Under the Copyright Act 1968 (several provision of which are referred to below), this thesis must be used only under the normal conditions of scholarly fair dealing for the purposes of research, criticism or review. In particular no results or conclusions should be extracted from it, nor should it be copied or closely paraphrased in whole or in part without the written consent of the author. Proper written acknowledgement should be made for any assistance obtained from this thesis.

Under Section 35(2) of the Copyright Act 1968 'the author of a literary, dramatic, musical or artistic work is the owner of any copyright subsisting in the work'. By virtue of Section 32(1) copyright 'subsists in an original literary, dramatic, musical or artistic work that is unpublished' and of which the author was an Australian citizen, an Australian protected person or a person resident in Australia.

The Act, by Section 36(1) provides: 'Subject to this Act, the copyright in a literary, dramatic, musical or artistic work is infringed by a person who, not being the owner of the copyright and without the licence of the owner of the copyright, does in Australia, or authorises the doing in Australia of, any act comprised in the copyright'.

Section 31(1)(a)(i) provides that copyright includes the exclusive right to 'reproduce the work in a material form'. Thus, copyright is infringed by a person who, not being the owner of the copyright, reproduces or authorises the reproduction of a work, or of more than a reasonable part of the work, in a material form, unless the reproduction is a 'fair dealing' with the work 'for the purpose of research or study' as further defined in Sections 40 and 41 of the Act.

Section 51(2) provides that "Where a manuscript, or a copy, of a thesis or other similar literary work that has not been published is kept in a library of a university or other similar institution or in an archives, the copyright in the thesis or other work is not infringed by the making of a copy of the thesis or other work by or on behalf of the officer in charge of the library or archives if the copy is supplied to a person who satisfies an authorized officer of the library or archives that he requires the copy for the purpose of research or study'.

*'Thesis' includes 'treatise', dissertation' and other similar productions.

Why do people with Parkinson's disease fall?

Mark Dominic Latt

This thesis is submitted in fulfilment of the requirements for the degree of Doctor of Philosophy.

Faculty of Medicine

The University of Sydney

March 2006

DECLARATION

This thesis contains no material which has been accepted for the award of any degree or diploma in any University and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

ACKNOWLEDGEMENTS

This project would not have been possible without the guidance and encouragement of my supervisors Professor Stephen Lord and Doctor Victor Fung and my associate supervisors Dr Hylton Menz, Professor John Morris and Dr Richard Fitzpatrick.

I wish to acknowledge the enormous debt of gratitude I owe to the many people who participated in my studies. Without them, this project would have been neither possible nor worthwhile.

Most importantly, I wish to thank my wife Sophie Chan and daughter Laryssa for their support and inspiration in this and every other of my endeavours.

I dedicate this thesis to my parents, Dr John Ming-Gee Chu and Dr Doreen Latt, and to my grandmother, Dora Latt.

ABSTRACT

The project described in this thesis identified risk factors for falls in people with Parkinson's disease (PD). Firstly, it identified impairments of physiological function, postural stability and gait pattern that distinguish PD patients from healthy control subjects. Secondly it determined if these impairments distinguish fallers from non-fallers with PD.

In the case-control study described in chapter 5, we found that PD patients have significantly weaker knee extension strength, slower simple reaction times, greater postural sway, smaller maximal balance ranges and worse coordinated stability than healthy controls. As a proportion of their limits of stability, PD patients sway more than healthy controls even in conditions without external or self-initiated perturbations.

The case-control study described in chapter 6 demonstrated that abnormalities in postural sway, maximal balance range and coordinated stability worsen as the Hoehn and Yahr stage of disease becomes more advanced and are significantly worse in fallers than in non-fallers with PD.

In a further case-control study (chapter 8), accelerometeric techniques were used to compare gait patterns between healthy controls and PD subjects and between fallers and non-fallers with PD. It was found that PD patients, unlike healthy control subjects, experience irregular self-generated perturbations of

the head (centre of balance) and pelvis (COG) when walking. These perturbations tend to be more irregular in fallers than in fallers with PD.

Finally, a cohort study (chapter 9) was performed to determine whether the abnormalities detected in the case-control studies could explain why people with PD fall. It was found that cognitive ('frontal') impairment, freezing of gait, abnormal axial posture, leg weakness and impaired coordinated stability are independent risk factors of falls and may be used predict falls in PD. Future intervention studies are required to determine whether improvement of leg strength and coordinated stability reduces the risk of falling.

CHAPTER SUMMARY

CHAPTER 1 Introduction to the project with explication of hypotheses and aims.

CHAPTER 2 Review of the literature on falls, postural stability and gait in Parkinson's disease.

CHAPTER 3 Description of the methods of the main prospective cohort study.

CHAPTER 4 Study of test-retest reliability of physiological measures used in the project.

CHAPTER 5 Case-control study comparing postural sway between PD and healthy control groups and crossover study comparing postural sway between 'on' and 'off' phases of levodopa therapy in PD patients.

CHAPTER 6 Case-control study examining postural sway across Hoehn and Yahr stages 1,2 and 3 and between falling and non-falling patients with PD.

CHAPTER 7 Study examining the effects of gait speed (experiment 1), cadence (experiment 2) and step length (experiment 3) on head and pelvic rhythm while walking.

CHAPTER 8 Experiment 1: Case-control study comparing gait accelerometry between PD and healthy control groups and crossover study comparing postural sway between 'on' and 'off' phases of levodopa therapy in PD patients. Experiment 2: Case-control study comparing gait accelerometry between falling and non-falling patients with PD.

CHAPTER 9 Prospective cohort study examining risk factors for falls in PD and developing a model using only variables obtained through standard clinical history and examination and models with both clinical and physiological variables.

CHAPTER 10 Discussion and conclusion of the thesis.

CONTENTS

CHAPTER 1

INTRODUCTION

1.1 BACKGROUND TO THE STUDIES

It could be argued that the greatest discovery in Parkinson's disease (PD) was published over 4,000 years ago. The Ayurvedic Ayurveda, an Indian medical text dating back to 2500 BC, described the use of Mucuna beans to treat tremor, rigidity and slowness. We know now that these beans contain levodopa, the active compound in most modern treatments of PD. In the last 200 years, history has finally come round full circle, with descriptions of the clinical characteristics of PD [Parkinson 1817], observations of reduced dopamine in the brains of patients [Ehringer and Hornykiewicz 1960] and evidence of the efficacy of levodopa [Birkmayer and Hornykiewicz 1961; Cotzias, van Woert et al. 1967]. What remains to be studied for the benefit of patients with this disabling disease?

In the vast majority of patients, we can not explain why PD develops, cure the disease definitively or prevent its consequences. Therefore, considerable research into the pathophysiology, treatment and prevention of complications is still required. This thesis deals with a major complication of PD - falling. It attempts to explain why falls occur in PD, predict which patients are most likely to fall and point towards possible therapies to prevent falls.

A fall has been defined as an 'event which results in the person coming to rest inadvertently on the ground or other lower level, and other than as a consequence of the following: sustaining a violent blow, loss of consciousness, sudden onset of paralysis, or an epileptic seizure'[1987]. Even with acute stroke, epilepsy, syncope and external perturbations excluded from this and similar definitions [Gibson 1987; Feder, Cryer et al. 2000], the impact of falls and fall-related injury on our community is enormous. Admissions to hospital due to falls cost the NSW Department of Health over $324 million each year [Moller 1998]. Failure to address falls in the aging population will increase costs to over $644 million by 2050 [Moller 2000], necessitating an additional 800 beds in hospitals and 1200 beds in facilities providing high level residential care. Falls are a major contributor to death and disability in the elderly, with one in four people over the age of 65 in Australia falling every year [Jorm, Astbury et al. 1995] and 5 to 11% of falls resulting in significant injuries [Kannus, Parkkari et al. 1999].

There is a strong relationship between falls and PD. PD affects about 2% of people over 65 years of age [Tanner 1992] but accounts for a disproportionately large percentage of subjects who fall in hospital [Salgado, Lord et al. 1994] and in the community [Campbell, Borrie et al. 1989]. PD patients are almost three times more likely to fall than people without PD after adjusting for age [Fink, Kuskowski et al. 2005]. As far as diseases are concerned, only dementia and perhaps stroke contribute more to falls.

Falls will occur at some time in up to 90% of people with PD [Koller, Glatt et al. 1989], with 68% falling at least once each year [Schrag, Ben-Shlomo et al. 2002; Wood, Bilclough et al. 2002], 13% falling at least once a week [Koller, Glatt et al. 1989] and 16% fracturing a hip [Sato, Kaji et al. 2001]. These statistics suggest that falls in PD are neither random nor infrequent. They also suggest risk factors peculiar to or magnified by PD. Falls in PD are associated with rapid disease progression and severe disability [Jankovic, McDermott et al. 1990]. The overall impact of falls on PD is indicated by a mortality that is two to five times higher among PD patients than among age-matched controls [Bennett, Beckett et al. 1996; Morens, Davis et al. 1996]. In spite of this impact, there have been few retrospective [Koller, Glatt et al. 1989; Ashburn, Stack et al. 2001; Fink, Kuskowski et al. 2005; Robinson, Dennison et al. 2005; Wielinski, Erickson-Davis et al. 2005] or prospective [Ashburn, Stack et al. 2001; Bloem, Grimbergen et al. 2001; Wood, Bilclough et al. 2002] studies of the causes of falls in PD.

Previous studies have highlighted some methods for predicting falls. The Tinetti mobility index [Tinetti 1986], for example, distinguishes fallers from non-fallers with a high degree of accuracy [Bloem, Grimbergen et al. 2001; Wood, Bilclough et al. 2002]. More research is required, however, to explain the pathophysiological mechanisms that cause a particular patient or group of patients to fall. Also, the studies have focussed on PD-specific risk factors for falls, such as severity or stage of disease. These risk factors, however, may not

be remediable. Ongoing research is necessary to consider a broader range of risk factors that are potentially treatable.

The studies mentioned above have documented the following independent risk factors for falls in PD:

1. previous falls,
2. fear of falling,
3. worse disease severity,
4. longer duration of disease,
5. loss of arm swing and
6. presence of dementia,

and hypothesised the following risk factors:

1. increasing age,
2. worse balance,
3. bradykinesia,
4. rigidity,
5. dyskinesia,
6. freezing of gait and
7. muscle weakness.

In addition to the above, it is also necessary to consider other risk factors contributing to falls in the wider, non-parkinsonian community:

1. slower simple reaction times,

2. impaired peripheral sensation,
3. poor visual acuity and contrast sensitivity [Lord, Clark et al. 1991],
4. use of medications [Tinetti, Speechley et al. 1988; Lord, Anstey et al. 1995] and
5. gait and balance abnormalities [Tinetti, Speechley et al. 1988].

The work detailed in this thesis will address some gaps in the scientific literature. It will explore important potential risk factors for falls that have not been investigated previously in a prospective study of PD, such as:

1. freezing of gait,
2. frontal lobe impairment, assessed by the Frontal Assessment Battery [Dubois, Slachevsky et al. 2000],
3. lower limb reaction times, strength and sensation assessed by the Physiological Profiles Approach (PPA) [Lord, Menz et al. 2003],
4. high- and low-contrast visual acuity and visual contrast sensitivity (PPA),
5. postural stability during self-initiated movements (PPA),
6. step-to-step variability in temporospatial measurements of gait, assessed by accelerometric methods [Smidt, Arora et al. 1971; Menz, Lord et al. 2003] and
7. anti-parkinsonian medications.

1.2 HYPOTHESES

It was hypothesised that falls in people with Parkinson's disease are multifactorial, due to:

1. deficits in specific physiological systems, such as muscle strength, vision and proprioception;
2. impaired postural stability while standing and walking;
3. impulsivity and cognitive impairment; and
4. PD-specific factors such as freezing of gait (FOG) and disease severity and stage.

1.3 AIMS

The aims of the studies were to:

1. identify physiological deficits associated with falls in PD,
2. identify deficits in postural stability associated with falls in PD,
3. identify deficits in gait control associated with falls in PD,
4. develop a model incorporating clinical and physiological measures that explains why falls occur in PD and
5. identify risk factors for falls that may be amenable to therapy.

CHAPTER 2

REVIEW OF FALLS IN PARKINSON'S DISEASE

2.1 INTRODUCTION

There are a number of double-blind randomised controlled trials demonstrating that modification of risk factors reduces the incidence of falls in the elderly [Tinetti, Baker et al. 1994; Campbell, Robertson et al. 1997; Close, Ellis et al. 1999; Gardner, Robertson et al. 2000; Salkeld, Cumming et al. 2000; Gardner, Buchner et al. 2001; Robertson, Devlin et al. 2001; Robertson, Devlin et al. 2001; Gardner, Phty et al. 2002]. This level of evidence is as yet unavailable in PD. Before appropriate randomised controlled trials can be performed, however, there is a need for more studies in the level III-2 category (cohort or case-control designs) that are powered to examine all possible risk factors for falls in PD. There have been a number of case-control, cross-sectional and cohort studies addressing falls in PD.

2.2 RETROSPECTIVE STUDIES

In a cross-sectional study, Koller and colleagues [Koller, Glatt et al. 1989] questioned 100 subjects with Parkinson's disease about the falls they had experienced in the past. A history of falling correlated significantly with age,

duration of disease, postural instability, bradykinesia and rigidity but not with tremor, dopaminergic therapy, postural hypotension, sensory loss, dementia, heart disease or antihypertensive treatment. Ashburn and colleagues [Ashburn, Stack et al. 2001] performed a cross-sectional study of 63 PD patients living in the community, 40 (64%) of whom had a fall in the preceding 12 months. Fallers performed worse than non-fallers in tests of postural stability when distracted. In addition, more advanced disease (higher Hoehn and Yahr stages), worse symptoms (UPDRS Scores), worse mobility and greater handicap were noted among the fallers.

