59309. https://doi.org/10.3791/59309

2) **Tan, J.L**., Perera, T., McGinley, J.L., Yohanandan, S.A.C., Brown, P., Thevathasan, W., 2018. Neurophysiological analysis of the clinical pull test. J. Neurophysiol. https://doi.org/10.1152/jn.00789.2017

A separate publication related to Study 4 describing postural control and the effects of PPN DBS in people with PD is included in Appendix 1.

1) Perera, T., **Tan, J.L.**, Cole, M.H., Yohanandan, S.A.C., Silberstein, P., Cook, R., Peppard, R., Aziz, T., Coyne, T., Brown, P., Silburn, P.A., Thevathasan, W., 2018. Balance control systems in Parkinson's disease and the impact of pedunculopontine area stimulation. Brain 141, 3009–3022. https://doi.org/10.1093/brain/awy216

The overall structure of this thesis is summarised by the concept map in Figure 1.1, followed by an outline of the individual chapters.

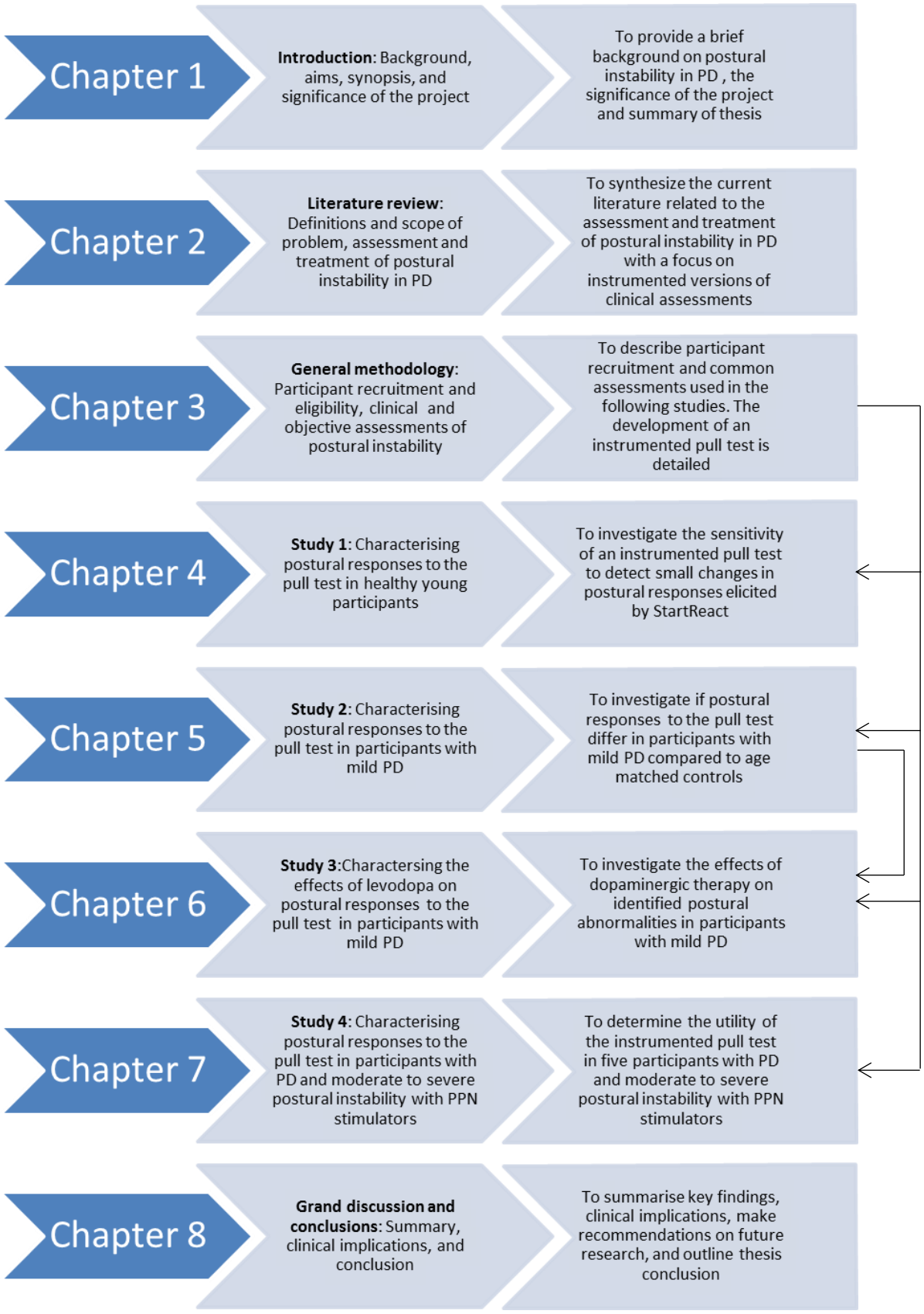

Figure 1.1: Concept map of the thesis structure

Chapter 1 is an overview of the thesis and introduction to the problem. It provides the background, aims, synopsis and significance of the thesis.

Chapter 2 provides a narrative review of the literature relevant to the thesis and is organised in three sections. Firstly, postural instability in PD is discussed, including definitions, pathophysiology and impact. Secondly, clinical and laboratory based assessments of postural instability (dynamic posturography) in PD are synthesized with a focus on reactive postural responses and the need to develop an instrumented pull test. Thirdly, a review of the literature relating to the advantages of dynamic posturography is undertaken, with a focus on the potential use of an instrumented pull test. This chapter identifies the shortcomings of current assessments of postural instability to quantify postural responses in PD. Findings from this chapter were used to inform the development of the pull test, and the four studies that comprise the research undertaken for this thesis.

Chapter 3 presents the general methods for participant recruitment, eligibility and common assessments used in the four studies undertaken in this thesis. This includes the use of a clinical balance assessment, the Unified Parkinson's disease rating scale (UPDRS), and an objective assessment, an instrumented pull test. The development of the instrumented pull test and protocol is detailed. Postural responses in the trunk and step are measured using 3D motion tracking sensors. As in clinical practice, the perturbation was delivered manually by an examiner. To deliver the pull, we employed a rope attached to a harness with a force gauge to record the force of each pull.

Chapter 4 presents a cross sectional study (Study 1) characterising postural responses to the instrumented pull test in healthy young participants. In this study of 33 participants, pulls were manually administered, with trunk and step responses measured using motion tracking. The capability of the instrumented pull test system to detect small changes in postural responses was evaluated using StartReact effects, where an intended movement is released early by a startling stimulus. Postural responses in the trunk and step were evaluated in 35 trials. Findings from Study 1 demonstrate the instrumented pull test was able to detect the speeding of truncal responses to a loud auditory stimulus (StartReact effects) and discriminate postural responses in the first trial from subsequent, habituated trials. Examiner pull force significantly affected the postural response, particularly the size of stepping. The

instrumented pull test could present an alternative assessment tool to the clinical pull test to quantify postural instability in patients with PD for clinical research.

Chapter 5 presents the methods and results of a cross sectional study (Study 2) characterising postural responses to the instrumented pull test in participants with mild PD (no clinically demonstrable postural instability). Findings were compared with age matched controls. In this study, postural responses from 18 participants with PD off levodopa, and 11 controls were assessed using the instrumented pull test. First and subsequent trial postural responses were compared to evaluate if differences were present in trunk and step responses between patients and controls. Findings from Study 2 demonstrate subclinical abnormalities in trunk and step responses are present in people with mild PD in first and subsequent trials compared to healthy controls.

Chapter 6 presents the methods and results of a cross sectional study (Study 3) characterising the effects of levodopa on postural responses elicited by the instrumented pull test in patients with mild PD. Patients and controls comprised the same cohort as Chapter 5. Findings from Study 3 demonstrate that levodopa did not restore trunk and step responses in people with mild PD to that of controls.

Chapter 7 presents the methods and results of a cross sectional study (Study 4) investigating the utility of an instrumented pull test to characterise postural responses in people with PD and moderate to severe postural instability implanted with PPN stimulators. Five participants were assessed off and on stimulation to evaluate the effects of PPN DBS on postural responses using an instrumented pull test. Two clinical tests, the UPDRS III sub score comprising items 27 to 30 (chair rise, posture, gait and pull test) and Mini-BESTest were further used to evaluate postural responses. Findings from Study 4 suggest the instrumented pull test is able to quantify postural responses with greater sensitivity compared to the clinical pull test. However, the feasibility of this technique in a cohort experiencing moderate to severe postural instability is questionable due to small sample sizes and multiple instrumented pull test trials where participants required catching by the assessor. Alternative measures of clinical assessments such as the Mini-BESTest may present a more practical method to quantify postural responses in patients with moderate to severe postural instability.

Chapter 8 integrates the findings of the previous studies and presents the contribution of this thesis to knowledge in the area of assessment and treatment of postural instability in people

with PD. The major strengths and limitations and clinical implications are summarised, and directions for future research are discussed.

1.4 Significance of the thesis

Postural instability is a common and severely disabling symptom for people with PD. It is a significant contributor to falls and fractures, resulting in devastating consequences (Kim et al., 2013; Sleeman et al., 2016). Targeted strategies to prevent falls are required, but this calls for an improved understanding of the mechanisms underlying postural instability. The assessment of postural instability is commonly assessed using the pull test in the clinical setting where an examiner grades the corrective postural response following a backward pull at the patient's shoulders (Fahn et al., 1987). However variabilities with test administration and interpretation can confound outcomes (Nonnekes et al., 2015; Visser et al., 2003). Laboratory measures of postural instability provide an objective method to assess postural instability in people with PD (Visser et al., 2008b).

This thesis investigates the use of an instrumented version of the clinical pull test to precisely quantify postural responses in people with PD. There is limited knowledge of postural responses in people with PD, particularly in mild disease when balance remains intact and falls are not reported. The instrumented pull test may provide new and important information regarding the characterisation of postural responses in people with PD and the effects of therapies on postural responses. Instrumentation also allows exploration of examiner and patient variables (e.g. examiner pull force, or participant height and weight) that may influence pull test responses in people with PD. Findings from this thesis may be used to inform clinicians of changes that occur in postural responses in people with mild PD. It is critical for clinicians to understand changes in postural instability that occur in people with PD so that treatments can be implemented that may reduce the risk of falls.

CHAPTER 2. LITERATURE REVIEW: POSTURAL INSTABILITY IN PEOPLE WITH PARKINSON'S DISEASE

2.1 Overview

Postural instability is a major contributor to falls and diminished quality of life in people with Parkinson's disease (PD). This chapter will provide a narrative review of the literature relevant to the assessment and treatment of postural instability in people with PD. The chapter firstly defines postural reflexes and reactive postural control, and outlines the pathophysiology underlying abnormalities of reactive postural responses in people with PD. Secondly, literature pertaining to the use of laboratory based techniques of dynamic posturography to capture early abnormalities in postural responses, monitor postural instability, and effects of therapy in people with PD are detailed. Thirdly, clinical, laboratory, and instrumented measures used to assess postural instability in people with PD are described, with a focus on the emerging development of instrumented clinical tests of postural instability.

2.1.1 Definitions of balance and postural instability

Balance is fundamental to perform daily activities such as standing and walking. It represents the ability to maintain the body's centre of mass relative to the base of support, and is crucial in standing to prevent a fall (Pollock et al., 2000). Postural equilibrium is achieved when the centre of mass is controlled over the base of support during static or dynamic activities (Horak, 2006). Postural control, or equilibrium can be reactive - in response to an externally generated perturbation displacing the centre of mass, or proactive – in response to an internally generated movement of the body (Horak et al., 1997). During dynamic activities, reactive postural control can be defined as the maintenance of upright body against external forces displacing the centre of mass (Horak et al., 1997; Kim et al., 2013).

Impairment in balance that compromises the ability to maintain or change posture during tasks of static or dynamic activities is termed 'postural instability' (Kim et al., 2013). For the purposes of this thesis, postural instability is described within the context of a dynamic task comprising a challenge to balance such as an externally generated perturbation. It is also acknowledged other activities including gait, comprise an aspect of dynamic balance that is not detailed within this literature review (Horak, 2006).

Postural equilibrium is achieved through the interaction of multiple sensorimotor strategies to move the centre of mass over the base of support (Horak, 2006). Feedback from the visual, proprioceptive, and vestibular systems plays a significant role. Reactive postural responses are subsequently shaped across a continuum modulated by cortical pathways based on experience, attention, voluntary intention, environmental constraints and predictability of the perturbation (Jacobs and Horak, 2007). Maintenance of postural equilibrium is modulated by the central nervous system to rapidly detect destabilising forces and initiate appropriate muscle synergies (Nashner, 1983, 1977). These automatic motor programs are thought to arise from the structures in the brain stem (Jacobs and Horak, 2007), most possibly in neurons of the pontomedullary reticular formation (Schepens et al., 2008; Yeomans and Frankland, 1995).

Several movement strategies aid in restoring postural equilibrium. A centre of mass movement within the base of support evokes a "feet-in-place" ankle or hip response whereas stepping involves unloading and loading of a lower limb to move the base of support under the falling centre of mass (Horak et al., 1997; Winter, 1995) (Figure 2.1). The ankle strategy is used to control anterior-posterior sway in quiet stance or in response to small forces perturbing balance. Hip and stepping strategies are used in response to large and fast perturbations where the ankle strategy is insufficient to maintain the centre of mass within the base of support (Horak and Kuo, 2000).

Source: Horak, F., Kuo, A., 2000. Postural Adaptation for Altered Environments, Tasks, and Intentions, in: Winters, J.M., Crago, P.E. (Eds.), Biomechanics and Neural Control of Posture and Movement. Springer New York, New York, NY, pp. 269

Figure 2.1: Movement strategies used to maintain postural equilibrium in standing during an external perturbation.

A subject may use a continuum of strategies during a postural perturbation task depending on prior experience and task conditions. Adapted with permission from Springer-Verlag New York, Inc.

A perturbation is a sudden change in condition resulting in displacement of body equilibrium (Horak et al., 1997). These could comprise sensory (Smith, 2018) (e.g. vestibular stimulation), visual (Brown et al., 2006) (e.g. removal of visual feedback) and somatosensory (Vaugoyeau et al., 2011) (e.g. tendon vibration) components that induce sensations of movement, or larger perturbations that involve mechanical displacement of body segments. In the laboratory, mechanical perturbations can be applied to any segment of the body, but the most common method to challenge a person's balance involves motorised platforms that induce a displacement beneath the feet similar to slip-like or tilting movement (Figure 2.2) (Horak et al., 1997; Nonnekes et al., 2013; Visser et al., 2008b). A backward perturbation is reported to be the most unstable of orientations in healthy individuals as well as people with PD (Horak et al., 2005; Oude Nijhuis et al., 2009). This appears to be due to the biomechanical difficulty in exerting a dorsiflexion torque around the ankles compared to producing a plantar flexion movement (Winter et al., 1996).

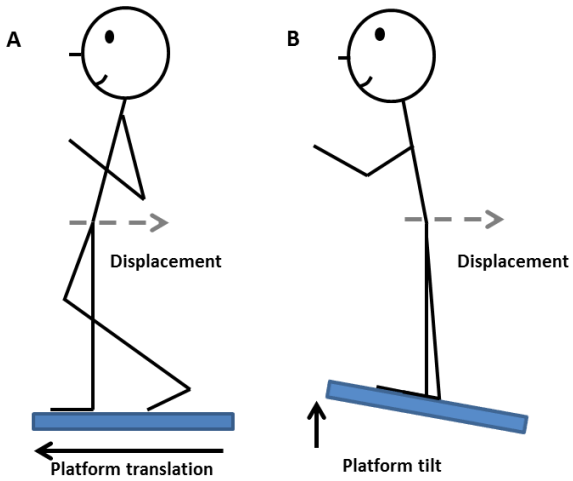

Figure 2.2: Schematic of types of platform perturbations inducing a backward displacement.
A backward displacement of centre of mass can be elicited by (A) forward translation or (B) upward tilting (B) of a motorised platform.

Postural reflexes act to maintain balance and upright stance in response to perturbations (Shemmell, 2015). Postural reflexes comprise the earliest reaction to a perturbation, with short, medium and long latency reflexes contributing as the first line of defence in balance recovery to prevent a fall (Horak, 2006). These reflexes are triggered involuntarily by afferent proprioceptive input to produce well-coordinated patterns of muscle activation (Brown et al., 2006; Dietz et al., 1988; Horak, 2006; Rinalduzzi et al., 2015). In particular, medium and long latency reflexes, with onset latencies between 80 to 100 ms, are suggested to be advantageous to maintain balance against perturbations occurring in real life (Bloem

1992). Impaired postural reflexes are a significant contributor to abnormalities in reactive postural control observed in people with PD (Kim et al., 2013).

2.1.2 Mechanisms of postural instability in PD

Abnormalities in reactive postural responses have largely been understood from the use of dynamic posturography (Nonnekes et al., 2013). Deficits of reactive postural control comprise one of the four domains that contribute to balance dysfunction in people with PD (Schoneburg et al., 2013). Other domains contributing to postural impairments are not discussed within this review.

There are marked difficulties in scaling the size of the postural response to an external perturbation. For example, healthy participants will adapt postural responses to account for the largest perturbation in a forewarned task involving small and large platform translations. In contrast, people with moderate PD select the same sized postural response regardless of perturbation magnitude (Beckley et al., 1993). There is poor adaptation of reflexes, with inability to modulate the response to changes to postural tasks - termed "postural inflexibility" (Bloem et al., 1992b; Chong et al., 2000; Horak et al., 1992).

In PD, postural responses are abnormally activated in people of moderate to severe disease severity (HY 2.5 - 4) (Carpenter et al., 2004; Dimitrova et al., 2004; Horak et al., 2005). There is increased responses in medium latency stretch reflexes and decreased responses in stabilising long latency reflexes (Beckley et al., 1991; Bloem et al., 1992a). Abnormally enhanced medium latency reflex amplitudes are observed in multiple muscles including the trunk, hip, arms in people with PD compared to healthy controls following multidirectional perturbations (Bloem et al., 1996, 1992a; Dietz et al., 1988). The increased gain in medium latency reflex amplitudes may contribute directly to impairment of postural responses in PD by resulting in a greater contraction in antagonist muscles prior to balance correction. Excessive afferent input to the central nervous system may also account for the unnecessarily large and disproportionate balance responses observed in PD resulting in greater instability (Bloem et al., 1996; Horak et al., 1996).

It is hypothesized that dysfunctional basal ganglia pathways and dopaminergic deficits may underlie impaired postural reflexes in PD. In people with PD, the enhanced medium latency reflex amplitudes in the stretched gastrocnemius muscle observed during platform rotations

are proposed to be related to reduced inhibitory output of the nigrostratial dopaminergic circuit (Scholz et al., 1987). In patients with 1-methyl-4-phenyl-I,2,3,6-tetrahydropyridine (MPTP) induced parkinsonism, similar increases in medium latency reflexes were found, with MPTP believed to selectively damage dopaminergic neurons in the substantia nigra (Bloem et al., 1990). In addition, reduced long latency lower limb muscle reflex responses in advanced PD is suggested to reflect basal ganglia dysfunction resulting in impaired selection and initiation of motor planning (Diener et al., 1987).

Increased rigidity has been found in both trunk and lower limb muscles during a postural perturbation in people with moderate to severe PD (Bloem et al., 1996; Carpenter et al., 2004; Horak et al., 1996). Increased muscle rigidity can lead to biomechanical impairments impeding the ability to perform corrective postural reactions effectively (Park et al., 2015). For example, people with PD tend to 'fall like a log' later in disease, which may be partly due to truncal rigidity (Carpenter et al., 2004). Furthermore, there are poor compensatory movements in the arms and legs, providing little functional protection. Where healthy participants tend to extend their arms to an external perturbation, people with PD often bring their arms closer to their bodies (Carpenter et al., 2004). Lesions of non-dopaminergic systems can also play a role in the pathophysiology of postural instability in PD, particularly in more advanced disease (Dimitrova et al., 2004; Horak et al., 1996). Using platform perturbations, studies have demonstrated levodopa has limited effects on axial symptoms such as postural instability, compared to appendicular symptoms (Bloem et al., 1996; Horak et al., 1996; Kam et al., 2014; King et al., 2010; King and Horak, 2008; Wright et al., 2007). These studies have conventionally focussed on patients who already demonstrate abnormalities in postural responses (Bloem et al., 1998; Horak et al., 2005; Kam et al., 2014; King et al., 2010; King and Horak, 2008). While some perturbation studies allude to aspects of postural responses that may be levodopa refractory in people with mild PD, the characterisation of reactive postural responses remain underexplored in this population (Ganesan et al., 2010; Lee et al., 2013; McVey et al., 2009) (Detailed in section 2.3.1.)

2.2 Measurement tools to quantify postural instability

A variety of clinical measures are available to assess postural instability in PD (Bloem et al., 2016a). For the purposes of this review, we focus specifically on the pull test which is commonly employed in clinical setting and assesses the reactive postural response. The pull test exists in various forms (warned versus un-warned, pull versus push and release), with the

aim of assessing a reactive postural response and corrective steps (Hunt and Sethi, 2006; Jacobs et al., 2006; Nonnekes et al., 2015; Visser et al., 2003). The push and release test is acknowledged as a recently developed alternative clinical test of postural stability in PD, but will not be discussed in the detail as methods of administration are different from the pull test (Smith et al., 2016). In the push and release test, corrective stepping is graded following the sudden release of the participant, as they lean backwards into the examiner's hands at shoulder level (Jacobs et al., 2006). This is in contrast to the pull test where corrective stepping is assessed following a backward pull on the participants' shoulders by an examiner. The advantages and limitations of the clinical pull test are outlined. The development of instrumented versions of clinical tests is discussed with a focus on the instrumentation of the clinical pull test.

2.2.1 The clinical pull test

The clinical pull test is commonly used in clinical practice to assess reactive postural responses in patients with movement disorders, particularly PD (Hunt and Sethi, 2006). The most well-known variant is the pull test described by item 30 of the Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn et al., 1987) - a primary rating scale in studies of PD. In this test, an examiner briskly pulls the patient backward at the shoulders and visually grades the response (Fahn et al., 1987; Hunt and Sethi, 2006; Visser et al., 2003). Corrective postural responses are graded using a five point integer scale (Fahn et al., 1987) (Table 2.1). The presence of postural instability according to the clinical pull test assessment marks a transition to Stage 3 of the Hoehn and Yahr (HY) scale, which describes disease staging and progression in PD (Hoehn and Yahr, 1967).

Despite the widespread use of the clinical pull test, outcomes can vary due to test administration and interpretation. The integer based scoring (score/4) is subjective and may not be sensitive to detect small but important changes of balance, particularly in mild disease (Mancini et al., 2012; McVey et al., 2009; Nonnekes et al., 2015; Visser et al., 2003). Variabilities in pull force by the examiner, positioning of the patient, and weight of the examiner and patient may contribute to the moderate intra and inter-rater reliability of the pull test (Bloem et al., 1998; Nonnekes et al., 2015; Visser et al., 2003). These variabilities may partly explain why the clinical pull test fails to accurately predict future falls (Bloem et al., 2001; Munhoz and Teive, 2014). Furthermore, rating of corrective step count only

provides a gross approximation of balance responses, with little elucidation of underlying balance impairments.

Table 2.1: Scoring of postural instability as defined by the UPDRS item 30

	Postural instability
0	Normal.
1	Retropulsion, but recovers unaided.
2	Absence of postural response; would fall if not caught by examiner.
3	Very unstable, tends to lose balance spontaneously.
4	Unable to stand without assistance

There remains debate on how the clinical pull test should be best performed and interpreted (Hunt and Sethi, 2006; Munhoz et al., 2004). According to revised guidelines produced by the International Movement Disorders Society (MDS), the MDS-UPDRS proposes that the patient should be fore-warned about the impending challenge, with an initial practice trial before a second trial is formally assessed (Goetz et al., 2008). In some studies, the average response from repeated pull test trials has been reported (Bloem et al., 2001; Nanhoe-Mahabier et al., 2012). However, others claim that an unexpected pull, performed only once, is most clinically meaningful (Bloem et al., 2001; Visser et al., 2003). Regardless of the method of administration, the clinical pull test fails to predict future falls in people with PD (Bloem et al., 2001). This may not only be due to inherent shortcomings of the clinical pull test, but the multi-factorial nature of falls, requiring multiple tests to address different aspects contributing to falls (Lamont et al., 2017; Wood et al., 2002).

2.2.2 Posturography

The most significant insights into identifying abnormalities in postural control have been gained from posturography. Posturography involves the evaluation of postural sway under differing conditions (Visser et al., 2008b). Posturography comprises two broad techniques; static posturography where posture is measured in quiet standing, or dynamic posturography, when perturbations of upright stance are induced. Utilising force plate technology, postural sway can be measured by analysing self-initiated fluctuations of centre of pressure within the base of support in quiet standing (Schoneburg et al., 2013). A range of variables of postural sway such as sway area, velocity and frequency is derived. With dynamic posturography, reactive postural responses are quantified to experimentally induced balance perturbations,

most commonly using movable platforms. Centre of pressure variables, and additional kinematic parameters from movement of body segments, and muscle activity from electromyography are then measured in response to balance challenges.

2.2.2.1 Static posturography

While postural instability is associated with advanced PD, growing evidence suggests postural sway is abnormal in the mild stages (HY < 2) (Beuter et al., 2008; Chastan et al., 2008; Nantel et al., 2012). Though some have reported no significant difference in sway variables in quiet standing between people with PD and controls, (Valkovič et al., 2008; Waterston et al., 1993), a number of studies report an increase in sway area, particularly in the mediolateral direction in people with PD (Chastan et al., 2008; Ebersbach and Gunkel, 2011; Mancini et al., 2012). These sway alterations are present at diagnosis and are not caused by medication (Chastan et al., 2008; Mancini et al., 2012). Abnormalities in sway (e.g. increased mediolateral jerk and decreased frequency) have been suggested as a measure to monitor progression of postural instability from time of diagnosis, before medication is initiated (Mancini et al., 2012). However, measures of postural sway have shown poor reliability in people with PD, particularly when dyskinesias are present (Paul et al., 2012). Furthermore, markers of sway abnormalities which reliably predict falls remain unclear. At present, static sway measures do not discriminate between PD fallers and non-fallers (Johnson et al., 2013) nor correlate to falls history in the previous year (Blaszczyk et al., 2007). This is not surprising as measurements in quiet stance do not capture deficits associated with reactive postural adjustments (Ebersbach and Gunkel, 2011).

2.2.2.2 Dynamic posturography

In the laboratory, conventional techniques of dynamic posturography include motorised platform translations or rotations beneath the feet. These techniques allow precise control of the intensity and direction of perturbation whilst measuring kinetic, kinematic and neurophysiological endpoints (Campbell, 2012; Campbell et al., 2013; Nonnekes et al., 2014). Laboratory based assessments therefore have greater sensitivity as measures to quantify changes in postural responses (e.g. step length), and capture different components of postural control (e.g. motor vs sensory) in comparison to clinical assessments.

Dynamic posturography may offer a more sensitive method of predicting falls in PD. A number of studies have reported multi-directional compensatory stepping impairments in

people with moderate PD (Dimitrova et al., 2004; King et al., 2010; King and Horak, 2008). These stepping deficits could represent a potential marker to identify patients with postural instability at greater risk of falls. Deficits in preparation prior to a backward step have been observed in response to a backward waist pull in mild disease before postural instability is clinically evident (HY Stage 2). These changes involve increased preparatory weight shift duration, and increased posterior shift of the centre of pressure in people with mild PD compared to controls (McVey et al., 2009). Later in disease, increased weight shift time was similarly observed in a separate cohort of people with PD of increased disease severity (HY Stage 3) using the same backward waist pull paradigm (McVey et al., 2013). This suggests weight shift time may be a marker of early changes to postural instability in people with mild PD. Although dynamic posturography is widely used to precisely quantify postural abnormalities in people with PD, there remains a lack of proven markers that can identify people with PD at greater risk of falls or monitor changes in postural responses over time (Visser et al., 2008b). One issue may be that markers of postural instability need to be present early in disease course, and be specific to postural instability (McVey et al., 2013). Another issue may be the many variations in methodologies (e.g. platform translations versus platform tilts) and outcome measures (e.g. whole body displacement measured using motion sensors, or muscle activity measured using electromyography) that can be extracted from dynamic posturography, making the outcomes of studies in people with PD difficult to interpret.

The inherent setup of motorised platforms can also confound corrective postural responses. Perturbations often comprise a quick acceleration and deceleration due to the short trajectories of platform movement. Individual muscles responses can therefore be blended, and difficult to distinguish (Carpenter et al., 2005; McIlroy and Maki, 1994). During the deceleration phase of platform movement, forces applied may also influence postural responses and aid participants' recovery of balance (Nonnekes et al., 2013). In other studies of platform rotations, postural responses are confined to a fixed base of support that prevent stepping (Bloem et al., 1996; Bohnen and Cham, 2006; Carpenter et al., 2004; Horak et al., 1992; Schieppati and Nardone, 1991). However, this does not reflect postural responses in real life, which often includes stepping (Horak, 2006).

To overcome these limitations, sophisticated platforms that translate over greater distances allow quantification of postural responses that do not restrain corrective stepping (Nonnekes et al., 2013). A shortcoming is that these setups require a dedicated space with customised

equipment such as 3D motion capture that can be relatively expensive (Di Giulio et al., 2016; Nonnekes et al., 2013). Accordingly, the use of dynamic posturography is restricted to specialised laboratories.

2.3 The utility of measurement tools for postural instability

The assessment of postural responses in people with PD is important as postural instability is associated with increased falls and diminished quality of life particularly in later disease. Clinical and posturographic studies have contributed significantly to the understanding of postural instability in PD. Studies utilising clinical and laboratory measures of balance have been used to detect abnormalities in postural responses, objectively quantify the outcomes of therapy, and to understand the underlying pathophysiology of postural instability in PD. These studies in people with PD conventionally recruit participants where abnormalities in postural responses are clinically evident (i.e. HY > 2) (Bloem et al., 1996; Dimitrova et al., 2004; Jacobs and Horak, 2006; Kam et al., 2014; King and Horak, 2008). The use of posturography has been proposed as a method to monitor the progression of postural instability through disease course, however current methodologies are limited by several challenges.

2.3.1 Detection of postural abnormalities in PD

Impairment of postural responses is often not apparent in mild PD. When assessed by the clinical pull test, patients typically regain balance to the backward pull within two steps, which is scored as normal. Yet abnormalities in postural control have been identified in people with PD using dynamic posturography (Ganesan et al., 2010; McVey et al., 2009).

Only five studies have investigated reactive postural responses in mild PD (HY $\leq$ 2) (Chastan et al., 2008; Ganesan et al., 2010; Halmi et al., 2019; Lee et al., 2013; McVey et al., 2009). All studies assessed participants with PD in the on medication state compared to controls except one, where participants were on limited or no medication (Chastan et al., 2008). Postural changes observed were subclinical. It did not affect overall step responses assessed by the clinical pull test (Ganesan et al., 2010) or kinematic measures (McVey et al., 2009). Findings were difficult to synthesize as studies employed different methods of perturbation and measures to quantify postural responses. With backward platform tilts, people with PD on medication demonstrated decreased limits of stability and increased centre of mass displacement compared to controls (Ganesan et al., 2010). Using backward waist pulls,

alterations of postural responses in people with PD were concentrated in movement preparation and increased weight shift prior to stepping when compared to controls (McVey et al., 2009). When performing a task of passing a weighted ball around the body, people with PD demonstrated increased centre of mass displacement and sway velocity compared to controls (Halmi et al., 2019). To backward platform tilts, no difference in sway area or path length were demonstrated in people with PD compared to controls (Chastan et al., 2008). (Chastan et al., 2008).

Using dynamic posturography, subclinical changes in postural control could be used to identify signs of postural instability in people with mild PD. Determining variables of balance recovery that are sensitive and specific to people with PD could potentially be used as biomarkers to identify people at greater risk of falls earlier in disease (McVey et al., 2009). Diagnosis of falls risk and consistency of clinical assessments of balance are imperative for optimal management of people with PD (Kerr et al., 2010; Latt et al., 2009; McVey et al., 2013; Nonnekes et al., 2013). However, there remains a lack of established markers for postural instability in people with PD. One reason may be the lack of standardisation of measurement methods and outcomes in studies of postural perturbations. Furthermore, methods utilised do not characterise postural responses in a similar manner as assessed by the clinical pull test in routine assessment.

2.3.2 Evaluating effects of therapy on postural instability

A main goal of medical therapy in people with PD is to provide symptomatic control through pharmacological and non-pharmacological interventions (e.g. deep brain stimulation) (DBS). Dopamine replacement therapy remains the mainstay of drug treatment for people with PD, of which levodopa is the best established. For the purposes of this review, the effects of levodopa and DBS on postural instability in people with PD are detailed.

2.3.2.1 Effects of levodopa

The loss of dopamine producing neurons in the substantia nigra contributes significantly to the pathological changes in people with PD (Lees et al., 2009). As motor impairments are mostly related to the loss of dopamine neurons, dopamine replacement therapy is commonly used to increase the availability of dopamine to remaining neurons in the basal ganglia. Dopaminergic medication includes levodopa and dopamine agonists including ergot and non-

ergot derivatives (Horstink et al., 2006). Of these, levodopa is the most well-established and effective, with treatment associated with improved quality of life and improved mortality (Horstink et al., 2006; Lang and Lees, 2002; Rascol et al., 2002; Sethi, 2008).

According to clinical guidelines, levodopa is indicated for the symptomatic treatment for people with early PD with recommendations to keep the effective dose as low as possible to reduce the development of motor complications (Horstink et al., 2006; National Collaborating Centre for Chronic Conditions (UK), 2006). After 4 to 6 years of treatment with levodopa, patients may begin to experience motor complications with fluctuations in motor performance (Fahn et al., 2004; Pedrosa and Timmermann, 2013). This refers to the alteration between "off" periods, where the patient has a poor response to medication and "on" periods where the patient experiences a good response to medication, and where dyskinesias may also occur (Goetz et al., 2008).

The effects of levodopa on postural instability are unclear. Studies of platform perturbations (Bloem et al., 1996; Carpenter et al., 2004; Horak et al., 1996; Kam et al., 2014; Rocchi et al., 2002) or truncal (Di Giulio et al., 2016; Foreman et al., 2012) typically explore postural responses in people with PD using heterogeneous samples, with postural abnormalities ranging from HY stage 1.5 to 4. In people with moderate PD, functional balance tests such as the Mini-BESTest and Berg Balance Scale report benefits of levodopa on balance (McNeely et al., 2012; Nova et al., 2004). Impaired responses, when present, are commonly observed in the off medication condition and improve with levodopa. However, laboratory measures demonstrate that some aspects of postural responses do not appear to improve. One study found improved performance on the Functional Gait Assessment, with no difference in stepping responses to a manual backward pull on medication in people with moderate PD (Foreman et al., 2012). Such discrepancies may arise due to the greater sensitivity of laboratory measures, or the effect of levodopa in other symptoms of PD such as bradykinesia or rigidity (Mancini et al., 2008; McNeely et al., 2012).

Numerous studies demonstrate the lack of effect of levodopa on postural responses in people with PD of increased disease severity (HY > 2) (Bloem et al., 1996; Carpenter et al., 2004; Kam et al., 2014; King et al., 2010; King and Horak, 2008). Using platform perturbations, deficits in stepping are demonstrated in people with moderate PD, with under-scaling of responses in all directions (Kam et al., 2014; King et al., 2010; King and Horak, 2008).

Similar findings have been observed in studies of truncal perturbations in people with PD ranging in disease severity from HY stages 2 to 4 (Di Giulio et al., 2016; Foreman et al., 2012). Using motors and pulleys, people with PD take multiple and abnormally small backward recovery steps to a backward perturbation with no differences between off and on medication compared to healthy controls (Di Giulio et al., 2016). Another study utilising manual backward pulls found no improvements in spatiotemporal variables of stepping in people with PD off and on levodopa (Foreman et al., 2012). Furthermore, administration of levodopa has been demonstrated to worsen postural responses in some instances. In people with moderate PD, levodopa not only reduced tonic activity of leg muscles in quiet stance but further reduced reactive forces opposing a platform perturbation. These changes resulted in less resistance to an external perturbation and greater instability with faster centre of mass displacements (Horak et al., 1996). Overall, axial symptoms such as postural instability are known to be less responsive compared to other appendicular symptoms such as rigidity and bradykinesia (Steiger et al., 1996) which may indicate separate neural circuits (Wright et al., 2007). Together, this could be taken to mean that postural deficits are caused by non-dopaminergic mechanisms, particularly in advanced stages of PD (Bohnen et al., 2009; Di Giulio et al., 2016; Müller et al., 2013).

In people with mild PD (HY $\leq$ 2), abnormalities of postural responses also appear to be levodopa refractory (Ganesan et al., 2010; Lee et al., 2013; McVey et al., 2009). Changes are subclinical, involving preparation of the initial step following a backward perturbation (McVey et al., 2009) or decreased limits of stability to platform tilts (Ganesan et al., 2010). To date, these studies have only explored the effects of levodopa in people with PD in the on medication state compared to controls (detailed in Section 2.3.1). Accordingly, the overall therapeutic efficacy of levodopa on postural responses in people with mild PD remains to be explored.

2.3.2.2 Effects of deep brain stimulation

Deep brain stimulation is an established therapy, commonly used in the mid to late stages of PD (Ashkan et al., 2017; Benabid, 2003; Bronstein et al., 2011; Deuschl et al., 2006), and more recently, also in mild disease at the onset of motor fluctuations (Schuepbach et al., 2013). It involves the implantation of electrodes into specific brain targets, delivering electrical stimulation from a subcutaneous battery to the electrode tips, modulating abnormal

brain activity. Conventional targets, such as the subthalamic nucleus (STN) and globus pallidus pars interna (GPi), are well recognised for treating motor fluctuations and dopaminergic medication responsive signs of tremor, rigidity and bradykinesia (Castrioto and Moro, 2013; Deuschl et al., 2006; Kleiner-Fisman et al., 2006; Weaver et al., 2009).

However, conventional DBS targets have not proven to be effective to alleviate postural instability in the long term, and may even worsen symptoms involving gait and posture (Bloem et al., 1996; Bonnet et al., 1987; Fasano et al., 2015; Horak and Nashner, 1986; St George et al., 2010; Vu et al., 2012). In one study, reactive postural responses to a backward perturbation were suggested to worsen, with smaller muscle burst amplitudes in tibialis anterior measured using electromyography at six months following STN DBS compared to pre surgery (St George et al., 2012). A longitudinal study found benefits to posture were not sustained compared to other segmental motor symptoms at five year follow up (St George et al., 2010). Although these outcomes may reflect underlying disease progression, postural deficits, particularly later in PD are suggested to involve extension of pathological processes into non-dopaminergic systems (Bohnen et al., 2009; Di Giulio et al., 2016; Kumar et al., 1998; Müller et al., 2013).

Effects of PPN DBS

To address these shortcomings, DBS of a new and alternative target, the pendunculopontine nucleus (PPN) was developed as a potential therapy for treatment resistant axial symptoms of gait and posture (Castrioto and Moro, 2013; Fasano et al., 2015). Cell loss in the PPN has been implicated in PD (Rinne et al., 2008), and associated with worsened balance, decreased attention to task, and increased falls (Bohnen et al., 2009). The PPN is considered a critical structure in control of balance (Jenkinson et al., 2009; Rinne et al., 2008) with direct connections to cortical motor areas via the thalamus, basal ganglia, cerebellum and spinal cord (Gut and Winn, 2016; Takakusaki et al., 2016). In healthy individuals, the most important predictor of better balance responses was brainstem volume of the PPN region and the basal ganglia (Boisgontier et al., 2017). Accordingly, lesions of the PPN produce PD-like symptoms (Pahapill and Lozano, 2000), with loss of cholinergic neurons in the PPN linked to increasing severity of symptoms in PD (Zweig et al., 1989).

Although clinical studies (typically recruiting 10 participants or less), show improvements in gait freezing and falls following PPN DBS, the effects on postural instability remain unclear.

The small sample sizes of clinical studies may contribute to discrepancies in findings (Morita et al., 2014; Thevathasan et al., 2018). Fewer than 100 cases of patients with PPN DBS have been reported in the past 10 years (Thevathasan et al., 2018). Postural instability was initially thought to improve with PPN DBS (Plaha and Gill, 2005; Stefani et al., 2007), however, results since have demonstrated variable or no effect when assessed using clinical tests of balance (Ferraye et al., 2010; Moro et al., 2010; Plaha and Gill, 2005; Stefani et al., 2007; Welter et al., 2015).

Studies of PPN DBS have yet to explore postural responses to external perturbations in the laboratory. Previous work has commonly used the UPDRS to quantify postural responses, and utilise composite scores comprising both gait and posture items of the UPDRS (e.g. items 27 to 30 comprising chair rise, posture, gait and postural instability). These composite scores do not clearly differentiate outcomes of postural responses. The lack of sensitivity of clinical assessments such as the UPDRS may also hinder detection of small changes to postural responses modulated by PPN DBS.

Using laboratory tests of balance with force plate measurement, three studies have demonstrated aspects of postural control that can be modulated by PPN DBS in quiet standing (Perera et al., 2018; Wilcox et al., 2011; Yousif et al., 2016). Changes were proposed to improve static postural control through increased somatosensory integration (Yousif et al., 2016), decreased mediolateral sway (Wilcox et al., 2011) and increased feedback control derived from models of postural sway (Perera et al., 2018). This may yield insights into reactive postural responses which may be modulated by this therapy.

2.3.3 Monitoring progression of postural instability

Static and dynamic variables of postural control have been proposed as markers to assess subclinical changes in postural control and monitor progression over time in people with PD (Beuter et al., 2008; Chastan et al., 2008; Ganesan et al., 2010; Mancini et al., 2011; McVey et al., 2013, 2009). However, no study to date has comprehensively monitored the progression of postural instability in people with PD over time in the laboratory. This may partly be due to the lack of proven objective markers of postural instability that signal the transition from non-faller to faller in people with PD and the cost of long term longitudinal studies. To be useful, potential markers of postural instability need to be present prior clinical assessment, and specific to postural instability (McVey et al., 2013). For example, when

postural responses to a backward pull were assessed separately in two different cohorts of patients, one with mild PD (McVey et al., 2009) and another with moderate PD (McVey et al., 2013), weight shift time prior to the first step was increased in both groups. Weight shift time may be a potential marker of postural instability; however, its specificity to postural instability has not been evaluated. More recently, development of body–worn sensors have facilitated objective monitoring of postural instability in people with PD in the community over time (Horak et al., 2015). These techniques may provide an alternative avenue to discover markers of postural instability in people with PD in the future.

2.4 Instrumentation of clinical tests of balance

Instrumented tests of postural responses warrant further exploration and development to consider whether they have potential to be used as a substitute for clinical scales in people with PD. However, extensive further studies of reliability and validity are required before they can be utilised as new screening tools in the clinic. These methods not only quantify postural responses more precisely compared to observational clinical rating scales, but also provide insights into variability and reliability influencing test administration and response (Smith et al., 2016). Initial attempts are currently being made to instrument the pull test for use in clinical populations, with two variants described – the clinical pull test, as performed by an examiner performing a brisk backward tug at the patient's shoulders, and the push and release test (Fahn et al., 1987; Jacobs et al., 2006). Outcome measures typically capture whole body kinematics with video-based motion capture and patterns of muscle recruitment using EMG.

2.4.1 Quantification of 'top down' postural responses

While dynamic posturography has been useful to elucidate abnormalities of postural responses in PD, moving platforms quantify responses to bottom up perturbations, where the 'feet go from under you' (Horak et al., 1997). However, the pull test quantifies responses to the top down perturbation, where there is initial displacement of the upper body and response of the trunk (Azevedo et al., 2016; Colebatch et al., 2016; Di Giulio et al., 2016; Govender et al., 2015).

In young healthy participants, patterns of EMG responses that follow displacements at the level of the ankles are fundamentally different from posterior perturbations at shoulder level (Colebatch et al., 2016). When brisk perturbations are applied at the trunk, initial quadriceps

activity is elicited with co-contraction in tibialis anterior, and soleus and forward acceleration of the lower legs in a 'limbo' position (Colebatch et al., 2016). This is followed by a more prolonged activation in tibialis anterior and quadriceps. Forward truncal lean provides limited benefit, with minimal muscle activity in hamstrings, rectus abdominis, and paraspinal muscles. This is in contrast to platform perturbations, where responses in healthy young individuals show there is sequential distal to proximal activation of lower limb activity from tibialis anterior to quadriceps to hip abductors, with reciprocal activation of trunk muscles (Horak et al., 1997). Postural responses arising from the lower limbs are shaped by patterns of sensory, proprioceptive and vestibular input, that are not directly comparable to those produced by a top down response (Colebatch et al., 2016; Di Giulio et al., 2016). Differing sites of force application (i.e. perturbation under the feet with platform movement versus perturbation at truncal level) yield kinematic chain responses that inevitably prioritise lower limb responses over the trunk.

The quantification of postural response of the trunk has hitherto been limited by suitable objective measures. Unlike bottom up postural perturbations that can be standardised using computerised platform translations, top down perturbations have proven more difficult to administer and assess (Azevedo et al., 2016; Colebatch et al., 2016; Di Giulio et al., 2016; Govender et al., 2015). To stimulate top down reflexes, complex setups have been developed in the laboratory. These techniques include anterior and posterior shoulder perturbations by motors (Di Giulio et al., 2016), lateral shoulder perturbations using pendulums (Azevedo et al., 2016), backward waist pulls (McVey et al., 2013, 2009) and manual shoulder taps or pulls (Colebatch et al., 2016; Foreman et al., 2011; Govender et al., 2015; Graus et al., 2013).

Due to the difficulty in eliciting truncal perturbations, limited studies of top down perturbations exist in PD. In mild disease, patients demonstrated small alterations in movement preparation, and increased weight shift prior to backward stepping (McVey et al., 2009). In moderate to advanced PD, patients took multiple small and inefficient (< 50 mm) steps to regain balance (Di Giulio et al., 2016; McVey et al., 2013). Postural impairments increased as postural instability became more evident (McVey et al., 2013). However, no study of truncal perturbations has quantified both truncal and step responses to the clinical pull test. Most studies of truncal perturbations in PD prioritise responses of the legs as the primary outcome (Di Giulio et al., 2016; Foreman et al., 2012; McVey et al., 2013, 2009). Lower limb measures fail to capture the key role of the truncal response that contributes to

initial balance recovery. Only two studies have explored truncal responses in people with PD to a feet-in-place response (Azevedo et al., 2016; Di Giulio et al., 2016). These studies demonstrate internally generated forces to resist the perturbation were smaller in people with PD compared to controls, resulting in a greater centre of mass displacement in static standing.

Whether truncal abnormalities present in people with PD influence step responses during the clinical pull test remain unknown. A step response is commonly generated when the truncal response is insufficient to maintain balance during the clinical pull test (Horak, 2006). However, stepping can also occur well within limits of stability in healthy older fallers, and is triggered by other contextual factors such as fear of falling, which is common in later stages of PD (Maki and McIlroy, 1997; Pai et al., 1998).

Furthermore, confounders of postural responses have not been routinely accounted for in studies of top down perturbations. Variables such as pull force, or participant height and weight are proposed to contribute to postural responses during the pull test. Some studies have accounted for pull force by applying precise perturbations individualised to the participant's height or weight using motor, pulleys and pendulums. When using a calibrated weight drop (20% participant body weight), subtle postural abnormalities in weight shift and stepping were detected to a posterior waist pull in people with PD that had no clinically detectable postural instability (HY < 2) compared to age matched controls (McVey et al., 2009). In contrast, studies of manual backward shoulder pulls have not accounted for pull force (Adkin et al., 2005; Foreman et al., 2012). This shortcoming may account for the lack of change in postural responses observed. Only one study has attempted to characterise postural responses in people with PD according to the clinical pull test, employing a manual backward perturbation (Foreman et al., 2012). However, truncal responses were not measured, and no differences in spatiotemporal variables of stepping were found in the off and on levodopa condition. More recently, a wearable pull test has also been attempted, with postural responses captured from sensors attached around the chest and waist of healthy young participants (Andò et al., 2018). The use of this technique remains to be investigated in people with PD.

2.4.2 The instrumented pull test

To a top down perturbation, quantitative assessment of trunk responses in PD might be important for several reasons. Firstly, falls are common in people with PD to sudden truncal

movements, for example when turning or bending (Chou and Lee, 2013; Horak, 2006). Secondly, abnormalities in truncal responses are suggested to contribute to postural instability (Carpenter et al., 2004). In previous studies of platform perturbations, people with PD display decreased trunk mobility in the pitch and roll directions (Carpenter et al., 2004; Horak et al., 1996). These abnormalities are particularly evident in later stages of PD, where stooping, decreased truncal flexibility and reduced early reactive movements of the trunk and legs contribute to result in patients 'falling like a log' in response to a backward perturbation (Dimitrova et al., 2004; Horak et al., 2005; Jacobs et al., 2005).

Abnormalities in truncal responses have also been found in other tasks of gait and posture including sitting, standing, reaching and turning (Bridgewater and Sharpe, 1998; Schenkman et al., 2001; van der Burg et al., 2006) with increased axial rigidity, abnormal upper and lower body coordination and altered upper body kinaesthesia (Klockgether et al., 1995; Konczak et al., 2007; Maschke et al., 2003; Wright et al., 2010). For example, one study found people with PD demonstrated decreased accuracy and perception of axial rotation with hip twisting (Wright et al., 2010). Deficits in upper body kinaesthesia may result in postural responses of reduced accuracy to restore balance. Assessment of trunk responses may therefore yield greater insights into postural deficits in people with PD, whilst providing greater sensitivity in quantification compared to the clinical pull test

Development of an instrumented pull test offers researchers a technique for objective assessment of postural responses to the pull test. Ideally, an objective method to characterise clinical pull test responses should have excellent psychometric properties, be easy to administer, simple to operate, widely accessible, and portable. This is important to facilitate widespread adoption of the technique as an alternative assessment tool to assess postural responses within research and potentially, clinical settings following further substantial research in reliability and validity.

This assessment tool would need to account for variabilities influencing pull test administration, such as pull force, and participant characteristics such as height and weight, and capture both trunk and step responses to a backward perturbation. Such methodology could then be applied to studies seeking to capture early abnormalities in postural responses, track postural instability over time, detect responses to therapy, and identify variables in test performance and administration contributing to postural responses.

2.5 Summary and conclusions

Postural instability is considered one of the cardinal symptoms of PD which results in the impairment of balance. This compromises the ability to maintain or change posture during tasks of static or dynamic activities. Postural instability is a major contributor to injurious falls and risk of fractures, resulting in increased burden of morbidity and mortality in people with PD (Lima et al., 2019; Malochet-Guinamand et al., 2015; Rudzińska et al., 2013; van den Bos et al., 2013). The assessment of postural instability is commonly assessed using the pull test in the clinical setting where an examiner grades the corrective postural response following a backward pull at the patient's shoulders (Fahn et al., 1987). However variabilities with test administration and interpretation can confound outcomes (Nonnekes et al., 2015; Visser et al., 2003). Laboratory measures of postural instability using static or dynamic posturography, can therefore provide an objective method to assess postural instability in people with PD (Visser et al., 2008b).

In particular, dynamic posturography has been used to capture reactive postural responses by using movable platforms to induce a balance perturbation. These techniques offer precise quantification of postural responses by capturing changes in centre of pressure variables, kinematic parameters from movement of body segments, and muscle activity from electromyography. Studies of dynamic posturography have been useful to detect abnormalities in postural responses, objectively quantify the outcomes of therapy, and understand the underlying pathophysiology of postural instability in PD. However, researchers conventionally recruit participants where abnormalities in postural responses are already clinically evident (i.e. HY > 2) (Bloem et al., 1996; Dimitrova et al., 2004; Jacobs and Horak, 2006; Kam et al., 2014; King and Horak, 2008). Furthermore, methods of balance perturbation comprise bottom up movement beneath the feet, which does not directly compare to the balance perturbation of a top down pull from truncal level as occurs during the clinical pull test.

To date, the quantification of postural responses evoked from the trunk has been limited by suitable objective measures. Unlike bottom up perturbations that can be standardised using motorised translations, top down perturbations have proven more difficult to administer and assess. Complex setups developed in the laboratory include motors (Di Giulio et al., 2016), pendulums (Azevedo et al., 2016) and weight drops (McVey et al., 2013, 2009). Preliminary findings of truncal perturbations confirm the presence of abnormalities of postural responses

in PD (McVey et al., 2009). However, more research is required to explore postural responses in people with PD, particularly in mild PD where postural instability is not detected by the clinical pull test.

Development of an instrumented pull test therefore offers researchers a technique for objective assessment of postural responses to the clinical pull test. Such an assessment tool can also be used in the laboratory to clarify the effects of therapies on postural responses, for example, medication in mild disease or PPN DBS in moderate to advanced disease. Instrumented tests of postural responses may potentially substitute clinical scales specific to people with PD in the future. However, further studies are required to determine its reliability, validity and feasibility before use in the clinical setting.

CHAPTER 3. DEVELOPMENT OF AN INSTRUMENTED PULL TEST

3.1 Overview

The assessment of postural instability presents several challenges in people with Parkinson's disease (PD). As detailed in Chapter 2, clinical assessments such as the pull test is commonly used to assess postural instability in people with PD. However outcomes vary due to inconsistencies with test administration and interpretation. Laboratory assessments using platform perturbations provide objective quantification of postural responses but do not characterise postural responses in a similar manner elicited by the pull test.

To overcome issues with reliability and scaling of the pull test, an instrumented version of the clinical test is developed to precisely quantify postural responses. Akin to the clinical pull test, pulls are manually administered by an examiner, with the participant's trunk and step responses captured using a semi-portable motion tracking system. This technique offers researchers a technique for objective assessment of postural responses to the pull test.

The instrumented pull test protocol was published as a methods paper with video demonstration in April 2019:

> **Tan, J.L.**, Thevathasan, W., McGinley, J., Brown, P., Perera, T., 2019. An Instrumented Pull Test to Characterize Postural Responses. JoVE J. Vis. Exp. e59309. https://doi.org/10.3791/59309

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3.2 The instrumented pull test

The instrumented pull test was used to investigate postural responses across all studies in this thesis. Prior to use in the clinical PD cohort (Chapters 5, 6, and 7), the instrumented pull test was used to investigate postural reflexes in healthy adults in Chapter 4. Development and outcomes of the instrumented pull test methods paper is derived from findings of the instrumented pull test in 33 young healthy participants (Chapter 4), which details postural responses following a manual backward perturbation by an examiner. The methods paper describes the generic protocol of the instrumented pull test to quantify postural responses in people across a range of disease conditions and ages where quantifying postural instability is of interest and assessment employs the pull test. For the purposes of this thesis, participant selection, recruitment, and variations in pull test methodology from the protocol paper are detailed in individual chapters.

Video Article

An Instrumented Pull Test to Characterize Postural Responses

Joy Tan[1,2,4], Wesley Thevathasan[2,3,4,5], Jennifer McGinley[6], Peter Brown[7], Thushara Perera[1,4]

[1]Department of Medical Bionics, The University of Melbourne

[2]Department of Neurology, The Royal Melbourne Hospital

[3]Department of Neurology, Austin Hospital

[4]The Bionics Institute

[5]Department of Medicine, The University of Melbourne

[6]Department of Physiotherapy, The University of Melbourne

[7]Medical Research Council Brain Network Dynamics Unit, University of Oxford

Correspondence to: Thushara Perera at tperera@bionicsinstitute.org

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Abstract

Impairment of postural reflexes, termed postural instability, is a common and disabling deficit in Parkinson's disease. To assess postural reflexes, clinicians typically employ the pull test to grade corrective responses to a backward perturbation at the shoulders. However, the pull test is prone to issues with reliability and scaling (score/4). Here, we present an instrumented version of the pull test to more precisely quantify postural responses. Akin to the clinical test, pulls are manually administered except pull force is also recorded. Displacements of the trunk and feet are captured by a semi-portable motion tracking system. Raw data represent distance traveled (in millimeter units), making subsequent interpretation and analysis intuitive. The instrumented pull test also detects variabilities influencing pull test administration, such as pull force, thereby identifying and quantifying potential confounds that can be accounted for by statistical techniques. The instrumented pull test could have application in studies seeking to capture early abnormalities in postural responses, track postural instability over time, and detect responses to therapy.

Video Link

The video component of this article can be found at https://www.jove.com/video/59309/

Introduction

Postural reflexes act to maintain balance and upright stance in response to perturbations[1]. Impairment of these postural responses in disorders such as Parkinson's disease results in postural instability, and commonly leads to falls, reduced walking confidence and diminished quality of life[2,3,4]. In clinical practice, postural reflexes are typically assessed with the pull test, where an examiner briskly pulls the patient backward at the shoulders and visually grades the response[5,6,7,8]. Postural instability is usually scored using the Unified Parkinson's Disease Rating Scale (UPDRS) (0 - normal to 4 - severe), as published by the International Movement Disorder Society[5]. This method has been used extensively in the assessment of individuals with Parkinson's disease but suffers poor reliability and very limited scaling (score/4)[6,7,9]. Pull test scores often do not correlate with important clinical endpoints such as falls and the integer-based rating lacks sensitivity to detect fine postural changes[10,11].

Laboratory-based objective measures offer precise information about the nature of balance response by quantifying kinetic (e.g., the center of pressure), kinematic (e.g., joint goniometry/limb displacement) and neurophysiological (e.g., muscle recruitment) endpoints[12]. These methods may identify abnormalities before postural instability is clinically evident and track changes over time, including responses to treatment[13,14].

Tools for Quantifying Postural Instability

Conventional techniques of dynamic posturography commonly employ moving platforms. Resulting postural responses are quantified using a combination of posturography, electromyography (EMG), and accelerometry[12,15,16]. However, the bottom-up responses of platform perturbations - which evoke a response like slipping on a wet floor, are fundamentally different from the top-down postural responses of the clinical pull test - as may occur when being bumped in a crowd. Emerging evidence suggests truncal perturbations yield different postural characteristics to those of moving platforms[17,18,19]. Accordingly, others have attempted truncal perturbations in the laboratory using complex techniques including motors, pulleys, and pendulums[15,20,21,22]. Methods of measurement are often expensive and inaccessible and comprise of video-based motion capture that requires dedicated space in specialized laboratories[20,21]. Ideally, an objective method to characterize pull test responses should have excellent psychometric properties, be easy to administer, simple to operate, widely accessible, and portable. This is important to facilitate widespread adoption of the technique as an alternative assessment tool to assess postural responses within research and potentially, clinical settings.

The Instrumented Pull Test

The aim of this protocol is to offer researchers a technique for objective assessment of postural responses to the pull test. A semi-portable and widely available electromagnetic motion capture system underpins the technique. The perturbation involves manual pulls that do not require specialized mechanical systems. This method has sufficient sensitivity to detect small differences in postural reaction times and response amplitudes; therefore, it is suited to capturing potential abnormalities rated from normal up to grade 1 postural instability according to the UPDRS (postural instability with unassisted balance recovery)[5]. This method may also be utilized to explore the effects of therapy on postural instability. The protocol described here is derived from that in Tan et al.[23].

Protocol

All methods described were reviewed and approved by the local human research ethics committee at Melbourne Health. Informed consent was obtained from the participant prior to the study.

1. Equipment setup

1. Prepare the electromagnetic motion tracker with 3 miniature motion sensors as per the manufacturer's guidelines. Prior to data collection, ensure each sensor is sampled at a minimum 250 Hz, displacement is measured in millimeter units and rotations (pitch, roll, and yaw) are in degrees. Ensure that all internal filterings are disabled, and the position of the sensors set to reference a static origin (usually the electromagnetic transmitter).
2. Affix a load cell (minimum tension range 100 N, S-type recommended) to the patient harness at shoulder-level using a rope with a minimum diameter of 10 mm.
   NOTE: The harness system and rope are suitable for use in participants weighing up to 120 kg.
3. Connect the load cell to data acquisition unit (A/D Converter).
4. Connect the trigger output from the data acquisition unit into a trigger input of the motion tracker to ensure synchronized recording. Set data acquisition unit sampling rate to match the motion tracker and disable all filtering.
5. Conduct the experiment in a quiet room to minimize distractions during the assessment. Allow enough space for participants to take several corrective steps to regain balance.
   NOTE: Patients with Parkinson's disease and retropulsion are known to take 5-6 steps backward during the pull test.
6. Place falls mat on the floor as a precautionary measure.
7. Clean the harness, sensors, and wires with a hospital grade disinfectant wipe before testing each participant.
   NOTE: Video recording (e.g., using a portable camera on a tripod) of the instrumented pull test procedure is recommended so that any irregularities during data processing can be referenced against the video data of a trial.

2. Participant selection and preparation

1. Identify appropriate participants for study: participants can comprise a range of ages, disease conditions and severity where postural responses are of interest and balance assessment typically employs the clinical pull test. Ensure that participants can stand independently and generate a corrective balance response not requiring assistance to recover (i.e., up to Grade 1 postural instability according to the UPDRS).
2. Exclude any persons with cardiovascular, vestibular, vision and musculoskeletal conditions (including persons requiring foot orthotics or splints), that may impair balance performance unless this is the subject of the investigation, those on contact precautions, and those on medication known to affect balance or attention (e.g., antidepressants, neuroleptics, benzodiazepines, antiepileptics, antiarrhythmics, and diuretics).
3. Have the participant wear comfortable loose clothing on the day of the experiment and remove shoes prior to the pull test procedure.
4. Assist the participant in putting on the customized trunk harness with the load cell. Click the buckles around the chest and waist. Ensure adjustment straps on the harness are tight but comfortable. Do not allow more than 50 mm of slack in the harness when pulling on the rope. In participants with known postural instability, ensure that an assistant is present when the harness is applied while the participant is standing.
5. Attach motion sensors using medical tape to the sternal notch (at the level of the second and third thoracic vertebra), and on the feet at the right and left ankle malleolus.
   NOTE: Apply the sensors on participants with known postural instability in sitting. All cables must be routed carefully to avoid trip hazards.
6. Ask the participant to stand bare feet, in a comfortable stance (according to the participant's preferred base of support) along vertical and horizontal line markings on the floor. Note the participant's feet position. Ask the participant to also note their own feet position in order to revert to the same position after every pull. Monitor the participant's feet placement after every trial and ask the participant to return to the original feet position if any deviations are observed.
7. Instruct the participant to focus on artwork 1.5 m ahead at the eye level with hands by their side to minimize distractions between pulls.

3. Instrumented pull test procedure

1. Perform the instrumented pull test in accordance with the clinical pull test guidelines described by the UPDRS[5].
2. Explain the test procedure, and let the participant know that stepping is allowed to regain balance following the backward pull. Discourage anticipatory responses such as forward trunk flexion, stiffening in posture or knee flexion prior to the pull. Note these responses if they occur during the experiment.
3. Prior to each pull, ensure the participant is attentive by asking the participant to focus on a picture hanging on the wall. Ensure the participant is standing upright, with eyes open, hands by their side, and their feet placed on the designated markers in a comfortable stance.
4. Stand behind the participant. Apply a brisk pull of sufficient force to generate a trunk and step response via the rope and load cell held perpendicular to the shoulder level of the participant.

5. After each pull ensure the participant returns to the original feet positioning. Reset the position back to designated markers on the floor and repeat 35 times.
   NOTE: The number of trials can be varied according to the experimental design and clinical population.
6. Allow participants a short rest of 2 min after every 10 trials or as required to reduce the effects of fatigue and ensure attention is focused on the task. Participants can choose to sit or stand. Request that participants refrain from talking in between pulls unless requesting a break or expressing discomfort during the procedure.
7. As an additional safety precaution, ensure that the assessor and assistant are standing with their backs close to a wall while allowing enough room for the participant to take several steps backward.
   NOTE: The assessor must always be prepared to catch the patient. An assistant is required for safety when participants with known postural instability are assessed.
8. Detach sensors and assist the participant out of the harness following completion of the instrumented pull test procedure.

4. Signal processing

NOTE: Use a suitable data science platform such as MATLAB, R, or Python. Commands shown here are for MATLAB and example code is available as **Supplementary File**.

1. Import data recorded during step 3.4 into a suitable data science platform: csvread().
2. Align the motion tracker and load cell data using trigger signals and resample to a higher sampling rate: 1 kHz resample() function if required.
3. High-pass filter all motion tracking and load cell data with a 0.05 Hz cut-off frequency to remove base-line drift: butter() and filtfilt().
4. Double differentiate the trunk motion tracking displacement data to obtain trunk velocity and acceleration: diff().
5. Using either the trigger signal or a peak-detection algorithm applied to the load cell data, slice recordings to obtain epochs of each individual pull test trial: findpeaks() function.
6. Detect and reject trials with the anticipatory truncal movement. A forward trunk displacement immediately prior to the pull administration usually presents as a peak at least three standard deviations above the baseline mean of the trunk sensor: std() and mean().
7. Determine postural reaction time as the difference between the onset of trunk displacement (3 standard deviations above baseline mean) following the pull and the turning point of the trunk velocity curve (indicating the beginning of trunk deceleration): differentiate, diff(), and use zero crossing detector, zcd().
8. Determine the magnitude of the postural response as the peak deceleration of the trunk: min() or max().
9. Calculate the step reaction time as the difference between the onset of truncal displacement (as per 4.7) to the initial movement of the stepping limb: 3 standard deviations above the baseline mean.
10. Determine the step response magnitude by calculating the total displacement of the foot in millimeters (mm), from initial foot lift-off to contact of the stepping limb arresting backward retropulsion. Exclude steps less than 50 mm, as the change in the base of support is considered negligible[24]: min() or max().
11. Calculate the peak pull force and rate of force development from the load cell: max() for pull; max() and diff() for rate of force.
    NOTE: The peak pull force indicates the instantaneous maximum force delivered, whereas the force rate is the slope of the force versus time curve indicating how rapidly the force was generated.

Representative Results

The instrumented pull test (**Figure 1**) was used to investigate trunk and step responses in a young, healthy cohort[23]. Thirty-five trials were presented serially, with an auditory stimulus delivered concurrently with each pull (**Figure 2**). The auditory stimulus was either 90 dB (normal) or 116 dB (loud). The loud stimulus has been demonstrated as sufficient to trigger StartReact effects, where pre-prepared responses are released early by a startling auditory stimulus[25]. StartReact effects can be used as a probe to explore mechanisms underlying motor preparation[26]. The first-trial was kept to analyze unhabituated responses, and four subsequent trials discarded to allow for practice effects, which have been shown to habituate over five initial trials[27]. Subsequent habituated trials comprised 20 normal-intensity and 10 loud trials randomly intermixed. Inter-trial intervals (10 - 15 s) were variable. The analysis was conducted using linear mixed models due to multiple contributing factors that could influence trunk and step postural responses (e.g., variability of pull force between trials or participant height and weight). Linear mixed models' analysis was conducted using the following equation:

$$Y_{ij}=(\beta_0+\theta_{0j})+\beta_1 TrialType_{ij}+\beta_2 Weight_j+\beta_3 Height_j+\beta_4 PeakForce_{ij}+\beta_5 ForceRate_{ij}+\epsilon_{ij}$$

where Y_{ij} is the participant's reaction time or response magnitude for trial i, $\beta_{0\text{-}5}$ are the fixed effect coefficients, θ_{0j} is the random effect for participant j (random intercept), ε_{ij} and is the error term.

The instrumented pull test distinguished first-trial responses and StartReact effects to a backward perturbation. During the first-trial, step reaction time was slower (first-trial vs. subsequent trials mean difference: 36.9 ms, $p = 0.009$), and stepping size was larger (first-trial vs. subsequent trials mean difference: 60 mm, $p = 0.002$) (**Table 1**). Trunk reaction time and response magnitude remained unchanged. StartReact effects were only present in the trunk to subsequent habituated pulls. A loud auditory stimulus accelerated truncal reaction time (loud vs. normal stimuli mean difference: 10.2 ms, $p = 0.002$) and increased truncal response magnitude (loud vs. normal stimuli mean difference: 588 $mm.s^{-2}$, $p < 0.001$) (**Figure 3** and **Table 2**). Variables contributing to the pull test responses were explored. Notably, examiner peak pull force was found to influence the size of stepping responses ($p < 0.001$) and trunk reaction times ($p < 0.001$) (**Tables 3** and **4**). Participant weight influenced step reaction times ($p = 0.008$) (**Table 3**). Otherwise, participant height and weight did not influence results.

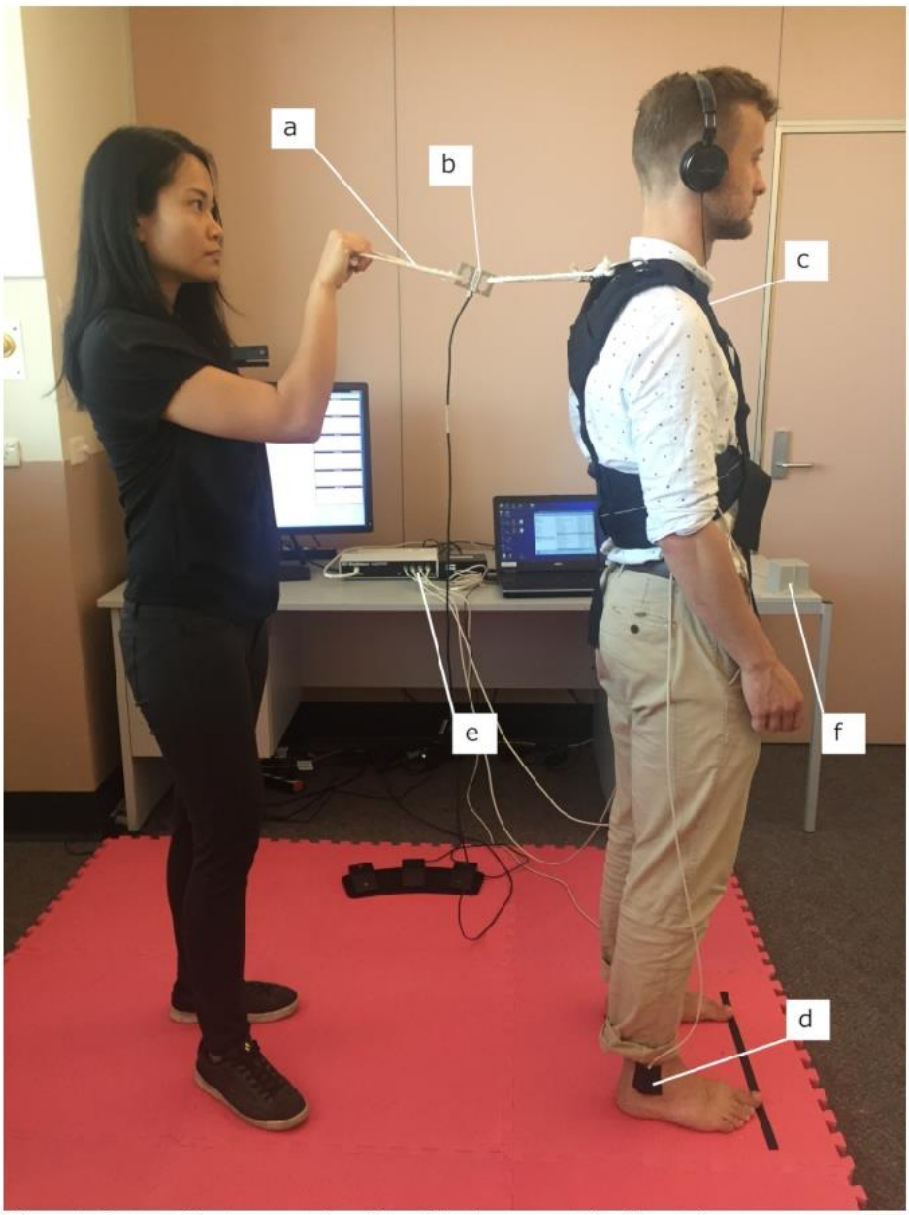

Figure 1. Set up of instrumented pull test. The instrumented pull test allows an assessor to apply a shoulder-level backward perturbation using a rope and harness **(a)**. The force of the perturbation is recorded using a force gauge **(b)**; the truncal response via a sensor placed at the sternal notch **(c)**; and stepping via sensors on the left and right ankle malleolus **(d)**. The motion tracking system encompasses a processing unit **(e)** which calculates three-dimensional positions of up to four sensors with respect to an electromagnetic transmitter **(f)**. Auditory stimuli are delivered via headphones.This figure has been modified from[23]. Please click here to view a larger version of this figure.

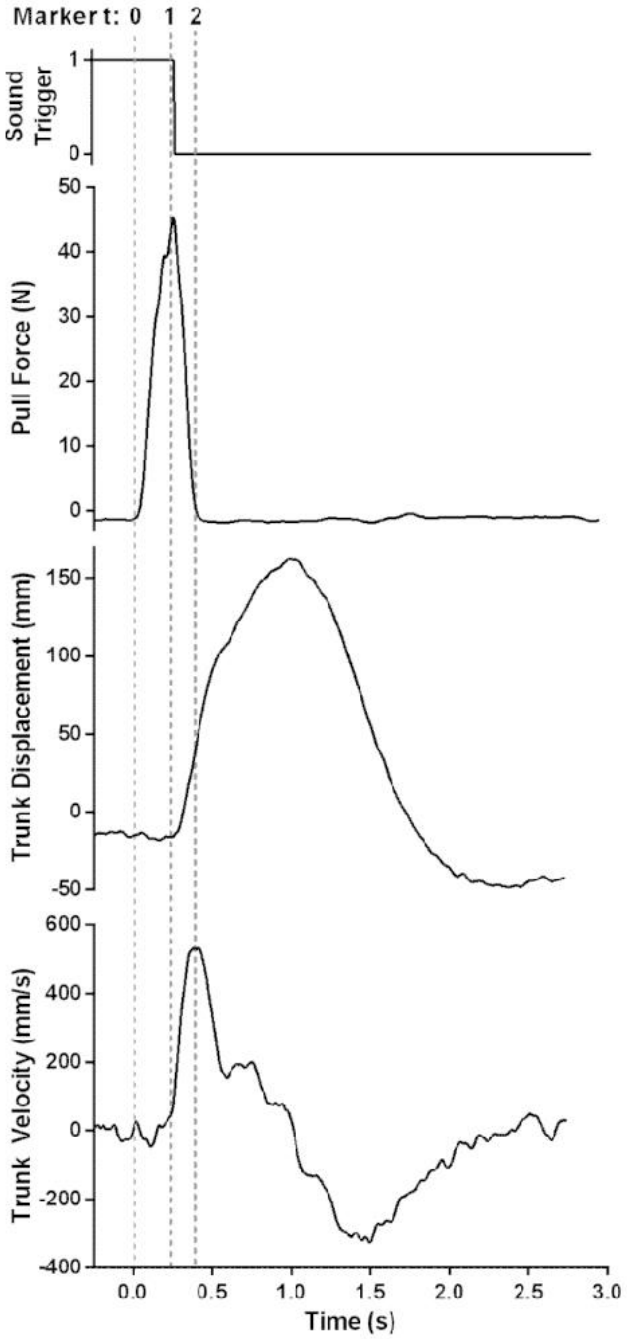

Figure 2. Data collected from a representative trial from the instrumented pull test. Vertical broken lines indicate markers on the time (t) axis. The onset of pull occurs at marker 0 with subsequent onset of trunk displacement at marker 1. Positive truncal displacement indicates backward movement. The auditory stimulus begins at the falling edge of the sound trigger, within 21 ± 6 ms of peak pull force. The onset of trunk deceleration at marker 2 occurs at the reversal of peak trunk velocity. The postural response (i.e., truncal reaction time) is defined as the difference between markers 2 and 1. This figure has been modified from[23]. Please click here to view a larger version of this figure.

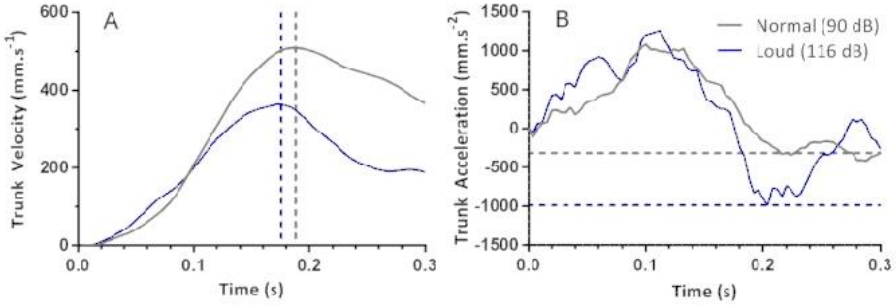

Figure 3. StartReact effects in truncal postural responses. Raw data representative of single trials associated with the normal stimulus at 90 dB (normal), indicated by the grey lines and loud auditory stimulus at 116 dB (loud), indicated by the blue lines. Vertical broken lines indicate markers on the time axis. StartReact is demonstrated by quicker reaction times in trunk velocity to the loud auditory stimulus, indicated by the blue broken vertical line, compared with the normal auditory stimulus, indicated by grey broken vertical line (**A**). Response magnitude to the postural task is derived from trunk acceleration. Horizontal broken lines indicate markers on the trunk acceleration axis. The largest response magnitude is shown in the loud trial, as indicated by the blue broken horizontal line representing the minimum point of the acceleration curve, compared to the normal trial, represented by the grey broken horizontal line (**B**). This figure has been modified from[23]. Please click here to view a larger version of this figure.

	Step Reaction Time			Step Response Magnitude		
Trial Type Comparison	**Mean Δ (ms)**	**95% CI**	**p-value**	**Mean Δ ($mm.s^{-2}$)**	**95% CI**	**p-value**
First vs. Normal	36.9	4.7, 69.2	0.009	60	17, 103	0.002
First vs. Loud	46.1	13.1, 79.2	0.002	53	9, 97	0.005
Normal vs. Loud	9.2	-3.1, 21.5	0.072	-7	-23, 9	0.315

Table 1. Mean differences (Δ) between the first pull test trial and subsequent trials with 90 dB (normal) or 116 dB (loud) auditory stimuli for step reaction time and response magnitude. This table has been modified from[23].

	Trunk Reaction Time			Trunk Response Magnitude		
Trial Type Comparison	**Mean Δ (ms)**	**95% CI**	**p-value**	**Mean Δ ($mm.s^{-2}$)**	**95% CI**	**p-value**
First vs. Normal	-6	-31.1, 19.0	0.692	162	-412, 737	0.497
First vs. Loud	4.2	-21.2, 29.6	0.692	-425	-1008, 158	0.12
Normal vs. Loud	10.2	3.0, 17.5	0.002	-588	-750, -425	< 0.001

Table 2. Mean differences (Δ) between the first pull test trial and subsequent trials with 90 dB (normal) or 116 dB (loud) auditory stimuli for trunk reaction time and response magnitude. This table has been modified from[23].

	Step Reaction Time			Step Response Magnitude		
Predictor	**Estimate**	**95% CI**	**p-value**	**Estimate**	**95% CI**	**p-value**
Peak Force	-0.12	-0.44, 0.19	0.436	1.02	0.55, 1.49	< 0.001
Force Rate	-0.01	-0.04, 0.02	0.575	0.01	-0.03, 0.06	0.528
Height	-64.65	-283.98, 154.69	0.542	240.26	-797.51, 1278.03	0.629
Weight	2.37	0.72, 4.03	0.008	-2.51	-10.56, 5.55	0.518

Table 3. Coefficient estimates, 95% confidence intervals (CI), and statistical significance of instrumented pull test predictors resulting from linear mixed models for step response. This table has been modified from[23].

	Trunk Reaction Time			Trunk Response Magnitude		
Predictor	**Estimate**	**95% CI**	**p-value**	**Estimate**	**95% CI**	**p-value**
Peak Force	0.36	0.22, 0.51	< 0.001	0.98	-2.95, 4.91	0.623
Force Rate	-0.01	-0.03, 0.00	0.062	-0.12	-0.47, 0.22	0.486
Height	45.97	-31.16, 123.11	0.233	-708.94	-3362.70, 1944.82	0.587
Weight	-0.17	-0.75, 0.42	0.566	2.08	-18.04, 22.19	0.834

Table 4. Coefficient estimates, 95% confidence intervals (CI), and statistical significance of instrumented pull test predictors resulting from linear mixed models for the truncal response. This table has been modified from[23].

Supplementary Coding File. Please click here to download this file.

Discussion

Here, we have demonstrated the protocol for instrumentation of the clinical pull test, taking a method widely used in clinical practice and yielding an objective measurement of postural responses in addition to the important aspect of the pull administration. Using semi-portable motion tracking, this method offers a means of measurement that is more accessible compared to conventional laboratory techniques[28]. Using this method, researchers can explore characteristics of postural responses to a top-down perturbation across populations of varying ages and conditions.

While the protocol was used successfully, several limitations should be noted. Motion tracking detects net movement rather than the onset of muscle recruitment, commonly measured by EMG[29,30,31]. If desired, EMG (e.g., measured from muscles including tibialis anterior, soleus, hamstrings, quadriceps, rectus abdominis and lumbar paraspinals) could be integrated into the protocol with relative ease. The motion sensors we employed are connected by wires to the base unit. These wires are of sufficient length in the laboratory to record pull test kinematics, yet a wireless system would be more practical particularly in a clinical setting. Further validity and reliability testing in cohorts of different disease states and severity is required before this method can find credibility as a standardized assessment tool to assess postural responses scored up to a grade 1 according to the UPDRS (postural instability with unassisted balance recovery)[5].

The Instrumented Pull Test as an Assessment Tool for Postural Instability

Electromagnetic motion tracking is relatively inexpensive and semi-portable compared to other solutions which report displacement data[21,32,33].Recording of displacement in millimeter units is crucial to the simplicity of the technique as it negates the requirement for complex signal processing, so the data can be intuitively comprehended. Other commonly used techniques such as accelerometry cannot be easily converted to displacement without the use of adequate sensor-fusion techniques to remove several confounds (gravitational artifact, drift over time, calibration error)[28,34,35].

Critical steps were discerned in this protocol to ensure accurate collection of data. Importantly, we defined postural reaction time in the instrumented pull test by the onset of truncal displacement, rather than the onset of the examiner-initiated pull. This was crucial to exclude any movement of the harness and rope at the time of the pull that contributes to the response latency. In previous work, the peak acceleration of postural responses occurred earlier, and with larger amplitudes in the upper body compared to the sacrum in response to a truncal perturbation[17]. The pull of non-standardized force was elicited manually, similarly to the clinical pull test. Stepping is defined as the foot moving past the stance foot in the backward direction, excluding movement in any other direction. We found peak force significantly affected step and trunk responses. Recording of force is therefore imperative to the methodology and results can account for pull force by using mixed effect models. Depending on the load cell specifications a pre-amplifier and separate power supply may be required. Use the calibration curve supplied by the manufacturer to convert the recorded voltage to pull force (Newtons). The trigger may also be used to time the delivery of auditory or visual stimuli for further characterization of balance mechanisms.

When 35 trials are performed, the instrumented pull test procedure takes approximately 20 minutes to complete. Users of this protocol will need to determine if timeframes required for the experiment are appropriate compared to their usual methods of assessing postural instability. During the task, participants are instructed to focus on the picture, as attention is known to attenuate with repeated exposure to a threat to balance control[36]. Attention to a postural task is associated with increased conscious monitoring of posture, and the corresponding decrease in amplitude of postural displacements[37]. During testing, the safety of participants and potential falls risk to both assessor and patient are of imperative concern. Additional safety precautions include the use of an assistant for patients with known postural instability and proximity to a wall to safeguard the assessor from falling together with the participant[9].

StartReact and Motor Preparation

The instrumented pull test has demonstrated the capability to detect small changes in response latency of postural responses. In the representative results, we delivered auditory stimuli concurrent with the perturbation to assess for acceleration in reaction time that occurs with loud (116 dB) compared with lesser intensity (90 dB) stimuli, known as the StartReact effect[25,38]. We were able to detect an average difference in truncal response latency of approximately 10 ms with the instrumented pull test protocol in a cohort of 33 participants[23]. Acceleration of such movement onsets to the StartReact effect typically occur with a magnitude of less than 20 ms using EMG[15]. Differences in stepping latency were also detected in first trial responses, with larger step responses. This is consistent with the greater destabilization found in 'first-trial effects' using moving platforms[39,40].

This method described in this manuscript has demonstrated the capability of the instrumented pull test to provide precise quantification of postural responses in response to the typically employed clinical pull test. At present, the instrumented pull test is intended as an alternative method to assess postural responses in the research setting. Further work in reliability and validity is required before its use in the clinic.

The number of instrumented pull test trials can be adjusted at the user's discretion dependant on statistical power calculations. To increase the participant's comfort during testing, particularly with females, a modified harness which fastens from behind could be considered in a future version of the instrumented pull test. Further research is required to fully explore these responses in patient populations with balance abnormalities (up to grade 1 postural instability according to the UPDRS) to investigate effects of therapy and elucidate mechanisms contributing to postural instability.

Disclosures

No conflicts of interest, financial or otherwise, are declared by the authors.

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Materials List for:

An Instrumented Pull Test to Characterize Postural Responses

Joy Tan[1,2,4], Wesley Thevathasan[2,3,4,5], Jennifer McGinley[6], Peter Brown[7], Thushara Perera[1,4]

[1]Department of Medical Bionics, The University of Melbourne

[2]Department of Neurology, The Royal Melbourne Hospital

[3]Department of Neurology, Austin Hospital

[4]The Bionics Institute

[5]Department of Medicine, The University of Melbourne

[6]Department of Physiotherapy, The University of Melbourne

[7]Medical Research Council Brain Network Dynamics Unit, University of Oxford

Correspondence to: Thushara Perera at tperera@bionicsinstitute.org

URL: https://www.jove.com/video/59309
DOI: doi:10.3791/59309

Materials

Name	Company	Catalog Number	Comments
Analog to Digital Convertor & Software	CED	Micro 1401-3	Any suitable digital acquisition system can be used
Load Cell	Omegadyne	LCM201-100N	
MATLAB Software	MathWorks Inc.	NA	Any data science platform can be used
Motion Sensor	Ascension	6DOF, type-800	
Motion Tracker	Ascension	3D Guidance trakSTAR	Mid-range transmitter
S&F Technical Harness and Belt	Lowepro	LP36282	

3.3 Summary and conclusions

This chapter details the development of the instrumented pull test. This technique was utilized to quantify postural responses to a manual backward pull in the studies reported in Chapters 4, 5, 6 and 7.

CHAPTER 4. NEUROPHYSIOLOGICAL ANALYSIS OF THE CLINICAL PULL TEST

4.1 Overview

Chapter 2 highlighted the potential utility of instrumented clinical tests of balance, and the limited availability of these measures in the research and clinical setting. Following the development of an instrumented pull test in Chapter 3, this chapter adds to the understanding of postural responses elicited by the clinical pull test using instrumentation in a cohort of healthy young participants (Study 1). The published manuscript of this study is reprinted in the chapter.

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RESEARCH ARTICLE | *Control of Movement*

Neurophysiological analysis of the clinical pull test

Joy Lynn Tan,[1,2] Thushara Perera,[1,3] Jennifer L. McGinley,[3,4] Shivanthan Arthur Curtis Yohanandan,[3] Peter Brown,[5] and Wesley Thevathasan[2,3,6]

[1]*Department of Medical Bionics, The University of Melbourne, Parkville, Victoria, Australia;* [2]*Department of Neurology, The Royal Melbourne Hospital, Parkville, Victoria, Australia;* [3]*The Bionics Institute, East Melbourne, Victoria, Australia;* [4]*Department of Physiotherapy, The University of Melbourne, Parkville, Victoria, Australia;* [5]*Medical Research Council Brain Network Dynamics Unit and Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, United Kingdom; and* [6]*Department of Medicine, The University of Melbourne, Parkville, Victoria, Australia*

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Tan JL, Perera T, McGinley JL, Yohanandan SA, Brown P, Thevathasan W. Neurophysiological analysis of the clinical pull test. *J Neurophysiol* 120: 2325–2333, 2018. First published August 15, 2018; doi:10.1152/jn.00789.2017.—Postural reflexes are impaired in conditions such as Parkinson's disease, leading to difficulty walking and falls. In clinical practice, postural responses are assessed using the "pull test," where an examiner tugs the prewarned standing patient backward at the shoulders and grades the response. However, validity of the pull test is debated, with issues including scaling and variability in administration and interpretation. It is unclear whether to assess the first trial or only subsequent repeated trials. The ecological relevance of a forewarned backward challenge is also debated. We therefore developed an instrumented version of the pull test to characterize responses and clarify how the test should be performed and interpreted. In 33 healthy participants, "pulls" were manually administered and pull force measured. Trunk and step responses were assessed with motion tracking. We probed for the StartReact phenomenon (where preprepared responses are released early by a startling stimulus) by delivering concurrent normal or "startling" auditory stimuli. We found that the first pull triggers a different response, including a larger step size suggesting more destabilization. This is consistent with "first trial effects," reported by platform translation studies, where movement execution appears confounded by startle reflex-like activity. Thus, first pull test trials have clinical relevance and should not be discarded as practice. Supportive of ecological relevance, responses to repeated pulls exhibited StartReact, as previously reported with a variety of other postural challenges, including those delivered with unexpected timing and direction. Examiner pull force significantly affected the postural response, particularly the size of stepping.

NEW & NOTEWORTHY We characterized postural responses elicited by the clinical "pull test" using instrumentation. The first pull triggers a different response, including a larger step size suggesting more destabilization. Thus, first trials likely have important clinical and ecological relevance and should not be discarded as practice. Responses to repeated pulls can be accelerated with a startling stimulus, as reported with a variety of other challenges. Examiner pull force was a significant factor influencing the postural response.

balance; postural reflex; pull test; StartReact

Address for reprint requests and other correspondence: W. Thevathasan, Dept. of Neurology, Royal Melbourne Hospital, Royal Parade, Parkville, Melbourne, 3050 Australia (e-mail: wesley.thevathasan@mh.org.au).

INTRODUCTION

Postural "reflexes" are crucial to the maintenance of upright stance (Currie and Carlsen 1985; Eaton and Emberley 1991; Shemmell 2015). Impairment of these reflexes in disorders such as Parkinson's disease results in postural instability and causes reduced walking confidence, falls, and even inability to stand (Bloem et al. 2004; Hely et al. 2005). In clinical practice, postural responses are routinely assessed using the "pull test." In the pull test, an examiner tugs the standing patient backward at the shoulders and grades the response (Fahn and Elton 1987). Patients typically respond by flexing at the trunk and sometimes by taking a corrective step (Hunt and Sethi 2006; Visser et al. 2003). However, pull test scores correlate poorly with important clinical end points such as falls, and poor validity of the pull test is cited as a factor confounding the detection of novel treatments (Bloem et al. 1998; Morita et al. 2014; Thevathasan et al. 2011). Such issues could simply reflect the limited scaling of the test (score/4). Additionally, inter- and intrarater reliability are often cited as confounds (Hunt and Sethi 2006; Munhoz et al. 2004). However, it is unclear whether variabilities in test administration, such as pull force, influence the response. Interpretation of the test is also controversial. For example, it is debated which trial to assess. Guidelines produced by the International Movement Disorders Society suggest that the patient should be forewarned about the impending challenge, with an initial practice trial before a second trial is formally assessed (Goetz et al. 2008). Others claim that an unexpected pull, performed only one time, is most clinically meaningful (Bloem et al. 2001; Visser et al. 2003). In some studies, the average response from repeated pull test trials has been measured (Bloem et al. 2001; Nanhoe-Mahabier et al. 2012). Whether these different techniques yield different motor responses is uncertain. For example, in contrast to repeated trials, initial perturbations could be more "startling" and the motor response less preprepared (Allum et al. 2011). This also raises the question of ecological relevance. An expected backward perturbation as occurs in the pull test may occur relatively infrequently in daily life, such as a passenger subject to anticipated acceleration of a train. Do such responses differ from those triggered by challenges that occur unexpectedly and in any direction (Carpenter et al. 2004; Dimitrova et al. 2004; Jacobs et al. 2005)?

Some of these questions have been addressed in laboratory studies, using a different perturbation, platform translation beneath the feet (Campbell 2012; Campbell et al. 2012, 2013; Nonnekes et al. 2013; Ravichandran et al. 2013). These studies suggest that first and subsequent postural challenges evoke different responses. "First trial postural responses" have many features that suggest superimposition of the generalized startle reflex, including muscle cocontraction, forward flexion of the trunk in a crouching posture, and subsequent habituation (Allum et al. 2011; Oude Nijhuis et al. 2009, 2010). This "first trial effect" may actually be maladaptive, at least for stance preservation, being associated with increased deviations in center of mass and propensity to falls (Horak and Nashner 1986; Oude Nijhuis et al. 2009). If such findings also apply to the pull test, this would be of great relevance to clinicians, suggesting that the very first pull test trial is crucial to assess and should not be discarded as practice. This may be particularly true in patients with Parkinson's disease, who are reported to have abnormalities integrating startle responses into movement (Nieuwenhuijzen et al. 2006). Platform translation studies also suggest that postural responses, averaged over repeated trials, exhibit prepreparation but keep in reserve latent potential to be accelerated (Campbell et al. 2012; Nonnekes et al. 2013). Prepreparation was assessed in these studies using the StartReact probe, where a concurrent startling stimulus, such as a loud sound, can speed responses that are preprepared (Campbell 2012; Nonnekes et al. 2013; Valls-Solé et al. 1995, 1999). Platform translation studies report that StartReact is present with backward and sideways challenges and regardless of whether the perturbation is expected in timing or direction (Campbell et al. 2012; Nonnekes et al. 2013). If repeated pull test trials also exhibit StartReact, this could support that pull test results reflect the integrity of pathways used by a broader range of responses than only those elicited by a forewarned backward challenge.

However, whether findings from platform translation studies apply to the pull test is uncertain. Platform translation involves intense "bottom up" perturbations, generating an initial lower limb response as occurs when slipping on a wet floor (Horak et al. 1997). In contrast, the pull test employs a "top down" perturbation, with initial displacement and response of the trunk, as may occur when bumped in a crowd, and this generates a different pattern of motor recruitment (Colebatch et al. 2016; de Azevedo et al. 2016; Di Giulio et al. 2016; Govender et al. 2015).

We therefore developed an instrumented version of the pull test to better characterize the nature of elicited postural responses and clarify how the test should be performed and interpreted. Like the clinical test, the perturbation was delivered manually by an examiner but with measurement of pull force. Both the trunk and step responses were assessed with motion tracking, akin to visual assessment by a clinician. The following three key questions were addressed: first, whether responses to the first pull test trial differ from subsequent repeated trials; second, whether averaged responses to repeated pulls exhibit StartReact; and third, whether variabilities in baseline subject characteristics such as height and weight, or in the examiner such as pull force, affect results.

MATERIALS AND METHODS

Participants

Thirty-three healthy young adults (age 28.0 ± 4.1 yr; height 1.72 ± 0.1 m; weight 68.8 ± 14.0 kg; 20 males) without known hearing, neurological, or musculoskeletal disorders were recruited as a sample of convenience. Repeated trial data were captured for all participants. In 18 participants, first trial data were also captured, and pulls were of sufficient force to always generate both a trunk and step response. In the remaining 15 participants, pulls were of lesser force and elicited only a trunk response. Local ethics committee approval was obtained, and participants gave written informed consent.

Experiments

The instrumented pull test was performed similarly to the clinical pull test (Fahn and Elton 1987). Participants stood in bare feet and focused on a picture 1.5 m ahead at eye level, wearing a customized trunk harness attached to a load cell (LCM201–100N; Omegadyne). A warning cue was not provided. The assessor manually generated a backward pull via the load cell held perpendicular to the shoulder level of the participant (Fig. 1). Thirty-five trials were presented serially, with an auditory stimulus (40-ms duration, 1,000 Hz) delivered within 30 ms of each pull. The auditory stimulus was either 90 (normal) or 116 (loud) dB. This loud stimulus has been demonstrated as sufficient to trigger StartReact and a startle reflex (Thevathasan et

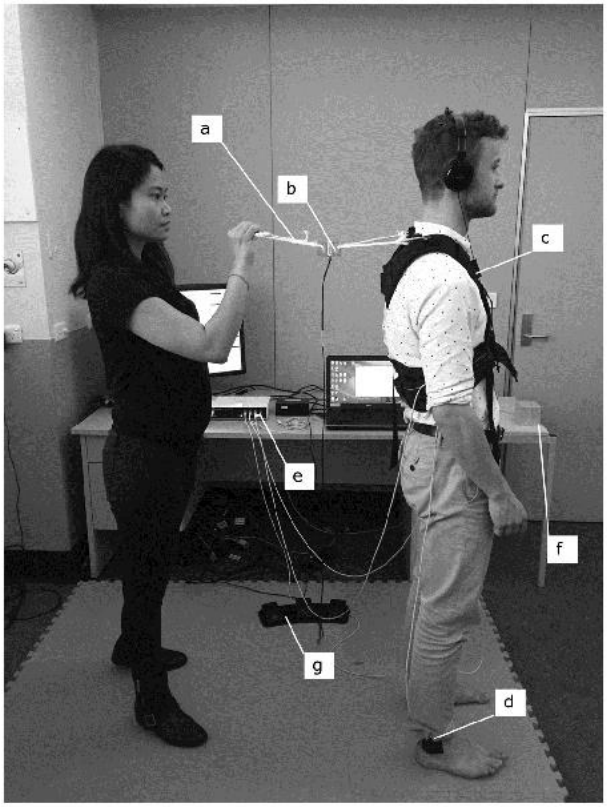

Fig. 1. Set up of instrumented pull test. The instrumented pull test allows an assessor to apply a shoulder-level backward perturbation using a rope and harness (*a*). The force of the perturbation is recorded using a force gauge (*b*); the truncal response via a sensor placed at the sternal notch (*c*); and stepping via sensors on the left and right ankle malleolus (*d*). The motion tracking system encompasses a processing unit (*e*) that calculates 3-dimensional positions of up to four sensors with respect to an electromagnetic transmitter (*f*). Real-time monitoring and feedback are displayed. Auditory stimuli are delivered via headphones. Computerized foot pedals (*g*) allow quick access to software functions.