Morris and colleagues (2000) [Morris, Iansek et al. 2000] compared 15 PD subjects with a previous fall with 15 PD subjects with no history of falls in a case-control study. They found that fallers tended to have worse balance than non-fallers while standing in a number of ways (feet apart, feet together, step stance, tandem stance and single leg stance). In another case-control study, Robinson and colleagues (2005) [Robinson, Dennison et al. 2005] compared 19 fallers with 21 nonfallers with PD. Fallers had greater duration and severity of disease and worse dyskinesia, freezing of gait, postural instability, fear of falling, impairment of fine motor control and proximal muscle weakness than non-fallers. In a retrospective study of 350 PD patients, fallers were significantly more likely to have advanced PD, urinary incontinence, increased Timed Up & Go times and increased PD duration than non-fallers [Balash, Peretz et al. 2005].

The retrospective nature of these studies introduces differential recall bias where recollections of symptoms, mobility problems and postural instability may be more vivid in fallers than in non-fallers, and selection bias, where subjects in the faller and non-faller groups may not be representative of fallers and non-fallers in the PD population. In other words, the observed differences between fallers and non-fallers may be due to the subjective nature of memory or the selection of idiosyncratic subjects rather than any objective discriminators.

2.3 PROSPECTIVE STUDIES

Recall bias can be minimised to a certain extent by prospective study designs. In a three-month prospective follow-up study of 57 PD patients, Ashburn and colleagues (2001) [Ashburn, Stack et al. 2001] found that one or more falls in the previous year and fear of future falls were independent predictors of falling. Bloem and colleagues (2001) [Bloem, Valkenburg et al. 2001] investigated risk factors for falls in a prospective study of 59 PD patients and 55 subjects without PD (patients' partners) recruited from a neurology outpatient department specialising in movement disorders. Measures of posture and balance at baseline were not associated with falls in the next six months. Significant differences were observed between fallers and non-fallers in fear of falling and use of walking aids. Fallers had significantly more advanced disease stage and worse symptoms and signs. Fallers performed

significantly worse in many performance-oriented tests of standing and walking. Most balance and gait tests were inadequate to predict falls. On multiple logistic regression analysis, more advanced stage of disease and a past history of recurrent falls increased the risk of recurrent falls in the next six months.

Wood and colleagues [Wood, Bilclough et al. 2002] assessed 109 people with Parkinson's disease recruited from a district hospital register. In addition to measures of disease severity, disability and functional mobility (including changes in posture and stair climbing), they assessed quality of life and changes in blood pressure. Fallers had significantly longer durations of symptoms, higher number of falls in the previous year, more advanced disease, worse cognition and less quality of life on univariate analysis. Independent risk factors were a history of previous falls, loss of arm swing, duration of disease and the presence of dementia.

2.4 CASE-CONTROL STUDIES

Risk factors might be significantly associated with falls but may not necessarily explain why the falls occurred. For example, reduced arm swing is independently associated with falls [Wood, Bilclough et al. 2002] but only hints vaguely at the pathophysiological mechanisms (such as slowed reaction times and displaced COG) leading to falls.

Previous studies into the mechanisms of falls have been case-control in design, comparing PD patients with healthy controls. They have tended to focus on stance and gait, implying that falls could result from impairments in these functions.

2.4.1 Stance and PD

Studies of balance have hypothesized that falls could be caused by difficulty controlling motion of the COG (*postural sway*), due to:

1. rigidity and stiffness,
2. impaired motor responses to unexpected external perturbations,
3. difficulty maintaining stability during self-initiated movements or following expected external perturbations (changing *postural set*) and
4. difficulty prioritizing different sensory inputs in order to maintain stability (sensory integration).

It has also been suggested that treatment with levodopa does not improve postural stability meaningfully or reduce falls.

2.4.1.1 Rigidity and stiffness

In an a priori manner, it is reasonable to suppose that problems with stance can cause falls in PD. A common finding in studies comparing PD patients to healthy controls is reduced or normal movement of the COG during undisturbed stance, in other words, less *postural sway* in PD patients [Horak, Nutt et al. 1992; Schieppati, Hugon et al. 1994].

Reduced sway can be explained partly by rigidity, which itself has several possible explanations. Firstly, reflexes for maintaining stability are abnormal. In PD patients, the following have been observed: excessive co-contraction in muscle groups not normally active during unperturbed stance (increased antagonistic muscle activity), slowness in adapting posture to changes in position of the floor (support surface translations) and difficulty ordering motor responses appropriately [Horak, Nutt et al. 1992; Schieppati, Hugon et al. 1994]. Secondly, the muscles in PD patients (eg. gastrocnemius) are inherently stiffer than in healthy controls [Dietz, Berger et al. 1988] and respond less to stretching despite equivalent background electromyographic activity. Thirdly, joints may become less flexible as a consequence of muscle stiffness [Dietz, Berger et al. 1988; Hayashi, Tokuda et al. 1997]. Fourthly, the stooped posture characteristic of PD may itself reduce sway, at least in the anteroposterior plane [Bloem, Beckley et al. 1999]. Finally, it has been hypothesized that PD patients consciously stiffen their lower limbs through co-contraction to keep their center of gravity within narrow stability limits

[Horak, Nutt et al. 1992; Schieppati, Hugon et al. 1994; Beckley, Panzer et al. 1995].

Although reduced sway may improve stability in undisturbed conditions, it is potentially dangerous under dynamic conditions, when the COG is displaced as a result of self-initiated movement (eg. turning and reaching) or external perturbations (eg. standing in a bus that stops suddenly or being pushed). An analogy has been drawn between the stance of a PD patient and that of a toy tin soldier [Bloem, van Vugt et al. 2001]. The tin soldier falls from even the smallest perturbation due to inflexibility and inability to adjust the COG to absorb the perturbation.

2.4.1.2 Standing and responding to external perturbations

A number of studies have shown that postural responses to external perturbations, such as toe-up surface rotations or backward surface translations, are coordinated poorly in PD [Dietz, Berger et al. 1988; Beckley, Bloem et al. 1991; Horak, Nutt et al. 1992]. When their COG is displaced forward (eg. by posterior displacements of the support surface), PD patients have weaker stabilizing responses (ie. contraction of the gastrocnemius) and stronger destabilizing responses (ie. contraction of the tibialis anterior) than healthy controls [Dietz, Berger et al. 1988]. PD patients respond to perturbations by activating muscle groups in an abnormal sequence [Beckley,

Bloem et al. 1991]. In response to toe-up support surface rotations, healthy controls activate distal muscle groups prior to proximal muscle groups to prevent excessive posterior displacement of their COG. In contrast, PD patients are more likely to activate proximal muscle groups prior to distal ones, are therefore less likely to limit posterior displacement of their COG and are more likely to fall backwards.

2.4.1.3 Standing and changing postural set

It has been demonstrated that PD patients have difficulty adapting motor responses to anticipated external perturbations (changing postural set), such as toe-up surface rotations of an expected magnitude [Beckley, Bloem et al. 1991; Bloem, Beckley et al. 1995; Chong, Horak et al. 2000] or self-generated perturbations such as rising to ones toes [Frank, Horak et al. 2000]. The result is that postural motor responses in PD patients tend to remain fairly constant but inadequate compared to the size of the perturbation. These abnormalities are thought to be secondary to defective basal ganglia that can not exercise appropriate control of spinal and supraspinal reflex centres [Marsden 1984].

2.4.1.4 Standing and sensory integration

In the early stages at least, PD patients have little difficulty using sensory information to maintain stability. Horak and colleagues (1992) [Horak, Nutt et

al. 1992] found that subjects with PD were able to maintain postural stability using visual, somatosensory (light touch and proprioception) and vestibular information. Their findings were supported by other investigators [Waterston, Hawken et al. 1993; Chong, Horak et al. 1999] who found no significant differences in sway between PD and control groups, although PD subjects tended to fall more frequently, across a range of conditions. These studies altered sensory conditions using the Sensory Organization Test (SOT) [Nashner, Black et al. 1982], in which the subject's visual inputs were eliminated by blindfolding or looking at a moving visual field and somatosensory inputs from the legs were modified by standing on a support surface that rotated in the anteroposterior plane. PD patients with more advanced disease encounter greater sway when sensory inputs are impaired, such as when vision is eliminated and the support surface is unstable [Bronte-Stewart, Minn et al. 2002].

PD patients at all stages, however, may have more difficulty maintaining balance in the presence of incongruent or misleading sensory information than in compensating for the absence of normal inputs. Bronstein (1990) [Bronstein, Hood et al. 1990] found that a greater increase in sway in PD patients than in controls when the visual field was displaced laterally, suggesting that patients had more problems maintaining stability in the presence of incongruent visual inputs. In contrast, PD patients are able to suppress misleading vestibular inputs, such as those generated by galvanic stimulation of the mastoid processes, and maintain normal postural stability

[Pastor, Day et al. 1993]. These studies suggest PD patients have greater difficulty suppressing incongruent visual than vestibular inputs.

2.4.1.5 Response to levodopa

Treatment with antiparkinsonian medication does not appear to improve postural stability meaningfully in PD [Bonnet, Loria et al. 1987; Koller, Glatt et al. 1989; Bloem, Beckley et al. 1996]. When postural stability is assessed using clinical motor examinations, the response to levodopa lessens as the disease becomes more advanced [Bonnet, Loria et al. 1987] and may eventually disappear altogether [Koller, Glatt et al. 1989]. A number of studies have demonstrated that sway increases following levodopa therapy [Bronte-Stewart, Minn et al. 2002; Rocchi, Chiari et al. 2002; Rocchi, Chiari et al. 2004]. The increased sway in these studies could be explained by a reduction in intrinsic stiffness or by hyperkinesia. Levodopa may improve the sequence [Horak, Nutt et al. 1992] and magnitude [Beckley, Panzer et al. 1995; Frank, Horak et al. 2000] of motor responses to perturbations but not the ability to change postural set [Horak, Nutt et al. 1992; Chong, Horak et al. 2000].

2.4.2 Gait and PD

While PD patients differ from healthy controls in many aspects of their gait, it is not clear whether these differences contribute to falls. The studies in the scientific literature tend to be case-control in design and compare PD patients with healthy controls. These studies do not compare PD patients who fall with those who do not.

2.4.2.1 Gait velocity and stride length

During free walking, people with PD walk more slowly than healthy age-matched controls, with speeds ranging from 0.8 - 1.0 m/s [Vieregge, Stolze et al. 1997; Ebersbach, Sojer et al. 1999; Lewis, Byblow et al. 2000; Stolze, Kuhtz-Buschbeck et al. 2001] compared to 1.0-1.3 m/s in healthy elderly people [Gabell and Nayak 1984; Ferrandez, Pailhous et al. 1990; Morris, McGinley et al. 1999]. Walking slowly reduces perturbation to the COG at push-off and may be a way to decrease destabilising forces [Morris, McGinley et al. 1999].

Difficulty increasing stride length is the main cause for slowness in PD [Morris, Iansek et al. 1994; Morris, Iansek et al. 1994]. Stride lengths in PD range from 0.2 to 1.0m [Blin, Ferrandez et al. 1990; Morris, Iansek et al. 1994;

McIntosh, Brown et al. 1997; Vieregge, Stolze et al. 1997; Morris, McGinley et al. 1999] compared with 0.76 to1.5 m in the elderly [Finley, Cody et al. 1969; Murray, Kory et al. 1970; Winter, Patla et al. 1990]. PD patients have more difficulty adjusting stride length than adjusting cadence (number of steps taken per unit time) [Bowes, Charlett et al. 1992; Morris, Iansek et al. 1994]. Unlike healthy individuals, they increase gait speed by increasing cadence alone rather than both cadence and step length. Similarly, PD patients reduce their gait speed by reducing cadence rather than by decreasing stride length. Although people with PD can vary their gait velocity, the range of gait velocity is therefore narrowed compared with controls [Morris, Iansek et al. 1994]. PD patients can regulate stride length more easily when external cues (eg. stripes on the floor to indicate where the feet should step). These cues may allow the supplementary motor area to control stride length by bypassing the basal ganglia.

2.4.2.2 Cadence

PD patients tend to have slower cadences (94.5 steps per minute) than healthy controls (98.5 steps per minute) although this difference is not significant [Vieregge, Stolze et al. 1997; Ebersbach, Sojer et al. 1999; Stolze, Kuhtz-Buschbeck et al. 2001]. The ability to modulate walking cadence appears intact in most people with Parkinson's [Morris, Iansek et al. 1994; Morris, McGinley et al. 1999]. PD patients can modulate cadence using both external

cues (stepping in time with a metronome) and internal control mechanisms (wanting to step faster or slower) [Morris, Iansek et al. 1996].

The ability to increase cadence but not stride length is exemplified by the clinical signs and symptoms of festination and freezing of gait (FOG). Three-dimensional studies of gait in 14 patients with PD [Nieuwboer, Dom et al. 2001] found that cadence increased and stride length decreased markedly during festination. Also, cadence tends to increase and stride length decrease in the steps immediately prior to an episode of FOG.

2.4.2.3 Double support time

When walking, people with PD spend more time in double support (up to 50% of the gait cycle) [Ferrandez and Blin 1991; Mitoma 1997; Mitoma 1997; Azulay, Mesure et al. 1999]. This can result in a shuffling pattern. In contrast, double support time constitutes only 11 to 40% of the gait cycle in healthy elderly people [Murray, Drought et al. 1964; Imms and Edholm 1981; Ferrandez, Pailhous et al. 1990; Winter, Patla et al. 1990] and 9 to 11% in healthy young adults [Murray, Drought et al. 1964].

An increase in double support time can result from a fear of falling [Maki 1997] or an attempt to avoid falls [Winter, Patla et al. 1990; Winter 1991]. Increasing the proportion of the gait cycle spent in double support allows more

time for stabilization. Weakness or lower limb discomfort in advanced PD may also impair ability to support the body's weight during the single stance phase and necessitate increased double support [Morris, McGinley et al. 1999].

2.4.2.4 Step width

Most studies have found no significant difference in step width between PD patients and healthy controls [Vieregge, Stolze et al. 1997; Stolze, Kuhtz-Buschbeck et al. 2001]. In a comparative analysis of gait, it was found that step width in PD (approximately 6 cm) was greater than in healthy controls (5 cm) but less than in people with normal pressure hydrocephalus (14 cm) [Stolze, Kuhtz-Buschbeck et al. 2001]. These differences were not significant. In contrast, a study of 16 Parkinson's disease patients and 16 elderly controls found that step width was greater both before and after anti-parkinsonian treatment (both approximately 12 cm) in patients than in controls (9 cm) [Mesure, Azulay et al. 1999].