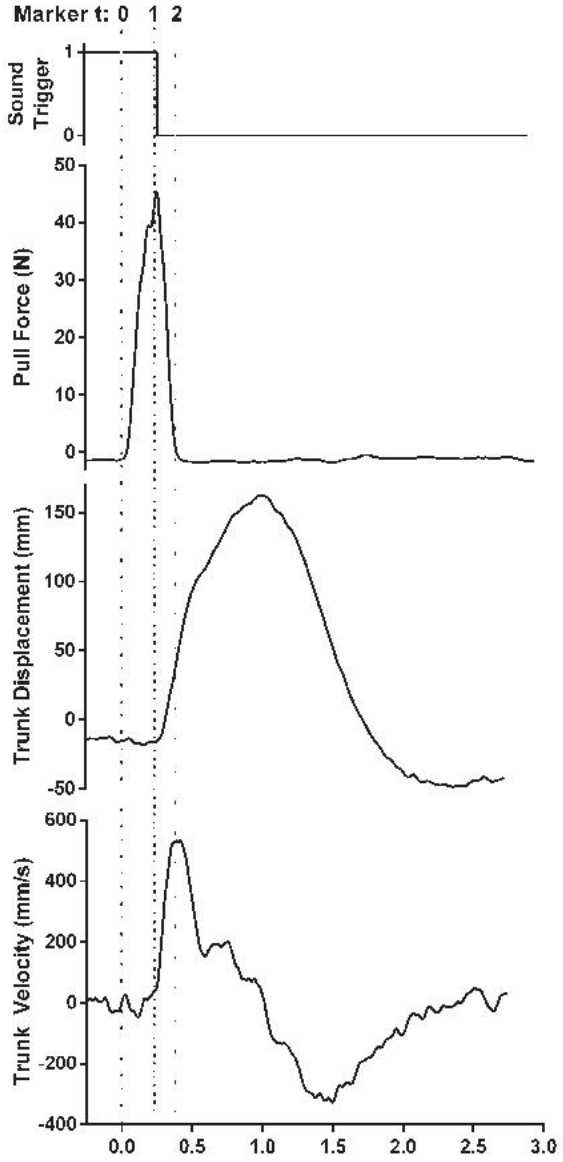

Fig. 2. Data collected from a representative trial from the instrumented pull test. Vertical broken lines indicate markers on the time axis. Onset of pull occurs at *time* (*t*) *0* with subsequent onset of trunk displacement at t_1. Positive truncal displacement indicates backward movement. The auditory stimulus begins at the falling edge of the sound trigger within 21 ± 6 ms of peak pull force. Onset of trunk deceleration at t_2 occurs at reversal of peak trunk velocity. The postural response, i.e., truncal reaction time, is defined as the difference between t_2 and t_1.

al. 2011). The first five trials involved normal sounds, followed by 20 normal and 10 loud trials randomly intermixed. Intertrial intervals (10–15 s) were variable. Participants had a short rest after each block of 10 pulls, or as requested.

Auditory stimuli were delivered through a custom hardware audio interface. Auditory tones were delivered binaurally through headphones (ATH-ES7; Audio Technica, Tokyo, Japan). Sound pressure levels were calibrated in a soundproof room with a modular precision sound analyzer (Observer 2260; Bruel and Kjaer, Naerum, Denmark) via an artificial ear and headphone adaptor. Tones were triggered when the force of each pull reached a maximum (Fig. 2). Triggering was processed within the hardware via an embedded microprocessor, resulting in a delay of 21 ± 6 ms between the onset of the pull and auditory stimulus delivery. This delay is well within the time window where a loud auditory stimulus can trigger StartReact (Castellote et al. 2013; Kumru and Valls-Solé 2006; Valls-Solé 2004).

Responses in both tasks were measured with electromagnetic three-dimensional motion tracking using type-800 miniature sensors (Ascension TrakStar). Sensors were attached at the sternal notch (at the level of the 2nd and 3rd thoracic vertebra) and on the right and left ankle malleolus. Each sensor, sampled at 250 Hz, measured triaxial displacement in millimeter units as well as pitch, roll, and yaw in degrees. The sensors were referenced to the origin of the transmitter. Data were acquired using custom software. Previous work has shown this system has a sensitivity of 0.45 mm and 0.02° with measurements accurate to ±0.4 mm and ±0.05° (Perera et al. 2016).

Tasks were administered in a quiet room with distractions minimized. The order of tasks was counterbalanced. Participants were blinded to experiment hypotheses. One researcher (Tan) conducted all assessments and continuously monitored participants to prevent falls.

Parameters

Data analysis was automated using a script written in MATLAB (MathWorks). Motion tracking data were high-pass filtered with a 0.05-Hz cut-off frequency. Trunk displacement data were differentiated to determine velocity and then acceleration.

The truncal response is the first strategy used to maintain upright posture in the pull test and is elicited in every trial (Di Giulio et al. 2016). Postural reaction time was defined as the difference between the onset of trunk displacement and the turning point of the trunk velocity curve (when the trunk started to decelerate) (Figs. 2 and 3). Notably, the imperative was defined as the onset of trunk displacement (3 SDs above the 1-s prestimulus baseline), rather than any threshold of pull force, since this removed the confound of variability due to slack in the harness or body. Magnitude of the postural response was defined as the peak deceleration of the trunk and is reported in units of millimeters per second per second (mm/s^2).

When the truncal response is insufficient to maintain balance, the step response is generated (Pai et al. 1998). Stepping can also occur early, well within stability limits and before balance is fully perturbed (Maki and McIlroy 1997). Stepping was defined as the foot moving past the stance foot in the backward direction, excluding movement in any other direction. Step reaction time was calculated as the difference between the onset of truncal displacement to the initial movement of the stepping limb (4 SDs above baseline). Response magnitude of stepping was determined by total displacement of the feet in millimeters, from initial foot lift off to contact of the stepping limb arresting backward retropulsion. Analysis excluded steps <50 mm, since the

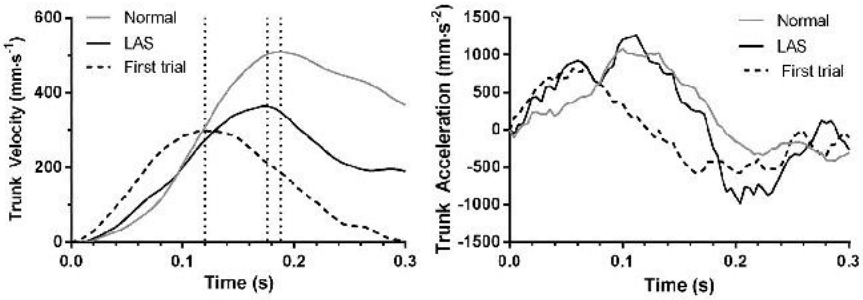

Fig. 3. Raw data (postural response task) from a participant demonstrating single trials associated with the first pull (first trial), normal stimulus at 90 dB (normal), and loud auditory stimulus at 116 dB (LAS). StartReact is demonstrated by quicker reaction times in trunk velocity to the first trial and LAS compared with the normal auditory stimulus. Response magnitude to the postural task is derived from trunk acceleration. The largest response magnitude is demonstrated in the LAS trial, as indicated by the peak of the acceleration curve.

Table 1. *Mean differences between the first pull test trial and subsequent trials with 90 (normal) or 116 (loud) dB auditory stimuli for trunk reaction time and response magnitude*

	Trunk Reaction Time			Trunk Response Magnitude		
Trial type comparison	Mean Δ, ms	95% CI	*P* value	Mean Δ, mm/s^2	95% CI	*P* value
First vs. normal	−6.0	−31.1, 19.0	0.692	162	−412, 737	0.497
First vs. loud	4.2	−21.2, 29.6	0.692	−425	−1008, 158	0.120
Normal vs. loud	10.2	3.0, 17.5	0.002	−588	−750, −425	<0.001

Δ, Difference; CI, confidence interval.

change in base of support is considered negligible (McVey et al. 2013).

Reaction times and response magnitudes were computed for every individual trial, including the first trial. For repeated trials, the first five trials were discarded to avoid first trial effects, which have been shown to habituate over several initial trials (Nanhoe-Mahabier et al. 2012). Repeated trial measures reflect averages over the subsequent 30 trials. Additionally, trials were rejected if there was an anticipatory truncal movement (a forward trunk displacement immediately before the auditory stimulus that exceeds 3 SDs above the 1-s prestimulus baseline). In one participant, anticipatory truncal movement was detected in most trials, so this data set was excluded.

Peak pull force and rate of force development were calculated from the load cell and reported in units of Newtons and Newtons per second, respectively. The peak pull force indicates the instantaneous maximum force delivered, whereas the force rate is the slope of the force vs. time curve indicating how rapidly the force was generated.

Data Analysis

A Kolmogorov-Smirnov Test demonstrated that all measures did not differ from a normal distribution.

Because of the number of contributing factors that could influence trunk and stepping reaction time and magnitude in the postural reflex task, a linear mixed models (LMM) analysis was conducted according to methods previously described (Boisgontier et al. 2017). LMM offers several advantages over ANOVA in the analysis of the postural reflex task by accounting for both nested (multiple observations in a single participant in one condition) and crossed (participant observed in multiple conditions) factors, controlling for increased probability of type 1 error (Boisgontier and Cheval 2016). At the participant level, it accounts for height and weight, and sampling variability of peak force and force rate at the trial level. LMMs prevent information loss by considering all trials individually rather than averaging data across multiple trials. Results can subsequently be generalized across the population and conditions tested (Boisgontier et al. 2017).

To determine effects of auditory stimulus and pull force variables on reaction time and response magnitude in the postural reflex task, LMM analysis was conducted using the following equation:

$$Y_{ij} = (\beta_0 + \theta_{0j}) + \beta_1 \text{TrialType}_{ij} + \beta_2 \text{Weight}_j + \beta_3 \text{Height}_j + \beta_4 \text{PeakForce}_{ij} + \beta_5 \text{ForceRate}_{ij} + \varepsilon_{ij}$$

where Y_{ij} is the participant's reaction time or response magnitude for *trial i*, β_{0-5} are the fixed-effect coefficients, θ_{0j} is the random effect for *participant j* (random intercept), and ε_{ij} is the error term.

This model was built using SPSS (IBM, Chicago, IL) version 22. The following factors were included: trial type, weight, height, peak force, and force rate. At the participant level, height and weight were included to account for the lever-arm mechanism of the pull and the impact inertia of the trunk (Delitto et al. 1989; Oliveira et al. 2011). To determine if the first trial was different from subsequent trials, the trial factor is coded as 0 for the first trial (90 dB), 1 for repeated trials at 90 dB, and 2 for repeated trials at 116 dB. Four LMMs relating to trunk reaction time, trunk response magnitude, stepping reaction time, and step response were used to analyze the data. Variance inflation factors for each predictor in all models fell below 10, and multicollinearity was considered absent (Hair et al. 1995). The variance component covariance structure was selected for the LMMs.

For each explanatory variable, an estimate of the effect, *P* value, and 95% confidence intervals are specified. Where the explanatory variable is continuous, the estimate of the effect is based on a regression coefficient (which gives the predicted increase in outcome for a 1-point increase in the variable). For categorical explanatory variables, post hoc pairwise comparisons were performed to determine the differences between trial types and were corrected for multiple comparisons (Benjamini and Hochberg 1995). Level of significance was $\alpha = 0.05$.

RESULTS

A summary of results from the LMM analysis is found in Tables 1, 2, 3, and 4.

First Trial Responses

Trunk reaction times from first trials did not differ from repeated trials with normal stimuli ($P = 0.692$) and repeated trials with loud stimuli ($P = 0.692$). Trunk response magnitudes from first trials did not differ from repeated trials with normal stimuli ($P = 0.497$) and repeated trials with loud stimuli ($P = 0.120$).

Step reaction times from first trials were slower than repeated trials with normal stimuli (mean difference 36.9 ms, $P = 0.009$) and repeated trials with loud stimuli (mean differ-

Table 2. *Mean differences between the first pull test trial and subsequent trials with 90 (normal) or 116 (loud) dB auditory stimuli for step reaction time and response magnitude*

	Step Reaction Time			Step Response Magnitude		
Trial type comparison	Mean Δ, ms	95% CI	*P* value	Mean Δ, mm/s^2	95% CI	*P* value
First vs. normal	36.9	4.7, 69.2	0.009	60	17, 103	0.002
First vs. loud	46.1	13.1, 79.2	0.002	53	9, 97	0.005
Normal vs. loud	9.2	−3.1, 21.5	0.072	−7	−23, 9	0.315

Δ, Difference; CI, confidence interval.

Table 3. *Coefficient estimates, 95% CI, and statistical significance of instrumented pull test predictors resulting from linear mixed models for truncal response*

	Trunk Reaction Time			Trunk Response Magnitude		
Predictor	Estimate	95% CI	*P* value	Estimate	95% CI	*P* value
Peak force	0.36	0.22, 0.51	<0.001	0.98	−2.95, 4.91	0.623
Force rate	−0.01	−0.03, 0.00	0.062	−0.12	−0.47, 0.22	0.486
Height	45.97	−31.16, 123.11	0.233	−708.94	−3,362.70, 1,944.82	0.587
Weight	−0.17	−0.75, 0.42	0.566	2.08	−18.04, 22.19	0.834

CI, confidence interval.

ence 46.1 ms, $P = 0.002$). Step response magnitudes from first trials were larger than repeated trials with normal stimuli (mean difference 60 mm, $P = 0.002$) and repeated trials with loud stimuli (mean difference 53 mm, $P = 0.005$).

StartReact in Repeated Trials

StartReact was present in the trunk response from repeated trials, that is, trunk reaction times in repeated trials were faster with loud compared with normal stimuli (mean difference 10.2 ms, $P = 0.002$). Trunk response magnitude in repeated trials was also larger with loud than normal stimuli (mean difference 588 mm/s^2, $P < 0.001$). However, there was no difference in repeated trials with normal and loud stimuli for step reaction time ($P = 0.072$) and step response magnitude ($P = 0.315$).

Impact of Examiner and Baseline Participant Variables

Increased peak pull force was associated with slower trunk reaction times ($b = 0.36$, $P < 0.001$) and larger step response magnitude ($b = 1.02$, $P < 0.001$). Increased participant weight was associated with slower step reaction time ($b = 2.37$, $P = 0.008$). Otherwise, participant weight and height did not influence results.

DISCUSSION

We sought to characterize the nature of postural responses generated by the pull test, to clarify how the test should be performed and interpreted. First pull test trials were significantly different from subsequent repeated trials, demonstrating a slower and larger step response. Despite the relative "surprise" of first trial perturbations (all with normal stimuli), the trunk response was no faster or larger than in repeated trials (with either normal or loud stimuli). In repeated trials, the trunk demonstrated StartReact, that is, loud stimuli were associated with faster responses. Increased peak pull force increased trunk response latency and increased the size of the step response. Increased subject weight increased step response latency. Otherwise, subject weight and height did not influence results.

Before further discussion, potential confounds need to be considered. It is important to note that, in this study, we employed motion tracking as the assessment tool, which detects net movement (akin to a clinician) rather than when muscle recruitment first begins, as is available with electromyography. Importantly, for first trials, we only employed normal stimuli and not also loud stimuli. Thus, we cannot directly assess whether first trials exhibited StartReact. One question is whether intensity effects (Kohfeld 1969; Woodworth 1938) contributed to our finding of StartReact in repeated trials. However, previous studies (Carlsen et al. 2007; Delval et al. 2012) that employed similar stimulus intensities report that the substantial reaction time benefit of StartReact is inconsistent with the modest and gradual reduction in reaction times seen with increasing stimulus intensities. Another potential confound is that of intersensory facilitation (Hershenson 1962). In this study, we excluded intersensory facilitation by employing a control sound of 90 dB in normal trials in addition to the potentially startling116 dB in loud trials (Thevathasan et al. 2011).

Characterization of Postural Responses to the Pull Test

First trial effects. We found that first pull test trials (with normal stimuli) differed significantly from repeated trials (with normal and loud stimuli). Although first trial trunk responses did not differ in latency or magnitude compared with repeated trials with normal and loud stimuli (see further discussion below), the step response was slower and the step magnitude bigger. We interpret this larger step as indicating that first pull test perturbations had a more destabilizing impact on stance. This is supported by our observation that greater peak pull force also generated a larger step response. This also corroborates findings that first trials provoked by platform translation result in greater displacement in center of mass and increased falls (Horak and Nashner 1986; Oude Nijhuis et al. 2009). Why

Table 4. *Coefficient estimates, 95% CI, and statistical significance of instrumented pull test predictors resulting from linear mixed models for step response*

	Step Reaction Time			Step Response Magnitude		
Predictor	Estimate	95% CI	*P* value	Estimate	95% CI	*P* value
Peak force	−0.12	−0.44, 0.19	0.436	1.02	0.55, 1.49	<0.001
Force rate	−0.01	−0.04, 0.02	0.575	0.01	−0.03, 0.06	0.528
Height	−64.65	−283.98, 154.69	0.542	240.26	−797.51, 1,278.03	0.629
Weight	2.37	0.72, 4.03	0.008	−2.51	−10.56, 5.55	0.518

CI, confidence interval.

would first trial responses be performed worse than subsequent repeated trials? First trials are performed slower even for a nonpostural nonstartling task of ankle dorsiflexion, and this may reflect the lesser opportunity for motor preparation compared with after practice (Sutter et al. 2016). This could explain why we found the step response in first trials to be slower (see further discussion below). However, a more specific issue for first postural challenges are findings reminiscent of a confounding startle reflex, including excessive muscle cocontraction, crouching body response, and subsequent habituation (Oude Nijhuis et al. 2009, 2010). The exact nature of the first trial effect is debated, and the pattern of muscle recruitment may not simply be explained by summation of the startle reflex and postural response (Oude Nijhuis et al. 2010). Nevertheless, like the startle reflex, the impact of first trial postural responses to stiffen and crouch the body may have provided evolutionary advantage to our ancestors. However, for the maintenance of upright stance, the first trial response appears to be maladaptive (Allum et al. 2011). In this study, we did not seek the full array of features characterizing the first trial postural response. However, discrimination of first trial from repeated postural responses can be difficult, for example, activation of sternocleidomastoid and masseter occurs in both (Campbell et al. 2013; Oude Nijhuis et al. 2010). Regardless, for the pull test we have found that first trial responses are different from repeated trial responses. This supports that the first pull test trial is worth assessing as a separate end point and could be argued to have greater ecological relevance (see below).

StartReact and motor preparation. For repeated trials, we found that postural responses of the trunk exhibited StartReact, supporting the existence of prepreparation (Valls-Solé et al. 1995, 1999). Only a weak trend suggested StartReact in the step response, which may reflect the secondary importance of stepping, being required only when the earlier trunk response is insufficient (Pai et al. 1998). That StartReact is present in the postural response of the trunk in repeated pull test trials is perhaps unsurprising, given these trials benefitted from practice and foreknowledge of the required response. These findings corroborate platform translation studies which report that repeated postural responses to both forward and sideways perturbations exhibit StartReact (Campbell 2012; Nonnekes et al. 2013). This suggests that repeated postural responses remain in reserve capacity to be released even quicker when there is a concurrent and suitably arresting stimulus. At least one study found that provoking this latent StartReact effect in postural responses is advantageous, improving balance preservation (Nonnekes et al. 2013). However, should not first postural trials also trigger StartReact (even in the absence of a loud stimulus) given their importance and propensity to generate a startle-like response? Indeed, one study found that a first postural challenge was itself a sufficiently arresting stimulus to provoke StartReact in wrist extension (Campbell et al. 2013). However, whether the postural response itself benefits from StartReact in first trials has not been explored (Campbell et al. 2013). Our results, on superficial review, suggest that this may not occur, since we found that first trial trunk reaction times were not different from repeated trials with normal stimuli. However, we did not compare postural responses with normal and loud sounds in first trials. Moreover, a recent study found that, for a nonpostural nonstartling ankle dorsiflexion task, first trials were actually performed slower than subsequent repeated trials (Sutter et al. 2016). Loud startling stimuli sped these first dorsiflexion trials so that they had a similar latency to repeated trials with normal stimuli (Sutter et al. 2016). Taken together, these findings raise the possibility that StartReact could actually have benefited our first pull test trunk responses but sufficed only to bring latencies in line with repeated trials with normal stimuli. This would also explain why the step response, which did not clearly benefit from StartReact in our study, remained slower in first trials compared with repeated trials. This is a hypothesis that could be addressed in future research.

Impact of examiner and baseline participant variables. Peak pull force varied sufficiently to be a factor affecting the latency of the trunk response and the size of stepping. The slower trunk response with increased peak pull force may reflect the greater recruitment of trunk muscles required before sufficient counteracting acceleration (deceleration) could be generated (our definition of response onset) (Cresswell et al. 1994). That increased peak pull force was associated with larger step size likely reflects the greater destabilization produced by a more forceful perturbation and thus the magnitude of the compensatory step required (Pai et al. 1998). Increased participant weight resulted in slower step reaction times. A relationship between increased body mass and slower reaction time has previously been reported (Skurvydas et al. 2009). This may be, at least partly, explained by Newton's second law (force = mass $\times$ acceleration), that is, increased recruitment of leg muscles may be required to generate sufficient force to produce step acceleration, when mass is greater (Skurvydas et al. 2009). Otherwise, weight and height did not influence pull test performance although this may reflect limited variance of these parameters in the participants.

Clinical relevance. We tested a cohort of young healthy controls, and whether these findings are applicable to older patients with Parkinson's disease is worthy of future investigation. For example, StartReact is reported to be delayed with aging (Tresch et al. 2014) and is reported to be absent in some patients with Parkinson's disease (Thevathasan et al. 2011). Regardless, our results are likely to have interest for clinicians who perform the pull test. Our findings support that the first trial response is important to capture as an end point in its own right rather than to be ignored in the primary assessment of the second trial (as suggested in the Movement Disorders Society Unified Parkinson's Disease Rating Scale) or averaged out in analysis of repeated trials (Goetz et al. 2008; Nonnekes et al. 2015; Oude Nijhuis et al. 2010; Visser et al. 2003). Interestingly, previous studies have suggested that the first trial may correlate best with other clinical measures of balance impairment such as falls (Nanhoe-Mahabier et al. 2012; Nonnekes et al. 2015; Oude Nijhuis et al. 2010; Visser et al. 2003). It is encouraging and supportive of ecological relevance that postural responses to the pull test exhibit similar characteristics (at least in terms of first trial responses and StartReact in repeated trials) to those generated in the laboratory from bottom up perturbations where the timing and directions of perturbations are unknown (Campbell 2012; Nonnekes et al. 2013). On the other hand, it seems clear that examiner performance, namely peak pull force, has a substantial impact on pull test results. Clinicians do not have the benefit of a pull force meter and a mixed linear model to adjust for such confounds. Although the pull test remains a very useful clinical test, these findings help

explain why reliability has been an issue and supports the call to develop more objective measures or biomarkers of postural instability (Perera et al. 2018).

Our results may have bearing on rehabilitation strategies that have been employed in patients with Parkinson's disease whereby patients are subject to repeated pulls to enhance the practiced response (Dijkstra et al. 2015; Peterson et al. 2016). It is unclear if this approach would benefit the first, and arguably most important, postural response given the propensity for first trial effects to confound movement execution. These first trial responses may be exaggerated in patients with Parkinson's disease, who have delays in habituation compared with controls (Nanhoe-Mahabier et al. 2012). It has been speculated that exaggerated first trial responses in Parkinson's disease patients may arise as a consequence of fear of falling (Adkin et al. 2003, 2008; Davis et al. 1993; Franchignoni et al. 2005; Grillon et al. 1991). Furthermore, one study (Nieuwenhuijzen et al. 2006) observed that patients with Parkinson's disease are less able to integrate the startle response into phases of gait. If diminished integration of the startle reflex can also involve first postural responses then this could conceivably be a factor in the risk of falls in patients with Parkinson's disease. If so, then it is worth noting that therapies exist to suppress startle and therefore falls in patients with hyperekplexia (exaggerated startle) (McAbee 2015).

The Instrumented Pull Test as a Potential Assessment Tool

This study highlights the capabilities of instrumentation of the clinical pull test with responses assessed with motion tracking. As in clinical practice, the perturbation was delivered manually by an examiner. To deliver the pull, we employed a rope attached to a harness with a force gauge to record the force of each pull. The recording of pull force appears important, since this was a significant cofactor affecting results. The use of an external motion tracker to measure responses was akin to visualization of movement used by clinicians. Of crucial importance was the method of analyzing motion tracking data with respect to the onset of trunk displacement rather than the pull itself. This decision to time lock to the onset of trunk displacement allowed us to exclude several confounds, including the variable time taken to tension the harness and rope by the assessor and the variable stiffening of the body between trials.

Recently, more precisely calibrated truncal perturbations have been attempted in the laboratory with motors and pendulums (de Azevedo et al. 2016; Di Giulio et al. 2016). In contrast, motion tracking is a relatively simple technique (albeit still requiring specialized equipment), and this has been previously employed to assess the "push and release test" (an alternative to the more widely used pull test) (Jacobs et al. 2006; Smith et al. 2016). The instrumented pull test reported here could therefore be a more accessible alternative to assess patients with Parkinson's disease for clinical research. However, we note that the instrumented pull test described here would only be able to finely grade responses in patients who can still maintain stance without falling, that is, patients with Parkinson's disease (up to Hoehn and Yahr stage 3/5) who exhibit up to grade 1 postural instability according to the Unified Parkinson's disease Rating Scale (Fahn and Elton 1987).

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

J.L.T., T.P., J.L.M., P.B., and W.T. conceived and designed research; J.L.T. and S.A.C.Y. performed experiments; J.L.T., T.P., and W.T. analyzed data; J.L.T., T.P., J.L.M., P.B., and W.T. interpreted results of experiments; J.L.T. prepared figures; J.L.T., T.P., and W.T. drafted manuscript; J.L.T., T.P., J.L.M., S.A.C.Y., P.B., and W.T. edited and revised manuscript; J.L.T., T.P., J.L.M., S.A.C.Y., P.B., and W.T. approved final version of manuscript.

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4.2 Summary and conclusions

This study provides preliminary insights into the nature of postural responses that can be elicited by the clinical pull test in healthy young participants. The instrumented pull test was able to detect small speeding of truncal responses (approximately 10 ms), and distinguish first and subsequent trial postural responses. The first pull triggers a different response, including a larger step size suggesting more destabilization. Thus, first trials likely have important clinical and ecological relevance and this finding suggests that they should not be discarded as practice. Furthermore, findings from the instrumented pull test informed test administration and performance. In healthy young participants, examiner pull force was a significant factor influencing the postural response. Findings from this study suggest the instrumented pull test could present an alternative assessment tool to quantify small changes in postural responses in participants with mild PD (Hoehn and Yahr stage ≤ 2) where postural responses to the clinical pull test are considered intact.

CHAPTER 5. CHARACTERISATION OF PULL TEST RESPONSES IN MILD PARKINSON'S DISEASE

5.1 Overview

In Chapter 4, postural responses were characterised in a cohort of young healthy participants using an instrumented pull test and StartReact effects. The current chapter extends the use of the instrumented pull test to investigate postural responses in participants with mild Parkinson's disease (PD). Clinical pull test responses are typically considered to be intact in mild PD (i.e. Hoehn and Yahr (HY) ≤ 2). However, subclinical changes in postural responses to external perturbations have been demonstrated using laboratory based measures (Ganesan et al., 2010; Lee et al., 2013; McVey et al., 2009). The instrumented pull test has potential to be used to characterise postural responses in people with mild PD and detect postural abnormalities. Postural responses elicited from participants with PD using the instrumented pull test could also be used to guide how the test should be performed and interpreted in the clinical assessment of postural responses in PD.

5.2 Introduction

Postural responses are integral to maintain upright stance while standing, walking and in response to an unexpected perturbation (Shemmell, 2015). In PD, impairment of postural responses results in postural instability, and is associated with falls and diminished quality of life (Allen et al., 2013; Hely et al., 2005; Schoneburg et al., 2013). Although postural instability commonly increases with disease progression, it is often not apparent in mild disease (Kim et al., 2013).

In clinical practice, postural responses are commonly assessed using the clinical pull test, where an examiner stands behind the patient and administers a brisk backward pull at their shoulders. The corrective response is subjectively scored according to the Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn S and Elton RL., 1987) and postural stability is assessed as normal when up to two steps are taken to arrest retropulsion (Goetz et al., 2008; Nonnekes et al., 2015). This method has been used extensively in the assessment of individuals with PD, but suffers poor reliability and limited scaling (Bloem et al., 1998; Munhoz et al., 2004). Moreover, the integer-based scoring limits its use in research to detect changes to postural instability in mild disease (Chapter 2).

Variants of pull test administration can confuse interpretation of test responses in clinical practice and research (Nonnekes et al., 2013). According to guidelines by the International Movement Disorders Society (MDS), a forewarned, initial practice trial is performed before the second trial is formally assessed (Goetz et al., 2008). Others claim that an unexpected pull, performed once, is most clinically meaningful, as this has the most ecological relevance to falls occurring in daily life (Bloem et al., 2001; Visser et al., 2003). In people with PD, the postural response during the first pull are more frequently abnormal compared to subsequent trials, with greater propensity to falls (Bloem et al., 2001). Due to the different nature of first trial responses, some studies have discarded the first trial, with the average response from repeated pull test trials measured (Bloem et al., 2001; Foreman et al., 2012; McVey et al., 2013, 2009). However, first trial responses may contain important information about postural control with PD of moderate disease severity (HY stage 2.5 - 3) and healthy participants following a backward platform tilt (Nanhoe-Mahabier et al., 2012). People with moderate PD demonstrated increased centre of mass displacement due to abnormally large trunk flexion and ankle plantarflexion during the first trial compared to healthy participants. Responses to habituated trials were similar in both groups. Habituated trials were defined by the average of subsequent trial responses from trials 5 to 8 as postural responses were demonstrated to take up to five trials to habituate in people with PD (Nanhoe-Mahabier et al., 2012).

Little attention has focused on postural responses that present in mild PD (HY $\leq$ 2). To date, only two studies have investigated postural responses to backward perturbations in people with mild PD (Chastan et al., 2008; Ganesan et al., 2010). These changes in postural responses are subclinical, and do not affect overall balance. People with mild PD demonstrate decreased limits of stability in the backward-left direction to platform tilts (Ganesan et al., 2010) and increased sway when balance is perturbed using platform oscillations compared to healthy individuals (Chastan et al., 2008). Subclinical postural instability experienced in people with PD is suggested to remain well compensated in early disease even during larger perturbations to balance such as platform perturbations (Chastan et al., 2008). However, studies of postural responses in people with mild PD commonly report the averaged outcomes across all trials and do not specifically investigate first trial postural responses. Whether differences are present in first trial postural responses in people with mild PD compared to healthy individuals remains to be explored.

While platform translations can provide insights into postural responses in people with PD, they differ in fundamental ways from the clinical pull test. Moving platforms employ a slip-like movement beneath the feet which elicits a bottom-up ankle to hip strategy (Horak, 2006) whereas the pull test aims to assess a top-down response where there is initial displacement of the trunk - a different challenge to slipping that may occur in daily life, for example, when being bumped in a crowd. In both young and old healthy individuals, emerging evidence suggests truncal perturbations yield different postural characteristics to those conventionally elicited using moving platforms (Colebatch et al., 2016; Colebatch and Govender, 2018; Govender et al., 2015). In healthy young participants, responses to posterior perturbations at truncal level were found to elicit a 'limbo-like' movement (Colebatch et al., 2016). To a posterior truncal perturbation, there is forward acceleration at the tibia (i.e. knee flexion) associated with a complex pattern of muscle activation including tibialis anterior, quadriceps and soleus, with no activation of abdominals (Colebatch et al., 2016). In contrast, posterior perturbations with platform perturbations generate a stereotypical pattern of distal to proximal muscle activation from tibialis anterior, quadriceps to abdominals (Horak and Nashner, 1986). The characterisation of top-down postural responses with truncal perturbations therefore deserves further investigation in people with PD.

Truncal responses are important as they represent the first strategy to maintain upright posture to the pull test, and contributes to initial balance recovery (Di Giulio et al., 2016; Tan et al., 2018). A step response is commonly generated when the truncal response is insufficient to maintain upright stance during the pull test (Horak, 2006), although it is acknowledged stepping can also be triggered by other contextual factors such as fear of falling (Maki and McIlroy, 1997; Pai et al., 1998). To date, studies of truncal perturbations have prioritised responses of the legs (Di Giulio et al., 2016; Foreman et al., 2012; McVey et al., 2013, 2009), with only one study exploring truncal responses to a backward perturbation in people with PD using feet-in-place responses (Di Giulio et al., 2016). To our knowledge, no study has quantified both truncal and step responses to the clinical pull test.

In the study described in this chapter, the instrumented pull test was used to characterise the nature of postural responses in people with mild PD (HY $\leq$ 2), and clarify how the clinical test should be performed and interpreted. First and subsequent postural responses are of interest to determine whether first trial postural responses discriminated people with PD from controls. Variables such as pull force by the examiner, and participant height and weight are

suggested to influence outcomes of the clinical pull test in people with PD (Bloem et al., 1998; Nonnekes et al., 2015; Visser et al., 2003), but have yet to be investigated in the laboratory. The instrumented pull test was previously used to investigate postural responses in a cohort of young healthy participants (Tan et al., 2018) (detailed in Chapter 4). Participants' trunk and step responses were quantified using motion tracking in response to a manual backward pull at shoulder level by an examiner. Pull force was concurrently recorded using a force gauge. Using mixed models analyses, this method replaced discrete clinical scoring to allow precise measurement of postural responses while accounting for variabilities in pull test performance such as examiner pull force and participant height and weight.

5.3 Aims and hypotheses

The aims of the study were to:

1) Investigate if first and subsequent postural responses in people with mild PD were different compared to age matched healthy controls using an instrumented pull test.
   Hypothesis 1a: In the first trial, trunk and step responses are slower and larger in people with mild PD compared to controls.
   Hypothesis 1b: In subsequent trials, truncal and step postural responses are improved in people with mild PD to levels of controls (similar to findings from a previous study which demonstrated no differences in postural responses to platform perturbations in participants with PD and controls in subsequent, habituated trials) (Nanhoe-Mahabier et al., 2012).

2) Determine variables in examiner performance (i.e. pull force produced by the examiner) and baseline participant characteristics (i.e. height and weight) that may influence instrumented pull test responses in people with mild PD.
   (Based on results from Chapter 4)
   Hypothesis 2a: Increased examiner pull force would increase the size of trunk and step postural responses, and the speed of truncal responses but not step responses.
   Hypothesis 2b: Rate of force production (i.e. speed of the pull) would not influence trunk and step postural responses.
   Hypothesis 2c: Participant height would not influence trunk and step postural responses.
   Hypothesis 2d: Participant weight would influence step postural responses with increased weight associated with slower step reaction time.

5.4 Participants and methods

5.4.1 Participants

People with PD were recruited through a private neurology clinic. Potential participants were initially identified by a neurologist (W.T.) based on inclusion and exclusion criteria. The author (J.LT.) then confirmed eligibility and approached potential participants. Healthy controls participants were age matched to participants with PD, and recruited as a sample of convenience. The author (J.L.T.) explained the study protocol to all participants before enrolment. Participants read and signed a Participant Information and Consent Form (Appendix 2) prior to assessment. The study was approved by the Melbourne Health Human Research Ethics Committee (2013.129) (Appendix 3).

5.4.2 Inclusion and exclusion criteria

Participants with PD were included based on the following criteria:

i) Fulfilment of the UK Brain Bank criteria for idiopathic PD (Gibb and Lees, 1988).
ii) A daily regime of oral dopaminergic medication, with beneficial response to medication.
iii) HY staging ≤ 2, off levodopa (i.e. unilateral disease to bilateral disease, with pull test item 30 responses ≤ 1) (Fahn et al., 1987), as the study focused on people with mild PD.
iv) A Mini Mental State Examination (MMSE) (Folstein et al., 1975) score of 24 or higher as lower scores indicate cognitive impairment (Crum et al., 1993). As the focus of the study was postural responses to a backward pull, cognitive decline could affect the ability to follow test instructions and task performance.

Participants with PD were excluded based on the following criteria:

i) Any co-existing neurological (e.g. stroke or prior brain surgery), cardiovascular, vestibular, vision and musculoskeletal conditions (e.g. hip and knee osteoarthritis, including use of foot orthotics or splints) that may impair postural stability.
ii) Use of any gait aid.
iii) Unable to stand independently in the off medication condition.
iv) Unable to comply with the study protocol (i.e. complete 35 instrumented pull test trials).

Age matched healthy controls were excluded based on the following criteria:

i) Any neurological, cardiovascular, vestibular, vision and musculoskeletal conditions (e.g. hip and knee osteoarthritis, including use of foot orthotics or splints) that may impair postural stability.
ii) On medications known to affect postural stability or attention (e.g. antidepressants, neuroleptics, benzodiazepines, antiepileptics, antiarrhythmics and diuretics).
iii) Use of any gait aid.
iv) Falls in the past year.
v) Unable to stand independently.
vi) Unable to comply with the study protocol (i.e. complete 35 instrumented pull test trials).

5.4.3 Experiments

Clinical Assessments

Participants with PD were assessed in the morning in the off condition (following overnight withdrawal of levodopa > 12 hours). We explored postural responses in participants with mild PD in the off levodopa condition to detect signs of postural abnormalities (Bonnet et al., 2014; Nanhoe-Mahabier et al., 2012). They were first clinically characterised using the motor subsection part III of the UPDRS (score/108) (Fahn et al., 1987) and Gait and Falls Questionnaire (GFQ, score/64) to assess for prior falls in the preceding 12 months (Giladi et al., 2000). A full description of the clinical assessments employed is provided below. All clinical assessments were rated by the thesis author, a physiotherapist with expertise in movement disorders (J.L.T.). Following clinical assessments, participants were assessed using the instrumented pull test.

Unified Parkinson's Disease Rating Scale (UPDRS)

The UPDRS was used to quantify disease severity and assess motor function in response to therapeutic interventions in participants with PD (Perlmutter, 2009; Ramaker et al., 2002). The UPDRS is widely accepted for the evaluation of PD, and used in many clinical trials (Mitchell et al., 2000). Overall, systematic evaluation of the UPDRS demonstrated high internal consistency and inter-rater reliability (Martínez-Martín et al., 1994; Ramaker et al., 2002; Richards et al., 1994; Stebbins and Goetz, 1998), particularly across the motor

subsection (Part III) (Forjaz and Martinez-Martin, 2006; Stebbins and Goetz, 1998) which quantifies the motor manifestations of PD (score/108). Only the motor subsection was used in our protocol as it was of interest to quantify physical function. Individual items are scored using a five-point ordinal scale (0 to 4) where a higher score indicates greater impairment and disability. Items 27 – 30 (score/16) assessing arising from a chair, posture, gait and postural instability respectively were summed to give a single axial score.

The clinical pull test

Postural instability was evaluated according to item 30 of the UPDRS (Fahn et al., 1987). A corrective stepping response is scored (between 0 to 4) by an examiner who administers a brisk tug backwards at shoulder level. Though it is the most commonly used measure by clinicians and researchers to evaluate postural instability and determine effects of therapeutic interventions (Ramaker et al., 2002), variability with test administration and interpretation can affect outcomes. Pull force by the examiner, and participant and examiner height and weight makes the test difficult to standardise. Controversies remain as to whether the test should be administered warned or un-warned, and whether responses to the first unexpected pull or second practiced pull is most informative (Visser et al., 2003). Accordingly, the clinical pull test has been found to be a poor and variable predictor of future falls, especially in the on medication state (Bloem et al., 2001; Foreman et al., 2011; Munhoz and Teive, 2014). To improve accuracy of evaluation, recommendations have been made to standardise technique and scoring (Munhoz et al., 2004). In 2007, a revised version of the UPDRS – the MDS-UPDRS was developed to address some of the limitations of the UPDRS by providing standardised instructions to examiners and detailed scoring criteria to differentiate milder levels of impairment (Goetz et al., 2008, 2007). While the clinical pull test (and scoring of motor subsection Part III) according to the MDS-UPDRS would have been the preferred clinical assessment, data collection for a related study to the thesis (Appendix 1) began before the MDS-UPDRS was released. To ensure comparability and consistency of data collection in studies across the doctoral project, the UPDRS was used instead of the MDS-UPDRS.

Regardless, the clinical pull test is not designed to assess underlying causes of postural disturbances. The observational nature of rating scales cannot distinguish subtle changes in postural instability, particularly in mild disease (Mancini et al., 2012; McVey et al., 2009). Furthermore, clinical assessments are not sensitive to detect changes that identify increased

falls risk, for example, when a person has moved their centre of mass too far out of base of support (Rocchi et al., 2002).

Despite its shortcomings, the clinical pull test is one of the few test of reactive postural control which is not confounded by other aspects of mobility (Hass et al., 2008). It is easy to administer, providing clinicians a gross approximation of potential postural abnormalities (Visser et al., 2003). Consequently, it represents a useful first step in quantifying the postural response in people with PD.

Mini-Mental State Examination

Participants' cognition were assessed with the Mini-Mental State Examination (MMSE, score/30) (Folstein et al., 1975). Inclusion criteria required a score of 24 or higher, as lower scores indicate cognitive impairment. Cognitive decline in PD could affect understanding of test instructions and influence task performance, as well as the ability to provide informed consent.

Gait and Falls Questionnaire

The gait and falls questionnaire (GFQ), (score/64) was administered to determine if participants demonstrated gait disturbances and falls prior to study enrolment. The GFQ assesses gait impairments including freezing of gait, festination and falls in people with PD (Giladi et al., 2000). An inclusion criterion of the clinical PD cohort was the recruitment of participants with no clinically demonstrated postural instability, where catching by an assessor was required. Though FOG is common in advanced PD it can also occur early in disease, and is a frequent cause of falls (Kerr et al., 2010; Latt et al., 2009; Okuma, 2014). To assess for presence of FOG, the FOGQ, (score/24) consisting of six items (items 2 to 7 of the GFQ) was used to identify FOG severity and gait disturbances. The falls question (item 12) was used to provide a report of prior falls in the past year. In particular, item 3 of the FOGQ is shown to be a good screening question of FOG frequency (Moore et al., 2007). Previous studies have reported the FOGQ is a well validated measurement tool and demonstrates satisfactory test-retest reliability and internal consistency (Baggio et al., 2012; Giladi et al., 2009, 2000; Nilsson and Hagell, 2009). It adequately correlates to the UPDRS ($r = 0.79$), and has excellent sensitivity (85.9%) to detect freezers (Giladi et al., 2009). Each item is scored from 0 to 4, with higher scores indicating worse motor function.

The instrumented pull test

The instrumented pull test was performed similarly to the clinical pull test (Fahn et al., 1987). Details of the experimental setup and equipment were previously described in Chapter 3. Briefly, the participant stood in bare feet and focused on artwork approximately 1.5m ahead, wearing a customised trunk harness attached to a load cell. The examiner generated a manual backward pull via a rope and load cell held perpendicular to the participant's shoulders. Stepping by participants was permitted and pulls were always of sufficient force to generate a step response in every trial. Thirty five trials were presented serially. Inter-trial intervals (10-15s) were variable. Participants were provided a short rest after every 10 trials, or as requested. The experiment was administered in a quiet room with distractions minimised. The thesis author (J.L.T.) conducted all assessments and continuously monitored participants to prevent falls.

Postural responses were measured using electromagnetic three-dimensional motion tracking sensors (Ascension TrakStar), attached at the sternal notch (at the level of the 2nd and 3rd thoracic vertebra) to record trunk parameters, and on the right and left ankle malleolus to record stepping parameters. Each sensor measured triaxial displacement in millimetre units as well as pitch, roll, and yaw in degrees. The sensors were referenced to the origin of the transmitter, which comprised the motion tracking system.

5.4.4 Parameters and data analysis

A separate researcher computed trunk and step parameters using custom scripts in MATLAB (MathWorks Inc, Massachusetts, USA). The same parameters related to trunk and step reaction time and response magnitude (i.e. trunk deceleration and feet displacement) were previously used to characterise postural responses in healthy young participants using StartReact effects (Chapter 4). A full list and description of trunk and step parameters in the present study are reported in Table 5.1. These parameters were chosen to examine responses of trunk and step known to be affected by PD (Adkin et al., 2005; Benatru et al., 2008; Carpenter et al., 2004). Peak pull force (Newtons) and rate of pull force development (Newtons/second) were calculated using data from the load cell.

Trunk and step parameters were computed for each trial. To investigate postural responses during first and subsequent pulls, the first trial response was included in analysis. After the first pull, the following four trials were considered 'practice' trials and discarded. Postural

responses are known to take up to five trials to habituate in people with PD (Nanhoe-Mahabier et al., 2012). The subsequent postural response was determined by the averages over the subsequent 30 trials (i.e. Trials 6 to 35). Trials were rejected if there was an anticipatory truncal movement (a forward trunk displacement that exceeds 3 SDs above baseline in the one second epoch prior to the pull).

Table 5.1: Postural response parameters and descriptions

Parameters	Description	Units
Trunk reaction time	Difference between the onset of trunk displacement and the start of trunk deceleration	Milliseconds (ms)
Trunk deceleration	Peak deceleration of the trunk	Millimetres per second per second (mm/s^2)
Posterior pitch angle	Angular displacement of the trunk from initial stance to peak trunk extension (prior to stepping)	Degrees (°)
Posterior pitch velocity	Peak posterior pitch angle divided by pitch duration (time between onset of trunk displacement to peak trunk extension)	Degrees per second (°/s)
Step reaction time	Time between onset of trunk displacement and initial foot lift off	Milliseconds (ms)
Initial step length	Displacement of the initial stepping limb from foot lift off to foot contact	Millimetres (mm)
Step velocity	Initial step length divided by the first step duration (initial foot lift off to initial foot contact time)	Millimetres per second (mm/s)
Retropulsion	Total posterior displacement between first foot lift off and landing of the final foot arresting movement	Millimetres (mm)
Step count	Number of foot falls over the retropulsion distance	Integer (e.g. 0, 1, 2)

5.4.5 Statistical analysis

A Kolmogorov Smirnov test demonstrated that all measures were sampled from an underlying normal distribution. Due to the number of contributing factors that could influence trunk and stepping parameters in the pull test, linear mixed models (LMM) analysis was conducted according to methods previously described (Boisgontier et al., 2017; Tan et al., 2018). To determine effects of pull force on trunk and step parameters in the postural response task, LMM analysis was conducted using the following equation:

$$Y_{ij} = (\beta_0 + \theta_{0j}) + \beta_1 \text{TrialType}_{ij} + \beta_2 \text{Group}_j + \beta_3 \text{Weight}_j + \beta_4 \text{Height}_j + \beta_5 \text{PeakForce}_{ij} + \beta_6 \text{ForceRate}_{ij} + \epsilon_{ij}$$

where Y_{ij} is the participant's trunk or step postural response parameter (Table 5.1) for trial_i, β_{0-6} are the fixed effect coefficients, θ_{0j} is the random effect for participant *j* (random intercept), ϵ_{ij} is the error term.

This model was built using SPSS (IBM, Chicago, IL) version 22. The following factors were included: trial type, group, weight, height, peak force and force rate. At the participant level, height and weight were included to account for the lever arm of the pull and inertia of the trunk (Delitto et al., 1989; Oliveira et al., 2011).

To determine if the first trial was different from subsequent trials, the trial type was coded as 0 for first trial and 1 for subsequent trials. Group was coded as 0 for healthy control participants, 1 for participants with PD. Nine independent LMM relating to trunk and step parameters were used to analyse the data. Variance inflation factors for each predictor in all models fell below 10 and multicollinearity was considered negligible (Hair et al. 1995). The variance components covariance structure was selected for the LMM. For categorical explanatory variables, post hoc pairwise comparisons were performed to determine differences between trial type and groups and were corrected for multiple comparisons (Benjamini and Hochberg, 1995). Results reported are mean and 95% confidence interval (CI).

For each explanatory variable, an estimate of the effect, p value and CI were calculated. To assess if explanatory variables (i.e. peak pull force, force rate, participant height and weight) differed between groups (participants with PD, controls), LMM was used within each group. Level of significance was set at $\alpha = 0.05$.

5.5 Results

Two cohorts were assessed: (i) 18 participants (age 59.1 ± 9.3 years; height 1.65 ± 0.1 m; weight 82.7 ± 16.5 kg; 12 males) with mild PD and no clinically detectable postural instability (HY ≤ 2); and (ii) 11 healthy age matched controls (58.8 ± 7.8 years; height 1.71 ± 0.1 m; weight 73.2 ± 13.2 kg; 5 males). The two groups did not significantly differ in age (p

= 0.9), height (p = 0.085), or weight (p = 0.099). Clinical characteristics of the participants with PD and age matched healthy controls are detailed in Table 5.2 respectively. No trials were excluded due to truncal anticipation prior to the pull. One healthy participant experienced a fall, requiring catching by the examiner during the first trial. Data from this trial were excluded. Otherwise no falls were reported with all participants. All participants adhered to the experimental protocol, with no participant withdrawals.

Table 5.2: Characteristics of participants with Parkinson's disease and age matched healthy controls

Group	Participant	Age/ Gender	Height (m)	Weight (kg)	HY Stage	PD Duration (years)	LED (mg/day)	UPDRS III, OFF meds	UPDRS It 30, OFF meds	GFQ	FOGQ	Falls Q	Supportive for UK brain bank criteria
PD	1	46F	1.51	67.4	2	1	600	18	0	3	0	0	T, A, P, D
PD	2	53F	1.57	43.8	2	2	400	32	0	7	4	0	T, A, P
PD	3	51M	1.85	85.0	2	4	500	15	0	5	2	0	T, A, P
PD	4	63M	1.90	101.7	2	4	850	23	0	2	2	0	T, A, P
PD	5	59M	1.70	88.2	2	6	500	53	0	5	3	0	T, A, P
PD	6	55M	1.84	106.1	2	8	1500	22	1	15	9	0	T, A, P
PD	7	59M	1.76	101.2	2	12	500	30	0	7	4	0	T, A, P, D
PD	8	55F	1.67	63.5	2	4	500	23	0	7	4	0	T, A, P D
PD	9	51F	1.55	88.9	2	3	600	11	0	3	2	0	A, P
PD	10	65F	1.66	84.7	2	15	400	33	0	9	4	1	T, A, P, D
PD	11	66M	1.78	75.2	2	9	650	32	1	7	3	0	T, A, P, D
PD	12	50F	1.57	64.5	2	2.5	600	16	0	7	2	0	T, A, P, D
PD	13	76M	1.75	70.0	1	6	350	12	0	0	0	0	T, A, P
PD	14	56M	1.68	83.2	2	3	450	14	0	4	1	0	T, A, P
PD	15	72M	1.70	85.4	2	7	600	22	0	4	2	0	A, P, D
PD	16	71M	1.73	80.2	2	5	300	19	0	1	0	0	T, A, P
PD	17	46M	1.79	103.5	2	2	800	13	0	1	0	0	T, A, P
PD	18	71M	1.76	96.5	2	8	550	19	0	3	1	0	T,A, P
HC	1	65M	1.73	77.7	-	-	-	-	-	-	-	-	-
HC	2	56M	1.73	100.3	-	-	-	-	-	-	-	-	-
HC	3	43F	1.63	61.3	-	-	-	-	-	-	-	-	-
HC	4	64M	1.68	78.5	-	-	-	-	-	-	-	-	-
HC	5	50F	1.59	67.1	-	-	-	-	-	-	-	-	-
HC	6	67F	1.53	71.8	-	-	-	-	-	-	-	-	-

Group	Participant	Age/ Gender	Height (m)	Weight (kg)	HY Stage	PD Duration (years)	LED (mg/day)	UPDRS III, OFF meds	UPDRS It 30, OFF meds	GFQ	FOGQ	Falls Q	Supportive for UK brain bank criteria
HC	7	57F	1.72	72.8	-	-	-	-	-	-	-	-	-
HC	8	66M	1.73	91.4	-	-	-	-	-	-	-	-	-
HC	9	67F	1.57	58.9	-	-	-	-	-	-	-	-	-
HC	10	54F	1.60	59.5	-	-	-	-	-	-	-	-	-
HC	11	58M	1.63	65.4	-	-	-	-	-	-	-	-	-

Clinical assessments were performed on the same day as experiments. LED = L-DOPA equivalent dose, mg/day; HC = Healthy control; HY = Hoehn and Yahr; UPDRS III = part III (motor subsection) of the Unified Parkinson's Disease Rating Scale (score/108), off medication state; Pull test (item 30;score/4), off medication state; GFQ = Gait and Falls Questionnaire (score/64); FOGQ = Freezing of Gait Questionnaire (score/24); Falls Q = Falls Question (score/4); UK Brain bank criteria: D = dyskinesias; A = asymmetry persistent; T = tremor at rest; P = progressive disease course; PD = Parkinson's disease.

5.5.1 First and subsequent postural responses in mild Parkinson's disease

Trunk responses

Mean trunk reaction time differed in participants with PD compared to controls ($F(2,480) = 4.45$, $p = 0.012$) across all trials. Post hoc tests revealed average trunk reaction time did not differ between groups during first trials (mean difference = - 31.8 ms; CI = - 76.3, 12.6; $p = 0.192$), but was faster in participants with PD compared to controls in subsequent trials (mean difference = - 44.5 ms; CI = - 61.5, - 27.4; $p < 0.001$). Mean pitch angle ($F(2, 61) = 7.01$, $p = 0.002$) and velocity ($F(2, 64) = 9.70$, $p < 0.001$) differed in participants with PD compared to controls. Post hoc tests revealed pitch angle and velocity were larger and faster in participants with PD compared to controls in first (pitch angle mean difference = 15°; CI = 2, 27; $p = 0.030$; pitch velocity mean difference = 114°/s; CI = 34, 194; $p = 0.006$) and subsequent trials (pitch angle mean difference = 20°; CI = 10, 31; $p < 0.001$; pitch velocity mean difference = 138°/s; CI = 72, 204; $p < 0.001$) (Figure 5.1).

There was no statistical difference detected in mean trunk deceleration between participants with PD and controls in first (mean difference = 510 mm/s^2; CI = - 2074, 3095; $p = 0.639$) and subsequent trials (mean difference = - 88 mm/s^2; CI = - 896, 719; $p = 0.826$). The trial x group interaction was not significant ($F(2, 1082) = 0.13$, $p = 0.881$).

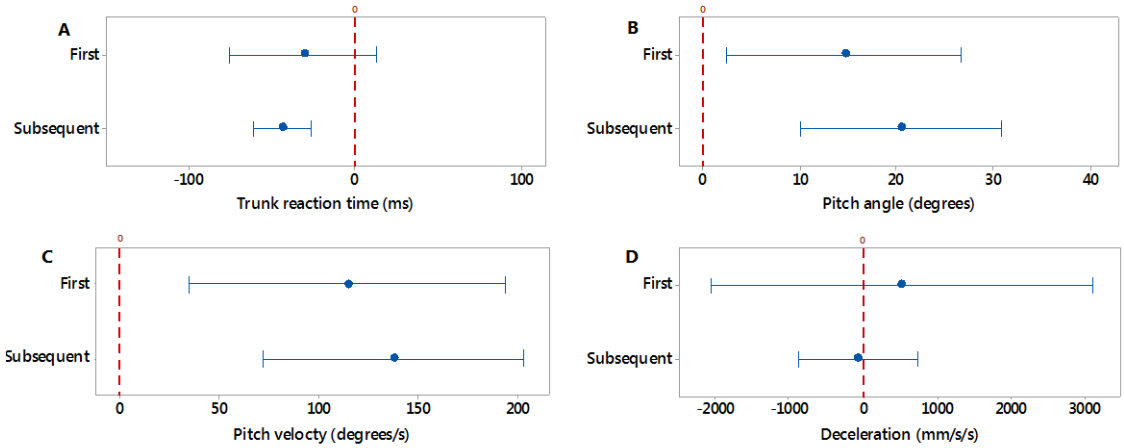

Figure 5.1: Mean difference in trunk parameters between participants with PD and controls during first and subsequent trials
(A) Trunk reaction time, (B) Pitch angle, (C) Pitch velocity and (D) Deceleration. Error bars represent the 95% confidence interval. Effect of group on trunk parameters is statistically significant between participants with PD and controls where error bars do not cross zero (dashed red vertical line).

Step responses

Mean initial step length (F (2, 62) = 7.87, p = 0.001) and retropulsion (F (2, 64) = 24.91, p < 0.001) differed in participants with PD compared to controls across all trials. Post hoc tests revealed step length did not differ during first trials between groups (mean difference = - 56 mm; CI = - 130, 17; p = 0.132), but was smaller in participants with PD compared to controls in subsequent trials (mean difference = - 81 mm; CI = - 144, - 19; p = 0.024). Retropulsion remained smaller on average in participants with PD compared to controls in first (mean difference = - 84 mm; CI = - 155, - 14; p = 0.024) and subsequent trials (mean difference = - 64 mm; CI = - 123, - 6; p = 0.033). Although there was a main effect of trial on step count (F (1, 1403) = 30.42, p < 0.001), post hoc tests revealed step count did not differ between participants with PD and controls in first (mean difference = - 0.2 step; CI = - 0.7, 0.4; p = 0.586) and subsequent trials (mean difference = - 0.1 step; CI = - 0.5, 0.3; p = 0.586) (Figure 5.2).

Mean step velocity differed in participants with PD compared to controls (F (2, 64) = 8.77, p < 0.001) across all trials. Post hoc tests revealed step velocity did not differ during first trials (mean difference = - 200 mm/s; CI = - 425, 26; p = 0.081), but was slower on average in subsequent trials in participants with PD compared to controls (mean difference = - 248 mm/s; CI = - 435, - 60; p = 0.018). Mean step reaction time was not statistically significant between groups (F (2, 70) = 0.38, p = 0.687). Post hoc tests revealed average step reaction time did not differ with PD compared to controls during first (mean difference = - 43.8 ms; CI = - 124.7, 37.2; p = 0.285) and subsequent trials (mean difference = - 4.5 ms; CI = - 68.4, 59.4; p = 0.885). The trial x group interaction was also not statistically significant (F (2, 1398) = 2.95, p = 0.053).

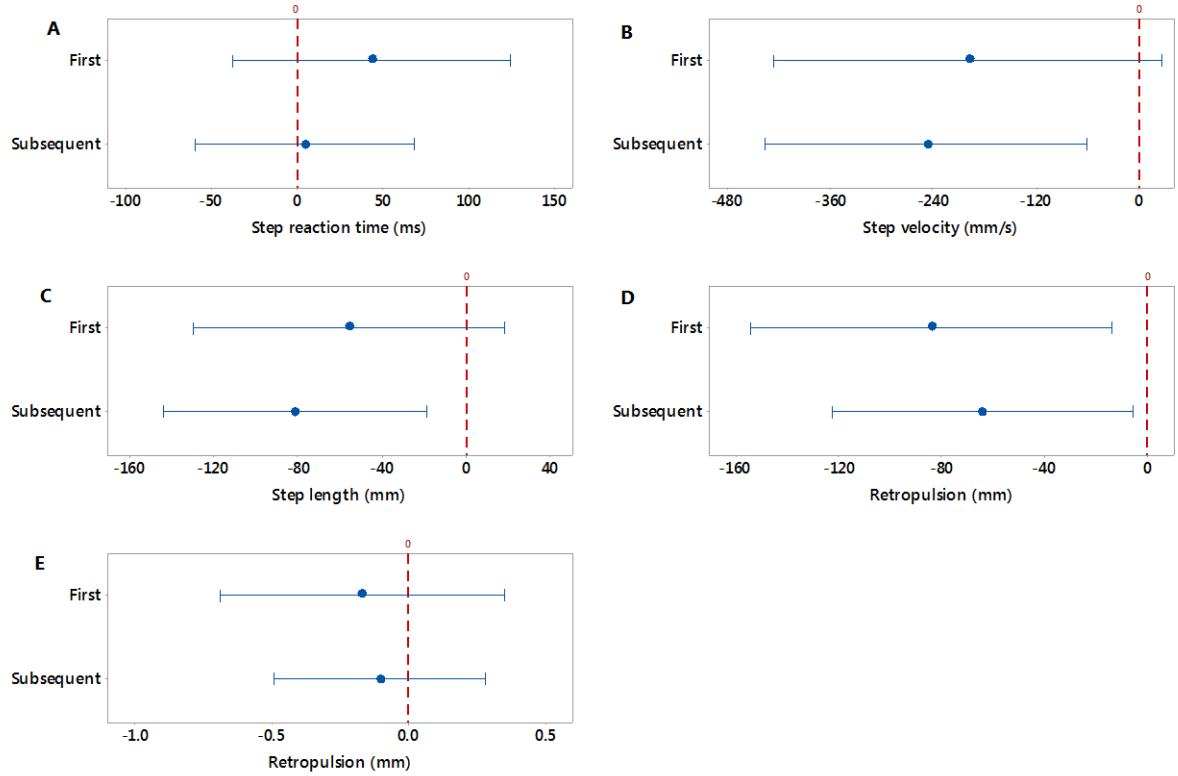

Figure 5.2: Mean difference in step parameters between participants with PD and controls during first and subsequent trials.
(A) Step reaction time, (B) Step velocity, (C) Step length, (D) Retropulsion and (E) Step count. Error bars represent the 95% confidence interval. Effect of group on step parameters is statistically significant between participants with PD and controls where error bars do not cross zero (dashed red vertical line).

5.5.2 Impact of examiner pull force and participant anthropometric characteristics

Linear mixed models analysis was conducted with random factors of participant, trial and group type, and fixed explanatory variables of weight, height, peak force and force rate. For each explanatory variable, an estimate of the effect and significance is provided (Figure 5.3). Outcomes are pooled from first and subsequent trials. When the explanatory variable is continuous, the estimate of the effect is based on the regression coefficient (denoted as b); it gives the predicted increase in outcome for a one point increase in the explanatory variable. Explanatory variables further detailing the estimate, p value and 95% confidence intervals in participants with PD and healthy controls are specified in Appendix 6.

In participants with PD and controls, peak pull force by the examiner was the main contributor to trunk and step parameters. In participants with PD, increased peak pull force was associated with larger pitch angles ($b = 0.11$, $p < 0.001$) and faster pitch velocities ($b = 0.57$, $p < 0.001$). With stepping, increased peak pull force was associated with increased step

velocity (b = 2.49, p < 0.001), initial step length (b = 0.70, p < 0.001) and retropulsion (b = 1.02, p < 0.001) (Figure 5.3). In controls, examiner pull force was associated with the same trunk and step parameters as PD, except pitch velocity which was not significant. Increased peak force was associated with increased step count (b < 0.01 p = 0.018) in controls. Increased weight was associated with a smaller pitch angle (b = - 0.84, p = 0.034) in participants with PD. Otherwise, height and weight did not influence results in participants with PD or controls.

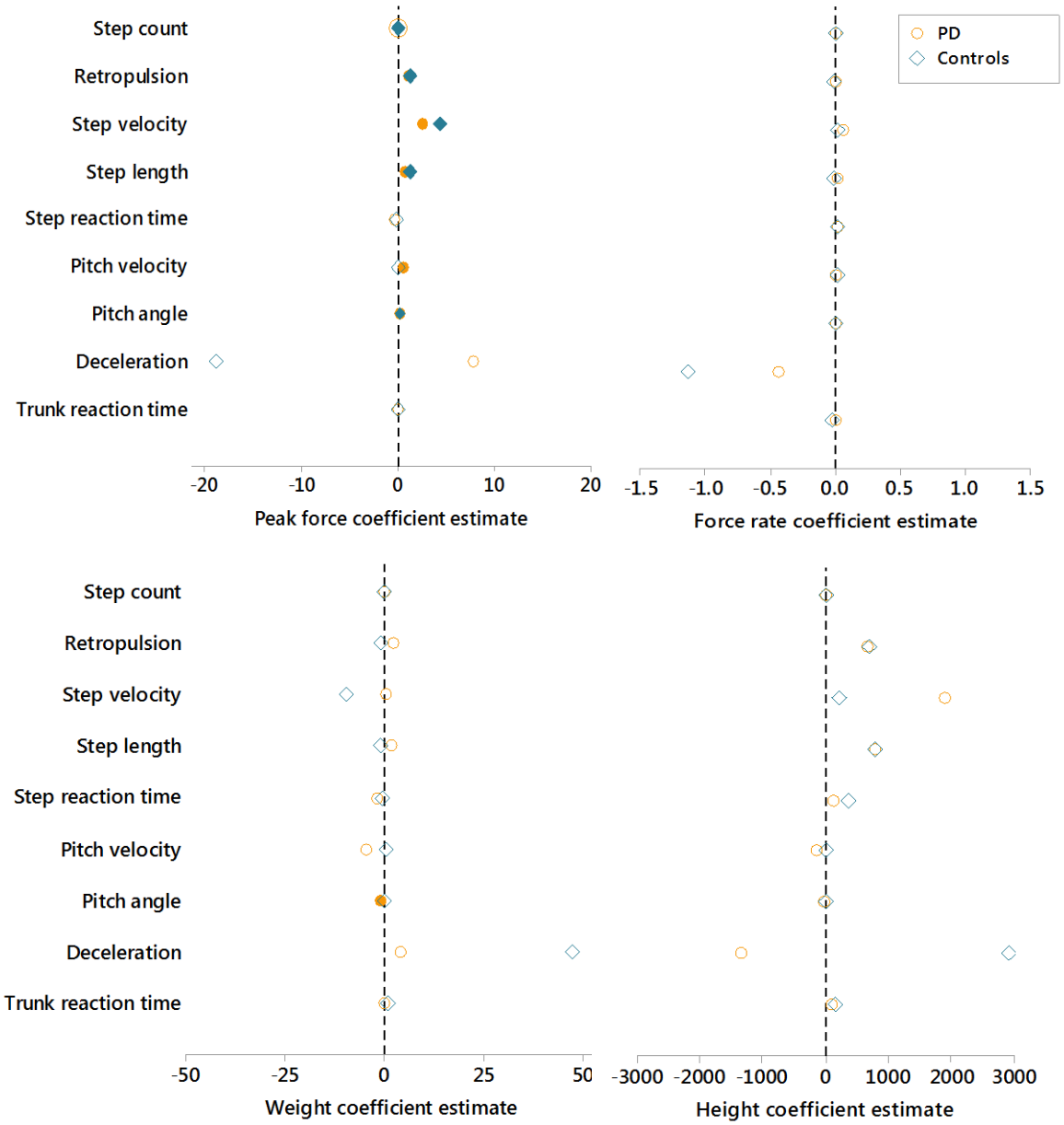

Figure 5.3: Coefficient estimates and statistical significance of instrumented pull test predictors resulting from linear mixed models for truncal and step responses.
Coefficient estimates and statistical significance of instrumented pull test predictors resulting from linear mixed models for truncal and step responses. Each panel illustrates the effect of an explanatory variable (i.e. peak pull force and force rate produced by the examiner, and participant height and weight) based on a regression coefficient using linear mixed models. Solid symbols represent significant effects ($p < 0.05$).

5.6 Discussion

This study sought to characterise the nature of postural responses in participants with mild PD compared to healthy age matched controls using an instrumented pull test. The key findings of this study are: 1) postural responses are affected in participants with mild PD in first and subsequent trials. In the first trial, trunk responses were larger and faster in trunk pitch in people with mild PD compared to controls. Step responses with initial step size and reaction time did not differ between groups. However, overall retropulsion was smaller in participants with PD compared to controls. Trunk and step abnormalities observed in participants with PD during the first trial remained in subsequent trials. Stepping abnormalities were more exaggerated, with stepping becoming even smaller and slower in participants with mild PD compared to controls. 2) Pull force exerted by the examiner significantly affected the postural response in participants with PD. Greater peak pull force led to an increase in the size and speed of trunk and step movement. Increased participant weight was associated with smaller trunk movement in participants with PD. Otherwise, participant height and weight did not influence results. These findings may have clinical implications when performing the pull test.

5.6.1 Postural responses to the pull test in mild Parkinson's disease

Our results showed abnormalities in trunk and step responses were detected in participants with mild PD. In PD, few researchers have investigated truncal perturbations in the laboratory (Azevedo et al., 2016; Colebatch et al., 2016; Di Giulio et al., 2016; Govender et al., 2015). This may be due to the difficulty of administering and assessing a perturbation at shoulder level compared to platform perturbations. For the first time, kinematics of trunk and step responses were characterised akin to the clinical test in people with mild PD. Furthermore, the instrumented pull test accounted for pull force, a significant variable confounding postural outcomes.

Postural instability that is clinically evident is not considered a presenting feature of PD (Beuter et al., 2008; Hermanowicz, 2001). Accordingly, the majority of studies of postural perturbations have focused on people with mild to moderate disease severity where postural instability is present on clinical assessment (Bloem et al., 1998; Dimitrova et al., 2004; Horak et al., 2005; Jacobs and Horak, 2006; Kam et al., 2014). Consistent with our findings, previous studies focussing on earlier disease stages also demonstrated subclinical changes in

postural responses in people with PD (Chastan et al., 2008; Ganesan et al., 2010; Lee et al., 2013; McVey et al., 2009). However, these studies examined either truncal (Chastan et al., 2008; Ganesan et al., 2010) or stepping responses (Lee et al., 2013; McVey et al., 2009), but not simultaneously. Several studies have reported subclinical postural changes in mild PD that include increased mediolateral sway (Chastan et al., 2008), increased weight shift times (Ganesan et al., 2010), and altered ankle joint motion (McVey et al., 2009) compared to controls. Although findings from our study cannot be directly compared to previous work due to differing methodology, we show stepping is directly impacted even in mild disease, with decreased initial step size and retropulsion in participants with PD. These findings have not previously been demonstrated and add to the growing body of evidence suggesting postural impairments occur in mild PD.

5.6.2 First trial postural responses

Faster and larger trunk responses detected in first (and subsequent) trials in participants with PD suggests the net torque used for postural correction was smaller or slower in participants with PD compared to controls, resulting in greater displacement. Smaller, weaker postural responses termed 'postural bradykinesia' have been previously reported in people with PD ranging from HY Stage 1.5 to 4 in a study using platform perturbations (Dimitrova et al., 2004). Here, we found truncal responses in the first trial were faster and larger in participants with PD compared to controls, suggestive of a less effective postural correction.

The greater backward trunk pitch prior to stepping may indicate a diminished initial response of the trunk to aid balance recovery. In this study, we did not specifically measure movement of the trunk from centre of pressure deviations and ground reaction forces. However, previous work have found that people with PD have smaller feet-in-place responses when resisting a backward perturbation compared to controls, resulting in increased displacements of the body (Di Giulio et al., 2016). Interestingly, no group x trial interaction in truncal deceleration was found. This meant that there were no differences in how fast participants slowed truncal movement in first and subsequent trials. This finding may be due to the large variability in deceleration, particularly during the first, unexpected trial. As shank movement of the lower limbs were not measured, we could not ascertain if trunk deceleration occurred as a result of a pure trunk movement or a 'limbo' type truncal response with forward bending of the knees, or combination of both. No change was found in other truncal parameters,

similar to previous findings of first trial truncal responses (in pitch and velocity) between participants with PD and controls (Adkin et al., 2005).

Alternatively, the greater trunk pitch in participants with PD may reflect an increased flexed or stooped posture in initial standing compared to control participants. Backward trunk pitch was calculated relative to the starting position of each participant just before the pull. Although stooped posture was not formally assessed, it is possible that greater stooping in participants with PD may contribute to larger pitch angle during the pull. Stooping is also known to be a destabilising posture (Jacobs et al., 2005). However, stooped posture does not fully account for postural abnormalities observed in people with moderate PD during platform translations such as increased co-activation of lower limb muscles (Bloem et al., 1992b; Jacobs et al., 2005).

In line with normal responses to the clinical pull test in participants with PD, step count did not differ between groups. However, overall retropulsion was smaller in participants with PD compared to controls, indicating smaller size in backward corrective steps. It is emphasized these statistically significant changes to retropulsion (84 mm smaller in participants with PD vs controls) did not affect instrumented pull test performance in both groups. Abnormal proprioceptive-motor integration likely contributes to the impaired scaling and control of movement amplitude observed (Jacobs and Horak, 2006). The smaller retropulsion in participants with PD in both first (and subsequent) trials, may represent one of the earliest abnormalities of protective stepping responses in mild PD that is yet to be well characterised. This findings are important for clinicians so that they can consider initiation of therapies earlier in disease course, such as those focussing on amplitude training (Farley and Koshland, 2005; Petzinger et al., 2013).

Consistent with our findings, a previous study also found first trial postural responses to platform rotation discriminated people with PD and controls. Larger truncal movement and ankle movements were demonstrated to toe-up rotations in participants with PD compared to controls (Nanhoe-Mahabier et al., 2012). However, participants recruited were of increased disease severity from HY Stage 2.5 to 3 and demonstrated postural instability. To our knowledge, no study has quantified first trial postural responses in trunk or step to a perturbation in mild disease.

It is unclear how postural instability develops as PD progresses, and how it relates to disease severity. Changes in truncal postural responses could contribute to the increased falls risk reported in people with mild PD (Kerr et al., 2010). Later in disease, impaired trunk and head control is associated with impairments in tasks of walking, balance and increased falls risk (Adkin et al., 2005; Cole et al., 2010). Accordingly, these biomechanical measurements could potentially be used as markers to identify postural instability in mild PD, and track change over time. However, abnormalities in truncal responses are not normally observable, nor considered in pull test criteria. Therefore, these changes may be useful to discriminate differences in postural responses in people with mild PD and controls in response to therapy (Chapter 6) or to monitor disease progression.

5.6.3 Subsequent trial postural responses

In subsequent trials, abnormalities of trunk and step responses in participants with PD detected during the first trial persisted, with further decreases in step size and speed compared to controls. Slower backward stepping was previously reported in people with mild PD compared to controls using platform translations (Lee et al., 2013). Hypometric stepping is also known to occur in PD in more advanced disease where patients produce steps of shorter length, requiring greater distances to regain balance to a backward pull (Jacobs and Horak, 2007; Kam et al., 2014; King and Horak, 2008). However, the presence of smaller initial steps has hitherto not been demonstrated in mild PD (Lee et al., 2013; McVey et al., 2009). A previous study investigating postural responses to a backward perturbation in mild PD found changes in movement preparation with increased weight shift time and dorsiflexion of the ankle prior to stepping, but no changes in initial step size (McVey et al., 2009). This may be due to different methodology which averaged responses from three trials, including the first trial which may have comprised different step characteristics. Furthermore, the perturbation employed a backward waist pull comprising a weight drop calibrated at 20% participant body weight. In contrast, the instrumented pull test employed manual pulls and pull force that was accounted in the statistical analyses for each trial.

Postural response latencies for people with PD are reported to be normal (Jacobs and Horak, 2006; Kam et al., 2014) or slightly faster than normal to an external perturbation (Dimitrova et al., 2004). In the current study, trunk reaction time was quicker in participants with PD compared to controls in subsequent trials. Quicker truncal reaction times in antagonist

muscles have been found using backward platform translations in people with PD, and postulated to arise from either abnormally increased background activity, decreased selectivity of muscle recruitment or anticipation of an expected perturbation (Dimitrova et al., 2004; Horak et al., 1996). These earlier onsets of muscle activity result in excessive co-contraction that interfere not only with normal response asymmetry in the trunk, but also the hips and legs to a backward perturbation (Carpenter et al., 2004; Horak et al., 1996). Although EMG responses were not specifically measured in this study, co-activation resulting in axial stiffening may have contributed to the quicker and larger truncal responses observed. In healthy young individuals, increased stiffening has been shown to induce early movements of the trunk and greater destabilisation to a backward platform tilts (Grüneberg et al., 2004). Additionally, participants with PD in our study were assessed off levodopa. Rigidity may contribute to truncal stiffening, as increased movement of the trunk off medication was found in participants with PD with increased truncal rigidity (Adkin et al., 2005). However, results are not directly comparable with our findings as patients ranged in disease severity from HY Stage 1 to 4, and increased disease severity may contribute to increased truncal stiffness and co-contraction.

No differences were found in the trunk reaction times in the first trial between participants with PD and controls. Previous work suggests that first trials evoke a superimposed startle-like reflex on the initial postural response (Nanhoe-Mahabier et al., 2012; Oude Nijhuis et al., 2010, 2009). Exaggerated trunk flexion with early onset of trunk muscle activation is observed during a startling stimulus (Nashner, 1976; Oude Nijhuis et al., 2009). A study found platform perturbations were sufficiently startling to evoke early onsets of movement, albeit in wrist extension (Campbell et al., 2013). Startle reflexes share common pathways, via reticulospinal tracts, to axial musculature of the trunk (Lawrence and Kuypers, 1968), and may contribute to the faster latencies in truncal reaction times demonstrated in this study. People with PD are suggested to be less able to integrate startle reflexes during gait (Nieuwenhuijzen et al., 2006). If this is also conceivable during a postural task, postural reaction times in subsequent trials may also be affected.

5.6.4 Impact of examiner pull force and participant anthropometric characteristics

Explanatory variables were explored within groups to determine if any differences were due to underlying disease. Peak pull force by the examiner significantly influenced trunk and step

responses in both participants with PD and controls. This is similar to findings in Chapter 4, where postural responses were investigated in young healthy participants. These results confirm the need to account for examiner pull force, particularly in laboratory based studies of truncal perturbations, and may also partly explain issues with variability and reliability encountered with the clinical pull test.

In PD, peak pull force varied sufficiently to influence speed and size of trunk and step responses. The increased size of trunk and step displacements (i.e. trunk pitch angle, initial step length and retropulsion) with increased peak pull force likely reflects the greater destabilisation produced by a larger force, and corresponding increase in compensatory postural correcting response (Pai et al., 1998). Increased trunk and step velocities with increased peak pull force may be explained by Newton's second law (force = mass x acceleration), where force is proportional to acceleration (i.e. the change in velocity). Increased participant weight was associated with smaller pitch angle. Weight may impact the inertia of the trunk, with participants of increased weight demonstrating less truncal displacement unless peak pull force is increased. Participants with PD tended to be shorter and heavier compared to controls. Although there were no statistical differences in height and weight between the two groups, this may be due to insufficient statistical power with relatively small sample sizes.

In control participants, examiner pull force was associated with the same trunk and step parameters as PD, except pitch velocity which was not significant. The finding that pitch velocity was associated with force of the pull in participants with PD and not controls may allude to impairments in force production in the trunk in PD. This may also be reflected in weight being associated with trunk pitch angle only in participants with PD. Alternatively, differences in findings between participants with PD and controls may be possibly due to the different sample sizes in each group. With controls, increased peak force was also associated with increased step count, although it was noted that changes to overall step count were subclinical.

5.6.5 Clinical relevance

While changes in trunk and step responses are statistically significant in participants with PD, the implications may be minimal as they produced corrective step counts to the backward pull that were no different to controls. Nevertheless, clinicians need to be aware that routine

assessments of postural stability may not be sensitive to detect changes in postural responses associated with mild disease. Another consideration is the consistency of examiner pull force during pull test performance, which is important for comprehensive assessment and long term management of postural instability of people with PD.

Our results showed differences in first and subsequent trial responses in participants with PD compared to controls. This suggests the first pull test trial may still be worth assessing as a separate endpoint before a second trial is formally assessed. Results from first perturbation trials are proposed to correlate better with important clinical outcomes such as falls (Nonnekes et al., 2015; Visser et al., 2010, 2003), providing closest ecological relevance to an unexpected perturbation in daily life.

5.6.6 Strengths, limitations and future recommendations

The current study was designed as a small feasibility study to explore use of an instrumented pull test to characterise postural responses in people with mild PD. Participants with PD were carefully screened for postural instability (HY $\leq$ 2), allowing for a study sample representative of individuals with PD where postural responses remained intact, but were relatively underexplored and understood.

The instrumented pull test was able to detect fine changes in postural responses in participants with mild PD in first and subsequent trials - demonstrating the capabilities of motion tracking as an alternative method to quantify postural responses compared to conventional methods of platform perturbations and electromyography. The instrumented pull test is the first to characterise whole body kinematics similar to the clinical pull test in people with PD, whilst accounting for pull force, a significant variable confounding stepping outcomes. When 35 pull test trial are performed, equipment preparation, set up of the participant and assessment time averaged twenty minutes. Researchers will need to determine if assessment timeframes are appropriate compared to their usual methods of assessing postural instability as this may vary depending on the participant's physical function. The use of the instrumented pull test system was also found to be safe and feasible in a clinical cohort of participants with mild PD. It is noted the usual precautions for examiners performing the clinical pull test applies. The examiner should be ready to catch the participant at all times, and the examiner should be positioned with their back close to a wall to prevent both from falling if the participant is unable to regain balance.

Several limitations of this study need to be considered. The small sample size of eighteen participants with PD limits generalisability of findings to the wider PD population. Furthermore, participants were recruited from a single clinic where individuals demonstrated adequate cognition and functional ability to participate in the experiments. It is reiterated (Chapter 4) that the instrumented pull test employs motion tracking, which detects net movement, similar to clinical observation rather than onset of muscle recruitment, as with electromyography. Truncal responses were investigated specifically in the anteroposterior direction as per the clinical pull test, whereas other studies have also found trunk roll contributions to postural instability (Adkin et al., 2005; Ganesan et al., 2010), particularly in mild PD (Ganesan et al., 2010). Although postural responses to perturbations in the anteroposterior direction are commonly studied in people with PD, impairments of postural responses in the lateral direction have also been found (Azevedo et al., 2016; King and Horak, 2008). To a large lateral platform perturbation requiring compensatory stepping, people with PD (HY 2 - 4) demonstrated greater postural instability and falls compared to age matched controls (King and Horak, 2008). People with PD lacked anticipatory lateral weight shift, and compensatory steps were slower, smaller and later than controls to the perturbation (King and Horak, 2008). The frequency of falls did not correlate with disease severity. Previous studies have also shown people with PD have reduced lateral stability in quiet stance (Wegen et al., 2001), and decreased anticipatory postural adjustments to feet-in-place responses to a lateral shoulder perturbation (Azevedo et al., 2016). As normal step initiation is associated with a lateral shift of the body's centre of mass towards the stance leg, it is possible impaired lateral weight shift in participants with PD prior to taking a compensatory backward step during the instrumented pull test procedure may have also contributed to the abnormalities in trunk and step responses observed.

The thesis author completed all clinical and objective assessments, and was not blinded to participant groups during the study. This could influence ratings of clinical assessments, or force produced by the examiner during pull test trials. However, instrumented pull test data was computed offline by a separate blinded researcher, and pull force accounted for in statistical analysis. An independent blinded examiner could be used to complete clinical ratings in future studies.

Changes to postural control such as increased rigidity or stooping can result in greater instability, particularly in the backward direction (Jacobs et al., 2005). Later in disease,

corrective arm responses to a backward perturbation are also known to be abnormally directed in PD, with participants bringing their arms closer to their bodies in adduction, instead of rapidly extending the arms out as a counterweight (Carpenter et al., 2004; McIlroy and Maki, 1995). Although not examined in this study, it is acknowledged these upper body abnormalities may contribute to the pull test responses observed in PD.

Future studies could investigate the use of instrumented pull test responses in people with PD with postural instability (e.g. HY 3) to understand how disease severity influences postural instability or to document postural responses to therapy such as levodopa. Changes to posture with axial rigidity may partly contribute to impaired clinical pull test responses observed later in disease progression (i.e. taking multiple steps to arrest backward retropulsion) (Kim et al., 2013; Park et al., 2015). Future research should consider the role of these truncal changes and how they relate to biomechanical impairments in people with PD during the pull test.

5.7 Summary and Conclusion

In this study, postural responses were characterised in people with mild PD and healthy age matched controls using an instrumented pull test. The instrumented pull test was able to detect differences in trunk and step postural responses in people with mild PD compared to controls in first and subsequent trials. In the first trial, trunk responses were larger and faster in trunk pitch in people with mild PD compared to controls. Overall retropulsion was smaller in participants with PD compared to controls, but initial step size and reaction time did not differ between groups. In subsequent trials, trunk and step abnormalities in participants with PD during the first trial persisted. Step responses became smaller and slower in people with mild PD compared to controls. This study corroborates the need for objective measures to detect changes to postural stability in people with mild PD, when outcomes of clinical assessments of postural instability remain unchanged. These findings also suggest clinicians should assess the first pull as an endpoint in itself, before a second trial is formally assessed.

Further studies are required to investigate how these abnormalities relate to disease severity and falls risk. Feasibility and safety of the instrumented pull test was demonstrated with all participants successfully completing the experimental procedure. The risk of falls to both participant and examiner during the experiment was similar to performing the pull test in the clinical setting. The instrumented pull test could have application in future studies of PD

seeking to capture abnormalities in postural responses in mild disease, track postural instability over time, and detect responses to therapies such as levodopa or DBS whilst simultaneously accounting for cofounders (e.g. pull force, height and weight) influencing postural responses. Using the instrumented pull test, identification of truncal and step abnormalities in PD may have the potential to act as markers of postural instability in mild PD.

CHAPTER 6. EFFECTS OF LEVODOPA ON PULL TEST RESPONSES IN MILD PARKINSON'S DISEASE

6.1 Overview

In Chapter 5, first and subsequent trial postural responses were characterised in a cohort of participants with mild Parkinson's disease (PD) using an instrumented pull test. The instrumented pull test methodology described in Chapter 3 was employed. Subclinical abnormalities in trunk and step responses were detected in participants with PD compared to age matched controls in first and subsequent trials. In the current chapter, postural responses are investigated in the same cohort of participants with mild PD on levodopa to determine the effects of medication on postural abnormalities in mild PD. Postural responses in participants with mild PD on medication are compared to age matched controls.

6.2 Introduction

Postural instability is a debilitating symptom in PD, often resulting in falls and diminished quality of life. Sixty eight percent of people with PD will experience a fall, with 46% reporting recurrent falls (Ashburn et al., 2001; Canning et al., 2009; Wood et al., 2002). Falls are not commonly assumed to occur in mild PD, however, it is now demonstrated people with PD are at increased falls risk even in mild disease (Albanese, 2007; Kerr et al., 2010; Pickering et al., 2007). The overall risk of falls is up to three times more likely in people with PD compared to older healthy individuals (Lima et al., 2019; Rudzińska et al., 2013). Impairments in trunk flexibility or preparation in stepping can occur in mild disease, and may contribute to postural instability observed in people with PD (McVey et al., 2009; Schenkman et al., 2011).

While levodopa is effective to alleviate other cardinal symptoms of PD such as rigidity bradykinesia and tremor, the treatment of postural instability presents a challenge (detailed in literature review Chapter 2, Section 2.3.2.1). Postural instability is less responsive compared to other symptoms, and becomes more prominent with disease progression (Koller et al., 1989; Steiger et al., 1996). This suggests non-dopaminergic pathways could be implicated in postural abnormalities, which may have important implications for interventions to manage postural instability (Bohnen et al., 2009; Thevathasan et al., 2018).

Furthermore, effects of levodopa on postural instability appear conflicting and dependent on the type of assessments used to quantify outcomes. Using clinical tests of balance, postural responses are reported to improve on levodopa in people with mild to moderate disease as measured with the Berg Balance Scale (Foreman et al., 2012; Franzén et al., 2009; McNeely et al., 2012; Nova et al., 2004). These improvements may result from benefit to other symptoms of PD such as bradykinesia or rigidity that aid overall postural responses. In contrast, when people with mild to moderate PD are assessed using precise laboratory measures, the effects of medication are minimal or even detrimental to postural responses. Some aspects, for example forward limits of stability in static standing, are suggested to improve, but not others which include early and late automatic postural responses involving backward perturbations (Bloem et al., 1996; Foreman et al., 2012; Franzén et al., 2009; Kam et al., 2014; King et al., 2010; King and Horak, 2008; McNeely et al., 2012; Wright et al., 2010). Using motion capture, averaged postural responses to five manual backward pulls delivered similarly to the clinical pull test demonstrated no difference in spatiotemporal variables of step reaction time, length and velocity in people with moderate PD off and on levodopa (Foreman et al., 2012). Similarly, studies using platform perturbations have found stepping does not improve on medication, remaining consistently under scaled in the forward, lateral and backward directions in people with moderate PD (Di Giulio et al., 2016; Kam et al., 2014; King et al., 2010; King and Horak, 2008). Levodopa was also found to worsen postural responses during a backward platform translation by reducing torque production and EMG magnitude in lower limb muscles in people with moderate PD. This resulted in greater instability with faster centre of mass displacement in the forward direction (Horak et al., 1996).

Previous studies investigating the effects of levodopa on postural instability in PD have conventionally recruited participants of greater disease severity where postural instability is clinically evident, or heterogeneous cohorts ranging from HY Stage 2 to 4 (Bloem et al., 1996; Di Giulio et al., 2016; Foreman et al., 2012; Kam et al., 2014). However, no study has investigated the effects of levodopa on postural responses to a perturbation in people with mild PD.

Dynamic posturography provides a method to identify changes of postural instability in people with mild PD even when balance is assessed as normal. In the clinical setting, the pull test is commonly used to assess postural stability in PD (Fahn et al., 1987; Hunt and Sethi,

2006). An examiner administers a backward tug at the patient's shoulder level and grades the corrective response (Fahn et al., 1987). Postural responses are graded as normal when less than two steps are taken to regain balance. Although quick and easy to administer, the clinical pull test is not sensitive to discriminate variables that may be altered in mild disease. In Chapter 5, postural responses were assessed in participants with mild PD (HY ≤ 2) while off levodopa using an instrumented pull test. Abnormalities in both trunk and step responses were demonstrated in participants with PD, with first and subsequent trial postural responses discriminating people with mild PD from controls. An increased number of observed differences between participants with PD off medication and healthy controls were detected in subsequent trials. Previous perturbation studies report people with mild PD demonstrate subclinical postural abnormalities in movement preparation that do not affect overall stepping (Ganesan et al., 2010; McVey et al., 2009) (Chapters 2 and 5). However, these studies (Ganesan et al., 2010; McVey et al., 2009) explored postural abnormalities of stepping in the on medication state, whereas our study in Chapter 5 investigated postural responses in people with PD in the off medication state. Furthermore, the effects of medication on truncal responses, which contribute to initial balance recovery is yet unknown. Whether these impairments in postural responses persist on medication to a perturbation remains to be explored.

6.3 Aims and hypotheses

The aim of the study was to:

1) Investigate postural responses in participants with mild PD off and on levodopa using an instrumented pull test.

   Hypothesis 1: Levodopa is not effective at improving trunk and step abnormalities (identified in Chapter 5) in people with mild PD using an instrumented pull test.

2) Examine if postural responses in participants with mild PD on levodopa differed from age matched controls using an instrumented pull test.

   Hypothesis 2: Truncal postural responses will remain larger and quicker in participants with mild PD compared to controls. Step responses are smaller in participants with PD compared to controls with no change in step reaction time.

6.4 Participants and methods

6.4.1 Participants

Participants with PD were recruited through a private neurology clinic and comprised the same participants assessed in Chapter 5. Inclusion and exclusion criteria of participants with PD and age matched healthy controls are detailed in Section 5.4.2. The author (J.L.T.) then confirmed eligibility and approached potential participants. Healthy controls were age matched to participants with PD, and recruited as a sample of convenience. The author (J.L.T.) explained the study protocol to all participants before enrolment. Participants read and signed a Participant Information and Consent Form (Appendix 2) prior to assessment. The study was approved by the Melbourne Health Human Research Ethics Committee (2013.129) (Appendix 3).

6.4.2 Experiment

Clinical Assessments

Participants with PD performed two sessions of the experimental protocol during a single visit. The PD cohort were assessed in the morning in the off levodopa condition (following overnight withdrawal of levodopa > 12 hours). Subsequently, they were re-assessed in the on condition, approximately 1 hour after a suprathreshold levodopa dose at 150% their usual morning dose (Visser et al., 2008a). Testing was always completed in this order.

In the off and on medication condition, participants with PD were first clinically characterised using the motor subsection (part III) of the Unified Parkinson' Disease Rating Scale (UPDRS, score/108) (Fahn et al., 1987). Assessments used to describe participant baseline characteristics are detailed in Chapter 5. All clinical assessments were rated by the thesis author, a physiotherapist with expertise in movement disorders (J.L.T.). Following clinical assessments, participants were assessed using the instrumented pull test.

The instrumented pull test

The instrumented pull test was performed similarly to the clinical pull test. Details of the experimental setup and equipment were previously described in Chapter 3. The same instrumented pull test protocol was used as per Chapter 5, and detailed in Section 5.4.3. Briefly, thirty five trials were presented serially. Inter-trial intervals (10-15s) were variable.

Participants were provided a short rest after every 10 trials, or as requested. The thesis author (J.L.T.) conducted all assessments and continuously monitored participants to prevent falls.

6.4.3 Parameters and data analysis

A separate researcher blinded to medication condition computed trunk and step parameters using custom scripts in MATLAB (MathWorks Inc, Massachusetts, USA) (Chapter 3). A list and description of trunk and step parameters used to characterise postural responses in participants with PD was previously described in Chapter 5, Table 5.1.

Trunk and step parameters were computed for each trial. To investigate the effects of levodopa on postural responses in participants with PD, the first five trials were considered 'practice' trials and discarded. First trial postural responses off and on levodopa were not compared, as participants with PD were already familiarised with the instrumented pull test procedure in the off levodopa condition (Chapter 5), and testing on levodopa was conducted an hour later. Postural responses take up to five trials to habituate in people with PD (Nanhoe-Mahabier et al., 2012). The postural response reflect averages over the subsequent 30 trials (i.e. Trials 6 to 35) – the subsequent postural response. Trials were rejected if there was an anticipatory truncal movement (a forward trunk displacement that exceeds 3 SDs above baseline in the one second epoch prior to the pull).

6.4.4 Statistical analysis

A Kolmogorov Smirnov test demonstrated that all measures did not differ from a normal distribution. Due to the number of contributing factors that could influence trunk and stepping parameters in the pull test, linear mixed models (LMM) analysis was conducted according to methods previously described (Boisgontier et al., 2017; Tan et al., 2018). This model was built using SPSS (IBM, Chicago, IL) version 22. The following factors were included: trial type, group, weight, height, peak force and force rate. At the participant level, height and weight were included to account for the lever arm of the pull and inertia of the trunk (Delitto et al., 1989; Oliveira et al., 2011).

To determine the effects of levodopa on postural responses in participants with PD, the trial type was coded as 0 for the first five practice trials and 1 for subsequent trials (Trials 6 - 35). Group was coded as 0 for healthy control participants, 1 for participants with PD off

levodopa and 2 for participants with PD on levodopa. LMM analysis was conducted using the following equation:

$$\mathrm{Y}_{ij} = (\beta_0 + \theta_{0j}) + \beta_1 \mathrm{TrialType}_{ij} + \beta_2 \mathrm{Group}_j + \beta_3 \mathrm{Weight}_j + \beta_4 \mathrm{Height}_j + \beta_5 \mathrm{PeakForce}_{ij} + \beta_6 \mathrm{ForceRate}_{ij} + \epsilon_{ij}$$

where Y_{ij} is the participant's trunk or step postural response parameter for trial i, $\beta_{0\text{-}6}$ are the fixed effect coefficients, θ_{0j} is the random effect for participant j (random intercept), ε_{ij} is the error term.

Nine independent LMM relating to trunk and step parameters were used to analyse the data. Variance inflation factors for each predictor in all models fell below 10 and multicollinearity was considered negligible (Hair et al. 1995). The variance components covariance structure was selected for the LMM. For categorical explanatory variables, post hoc pairwise comparisons were performed to determine differences between conditions and were corrected for multiple comparisons (Benjamini and Hochberg, 1995). Level of significance was set at $\alpha = 0.05$.

6.5 Results

Two cohorts were assessed: (i) 18 patients (age 59.1 ± 9.3 years; height 1.65 ± 0.1 m; weight 82.7 ± 16.5 kg; 12 males) with mild PD and no clinically detectable postural instability (HY ≤ 2); and (ii) 11 healthy age matched controls (58.8 ± 7.8 years; height 1.71 ± 0.1 m; weight 73.2 ± 13.2 kg; 5 males). The two groups did not significantly differ in age ($p = 0.9$), height ($p = 0.085$) or weight ($p = 0.099$). Clinical characteristics of all participants are described in Table 5.2. No trials were excluded due to truncal anticipation prior to the pull. As stated in Chapter 5, one healthy control participant experienced a fall in the first trial, requiring catching by the examiner. No participant with PD experienced a fall. Sixteen out of eighteen participants demonstrated a minimum of 30% of improvement in UPDRS III scores, which is considered to be clinically relevant (Albanese et al., 2001). The mean UPDRS III motor score significantly improved to 10.5 (± 5.2 SD) on levodopa, from 22.6 (± 10.4 SD) while off levodopa ($p < 0.001$). This represented a mean change of 12.1 on the UPDRS III motor score, indicating a large clinically important difference (Shulman et al., 2010).

6.5.1 Effects of levodopa

The results focus on our primary analysis, examining the effects of levodopa in trunk and step responses between participants with PD and healthy controls in subsequent trials.

Participants with PD

Mean trunk reaction time was not statistically different in participants with PD on and off levodopa (mean difference ON vs OFF PD = 6.0 ms; CI = - 0.6, 12.5; p = 0.077). Mean pitch angle was smaller and mean pitch velocity was slower on levodopa compared to off levodopa (pitch angle mean difference = - 4°; CI = - 5, - 3; $p < 0.001$; pitch velocity mean difference = - 24°/s; CI = - 30, - 16; $p < 0.001$). Deceleration was not statistically significant in participants with PD on and off levodopa (mean difference ON vs OFF PD = 221 mm/s^2; CI = - 188, 629; p = 0.289) (Figure 6.1).

Step length and retropulsion was smaller in participants with PD on levodopa compared to off levodopa (step length mean difference = - 25 mm; CI = - 31, - 18; $p < 0.001$; retropulsion mean difference = - 35 mm; CI = - 41, - 28; $p < 0.001$). Step count was reduced in participants with PD on levodopa compared to off levodopa (step count mean difference = - 0.2 step; CI = - 0.3, - 0.1; $p < 0.001$). Step reaction time was slower in participants with PD on levodopa compared to off levodopa (mean difference ON vs OFF PD = 9.1 ms; CI = 0.1, 17.3; p = 0.029). Step velocity was slower in participants with PD on levodopa compared to off levodopa (mean difference = - 56 mm/s; CI = - 77, - 36; $p < 0.001$) (Figure 6.2).

Participants with PD on levodopa and controls

Mean trunk reaction time differed in participants with PD compared to controls ($F(2,480) = 4.45$, p = 0.012). Trunk reaction time remained faster for participants with PD on levodopa compared with controls (mean difference = - 38.5 ms; CI = - 55.5, -21.6; $p < 0.001$). Mean pitch angle ($F(2, 61) = 7.01$, p = 0.002) and mean velocity ($F(2, 64) = 9.70$, $p < 0.001$) differed in participants with PD compared to controls. Mean pitch angle and mean velocity remained larger and faster with participants with PD on levodopa compared to controls (pitch angle mean difference = 16°; CI = 6, 27; p = 0.003; pitch velocity mean difference = 114°/s; CI = 48, 180; p = 0.001). Deceleration did not differ in participants with PD compared to controls ($F(2, 1082) = 0.126$, p = 0.881). There was no statistically significant effect of

levodopa between participants with PD on levodopa compared with controls (mean difference = 132 mm/s^2; CI = - 663, 927; p = 0.738).