2.4.2.5 Coefficients of variation

The coefficient of variation (CV) of any variable is the standard deviation (SD) of that variable expressed as a percentage of the variable's mean. In gait analyses, the CV is simply a measure of the variability between steps in a gait

trial. For example, the CV of a patient's step length during a walking trial is the SD of that individual's step length divided by the individual's mean step length. Step-to-step variability in step length, and hence step length CV, is greater in PD patients than in healthy controls and increases as the stage of PD increases [Blin, Ferrandez et al. 1990; Hausdorff, Cudkowicz et al. 1998; Ebersbach, Sojer et al. 1999; Stolze, Kuhtz-Buschbeck et al. 2001]. The basal ganglia appear to be involved in motor programs controlling spatial regularity.

2.4.2.6 Freezing of gait

Freezing of gait (FOG) is a relatively late complication in PD patients [Giladi, McDermott et al. 2001] and results in a sudden halting of gait or an inability to start walking. Anecdotally, in the doctor's surgery, this problem appears to be associated with falls in PD patients [Bloem, Hausdorff et al. 2004] although a relationship has not been demonstrated in a scientific study.

2.4.2.7 Effect of levodopa on gait characteristics in Parkinson's disease

In PD gait problems may arise from an imbalance of neurotransmitters in the basal ganglia [Morris, McGinley et al. 1999]. Bowes and colleagues (1990) analysed gait in 14 PD patients aged 64 to 88 years receiving maintenance levodopa therapy [Bowes, Clark et al. 1990] in a randomized crossover study. A 7% mean increase in stride length and a 20% decrease in double support

time were observed on active treatment ($p < 0.0001$, in each case). Following therapy, stride length and peak velocity increase [Blin, Ferrandez et al. 1991] and signs of PD improve (shown by reduced scores on clinical rating scales) [O'Sullivan, Said et al. 1998]. In contrast, stride time, stride duration variability, stride length variability, cadence and double limb support were resistant to levodopa.

Studies using two-dimensional cinematography showed that people with PD walk with more flexion of the trunk, arms, hips and knees during stance phase and less clearance of the toe above the floor during swing phase of the gait cycle [Knutsson and Martensson 1971; Knutsson 1972]. Arm swing amplitude was also reduced. It is unclear whether levodopa therapy improves these kinematic variables.

2.5 CONCLUSION

The above studies have identified several possible clinical and physiological risk factors for falls in PD. The relative importance of these risk factors remains unclear as the studies focus on either clinical variables (cohort studies) or pathophysiological factors (case-control studies respectively) but seldom both. For example, longer disease duration has been identified as a risk factor for falls [Bloem, Grimbergen et al. 2001; Wood, Bilclough et al. 2002] but it is unclear whether its effect is independent of FOG or muscle weakness.

In addition to case control studies, we have performed a cohort study examining both physiological and clinical variables to identify independent risk factors for falls and determine why falls occur in PD.

CHAPTER 3

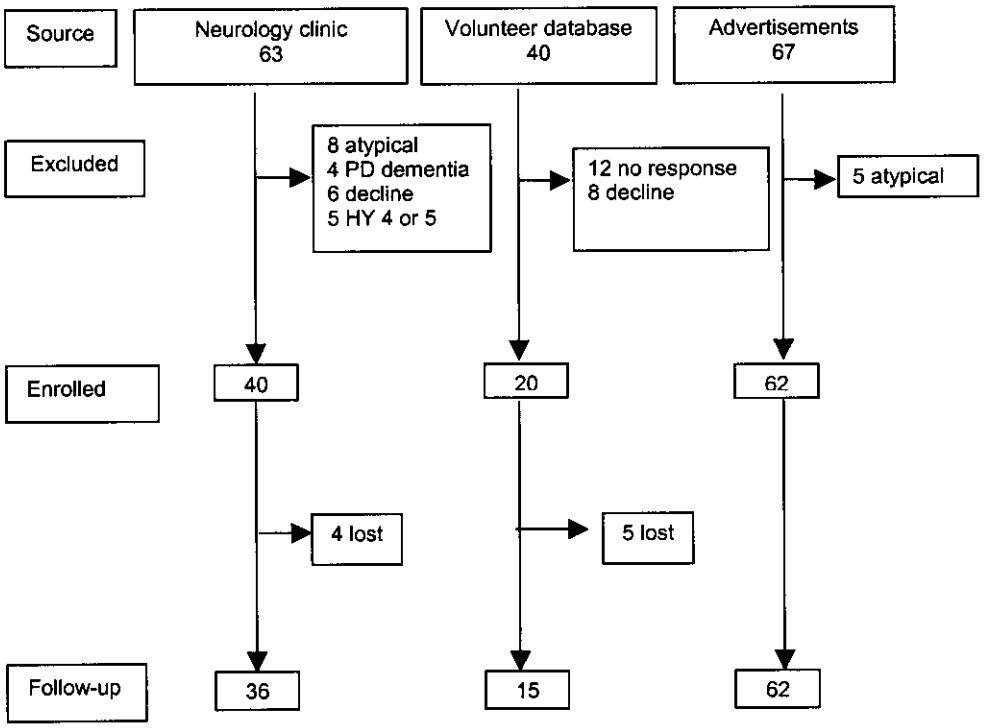
METHODS OF THE MAIN STUDY

3.1 SUBJECTS

For the main prospective study, 113 subjects with PD (age 66 ± 95% confidence interval 1.6 years, 66 male, height 171 ± 1.4 cm and weight 72 ± 2.9 kg) were recruited from a variety of sources (fig. 3.1): 36 (32%) from an outpatient movement disorders clinic at a secondary referral hospital, 15 (13%) from a database of volunteers at the Prince of Wales Medical Research Institute, 42 (37%) from PD support groups and 20 (18%) from the general community via television and newsletter advertisements. Subjects were eligible if they had a diagnosis of PD as defined by the United Kingdom Parkinson's Disease Brain Bank criteria [Hughes, Ben-Shlomo et al. 1992] (appendix A), lived in the community, were able to walk unassisted without a walking stick and could perform activities of daily living (eating, dressing and attending to hygiene) independently. Subjects were excluded if they had a MMSE score less than 24 [Folstein and Folstein 1981] or clinical signs or symptoms of an atypical parkinsonian syndrome (eg. progressive supranuclear palsy or multiple system atrophy). No subjects had evidence on history or examination of psychosis, neuroleptic use, vertigo, epilepsy, stroke, transient

ischaemic attack, syncope, uncompensated heart failure or moderate or severe valvular heart disease.

Figure 3.1. **Recruitment and follow-up of subjects**



3.2 MEASURES

All measures in the studies were performed by one rater (the author of this thesis). In selecting the instruments for the studies in this thesis I have endeavoured as far as possible to adhere to the following principles:

1. Measures should have criterion, construct and content validity.
2. Measures should be reliable.
3. Tests should not interfere with the subject's treatment regimen or schedule.
4. Tests should not cause discomfort or fatigue.

The following measures and instruments were used:

Clinical measures:

1. Clinical history and examination
2. Disease stage: Hoehn and Yahr (HY) scale [Hoehn and Yahr 1967],
3. Disability or disease severity: Unified Parkinson's Disease Rating Scale (UPDRS) [Fahn, Elton et al. 1987]
4. Handicap: Schwab and England scale [England and Schwab 1956; Schwab and England 1969]
5. Assessment of cognition: Mini Mental State Examination (MMSE) [Folstein and Folstein 1975] and Frontal Assessment Battery (FAB)[Dubois, Slachevsky et al. 2000]

Measures of physiological function:

1. High and low-contrast visual acuity: Australian Vision Charts [Verbaken and Johnston 1986]
2. Visual contrast sensitivity: Melbourne Edge Test [Verbaken and Johnston 1986]
3. Proprioception: knee angle protractor [De Domenico and McCloskey 1987]
4. Peripheral light touch sensation: Semmes-Weinstein aesthesiometers [Semmes, Weinstein et al. 1960]
5. Isometric leg strength: Strain gauges [Lord, Clark et al. 1991]

6. Simple reaction time: finger-press and foot-press [Lord, Clark et al. 1991]
7. Postural stability: dorsal sway rod [Lord, Clark et al. 1991]
8. Dynamic postural stability: Coordinated Stability Test (CST) and maximal balance range test [Lord, Ward et al. 1996]
9. Gait analysis: accelerometers [Menz, Lord et al. 2003]

Counting the number of falls:

1. Monthly falls calendars and
2. Monthly telephone interviews.

3.2.1 Clinical measures

3.2.1.1 Clinical history and examination

All subjects had assessments performed when their antiparkinsonian medications were providing benefit (i.e. an 'on' state) typically in the mid morning as there is some evidence to imply that falls tend to occur when patients are most mobile and active (usually in the 'on' state) [Bloem, Grimbergen et al. 2001]. The clinical assessments usually took 25 minutes (range 20 to 52 minutes). No assessments caused discomfort or fatigue and all were completed before the effects of levodopa 'wore off'. Medical histories (including details of falls in the previous year) were taken using a standardized interview. Blood pressure was measured using a mercury sphygmomanometer

after 10 minutes of lying supine, immediately after rising unassisted to a standing position and again after three minutes of standing still.

The "Timed Up and Go" test (TUAG) [Mathias, Nayak et al. 1986] was used as a general indicator of the subject's mobility, measuring the time taken to rise from a seated position, walk three metres, turn 180 degrees, walk back to the seat and sit down. The number of steps taken to turn 180° from a stationary standing position was recorded.

3.2.1.2 Stage of Parkinson's disease

Since its introduction into the scientific literature in 1967, the Hoehn and Yahr (HY) scale has been the most commonly used method of quantifying the stage of Parkinson's disease [Hoehn and Yahr 1967] (appendix C). The clinical features used in the scale, such as unilateral or bilateral disease, presence or absence of postural instability and independence while walking, can be assessed by researchers with a high degree of inter-rater reliability [McRae, Diem et al. 2002].

3.2.1.3 Measures of disability

The first disability scale to be used in the literature was the Northwestern University Disability Scale (NUDS) [Canter, de la Torre et al. 1961] which

included items assessing ability to dress, attend to personal hygiene, speak and feed. Subsequent rating scales added items assessing bradykinesia, rigidity, posture, arm swing, gait, tremor [Webster 1968], salivation, postural instability and rapid movements of the fingers, hands and feet [Parkes, Calver et al. 1970; Duvoisin 1971]. Unfortunately, the reliability, validity and responsiveness of each of these scales were not adequately established[Clarke; Hobart, Lamping et al. 1996].

The Unified Parkinson's Disease Rating Scale (UPDRS) [Fahn, Elton et al. 1987] (appendix D) has become the standard clinician-rated measurement of disability in Parkinson's disease [Hobart, Lamping et al. 1996] and is the one used in my studies. It is divided into 4 sections covering cognition, mood, disability, motor function and complications of therapy. It includes an item addressing the presence of freezing of gait.

The UPDRS has shown high inter-observer reliability [Richards, Marder et al. 1994; Louis, Lynch et al. 1996], internal consistency and convergent validity [Martinez-Martin, Gil-Nagel et al. 1994]. When inter-rater reliability of the UPDRS motor examination was assessed by three experienced neurologists, intra-class correlation coefficients indicated high agreement for observations of timed movements, resting tremor, rising from a chair and gait pattern. There was moderate agreement for observations of action tremor, rigidity, posture, postural stability and bradykinesia, but poor agreement for speech impairment and facial immobility [Richards, Marder et al. 1994]. These results suggested

that satisfactory reliability can be obtained by the motor component of the UPDRS. These results were confirmed by a study in which 40 people with PD were simultaneously assessed by five raters who applied the UPDRS [Martinez-Martin, Gil-Nagel et al. 1994]. The inter-rater reliability was satisfactory (all the items had $k > 0.40$).

The inter-rater reliability between physician and patient in the historical section of the UPDRS was examined in a study of thirty consecutive subjects with idiopathic PD [Louis, Lynch et al. 1996]. Firstly, these subjects filled out the historical section of a modified UPDRS. This instrument was then administered again to the same subjects by a neurologist. The weighted kappa statistic for each of the 17 items in the historical section of the UPDRS ranged from 0.63 to 1.0, suggesting moderate to excellent agreement, with a total weighted kappa of 0.83 (95% confidence interval of 0.79 to 0.87). It was concluded that disability in non-demented PD patients can be assessed reliably by self-administering the historical section of the UPDRS. [Louis, Lynch et al. 1996].

In a validation study of the UPDRS [Martinez-Martin, Gil-Nagel et al. 1994], there was high internal consistency (Cronbach's alpha of 0.96). The UPDRS correlated well with the HY stage, some timed tests (finger tapping and standing from a seated position) and the Folstein Mini-Mental State Examination (MMSE) ($p < 0.001$). It had excellent convergent validity with

the Schwab and England Scale of disability ($p < 0.001$). These results suggest that the UPDRS has high validity as a measure of disability in PD.

The severity of dyskinesia was quantified by the Abnormal Involuntary Movement Scale [Guy 1976] (appendix H).

3.2.1.4 Measurements of handicap

The Schwab and England scale [England and Schwab 1956; Schwab and England 1969] (appendix E) assesses the patient's ability to perform activities of daily living in both "on" and "off" states, where 100% denotes normal ability and 0% complete dependence. Its validity and reliability has not been investigated thoroughly.

3.2.1.5 Assessment of Cognition

Two bedside tests of cognitive function were used. General cognitive function was assessed with the Mini Mental State Examination (MMSE) (appendix F), and cognitive impairment was defined as a MMSE [Folstein and Folstein 1975] score $\leq$27/30. Frontal lobe function was assessed with the Frontal Assessment Battery (FAB) and impairment defined as a score $\leq$ 17/18 [Dubois, Slachevsky et al. 2000]. The FAB tests domains of cognition not assessed by the MMSE, including conceptualisation, verbal fluency, motor programming, inhibitory control, environmental autonomy and sensitivity to

interference. It is an appropriate screening tool in the PD population as only one out of six items (i.e. the verbal fluency component) is timed and requires motor dexterity.