Mean initial step length (F (2, 62) = 7.87, p = 0.001) and retropulsion (F (2, 64) = 24.91, p < 0.001) differed in participants with PD compared to controls. Levodopa reduced size of step length and retropulsion with participants with PD compared to controls (step length mean difference = - 106 mm; CI = - 168, - 44; p = 0.003; retropulsion mean difference = - 99 mm; CI = - 157, - 41; p = 0.003). Step count differed with participants with PD compared with controls (F (2, 79) = 12.43, p < 0.001). Step count did not differ compared to controls (step count mean difference = - 0.3 step; CI = - 0.7, 0.1; p = 0.182).

Mean step velocity differed in participants with PD compared to controls (F (2, 64) = 8.77, p < 0.001). Levodopa reduced step velocity with participants with PD compared to controls (mean difference = - 304 mm/s; CI = - 492, - 116; p < 0.001). With step reaction time, there was no differences in participants with PD compared to controls (F (2, 1398) = 2.947, p = 0.053; mean difference = 4.6 ms; CI = -59.2, 68.4; p = 0.884).

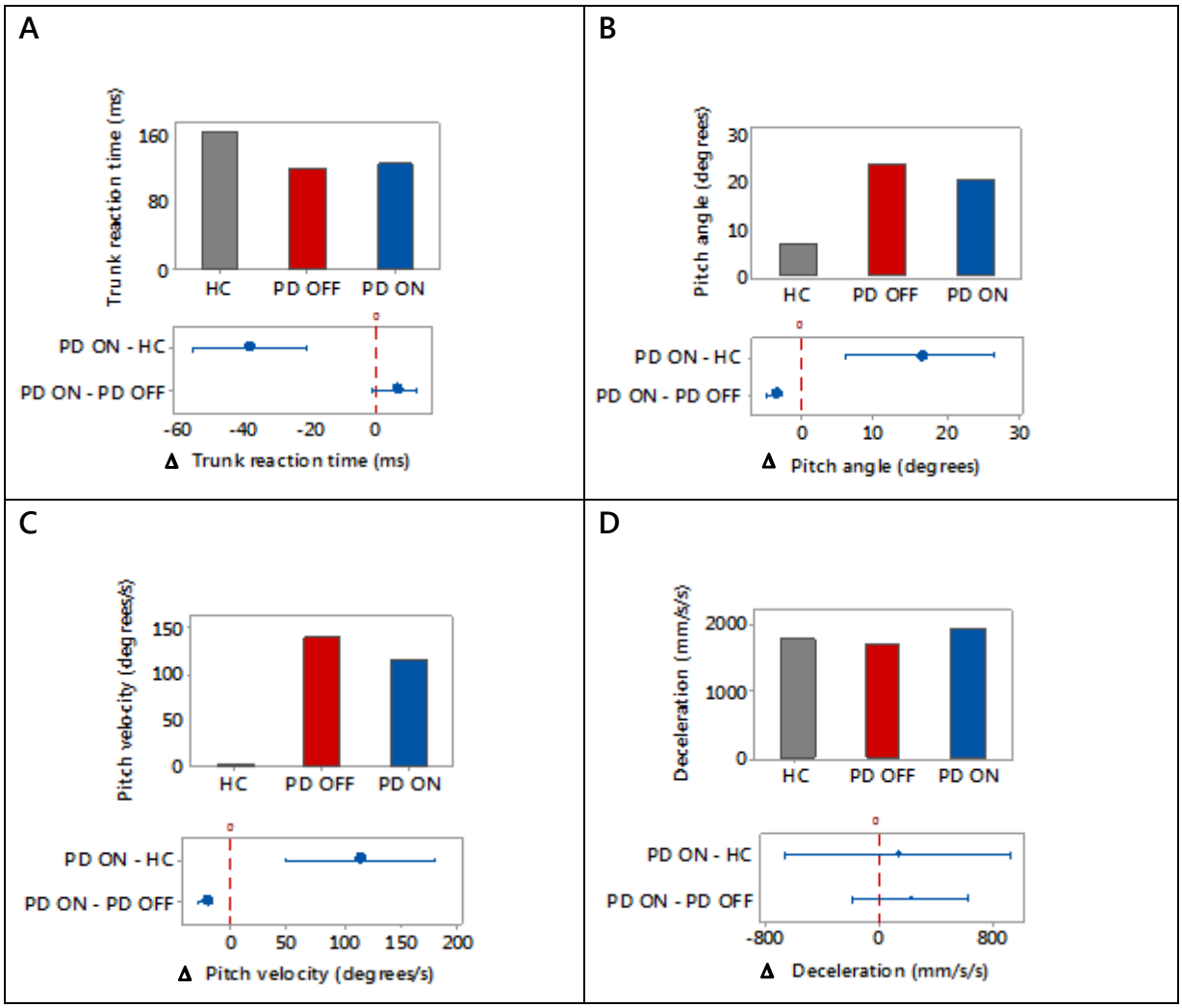

Figure 6.1: Mean difference in trunk parameters between PD and controls and effects of levodopa.

(A) Trunk reaction time, (B) Pitch angle, (C) Pitch velocity and (D) Deceleration. Bar graphs represent the mean of each group (PD OFF = participants with PD off levodopa, PD ON = participants with PD on levodopa and HC = healthy controls) in subsequent trials. Error bars represent the 95% confidence interval. Effect of group on trunk parameters is statistically significant between participants with PD and controls where error bars do not cross zero (dashed red vertical line). Statistically significant mean differences (Δ) in trunk parameters remained on medication in participants with PD and controls in all parameters.

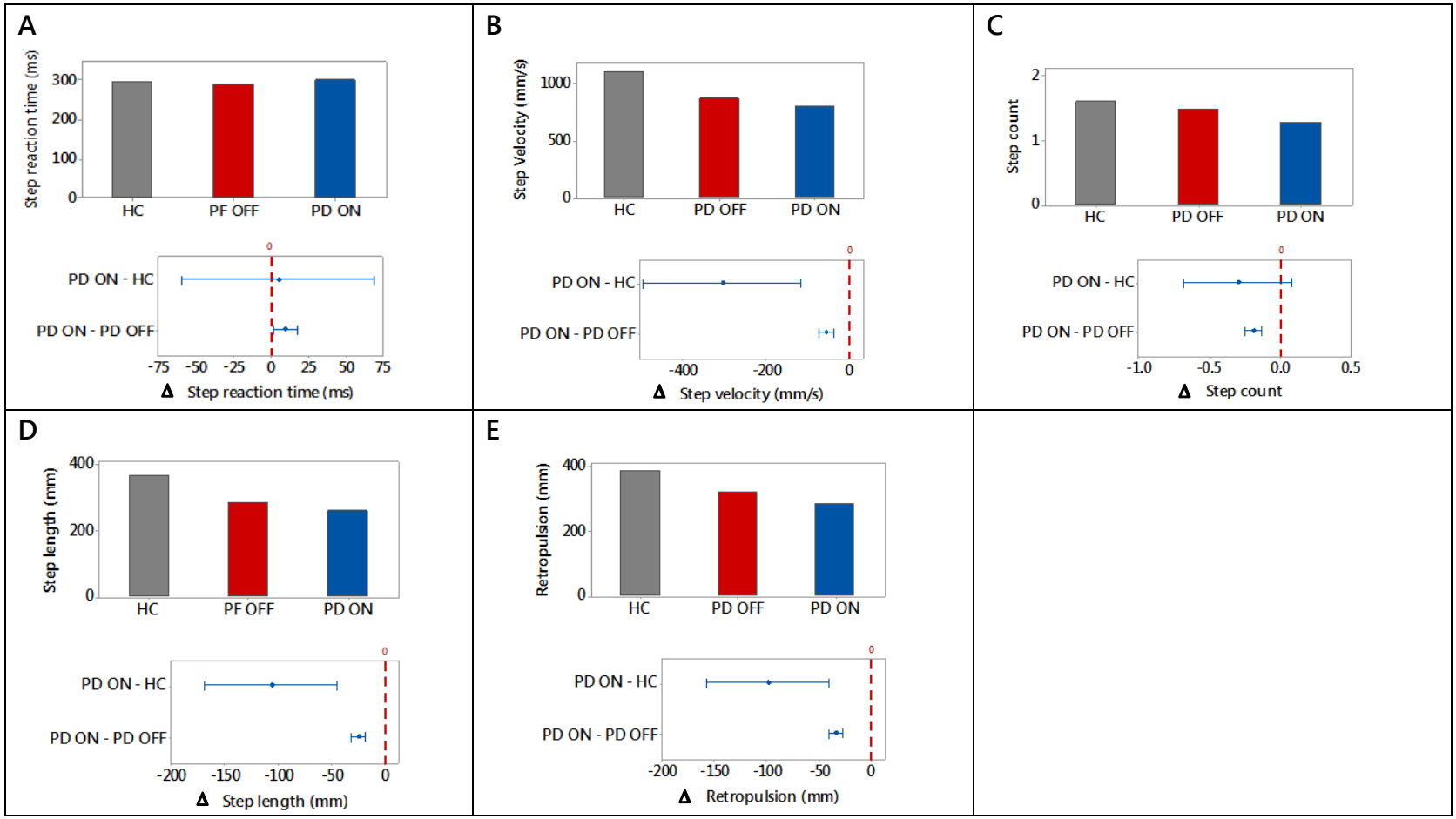

Figure 6.2: Mean difference in step parameters between PD and controls and effects of levodopa.
(A) Step reaction time, (B) Step velocity, (C) Step count (D) Step length and (E) Retropulsion. Bar graphs represent the mean of each group (PD OFF = participants with PD off levodopa, PD ON = participants with PD on levodopa and HC = healthy controls) in subsequent trials. Error bars represent the 95% confidence interval. Effect of group on step parameters is statistically significant between participants with PD and controls where error bars do not cross zero (dashed red vertical line). Statistically significant mean differences (Δ) in step parameters remained on medication in participants with PD and controls in all parameters except step count.

6.6 Discussion

This study sought to characterise the effects of levodopa on postural responses in participants with mild PD (HY ≤ 2) compared to controls using an instrumented pull test. On levodopa, participants with mild PD demonstrated abnormalities in trunk and step responses following a manual backward pull. These postural responses altered with levodopa but remained different to responses of healthy age matched controls. In participants with PD, levodopa improved the size and speed of truncal responses towards levels of control participants with smaller pitch angle and slower pitch velocity on levodopa compared to off levodopa. Conversely, the size and speed step responses worsened on levodopa away from levels of control participants, with smaller and slower stepping compared to the off levodopa condition. For the first time, the effects of levodopa on postural responses to the pull test were characterised in mild PD. These findings are particularly relevant as the pull test is routinely used as an assessment of postural stability in clinical practice and outcomes may have implications for therapies to address postural instability in people with PD.

6.6.1 Characterisation of postural responses using the pull test

The mixed responsiveness of trunk and step responses to levodopa has several implications. First, changes in postural responses can occur in mild disease, with no relationship to dopaminergic state (Di Giulio et al., 2016; Mancini et al., 2011; Rocchi et al., 2002). Even though participants with mild PD were on levodopa, they did not demonstrate trunk postural responses comparable to that of healthy controls. Levodopa was demonstrated to benefit postural responses, but this benefit was small. On medication, differences in mean truncal pitch, velocity and onset of truncal movement were reduced towards levels of healthy controls, which suggest an improvement in initial response of the trunk to aid balance recovery. Forces used to resist a backward movement to a feet-in-place response following a truncal perturbation are known to be smaller in people with moderate PD, leading to increased displacements of the body with no improvements on levodopa (Di Giulio et al., 2016). Other abnormalities of truncal responses including excessive trunk pitch and stiffening are also known to persist on levodopa to a manual backward pull (Adkin et al., 2005) and backward platform rotations (Carpenter et al., 2004). However, it was unclear if a heterogeneous cohort contributed to these findings as participants ranged from mild to severe disease severity (HY 1.5 to 4). Here, our study clearly demonstrates truncal abnormalities are also present in people with mild PD on levodopa.

Secondly, levodopa may be detrimental to postural responses, even in mild PD. Participants with mild PD demonstrated smaller and slower stepping. In line with our study, slower backward corrective steps have also been reported in response to platform translations in patients with mild PD in the on medication state compared to healthy controls, but no differences in step size was found (Lee et al., 2013). In later disease, it is well established that levodopa does not effectively alleviate abnormalities in postural responses. Abnormally under scaled step size and slower step velocity have been demonstrated to persist on medication in people with PD (Bloem et al., 1998; Jacobs and Horak, 2006; Kam et al., 2014; King et al., 2010; King and Horak, 2008). Smaller initial balance recovery steps have also been found to a backward truncal perturbation in people with mild to moderate PD compared to healthy participants with no changes off and on medication (Di Giulio et al., 2016). Although our findings suggested step reaction time was slower (by an average 9 ms) in participants with PD on levodopa compared to off, these results may have arisen due to sensitivity of the instrumented pull test system and analyses as no effect was demonstrated at group level. Accordingly, previous studies demonstrate step reaction time does not differ in people with moderate PD compared to controls (Jacobs and Horak, 2006; Kam et al., 2014).

However, what may account for the apparent worsening of step responses in participants with mild PD on levodopa? In our study, postural responses to the pull in participants with PD on levodopa comprised a larger and faster trunk response, but a smaller and slower step compared to controls. Before discussing the possible involvement of dopaminergic pathways, we first explored whether these findings may due to impairments in balance correcting mechanisms or kinematics of the pull. Under scaling of step size may indicate impairments in predictive central set that is known to worsen on compared to off levodopa (Horak et al., 1996). Central set refers to the descending pathways that prepare sensory and motor systems for an anticipated stimulus and task condition (Schmidt, 1982). Setting the response is particularly advantageous in predicable tasks; such as a series of anticipated pulls in the backward direction, so that motor output can be optimised in speed and amplitude to the impending stimulus (Rinalduzzi et al., 2015). However, people with PD on medications when compared to controls, demonstrate a fundamental difficulty in shifting the central set even to a predictable perturbation (Beckley et al., 1993). To small perturbation amplitudes, people with PD off medication are able to successfully scale the size of postural responses, but were unable as perturbation amplitudes became larger (Horak et al., 1996). Difficulties with central

set scaling have been shown to worse on levodopa, resulting in muscle activation that is fragmented and reduced in torque (Beckley et al., 1993; Horak et al., 1996). These findings suggest participants with PD on levodopa generate less corrective postural force to a perturbation compared to healthy controls, even in mild disease. Less corrective force production is expected to affect both trunk and step responses similarly (i.e. a larger trunk pitch and larger step). Our findings are therefore surprising, and may reflect either the biomechanics of a top down perturbation and 'limbo-like' movement, the possibility of increased flexed posture in participants with PD or the relatively small sample size.

Alternatively, reduced step length may arise as a consequence of initial truncal responses. As the truncal response is the first strategy used to maintain balance to a perturbation at shoulder level, abnormalities in truncal responses may contribute to the kinematics of subsequent step deficits during the pull test. On levodopa, the speed and size of trunk movement was improved but was still abnormally larger and quicker compared to controls. Accordingly, deceleration values (i.e. how fast a participant slowed truncal movement) were not different between participants with PD and healthy controls. It is speculated that smaller stepping may be due to a maladaptive compensatory strategy where participants with PD prioritise the truncal response to arrest movement over stepping, during a predictable, practised postural task, even though it results in greater instability in the trunk.

6.6.2 Non-dopaminergic pathways involvement

In our study, participants with PD received a suprathreshold dose of levodopa in the on medication condition. The large clinically important difference in motor scores off and on levodopa reflected motor symptoms (i.e. tremor, bradykinesia and rigidity) and axial symptoms (i.e. postural instability) that were optimised (Visser et al., 2008a). Impairments in postural responses are known to be unresponsive to levodopa in people with moderate to severe PD, and usual medication regimes may not be sufficient to alleviate deficits in postural control (Kam et al., 2014). Here, we found postural abnormalities were still present on medication in people with mild PD, similar to a previous study of platform perturbation that administered a suprathreshold dose of levodopa in participants with moderate PD (Visser et al., 2008a).

The worsened stepping responses in participants with PD on levodopa also suggest that dopaminergic dysfunction within the basal ganglia may not be primarily responsible for the

smaller compensatory step size to the backward pull. In people with moderate to severe PD, improvements in the length and accuracy of compensatory stepping can be variable to platform perturbations (Jacobs and Horak, 2006). These variabilities and under scaling of compensatory stepping are postulated to involve impairment of neural circuits outside the basal ganglia involving the supplementary motor area, particularly in more advanced disease (Jacobs and Horak, 2007). Accordingly, imaging studies have also identified abnormalities in cortical, cerebellar and brainstem pathways of locomotor networks in addition to basal ganglia dysfunction in people with PD (Jahn et al., 2008).

Deficient non-dopaminergic pathways could be implicated in postural abnormalities identified in people with mild PD (Bohnen et al., 2009; Thevathasan et al., 2018). For example, degeneration of cholinergic pathways from the pedunculopontine nucleus (PPN) can occur early in disease (Bohnen and Albin, 2011, 2009; Müller and Bohnen, 2013). Preliminary evidence demonstrates therapies that target cholinergic pathways such as PPN stimulation and cholinesterase inhibitors may benefit axial symptoms of gait and postural instability in PD resulting in decreased falls in moderate to advanced PD (Alp et al., 2016; Moro et al., 2010). Therefore, cholinergic neurons in the PPN may present an alternative target to alleviate non-levodopa responsive postural abnormalities identified in this study (Chapter 7).

6.6.3 Clinical relevance

Postural responses in participants with PD would not be scored differently from that of control participants according to the clinical pull test. However, the examiner may observe differences in the quality of corrective postural responses in participants with PD that is not taken into account with clinical scoring. For example, participants with PD may take only one or two steps backwards, but steps taken may be smaller or slower, with increased body sway, or with protective forward arms extension.

Overall, balance mechanisms still appear well compensated in mild disease as postural changes identified were subclinical. However, clinicians should be mindful that abnormalities in postural responses exist in patients who are optimally medicated even in mild PD. As postural instability can comprise deficits of different domains, clinicians should also consider assessing postural responses using other clinical assessments of balance recommended by the movement disorders society guidelines in complement to the clinical pull test (Bloem et al.,

2016b; Horak, 2006; Schoneburg et al., 2013). Impairments in truncal control are implicated in deficits of walking and balance with disease progression (Adkin et al., 2005; Cole et al., 2010). Furthermore, people with PD commonly take small and multiple backward steps to the clinical pull test in later in disease – termed retropulsion (Nonnekes et al., 2015). Retropulsion can contribute to postural instability and falls in people with PD (Di Giulio et al., 2016; Jacobs and Horak, 2006; King et al., 2010; King and Horak, 2008). Although falls are assumed to be relatively rare in mild PD (Albanese, 2007), people with PD have an increased falls risk even in mild disease (Kerr et al., 2010).

The identification of smaller step sizes in people with mild PD on levodopa that is not restored to levels of controls may have implications for non-pharmacological interventions such as rehabilitation (Bloem et al., 2015). Strategies that target protective postural responses with perturbation training may benefit stepping. Repeated exposure to a perturbation is suggested to improve compensatory stepping in subsequent trials (Jobges et al., 2004; Peterson and Horak, 2016), and crucially, stepping responses of first trials (Barajas and Peterson, 2018). Further studies are required to explore the retention and training dosage to sustain such benefits in people with PD.

6.6.4 Strengths, limitations and future recommendations

This study adds new knowledge to the understanding of postural instability in people with mild PD. The instrumented pull test was sensitive to detect effects of levodopa in trunk and step responses. To date, laboratory studies of postural perturbation in people with mild PD have only been explored in the on medication state (Lee et al., 2013; McVey et al., 2009). Previous work have either found no difference in stepping responses to a postural perturbation or explored feet-in-place responses using platform tilts (Chastan et al., 2008; Ganesan et al., 2010). Our study is therefore the first to characterise whole body kinematics similar to the clinical pull test whilst accounting for pull force - which was previously found to significantly influence step responses.

The current study involved the same participants described in Chapter 5. Limitations relating to methodology of the motion tracking system, direction and predictability of pulls are previously described (Chapters 4 and 5). Several additional limitations of this study need to be considered. The effects of levodopa in people with mild PD were characterised only for subsequent trials. First trial postural responses, which would be of most interest, were not

compared off and on levodopa. This was because participants with PD were familiarised with the instrumented pull test protocol during the first block of trials in the off levodopa condition and testing in both conditions were conducted an hour apart. Counterbalancing of levodopa conditions could be considered in future studies to investigate effect of levodopa on first trial responses. Alternatively, the control group could be assessed with the pull test protocol twice, to account for learning effects or fatigue that may influence the second block of trials. Another consideration with the overnight withdrawal of levodopa in participants with PD on chronic levodopa therapy is the effects of the long duration response (Nutt et al., 1995). The long duration response of levodopa results in a sustained improvement in symptoms, and is suggested to be present by 15 days of treatment (Quattrone et al., 1995). This response represents approximately a third of the total response to levodopa and can be measured by the deterioration in overall function after total drug withdrawal (Morris et al., 1998). Therefore, true baseline assessment off levodopa with a participant with PD may not be attained for up to two weeks (Morris et al., 1998). The thesis author completed all assessments, and was not blinded to levodopa conditions during the study. This could influence ratings of clinical assessments; however, instrumented pull test data was computed offline by a separate blinded researcher. A separate examiner could be used to complete clinical ratings in future studies.

6.7 Summary and conclusions

Findings from the current study suggest subclinical postural abnormalities to the pull test are present in people with mild PD and levodopa has a small, but incomplete benefit to postural responses. In participants with PD, deficits in trunk and step responses remained on medication, with smaller and slower stepping compared to controls. Although these findings were statistically significant, the effect of levodopa may be small as postural responses were assessed as normal according to clinical pull test ratings off and on medication. The lack of levodopa effect on postural responses to an external perturbation has previously been investigated in people with PD of greater disease severity (HY 2 - 4). The current study extends these findings to people with mild PD (HY $\leq$ 2). Clinicians and patients should be aware of these changes to postural stability, as smaller protective step size is associated with increased falls risk in more advanced PD (Kim et al., 2013). Although falls tend to be rare in mild disease, people with PD have a higher incidence of falls risk compared to the older healthy population (Lima et al., 2019; Pickering et al., 2007). This may have implications for the implementation of interventions to target protective stepping responses. The use of the

instrumented pull test may also be useful to assess the effects of different therapies that may improve postural responses in people with PD. As the absence of levodopa responsiveness suggests the involvement of non-dopaminergic pathways, rehabilitation strategies that focus on protective postural responses with perturbation training in mild disease or therapies that target cholinergic pathways such as PPN DBS may benefit postural stability in PD.

CHAPTER 7. AN EXPLORATION OF PULL TEST RESPONSES IN PEOPLE WITH PARKINSON'S DISEASE AND PEDUNCULOPONTINE NUCLEUS STIMULATION

7.1 Overview

In Chapter 5, subclinical abnormalities in postural responses in participants with mild Parkinson's disease (PD) were detected by an instrumented pull test. Findings from Chapter 6 demonstrated levodopa did not restore postural responses in participants with PD to that of healthy controls, indicating non-dopaminergic pathways may be involved in the pathophysiology of postural instability in PD.

The current chapter describes the use of the instrumented pull test to assess postural responses in participants with moderate to severe PD chronically implanted with bilateral pedunculopontine nucleus (PPN) stimulators. PPN deep brain stimulation (DBS) is a therapy developed specifically to alleviate axial symptoms of gait and postural abnormalities unresponsive to conventional therapies such as levodopa or DBS of the subthalamic nucleus or globus pallidus. Previous work suggests scoring of commonly used clinical assessments such as the pull test may not be sensitive to small changes to postural responses induced by PPN DBS.

To this aim, the instrumented pull test, together with a clinical balance assessment – the MiniBESTest – is used to characterise postural responses in participants with PD with moderate to severe postural instability, and explore any changes in postural responses on and off stimulation.

7.2 Introduction

Postural instability is a common and disabling deficit in PD becoming more prominent with disease progression (Kim et al., 2013). In a longitudinal study, 34% of participants with PD demonstrated postural instability within 2 years of diagnosis (Hely et al., 1989), with 92% of surviving participants reporting postural instability at 15 year follow up (Hely et al., 2005). Postural instability results in difficulties during tasks of walking, transfers and standing, and is a major contributor to falls and disability in people with PD (Allen et al., 2013; Giladi et al., 2005; Kerr et al., 2010; Kim et al., 2013; Latt et al., 2009; Robinson et al., 2005). In the clinical setting, postural instability is commonly assessed using the pull test, where an examiner briskly pulls the patient backward at the shoulders and visually grades the response (Fahn et al., 1987; Hunt and Sethi, 2006; Visser et al., 2003) (Chapter 2). Despite several shortcomings of previously identified of the clinical pull test (Chapter 2), it remains widely used in research as an outcome of postural instability in people with PD.

Postural instability presents a significant therapeutic challenge in PD. Conventional therapies such as dopaminergic medication and DBS of the subthalamic nucleus and global pallidus internus are not effective to alleviate postural instability and may even worsen symptoms involving gait and posture (Bloem et al., 1996; Bonnet et al., 1987; Fasano et al., 2015; Horak and Nashner, 1986; St George et al., 2010; Vu et al., 2012). In Chapter 6, it was found dopaminergic medication did not restore trunk and step responses in people with mild PD to that of control participants. The lack of effect of dopaminergic medication on postural responses has previously been demonstrated in people with PD of increased disease severity (Bloem et al., 1996; Di Giulio et al., 2016; Kam et al., 2014). Postural deficits, particularly later in PD are suggested to involve non-dopaminergic lesions (Bohnen et al., 2009; Di Giulio et al., 2016; Müller et al., 2013). Cell loss in the PPN have been implicated in PD (Rinne et al., 2008), and associated with worsened balance, decreased attention to task, and increased falls (Bohnen et al., 2009). The PPN is considered a critical structure in control of balance (Jenkinson et al., 2009; Rinne et al., 2008) with direct connections to cortical motor areas via the thalamus, basal ganglia, cerebellum and spinal cord (Gut and Winn, 2016; Takakusaki et al., 2016). Previous studies of animal models show lesions of the PPN produce PD-like symptoms (Pahapill and Lozano, 2000), and the loss of cholinergic neurons in the PPN has been linked to increasing severity of symptoms in people with PD (Zweig et al., 1989).

To date, the impact of PPN DBS on postural instability remains unclear. In early studies, postural instability was initially thought to improve with PPN DBS (Plaha and Gill, 2005; Stefani et al., 2007). These small clinical studies comprising two (Plaha and Gill, 2005) and six (Stefani et al., 2007) patients respectively, reported improvements in composite scores of postural stability comprising axial symptoms of gait and posture (UPDRS items 27 to 30) (Plaha and Gill, 2005; Stefani et al., 2007). In particular, improvements in postural responses according to the clinical pull test (item 30 of the UPDRS) were found (Plaha and Gill, 2005). However, results in subsequent studies have been conflicting. Some studies have reported variable or no improvement in postural instability as rated according to the clinical pull test (item 30 of UPDRS), while others have reported inconsistent outcomes in composite scores of postural stability (UPDRS items 27 to 30) (Ferraye et al., 2010; Moro et al., 2010; Plaha and Gill, 2005; Stefani et al., 2007; Welter et al., 2015). One problem has been the limited sensitivity of clinical assessment measures to precisely quantify outcomes. The clinical pull test is the most frequently used measure of postural instability in studies of PPN DBS (Thevathasan et al., 2018). However, the clinical pull test may not be able to capture small but important changes to balance. In Chapter 5, the instrumented pull test was able to detect subclinical changes in postural responses in a cohort of participants with mild PD (HY $\leq$ 2). On the contrary, patients in PPN studies comprise a cohort who commonly do demonstrate postural instability, where responses to the pull test may include multiple, small steps to arrest backward movement (termed retropulsion), or those that tend to fall 'like a log' requiring catching by an examiner (Kim et al., 2013; Nonnekes et al., 2015). Corrective postural responses in this cohort of patients with PD thus warrant separate investigation. Another confounder has been the use of composite axial scores of the UPDRS (i.e. items 27 to 30 comprising chair rise, posture, gait and postural stability) to report improvements to axial symptoms in PPN studies (Fasano et al., 2015). Summation of these scores does not adequately discriminate between improvements to gait or postural responses.

In the laboratory, precise methods to quantify postural responses commonly employ platform perturbations capturing kinetic, kinematic and neurophysiological endpoints (e.g. electromyography) (Ebersbach and Gunkel, 2011; Horak and Nashner, 1986; Nonnekes et al., 2013; St George et al., 2010; Visser et al., 2008b). These techniques are sensitive to assist clinicians in detecting abnormalities in balance in mild PD (Chastan et al., 2008; Ganesan et al., 2010; McVey et al., 2009), and the detection of changes to treatment such as

dopaminergic therapy and DBS (Horak et al., 1996; Kam et al., 2014; Rocchi et al., 2012; St George et al., 2010). Using posturography, three clinical studies have demonstrated aspects of postural control can be modulated by PPN DBS in quiet stance (Perera et al., 2018; Wilcox et al., 2011; Yousif et al., 2016). Changes were proposed to improve static postural control through increased somatosensory integration (Yousif et al., 2016), decreased mediolateral sway (Wilcox et al., 2011) and sway abnormalities (Perera et al., 2018). Whether postural responses to a perturbation can be directly modulated by PPN DBS remains to be investigated.

The instrumented pull test (Chapters 3 and 4) presents an objective method to assess reactive postural responses to perturbation in the research setting. An examiner performs a manual backward tug at the participant's shoulder level with the corrective postural response quantified using a semi portable 3D motion tracking system. This methodology was previously used to detect small (< 20 ms) differences in postural reaction times and amplitudes in young healthy participants (Tan et al., 2018) (Chapter 4) and differences in postural responses in a cohort of participants with mild PD compared to controls (Chapter 5). In this chapter, the instrumented pull test is used to probe any potential changes to postural responses in people with PD and moderate to severe postural instability on and off PPN stimulation.

In conjunction, clinical tests of balance which possess excellent reliability and validity in PD can be used to explore effects of PPN DBS on postural instability (Duncan et al., 2013; King et al., 2012; Leddy et al., 2011; Mak and Auyeung, 2013; Potter and Brandfass, 2015). The Mini-BESTest presents one such alternative clinical measure of dynamic balance in PD that is recommended by the movement disorders society (MDS) taskforce on rating scales (Bloem et al., 2016a). It comprises four domains of balance including anticipatory postural adjustments (e.g. standing on one leg), reactive postural control (e.g. the ability to react to postural perturbations in the forward, lateral and backward direction), sensory orientation (e.g. standing on an incline or foam surface) and dynamic gait (e.g. walking and performing a cognitive task) (Franchignoni et al., 2010). Of these, the reactive postural control domain of the Mini-BESTest is of interest as an alternative assessment of postural responses to the clinical pull test. The utility of the Mini-BESTest has yet to be explored in patients with PPN DBS. Previous studies have found the Mini-BESTest was able to quantify postural responses across disease severity from Hoehn and Yahr (HY) Stages 1 to 4, with sensitivity to predict

future fallers (Duncan and Earhart, 2012; Leddy et al., 2011; Löfgren et al., 2017), and discriminate postural responses to therapies including medication and subthalamic DBS (McNeely et al., 2011; McNeely and Earhart, 2013).

7.3 Aims

The primary aim of the study was to:

1) Examine the utility of the instrumented pull test to discriminate effects of PPN DBS on postural responses in people with moderate to severe PD.

The secondary aim was to:

2) Explore clinical assessment tools (i.e. UPDRS and Mini-BESTest) that may discriminate effects of PPN DBS on postural responses in people with moderate to severe PD.

7.4 Participants and methods

7.4.1 Participants

Five participants with PPN stimulators were recruited. The participants were a subset of a larger cohort of 13 patients previously published in a related study describing postural control in PPN DBS (Perera et al., 2018) (Appendix 1). Patients with PD received PPN DBS for severe freezing of gait and postural instability, which persisted in the on medication state, resulting in falls. Participants were recruited from centres in Brisbane, Sydney and Melbourne (Australia) from a PPN database and were a sample of convenience screened by a movement disorders neurologist (W.T.) for ability to participate. Eight of the 13 participants were assessed prior to the commencement of thesis studies and excluded in the current study according to eligibility criteria. Recruitment and eligibility for the prior study are detailed in a previous publication (Perera et al., 2018). Eligible participants read and signed a Participant Information and Consent Form (Appendix 2), with the author (J.L.T.) explaining the study prior to enrolment. Ethics committee approval was obtained from all centres (Appendix 3).

7.4.2 Inclusion and exclusion criteria

Participants were included based on the following criteria:

i) Fulfilment of the UK Brain Bank criteria for idiopathic PD (Gibb and Lees, 1988).

ii) HY stage 3 to 4 (i.e. moderate disease with impaired postural reflexes to severe disease, able to walk or stand unassisted) (Fahn et al., 1987), as the study focussed on people with moderate to severe postural instability.

iii) Chronically (> 6 months) implanted with bilateral PPN stimulators.

Participants were excluded based on the following criteria:

i) Death.

ii) Device explantation due to lack of efficacy.

iii) Cognitive impairment (assessed by the Mini Mental State examination score < 24).

iv) Inability to stand independently without aids.

v) Geographical distance limiting travel to research site.

7.4.3 Experiments

All assessments occurred off medication, with overnight withdrawal (> 12 hours) of dopaminergic therapy. Participants were assessed off and on stimulation, in counter balanced order, and were blinded to conditions. On stimulation, participants received lone bilateral stimulation to the PPN region, without implantation of other targets (Hamani et al., 2016). Choice of contacts and stimulation parameters were as employed for chronic therapy when on stimulation. Assessments occurred with a minimum 1 hour washout period between conditions in accordance with previous work demonstrating changes to axial symptoms of gait and posture (Perera et al., 2018; Thevathasan et al., 2011b).

In each condition, participants were clinically assessed using the motor subsection (Part III) of the UPDRS, (score/108) (Fahn et al., 1987), which was further segmented into the UPDRS III subscore comprising items 27 to 30 (chair rise, posture, gait and pull test), and the Mini-Balance Evaluations Systems Test (Mini-BESTest, score/28) (Franchignoni et al., 2010). The Mini-BESTest assesses four domains of balance control; anticipatory (score/6), reactive (score/6), sensory integration (score/6), and dynamic gait (score/10). The Mini-BESTest was selected as a complimentary assessment tool to identify aspects of postural control contributing to impairment of postural stability in participants with PD with moderate to severe PD. Previous research demonstrates strong reliability, validity, and high clinical utility of the Mini-BESTest in people with PD (Duncan et al., 2013; Leddy et al., 2011; Mak and Auyeung, 2013; Potter and Brandfass, 2015), with strong correlations to the Berg Balance

Scale and Timed Up and Go (Bergström et al., 2012). Furthermore, the Mini-BESTest is able to discriminate between fallers and non-fallers (Duncan et al., 2013) and people with and without balance deficits (King et al., 2012). Each item is rated on a three-point ordinal scale (0 to 2), where a lower score indicates greater severity of balance dysfunction.

Clinical assessments were rated unblinded by the thesis author (J.L.T.). Other gait and reaction time measures were concurrently measured as part of an unrelated study not reported in this thesis.

Postural responses were measured using the instrumented pull test previously described in Chapter 3. Briefly, the instrumented pull test was performed similarly to the clinical pull test. The participant wore a customised harness and stood in bare feet, looking ahead focussing on a picture. The examiner generated a manual backward pull via a rope attached to the harness, held perpendicular to the participant's shoulders. The pull was always of sufficient force to generate a step response, and participants were advised stepping was allowed to recover balance. As postural instability was a significant symptom in this cohort, 10 trials (instead of 35 trials in all previous studies) were performed to minimise participant fatigue. Unlike previous chapters (4, 5 and 6), five practice pulls were not performed. A similar number of perturbations have previously been performed by others investigating balance in patients with PD with moderate to severe postural instability (Foreman et al., 2012; McVey et al., 2013). Testing was ceased if participants required assistance to recover balance in five consecutive trials to minimise distress. An additional assistant was present, and was prepared to catch the participant at all times. Safety of participants and examiner were ensured, with the use of fall mats and positioning of the examiner and participant close to a wall to safeguard against falls. The thesis author (J.L.T.) conducted all experiments, monitored patient safety, and altered stimulation parameters under the instruction of a neurologist specialised in movement disorders (W.T.).

7.4.4 Parameters and data analysis

Balance was assessed using clinical assessments of the motor subsection III of the UPDRS, the Mini-BESTest, and an objective instrumented pull test. Higher scores with the UPDRS indicate worse motor function. In contrast, higher scores with the Mini-BESTest indicate better balance function.

Data analysis for the instrumented pull test was automated using a script written in MATLAB (MathWorks). Motion tracking data were high-pass filtered with a 0.05-Hz cut-off frequency. Trunk and step variables were computed according to methods described in Chapter 3. In the trunk, variables included reaction time, response magnitude, pitch angle and pitch velocity. In the step, variables included step reaction time, step velocity, initial step length, retropulsion and step count. One participant declined assessment with the instrumented pull test due to fatigue. Data from this participant was excluded in analysis.

As statistical analysis was not appropriate due to the small sample size, individual and group data are presented for clinical assessments. With instrumented pull test trials, variables are reported as means ± and standard deviation (SD). Step count is reported as a range.

7.5 Results

Four participants (4 males; age 67.8 ± 6.1 years) with moderate to severe PD (HY Stage 3 and 4), chronically implanted with bilateral PPN stimulators were assessed off and on simulation. Clinical characteristics of the participants are shown in Table 7.1.

Table 7.1: Participants with Parkinson's disease and PPN DBS

Participant	Age/ Gender	Centre	PD duration	HY	PPN DBS duration (years, months)	MMSE	UK Brain Bank criteria	LED (mg/day)	UPDRS III Total Score Off/On DBS	UPDRS III Items 27-30 Off/On DBS
P1	63M	Melbourne	8	4	4,0	28	D,A,T,P	1500	44/40	6/6
P2	72M	Brisbane	8	4	2,7	30	D,A,P	800	33/25	6/3
P3	74M	Brisbane	9	4	4,6	30	A,T,P	1200	54/48	8/7
P4	62M	Brisbane	14	4	4,5	29	D,A,T,P	800	38/28	5/5

Clinical assessments were performed on the same day as experiments.
HY= Hoehn and Yahr Stage; Items 27–30 = items 27–30 of UPDRS, assessing gait, posture and balance (score/16); MMSE = Mini Mental State Examination (score/30); UK Brain bank criteria: D = dyskinesias; A = asymmetry persistent; T = tremor at rest; P = progressive disease course; UPDRS III = part III (motor) of the Unified Parkinson's Disease Rating Scale (score/108). LED = Levodopa equivalent dose, mg/day.

7.5.1 Instrumented pull test

Four participants were assessed with the instrumented pull test. One participant (P1) was unable to regain balance independently under both stimulation conditions for five sequential trials, requiring catching by an examiner. Catching occurred when the participant did not

generate a step or produced ineffective stepping with small multiple steps in response to the pull. A further two participants (P2, P3) were unable to regain balance off stimulation, but were able to regain balance in three trials on stimulation. Only one participant (P4) was able to independently regain balance in 8 and 9 trials off and on stimulation respectively (Table 7.2). Variables of trunk and step responses from the instrumented pull test are detailed in Figure 7.1 and Table 7.3.

Table 7.2: Effects of PPN DBS on instrumented pull test responses for participants with PD

	Participant 1	**Participant 2**	**Participant 3**	**Participant 4**
OFF DBS	●●●●●	●●●●●	●●●●●	●●●●●●●●●
ON DBS	●●●●●	●●●●●●●●●	●●●●●●●●●	●●●●●●●●●●

Circles represent number of instrumented pull test trials (score/10) performed. Red circles represent trials where participants required catching by an examiner to prevent a fall. Testing was ceased if the participant required catching in five consecutive trials. Green circles represent trials where the participant was able to regain balance independently. Trials 1 to 10 are ordered sequentially from left to right.

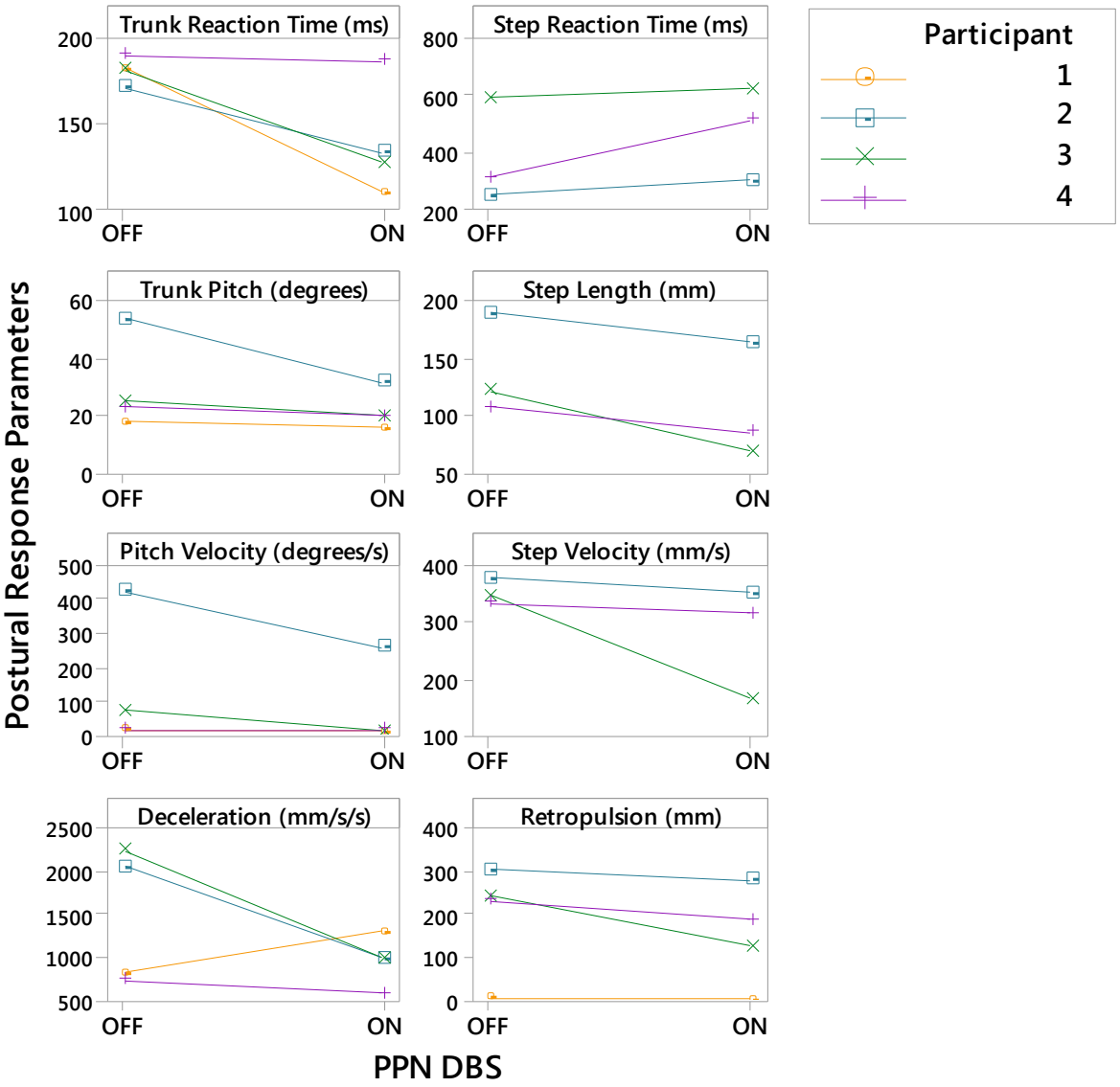

Figure 7.1: Effects of PPN DBS on postural responses for participants with PD using the instrumented pull test.

Mean trunk and step parameters derived from the instrumented pull test on and off PPN DBS. Participant 1 did not generate a step response to the pull in both conditions (i.e. retropulsion score of 0 mm) and values for step reaction time, step length and step velocity were therefore not computed. PPN DBS = pedunculopontine deep brain stimulation**.**

Table 7.3: Instrumented pull test variables in participants with Parkinson's disease and PPN DBS

	Participant 1		**Participant 2**			**Participant 3**			**Participant 4**			
	OFF	**ON**	**OFF**	**ON**		**OFF**	**ON**		**OFF**		**ON**	
	● Trials	● Trials	● Trials	● Trials	● Trials	● Trials	● Trials	● Trials	● Trials	● Trials	● Trials	● Trials
Number of trials	5	4*	5	7	3	5	7	3	2	8	1	9
Trunk RT (ms)	182 ± 23	109 ± 13	170 ± 88	169 ± 52	96 ± 46	181± 51	128 ± 15	124 ± 42	180 ± 11	198 ± 70	184	188 ± 43
Trunk deceleration ($mm.s^{-2}$)	827 ± 539	1310 ± 646	2058 ± 679	1010 ± 530	984 ± 40	2259 ± 1292	993 ± 418	982 ± 234	1094**	385 ± 226	736	407 ± 315
Pitch angle (°)	18 ± 3	16 ± 3	54 ± 28	35 ± 10	29 ± 11	25 ± 16	28 ± 9	12 ± 3	29 ± 5	17 ± 5	26	13 ± 5
Pitch velocity (°/s)	14 ± 4	9 ± 2	419 ± 107	256 ± 128	259 ± 104	71 ± 60	14 ± 5	4 ± 2	19 ± 1	11 ± 4	9	21 ± 16
Step RT (ms)	NA	NA	243 ± 71	356 ± 112	235 ± 14	584 ± 344	667 ± 76	563 ± 63	308 ± 40	397 ± 102	632	381 ± 154
Step length (mm)	NA	NA	190 ± 70	231 ± 52	96 ± 33	122 ± 63	78 ± 30	60 ± 6	57 ± 1	126 ± 68	68	103 ± 32
Step velocity (mm/s)	NA	NA	376 ± 139	458 ± 103	239 ± 77	344 ± 209	155 ± 60	171 ± 91	231 ± 43	434 ± 192	281	346 ± 97
Retropulsion (mm)	4 ± 1	3 ± 1	304 ± 42	318 ± 40	248 ± 45	242 ± 216	131 ± 47	121 ± 48	241 ± 16	224 ± 32	219	158 ± 35
Step count	NA	NA	5 to 10	5 to 8	3 to 6	0 to 11	0 to 5	3 to 4	4 to 6	4 to 8	10	4 to 7

Red circles represent trials where participants required catching by an examiner to prevent a fall. Testing was ceased if the participant required catching in five consecutive trials denoted by red circles. Green circles represent trials where the participant was able to regain balance independently. *Data from one trial was not computed due to technical error. **Deceleration values from one trial were not available due to technical error. NA = Data not available as a step response was absent in all trials on and off DBS. All variables are mean ± SD, except in Participant 4, ON DBS where data from one trial was available. Step count is reported as a range.

7.5.2 Clinical assessments

All participants completed clinical assessments of the UPDRS III and Mini-BESTest. UPDRS III motor scores decreased with all participants on stimulation, indicating better overall motor function (Table 7.1). On stimulation, axial scores of gait and balance according to UPDRS III It 27 to 30 improved in two participants, and remained unchanged in two participants (Figure 7.2). With clinical pull test item 30 of the UPDRS, only one participant (P3) improved on stimulation. With the Mini-BESTest, total scores increased with all participants on stimulation compared to off stimulation, indicating better overall balance responses (Figure 7.3). With the reactive balance component of the Mini-BESTest, no improvements were found in all participants on stimulation.

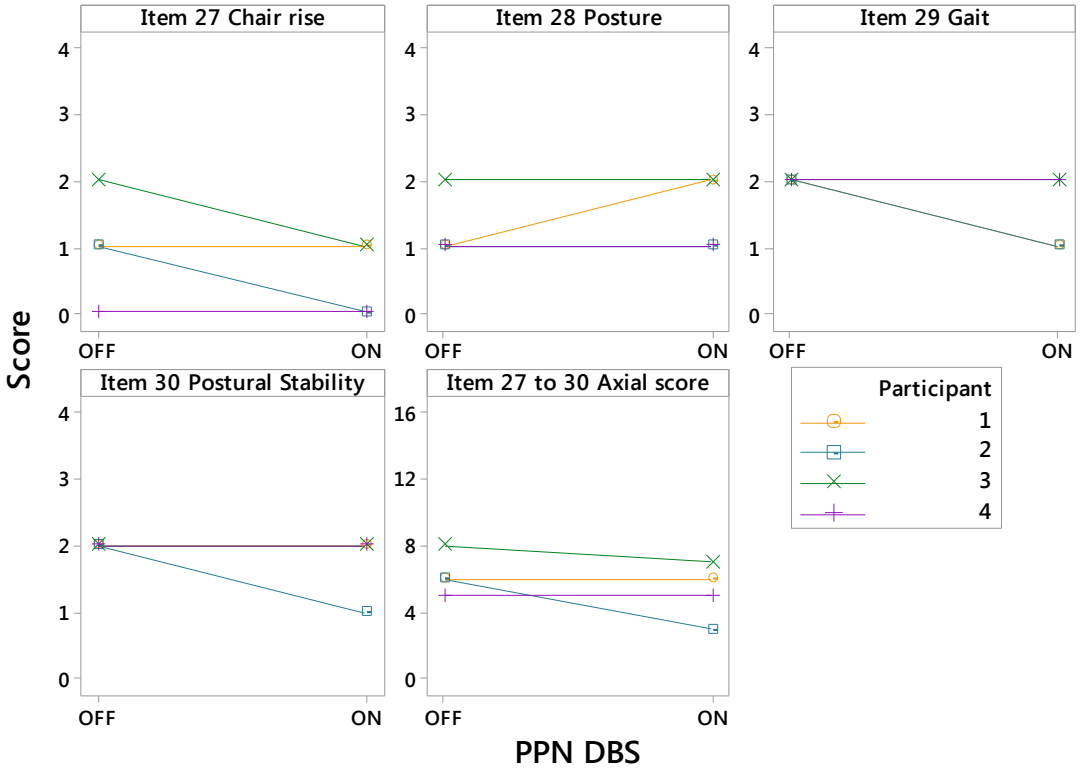

Figure 7.2: Effects of PPN DBS on UPDRS III subscores for participants with PD.
Participants were assessed with the UPDRS III motor subsection on and off stimulation. Panels describe items related to gait and posture outcomes of the UPDRS III motor subsection. Abbreviations: Item 27 chair rise (score/4), item 28 posture (score/4), item 29 gait (score/4), item 30 postural stability (score/4), Axial score = sum of items 27 to 30 of the UPDRS (score/16). Lower scores indicate improved motor function. PPN DBS = pedunculopontine deep brain stimulation. UPDRS = Unified Parkinson's disease rating scale. With item 30 postural stability, scores remained unchanged participants 1, 3 and 4 off and on stimulation.