3.2.2 Tests of physiological function

Physiological functions in multiple domains were quantified using the Physiological Profiles Approach (PPA) [Lord, Menz et al. 2003], a battery of reliable measures that has been validated in prospective studies of older people [Lord, Clark et al. 1991; Lord, Clark et al. 1991; Lord, Clark et al. 1991; Lord, McLean et al. 1992; Lord, Sambrook et al. 1994; Lord, Ward et al. 1994]. The PPA battery was able to classify subjects into multiple faller (two or more falls) and non-multiple faller (less than two falls) groups with an accuracy of 75 to 79%. The reliability of the PPA will be the subject of chapter 4. The components of the PPA used in my studies are outlined below.

3.2.2.1 Visual acuity

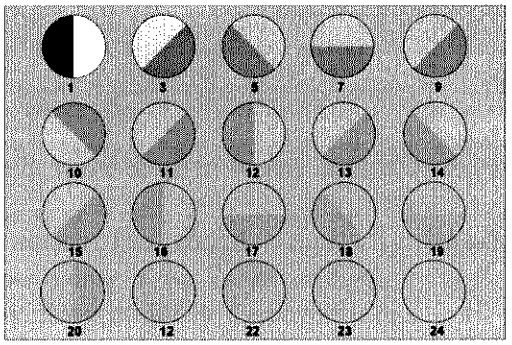
Visual acuity is measured using the Australian Vision Chart 5 letter chart with high- and low-contrast letters at a test distance of 3m [Verbaken and Johnston 1986]. The letters on the chart varied in size by 0.01 $\log_{10}$MAR units (fractions 6/5 to 6/6), 0.1 $\log_{10}$MAR units (Snellen fractions 6/6 to 6/15) and 0.3 $\log_{10}$MAR units (fractions 6/15 to 6/60) according to rows. Acuity is

assessed binocularly with subjects wearing their distance glasses (if applicable) at a test distance of 3 m and measured in terms of the minimum angle resolvable (MAR) in minutes of arc. Starting with the high-contrast chart, subjects are asked to read aloud the letters on the chart. The lowest line that could be read with no more than 2 errors and the corresponding score in minutes of arc (MAR) were recorded.

3.2.2.2 Visual contrast sensitivity

Edge contrast sensitivity was assessed using the Melbourne Edge Test [Verbaken and Johnston 1986] (fig.3.2) with subjects wearing near-vision spectacles whenever appropriate. The chart consisted of twenty 25 mm circles, each containing paler and darker halves. The contrast between darker and paler halves decreased progressively with each circle, making it gradually harder for the subject to discriminate the interface between the halves. The subject had to identify the interface (along a diameter) between the halves which was oriented in four alternative ways: horizontal, vertical, 45 degrees going up to the left, and 45 degrees going up to the right. The examiner noted the circle with the lowest contrast whose diameter the subject correctly identified. The corresponding number of the circle represented the subject's contrast sensitivity threshold in decibels.

Figure 3.2 **Melbourne Edge Test**

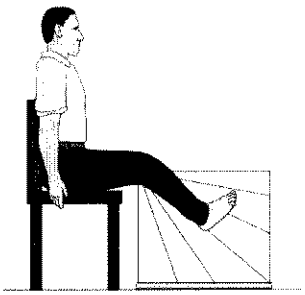


The numbers under the circles represent contrast between lighter and darker halves in decibels (dB).

3.2.2.3 Proprioception

Proprioception at the knee was measured using a lower limb-matching task with the subject seated [De Domenico and McCloskey 1987] (fig. 3.3). Discrepancies between referent and test legs in the angle of passive knee flexion were recorded using a large acrylic protractor placed between the legs.

Figure 3.3 **Proprioception test**

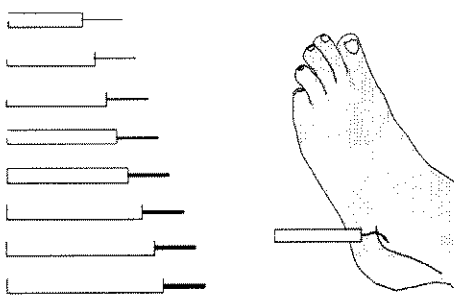


3.2.2.4 Light touch sensation

Tactile sensitivity was measured at the lateral malleolus using a Semmes-Weinstein aesthesiometer [Semmes, Weinstein et al. 1960] (fig. 3.4). This

instrument contained 8 nylon filaments of equal length, but varying in diameter. The force (in grams) required to bend each filament was calibrated and ranged from 4.5 mg (smallest diameter) to 447000 mg (thickest diameter). The filaments were applied to the centre of the lateral malleolus of the ankle. Filaments above the touch sensitivity threshold were applied initially, followed by progressively narrower ones until the subject could no longer detect their application. The examiner then applied progressively broader filaments until a filament was detected. The touch threshold (narrowest filament detected) was determined from a minimum of three ascending and descending steps. The pressure exerted by this filament was converted into milligrams.

Figure 3.4 **Semmes-Weinstein aesthesiometers**

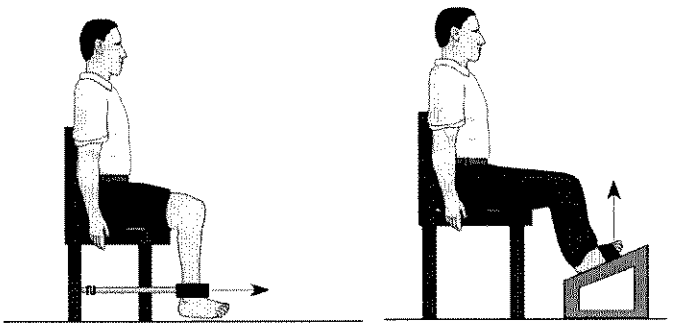


3.2.2.5 Leg strength

The average maximal voluntary strength of the knee extensor, knee flexor and ankle dorsiflexor muscle groups in the subjects' stronger and weaker legs was measured under isometric conditions in a seated position [Lord, Clark et al. 1991] (fig. 3.5). Knee extensor and flexor strength was measured using a

strain gauge attached to the subject's leg with a Velcro strap. The force of knee extension and flexion was measured with the subject sitting in a tall chair with a strap around the leg 10 cm above the ankle joint, and the hip and knee joint angles positioned at 90 degrees. In 3 trials per muscle group, the subject attempted to pull against the strain gauge assembly with maximal force for 2 to 3 seconds and the greatest force for each muscle group was recorded. Ankle dorsiflexion strength was measured using a footplate attached to a spring gauge. While the subject sat in a tall chair, the foot was secured to the footplate using a Velcro strap with the knee flexed approximately 70 degrees. In 3 trials, the subject attempted maximal dorsiflexion of the ankle, and the greatest force was recorded.

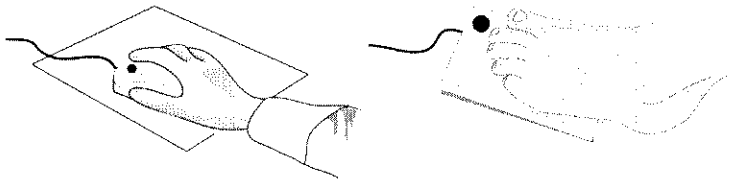
Figure 3.5 **Knee extension and ankle dorsiflexion strength tested with strain gauges**



3.2.2.6 Simple reaction time

Simple reaction time was assessed in milliseconds with subjects seated using a light as the stimulus and a finger-press or a foot-press as the response [Lord, Clark et al. 1991] (fig 3.6). Subjects had 5 practice trials and 10 test trials, and the average of the 10 test trials was the test measure.

Figure 3.6 **Tests of simple reaction times in the hand and foot**



3.2.2.7 Postural sway

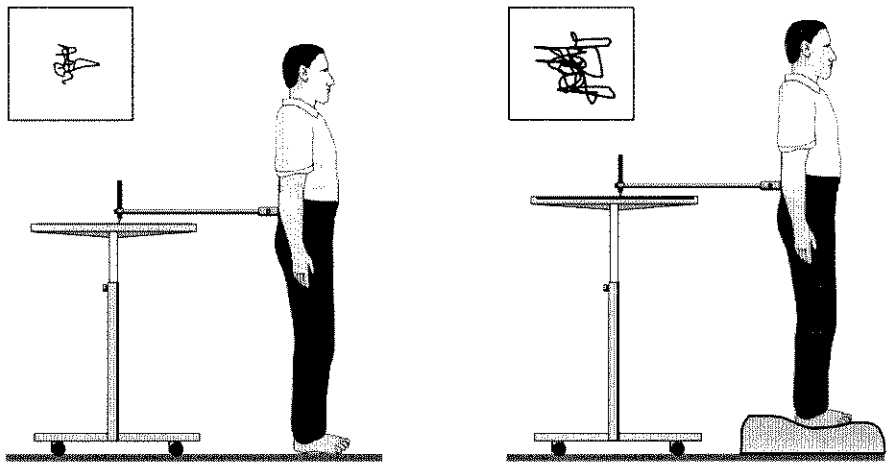
Postural sway was measured using a sway meter that measured displacement of the body at the level of the waist [Lord, Clark et al. 1991] (fig. 3.7) . The sway meter consisted of a pen on the end of a lightweight aluminium rod attached around the subject's waist at the level of the second lumbar vertebra by a Velcro belt. The pen traced the subject's sway pathway on 1 mm graph paper. Testing was performed with subjects standing on the floor and on a foam rubber mat (60cm x 60cm x 15cm thick) with eyes open and eyes closed. Each test trial lasted 60 seconds. A number of measures were obtained for each of the visual (eyes open or closed) and support surface (firm or compliant) conditions:

1. Anterior-posterior (A-P) sway: the displacement between anterior- and posterior-most points of the subject's sway pathway along the A-P axis;

2. Medial-lateral (M-L) sway: the displacement between the left and right-most points of the subject's sway pathway along the M-L axis; and

3. Sway distance: the total distance of the subject's sway pathway, measured by counting the number of 1 mm squares traversed by the pen on the sway meter.

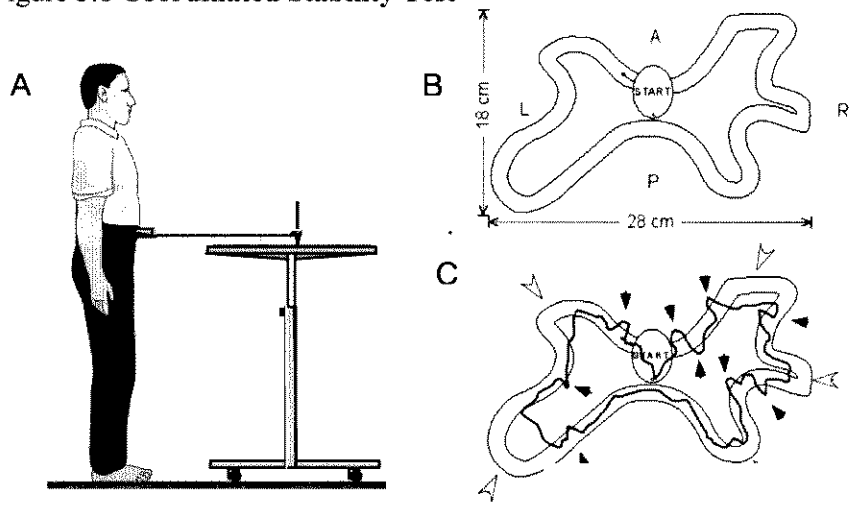
Figure 3.7 **Tests of sway on firm and compliant support surfaces**



3.2.2.8 Postural stability during tests of self-initiated movement

This was assessed using the coordinated stability test (CST) (fig. 3.8), a test that requires subjects to move their COG in a steady and coordinated manner when near the limits of their base of support, and the maximal A-P range test, a test measuring the total distance subjects could move their centre of gravity in the A-P plane without lifting their feet or toes off the ground [Lord, Ward et al. 1996]. In CST, the subject had to trace the pen on the end of the sway meter in an anticlockwise direction around a convoluted track but stay within the sides of the track. Each time the pen crossed an interior or exterior side of the track, the subject accrued one point. Each time the pen cut across a corner, the subject accrued five points. Higher scores were indicative of worse coordinated stability.

Figure 3.8 **Coordinated Stability Test**



A. Experimental set-up. B. Convoluted track (A anterior, P posterior, R right and L left). C. Example of a subject's performance. Here the subject has crossed the sides 9 times (black arrows) and cut all 5 corners (white arrows). The score was 34 (9 x 1 + 5 x 5).

In the maximal A-P range test, subjects were instructed to stand as straight as possible with the feet shoulder width apart. For the anterior component of the test, subjects were asked to lean forward as far as possible while keeping the back straight and the heels stationary on the ground. For the posterior component, subjects were asked to lean back as far as possible while keeping a straight back and the toes stationary on the ground. Three trials were performed for both the anterior and posterior components. The highest displacements moved by the rod in anterior and posterior directions were summed and recorded as the maximal A-P range.

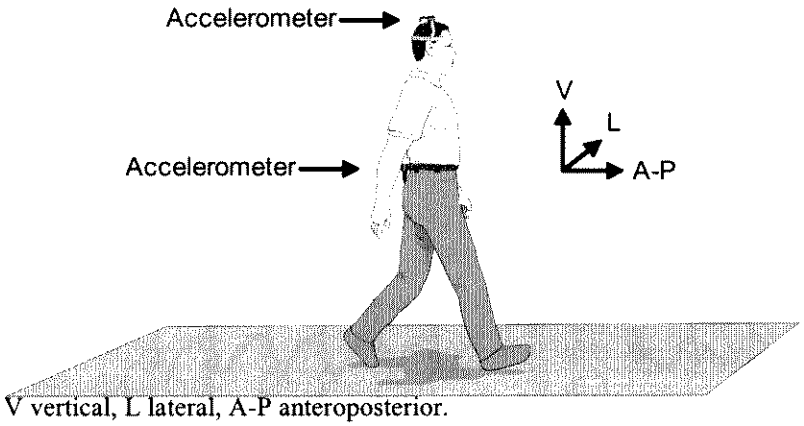
To determine whether subjects encroach upon their limits of stability when they stand with all sensory inputs present, we calculated the percentage of A-P sway (with eyes open on the floor) to the maximal A-P range.