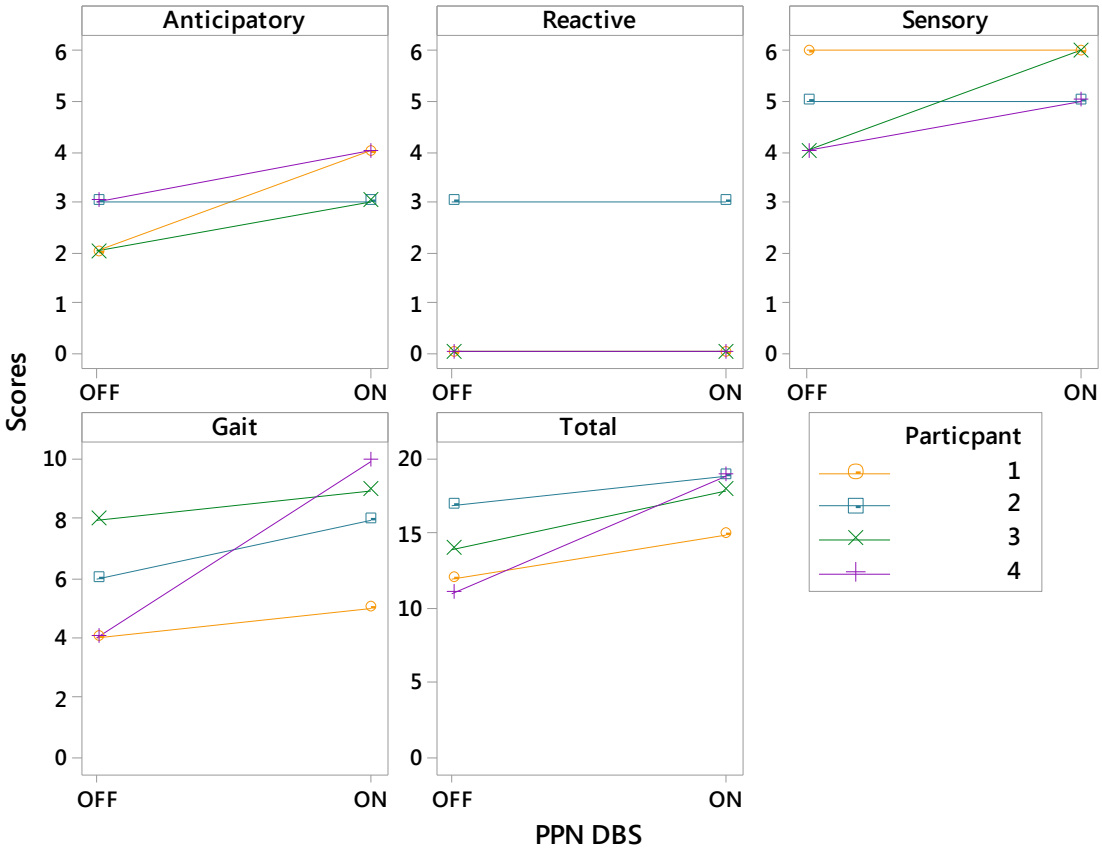

Figure 7.3: Effects of PPN DBS on Mini-BESTest scores for participants with PD.
Participants were assessed with the Mini-BESTest on and off stimulation. Panels describe the Mini-BESTest domains of balance and sum of the total score. Abbreviations: Anticipatory = Anticipatory postural adjustments subscale of Mini-BESTest (score/6); Reactive = Reactive postural responses subscale of Mini-BESTest (score/6); Sensory = Sensory orientation subscale of Mini-BESTest (score/6); Gait = Dynamic balance during gait subscale of Mini-BESTest (score/6); Mini-BESTest Total (score/28). Higher scores indicate improved balance performance. In the reactive domain, scores remained unchanged for participants 1, 3 and 4 off and on stimulation.

7.6 Discussion

In this study, the effects of PPN DBS on postural instability were explored off and on stimulation in four participants with moderate to severe PD using an instrumented pull test. While findings need to be interpreted with caution due to the small sample size, the instrumented pull test was able to quantify postural responses with greater resolution compared to clinical assessments. Where the clinical pull test was unable to differentiate between types of falls that required catching (e.g. a “log fall” with no step response versus fall with retropulsion), postural response variables were quantified in every

instrumented pull test trial, even when the participant required catching due to an imminent fall. With the clinical pull test, postural responses remained unchanged in three out of four participants on stimulation. No change in the reactive postural responses of the Mini-BESTest, which assesses forward, lateral and backward corrective stepping, was found in all participants.

7.6.1 The instrumented pull test as an assessment tool

The instrumented pull test was used to assess postural responses in participants with moderate to severe PD, and included all participants that were able to stand independently. While the instrumented pull test was able to quantify small changes in postural responses in people with mild PD (Studies 2 and 3), quantification of postural responses in participants with moderate to severe PD presented greater challenges. Out of five participants, one was unable to complete assessment with the instrumented pull test due to fatigue, and another required catching in all trials. In the remaining three participants, catching was required in multiple trials. Consequently, limited data from trials where participants were able to regain balance independently were available. Furthermore, data from postural responses were highly variable, with no clear trends between off and on stimulation. Although the small sample size limits interpretation of instrumented pull test findings, the inter-individual variability in reactive postural responses may also reflect the complex nature of balance, with multi factorial systems involvement from attentional processing, visual, vestibular and proprioceptive centres (Schoneburg et al., 2013).

Postural response variables such as trunk reaction times were found to be quicker in three out of the four participants on stimulation compared to off. Although these findings demonstrate the instrumented pull test was able to quantify postural responses with greater resolution compared to the clinical pull test, future use of the instrumented pull test in participants with PD demonstrating moderate to severe postural instability may not be practicable. It may be more feasible to explore trends in postural responses in a larger cohort of people with PD demonstrating moderate postural instability who are still able to regain balance independently (screened using the clinical pull test). Postural response variables obtained may then be useful as markers to monitor changes in postural stability over time.

7.6.2 Clinical assessments

In this study, effects of PPN DBS were evaluated using commonly utilised clinical balance assessments comprising UPDRS III motor subsection items 27 to 30 and the Mini-BESTest. UPDRS items 27 to 30 improved in two participants, and remained unchanged in two participants. In previous studies of PPN DBS, the common use of composite UPDRS axial scores items 27 to 30 to describe benefits to postural instability did not discriminate changes between posture and gait. Accordingly, effects of PPN DBS on postural instability remained unclear (Thevathasan et al., 2018). Discrepancies in findings remain even when researchers attempt to quantify postural instability specifically with the clinical pull test - most likely due to small sample sizes. Fewer than 100 cases of patients with PPN DBS have been reported in the past 10 years (Thevathasan et al., 2018). One study found postural responses improved in two participants to the clinical pull test on PPN DBS (Plaha and Gill, 2005). However, another study found pull test scores did not improve in five participants at one year follow up (Ferraye et al., 2010).

Discrepancies were also found when postural responses were quantified using the clinical pull test and reactive postural domain of the Mini-BESTest as compared to the instrumented pull test. For example, postural responses with clinical assessments did not improve in line with two out of four participants' ability to regain balance to the instrumented pull test. Participant 3 (P3) and 4 (P4) were able to independently regain balance to several trials of the instrumented pull test, although they did not regain balance during the clinical pull test. This may be due to learning effects, as the instrumented pull test procedure involved a series of 10 consecutive pulls, whereas clinical assessments were only performed once.

Unlike Chapter 6 where the first five pulls were discarded as 'practice pulls', the averaged trial responses of all trials in the off and on conditions were reported. Averaging of postural responses (or initial flexed posture) may have contributed to the large pitch angle observed in Participant 2 in the off stimulation condition. A drawback of this methodology is inability to identify if the first trial contained information about postural responses that were different to subsequent, habituated trials (Visser et al., 2010).

To date, the effects of PPN DBS on postural responses have not been investigated using the Mini-BESTest. All four participants demonstrated improvements in total Mini-BESTest scores on stimulation. However, no change was found with reactive postural responses subscores. Better overall balance as assessed by the Mini-BESTest appeared to arise due to improvements in other domains of postural control, particularly dynamic gait where all participants recorded increased scores on stimulation. For example, total Mini-BESTest scores improved on stimulation from 11 to 19 in Participant 3. The largest improvement was found in the domain of dynamic gait, which increased by 6 points, with no change in reactive balance scores. Such findings may be due to improvements in gait freezing which is a well reported benefit of PPN DBS (Moro et al., 2010; Thevathasan et al., 2011b, 2011a; Welter et al., 2015).

Furthermore, the Mini-BESTest employs a different method of balance perturbation which is not directly comparable to the pull test. Reactive postural responses are assessed in multiple directions (forward, lateral and backwards), and administration of the backward perturbation is elicited using the 'push and release', where the patient has to regain balance to a sudden release from a backward lean induced by an examiner as compared to the brisk backward shoulder tug administered by an examiner during the clinical pull test (Jacobs et al., 2006; Smith et al., 2016). Variabilities of postural responses with the clinical pull test relate mainly to peak pull force of the examiner (Chapter 4 and 5) whereas variabilities in the 'push and release' postural responses relate to backward lean and participant height (Smith et al., 2016).

Comprehensive measures of balance are recommended by the MDS taskforce for clinicians and researchers to capture balance responses specific to PD. The Mini-BESTest represents a clinical balance assessment with excellent inter-rater (Intraclass correlation coefficient = 0.91) and test-retest reliability (Intraclass correlation coefficient = 0.92), with adequate correlation for disease severity with the UPDRS (r = -0.51) in patients with PD (Franchignoni et al., 2010; Godi et al., 2012; King et al., 2012; Leddy et al., 2011). These assessments may present an additional method to explore postural responses in people with moderate to severe PD in conjunction to commonly used clinical assessment such as the UPDRS. The Mini-BESTest is considered a

'recommended' measure (Bloem et al., 2016b), providing insights into domains that contribute to overall balance.

7.6.3 Postural instability and effects of pedunculopontine deep brain stimulation

Postural deficits tend to be levodopa resistant particularly in more severe disease, suggesting the involvement of non-dopaminergic circuits (Bloem et al., 1996; Bonnet et al., 1987). The involvement of cholinergic pathways are thought to partly underlie pathophysiology of postural instability in PD (Dimitrova et al., 2004; Horak et al., 1996). However, dysfunctional basal ganglia pathology and dopaminergic deficits can also contribute, and become more apparent with disease progression (Bloem et al., 1990; Diener et al., 1987; Scholz et al., 1987).

PPN DBS has been previously shown to alter postural control in quiet stance, though benefits to functional balance remain unclear. On stimulation, benefits to balance were suggested through improved somatosensory integration and decreased mediolateral sway (Yousif et al., 2016). These changes were proposed to improve postural control, although no clinical benefits to balance were found. Separately, decreased mediolateral sway was also found in a case study of a patient followed over 14 months, with improvements to clinical and spatiotemporal measures of gait and falls (Wilcox et al., 2011). More recently, sway abnormalities in people with PD not only correlated to clinical balance outcomes (composite score of UPDRS items 27 and 30 - chair rise and pull test), but were also partly reversible and improved by PPN DBS (Perera et al., 2018).

Taken together, findings from the current study suggest some aspects of postural control may be modulated by PPN DBS. However, definitive conclusions on the therapeutic effects of PPN on postural instability cannot be drawn due to the small sample size. The effects of stimulation specifically on reactive postural responses seem to be circumscribed when participants with severe postural instability experience larger perturbations to balance such as an external perturbation. Between participants, the variability in postural responses to stimulation may also reflect an inherent limitation of the target, or challenges in surgical targeting due to the heterogeneous structure and poorly defined boundaries of the PPN (Benarroch, 2013; Hamani et al., 2016).

7.6.4 Strengths, limitations and future directions

In four participants with PD receiving PPN stimulation, the instrumented pull test was able to characterise postural responses with greater resolution compared to the clinical pull test. However, it is acknowledged participants required catching in multiple trials, making it difficult to interpret or explore trends in the data. For the first time, the effects of PPN DBS on postural responses were quantified using the Mini-BESTest. The Mini-BESTest demonstrated improvements in balance in participants receiving PPN stimulation resulted mainly from improvements in dynamic gait, and not reactive postural responses. This is in line with the therapeutic indications of PPN as a treatment particularly for gait freezing and falls (Thevathasan et al., 2018).

Several limitations are acknowledged in this study. The small sample size of five participants limits any conclusive findings on the therapeutic outcomes of PPN DBS on postural instability. Small sample sizes of typically 6-8 are common in clinical studies of PPN, indicative of the challenges and debate surrounding PPN targeting and programming (French and Muthusamy, 2018; Morita et al., 2014; Thevathasan et al., 2018). Another limitation is the relatively short stimulation washout time allowed which may have impaired the ability to detect changes to posture on and off stimulation. Axial symptoms of posture and gait may require longer adaptation periods with studies of PPN DBS reporting washout periods ranging from 1 hour to 2 weeks (Ostrem et al., 2010; Perera et al., 2018; Thevathasan et al., 2011b). In this study, the washout period was approximately 1 hour, in the interest of participant comfort and adherence. This washout period was sufficient to produce changes to posture and gait in previous studies of PPN DBS (Perera et al., 2018; Thevathasan et al., 2011b). Clinical assessments and the instrumented pull test were performed unblinded by the thesis author. Although participants were blinded to stimulation condition, outcomes could be biased by the examiner. Future studies could utilise a separate researcher to alter stimulation settings and the use of video recordings to score clinical outcomes by a blinded examiner. The severe postural instability experienced in this cohort also limited the interpretation of instrumented pull test findings. Future studies assessing people with PD and postural instability need to carefully screen those who are suitable for assessment using the instrumented pull test (i.e. people with Grade 1 postural instability according to the

UPDRS, able to regain balance independently) to explore trends in postural response variables that may be useful to detect or predict patients with PD at greater risk of falls, or the combined therapeutic efficacy of interventions such as levodopa and deep brain stimulation.

7.7 Summary and conclusions

The instrumented pull test and two clinical tests of postural responses (UPDRS items 27 to 30 and the Mini-BESTest) were used to assess postural responses in four participants with moderate to severe PD chronically implanted with bilateral PPN stimulators. Although findings suggest the instrumented pull test was able to quantify postural responses with greater resolution compared to clinical assessments, use of the instrumented pull test may not be feasible in patients with PD demonstrating severe postural instability as they required catching in multiple trials by an examiner. Definitive conclusions cannot be drawn on the therapeutic effects of PPN DBS for postural instability due to the small sample size and limited interpretation of data. From the trials where participants were able to regain balance independently, there was no clear trends in postural response variable between off and on stimulation. The effects of PPN stimulation on postural responses may also be circumscribed, particularly in moderate to severe PD when other postural deficits contribute to overall postural instability. The instrumented pull test may still present a useful tool in the research setting to explore postural responses in people with PD demonstrating moderate postural instability who are able to regain balance independently. Participants will need to be carefully screened to select those who are able to generate a corrective balance response according to the clinical pull test. The Mini-BESTest provided insights into domains of balance (i.e. dynamic gait) improved by PPN stimulation. Although findings need to be interpreted with caution due to the small sample size, the Mini-BESTest could be considered in future studies as an alternative or adjunct clinical assessment to the UPDRS to quantify postural responses in participants with PD who experience moderate to severe postural instability.

CHAPTER 8. GRAND DISCUSSION

8.1 Introduction

The primary goal of the thesis was to characterise postural responses in people with Parkinson's disease (PD) and the effects of levodopa and pedunculopontine nucleus (PPN) deep brain stimulation (DBS) on these responses using an instrumented version of the clinical pull test. This final chapter will synthesize findings from the four main studies within the thesis which utilised the instrumented pull test to: 1) determine its capability to detect small changes in postural responses in healthy young participants (Study 1, Chapter 4); 2) quantify postural responses in people with mild PD (HY Stage $\leq$ 2) (Study 2, Chapter 5); 3) determine the effects of levodopa therapy on postural responses in people with mild PD (Study 3, Chapter 6); and 4) evaluate the utility of the instrumented pull test to quantify postural responses in people with PD with moderate to severe postural instability (Study 4, Chapter 7). The strengths, limitations and clinical implications of the research are then considered. Next, directions for future research will discuss how the instrumented pull test may be refined as a potential assessment tool for postural instability in the clinical setting, and its use in clinical populations. Finally, the main conclusions from each study will be summarised with respect to the aims in Chapter 1.

8.2 Synthesis of main findings

The first major theme of this thesis was the development of an instrumented version of the clinical pull test. Although the clinical pull test is typically used to identify postural abnormalities in people with PD, it is not sensitive to detect mild changes to postural stability. Earlier detection of postural abnormalities is important due to the high prevalence and significant impact of postural instability in people with moderate to severe PD (Chapter 2). The risk of falls remains higher in people with PD compared to older healthy individuals (Ashburn et al., 2001; Contreras and Grandas, 2012; Pickering et al., 2007). A review of the assessment and treatment of postural instability in PD is described in Chapter 2, with a focus on reactive balance responses using laboratory based measures. Limitations of current assessments contributing to knowledge gaps in postural responses, and effects of therapy in PD were highlighted. To overcome some of

the limitations of conventional laboratory based assessments, instrumented versions of clinical tests have been developed. The review further discusses challenges faced in the development of these techniques.

The review in Chapter 2 guided development of an instrumented pull test to quantify trunk and step responses using 3D motion tracking sensors (Chapter 3). The utility of the instrumented pull test was investigated in Study 1, where postural responses to the pull test were characterised in healthy young participants. Using StartReact effects (where a startling loud auditory stimulus accelerates a pre-prepared movement), the instrumented pull test was able to detect a small speeding of truncal responses (approximately 10 ms), and distinguish first and subsequent trial postural responses. Findings from Study 1 suggested the instrumented pull test could present an alternative assessment tool to assess postural instability in patients with Parkinson's disease for clinical research.

A second major theme was the characterisation of postural responses in participants with mild PD (HY $\leq$ 2). The literature review (Chapter 2) found most studies of postural perturbations investigated patients with PD who already demonstrated postural abnormalities (HY > 2). In mild PD, falls are assumed to be rare (Albanese, 2007). However, it has become evident people with PD have an increased falls risk even in mild disease when optimally medicated (Kerr et al., 2010; Schenkman et al., 2011). The review highlighted postural abnormalities can occur in mild PD, and appear unrelated to medication state. Postural abnormalities in people with mild PD were not well identified or understood (Chastan et al., 2008; Ganesan et al., 2010; Lee et al., 2013; McVey et al., 2009). Consequently, Study 2 characterised postural responses to the instrumented pull test in participants with mild PD and healthy age matched controls. First and subsequent trial postural responses to the pull test were compared to evaluate if differences were present in trunk and step responses between participants with mild PD and controls. Findings from Study 2 suggest subclinical abnormalities in trunk and step responses are present to the pull test in participants with mild PD.

Thirdly, the effect of levodopa therapy was explored on postural responses in participants with mild PD using the instrumented pull test. Although it is well reported

that levodopa has little or no effect on postural responses to perturbations, these effects have yet to be explored in detail in people with mild PD. Therefore, Study 3 investigated the effects of levodopa on postural responses to the instrumented pull test in participants with mild PD compared to healthy age matched controls. Findings from Study 3 suggest mixed effects of levodopa on postural responses in participants with mild PD. Levodopa improved trunk postural responses, but did not restore trunk responses to levels comparable to controls. Conversely, some aspects of stepping responses appeared to worsen in participants with mild PD.

Finally, we evaluated the utility of the instrumented pull test to quantify postural responses in four participants with PD and moderate to severe postural instability receiving PPN DBS. PPN DBS is an alternative therapy targeting non-dopaminergic pathways which may be beneficial to postural instability. The instrumented pull test was used to characterise postural responses in participants with PD on and off stimulation. Two clinical tests, the Unified Parkinson's disease Rating Scale (UPDRS) III subscore comprising items 27 to 30 (chair rise, posture, gait and postural stability) and Mini-BESTest, were further used to evaluate postural responses. The findings from Study 4 suggest the instrumented pull test may be able to quantify postural responses with greater sensitivity compared to the clinical pull test in people with PD and moderate to severe postural instability. However, findings need to be interpreted with caution due to the small sample size, and variability of results with no clear trends from the data between off and on stimulation. The use of the instrumented pull test does not appear practicable in this cohort as participants required catching in multiple trials. Given the experimental nature of PPN DBS, participants were few, and definite conclusions cannot be drawn on the therapeutic efficacy of PPN DBS for postural instability. Using the Mini-BESTest, aspects of overall balance improved in participants with PD particularly in the dynamic gait domain on stimulation. The Mini-BESTest may be considered in future studies as a complimentary clinical assessment tool to assess balance in participants with PD and moderate to severe postural instability.

8.3 Strengths and limitations

The studies in this thesis present characterisation of postural responses to the pull test in people with PD according to an assessment commonly utilised in the clinical setting. They add to the understanding of abnormalities of postural responses that occur in mild PD, provide an initial exploration of the limits of its use in moderate to severe PD, and examine the efficacy of dopaminergic and non-dopaminergic therapies on postural responses to the pull test. These studies contribute to the understanding of postural responses in people with PD, and will help to guide future research and understanding of therapies to alleviate postural instability which is of importance due to its devastating consequences.

To the thesis author's knowledge, the instrumented pull test is the first to characterise whole body kinematics similar to the clinical pull test in people with PD (Studies 2 and 3). Studies of perturbations in mild PD have either identified subclinical postural abnormalities to feet-in-place responses (Chastan et al., 2008; Ganesan et al., 2010) or stepping responses (Lee et al., 2013; McVey et al., 2009), but not both. Although pull force by the examiner was previously hypothesized to influence pull test responses (Nonnekes et al., 2015), no study to date has objectively quantified the effects of examiner performance on the clinical pull test. Examiner pull force was found to be a significant variable influencing outcome of postural responses. These findings may explain issues with intra and inter reliability and poor correlation to objective endpoints such as dynamic posturography (Bloem et al., 1998). Studies 2, 3 and 4 also demonstrated the use of an instrumented pull test was safe and feasible as a potential assessment tool to assess postural instability in people with PD. The safety precautions employed during the instrumented pull test were no different from that performed with the pull test in clinical practice. This included an assistant to help with catching participants with known postural instability at higher risk of falls, and backward positioning of the examiner and participant close to a wall to prevent the examiner from falling together with the participant if they were unable to regain balance (Nonnekes et al., 2015).

Participants with PD in Studies 2 and 3 were carefully screened for disease staging (i.e. HY $\leq$ 2). This allowed for a sample representative of individuals with mild PD where postural responses have been relatively underexplored. It is acknowledged Studies 2 and 3 comprised a small cohort of eighteen participants with PD. Therefore, these results may not be representative of the wider PD population, and need to be interpreted with caution. Study 3 contributes to the understanding of levodopa effects on postural responses in mild PD. To our knowledge, no laboratory study has investigated the effects of levodopa on postural responses to the pull test in people with mild PD off and on medication. Previous work have only explored postural responses to an external perturbation in the on medication state (Lee et al., 2013; McVey et al., 2009). Although postural responses in the first trial were not assessed, study 3 confirmed postural abnormalities were present in people with mild PD on levodopa, similar to previous findings in later disease (Bloem et al., 1996; Curtze et al., 2015; Di Giulio et al., 2016; Horak et al., 1996; Kam et al., 2014).

In participants with PD and moderate to severe postural instability, the instrumented pull test appeared to assess postural responses with greater resolution compared to the clinical pull test (Study 4). However, the study consisted of a small sample of four participants, who required catching in multiple trials, making it difficult to interpret or explore trends of postural responses from instrumented pull test data. The relatively short stimulation washout time allowed (1 hour) may have also impaired the ability to detect changes to posture on and off stimulation. However, the washout period employed was sufficient to produce changes to posture and gait in previous studies of PPN DBS (Perera et al., 2018; Thevathasan et al., 2011b). The Mini-BESTest may present an alternative clinical assessment tool to assess postural responses in participants with PD and moderate to severe postural instability.

A number of limitations relate to, and are common in studies 2, 3 and 4. The thesis author completed all assessments. The use of one examiner precludes the reporting on inter-examiner variability of the instrumented pull test. Furthermore, the thesis author was not blinded to participant groups, which could influence ratings of clinical assessments, or force generated during pull test trials. To address potential examiner bias, data from the instrumented pull test was computed offline by a second researcher

who was blinded to participant groups, and the force of each pull test trial was accounted for in analyses. At group level, Studies 2 and 3 identified abnormalities of postural responses in people with mild PD to the pull test. However, it is acknowledged these results are not currently able to inform clinical decision making on the individual level.

8.4 Clinical implications

8.4.1 Clinical pull test administration and performance

The clinical pull test according to the UPDRS is widely used, and a key component in the neurological examination of postural responses in people with PD (Hunt and Sethi, 2006; Nonnekes et al., 2015). However, variability in pull test execution and interpretation can confound clinical practice and research (Hunt and Sethi, 2006; Munhoz et al., 2004). It is unclear whether variabilities in test administration, such as pull force, influence the response. Interpretation of the test is also controversial. Outcomes can vary depending on whether the first or subsequent trial is assessed (Nanhoe-Mahabier et al., 2012; Visser et al., 2003). This may partly explain the limitations of the clinical pull test as a sensitive predictor of future falls in PD (Chapter 2). To address this gap, this thesis provided new evidence to inform how the pull test should be administered and interpreted in people with PD.

Prior evidence suggests postural responses from the first, unpractised trial may be most clinically meaningful (Bloem et al., 2001; Visser et al., 2003). These responses are demonstrated to induce greater instability and propensity to falls compared to subsequent trial responses. Findings from studies 1 and 2 demonstrate first trial postural responses are significantly different from postural responses of subsequent trials. This was found not only in healthy individuals, but also people with PD of mild disease severity. Our findings demonstrate that the first trial response is important to capture as an end point in itself.

Guidelines from the movement disorders society (MDS) recommend performing an initial practice pull before the second trial is formally assessed for the accurate evaluation of postural responses (Goetz et al., 2008). Elderly patients may initially

misunderstand the corrective movement required, or may not comprehend the test instructions due to language barrier (Hunt and Sethi, 2006). This may result in the patient falling into the arms of the examiner following the pull without any attempt to generate a corrective step response. Although we did not correlate first trial postural responses with clinical measures, the utility of first trial responses may be its ecological relevance to correlate to important clinical endpoints such as falls (Nonnekes et al., 2015; Visser et al., 2010, 2003). An unexpected shoulder pull, performed once, is suggested to be more sensitive when retrospectively assessing falls or near falls in people with PD compared to the expected shoulder pull recommended of clinical guidelines (Visser et al., 2003). Regardless of the method of administration, the clinical pull test fails to predict future falls in people with PD (Bloem et al., 2001). This may not only be due to inherent shortcomings with variabilities of test administration and subjective scoring, but the complex, and multi-factorial nature of falls (Lamont et al., 2017; Wood et al., 2002). Nevertheless, our findings support that clinicians should perform and score an initial unpractised trial, before the pull test is performed according to clinical guidelines. The pull should be administered of sufficient force to elicit both a trunk and step response, as pull force was found be the main influence on the size of postural responses (detailed in section below).

In the laboratory, first trial postural responses have greater ability to discriminate between people with PD off levodopa and healthy controls when participants are of moderate disease severity (HY 2.5 - 3) compared to subsequent trials with use of platform rotations (Nanhoe-Mahabier et al., 2012). Studies 2 and 3 found subclinical postural abnormalities not only in the first trial in people with PD off and on levodopa, but also in participants with mild PD on levodopa in subsequent trials compared to healthy participants. Clinicians should be mindful that abnormalities in postural responses are present in patients who are optimally medicated even in mild PD. These abnormalities may manifest as a decrease in the quality of corrective postural responses (e.g. increased postural sway) in participants with PD that is not taken into account with clinical scoring. A limitation of study 4 was that we did not specifically investigate first trial responses in participants with moderate to severe PD (HY 4). Unlike previous work (Nanhoe-Mahabier et al., 2012), participants in our study demonstrated moderate to severe postural instability (and gait freezing), who required frequent catching by the

examiner to prevent a fall. As the clinical pull test does not distinguish between types of falls (i.e. 'log fall' with no step response, or fall with retropulsion), the instrumented pull test may be useful in future studies to identify markers of postural responses that signal the transition from non-faller to faller. By assessing larger cohorts of people with PD across the spectrum of postural instability, aspects of truncal or step variables may be identified as biomarkers indicative of increased falls risk.

8.4.2 Impact of examiner pull force and participant anthropometric characteristics

Examiner performance during the pull, in particular peak pull force, had a substantial impact on pull test results (Studies 1 and 2). In participants with PD, peak pull force varied sufficiently to influence speed and size of trunk and step responses. Interestingly, participant height and weight were of lesser influence. It is acknowledged clinicians do not have the benefit of a pull force meter and a mixed linear model to adjust for such confounds. In the studies contained in this thesis, all pulls by the examiner were of sufficient force to elicit a trunk and step response. In practice, clinicians need to estimate the force necessary to elicit a step in the patient prior to the pull, and position themselves and the patient appropriately with their backs close to a wall to safeguard against any unexpected falls, particularly in patients with known postural instability. The experience of examiners performing the pull test can create variability in outcomes due to inconsistency in strength of the pull (Nonnekes et al., 2015). Some examiners may be wary of administering a larger pull force as they may not be able to support the patient in case of a fall. Training of examiners performing the clinical pull test is therefore imperative, particularly when the clinical pull test is administered in clinical trials (Hunt and Sethi, 2006).

8.4.3 Implications for rehabilitation

For clinicians, it is important to consider that the clinical pull test is not sufficiently sensitive to detect trunk and step abnormalities observed in mild PD even in the off levodopa state. People with PD are known to be at increased risk of falling, even in mild disease (HY $\leq$ 2) when optimally medicated (Kerr et al., 2010). Accordingly, a study

found 45% of people with mild PD reported a fall or near fall, with fear of falling being an important predictor of falls or near falls (Lindholm et al., 2015).

More importantly, abnormalities of trunk and step responses identified in people with mild PD were not sufficiently restored on levodopa to be comparable to levels of healthy participants (Study 3). Clinicians need to be mindful that a patient with mild PD optimised on medications may still present with subclinical abnormalities in postural responses to the pull test. Given the importance of protective postural responses in falls prevention, the identification of smaller step sizes in people with mild PD presents a potential role for interventions to optimise stepping responses (Adkin et al., 2005). Rehabilitation strategies that target protective postural responses with perturbation training may benefit stepping. Repeated exposure to a perturbation is suggested to improve compensatory stepping in first (Barajas and Peterson, 2018) and subsequent trials (Jobges et al., 2004; Peterson and Horak, 2016). However, the degree of retention and training dosage to sustain these benefits remains unknown. A previous study suggests an 8 week program targeting multi domains of balance including step training was beneficial to overall balance in people with mild to moderate PD (average HY 2.5) at 12 months follow-up (Wong-Yu and Mak, 2015).

It is acknowledged that postural responses to an external perturbation such as pull test only reveal one aspect of postural stability. This is particularly evident in moderate to severe PD and highlighted in study 4, where large variations in postural responses and effects of PPN stimulation were observed between participants. In terms of postural stability, clinicians need to consider other domains that contribute to postural control which include postural control during quiet stance (e.g. during standing), anticipatory postural adjustments prior to voluntary movement (e.g. prior to taking a step) and dynamic balance during walking (Schoneburg et al., 2013). Impairment in one or a combination of domains can contribute to postural instability. According to the European Physiotherapy Guidelines for Parkinson's disease, the selection of assessment tools to evaluate domains of postural control should depend on whether deficits in relate to difficulties in static or dynamic activities (Keus et al., 2014). In addition to the clinical pull test, comprehensive assessment of postural responses in people with PD should comprise a range of assessments as recommended by the MDS taskforce (Bloem

et al., 2016b). These should include measures that evaluate the ability to change and maintain body equilibrium during daily tasks. For example, the timed up and go test which evaluates rising, walking and turning is recommended by the MDS and European clinical guidelines as a functional measure of balance (Bloem et al., 2016a; Keus et al., 2014; Podsiadlo and Richardson, 1991). The choice of assessment tool also depends on the context of how the information is used, such as to estimate falls risk or identify deficits in domains of postural control for interventions (Keus et al., 2014).

8.4.4 The instrumented pull test as an assessment tool for postural instability

The preliminary evidence from studies in this thesis suggests the instrumented pull test may offer an alternative method to assess postural responses in the research setting. Compared to conventional laboratory techniques of moving platforms that require a dedicated space, the instrumented pull test is semi-portable. Electromagnetic motion tracking is relatively inexpensive compared to conventional methods which report displacement data (Di Giulio et al., 2016; Kam et al., 2014). Recording of displacement in millimeter units negates the requirement for complex signal processing, so the data can be intuitively comprehended. Although the pull test remains a very useful clinical test, subclinical postural abnormalities detected in people with mild PD further support the need to develop more objective measures or biomarkers of postural instability with predictive value for falls risk (Nonnekes et al., 2015).

No single balance assessment is able to accurately capture overall postural stability within a group of participants. However, evaluation of postural responses to an external perturbation may provide insights into how patients integrate sensorimotor programs, how they learn, and how they execute a pre-planned, coordinated motor program, under different environmental contexts (Horak et al., 1997). In PD, various factors may contribute to deficits in reactive postural responses including inappropriate strategy selection, impaired sensory-reweighting, biomechanical limitations and cholinergic deficiency (Chong et al., 2000; Horak and Nashner, 1986; Mancini et al., 2008; Rinne et al., 2008; Schoneburg et al., 2013). This is particularly so in moderate to severe postural instability where individuals may experience different constraints that affect postural stability (Horak et al., 1997). Clinicians need to consider other domains that contribute to overall balance which include postural control during quiet stance, anticipatory

postural adjustments prior to voluntary movement and dynamic balance during walking (Schoneburg et al., 2013).

Further studies may be warranted in people with PD experiencing moderate to severe postural instability (Study 4) to assess if the instrumented pull test is useful in identifying markers of postural responses in patients at greater falls risk. At present, the instrumented pull test may find greatest utility in laboratory studies seeking to capture abnormalities in postural responses, track postural instability over time, and detect responses to therapy.

8.5 Future directions

Postural instability and falls are debilitating features of PD, with devastating consequences to both patients and caregivers (Kim et al., 2013). Falls interventions are most effective when implemented prior to falls occurring, however, current clinical assessments lack sensitivity to track the progression of postural instability in PD (McVey et al., 2013). The use of laboratory based assessments holds promise to expand our understanding of this important topic, and to understand the progression of postural instability so that interventions can be appropriately targeted. Furthermore, recent studies have included analyses of first trial postural responses which may be most pertinent to falls that occur in daily life (Barajas and Peterson, 2018; Liu et al., 2017; Nanhoe-Mahabier et al., 2012). Based on the findings of the studies in this thesis, a number of future research directions have been identified.

The development of instrumented versions of clinical tests of balance is of increasing interest (Andò et al., 2018; Di Giulio et al., 2016; Smith et al., 2016). Instrumentation of the clinical pull test could potentially be used as a substitute for clinical scales, with increased sensitivity of measurement. However, future research needs to validate and examine the utility of this approach if it is to be considered for use in the clinical setting. As the studies in this thesis were cross-sectional, future work needs to assess the responsiveness of the instrumented pull test to detect changes in postural responses in the same cohort over time. As 35 pulls is not practicable in the clinic, the number of pull test trials will need to be reduced through future studies of validity and reliability. Testing by multiple examiners in cohorts of different disease states and severity is also

required. As pull force by the examiner was also found to be a factor influencing the postural outcomes, future studies will also need to consider consistency of pull force though systems that may automatically feedback the amount of force from the pull. Examiners will need to be trained to elicit a pull always requiring a step response from the participant (as per the research protocol presented in Chapters 3 and 4). For ease of use, the linear mixed models employed in the studies could be incorporated into the software to produce data in real time. Other factors such as cost of the system and interpretability of outcomes also need to be considered before this method can find credibility as a standardised tool to assess postural responses in the clinical setting.

While the instrumented pull test was used successfully, additional measurements may benefit understanding of body kinematics to the pull or to underlying disease mechanisms. The instrumented pull test employed motion tracking – capturing net movement rather than the onset of muscle recruitment – akin to a clinician detecting movement of the participant during the pull. If desired, future studies may wish to integrate electromyography into the protocol (e.g. measured from muscles including tibialis anterior, soleus, hamstrings, quadriceps, rectus abdominis and lumbar paraspinals). Alternatively, placement of additional motion sensors on the shank may also help to identify if different postural strategies were used in participants with PD compared to healthy age matched controls, and contributed to the large variabilities in trunk movement observed (Studies 2 and 3).

Future iterations of the instrumented pull test need to further consider the user experience of the examiner and participant. With the current setup, motion sensors employed are connected by wires to the base unit. These wires are of sufficient length in the laboratory to record pull test kinematics. However a wireless system would be more practical in a clinical setting. To increase the participant's comfort during testing, particularly with females, a modified harness which fastens from behind could be considered.

Findings from this thesis are a small step towards identifying abnormalities of postural responses that are able to predict the risk of falls in people with PD before they occur. Future studies assessing people with PD and postural instability need to explore

variables in postural responses across a range of disease severity, and over time, in order to identify these markers of falls risk.

8.6 Conclusions

The overall aim of this thesis was to characterise postural instability in people with PD and the effects of therapies using an instrumented version of the pull test. The main conclusions are summarised:

1) A comprehensive narrative review:
   i) Described and synthesized the literature related to the assessment of postural instability in people with PD, with a focus on instrumented versions of clinical assessments.
   ii) Critically appraised the literature related to the management of postural instability in people with PD, with a focus on laboratory based assessments of dynamic posturography.
2) The methodology chapter:
   i) Described the development of an instrumented pull test where displacements of the trunk and feet are captured by a semi-portable motion tracking system.
   ii) Described the instrumented pull test protocol for use in populations where postural responses are of interest and balance assessment typically employs the clinical pull test.
3) A cross-sectional study investigating the utility of an instrumented pull test in healthy young individuals showed that:
   i) The instrumented pull test was sensitive to detect small changes in postural responses by capturing the speeding of postural responses in the trunk to a loud auditory stimulus (StartReact effects).
   ii) The instrumented pull test was able to discriminate postural responses between first and subsequent trials.
   iii) The instrumented pull test was able to detect variables influencing pull test administration (e.g. pull force by the examiner) to identify and quantify potential confounds that were accounted for by statistical techniques.

iv) Examiner pull force significantly affected the postural response in stepping in healthy young individuals.

4) A cross-sectional study investigating the utility of an instrumented pull test in people with mild PD showed that:
   i) The instrumented pull test was sensitive to detect subclinical abnormalities in trunk and step responses in people with mild PD compared to healthy age matched individuals.
   ii) First and subsequent trial postural responses discriminated people with mild PD and healthy age matched individuals.
   iii) Examiner pull force significantly affected the postural response in trunk and stepping in people with mild PD.

5) A cross-sectional study investigating the effects of levodopa on postural responses using an instrumented pull test in people with mild PD showed that:
   i) Levodopa produced mixed effects in trunk and step responses in people with mild PD.
   ii) Levodopa improved the size and speed of truncal responses in people with PD towards levels of age matched healthy individuals. Conversely, levodopa worsened the size and speed step responses away from levels of age matched healthy individuals.
   iii) Subclinical abnormalities in trunk and step responses in people with mild PD on levodopa were not restored to levels of age matched healthy individuals.

6) A cross-sectional study investigating the utility of an instrumented pull test in people with PD and moderate to severe postural instability receiving PPN DBS showed that:
   i) The instrumented pull test was able to detect postural responses with greater resolution off and on stimulation, compared to clinical assessments in a cohort of four participants.
   ii) Interpretation of findings was limited by the small sample size and highly variable postural responses in people with PD and moderate to severe postural instability who required catching in multiple trials.

iii) Use of the instrumented pull test may be best suited to participants with PD and postural instability who are still able to regain balance to a backward pull according to the clinical pull test in future studies.

Postural instability can present in mild disease even when overall balance is assessed as normal according to the clinical pull test. Consequently, people with PD have historically not been referred for interventions to address falls and risk of falls until later stages of the disease (Ashburn et al., 2004). More recently, increasing evidence has recognised the importance of exercise and rehabilitation in the management of people with PD and advocacy for referrals to allied health professionals in mild disease (Abbruzzese et al., 2016; Bloem et al., 2015; Earhart et al., 2015). The studies in this thesis have provided new insights into the abnormalities in postural responses experienced by people with mild PD and the effects of levodopa on these impairments using an instrumented version of the pull test. This thesis adds to the understanding of postural abnormalities that arise in people with mild PD, augmenting the established body of evidence previously describing abnormalities in postural responses in people with PD of greater disease severity. Findings from this thesis support the call for targeted interventions to be implemented early. The instrumented pull test presents an objective method for the assessment and tracking of postural responses in people with PD with disease progression. Knowledge gained from this thesis is a small step towards the goal of identifying abnormalities of postural responses that are able to predict the risk of falls in people with PD before they occur. The future presents many interesting opportunities and challenges for researchers and clinicians involved in the management of postural instability in PD.

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Appendices

Appendix 1. Publication

Publication related to Study 4, Chapter 7

Perera, T., **Tan, J.L.**, Cole, M.H., Yohanandan, S.A.C., Silberstein, P., Cook, R., Peppard, R., Aziz, T., Coyne, T., Brown, P., Silburn, P.A., Thevathasan, W., 2018. Balance control systems in Parkinson's disease and the impact of pedunculopontine area stimulation. Brain 141, 3009–3022. https://doi.org/10.1093/brain/awy216

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Balance control systems in Parkinson's disease and the impact of pedunculopontine area stimulation

Thushara Perera,[1,2] Joy L. Tan,[1,2] Michael H. Cole,[3] Shivy A. C. Yohanandan,[1] Paul Silberstein,[4] Raymond Cook,[4] Richard Peppard,[1,5] Tipu Aziz,[6] Terry Coyne,[7] Peter Brown,[6,8] Peter A. Silburn[7] and Wesley Thevathasan[1,9,10]

Impaired balance is a major contributor to falls and diminished quality of life in Parkinson's disease, yet the pathophysiology is poorly understood. Here, we assessed if patients with Parkinson's disease and severe clinical balance impairment have deficits in the intermittent and continuous control systems proposed to maintain upright stance, and furthermore, whether such deficits are potentially reversible, with the experimental therapy of pedunculopontine nucleus deep brain stimulation. Two subject groups were assessed: (i) 13 patients with Parkinson's disease and severe clinical balance impairment, implanted with pedunculopontine nucleus deep brain stimulators; and (ii) 13 healthy control subjects. Patients were assessed in the OFF medication state and blinded to two conditions; off and on pedunculopontine nucleus stimulation. Postural sway data (deviations in centre of pressure) were collected during quiet stance using posturography. Intermittent control of sway was assessed by calculating the frequency of intermittent switching behaviour (discontinuities), derived using a wavelet-based transformation of the sway time series. Continuous control of sway was assessed with a proportional–integral–derivative (PID) controller model using ballistic reaction time as a measure of feedback delay. Clinical balance impairment was assessed using the 'pull test' to rate postural reflexes and by rating attempts to arise from sitting to standing. Patients with Parkinson's disease demonstrated reduced intermittent switching of postural sway compared with healthy controls. Patients also had abnormal feedback gains in postural sway according to the PID model. Pedunculopontine nucleus stimulation improved intermittent switching of postural sway, feedback gains in the PID model and clinical balance impairment. Clinical balance impairment correlated with intermittent switching of postural sway (rho = -0.705, $P < 0.001$) and feedback gains in the PID model (rho = 0.619, $P = 0.011$). These results suggest that dysfunctional intermittent and continuous control systems may contribute to the pathophysiology of clinical balance impairment in Parkinson's disease. Clinical balance impairment and their related control system deficits are potentially reversible, as demonstrated by their improvement with pedunculopontine nucleus deep brain stimulation.

1 The Bionics Institute, East Melbourne, Victoria, Australia
2 Department of Medical Bionics, The University of Melbourne, Parkville, Victoria, Australia
3 School of Exercise Science, Australian Catholic University, Brisbane, Queensland, Australia
4 Royal North Shore and North Shore Private Hospitals, Sydney, New South Wales, Australia
5 Clinical Neurosciences, St Vincent's Hospital, Melbourne, Victoria, Australia
6 Nuffield Department of Clinical Neurosciences, John Radcliffe Hospital, University of Oxford, Oxford OX1 3TH, UK
7 Asia-Pacific Centre for Neuromodulation, Queensland Brain Institute, The University of Queensland, Brisbane, Queensland, Australia
8 Medical Research Council Brain Network Dynamics Unit, University of Oxford, Oxford OX1 3TH, UK
9 Departments of Neurology, The Royal Melbourne and Austin Hospitals, Victoria, Australia
10 Department of Medicine, The University of Melbourne, Parkville, Victoria, Australia

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Correspondence to: Dr Wesley Thevathasan
Department of Neurology, Royal Melbourne Hospital, Royal Parade, Parkville, Melbourne, 3050 Australia
E-mail: wesley.thevathasan@mh.org.au

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Abbreviations: DBS = deep brain stimulation; PID = proportional integral derivative; PPN = pedunculopontine nucleus; UPDRS = Unified Parkinson's Disease Rating Scale

Introduction

Impaired balance is a major contributor to diminished quality of life in Parkinson's disease (Marras *et al.*, 2008). Balance impairment in Parkinson's disease leads to symptoms such as falls, a sense of unsteadiness when walking and difficulty transitioning between positions such as sitting to standing (Schoneburg *et al.*, 2013). Such symptoms are common at diagnosis and become more prominent and treatment refractory with disease progression (Kim *et al.*, 2013). However, the pathophysiology of such balance impairment in Parkinson's disease is inadequately understood. Deficits associated with balance impairment in Parkinson's disease have included cholinergic deficiency, impaired attentional processing, increased body rigidity, abnormal patterns of leg muscle recruitment and increased body sway (Muller *et al.*, 2013; Schoneburg *et al.*, 2013; Rinalduzzi *et al.*, 2015). However, the precise nature of the underlying network dysfunction that causes balance impairment is unclear.

Recently, analysis of postural sway has attempted to explore the underlying control systems proposed to maintain upright stance (Gawthrop *et al.*, 2014; Morasso *et al.*, 2014). Postural sway is the constant movement in centre of mass which occurs even during quiet standing (Winter *et al.*, 1990). This can be approximated using posturography, which involves standing on a pressure sensitive plate to track variations in centre of pressure (an approximation of centre of mass) (Rocchi *et al.*, 2006; Visser *et al.*, 2008). Maintenance of upright stance requires a constant and active process of leg muscle modulation, as ankle stiffness alone can be insufficient to counteract torque from gravity (Schoneburg *et al.*, 2013). This continuous process of maintaining centre of mass around a specific balancing point is reflected in postural sway and represents a control theory challenge, akin to regulating temperature with a thermostat or speed of a car with cruise control (Morasso *et al.*, 2014; Glasauer and Straka, 2017). Indeed, many of the models of biological control systems have developed along with those used in machines (Gawthrop *et al.*, 2014). It is important to stress that these control system models are conceptual representations that aim to capture brain function rather than recreate neural circuitry.

A long-held view is that postural sway is regulated by a continuous feedback controller, such as the proportional–integral–derivative (PID) model, where the state of the control variable (position of centre of mass) continuously updates the output (motor response) (Peterka, 2000, 2002). PID continuous controllers use information from three time domains regarding error in the control variable in order to shape the output (Aström and Murray, 2010). Present ('proportional') information reflects the current error (e.g. distance of centre of mass from the setpoint). Past ('integral') information accounts for accrued errors (e.g. from a previous lurch backwards) and helps avoid drift from the set point. Future ('derivative') information predicts the error of the current trajectory (e.g. over/undershoot) and helps reduce oscillations around the set point. Importantly, these three time factors are not treated equally, but are weighted by the system—and this weighting shapes the characteristics of control (e.g. how quickly deficits are made up and how much oscillation occurs). A range of indirect phenomena have suggested that continuous sway control systems may be affected in Parkinson's disease, for example the detection of abnormal resonance in sway including limit cycle oscillations (Maurer *et al.*, 2004; Chagdes *et al.*, 2016). However, there is a lack of research directly addressing whether PID error signal processing in the control of sway is affected by Parkinson's disease and its treatment.