3.2.2.9 Gait analysis

Quantitative gait analysis was performed using accelerometers. Details of the components, validity and test-retest reliability of this method have been described in the scientific literature [Menz, Lord et al. 2003].

Linear accelerations of the head and pelvis were measured along vertical, anterior-posterior (A-P) and lateral axes using piezoresistant accelerometers with ranges of -10 to +10 gravities (fig.3.9) and sampling frequencies of 200 Hz. While head and centre of gravity movements typically have angular components, linear accelerometers were chosen *a priori* as gait (walking forward) and avoiding falls (keeping the body upright against gravity) involve linear motion.

Figure 3.9 **Experimental set-up of accelerometers**

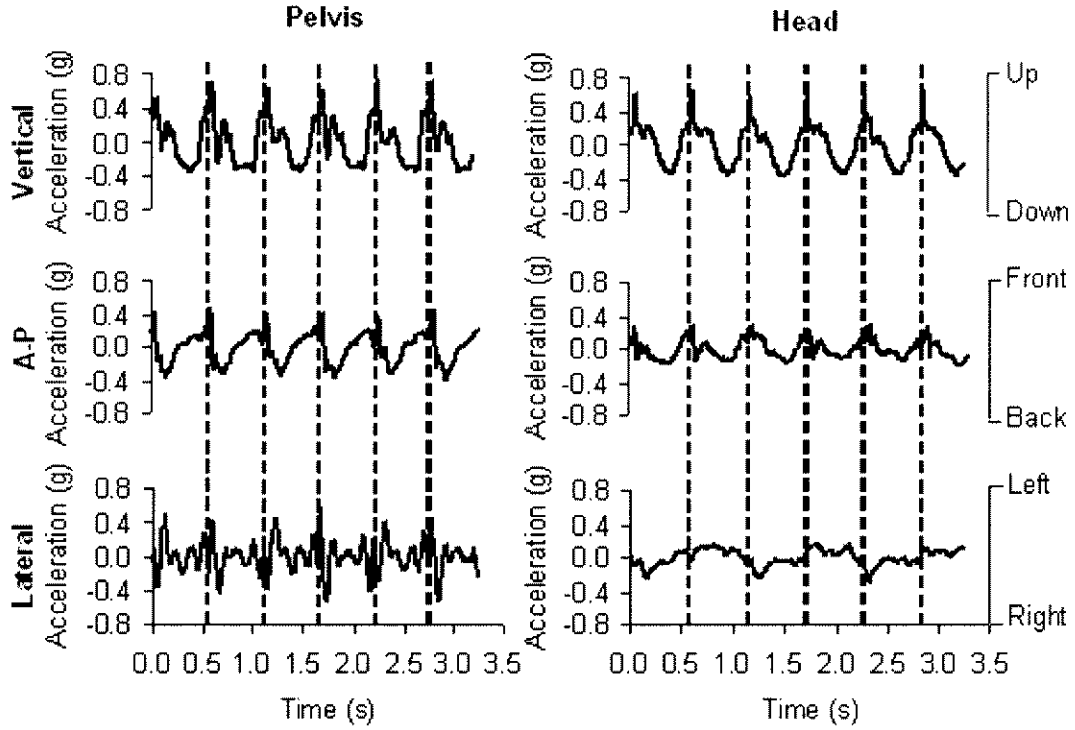


V vertical, L lateral, A-P anteroposterior.

The head accelerometer was attached firmly to the vertex using a light plastic frame. The pelvis accelerometer was attached to the back at the level of the second lumbar vertebral body using a Velcro™ belt. The accelerometers were wired to a lightweight laptop computer via a data acquisition card interface. The computer was carried by an assistant walking behind the subject during gait trials. All subjects wore comfortable, appropriately fitted, low-heeled walking shoes for all the trials. Gait trials were conducted along a smooth, horizontal 15 m length of the laboratory.

Before each testing session, the accelerometers were calibrated statically against gravity to estimate ± 1 g values. Head and pelvis accelerations for each walking trial were recorded at 200 Hz (fig. 3.10).

Figure 3.10 **Sample accelerometry tracings**



The mean vertical, A-P and lateral accelerations over the duration of each walking trial were assumed to be zero as the subjects were walking on a horizontal surface at a constant gait speed. The following variables were calculated:

(i) Average step length (cm), as measured by the instrumented walkway.

(ii) Cadence (steps/minute), calculated as the number of vertical pelvis acceleration peaks (heel strike transients) divided by the duration of the walking trial.

(iii) Gait speed (m/s), calculated as distance walked (10 m) divided by duration of the walking trial.

(iv) Step time coefficient of variation (CV), or the step-to-step variability in time between heel strike transients (step time standard deviation) expressed as a percentage of the mean step time over each walking trial.

(v) Acceleration root mean square (RMS), obtained from acceleration values sampled at 200 Hz and calculated as:

$$RMS = \sqrt{[(a_0^2 + a_1^2 + \ldots + a_n^2)/N]}$$

where a is the acceleration amplitude for each 0.005 s of the walking trial from time 0 s to time $0.005n$ s and N is the number of acceleration amplitudes recorded. The RMS was used to measure dispersion of acceleration values about zero.

(vi) Harmonic ratios (HR). The HR is a measure of the rhythm of acceleration patterns across a walking trial [Smidt, Arora et al. 1971; Yack and Berger 1993]. The acceleration signals of each stride were broken down into individual sinusoidal waveforms using Fourier transformations. Even harmonic waveforms were those that occurred twice or an even number of times in each stride. Odd harmonic waveforms occurred once or an odd number of times in each stride. In vertical and A-P planes, the HR was calculated as the sum of the amplitudes of even harmonic waveforms divided by the sum of the amplitudes of the odd harmonic waveforms.

$$HR = \Sigma \text{ Amplitudes of even harmonics} / \Sigma \text{ Amplitudes of odd harmonics}$$

The underlying premise of this measure is that bipedal gait involves two steps within a stride. In vertical and A-P planes, a stable rhythmic gait pattern should therefore consist of acceleration patterns that repeat in multiples of two within any given stride, as these patterns are in phase with heel strike, foot flat or toe-off and are resolved prior to taking subsequent strides. Accelerations patterns that do *not* repeat in multiples of two produce accelerations that are not resolved within each stride. In rhythmic bipedal gait, even harmonic waveforms should predominate and odd harmonic waveforms should be minimized in vertical and A-P planes.

The HR for lateral acceleration patterns is calculated differently to HRs for vertical and A-P patterns. This is because heel strike by any foot causes head and pelvic accelerations to the contralateral side, creating acceleration patterns that are monophasic in every stride [Menz, Lord et al. 2003]. Acceleration patterns in the lateral plane that occur an *even* number of times in any stride produce accelerations that are not resolved within that stride. The HR for the lateral plane is therefore calculated as:

$$HR = \Sigma \text{ Amplitudes of odd harmonics} / \Sigma \text{ Amplitudes of even harmonics}$$

The HR was chosen a priori as the main measure of head and pelvic rhythm, as higher HRs imply stable and regular acceleration patterns that are more in

phase with the subject's strides [Menz, Lord et al. 2003; Menz, Lord et al. 2003; Menz, Lord et al. 2004].

In one study in this thesis (Chapter 7), an instrumented walkway (the GAITRite® mat) was used in addition to the accelerometric equipment. The instrumented walkway was 460 cm long with an active area of 366 cm long by 61 cm wide, containing pressure sensors arranged in a grid pattern with a spatial resolution of 1.27 cm and a sampling frequency of 80 Hz.

3.2.3 Measurement of number of falls

The initial studies on falls were retrospective. Subjects were asked how many times they fell in the past 6 or 12 months. The major limitation of this approach is that subjects have difficult remembering their number of falls over long periods [Cummings, Nevitt et al. 1988]. The only feasible method of ascertaining falls is by the prospective approach and by asking subjects, their carers or their housemates to report on the number of falls. There are several methods available for the reporting of falls in prospective studies: monthly or bi-monthly mail-out questionnaires [Lord, Clark et al. 1991; Lord, Ward et al. 1994], weekly [Nevitt, Cummings et al. 1989], monthly falls calendars [Tinetti, Speechley et al. 1988] and monthly telephone interviews [O'Loughlin, Robitaille et al. 1993].

Each method has different effects on accuracy, compliance by the subjects and efficiency. Calendars and diaries allow subjects to indicate daily whether or not they have fallen. Telephone interviews often require many calls to contact active older people. Even with the most rigorous method of reporting, it is probable that falls are under-reported and described inaccurately. This could be due to denial, memory loss and distress on the part of some people who fall [Lord, Sherrington et al. 2001].

In the studies detailed in subsequent chapters, subjects were asked to document the number or falls on a daily basis in standardized diaries for twelve months. Subjects were also asked to record on a daily basis the number of near falls; injuries sustained during falls; and the number of episodes of gait freezing or start hesitation during the day. Subjects were asked to return the completed diaries by mail each month. To increase the accuracy of follow-up data, all subjects were also contacted by telephone each month for a structured interview to obtain or verify the above information.

CHAPTER 4

RELIABILITY OF MEASURES OF PHYSIOLOGICAL FUNCTION

4.1 INTRODUCTION

The battery of measures forming the Physiological Profiles Approach (PPA) have been used in studies of elderly people [Lord, Clark et al. 1991; Lord, Clark et al. 1991; Lord, Clark et al. 1991; Lord, McLean et al. 1992; Lord, Sambrook et al. 1994; Lord, Ward et al. 1994], but the reliability of only a few of these measures has been published in the medical literature [Anstey, Smith et al. 1997]. The reliability, especially the test-retest repeatability, is of fundamental importance as these instruments are used in the assessment of patients in both clinical and research settings. The measures need to be sensitive to real change in the subject's condition but resistant to measurement error. This study evaluates the test-retest reliability of these physiological measures.

Previous studies in the elderly population have used similar tests of visual acuity [Wildsoet, Wood et al.], visual contrast sensitivity [Haymes, Johnston et al.; Grey and Yap; Wood and Lovie-Kitchin; Wolffsohn and Cochrane] and peripheral sensation [Kumar, Fernando et al.; Nakazumi and Hamasaki;

Olmos, Cataland et al.; Perkins, Olaleye et al.; Sosenko, Sparling et al.; Pratorius, Kimmeskamp et al.] and identical tests of simple reaction time [Lord, Caplan et al. 1993; Lord, Caplan et al. 1993; Lord, Allen et al. 2002], postural sway and lower limb strength [Lord, Caplan et al. 1993; Lord, Caplan et al. 1993; Lord, Allen et al. 2002].

The PPA, however, has not been used, nor its reliability and validity tested previously in a sample of subjects with PD. While subsequent chapters assess the validity of the PPA in predicting falls in subjects with PD, this chapter examines its test-retest reliability in a sample of elderly subjects.

4.2 METHODS

4.2.1 Subjects

A sample of 30 elderly subjects (13 males and 17 females) aged between 76 and 87 years (mean 81, S.D. 3.1), with heights between 149 and 185 cm (mean 165, S.D. 9.8) and weights ranging from 45 to 104 kg (mean 69, S.D. 13.6) was recruited from the volunteer database of the Prince of Wales Medical Research Institute after informed consent was obtained. All subjects were free of medical conditions that would contraindicate any of the tests. The Human

Studies Ethics Committee at the University of New South Wales gave approval for the study.

4.2.2 Apparatus

The equipment used in this study have been described in more detail in previous studies [Lord, Clark et al. 1991; Lord, Clark et al. 1991; Lord, Clark et al. 1991; Lord, Caplan et al. 1993; Lord and Clark 1996; Lord, Menz et al. 2003] and in the preceding chapter.

High- and low-contrast acuity was measured with the Australian Vision Chart 5 [Verbaken and Johnston 1986]. Contrast sensitivity was assessed using the Melbourne Edge Test [Verbaken and Johnston 1986]. Light touch sensation thresholds were measured at the ankle with a selection of eight Semmes-Weinstein pressure aesthesiometers [Semmes, Weinstein et al. 1960] ranging from 0.0045 to 447 g. Proprioception was measured using the technique described by De Domenico and colleagues (1987) [De Domenico and McCloskey 1987]. The strength of knee flexion and extension and ankle dorsiflexion was measured using strain gauges. Reaction time was assessed by a simple reaction time task, using a light as the stimulus and depression of a switch by the hand or the foot as the response. Body sway was measured with the subject standing firstly on a firm surface (the linoleum-covered floor) with the eyes open and then with the eyes closed and secondly on a compliant

surface (a 10 cm-high rectangle of foam, 40 x 40 cm wide) with the eyes open and then closed. Each test of postural sway was performed once and lasted for 30 s. Subjects were instructed to stand as still as possible looking at a point on the wall straight ahead. The Coordinated Stability Task measured each subject's ability to adjust balance in a steady and controlled way while placing them near or at the limits of their equilibrium.

4.2.3 Procedure

Each subject had all tests at their first session and repeated 2 weeks later at approximately the same time of the day by the same investigator. All subjects underwent a structured interview to exclude any change in their clinical status from one session to the next.

4.2.4 Statistics

All data were examined for outliers and normality using stem and leaf plots. Outliers were included in the reliability analyses as they all had physiologically plausible values and were not the result of instrument or observer error. The skewness statistic was used to confirm normality. Variables with non-parametric distributions were log 10 transformed to fit a Gaussian pattern. Paired *t*-tests were performed to test for any significant

differences between test and retest results. Intra-class correlation coefficients (ICC) of the type (1,1) (one-way random model) were then used to evaluate the test-retest repeatability of each measurement between the two sessions. ICCs greater than 0.75 suggest excellent repeatability, 0.40 to 0.75 fair-to-good repeatability and less than 0.40 poor repeatability for any particular measure.

The degree of agreement between test and retest measurements was further assessed by determining the coefficient of variation (CV) of the method error (ME) and the limits of agreement (LoA) [Bland and Altman 1986]. For each of the measures, a plot was performed to exclude any relationship between the difference and the mean of test and retest values. Histograms of differences between test and retest measurements were performed to check for a normal distribution.