In contrast, intermittent control has recently arisen as an attractive additional or alternative model to maintain sway, which may better account for the significant and variable feedback delays from neural processing, which would confound continuous control (Bottaro *et al.*, 2005, 2008; Gawthrop *et al.*, 2011; Loram *et al.*, 2011). Continuous and intermittent control systems are not mutually exclusive. For example, a process of continuous monitoring with intermittent responses has been postulated (Gawthrop *et al.*, 2011). Intermittent control of sway is proposed to involve the event triggered episodic release of ballistic, pre-programmed corrective responses (Bottaro *et al.*, 2005; Gawthrop *et al.*, 2014). Interestingly, the expression of such motor programmes may be impaired in patients with Parkinson's disease and axial deficits—evidenced by our previous finding that such patients fail to exhibit the 'Start-React' phenomenon (Thevathasan *et al.*, 2011*b*). 'Start-React' refers to the accelerated release of ballistic, pre-programmed movement in response to startling stimuli, such as very loud sounds (Valls-Sole *et al.*, 1999). Importantly, we found that Start-React in Parkinson's disease could be restored by pedunculopontine nucleus (PPN) deep brain stimulation (DBS). Thus, taken together, these findings raise the possibility of an associated impairment in the output of intermittent sway control, which may be

amenable to recovery, along with related clinical balance impairment.

Indeed, the reversal of balance impairment in Parkinson's disease has become a major therapeutic challenge. Conventional treatments for Parkinson's disease such as levodopa and subthalamic or pallidal DBS are often minimally effective or can even worsen balance (Hariz *et al.*, 2008; Visser *et al.*, 2008; St George *et al.*, 2010). PPN DBS therefore arose as an experimental therapy for otherwise refractory gait and balance impairment. Small clinical studies have found that PPN DBS can improve gait freezing and falls (Ferraye *et al.*, 2009; Moro *et al.*, 2010; Thevathasan *et al.*, 2011*a*; Welter *et al.*, 2015). However, it is unclear if the benefit of PPN DBS on falls is because of improved balance or due to less gait freezing or some other factor (Thevathasan *et al.*, 2018). Clinical studies of PPN DBS have detected little or no specific benefit on postural instability, as assessed by clinical scales such as the pull test (Ferraye *et al.*, 2009; Moro *et al.*, 2010; Thevathasan *et al.*, 2011*b*; Welter *et al.*, 2015). However, this may reflect a lack of sensitivity of the assessment tools particularly where statistical power was low. Thus currently, it is unknown whether PPN DBS improves balance in Parkinson's disease. The potential of any therapy to improve balance in Parkinson's disease would be important information, even if only to reveal a viable therapeutic mechanism.

In this study, we acquired posturography data from patients with Parkinson's disease severely affected by clinical balance impairment, whilst off and on PPN DBS and compared results to healthy controls. Novel analysis methods were applied to derive measures of control system performance. We hypothesized that balance impairment in Parkinson's disease is associated with deficits in intermittent and continuous sway control and that these deficits would improve with PPN DBS. We also assessed if balance control system metrics correlated with clinical balance impairment, and thus may have potential as biomarkers.

Materials and methods

Subjects and clinical assessments

Two subject groups were assessed: (i) 13 patients (10 males) with Parkinson's disease complicated by severe clinical balance impairment, chronically implanted with bilateral PPN stimulators; and (ii) 13 age and gender matched (10 males) healthy controls. The two groups did not differ in age (70.0 ± 6.95 versus 69.8 ± 5.57 years; $U = 183.5$, $P = 0.699$). Subjects were recruited from centres in Oxford (England, UK), and Brisbane, Sydney and Melbourne (Australia). Data were collected over a 7-year period from December 2009 to December 2016. A database identified 28 patients implanted with bilateral single target PPN DBS for Parkinson's disease across the centres during the assessment period (up to March 2011 in Oxford and December 2016 in Australia). All patients were considered for inclusion and patients were not selected based on their benefit from DBS. Twelve patients were not assessed with posturography because of: death ($n = 1$), device explantation due to lack of efficacy ($n = 1$), dementia/frailty ($n = 4$), living in a remote location ($n = 4$), or involvement in other research ($n = 2$). Posturography was performed in 16 patients. Incomplete data from three patients were rejected before analysis. Of the 13 patients included, clinical outcomes of eight and reaction times of seven are previously reported (Thevathasan *et al.*, 2010, 2011*a*, *b*, 2012*a*). Ethics committee approval was obtained from all centres and participants gave written informed consent. Clinical details of the Parkinson's disease patients are shown in Table 1.

Patients with Parkinson's disease were selected for PPN stimulation because of severe gait freezing and postural instability persisting even ON medication, causing frequent falls. The persistence of these deficits despite adequate dopaminergic medication was determined clinically, via examination in a practically defined ON medication state (Thevathasan *et al.*, 2018). This was the dominant symptomatic issue at surgery and motor fluctuations, if present, were not severe. In Parkinson's disease, gait freezing and postural instability become more common and less medication responsive with disease progression (Giladi *et al.*, 2001*a*; Bloem *et al.*, 2004). However, it is unusual in Parkinson's disease for severe ON medication gait freezing and postural instability to be the predominant issue (Factor, 2008; Jankovic, 2008). As there is no definitive test for Parkinson's disease in life, we stress that the diagnosis of Parkinson's disease here is presumptive.

Patients with Parkinson's disease were receiving lone bilateral stimulation to the caudal PPN region, without implantation of other targets (Hamani *et al.*, 2016*b*). Surgical implantation of the PPN from two of the centres has been described previously (Pereira *et al.*, 2008; Thevathasan *et al.*, 2011*b*). Figure 1 demonstrates the stimulation locations (midpoint between active contacts for bipolar stimulation and cathodes for monopolar). Contacts were identified on postoperative CT fused with preoperative MRIs and referenced to local landmarks in the brainstem as described previously (Ferraye *et al.*, 2009). Coordinates were calculated as follows: laterality from midline (mean 6.481 mm, range 2.465–8.670 mm), ventrodorsal distance (d) from floor of the fourth ventricle (mean 6.403 mm, range 4.050–9.160 mm), and rostro-caudal distance (h) from a pontomesencephalic line connecting the pontomesencephalic junction to the inferior colliculi (mean −6.136 mm, range −2.185 to −12.544 mm). Chronic stimulation parameters were as follows: frequency 30 Hz (except one patient: 40 Hz), voltage range 2.5–4.9 V and pulse width 60 µs (except one patient: 90 µs).

Patients prospectively completed the Gait and Falls Questionnaire (GFQ, score/64), which assesses parkinsonian freezing, festination and falls (Giladi *et al.*, 2000). The Freezing of Gait Questionnaire (FOGQ, score/24) and Falls Question (FallsQ, score/4) are components of the GFQ (Giladi *et al.*, 2000, 2009). These questionnaires were administered prior to surgery and on the day of experiments and reflected function in patients' usual environments and medication states in the preceding weeks. Cognition was assessed with the Mini-Mental State Examination (score/30).

Experiments

In patients with Parkinson's disease, assessments were performed after overnight withdrawal of dopaminergic

Table 1 Parkinson's disease patients with balance impairment and PPN DBS

Patient	Age/ gender	Centre	PD duration, years	MMSE	UK Brain Bank criteria	LED (postop)	UPDRS III off/on meds (postop)	IT27–30 off/on meds (postop)	PPN DBS duration, years, months	GFQ pre/ postop	FOG pre/ postop	Falls Q pre/ postop	Clinical balance impairment (off/on DBS)
1	61 F	Brisbane	10	30	D,A,P	800	40/23	10/9	2, 0	61/36	24/16	4/3	5/4
2	72 M	Brisbane	18	30	D,A,T,P	2500	25/17	6/6	2, 6	30/16	14/11	4/2	3/3
3	76 M	Brisbane	6	28	A,P	600	26/14	6/4	2, 0	51/18	22/7	3/3	2/1
4	72 F	Brisbane	10	28	A,T,P	950	38/22	11/8	2, 0	48/26	22/13	4/2	5/3
5	71 M	Brisbane	4	29	D,T,P	1550	27/18	5/5	0, 6	48/21	18/9	4/3	2/2
6	77 M	Brisbane	6	30	A,P	1400	31/17	10/10	0, 6	31/14	16/6	1/2	5/5
7	56 M	Oxford	20	30	D,A,P	850	51/19	8/6	1, 0	38/40	14/15	4/4	3/2
8	78 F	Brisbane	11	27	A, T, P	1450	26/10	13/5	0, 7	46/30	20/16	4/3	^/^
9	74 M	Brisbane	9	30	A,T,P	1200	54/42	8/5	4, 6	^/37	^/15	^/3	4/3
10	75 M	Sydney	12	26	A,T,P	1200	32/24	7/6	1, 4	^/26	^/14	^/1	4/3
11	72 M	Brisbane	8	30	D,A,P	800	33/25	6/4	2, 7	^/20	^/8	^/2	3/1
12	62 M	Brisbane	14	29	D,A,T,P	800	38/28	5/5	4, 5	^/32	^/11	^/3	2/2
13	64 M	Melbourne	9	28	D,A,T,P	1000	44/26	6/4	5, 0	^/47	^/19	^/4	3/3

Postoperative (postop) clinical assessments were performed on the same day as experiments.

^ = not known; Clinical balance impairment (score/8) representing summation of UPDRS items of chair rise (item 27; score/4) and the pull test (item 30; score/4); FallsQ = Falls Question (score/4); FOGQ = Freezing of Gait Questionnaire (score/24); GFQ = Gait and Falls Questionnaire (score/64); IT27–30 = items 27–30 of UPDRS, assessing gait, posture and balance (score/16); MMSE = Mini Mental State Examination (score/30); UK Brain bank criteria: D = dyskinesias; A = asymmetry persistent; T = tremor at rest; P = progressive disease course; UPDRS III = part III (motor) of the Unified Parkinson's Disease Rating Scale (score/108).

LED = L-DOPA equivalent dose, mg/day.

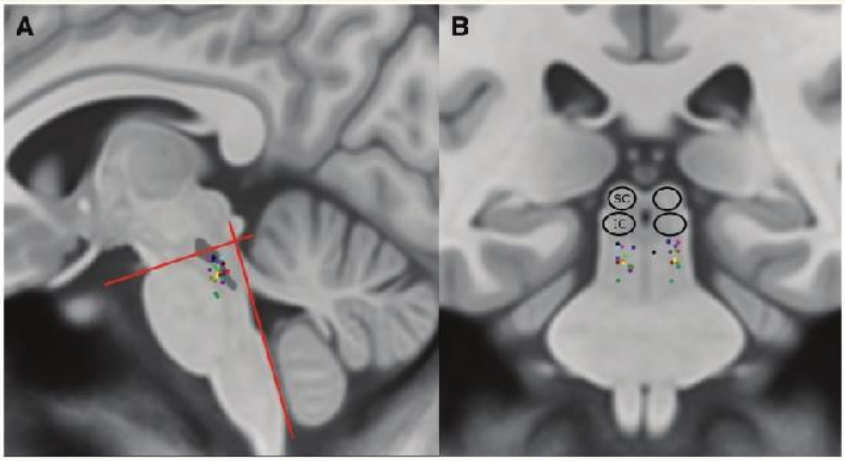

Figure 1 Localization of stimulation locations (coloured dots) represented in Montreal Neurological Institute (MNI) space (sagittal and coronal views). The relative location/extent of the pedunculopontine nucleus has been outlined on the sagittal view, based on cholineacetyltransferase immunohistochemical (ChAT5) staining in the human. Coordinates were calculated in millimetres from midline (laterality), ventrodorsal distance (d) from floor of the fourth ventricle and rostro-caudal distance (h) from a pontomesencephalic line connecting the pontomesencephalic junction to the inferior colliculi caudal margin, as described previously (Ferraye *et al.*, 2009). The mean (ranges) of these stimulation site coordinates were as follows: laterality 6.481 mm (2.5 to 8.7 mm), ventrodorsal distance (d) 6.4 mm (4.1 to 9.2 mm), rostro-caudal distance (h) 6.1 mm (−2.2 to −12.5 mm). IC = inferior colliculus; PM = ponto-mesencephalic line connecting the pontomesencephalic junction to the caudal end of the inferior colliculi; SC = superior colliculus.

medication and after 12 h of PPN DBS washout. Patients were assessed during two conditions, presented in counterbalanced order (using the Latin square method): Off PPN DBS and on bilateral PPN DBS. Patients were blinded to condition. The effectiveness of blinding was assessed in seven patients who were unable to guess the condition of stimulation better than chance after the wash-in period. Choice of contacts and stimulation parameters were as used for chronic therapy. After changing stimulation, a minimum 30 min wash-in period was enforced between conditions. Data were acquired using the same equipment and recording parameters across sites.

All posturography was performed using an AccuGait force-plate and accompanying NetForce Software (AMTI) with a measurement resolution of 0.003 N. Subjects were instructed to stand on the force-plate with eyes focussed on a wall mounted marker 1.5 m ahead. Feet were placed symmetrically across standardized markings on the force-plate. Distractions were minimized, and subjects requested not to talk. After the researcher observed that a state of quiet and stable stance had been achieved, data were acquired in 30-s trials. Four trials were obtained per condition. Patients were permitted to get off the force-plate and rest between trials if necessary to reduce fatigue. During experiments, one researcher (W.T. or J.L.T.) supervised proceedings, and monitored patient safety and altered stimulation. A second, blinded researcher operated the force-plate system and tagged the data according to the order of condition.

In a subgroup of eight patients with Parkinson's disease, a warned simple reaction time task was administered, providing an estimate of feedback delay for the PID model. As described and reported in seven of the patients previously, the task consisted of the serial presentation of 35 trials, each consisting of an auditory warning cue (92 dB, 40-ms duration, 300 Hz) followed (after a variable interval) by the auditory imperative 'go' cue (40-ms duration, 1000 Hz) (Thevathasan *et al.*, 2011*b*). The imperative stimulus was either normal intensity (89 dB) or loud (122 dB). Normal intensity trial results were used in analyses here. Patients were seated comfortably in a quiet room and instructed to react as quickly as possible with ballistic elbow flexion. Stimuli were controlled through a digital to analogue converter (1401, Cambridge electronic design). Auditory tones were delivered binaurally through headphones (Audio Technica ATH-ES7). Reaction times were assessed with a triaxial accelerometer taped to the radial styloid. Data were sampled at 256 Hz (Porti amplifier, TMSI). Accelerometry (TMSI) was band-pass filtered between 2 and 60 Hz.

Patients with Parkinson's disease were clinically assessed using the motor subsection (part III) of the Unified Parkinson's Disease Rating Scale (UPDRS, score/108), rated unblinded by the same neurologist or physiotherapist specialized in movement disorders (W.T., J.L.T.).

Anonymized data were transferred to a single centre (Bionics Institute) where researchers blinded to stimulation condition computed parameters using custom scripts in MATLAB (MathWorks Inc., Massachusetts, USA). Conditions were then revealed to permit statistical analysis.

Parameters and data analysis

Prior to analysis, all force-plate raw time series data were band-pass filtered between 0.001 and 10 Hz. For all sway values, the mean of the four trials per condition was used in statistical analysis.

The primary outcome measure was the frequency of intermittent switching in postural sway. Switching behaviour reflects abrupt changes or discontinuities in the preceding linear trajectory of the sway path when viewed at a particular time scale (Mosterman and Biswas, 1998). For example, this

may reflect switching between one subsystem of control to another. Intermittent switching of postural sway was calculated according to a published algorithm designed to detect such behaviour in posturography datasets based on a combination of wavelet analysis and Hilbert transformation (Nema *et al.*, 2017). This included (i) decomposing the filtered posturography time series data using a Daubechies wavelet transform. Like Fourier transformation, wavelet transforms extract temporal and frequency characteristics of time series. Wavelet analysis is particularly beneficial to analyse signals where frequency components vary over time. A relative strength of the Daubechies technique is to identify signal discontinuities; (ii) low-energy components were attenuated to reduce noise before reconstructing the components to obtain a filtered version of the original signal; and (iii) applying a Hilbert transform of the filtered signal to compute a time-frequency representation of the sway where discontinuities manifest as prominent peaks (Nema *et al.*, 2017). These peaks represent instances where intermittent changes (rapidly arising redirections of sway) had occurred. Peaks occurring above a threshold were counted to yield the rate of intermittent switching of postural sway (represented as Hz). The threshold was set at 10% of the standard deviation (SD) above the signal floor—a level determined after direct visualization of the dataset as best able to capture peaks in instantaneous frequency due to their large variance in amplitude (Supplementary Fig. 1). The amplitude of each peak represents the instantaneous frequency at the switching moment and has no clear physical meaning when considering complex multicomponent signals such as postural sway (Boashash, 1992). Thus, amplitude was not measured as an endpoint in its own right.

Sway data were also analysed according to a continuous PID control model in a subgroup of eight patients (where reaction time was available) in addition to the healthy controls using a custom script developed in MATLAB according to the following established method where standing is considered analogous to an inverted pendulum (Hidenori and Jiang, 2006) (Fig. 2). Assumptions included using ballistic elbow reaction time as a measure of delay in feedback control and that the body was rigid (without pivot points around limb or axial joints). Ballistic elbow flexion was considered a reasonable estimate of postural reaction times given its strong reticulospinal innervation (Lawrence and Kuypers, 1968; Carlsen *et al.*, 2009*a*). Patient height (measured in millimetres) was used to convert sway data to angular displacement according to trigonometry. The resultant parameters were gains in time domains of future, present and past scaled in arbitrary units (AU). To facilitate statistical analysis, we normalized these values in the Parkinson's disease patients relative to the data for healthy controls and expressed the difference as a percentage. The mean of each percentage (future, present and past) yielded a single value of PID model function for each patient/condition relative to healthy controls.

We computed standard measures of sway using custom scripts written in MATLAB. Two parameters were derived: (i) C90 area, which represents the area of an ellipse (measured in millimetres squared) that encompasses 90% of data points; and (ii) sway velocity, which represents the mean of the differentiated force-plate time series.

For the reaction time data, analysis was automated by a script developed in MATLAB including initial baseline removal (time constant individualized for each trial from the average baseline level 0.45 ms prior to the imperative) before rectification. The first five trials were rejected as practice. Response onset was defined as an amplitude rise exceeding the mean of the prestimulus (0.5 s) baseline by 3 SD. The mean normal intensity (89 dB) reaction time was used in statistical analysis.

For the clinical data, items of the UPDRS part III yielded two subscores (Fahn *et al.*, 1987). First, a balance subscore (score/8) representing summation of UPDRS items of chair rise (item 27; score/4) and the pull test (item 30; score/4). Second, the UPDRS item representing gait (item 29; score/4).

Statistical analysis

Given the small sample sizes, we adopted conservative non-parametric tests. Differences between subject groups were assessed with the Kruskal-Wallis test and *post hoc* Mann-Whitney U-test. Differences in patients with Parkinson's disease between conditions (on versus off PPN DBS) were assessed with the Wilcoxon signed ranks test. *Post hoc* tests were corrected for multiple comparisons using the false discovery rate (FDR) procedure (Bejamini and Hochberg, 1995). Level of significance was $P < 0.05$.

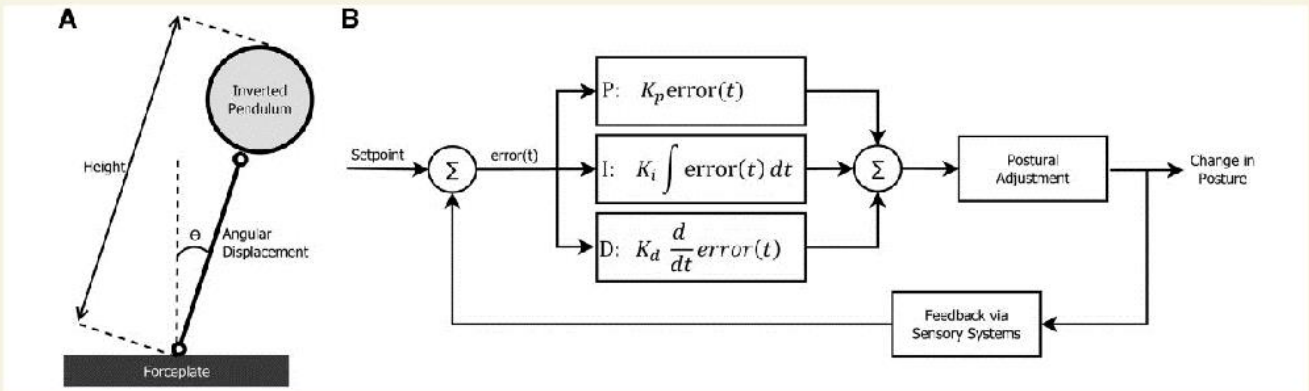

Figure 2 Schematic showing the inverted pendulum model of human balance (A) used in the PID control system (B). The setpoint input of the PID controller is fixed at zero and acquired posturography time-series data (converted to angular displacement using participant's height) gives the output allowing estimation of the factors K_p (proportional), K_i (integral) and K_d (derivative).

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Results

Control system primary outcomes

Intermittent switching of postural sway

There was a significant difference in intermittent switching of postural sway between groups [$\chi^2(38) = 10.292$, $P = 0.006$] (Figs 3A and 4). *Post hoc* tests revealed that Parkinson's disease patients off DBS had reduced intermittent switching of postural sway compared to healthy controls (1.908 Hz versus 2.517 Hz, U = 230, $P = 0.016$). PPN DBS significantly increased intermittent switching of postural sway (1.908 Hz versus 2.350 Hz, W = 8, $P = 0.016$). This meant that intermittent switching of postural sway in Parkinson's disease patients when on DBS did not differ from healthy controls (2.350 Hz versus 2.517 Hz, U = 185, $P = 0.703$).

Gains in the PID model

There was a significant difference in PID model gains between groups [$\chi^2(28) = 6.199$, $P = 0.045$]. *Post hoc* tests revealed that Parkinson's disease patients off DBS were significantly different in PID model gains compared to healthy controls (difference 27.446%, U = 107, $P = 0.010$). PPN DBS significantly improved PID model gains towards normal (difference 5.016% versus difference 27.446%, W = 35, $P = 0.016$). This meant that the PID model gains were not different between Parkinson's disease patients when on DBS and healthy controls (difference 5.016%, U = 135, $P = 0.587$). Looking at each PID time factor individually revealed that PPN DBS increased past (1.797×10^{-5} versus 3.654×10^{-5}, W = 3, $P = 0.039$), reduced present (0.957 versus 0.902, T = 35, $P = 0.016$), and reduced future (9.938 versus 7.268, W = 34, $P = 0.023$) PID gains towards values seen in healthy controls (Fig. 3D–F).

Secondary outcomes

Sway area and velocity

There was a significant difference in C90 area between groups [$\chi^2(38) = 23.494$, $P < 0.001$]. *Post hoc* tests revealed that Parkinson's disease patients off DBS had larger C90 areas compared to healthy controls (109.899 mm^2 versus 21.451 mm^2, U = 95, $P < 0.001$). PPN DBS did not change C90 area (93.094 mm^2 versus 109.899 mm^2, W = 58, $P = 0.5$). This meant that C90 area remained significantly larger in Parkinson's disease patients when on

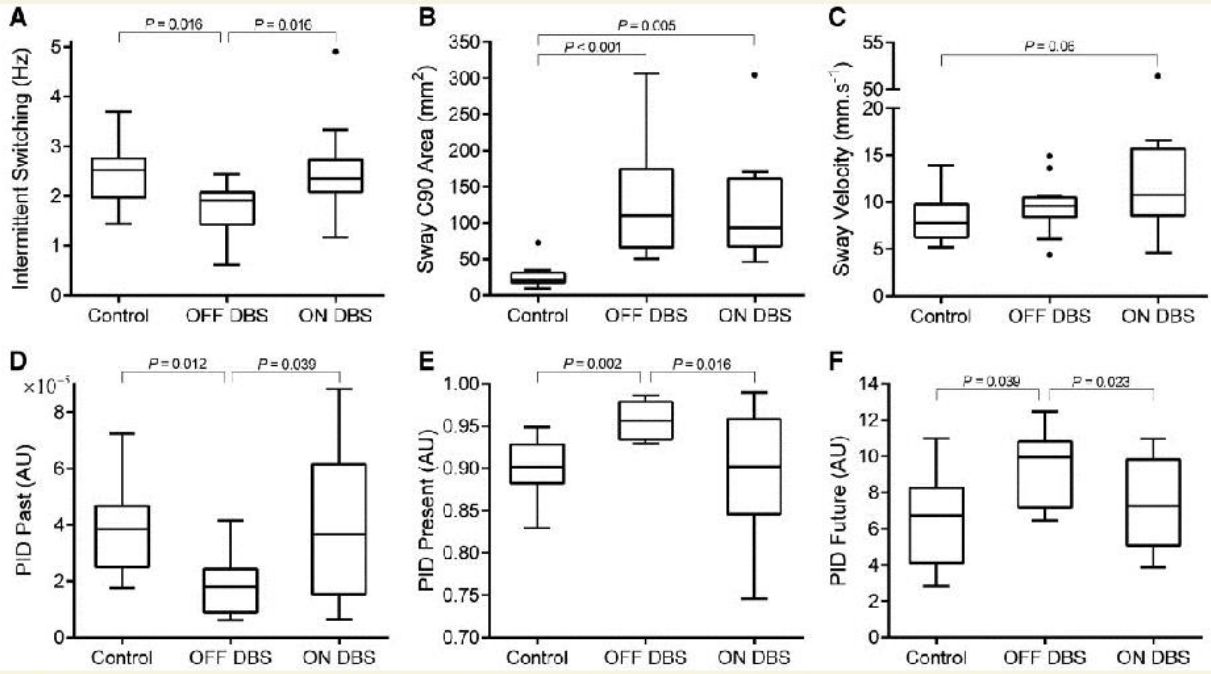

Figure 3 Postural sway parameters (medians and interquartile ranges) for healthy controls and Parkinson's disease patients (off and on PPN DBS). (**A**) Intermittent switching (abrupt, high amplitude redirections) of postural sway. (**B**) Sway C90 area (of an ellipse measured in millimetres squared that encompasses 90% of data points). (**C**) Sway velocity (mean of the differentiated time series). (**D**–**F**) PID continuous control model gains in time domains of past (**D**), present (**E**) and future (**F**) scaled in arbitrary units (AU). Differences between groups and conditions are indicated by bridges with *P*-values.

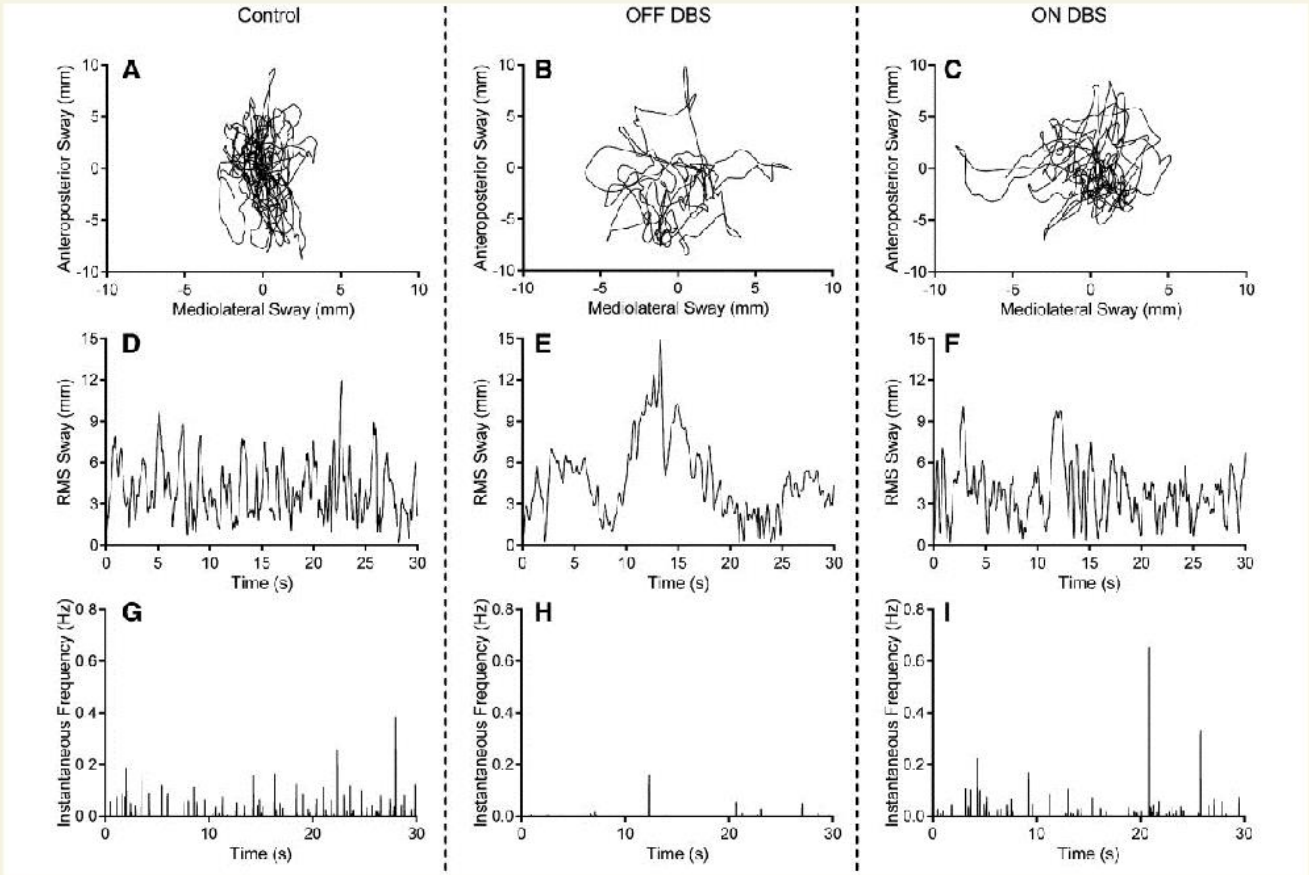

Figure 4 Example postural sway traces of a healthy control subject and Parkinson's disease Patient 5 (off and on PPN DBS) acquired during quiet stance on a force-plate (30-s trial). (**A**–**C**) Panels show movements in centre of pressure in two planes. Patients with Parkinson's disease have increased sway area but this did not change with PPN DBS. (**D**–**F**) Root mean square (RMS) of sway in millimetres. (**G**–**I**) The results of the wavelet-based transformation of the RMS sway time series with intermittent switching behaviour (abrupt redirections) clearly evident as instances of high frequency arising from the baseline.

PPN DBS compared with healthy controls (93.094 mm^2 versus 21.451 mm^2, U = 94, $P = 0.005$) (Figs 3B and 4).

There was no significant difference in sway velocity between groups [$\chi^2(38) = 4.931$, $P = 0.085$]. However, *post hoc* tests revealed a strong trend for PPN DBS to increase sway velocity (9.573 mm/s off DBS versus 10.785 mm/s on DBS, W = 16, $P = 0.060$] (Fig. 3C).

Correlations between sway parameters

Intermittent switching of postural sway correlated significantly with PID factors past (rho = 0.603, $P = 0.015$), present (rho = −0.829, $P < 0.001$) and future (rho = − 0.659, $P = 0.007$). There was a trend suggesting a positive correlation between intermittent switching and sway velocity (rho = 0.401, $P = 0.053$). There was no correlation between intermittent switching of postural sway and C90 area ($P = 0.106$).

Clinical measures

PPN DBS significantly improved the clinical balance score (expressed as mean/median) (3.417/3.000 off DBS versus 2.667/3.000 on DBS, W = 28, $P = 0.016$) but not the UPDRS gait subscore (2.417/2.000 off DBS versus 2.083/2.000 on DBS, W = 10, $P = 0.125$).

Correlations of clinical measures with sway parameters

The clinical balance score correlated significantly with intermittent switching of postural sway (rho = −0.735, $P < 0.001$) and overall PID gains (rho = 0.619, $P = 0.011$) (Fig. 5). There was no correlation between clinical balance score and C90 area ($P = 0.408$) or sway velocity ($P = 0.179$). Interestingly, the UPDRS gait score also correlated significantly with intermittent switching of postural sway (rho = −0.414, $P = 0.045$) but did not correlate with overall PID gains (rho = 0.096; $P = 0.726$) (Fig. 5).

Stimulation location

Stimulation locations varied considerably (Fig. 1), particularly in depth (h-value; mean −6.136 mm, range −2.185 to −12.544 mm) and extending beyond where immunohistochemistry is reported to have identified cholinergic neurons

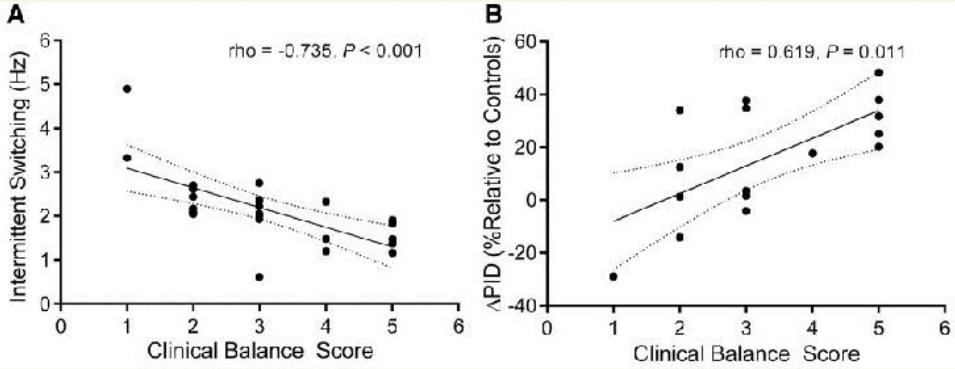

Figure 5 Correlations between clinical balance impairment and control system metrics. Correlations between clinical balance impairment (score/8), which represents summation of UPDRS items of chair rise (item 27; score/4) and the pull test (item 30; score/4) with measures of intermittent and continuous control of sway, namely: (**A**) intermittent switching (more switching behaviour correlates with lower balance impairment); and (**B**) the difference in normalized PID values relative to healthy controls (lower PID model gains relative to controls correlates with lower balance impairment).

(and, by inference, PPN location) in post-mortem samples (Mesulam *et al.*, 1989; Manaye *et al.*, 1999). However, we found no correlation between h-value (averaged per patient between the two sides) and intermittent switching of postural sway (rho = 0.451; $P = 0.125$) or clinical balance score (rho = 0.268; $P = 0.399$). Furthermore, we found no difference between patients with stimulation sites within the PPN region (defined as h-value between +2 and −6) and those with stimulation sites outside this region regarding the impact of DBS on intermittent switching of postural sway (50.847% improvement within the PPN versus 31.724% outside the PPN, U = 32, $P = 0.181$) or clinical balance score (10.000 % reduction within the PPN versus 14.286% outside the PPN, U = 30, $P = 0.747$).

Discussion

In this study, we found that patients with Parkinson's disease and severe clinical balance impairment demonstrated reduced intermittent switching of postural sway compared with healthy controls. Patients with Parkinson's disease also had abnormal feedback gains according to a PID model of continuous control. Intermittent switching of postural sway and gains in the PID model were returned to normal values by PPN DBS. However, PPN DBS improved but did not resolve clinical balance impairment (summed UPDRS items for arising from a chair and the pull test). Clinical balance impairment correlated substantially with both intermittent switching of postural sway (rho = −0.735) and gains in the overall PID model (rho = 0.619). Intermittent switching of postural sway and gains in the PID model were highly correlated. However, we found no correlation between control systems measures and sway area. In patients with Parkinson's disease, sway area was significantly greater than in healthy controls but did not change with PPN DBS. Sway velocity in patients with Parkinson's disease did not differ from healthy subjects. Neither sway area nor sway velocity correlated with clinical balance impairment. The location of stimulation in the PPN region varied greatly in rostro-caudal location between patients. Despite this variance, we found no correlation between stimulation depth and the therapeutic impact on sway control systems or on clinical balance impairment.

First, we acknowledge limitations and potential confounds in this study. It should be noted that the control models we refer to are conceptual representations of brain functioning that aim to capture performance of the actual underlying neural circuitry. This is particularly true of the PID parameters, which were derived by assessing conformance of the raw sway data to the model and assumptions that elbow flexion reaction time reflected postural feedback delays and the body acted as a rigid inverted pendulum (Peterka, 2002; Hidenori and Jiang, 2006). However, intermittent switching of postural sway was derived solely from the postural sway data with a time-frequency representation (via wavelet analysis) (Nema *et al.*, 2017). This yielded information of when switching behaviour (abrupt redirections) were detected in the continuous sway pattern. The occurrence of these sudden changes to sway are real but it is an assumption that these represent the function of an underlying intermittent control system. The sample size of patients here is modest; however, this represents a large cohort of patients implanted with PPN DBS, and required 7 years to recruit between multiple centres. Only around 100 patients with PPN DBS have been reported in the literature (Thevathasan *et al.*, 2018). Selection bias may have influenced results; however, we did not attempt to 'enrich' the cohort by selecting patients based on their response to DBS. We included almost half of the implanted cohort available across the study centres. Disease-related events that prevented assessment such as dementia, frailty and death are not unexpected given the prognosis of Parkinson's disease especially where associated with severe axial deficits (Hely *et al.*, 1999). Patients implanted

with PPN DBS are a highly selected and unusual subgroup of patients with Parkinson's disease who suffer severe gait freezing and postural instability as their predominant form of motor impairment, so these results may not be completely generalizable to the Parkinson's disease population as a whole. Assessment of the clinical impact of PPN DBS was measured by retrospective use of UPDRS items that suffer limited scaling and reliability, and more comprehensive tools to assess balance impairment are now available (Bloem *et al.*, 2016). The scoring of clinical endpoints was performed by unblinded clinicians. However, patients in this study were blinded to the condition of stimulation and postural sway analysis was performed by a computer algorithm and blinded researchers.

Balance impairment in Parkinson's disease

This study suggests that dysfunction in sway control systems contributes to the pathophysiology of balance impairment in Parkinson's disease and is potentially reversible with therapy, at least in patients similar to those studied here. It has been relatively unexplored whether such control systems are dysfunctional in Parkinson's disease and contribute to the pathophysiology of balance impairment (Maurer *et al.*, 2004; Yamamoto *et al.*, 2011; Chagdes *et al.*, 2016). Here, we explicitly measured feedback gains according to the PID model of continuous control and calculated the frequency of intermittent switching behaviour in the sway dataset (Hidenori and Jiang, 2006; Nema *et al.*, 2017). We found that in healthy controls and Parkinson's disease patients, gains in PID model factors future and present were greatest with relatively little input from factor past—as previously reported in healthy subjects (Peterka, 2002; Masani *et al.*, 2006). This reliance on present and future and not past error information (i.e. proportional-derivative rather than proportional-integral-derivative control) could prioritize the damping of oscillations over the diminution of steady state error. Such proportional-derivative control of sway has been argued to be sufficiently effective while less computationally demanding (Masani *et al.*, 2006). We found that in Parkinson's disease compared to healthy subjects, the gains in future and present factors were increased and restored to normal levels by PPN DBS. For intermittent control, we found that in healthy subjects, intermittent switching of postural sway occurred at median 2.517 Hz. This is a similar value to a study reporting that in control of a virtual load, intermittent taps of a joystick were optimally deployed at a rate of around 2 Hz (Loram *et al.*, 2011). Here, we found that in patients with Parkinson's disease and balance impairment, intermittent switching of postural sway was reduced to median 1.908 Hz and restored by PPN DBS to median 2.350 Hz.

Thus, it may seem that both continuous and intermittent systems are active in healthy subjects and dysfunctional in patients with Parkinson's disease but can be improved towards normal with therapy. An interaction between the two control systems could even be speculated, for example failure of the intermittent system in Parkinson's disease leading to compensatory overdrive of the PID system (which reverts to normal levels with therapy). Alternatively, the switching behaviour observed could represent continuous control acting intermittently. However, it could be argued that we directly found evidence only of intermittent switching behaviour in sway and the continuous control system findings simply reflect how the primary dataset aligns to the PID model and does not prove the existence of a continuous control system in neural circuitry. Furthermore, it has been demonstrated mathematically, that an intermittent control system can mimic or improve upon the performance of a continuous control system beset by the type of long and variable feedback delays encountered in the nervous system (Gawthrop *et al.*, 2011; Tanabe *et al.*, 2016).

Thus, the most robust findings from this study relate to the impairment and recovery of switching behaviour detected in sway patterns, interpreted as the impact of intermittent control (but without proving the existence of this model in neural circuitry), with substantial correlations with clinical balance impairment. A possible mechanism for reduced intermittent control in Parkinson's disease, is impaired release of ballistic, pre-programmed motor responses that use reticulospinal pathways (Valls-Solé *et al.*, 1995, 2008; Thevathasan *et al.*, 2011*b*). In patients with Parkinson's disease and severe axial motor impairment, we previously reported that the Start-React phenomenon was absent but restored by PPN DBS, in line with the benefit on gait freezing (Thevathasan *et al.*, 2011*b*). Intermittent adjustments to postural sway, like the responses elicited by Start-React, are considered to be pre-programmed (prepared in advance and ready for automatic release), ballistic (triggered off as a whole) and predominantly use reticulospinal pathways (Gawthrop *et al.*, 2014). The lack of Start-React in Parkinson's disease has since been corroborated by others, and associated with gait freezing but not yet with postural instability (Carlsen *et al.*, 2009*b*; Nonnekes *et al.*, 2014, 2015). In healthy subjects, Start-React has been observed not only in automatic adjustments to gait (e.g. obstacle avoidance and stepping) but also to posture (e.g. leg responses to platform translation) (MacKinnon *et al.*, 2007; Queralt *et al.*, 2008; Nonnekes *et al.*, 2013). Indeed, balance impairment and gait freezing in Parkinson's disease often co-exist, which raises the possibility of shared mechanisms (Giladi *et al.*, 2001*b*; Bekkers *et al.*, 2017). Impairment in the release of relatively small amplitude intermittent adjustments to sway could be considered analogous to the impaired release of larger amplitude responses to a postural challenge, as assessed with the 'pull test' (Munhoz *et al.*, 2004). Indeed, we found a close correlation between intermittent switching of postural sway and clinical balance impairment (combined score for the pull test and arising from a chair). Intermittent switching

of postural sway also correlated with the Parkinson's disease gait subscore, supporting the concept of a partly shared pathophysiology. This proposed 'unblocking' of pre-programmed movement with PPN DBS could be seen as analogous to the improvement in gait observed with external cues and with startling stimuli (Keefe *et al.*, 1989; Glickstein and Stein, 1991; Nieuwboer *et al.*, 2007).

Consistent with the variable results reported in previous studies we found that simple sway parameters of sway area and velocity did not correlate with clinical balance impairment in Parkinson's disease (Horak *et al.*, 1992; Matinolli *et al.*, 2007; Frenklach *et al.*, 2009; Ebersbach and Gunkel, 2011; Johnson *et al.*, 2013). Levodopa and subthalamic nucleus DBS have been reported across studies to have an inconsistent impact on sway area and velocity—although this could well reflect the variable impact of these therapies on balance as well as the confounding effects of dyskinesia (Maurer *et al.*, 2003; Revilla *et al.*, 2013; De la Casa-Fages *et al.*, 2017). We did find that sway area was abnormally large in Parkinson's disease, corroborating a wealth of previous research (Schoneburg *et al.*, 2013). However, PPN DBS did not change sway area despite the improvements observed in clinical balance impairment and control system performance. In this study, sway velocity did not differ between subject groups although a trend suggested that PPN DBS increases sway velocity—from being similar to controls to being increased compared to controls. In the one previous study of the impact of PPN DBS on sway (four patients), a possible albeit modest increase in path length (related to velocity) was also observed (Yousif *et al.*, 2016). That PPN DBS drives sway velocity to abnormally high values could represent worsening of an aspect of sway control or the activation of a compensatory mechanism. The increase in velocity may be related to the increase in switching behaviour as a strong trend suggested a correlation between intermittent switching and sway velocity although the nature of this relationship remains to be established.

The balance control system methods and findings in this study are novel and thus require more extensive investigation to assess their significance in a larger cohort of subjects including Parkinson's disease patients with a broader range of phenotypes. One question is whether sway control system metrics could be useful as biomarkers of balance impairment in Parkinson's disease. PID model parameters correlated with clinical balance impairment but required the additional assessment of reaction time and the assumption that the body conformed to a rigid inverted pendulum. The assessment of intermittent switching of postural sway may therefore be a simpler candidate biomarker; however, further investigation will be needed to assess validity.

Therapeutic potential of PPN DBS

Whilst we found that sway control system metrics returned to normal values with PPN DBS, there was only partial improvement on clinical balance impairment. A partial therapeutic benefit has also been the experience for PPN DBS for gait freezing (Thevathasan *et al.*, 2018). This limited clinical efficacy may reflect that the clinical application of PPN DBS has not yet been optimized or alternatively may reflect a fundamental limitation of the therapeutic mechanism. For example, if all that PPN DBS achieves is a circumscribed unblocking of pre-prepared ballistic motor programmes (such as adjustments to gait and balance), then this may be insufficient for patients in whom other varied systems, such as attentional processing, leads to clinical impairment (Snijders *et al.*, 2016). If so, then one strategy may be to identify patients in whom such blocked ballistic adjustments is the major issue and could therefore benefit most from PPN DBS. Impaired Start-React and reduced intermittent switching of postural sway could be investigated as markers of such reversibility.

There has been much debate regarding the ideal clinical application of PPN DBS, particularly the location of electrodes and stimulation (Hamani *et al.*, 2016*b*). Over time, two PPN regions have been posited; caudal and rostral (Thevathasan *et al.*, 2012*b*; Tattersall *et al.*, 2014). These two regions span a large distance relative to the brainstem, with the rostral PPN proposed as lying 2 mm above and below the pontomesencephalic junction and caudal PPN from 2 mm to 6 mm below the pontomesencephalic junction (Thevathasan *et al.*, 2012*a*). It is reported that alpha band oscillations in local field potentials in the caudal PPN correlated with gait (real and imagined) whereas beta band oscillations in the rostral PPN region did not (Thevathasan *et al.*, 2012*b*; Fraix *et al.*, 2013; Tattersall *et al.*, 2014; Lau *et al.*, 2015). Two studies have offered very preliminary evidence suggesting that caudal PPN DBS may be more effective for gait than rostral PPN DBS (Thevathasan *et al.*, 2012*a*; Fu *et al.*, 2014). In this study, all the patients were stimulated in the caudal PPN (or further below). Within this group, we found no association between stimulation depth and benefit on balance. The question of ideal PPN DBS location would be better addressed in a repeated measures assessment within patients whose electrodes span both rostral and caudal regions. Regardless, it is intriguing that the disparate locations of stimulation applied in this study were capable of yielding a clinical benefit for balance. Some variance in stimulation location is inevitable in clinical practice and reflects both surgical targeting and the contact chosen at the end of the electrode to apply stimulation. In some cases, stimulation locations in this study appear to extend beyond what would typically be considered to be the PPN region (Hamani *et al.*, 2016*a*). This could reflect that stimulation parameters typically used by PPN DBS generate a wide enough field of influence in the compact brainstem to overcome any targeting inconsistencies. Alternatively, the impact of what is termed 'PPN' DBS may actually reflect a fairly non-specific disinhibition of motor responses available in a wide dorsal brainstem region. This recalls a similarly large region where locomotion could be induced in decerebrate animals known historically as the 'mesencephalic locomotor region' (Jenkinson

et al., 2009). However, the current clinical consensus is to accurately target the PPN, ideally with electrode contacts on both rostral and caudal subregions, giving the option to stimulate either (Thevathasan et al., 2018).

Much work is yet needed to see if the clinical application of PPN DBS can be refined to a stage where it is ready to be assessed in a randomized controlled trial evaluating impact on quality of life. However, this study is encouraging that balance impairment in Parkinson's disease may be partly reversible, and may offer mechanistic insights that could assist other emerging therapies.

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Competing interests

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Supplementary material

Supplementary material is available at *Brain* online.

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Appendix 2. Participant information and consent forms

Studies 1 and 2

Participant Information Consent Form

MELBOURNE BRAIN CENTRE
at The Royal Melbourne Hospital

Title	Deep Brain stimulation for postural instability in Parkinson's disease
Protocol Number	HREC 2013.129
Coordinating Principal Investigator/ Principal Investigator	Dr Wesley Thevathasan
Location	**MASTER**

1. Introduction

You are invited to take part in this research project. This is because you are a healthy adult and do not have significant problems with balance.

This Participant Information and Consent Form tells you about the research project. It explains the procedures involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or healthcare worker.

Participation in this research is voluntary. If you don't wish to take part, you don't have to.

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:

- Understand what you have read;
- Consent to take part in the research project;
- Consent to participate in the research processes that are described;
- Consent to the use of your personal and health information as described

You will be given a copy of this Participant Information and Consent Form to keep.

2. What is the purpose of this research project?

We would like to test your balance in order to compare your results with those of patients with Parkinson's disease (with and without balance problems). This will help us to understand the cause of balance problems in Parkinson's disease. Furthermore, it will help us find out if deep brain stimulation (DBS) can be used to treat balance disturbance in Parkinson's disease.