LoA for each of the measures were calculated to determine the interval between which 95% of the differences would lie, using the mean difference ($\bar{d}$) and the standard deviation (s) of the differences between test and retest scores:

$$\text{LoA} = \bar{d} \pm 2s$$

The method error was calculated as:

$ME = s/\sqrt{2}$

The method error was used to determine the CV using the following equation (where x_1 and x_2 are means of test and retest scores respectively):

$CV = (2ME \times 100)/(x_1 + x_2)$

The CV reflects the amount of variation in the difference between test and retest scores.

4.3 RESULTS

There were significant differences ($p < 0.05$) between test and retest values only for measures of proprioception and coordinated stability. Test and retest reliability data for each of the measures are shown in tables 4.1 to 4.3.

Table 4.1 **Test-retest reliability of measures**

Variable	Mean (95% CI)	Difference (95% CI)	LoA	ICC (95% CI)	CV (%)
High contrast (MAR)	1.16 (0.96-1.37)	0.02 (-0.13-0.17)	-0.77-0.81	0.82 (0.67-0.91)	24.8
Low contrast (MAR)	2.08 (1.69-2.47)	0.06 (-0.20-0.32)	-1.33-1.44	0.81 (0.65-0.90)	24.4
MET (Db)	19.6 (18.8-20.3)	0.1 (-0.6-0.8)	-3.7-3.9	0.62 (0.35-0.80)	6.9
Hand reaction (ms)	242 (231-253)	5 (-3-13)	-38-47	0.69 (0.45-0.84)	6.4
Foot reaction (ms)	284 (272-297)	1 (-7-9)	-42-45	0.79 (0.61-0.89)	5.5
Touch (log_{10}0.1mg)	4.3 (4.2-4.4)	0.0 (-0.1-0.2)	-0.8-0.9	0.40 (0.06-0.66)	7.4
Proprioception (°)*	2 (1-2)	0 (-1-0)	1.4-2.1	0.12 (-.24-0.45)	45.9
Coordinated stability *	4.6 (2.5-6.6)	1.3 (0.3-2.2)	-3.8-6.3	0.64 (0.26-0.83)	46.0

LoA limits of agreement; ICC intra-class correlation coefficient, CV coefficient of variation of the method error, MAR minutes of arc, MET Melbourne Edge Test

* significant difference between test and retest values at $p < 0.05$.

Table 4.2 **Test-retest reliability for tests of sway**

Plane	Surface	Eyes	Mean (95% CI)	Difference (95% CI)	LoA	ICC (95% CI)	CV
AP	Firm	O	19 (16-21)	-1 (-4-2)	-18-16	0.40 (0.06-0.65)	31.2
Lat	Firm	O	15 (11-18)	1 (-4-6)	-26-27	0.28 (-0.08-0.57)	67.2
Total	Firm	O	301 (184-418)	-10 (-137-117)	-690-670	0.46 (0.13-0.69)	80.1
AP	Firm	C	27 (22-31)	3 (-2-7)	-20-25	0.53 (0.23-0.74)	32.3
Lat	Firm	C	17 (13-21)	2 (-3-7)	-24-29	0.26 (-0.10-0.56)	59.0
Total	Firm	C	504 (341-668)	111 (-67-288)	-839-1060	0.44 (0.11-0.69)	76.3
AP	Compl	O	25 (22-28)	-4 (-9-1)	-31-22	0.19 (-0.17-0.50)	34.9
Lat	Compl	O	21 (17-26)	-5 (-12-1)	-40-29	0.20 (-0.16-0.51)	51.8
Total	Compl	O	568 (404-732)	-246 (-459--33)	-1382-890	0.38 (-0.03-0.64)	59.0
AP	Compl	C	61 (53-68)	-1 (-8-6)	-38-36	0.70 (0.47-0.84)	21.8
Lat	Compl	C	48 (40-57)	0 (-8-9)	-45-45	0.44 (0.12-0.69)	33.7
Total	Compl	C	3111 (2352-3870)	-129 (-859-601)	-4030-3772	0.68 (0.43-0.83)	44.3

AP anterior-posterior, Lat medial-lateral, Compl Compliant, CI confidence interval, LoA limits of agreement, ICC Intra-class correlation coefficient, CV coefficient of variation of the method error

Table 4.3 **Test-retest reliability for tests of strength**

Strength (kg)	Mean (95% CI)	Difference (95% CI)	LoA	ICC (95% CI)	CV
Ankle dorsiflexion	11.8 (10.1-13.5)	-0.8 (-1.7-0.1)	-5.6-4.0	0.87 (0.75-0.93)	14.3
Knee extension	30.8 (25.1-36.5)	0.5 (-0.9-2.0)	-7.2-8.2	0.97 (0.93-0.98)	9.1
Knee flexion	15.7 (13.5-18.0)	-0.8 (-2.0-0.3)	-7.1-5.4	0.88 (0.76-0.94)	13.9

CI confidence interval, LoA limits of agreement, ICC Intra-class correlation coefficient, CV coefficient of variation of the method error

In spite of the high ICCs, tests of visual acuity had wide LoA (the high contrast visual acuity on retest for any particular subject differed from the initial measurement by between 0.77 MAR lower to 0.81 MAR higher) and high CVs (24.8% variability between test and retest). In contrast, tests of visual contrast sensitivity and light touch had lower ICCs (0.62 and 0.40 respectively) but narrow LoA (-3.7 to 3.9 and –0.8 to 0.9) and low CVs (6.9 and 7.4).

Hand and foot reaction times had high ICCs (0.69 and 0.79 respectively) as well as low CVs (6.4 and 5.5%) and narrow, clinically insignificant LoA (-38 to 47 and –42 to 45 ms).

Measures of postural sway (table 4.2) had variable ICCs, ranging from poor for medial-lateral sway on a compliant surface with eyes open (0.20) to good for anterior-posterior sway on a compliant surface with the eyes closed (0.70). The CVs however were large and the LoA wide for all these measures.

The best test-retest reliability was seen in tests of lower limb strength, which had excellent ICCs (87 to 97), moderately low CVs (9.1-14.3%) and narrow LoA (-5.6 to 4.0 and -7.2 to 8.2).

4.4 DISCUSSION

The most reliable measures examined were those of leg strength (table 4.3), shown by relatively narrow LoAs, small CVs and ICCs. Measures of simple reaction time were the next most reliable (table 4.1). The least reliable measures were those of coordinated stability (CST) and proprioception, demonstrating significant differences ($p < 0.05$) between test and retest values (table 4.1) and high CVs. Measures of postural sway, in general, were unreliable.

Reliability, or test-retest repeatability, is essential for tests that will be applied to subjects in a clinical or research setting. A high reliability improves the likelihood that any change in test results between one time and the next is due to change in the ability of the subject, rather than observer or instrument error. For all subjects, there was an approximately 2-week interval between one session and the next. This interval was chosen a priori as a compromise between a sufficient duration of time to prevent practice effects between sessions 1 and 2 and a minimal duration to avoid substantial changes due age or alteration in health. This assumption appears to hold in this study as almost

all of the measures (apart from proprioception and coordinated stability) lacked statistically significant improvement or deterioration and all lacked clinically significant change on average.

In this study, we have used a number of statistical tests to examine the reliability of the physiological measures. ICCs were used to assess consistency between test and retest measurements. On its own, the ICC can be misleading, as it is strongly influenced by the range of scores in test and retest measurements. If there is a very wide range of scores, clinically important intra-subject differences between test and retest will not be reflected by the ICC.

The coefficient of variation of the method error provides a relative measure of repeatability between test and retest scores and is not affected by a wide range of scores in the sample. However, this statistic does not express in absolute terms the amount of variability that can be expected between test and retest.

Bland and Altman (1986) [Bland and Altman 1986] described the LoA as absolute estimates of inter-instrument or test-retest reliability. The LoA have been used in this study, in preference to the more traditional intra-class and Pearson correlation coefficients, as the most appropriate expression of reliability. The advantage of the LoA is their description of the range of values in absolute terms within which 95% of retest results will lie. If the limits of agreement are both narrow and clinically insignificant, then the measure

shows good reliability. For example, measures of knee extension strength showed good reliability, with narrow LoA – there was a 95% chance that the repeat measurement of knee extension strength would be at most 7.2 kg lower or 8.2 kg higher than the initial measurement. Knee extension strength also had a low CV and a high ICC, providing further confirmation of the reliability of this measure.

Anstey and colleagues (1997) [Anstey, Smith et al. 1997] examined the test-retest reliability of similar tests of visual acuity, vibration sense, proprioception and postural sway using correlation coefficients. They too found better correlation between test and retest for measurement of visual acuity (r = 0.82) than for measurement of proprioception (between 0.30 to 0.61). The correlation coefficients for tests of sway on a firm surface with the eyes open were variable (r = 0.55 for anterior-posterior sway and 0.81 for total sway distance). Although these results are similar to the findings of the present study, direct comparisons are difficult as the earlier study did not calculate CVs or LoA.

Both studies suggest problems with our current methods of measuring postural sway and proprioception. Many authors have outlined the importance of postural set when examining body sway [Schieppati and Nardone 1991; Chong, Jones et al. 1999]. The instructions "look straight ahead and stand as still as possible" may be interpreted in many different ways by different subjects. The same subject may use different sensory, muscular and

mechanical sets each time to carry out this instruction, resulting in differences between test and retest in sway pattern. One way to improve the reliability of this test may be to take the average measurement of several sway trials, where subjects might use their full range of postural sets, for both test and retest sessions. The increased reliability would come at the price of increased duration of the session, fatigue of the subject and work by the investigator.

Tests of proprioception required the subject to extend both knees and position the left and right first metatarso-phalangeal joints at the same position on either side of a clear 1 cm thick Perspex sheet. Differences in the angle of knee flexion between one leg and the other could only be measured to a resolution of $\pm$ 1°. Even slight differences in the position of the Perspex sheet or amount of knee flexion between one session and the next could have led to differences between test and retest results. The reliability of this test could potentially be improved by using passive movements of the subject's legs, with one side being the referent limb.

Variation in the subject's attention influences test reliability in experimental and clinical settings [Fagius and Wahren 1981]. Attention can be affected by motivation, level of distraction, fatigue and psychological stress, all of which can vary from one session to the next. Variation in attention may explain the poor reliability of the coordinated stability task, which differed significantly in average score ($p < 0.05$) between test and retest. This task required more concentration and physical exertion by subjects than some of the other tests, as

it attempted to push them to the limits of their stability. The coordinated stability test is also prone to a learning effect, which could explain the significantly better (lower) scores on retesting.

Morgan and Fevens found a high reliability coefficient (0.93) for measures of visual acuity [Morgan and Fevens 1972.]. Our study had similarly high ICCs for both high- and low-contrast visual acuity (0.82 and 0.81 respectively). Both measures had unacceptably wide limits of agreement (-0.77 to 0.81 and –1.33 to 1.44 MAR) and high CVs (24.8 and 24.4), suggesting sub-optimal reliability. There are several possible reasons for the variability from one session to the next. The vision chart used in our study features many different letters of the alphabet, some of which may be easier to identify than others. An "unlucky error" or a "lucky guess" of a single letter may change the subject's score by as little as 0.03 to as much as 1.0 MAR. In addition, changes in attention between one session and the next could alter the scores considerably.

In our study, measures of leg strength and simple reaction time appeared to have the best reliability, evinced by higher ICCs, lower CVs and narrower LoA. For the tests of strength, subjects were asked to push or pull as hard as possible. Only the maximum strength, not the average of several trials, was recorded in order to eliminate the effects of muscle fatigue and practice from repeated measurements. This procedure is advantageous only for tests and in circumstances where it is safe and possible for subjects to be pushed to their limits. In the tests of simple hand and foot reaction time, subjects were

allowed practice trials to familiarize themselves with the task, as well as several experimental trials. The results of the experimental trials were averaged to reduce the influence of "luck" in this measure.

The results of this reliability study need to be interpreted with caution. The sample size of 30 was decided upon ad hoc as the minimum number that would enable parametric statistical analyses. A larger sample size might have resulted in a more homogeneous sample and hence more appropriate ICCs, CVs and LoA.

Given their lack of test-retest repeatability in an elderly population, can the measures of proprioception, coordinated stability and sway be justified in a population of PD patients? Most of these measures test several cognitive and physiological functions. For example, the proprioception test is influenced by attention, leg strength and joint stiffness. The coordinated stability task assesses attention, executive function, leg strength, vision, trunk coordination and sway. Proprioception is also likely to be an important component of this test. It is not inconceivable that the session-to-session variability reflected substantial changes in these physiological functions or their interactions over the two-week interval. For each instrument, several measurements conducted over the course of a typical day or week would provide a more robust, but less time efficient, assessment of physiological function than a single measurement. The subject's worst performance on each of these instruments may have a higher correlation with falling than a single measurement. The

question that will be asked in subsequent studies is whether these tests can identify PD patients who are likely to fall in the future, even though performance in the tests fluctuates over time.

Although not ideal, there are several reasons why this reliability study was performed using a sample of healthy older people rather than PD patients. In PD patients, there is considerable intra-subject variability in test performance secondary to phase of antiparkinsonian medication cycle. For example, PD patients perform differently at times of the day when their symptoms are controlled by levodopa ("on" phase) compared to times when the effects of levodopa are waning ("off" phase). Repeating the test at the same time of the day does not eliminate these problems, as there is considerable variability in the effects of the "on" phase (ie. "typical on" versus "best on") and the severity of the "off" phase (ie. "typical" versus "worst off"). In other words, performance differences between initial and repeat tests could reflect real changes in function rather than a lack of reliability.

4.5 CONCLUSION

This study illustrates the high test-retest reliability of the measures of lower limb strength and simple reaction time, the moderate reliability of visual contrast sensitivity and light touch, the low reliability of visual acuity, stereoscopic depth perception and vibration and the poor reliability of postural

sway, coordinated stability and proprioception. The results of this study need to be interpreted with caution as the variability in some measures between test and retest may reflect real change in the subject's condition.

CHAPTER 5

POSTURAL STABILITY AND TESTS OF SWAY IN PD

5.1 INTRODUCTION

Impaired balance, or postural instability, is a disabling complication of Parkinson's disease (PD) [Koller, Glatt et al. 1989; Rogers 1996; Sato, Kaji et al. 2001; Schrag, Ben-Shlomo et al. 2002; Wood, Bilclough et al. 2002]. Its pathophysiology and response to treatment have received considerable attention in the scientific literature, although several fundamental issues remain unresolved:

(1) How does PD affect postural sway? Investigators have found that sway in PD can be decreased [Dietz, Berger et al. 1988; Horak, Nutt et al. 1992], increased [Schieppati and Nardone 1991; Waterston, Hawken et al. 1993; Schieppati, Hugon et al. 1994; Rocchi, Chiari et al. 2002; Viitasalo, Kampman et al. 2002; Maurer, Mergner et al. 2003] or normal [Bronstein, Hood et al. 1990; Chong, Horak et al. 1999], depending upon measure of sway, sensory modifications, support surface, selection of patients with PD and healthy controls and timing of investigations with respect to antiparkinsonian therapy.
(2) In PD, can postural stability be maintained across a range of visual input/support surface conditions? A number of studies have examined whether

PD patients can maintain balance by distinguishing useful sensory inputs from those that have been tampered with experimentally and are potentially destabilizing. Bronstein and colleagues (1990) [Bronstein, Hood et al. 1990] found that PD patients had normal sway when standing with their eyes open or closed but that sway increased to a greater extent in these patients compared with controls when the visual field was moved laterally. This implied that PD patients have difficulty minimizing their dependence upon destabilizing visual stimuli. Abnormalities of sensorimotor integration were suggested by other studies that found that PD patients had worse postural stability when relying predominantly on vestibular inputs, such as when standing with eyes closed on a surface that rotated about the axis of the ankle joints [Bronte-Stewart, Minn et al. 2002] or when the visual field tilted to the same extent as the support surface [Maurer, Mergner et al. 2003]. In contrast, other investigators have found no abnormalities of sensory integration in similar conditions where sensory inputs conflict [Horak, Nutt et al. 1992; Waterston, Hawken et al. 1993; Chong, Horak et al. 1999]. To address these issues, we examined differences between PD patients and healthy age- and sex-matched controls in measures of postural sway in a range of sensory conditions: usual conditions, visual inputs removed by blindfolding, somatosensory inputs from the legs modified by standing on a compliant surface, and vision removed and somatosensory inputs modified. We used a pen-and-paper sway meter that traced movements of the body at the level of the second lumbar vertebra.

(3) Do patients with PD perform appropriately in tasks that require leaning or inclining postures? This aspect of postural stability is important as the purpose

of postural stability is to enable activities of daily living, such as grooming, food preparation and mobilization, which require controlled movements of the body segments and COG. Even when standing with their usual posture, people with severe PD tended to lean forwards, with their centre of foot pressure lying anterior to that of healthy controls [Schieppati and Nardone 1991]. When PD patients attempted to lean as far possible in forward and backward directions, they were unable to displace their centre of foot pressure as far as young subjects or elderly controls [Schieppati, Hugon et al. 1994]. To examine how anterior and posterior limits of stability are changed by PD, subjects were required to move the sway meter as far forwards and backwards as possible without bending the back or taking the heels and toes off the ground. In addition we investigated control of the COG movements at or near the limits of stability using a visual feedback task [Lord, Menz et al. 2003].

(4) How does levodopa affect stability in usual standing conditions, situations where sensory inputs are modified and tasks requiring controlled movements of the COG? There have been a number of studies examining the effects of levodopa and neurosurgery on postural sway, suggesting that levodopa tends to reduce sway following unilateral pallidotomy [Bronte-Stewart, Minn et al. 2002] but increase sway following the insertion of subthalamic [Rocchi, Chiari et al. 2002; Maurer, Mergner et al. 2003; Rocchi, Chiari et al. 2004] or globus pallidus internus stimulators [Rocchi, Chiari et al. 2002; Rocchi, Chiari et al. 2004], when the stimulators are turned off. When the stimulators are turned on, levodopa either increases postural sway further [Maurer, Mergner et al. 2003] or fails to reduce sway to levels experienced when stimulators are

used alone or when patients are 'off' both stimulation and levodopa. These studies, however, tended to use doses of levodopa that were much lower than the doses patients used prior to surgery and may not reflect accurately the influence of levodopa on postural sway. The effects of levodopa alone on postural stability has been less extensively examined in the scientific literature. Horak and colleagues (1992) [Horak, Nutt et al. 1992] found that levodopa therapy did not improve postural stability or anticipatory postural adjustments even though it improved the coordination of muscle activation in response to backward support surface translations. Similarly, Bloem and colleagues (1996) [Bloem, Beckley et al. 1996] found that backwards sway of the centre of foot pressure and COG in response to toe-up surface rotations was not improved by levodopa therapy, even though therapy reduced the magnitude of destabilizing medium latency responses. Other investigators have found that levodopa did not improve the ability of patients to adapt their response to external perturbations, such as resisting or yielding to surface movements [Chong, Horak et al. 2000], or internally-generated perturbations, such as rise-to-toes movements [Frank, Horak et al. 2000]. In order to assess the effects of levodopa on PD, we performed sway measurements in both 'on' and 'off' conditions on a sample of patients with mild to moderate PD (Hoehn and Yahr stages I to III) that did not require neurosurgical treatment.

5.2 METHODS

5.2.1 Subjects

Thirty subjects with PD as defined by the UKPDBB criteria [Hughes, Ben-Shlomo et al. 1992] (age 67 ± 95% confidence interval 4 years, 14 male, height 170 ± 8 cm, and leg length 86 ± 1 cm) were matched 1:1 for age, gender and leg length with thirty healthy controls from a database of volunteers at the Prince of Wales Medical Research Institute (table 5.1).

Table 5.1 **PD subjects and controls**

Factor	**Control** (n=28)	**PD** (n=28)
Duration of PD (years)	0	10 (6-13)
Age (years)	69 ± 4	67 ± 4
Male:female ratio	1:1	1:1
Height (cm)	169 ± 3	170 ± 3
Leg length (cm)	85 ± 1	86 ± 1
Weight (kg)	69 ± 5	70 ± 4
Levodopa (short-acting)		
Number of subjects		28
Dose (mg)		400 (300-1000)
Levodopa (slow-release)		
Number of subjects		3
Dose (mg)		200 (200 – 400)
COMT[‡] inhibitor		
Number of subjects		5
Dose (mg)		600 (600 – 1000)
Cabergoline		
Number of subjects		3
Dose (mg)		3.5 (2-5)

Values are presented as means ± 95% confidence intervals or medians (with inter-quartile ranges).

All patients were free of truncal dyskinesia, leg dyskinesia and leg tremor on clinical examination in both 'on' and 'off' phases of levodopa therapy. Patients and controls were free on history, clinical examination and review of medical files of other neurological, muscular-skeletal disorders that could affect their standing balance and were not taking antihypertensive, antiarrhythmic, antidepressant or psychoactive medications. Patients had normal scores on Folstein Mini-Mental State Examination (30/30) [Folstein and Folstein 1975] and the Frontal Assessment Battery (18/18) [Dubois, Slachevsky et al. 2000]. In addition, all subjects had normal leg strength, proprioception at the first metatarso-phalangeal joint, vestibular ocular reflexes and negative Unterberger's sign on clinical examination.

In patients, the severity of PD was assessed by the Unified Parkinson's Disease Rating Scale [Fahn, Elton et al. 1987], the stage of disease was rated by the Hoehn and Yahr scale [Hoehn and Yahr 1967] and the severity of dyskinesia was quantified by the Abnormal Involuntary Movement Scale [Guy 1976]. The protocol was approved by the Human Studies Ethics Committees at the University of Sydney and the University of New South Wales and informed consent was obtained from all subjects.

5.2.2 Measures of posture, rigidity, strength, reaction time, light touch sensation and proprioception

Posture was evaluated using the posture item of the UPDRS (0 = normal, 1 = slightly stooped, 2 = moderately stooped or leaning to one side, 3 = severely stooped or moderately leaning to one side and 4 = marked flexion with extreme abnormality of posture). Rigidity in the lower legs was quantified using a scale similar to the rigidity item of the UPDRS (0 = no leg rigidity, 1 = slight rigidity in any leg or rigidity detectable by contralateral movements, 2 = mild to moderate rigidity, 3 = marked rigidity in any leg but full range of movement easily achieved and 4 = severe rigidity in any leg with full range of motion achieved with difficulty).

The strength of knee flexion and extension and ankle dorsiflexion was measured in both legs using strain gauges while subjects were seated. For each movement, three trials were performed on both legs as the subject was instructed to "move as strongly as possible". The highest measurement of each of the three trials was recorded for each leg. Only the strength of the weaker leg was included in statistical analyses.

Reaction time in both legs was assessed by a simple reaction time task, using a light as the stimulus and depression of a switch by the hand or the foot as the response. For each leg, subjects were allowed 5 practice trials prior to 10

recorded trials. The average of the recorded trials was calculated for each leg. Only the reaction time of the slower leg was included in statistical analyses.

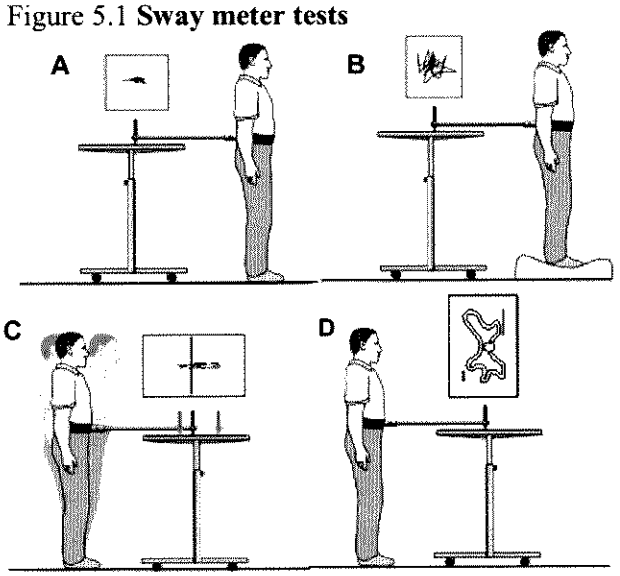
Light touch sensation thresholds were measured at the ankle with a selection of eight Semmes-Weinstein pressure aesthesiometers [Semmes, Weinstein et al. 1960] ranging from 0.0045 to 447 g, applied in order of heaviest to lightest to the centre of the right lateral malleolus until a threshold of sensation was reached. Proprioception was measured by asking blindfolded, seated subjects to align their lower limbs simultaneously on either side of a vertical acrylic sheet placed between their legs [De Domenico and McCloskey 1987]. This sheet had 2-degree protractor markings on either side, with the focal point placed in between the knees. Each subject had two practice trials and 6 experimental trials across a 90-degree range of ankle flexion. The average of the 6 experimental trials was calculated.

5.2.3 Tests of postural stability

The order of all sway tests was the same for all subjects. Subjects removed their shoes and socks for the tests and were allowed to rest between trials. Postural sway was measured using a lightweight aluminium rod, attached horizontally and dorsally at the level of the second lumbar vertebra (L2) via a Velcro belt. The extremity of the rod held a pen that traced the sway pathway onto 1 mm graph paper. Testing was performed with the subject standing

firstly on a non-compliant surface (the linoleum-covered floor) (fig. 5.1A) with the eyes open and then with the eyes closed and secondly on a compliant surface (a 10 cm-high rectangle of foam, 40 x 40 cm wide) (fig. 5.1B) with the eyes open and then closed.

Figure 5.1 **Sway meter tests**



(A) Postural sway on the firm surface (floor). (B) Postural sway on the compliant surface (40 x 40 x 10 cm foam). (C) Maximal anterior-posterior (A-P) range and (D) coordinated stability task. Insets show typical sway trajectories (A and B), maximal A-P range (C) and track for coordinated stability task (D).

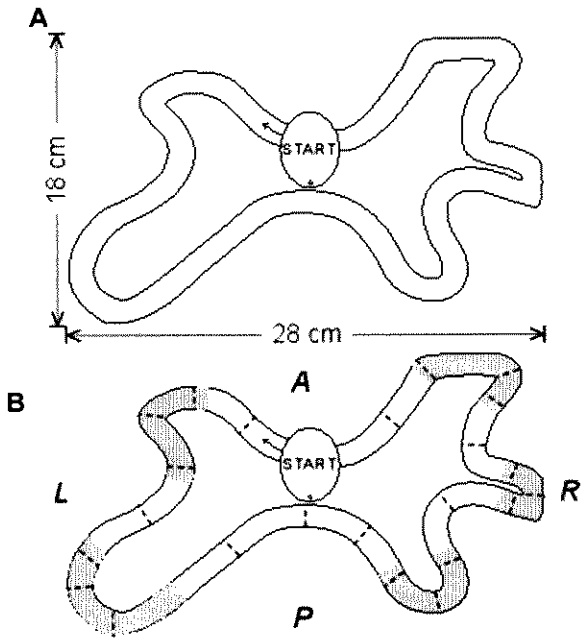
These visual and support surface constraints were used to assess the subject's postural stability in the following sensory conditions: (1) with all sensory inputs present, (2) with vision absent, (3) with leg somatosensory inputs modified and (3) with vision absent and leg somatosensory inputs modified. Each test of postural sway was performed lasted 30 s. Subjects were instructed to stand as still as possible, with feet shoulder width apart, looking at a point on the wall horizontally in front. For each of these tests, the investigator recorded the distance along the A-P axis between the most anterior and posterior points of the sway trajectory.

Limits of stability and control of COG movement were then assessed using the maximal A-P range test (fig. 5.1C) and the coordinated stability task (fig. 5.1D). For these tests, subjects wore the rod on the ventral aspect at the L2

level. The table was placed in front of the subject and its height was adjusted so that the rod of the sway meter could remain horizontal while the pen marked movements of the body at the L2 level. The maximal A-P range tests were used to determine how far subjects could move their COG in anterior and posterior directions without lifting the toes or the heels off the floor. Subjects were instructed to stand as straight as possible with the feet shoulder width apart. For the anterior component of the test, subjects were asked to lean forward as far as possible while keeping the back straight and the heels stationary on the ground. For the posterior component, subjects were asked to lean back as far as possible while keeping a straight back and the toes stationary on the ground. Three trials were performed for both the anterior and posterior components. The highest distances moved by the rod in anterior and posterior directions were summed and recorded as the maximal A-P range. To determine whether subjects encroach upon their limits of stability when they stand with all sensory inputs present, we calculated the percentage of A-P sway (with eyes open on the floor) to the maximal A-P range.