The major aim of this study is to assess if DBS helps balance disturbance in patients with Parkinson's disease.

So far, we know that DBS can help walking problems in Parkinson's disease. Many patients have reported that their balance is also improved by this treatment. In this research, we

will assess the degree of any such benefit on balance – so we can know if this treatment should be used for that purpose.

This study is being run in Melbourne (Royal Melbourne Hospital and The Bionics Institute) and Brisbane (Australian Catholic University). Overall, we plan to recruit 40 patients with deep brain stimulators, 11 patients with Parkinson's disease but without deep brain stimulators, and 20 healthy subjects

This project is internally funded by these centres (run out of their own research budgets) and grant funding is being sought (e.g. from the National Health and Medical Research Council, Australia). This study was initiated by Dr Wesley Thevathasan, a clinical neurologist (at the Royal Melbourne Hospital) and researcher (Melbourne University and Bionics Institute). At certain times, students doing honours or doctoral degrees may also be helping carry out the research (for example, Dr Simon Sung may use this data to help obtain his PhD).

3. What does participation in this research project involve?

If you take part, you will attend one of the research sites (Royal Melbourne Hospital, St Vincent's Hospital, Melbourne or Australian Catholic University, Banyo, Queensland) for 1-2 hours. When you arrive for your appointment one of the researchers will be available to explain in person the nature of the study. If you agree to volunteer, we will ask you to sign a consent form. We will record information such as your age and gender so that we can compare your results to similar participants in the other groups (called 'matching').

In one arm of the study, we will assess your balance whilst you stand on a platform that monitors adjustments to balance and also asking you to turn on the spot whilst having some probes taped over your skin in various places. We will also assess your reaction time – how quickly you can flex your elbow in response to sounds delivered through headphones.

In another arm of the study, we will test your balance using the 'pull test'. It involves you standing straight with your feet together then a researcher standing behind you tugs on your shoulders and sees how well you correct your balance. The pull test will be conducted whilst you stand on the pressure sensitive platform (as above) and also by using probes that we tape over your skin in various places

Assessments will be video recorded and any identifiable features (e.g. face, tattoos) will be blurred out to protect your privacy.

We will reimburse travel costs incurred by you in coming to and from the study appointment, for example taxi expenses or fuel and parking if you drive yourself and parking.

4. What are the possible benefits?

This study is for research and will not be of benefit to you personally. However, the information acquired during this study will help us better understand the causes of balance problems in Parkinson's disease and whether DBS can be used to treat balance disturbance.

5. What are the possible risks?

There is a risk of falling during the balance tasks. However, the techniques used in this study are the same as those that have been safely used in routine clinical practice (eg the 'pull test'). During the testing, you will always have a researcher standing by you.

There may be additional risks that the researchers do not expect or do not know about. Tell a member of the research team immediately about any new or unusual symptoms that you get.

6. What if new information arises during this research project?

During the research project, new information about the risks and benefits of the project may become known to the researchers. If this occurs, you will be told about this new information and the researcher will discuss whether this new information affects you.

7. Can I have other treatments during this research project?

There is no need to alter any treatment you may already be receiving for any condition.

8. Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part you don't have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment **OR** your relationship with the Royal Melbourne Hospital or collaborating centres.

9. What if I withdraw from this research project?

If you decide to withdraw from the study before it is finished, the researchers will keep and continue to use your information that has already been collected. This is to ensure that the results of the study can be measured properly. However, no further information will be collected. If you do not want this to happen, you should choose not to enter into the study.

10. How will I be informed of the results of this research project?

We hope to publish the results of this study in a scientific journal. We may also present the results at a scientific conference or a seminar in a university and publish results on our website. We would be happy to discuss the results of the study with you and to send you a copy of the published results.

11. What else do I need to know?

- **What will happen to information about me?**

Any information obtained in connection with this research project that can identify you will remain confidential and will only be used for the purposes stated in this document. It will only be disclosed with your permission, except as required by law. We plan to publish the results of this study. In any publication and/or presentation, information will be provided in such a way that you cannot be identified, except with your permission.

Personally identifiable information about you will be kept separately from the research data, in a locked filing cabinet in a swipe card secured building (at the Melbourne Brain Centre, Royal Melbourne Hospital). Researchers who analyse your data at non-Melbourne sites will not be given any personally identifiable information about you (eg will not know your name). All data from this study will be destroyed after 5 years (enough time to fully analyse and publish the results). The only way the study data will identify you is by a study participant ID number. No documents containing your personal information will be permitted to leave the hospital, and any document containing any personal information

will first be de-identified (your personal details will be removed, and only your ID number will be used).

Information about you may be obtained from your medical record held at this, and other, health services such as from your local doctor or other hospitals, for the purposes of this research.

- **Your medical record and any information obtained during the study are subject to inspection, for the purpose of verifying study procedures and the data, by the Therapeutic Goods Administration of Australia, this organisation [organisation's name, eg Melbourne Health], the Melbourne Health Human Research Ethics Committee or as required by law. How can I access my information?**

In accordance with relevant Australian and/or Victorian privacy and other relevant laws, you have the right to access the information collected and stored by the researchers about you. You also have the right to request that any information, with which you disagree, be corrected. Please contact one of the researchers named at the end of this document if you would like to access your information.

- **What happens if I am injured as a result of participating in this research project?**

If you suffer an injury as a result of participating in this research project, hospital care and treatment will be provided by the public health service at no extra cost to you if you elect to be treated as a public patient.

- **Is this research project approved?**

The ethical aspects of this research project have been approved by the Human Research Ethics Committee of Melbourne Health.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research* (2007) produced by the National Health and Medical Research Council of Australia. This statement has been developed to protect the interests of people who agree to participate in human research studies.

- **Complaints and compensation**

If you suffer any injuries or complications as a result of this research project, you should contact the study team as soon as possible and you will be assisted with arranging appropriate medical treatment. You can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

12. Further information or appointments:

If you want any further information concerning this project you can contact the principal researcher (Dr Wesley Thevathasan) on the following phone number: 03 9342 4412

13. For complaints:

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Name: Angela Gray

Position: *Manager Melbourne Health Human Research Ethics Committee*

Telephone: 03 9342 3006

Consent Form

Title	Deep Brain stimulation for postural instability in Parkinson's disease
Protocol Number	HREC 2013.129
Coordinating Principal Investigator/ Principal Investigator	Dr Wesley Thevathasan
Location	MASTER

Declaration by Participant

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the project without affecting my future health care.

I understand that I will be given a signed copy of this document to keep.

Name of Participant (please print) _____

Signature _____ Date _____

Name of Witness* (please print) _____

Signature _____ Date _____

* Witness is required when the participant cannot read the document for him/her self.

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, the research project.

Note: All parties signing the consent section must date their own signature.

Studies 2 and 3

Participant Information Consent Form

MELBOURNE BRAIN CENTRE
at The Royal Melbourne Hospital

Title	Deep Brain stimulation for postural instability in Parkinson's disease
Protocol Number	HREC 2013.129
Coordinating Principal Investigator/ Principal Investigator	Dr Wesley Thevathasan
Location	**MASTER**

1. Introduction

You are invited to take part in this research project. This is because you have Parkinson's disease and do not have significant problems with balance.

This Participant Information and Consent Form tells you about the research project. It explains the procedures involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or healthcare worker.

Participation in this research is voluntary. If you don't wish to take part, you don't have to. You will receive the best possible care whether you take part or not.

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:

- Understand what you have read;
- Consent to take part in the research project;
- Consent to participate in the research processes that are described;
- Consent to the use of your personal and health information as described

You will be given a copy of this Participant Information and Consent Form to keep.

2. What is the purpose of this research project?

The major aim of this study is to assess if Deep Brain Stimulation (DBS) helps balance disturbance in patients with Parkinson's disease. We would like to test your balance in order to compare your results with healthy participants and patients with Parkinson's disease who do have balance problems. This will help us to understand the cause of balance problems in Parkinson's disease. Furthermore, it will help us find out if DBS can be used to treat balance disturbance in Parkinson's disease.

So far, we know that DBS can help walking problems in Parkinson's disease. Many patients have reported that their balance is also improved by this treatment. In this research, we will assess the degree of any such benefit on balance – so we can know if this treatment should be used for that purpose.

This study is being run in Melbourne (Royal Melbourne Hospital and The Bionics Institute) and Brisbane (Australian Catholic University). Overall, we plan to recruit 40 patients with deep brain stimulators 11 patients with Parkinson's Disease without deep brain stimulators, and 20 healthy participants. This project is internally funded by these centres (run out of their own research budgets) and grant funding is being sought (e.g. from the National Health and Medical Research Council, Australia). This study was initiated by Dr Wesley Thevathasan, a clinical neurologist (at the Royal Melbourne Hospital)and researcher (Melbourne University and Bionics Institute). At certain times, students doing honours or doctoral degrees may also be helping carry out the research (for example, Dr Simon Sung may use this data to help obtain his PhD)

3. What does participation in this research project involve?

If you take part, you will attend one of the research sites (Royal Melbourne Hospital, St Vincent's Hospital, Melbourne or Australian Catholic University, Banyo, Queensland) for around 2 hours. We ask that you not take your Parkinson's disease medication on the morning of the study (this will be explained by a researcher to you before you arrive). When you arrive for your appointment one of the researchers will be available to explain in person the nature of the study. If you agree to volunteer, we will ask you to sign a consent form. We will record information such as your age and gender and details about your Parkinson's disease such as the duration of the disease - so that we can compare your results to similar participants in the other groups (called 'matching'). We will also assess your Parkinson's disease using rating scales and questionnaires.

We will assess you balance whilst you stand on a pressure-sensitive platform that monitors adjustments to balance, and when turning on the spot. We will also assess your reaction time – how quickly you can flex your elbow in response to sounds delivered through headphones. We will give you your usual Parkinson's disease medication, and assess your balance again using the same exercises.

As you will be assessed 'off medication' you should not drive yourself to the research appointment. We will reimburse travel costs incurred by you in coming to and from the study appointment, for example taxi expenses or fuel if driven in by a companion and parking.

Assessments will be video recorded and any identifiable features (e.g. face, tattoos) will be blurred out to protect your privacy.

We will also present you with a visual (flashing a laser dot on the floor), auditory (playing a sound through headphones) or tactile (using vibration motors similar to those found in mobile phones) cue while you perform the turning exercises to see if it improves your freezing.

4. What are the possible benefits?

This study is for research and will not be of benefit to you personally. However, the information acquired during this study will help us better understand the causes of balance problems in Parkinson's disease and whether DBS can be used to treat balance disturbance.

5. What are the possible risks?

There is a risk of falling during the balance task, especially as you will be off medication. However, the techniques used in this study are the same as those that have been safely used in routine clinical practice. During the testing, you will always have a researcher standing by you.

There may be additional risks that the researchers do not expect or do not know about. Tell a member of the research team immediately about any new or unusual symptoms that you get.

6. What if new information arises during this research project?

During the research project, new information about the risks and benefits of the project may become known to the researchers. If this occurs, you will be told about this new information and the researcher will discuss whether this new information affects you.

7. Can I have other treatments during this research project?

Apart from withholding your Parkinson's disease medication on the morning of the study, you can otherwise continue all other treatment as needed.

8. Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part you don't have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment **OR** your relationship with those treating you **OR** your relationship with the Royal Melbourne Hospital or collaborating institutions.

9. What if I withdraw from this research project?

If you decide to withdraw from the study before it is finished, the researchers will keep and continue to use your information that has already been collected. This is to ensure that the results of the study can be measured properly. However, no further information will be collected. If you do not want this to happen, you should choose not to enter into the study.

10. How will I be informed of the results of this research project?

We hope to publish the results of this study in a scientific journal. We may also present the results at a scientific conference or a seminar in a university and publish results on our website. We would be happy to discuss the results of the study with you and to send you a copy of the published results.

11. What else do I need to know?

- **What will happen to information about me?**

Any information obtained in connection with this research project that can identify you will remain confidential and will only be used for the purposes stated in this document. It will only be disclosed with your permission, except as required by law. We plan to publish the results of this study. In any publication and/or presentation, information will be provided in such a way that you cannot be identified, except with your permission.

Personally identifiable information about you will be kept separately from the research data, in a locked filing cabinet in a swipe card secured building (at the Melbourne Brain Centre, Royal Melbourne Hospital). Researchers who analyse your data at non-Melbourne sites will not be given any personally identifiable information about you (eg will not know your name). All data from this study will be destroyed after 5 years (enough time to fully analyse and publish the results). The only way the study data will identify you is by a study participant ID number. No documents containing your personal information will be permitted to leave the hospital, and any document containing any personal information will first be de-identified (your personal details will be removed, and only your ID number will be used).

Information about you may be obtained from your medical record held at this, and other, health services such as from your local doctor or other hospitals, for the purposes of this research.

- **Your medical record and any information obtained during the study are subject to inspection, for the purpose of verifying study procedures and the data, by the Therapeutic Goods Administration of Australia this organisation [organisation's name, eg Melbourne Health], the Melbourne Health Human Research Ethics Committee or as required by law. How can I access my information?**

In accordance with relevant Australian and/or Victorian privacy and other relevant laws, you have the right to access the information collected and stored by the researchers about you. You also have the right to request that any information, with which you disagree, be corrected. Please contact one of the researchers named at the end of this document if you would like to access your information.

- **What happens if I am injured as a result of participating in this research project?**

If you suffer an injury as a result of participating in this research project, hospital care and treatment will be provided by the public health service at no extra cost to you if you elect to be treated as a public patient.

- **Is this research project approved?**

The ethical aspects of this research project have been approved by the Human Research Ethics Committee of Melbourne Health.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research* (2007) produced by the National Health and Medical Research Council of Australia. This statement has been developed to protect the interests of people who agree to participate in human research studies.

- **Complaints and compensation**

If you suffer any injuries or complications as a result of this research project, you should contact the study team as soon as possible and you will be assisted with arranging appropriate medical treatment. If you are eligible for Medicare, you can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

12. Further information or appointments:

If you want any further information concerning this project or if you have any medical problems which may be related to your involvement in the project (for example, any side effects), you can contact the principal researcher (Dr Wesley Thevathasan) on the following phone number: 03 9342 4412

13. For complaints:

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Name: Angela Gray

Position: *Manager Melbourne Health Human Research Ethics Committee* Telephone: 03 9342 8530

Consent Form

Title	Deep Brain stimulation for postural instability in Parkinson's disease
Protocol Number	HREC 2013.129
Coordinating Principal Investigator/ Principal Investigator	Dr Wesley Thevathasan
Location	MASTER

Declaration by Participant

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the project without affecting my future health care.

I understand that I will be given a signed copy of this document to keep.

Name of Participant (please print) _____

Signature _____ Date _____

Name of Witness* (please print) _____

Signature _____ Date _____

* Witness is required when the participant cannot read the document for him/her self.

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, the research project.

Note: All parties signing the consent section must date their own signature.

Study 4

Participant Information Consent Form

MELBOURNE BRAIN CENTRE
at The Royal Melbourne Hospital

Title	Deep Brain stimulation for postural instability in Parkinson's disease
Protocol Number	HREC 2013.129
Coordinating Principal Investigator/ Principal Investigator	Dr Wesley Thevathasan
Location	**Royal Melbourne Hospital**

1. Introduction

You are invited to take part in this research project. This is because you have Parkinson's disease and have undergone, deep brain stimulation surgery
This Participant Information and Consent Form tells you about the research project. It explains the procedures involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or local doctor.

Participation in this research is voluntary. If you don't wish to take part, you don't have to. You will receive the best possible care whether or not you take part.

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:

- Understand what you have read;
- Consent to take part in the research project;
- Consent to participate in the research processes that are described;
- Consent to the use of your personal and health information as described

You will be given a copy of this Participant Information and Consent Form to keep.

2. What is the purpose of this research project?

The major aim of this study is to assess if Deep Brain Stimulation (DBS) helps balance disturbance in patients with Parkinson's disease.

So far, we know that DBS can help walking problems in Parkinson's disease. Many patients have reported that their balance is also improved by this treatment. In this research, we will assess the degree of any such benefit on balance – so we can know if this treatment should be used for that purpose.

This study is being run in Melbourne (Royal Melbourne Hospital and The Bionics Institute) and Brisbane (Australian Catholic University). Overall, we plan to recruit 40 patients with deep brain stimulators, 11 patients with Parkinson's Disease without deep brain stimulators and 20 healthy participants. This project is internally funded by these centres (run out of their own research budgets) and grant funding is being sought (e.g. from the National Health and Medical Research Council, Australia). This study was

initiated by Dr Wesley Thevathasan, a clinical neurologist (at the Royal Melbourne Hospital)and researcher (Melbourne University and Bionics Institute). At certain times, students doing honours or doctoral degrees may also be helping carry out the research (for example, Dr Simon Sung may use this data to help obtain his PhD).

3. What does participation in this research project involve?

If you take part, you will attend one of the research sites (Royal Melbourne Hospital, Bionics institute at St Vincent's Hospital, Melbourne or Australian Catholic University, Banyo, Queensland) for a half day (and for some patients who agree, over 2 half days).

We ask that you not take your Parkinson's disease medication on the morning of the study (this will be explained by a researcher to you before you arrive). When you arrive for your appointment one of the researchers will be available to explain in person the nature of the study. If you agree to volunteer, we will ask you to sign the consent form. We will record information such as your age and gender and details about your Parkinson's disease such as the duration of your disease - so that we can compare your results to similar participants in the other groups (called 'matching'). We will also assess your Parkinson's disease using rating scales and questionnaires.

During the study, tests will be performed with your stimulation off and on or with only one side turned on. However, we will not tell you which stimulation you receive at any particular time during testing. This is called 'blinding' and ensures that we exclude a 'placebo' effect (where a patient's knowledge about their treatment subconsciously influences their performance on testing).

There are 2 arms to the study. Some patients will be asked to consider taking part in both arms. Each arm of the study will take around half a day. In one arm of the study, we will assess your balance whilst you stand on a platform that monitors adjustments to balance (with stimulation off, on or with only one side turned on) and also by asking you to turn on the spot whilst having some probes taped over your skin in various places.

We will also assess your reaction time – how quickly you can flex your elbow in response to sounds delivered through headphones.

In the other arm of the study, we will test your balance using the 'pull test' and ability to turn on the spot (with stimulation off and on). You may recall having this pull test already with your neurologist. It involves you standing straight with your feet together then the neurologist standing behind you tugs on your shoulders and sees how well you correct your balance. In this study, the pull test will be conducted whilst you stand on a special platform that tracks foot pressure and also by using probes that we tape over your skin in various places.

At the conclusion of the study, we will switch you back to your normal stimulation settings and you can take your usual Parkinson's disease medication.

As you will be assessed 'off medication' you should not drive yourself to the research appointment. We will reimburse travel costs incurred by you in coming to and from the study appointment, for example taxi expenses or fuel if driven in by a companion and parking.

Assessments will be video recorded and any identifiable features (e.g. face, tattoos) will be blurred out to protect your privacy.

4. What are the possible benefits?

The results of the testing may reveal how well stimulation is helping your balance. This may be useful information for your treating doctor. However, the study is primarily for research and may not necessarily provide information that would benefit you personally.

5. What are the possible risks?

There is a risk of falling during the balance task, especially as you will be off medication and, some of the time, off=deep brain stimulation as well. However, the techniques used in this study are the same as those that have been safely used in routine clinical practice (eg the 'pull test'). During the testing, you will always have a researcher standing by you.

There may be additional risks that the researchers do not expect or do not know about. Tell a member of the research team immediately about any new or unusual symptoms that you get.

6. What if new information arises during this research project?

During the research project, new information about the risks and benefits of the project may become known to the researchers. If this occurs, you will be told about this new information and the researcher will discuss whether this new information affects you.

7. Can I have other treatments during this research project?

Apart from withholding your Parkinson's disease medication on the morning of the study, you can otherwise continue all other treatment as needed.

8. Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part you don't have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment **OR** your relationship with those treating you **OR** your relationship with the Royal Melbourne Hospital.

9. What if I withdraw from this research project?

If you decide to withdraw from the study before it is finished, the researchers will keep and continue to use your information that has already been collected. This is to ensure that the results of the study can be measured properly. However, no further information will be collected. If you do not want this to happen, you should choose not to enter into the study.

10 How will I be informed of the results of this research project?

We hope to publish the results of this study in a scientific journal. We may also present the results at a scientific conference or a seminar in a university and publish results on our website. We would be happy to discuss the results of the study with you and to send you a copy of the published results.

11. What else do I need to know?

- **What will happen to information about me?**

Any information obtained in connection with this research project that can identify you will remain confidential and will only be used for the purposes stated in this document. It will only be disclosed with your permission, except as required by law. We plan to publish the results of this study. In any publication and/or presentation, information will be provided in such a way that you cannot be identified, except with your permission.

Personally identifiable information about you will be kept separately from the research data, in a locked filing cabinet in a swipe card secured building (at the Melbourne Brain Centre, Royal Melbourne Hospital). Researchers who analyse your data at non-Melbourne sites will not be given any personally identifiable information about you (eg will not know your name). All data from this study will be destroyed after 5 years (enough time to fully analyse and publish the results). The only way the study data will identify you is by a study participant ID number. No documents containing your personal information will be permitted to leave the hospital, and any document containing any personal information will first be de-identified (your personal details will be removed, and only your ID number will be used).Information about you may be obtained from your medical record held at this, and other, health services such as from your local doctor or other hospitals, for the purposes of this research.
Your medical record and any information obtained during the study are subject to inspection, for the purpose of verifying study procedures and the data, by the Therapeutic Goods Administration of Australia, this organisation [organisation's name, eg Melbourne Health], the Melbourne Health Human Research Ethics Committee or as required by law.

- **How can I access my information?**

In accordance with relevant Australian and/or Victorian privacy and other relevant laws, you have the right to access the information collected and stored by the researchers about you. You also have the right to request that any information, with which you disagree, be corrected. Please contact one of the researchers named at the end of this document if you would like to access your information.

- **What happens if I am injured as a result of participating in this research project?**

If you suffer an injury as a result of participating in this research project, hospital care and treatment will be provided by the public health service at no extra cost to you if you elect to be treated as a public patient.

- **Is this research project approved?**

The ethical aspects of this research project have been approved by the Human Research Ethics Committee of Melbourne Health.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research* (2007) produced by the National Health and Medical Research Council of Australia. This statement has been developed to protect the interests of people who agree to participate in human research studies.

- **Complaints and compensation**

If you suffer any injuries or complications as a result of this research project, you should contact the study team as soon as possible and you will be assisted with arranging appropriate medical treatment. You can receive any medical treatment required to treat

the injury or complication, free of charge, as a public patient in any Australian public hospital.

12 Further information or appointments:

If you want any further information concerning this project you can contact the principal researcher (Dr Wesley Thevathasan) on the following phone number: 03 9342 4412

13. For complaints:

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Name: Angela Gray

Position: *Manager Melbourne Health Human Research Ethics Committee*

Telephone: 03 9342 8530

Consent Form

Title	Deep Brain stimulation for postural instability in Parkinson's disease
Protocol Number	2013.129
Coordinating Principal Investigator/ Principal Investigator	Dr Wesley Thevathasan
Location	MASTER

Declaration by Participant

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the project without affecting my future health care.

I understand that I will be given a signed copy of this document to keep.

Name of Participant (please print) _____

Signature _____ Date _____

Name of Witness* (please print) _____

Signature _____ Date _____

* Witness is required when the participant cannot read the document for him/her self.

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, the research project.

Note: All parties signing the consent section must date their own signature.

Appendix 3. Ethics approval letters

PO Royal Melbourne Hospital
Parkville Victoria 3050
Telephone 61 3 9342 8530
Facsimile 61 3 9342 8548
Email: research@mh.org.au
Website: http://research.mh.org.au
ABN 73 802 706 972

OFFICE FOR RESEARCH

MELBOURNE HEALTH

MELBOURNE HEALTH HUMAN RESEARCH ETHICS COMMITTEE

ETHICAL APPROVAL OF A RESEARCH PROJECT

Dr Wesley Thevathasan
University of Melbourne
Melbourne Brain Centre
Department of Medicine
PARKVILLE VIC 3010

30th September 2013

Dear Dr Thevathasan,

AU RED HREC Reference Number: HREC/13/MH/154

MH Project Number: 2013.129

Project Title: Pedunculopontine nucleus stimulation for postural instability in Parkinson's disease - HREC/13/MH/154

I am pleased to advise that the above project has received ethical approval from the Melbourne Health HREC. The Melbourne Health HREC is accredited by the Consultative Council for Human Research Ethics under the single ethical review system.

HREC Approval Date: 25th September 2013

Participating Sites:

- Royal Melbourne Hospital
- The Bionics Institute
- Australian Catholic University - Queensland

Approved Documents:

- Research Protocol Version 1 dated April 2013
- Master Participant Information and Consent Form – PD Group Version 2 dated September 2013
- Royal Melbourne Hospital Participant Information and Consent Form – PD Group Version 2 dated September 2013
- Master Participant Information and Consent Form – PPN Group Version 2 dated September 2013
- Royal Melbourne Hospital Participant Information and Consent Form – PPN Group Version 2 dated September 2013
- Master Participant Information and Consent Form – Healthy Controls Version 2 dated September 2013

- Royal Melbourne Hospital Participant Information and Consent Form - Healthy Controls Version 2 dated September 2013
- Gait and Falls Questionnaire (GFQ)
- Flyer Version 1 dated 26th January 2013

Site Specific Assessment:

Site
You are now required to submit this HREC Approval letter with an electronic copy of the approved documents named above as part of the Site Specific Assessment application to the Research Governance Officer at each site of the above listed participating sites, to obtain approval to commence the project at each site.

Conditions of Ethics Approval:

In order to comply with the National Statement on Ethical Conduct in Human Research 2007, Guidelines for Good Clinical Research Practice and Melbourne Health Research Policies and Guidelines you are required to:

- Submit a copy of this letter (via the principal investigator at each site) to the person responsible for radiation safety at each participating site – ***do this if*** the project involves exposure to ionising radiation and the Radiation Safety Officer (RSO) / Medical Physicist for that site has advised that the project needs to be added to the site's Licence for Research Involving Human Volunteers issued by the Department of Health Radiation Safety Section. (See information re radiation requirements at www.health.vic.gov.au/cchre). *Note:* A project cannot commence at a site until the Principal Investigator at that site has received notification from his/her RSO that the project has been added to that site's licence;
- Notify the HREC of the actual start date of the project at each Victorian site;
- Submit to the HREC for approval any proposed amendments to the project including any proposed changes to the Protocol, Participant Information and Consent Form/s and the Investigator Brochure;
- Notify the reviewing HREC of any adverse events that have a material impact on the conduct of the research in accordance with the NHMRC Position Statement: Monitoring and reporting of safety for clinical trials involving therapeutic products May 2009;
- Notify the HREC of any unforeseen events;
- Notify the HREC of your inability to continue as Principal Investigator or any other change in research personnel involved in the project;
- Notify the HREC if a decision is taken to end the study at any of the Victorian sites prior to the expected date of completion or failure to commence the study within 12 months of the HREC approval date at any of the Victorian sites;
- Notify the HREC of any other matters which may impact the conduct of the project.

Reporting

You are required to submit to the HREC:

- An Annual Progress Report every 12 months (or more frequently as requested by the reviewing HREC) for the duration of the project. This report is due on the anniversary of HREC approval. Continuation of ethics approval is contingent on submission of an annual report in a timely manner; and
- A comprehensive Final Report upon completion of the project.

The HREC may conduct an audit of the project at any time.

Please Note: Templates for reporting Amendments, Adverse Events, Annual Report/Final Reports, etc. can be accessed from: www.health.vic.gov.au/cchre

Please refer to the Melbourne Health Office for Research website to access guidelines and other information and news concerning research at Melbourne Health:
http://www.mh.org.au/www/342/1001127/displayarticle/1001352.html

A list of those HREC members present at the review of this project can be obtained from the above website.

Yours sincerely,

Ms Angela Gray
Manager, Human Research Ethics Committee
Ph: 9342 8530
E-mail: angela.gray@mh.org.au

The Royal Melbourne Hospital
Parkville Victoria 3050
Telephone 61 3 9342 8530
Facsimile 61 3 9342 8548
Email: research@mh.org.au
Website: http://research.mh.org.au
ABN 73 802 706 972

MELBOURNE HEALTH

OFFICE FOR RESEARCH

APPROVAL OF AMENDMENT

24 February 2016

Dear Dr Wesley Thevathasan

HREC Reference Number: HREC/13/MH/154
SSA Reference Number: SSA/13/MH/170
Local Project Number: 2013.129

Research Title: Deep brain stimulation for postural instability in Parkinson's disease - HREC/13/MH/154

Type of review: Ethics Review Only

I am pleased to advise that the amendment to the above project reviewed and approved by the Melbourne Health HREC. This approval applies to all sites for which the Melbourne Health HREC has issued ethical approval.

Amendment Approval Date: 24 February 2016

Approved Documents:

- Protocol, Version 4, dated February 2016
- Addition of Personnel to a Research Study Form for Mr David Begg and Mr Bastian Oetomo, dated 17 February 2016
- Master PICF PD Controls Group, Version 5, dated February 2016

Noted Documents:

- CV for David Begg
- CV for Bastian Oetomo

Please refer to the Melbourne Health Office for Research website to access guidelines and other information and news concerning research at:
http://www.mh.org.au/www/342/1001127/displayarticle/1001352.html

Please Note: Template forms for reporting Amendments, Adverse Events, Annual Report/Final Reports, etc. can be accessed from:: www.health.vic.gov.au/cchre.

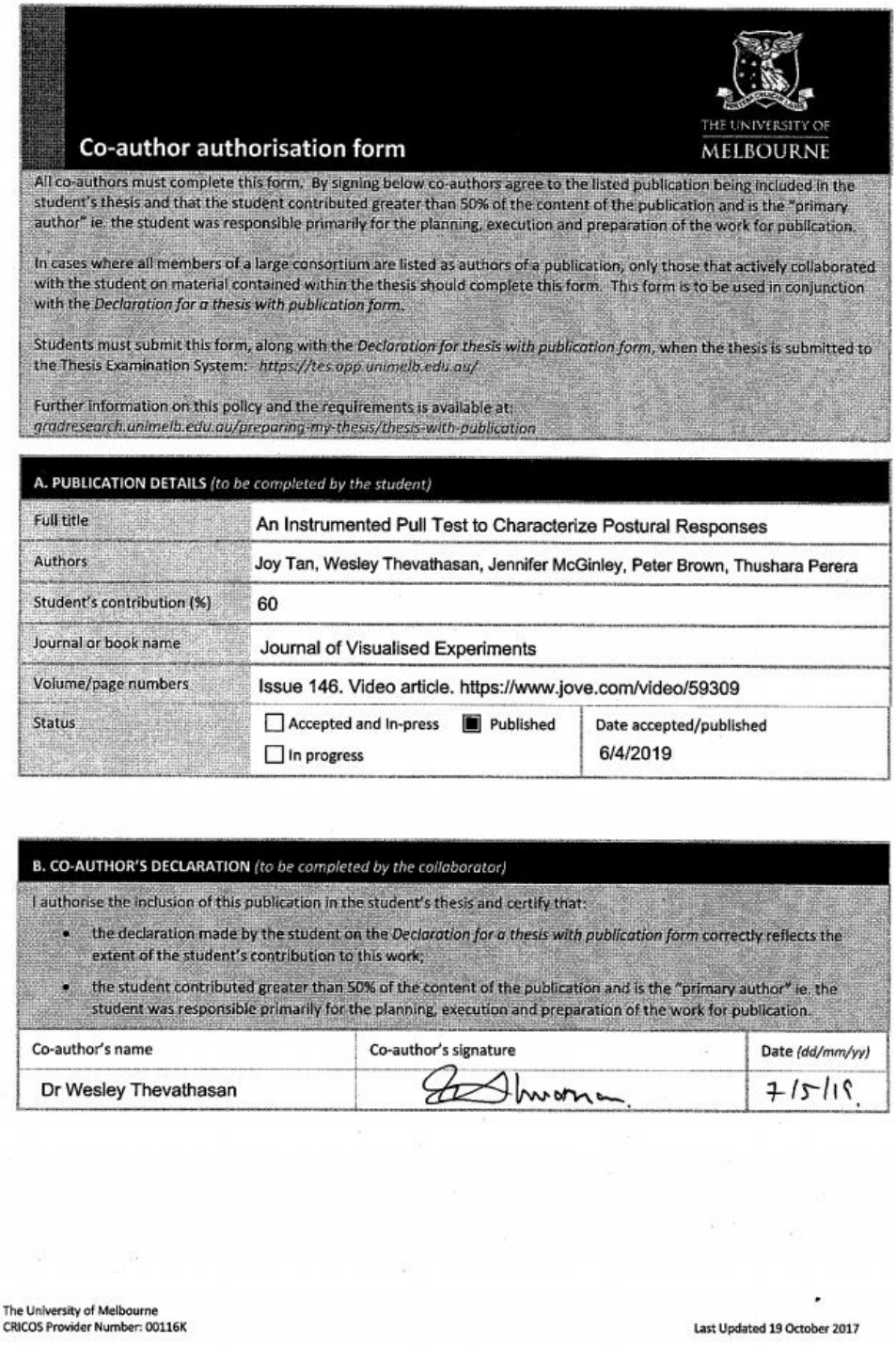
For any queries about this matter, please contact Ms Jessica Turner on 9342 8530 or via email on: Jessica.Turner@mh.org.au

Yours sincerely,

Ms Jessica Turner
Manager - Human Research Ethics Committee
Ph: 9342 8530

Appendix 4. Co-author authorisation forms

Chapter 3



Co-author authorisation form

THE UNIVERSITY OF MELBOURNE

All co-authors must complete this form. By signing below co-authors agree to the listed publication being included in the student's thesis and that the student contributed greater than 50% of the content of the publication and is the "primary author" ie. the student was responsible primarily for the planning, execution and preparation of the work for publication.

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Full title	An Instrumented Pull Test to Characterize Postural Responses	
Authors	Joy Tan, Wesley Thevathasan, Jennifer McGinley, Peter Brown, Thushara Perera	
Student's contribution (%)	60	
Journal or book name	Journal of Visualised Experiments	
Volume/page numbers	Issue 146. Video article. https://www.jove.com/video/59309	
Status	☐ Accepted and In-press ■ Published ☐ In progress	Date accepted/published 6/4/2019

B. CO-AUTHOR'S DECLARATION *(to be completed by the collaborator)*

I authorise the inclusion of this publication in the student's thesis and certify that:

- the declaration made by the student on the *Declaration for a thesis with publication form* correctly reflects the extent of the student's contribution to this work;
- the student contributed greater than 50% of the content of the publication and is the "primary author" ie. the student was responsible primarily for the planning, execution and preparation of the work for publication.

Co-author's name	Co-author's signature	Date *(dd/mm/yy)*
Dr Wesley Thevathasan		7/5/19

The University of Melbourne
CRICOS Provider Number: 00116K

Last Updated 19 October 2017

Co-author authorisation form

THE UNIVERSITY OF MELBOURNE

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Co-author's name	Co-author's signature	Date *(dd/mm/yy)*
A/Prof Jennifer McGinley		11/09/2019

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Co-author's name	Co-author's signature	Date *(dd/mm/yy)*
Prof Peter Brown		7/5/19

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Co-author's name	Co-author's signature	Date *(dd/mm/yy)*
Dr Thushara Perera	Tperera	07/05/19

Chapter 4

Co-author authorisation form

THE UNIVERSITY OF MELBOURNE

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Full title	Neurophysiological analysis of the clinical pull test	
Authors	Joy Lynn Tan, Thushara Perera, Jennifer McGinley, Shivanthan Arthur Curtis Yohanandan, Peter Brown, Wesley Thevathasan	
Student's contribution (%)	80	
Journal or book name	Journal of Neurophysiology	
Volume/page numbers	Vol 120, pg 2325 - 2333	
Status	☐ Accepted and In-press ■ Published ☐ In progress	Date accepted/published 15/8/2018

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Co-author's name	Co-author's signature	Date *(dd/mm/yy)*
Dr Thushara Perera		07/05/19

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Co-author's name	Co-author's signature	Date *(dd/mm/yy)*
A/Prof Jennifer McGinley		11/09/2019

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Co-author's name	Co-author's signature	Date *(dd/mm/yy)*
Shivanthan Yohanandan		8/5/2019

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Co-author's name	Co-author's signature	Date *(dd/mm/yy)*
Prof Peter Brown		7/3/19

Co-author authorisation form

THE UNIVERSITY OF MELBOURNE

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Co-author's name	Co-author's signature	Date *(dd/mm/yy)*
Dr Wesley Thevathasan		7/5/19

Appendix 5. Declaration for thesis with publication forms

Declaration for a thesis with publication

THE UNIVERSITY OF MELBOURNE

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A. PUBLICATION DETAILS *(to be completed by the student)*

Full title	An Instrumented Pull Test to Characterize Postural Responses	
Authors	Joy Tan, Wesley Thevathasan, Jennifer McGinley, Peter Brown, Thushara Perera	
Student's contribution (%)	60	
Journal or book name	Journal of Visualised Experiments	
Volume/page numbers	Issue 146. Video article. https://www.jove.com/video/59309	
Status	☐ Accepted and In press ■ Published ☐ In progress	Date accepted/ published 6/4/2019

B. STUDENT'S DECLARATION

I declare that the publication above meets the requirements to be included in the thesis

Student's name	Student's signature	Date *(dd/mm/yy)*
Joy Lynn Tan		07/05/2019

C. PRINCIPAL SUPERVISOR'S DECLARATION

I declare that:

- the information above is accurate
- The advisory committee has met and agreed to the inclusion of this publication in the student's thesis
- All of the co-authors of the publication have reviewed the above information and have agreed to its veracity
- 'Co-Author Authorisation' forms for each co-author are attached.

Supervisor's name	Supervisor's signature	Date *(dd/mm/yy)*
Dr Wesley Thevathasan		7/5/19.

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A. PUBLICATION DETAILS *(to be completed by the student)*

Full title	Neurophysiological analysis of the clinical pull test	
Authors	Joy Lynn Tan, Thushara Perera, Jennifer McGinley, Shivanthan Arthur Curtis Yohanandan, Peter Brown, Wesley Thevathasan	
Student's contribution (%)	80	
Journal or book name	Journal of Neurophysiology	
Volume/page numbers	Vol 120, pg 2325 - 2333	
Status	☐ Accepted and In press ■ Published ☐ In progress	Date accepted/ published 15/8/2018

B. STUDENT'S DECLARATION

I declare that the publication above meets the requirements to be included in the thesis

Student's name	Student's signature	Date *(dd/mm/yy)*
Joy Lynn Tan		7/05/2019

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Dr Wesley Thevathasan		7/5/19.

Appendix 6. Supplementary data

Chapter 5: Predictors of postural responses in participants with PD and healthy controls

Table 4.1: Coefficient estimates (b), 95% confidence intervals (CI), and *p*-values of instrumented pull test predictors resulting from linear mixed models for trunk responses in participants with PD

	Trunk Reaction Time		Deceleration		Pitch Angle		Pitch Velocity	
Predictor	**b (95 %CI)**	***p***	**b (95 %CI)**	***p***	**b (95 %CI)**	***p***	**b (95 %CI)**	***p***
Peak Force	0.03 (- 0.32, 0.39)	0.851	7.77 (-7.39, 22.94)	0.308	0.11 (0.06, 0.15)	< 0.001	0.57 (0.28, 0.87)	< 0.001
Force Rate	0.00 (- 0.03, 0.02)	0.758	-0.44 (-1.51, 0.63)	0.416	0.00 (0.00, 0.00)	0.512	0.00 (-0.01, 0.02)	0.674
Height	103.15 (-32.55, 238.85)	0.126	- 1356.07 (-6105.40, 3393.26)	0.551	-15.82 (-131.73, 100.08)	0.775	-143.46 (-886.30, 599.38)	0.686
Weight	-0.05 (- 1.04, 0.94)	0.917	4.12 (-31.96, 40.20)	0.813	-0.84 (-1.60, -0.07)	0.034	-4.63 (-9.53, 0.28)	0.063

Table 4.2: Coefficient estimates (b), 95% confidence intervals (CI), and *p*-values of instrumented pull test predictors resulting from linear mixed models for step responses in participants with PD

	Step Reaction Time		Initial Step length		Step Velocity		Retropulsion		Step count	
Predictor	**b (95 %CI)**	***p***	**b (95% CI)**	***p***	**b (95 %CI)**	***p***	**b (95% CI)**	***p***	**b (95 %CI)**	***p***
Peak Force	-0.36 (-0.83,0.12)	0.143	0.71 (0.34, 1.08)	< 0.001	2.49 (1.38, 3.59)	< 0.001	1.02 (0.67, 1.37)	< 0.001	0.00 (0.00, 0.00)	0.987
Force Rate	0.02 (-0.01,0.04)	0.226	0.02 (0.00, 0.04)	0.052	0.05 (-0.01, 0.11)	0.088	0.00 (-0.02, 0.02)	0.836	0.00 (0.00, 0.00)	0.969
Height	429.81 (-133.69, 993.30)	0.125	-249.52 (-789.01, 289.97)	0.340	-437.07 (-1898.38, 1024.24)	0.533	-139.57 (-657.76, 378.62)	0.574	1.08 (-2.27, 4.42)	0.503
Weight	-2.01 (-5.76, 1.73)	0.271	1.54 (-2.03, 5.12)	0.373	0.40 (-9.30, 10.10)	0.932	1.93 (-1.50, 5.36)	0.250	0.01 (-0.01, 0.03)	0.438

Table 4.3: Coefficient estimates (b), 95% confidence intervals (CI), and *p*-values of instrumented pull test predictors resulting from linear mixed models for trunk responses in healthy controls

	Trunk Reaction Time		Deceleration		Pitch Angle		Pitch Velocity	
Predictor	**b (95 %CI)**	***p***	**b (95 %CI)**	***p***	**b (95 %CI)**	***p***	**b (95 %CI)**	***p***
Peak Force	0.04 (-0.35, 0.43)	0.822	-19.06 (-54.32, 16.20)	0.279	0.06 (0.03, 0.08)	< 0.001	-0.10 (-0.25, 0.04)	0.153
Force Rate	-0.03 (-0.06, 0.00)	0.070	-1.14 (-3.82, 1.54)	0.400	0.00 (0.00, 0.00)	0.691	0.01 (0.00, 0.02)	0.164
Height	144.13 (-59.26, 347.51)	0.138	2905.16 (-15291.99, 21102.31)	0.724	-10.93 (-66.05, 44.20)	0.660	-14.44 (-397.51, 368.64)	0.933
Weight	0.66 (-0.73, 2.04)	0.328	47.55 (-78.40, 173.50)	0.435	-0.07 (-0.37, 0.24)	0.626	0.44 (-1.67, 2.56)	0.644

Table 4.4: Coefficient estimates (b), 95% confidence intervals (CI), and *p*-values of instrumented pull test predictors resulting from linear mixed models for step responses in healthy controls

	Step Reaction Time		Initial Step length		Step Velocity		Retropulsion		Step count	
Predictor	**b (95 %CI)**	***p***	**b (95 %CI)**	***p***	**b (95 %CI)**	***p***	**b (95 %CI)**	***p***	**b (95 %CI)**	***p***
Peak Force	-0.30 (-0.60, 0.01)	0.057	1.18 (0.87, 1.48)	< 0.001	4.35 (3.40, 5.30)	< 0.001	1.23 (0.84, 1.62)	< 0.001	0.00 (0.00, 0.01)	0.018
Force Rate	0.01 (-0.02, 0.03)	0.558	-0.01 (-0.03, 0.02)	0.578	0.01 (-0.06, 0.07)	0.829	-0.01 (-0.04, 0.02)	0.423	< 0.01 (- 0.0003, 0.003)	0.307
Height	452.97 (-361.53, 1267.47)	0.235	123.61 (-777.21, 1024.43)	0.760	2058.87 (-202.99, 4320.73)	0.069	114.74 (-675.26, 904.75)	0.746	0.54 (-6.69, 7.76)	0.868
Weight	-0.72 (-5.21, 3.78)	0.724	-0.96 (-5.93, 4.00)	0.669	-9.68 (-22.18, 2.82)	0.113	-1.10 (-5.48, 3.28)	0.583	-0.02 (-0.06, 0.02)	0.334

JoVE: Supplemental coding file

```
% Instrumented Pull Test Analysis Workflow
% MATLAB Pseudocode

% This function returns the experimental parameters (postural reaction
% time, peak trunk deceleration, step reaction time, total step
% displacement, peak pull force, and rate of force development) as a
struct
% object (Results). Inputs required are *.csv file paths to the motion
% tracking and load cell data.
function Results = GetPullTestResults(MotionTrackerPath, LoadcellPath)
    % Read data from files
    MotionData = array2table(csvread(MotionTrackerPath));
    LoadcellData = array2table(csvread(LoadcellPath));
    % Align data using trigger signal
    MotionIdx = find(MotionData.Trigger, 1);
    LoadcellIdx = find(LoadcellData.Trigger, 1);
    MotionData(:, MotionIdx) = [];
    LoadcellData(:, LoadcellIdx) = [];
    % Resample to 1kHz
    fs = 1000;
    MotionData = resample(MotionData, MotionData.t, fs);
    LoadcellData = resample(LoadcellData, LoadcellData.t, fs);
    % High-pass filter with cut-off at 0.05 Hz
    fc = 0.05;
    wc = fc/(fs/2);
    [B, A] = butter(20, wc, 'high');
    MotionData = filtfilt(B, A, MotionData);
    LoadcellData = filtfilt(B, A, LoadcellData);
    % Differentiate displacement data
    MotionData.TrunkVelocity.Y = diff(MotionData.Trunk.Y);
    MotionData.TrunkAcceleration.Y = diff(MotionData.TrunkVelocity.Y);
    % Slice data to find single trial epochs
    [~, TriggerIdx] = findpeaks(MotionData.Trigger);
    % Loop through epochs and generate results
    Results.N = length(TriggerIdx);
    for i = 1:Results.N-1
        s = TriggerIdx(i); % start index
        e = TriggerIdx(i+1); % end index
        % Check for anticipation
        reject = FindAnticipation(MotionData.Trunk.Y(s:e),...
            LoadcellData.Force(s:e));
        if ~reject
            % Populate results struct
            Results.TrunkReactionTime(i) = ...
                GetTrunkReactionTime(MotionData.Trunk.Y(s:e),...
                MotionData.TrunkAcceleration.Y(s:e), fs);
            Results.PeakTrunkDeceleration(i) = ...
                max(MotionData.TrunkAcceleration.Y(s:e));
            Results.LeftStepReactionTime(i) = ...
                GetStepReactionTime(MotionData.Trunk.Y(s:e),...
                MotionData.LeftFoot.Y(s:e), fs);
            Results.RightStepReactionTime(i) = ...
                GetStepReactionTime(MotionData.Trunk.Y(s:e),...
```

```
                MotionData.RightFoot.Y(s:e), fs);
            Results.LeftTotalStepDisplacement(i) = ...
                GetTotalStepDisplacement(MotionData.LeftFoot.Y(s:e));
            Results.RightTotalStepDisplacement(i) = ...
                GetTotalStepDisplacement(MotionData.RightFoot.Y(s:e));
            Results.PeakPullForce(i) = ...
                max(LoadcellData.Force(s:e));
            Results.ForceRate(i) = ...
                max(diff(LoadcellData.Force(s:e)));
        end
    end
end

function CanReject = FindAnticipation(TrunkDisplacement, PullForce)
    CanReject = 0;
    % Find onset of trunk displacement
    BaselineMean = mean(TrunkDisplacement);
    BaselineSTD = std(TrunkDisplacement);
    thresh = BaselineMean + 3*BaselineSTD;
    onset = find(TrunkDisplacement>thresh, 1);
    % Find onset of pull
    BaselineMean = mean(PullForce);
    BaselineSTD = std(PullForce);
    thresh = BaselineMean + 3*BaselineSTD;
    pull = find(PullForce>thresh, 1);
    % If trunk displacement occurs before pull, then reject trial
    if onset < pull
        CanReject = 1;
    end
end

function RT = GetTrunkReactionTime(TrunkDisplacement,
TrunkAcceleration, fs)
    % Find onset of trunk displacement
    BaselineMean = mean(TrunkDisplacement);
    BaselineSTD = std(TrunkDisplacement);
    thresh = BaselineMean + 3*BaselineSTD;
    onset = find(TrunkDisplacement>thresh, 1);
    % Use zero crossing detector to find start of deceleration
    decel = zcd(TrunkAcceleration);
    % Calculate reaction time
    RT = (decel-onset)/fs;
end

function RT = GetStepReactionTime(TrunkDisplacement, StepDisplacement,
fs)
    % Find onset of trunk displacement
    BaselineMean = mean(TrunkDisplacement);
    BaselineSTD = std(TrunkDisplacement);
    thresh = BaselineMean + 3*BaselineSTD;
    onset = find(TrunkDisplacement>thresh, 1);
    % Find onset of step displacement
    BaselineMean = mean(StepDisplacement);
    BaselineSTD = std(StepDisplacement);
    thresh = BaselineMean + 3*BaselineSTD;
    step = find(StepDisplacement>thresh, 1);
    % Calculate reaction time
    RT = (step-onset)/fs;
```

```
end

function Step = GetTotalStepDisplacement(StepDisplacement)
    Step = max(StepDisplacement);
    if Step < 50 % reject if step is less than 50 mm
        Step = NaN;
    end
end
```