The coordinated stability task (fig. 5.2A) was used to determine subjects' ability to move their centres of mass at their limits of stability.

Figure 5.2 **Coordinated Stability Task**



Pathway (A) and marking stencil (B). Grey regions indicate corners and white strips indicate sides. *A* anterior, *P* posterior, *L* left, *R* right

Each subject was asked to guide the pen on the end of the sway rod in an anticlockwise direction around a tortuous track printed on a piece of paper and placed on the table. Subjects were instructed to stand as straight as possible prior to test commencement and not to use their hands or move their feet. To complete the test without penalties, the subject had to remain within the borders of the 1.5 cm wide track, and adjust the position of the pen 140 mm laterally left or right and 90 mm forwards or backwards in the A-P plane. To assist in scoring, a transparency indicating the corners (grey regions) was placed over the track after completion of the test (fig. 5.2B). All subjects were able to transect the dotted lines across the white portions (in between the sides) of the track. A corner of the track was defined as 'cut' if the pen did not

transect all three dashed lines in a grey region of the track. Each time a corner was cut, the subject accrued 5 penalty points. A side of the track was defined as 'crossed' if the pen moved beyond the inner or outer boundaries of the track. Each time a side was crossed, the subject accrued 1 penalty point. No more than five penalty points could be accrued in each grey region of the track. This convention was adopted to avoid over-penalizing subjects who attempted to negotiate the grey regions. For example, a subject who attempted to transect all three dashed lines in a grey region but succeeded only in transecting one or two of them and crossing the sides seven or eight times in the process would accrue only 5 penalty points for that region, as would a subject who immediately cut the corner altogether. The total score was the sum of all penalty points the subject had accumulated during the trial. Subjects performed one practice trial prior to the experimental trial.

5.2.4 Procedure

PD subjects were instructed to take their usual morning doses of short-acting antiparkinsonian medications but to withhold their long-acting ones (eg. slow-release preparations of levodopa and cabergoline). All rating scale, leg strength, simple reaction time, proprioception and postural sway measurements were performed twice in PD subjects and controls. PD subjects were allocated at random into two counterbalanced groups to reduce the effects of fatigue and practice on tests of sway. One group of PD subjects took

their second morning dose of short-acting levodopa, waited until they began to experience a typical 'on' phase (usually within thirty to forty-five minutes), had UPDRS (motor subscale), sway, leg strength, reaction time and proprioception measurements (completed within an hour while the subject was still 'on'), rested for at least one hour and had all measurements repeated in the same order when the subject was beginning to experience a typical 'off' phase. The other group of PD subjects had initial measurements performed before their second morning dose of levodopa (usually within one hour) while they were experiencing a typical 'off' phase, rested an hour during which time they took their second dose of levodopa and had repeated measurements in a typical 'on' phase after this dose.

A typical 'off' phase was defined as the time period when the patient felt that the effect of the antiparkinsonian medications had worn off and that the symptoms of PD were uncontrolled. A typical 'on' phase was defined as the period when the patient felt that the parkinsonian symptoms were controlled at least as well as usual when the medications were working. In controls, initial measurements were performed in the mid morning between 9 and 10 am and repeated two to three hours later at approximately the same times of the morning as measurements in PD subjects. The repeat measurements in controls were necessary to determine if any of the sway tests had significant practice or fatigue effects and to provide measurements that could be compared with 'off' and 'on' measures in the PD group.

5.2.5 Statistics

All analyses were performed using SPSS 12 for Windows. Measures of leg strength, reaction time, light touch sensation, proprioception, A-P sway for each of the sensory conditions, maximal A-P range, A-P sway:maximal range ratio and the coordinated stability task in 'off' and 'on' phases in PD subjects and in initial and repeat tests in controls were examined for normality using stem-and-leaf plots and the Kolmogorov-Smirnov test statistic. Measures of leg length and maximal A-P range were normally distributed. Leg strength, reaction time, light touch sensation, proprioception, A-P sway measures, A-P sway:maximal range percentages and coordinated stability task scores were negatively skewed and needed to be log 10 transformed in order to achieve parametric distributions. In all comparisons between groups, 'off' phase measurements in PD subjects were compared with initial measurements in controls and 'on' phase measurements in the PD group were compared with repeat measurements in controls. Two-sample t-tests were used to detect differences in leg strength, reaction time and proprioception between PD subjects and controls. As light touch sensation could not be transformed into a parametric distribution, differences between PD subjects and controls were examined using the Mann-Whitney U test. Differences in UPDRS total, UPDRS sub-item and AIMS scores between the 'on' and 'off' phases of PD were examined using the Wilcoxin Signed Ranks Test.

Paired t-tests, bivariate product-moment (Pearson) correlations and intra-class correlations (ICCs) (two-way mixed effects model looking for absolute agreement between initial and retest measures by a single observer) were performed to examine reliability and possible effects of fatigue or practice on repeated measures in controls. The effects of fatigue and practice were also examined in PD subjects using paired t-tests to determine whether significant systematic differences existed between initial (14 subjects 'on' and 14 subjects 'off') and repeat tests (with swapping of 'on' and 'off' phases in subjects).

Pearson coefficients were used to screen for any significant correlations between all measures of sway and leg length, strength, reaction time and proprioception in all subjects. Two separate correlation matrices were formed. The first included the measures of all PD subjects in the 'off' phase and of all controls from their initial testing session (table 5.5). The second matrix included the measures of all PD subjects in the 'on' phase and all controls from their repeat testing session (table 5.6). Linear regression with backward elimination of redundant variables was used to determine relationships between tests of postural stability and subject group, knee extension strength, simple reaction time, posture and leg rigidity. Posture, leg rigidity and subject group were used as categorical variables in regression models. The residuals of these regression models had normal distributions when examined in histograms.

For sway measures involving modifications of visual input and support surface, repeated measures generalized linear models (GLM) with two within-subject factors (support surface and visual input), and one between-subjects factor (subject group) were used to determine whether changing visual and support conditions had different effects upon sway in PD patients than in healthy controls. Box's M was used to verify that observed covariance matrices of the A-P sway variables were equal across the groups of subjects.

Differences between PD subjects and controls in A-P balance range, A-P sway:range ratio and the coordinated stability task score were examined using linear regression.

In PD subjects, differences between 'on' and 'off' phase measures were examined using paired samples t-tests.

5.3 RESULTS

Table 5.2 **PD subjects and controls**

	Control (n=28)	PD (n=28)	
		"Off"	"On"
Knee extension (kg)	37.8 ± 6.6	24.1 ± 4.3***	25.9 ± 4.4**
Knee flexion (kg)	16.2 ± 2.3	15.6 ± 2.4	15.6 ± 2.9
Ankle dorsiflexion (kg)	12.2 ± 1.7	11.8 ± 2.1	12.5 ± 2.1
Leg reaction time (ms)	280 (257-306)	382 (290-444) ***§	335 (280-397) **
Light touch sensation (g)	4.3 (4.1-4.6)	Not performed	5 (4.0-5.0)
Proprioception (degrees)	2 (1-2)	2 (0-3)	1 (1-3)
Hoehn and Yahr Stage	0	2 (2-3)*** §	2 (1-2)***
UPDRS‡ total score	0	62 (40-76)*** §	43 (32-58)***
UPDRS motor subscale	0	22 (14-31) *** §§§	14 (7-24) ***
UPDRS tremor item	0	1 (0-2) ***§§	0 (0-1) *
UPDRS posture item	0	1 (0-2) ***§	1 (0-1) ***
UPDRS leg rigidity item	0	2 (0-2) ***	1 (0-2) ***
UPDRS retropulsion item	0	1 (0-1)***	1 (0-1) ***
AIMS† score	0	0 (0-0)	0 (0-0)

Values are presented as means ± 95% confidence intervals or medians (with inter-quartile ranges).
** $p < 0.005$, *** $p < 0.001$ for differences in measurements between 'off' measurements in PD subjects and initial measurements in controls and between 'on' measurements in PD subjects and repeat measurements in controls.
§ $p < 0.05$, §§ $p < 0.005$ and §§§ $p < 0.001$ for paired differences between 'on' and 'off' phases of levodopa therapy in PD subjects.
‡UPDRS = Unified Parkinson's Disease Rating Scale. †AIMS = Abnormal Involuntary Movements Scale [Guy 1976].

5.3.1 Hoehn and Yahr stage and UPDRS

5.3.1.1 Differences between PD patients and controls

In both 'on' and 'off' phases, PD subjects had significantly worse total UPDRS ($z = -6.6$ 'off', $p < 0.001$; $z = -6.8$ 'on', $p < 0.001$), UPDRS motor subscale ($z = -6.5$ 'off', $p < 0.001$; $z = -6.6$ 'on', $p < 0.001$), tremor ($z = -4.6$ 'off', $p < 0.001$; $z = -2.8$ 'on', $p < 0.05$), posture ($z = -3.6$ 'off', $p < 0.001$; $z = -4.8$ 'on', $p < 0.001$) and retropulsion ($z = -5.2$ 'off', $p < 0.001$; $z = -4.4$ 'on', p

< 0.001) scores than controls (table 5.2). The majority of PD subjects, however, scored 1 or less on the tremor item (no tremor or slight and infrequently present) in the 'off' phase and 0 (no tremor) in the 'on' phase. Those PD subjects with tremor had the problem isolated to their upper limbs. Differences between groups on the posture item were unlikely to be clinically significant as almost all of the PD subjects had a normal or slightly stooped posture in both phases. Only one subject scored greater than 2 on the posture item – this subject was severely stooped in the 'off' phase (score of 3) but only moderately stooped in the 'on' phase. There were significant differences between PD subjects and controls in rigidity item scores of the whole body ($z = -5.3$ 'off', $p < 0.001$, and $z = -4.6$ 'on', $p < 0.001$). When the legs were examined in isolation, PD subjects still had significantly more rigidity than controls ($z = -5.6$ 'off', $p < 0.001$, and $z = -4.4$ 'on', $p < 0.001$). Rigidity in the majority of PD subjects was usually slight or detectable only on mirror movements of the contralateral leg. In the 'off' phase, the median score 0.5 with an interquartile range of 0 to 0.5 for the most rigid side. In the 'on' phase, the median score was 0 with an interquartile range of 0.

5.3.1.2 Differences between 'on' and 'off' phases in PD patients

In the PD group, there were significant improvements as a result of levodopa in Hoehn and Yahr stage ($z = -1.9$, $p < 0.05$) and total UPDRS ($z = -2.1$, $p < 0.05$), motor subscale ($z = -4.0$, $p < 0.001$), tremor ($z = -2.6$, $p < 0.005$) and

posture ($z = -2.3$, $p < 0.05$) scores. The improvement in posture is unlikely to be of major clinical significance as the majority of PD subjects were only slightly stooped or normal in both 'off' and 'on' phases. There were no significant differences between phases in leg rigidity ($z = -1.6$, $p > 0.05$) or retropulsion scores ($z = -1.5$, $p > 0.05$).

5.3.2 Leg strength, reaction time, light touch sensation and proprioception

5.3.2.1 Differences between PD patients and controls

PD subjects were significantly weaker than healthy controls in knee extension in both 'on' ($t_{54} = 2.9$, $p < 0.005$) and 'off' ($t_{54} = 3.4$, $p < 0.001$) phases (table 5.2). Simple reaction time in the legs was significantly longer in PD patients in both 'on' ($t_{54} = -3.6$, $p < 0.005$) and 'off' ($t_{54} = -5.4$, $p < 0.001$) phases than in controls. There were no significant differences between PD subjects and controls in knee flexion and ankle dorsiflexion strengths, proprioception or light touch sensation.

5.3.2.2 Differences between 'on' and 'off' phases in PD patients

In PD subjects, knee extension was significantly weaker in the 'off' than in the 'on' phase. Simple reaction time in the legs was significantly longer in the 'off' phase than in the 'on' phase. There were no significant differences

between 'on' and 'off' phases in knee flexion and ankle dorsiflexion strengths, proprioception or light touch sensation.

5.3.3 Reliability and fatigue or practice effects

All A-P sway measures had fair-to-good test-retest reliability in healthy controls, with ICCs ranging from 0.46 ($p < 0.05$) to 0.66 ($p < 0.001$) (table 5.3).

Table 5.3 **Reliability and differences between initial and repeat measurements in healthy controls**

Variable	Mean (95%CI)	Pearson	Intraclass
A-P sway (mm)			
Eyes open/firm	-1.4 (-3.5-0.8)	0.46*	0.46 (0.12-0.71)*
Eyes closed/firm	0.8 (-2.6-4.2)	0.66***	0.66 (0.39-0.83)***
Eyes open/compliant	-4.0 (-8.9-0.9)	0.52**	0.52 (0.17-0.74)**
Eyes closed/compliant	3.0 (-3.9-9.9)	0.51*	0.51 (0.17-0.74)**
Maximal A-P range (mm)	-0.5 (-1.7-0.7)	0.99***	0.99 (0.98-1.0)***
A-P sway:range ratio (%)	0.8 (-2.0-0.3)	0.52**	0.51 (0.19-0.74)**
Coordinated stability			
Total score	-0.12 (-1.1-0.8)	0.44*	0.45 (0.10-0.70)*
Sides	-0.10 (-0.6-0.4)	0.40*	0.41 (0.04- 0.67)*
Corners	0.0 (-0.1-0.1)	0.87***	0.87 (0.74-0.94)***

Table shows mean intra-subject differences between test and retest, Pearson and intraclass correlation coefficients and significance for sway measures in 28 controls. * $p < 0.05$, ** $p < 0.005$, *** $p < 0.001$ for test-retest differences and Pearson and intraclass correlation coefficients.

Maximal A-P range had the best reliability with a Pearson coefficient of 0.99 and an ICC of 0.99 (0.98-1.0). This measure was 0.5 mm less on retest in phase 2, although this difference was not statistically significant. Similarly, there were no significant differences between test and retest in A-P

sway:range percentage or coordinated stability task score, both of which had fair-to-good reliability with ICCs 0.51 (0.19-0.74) and 0.45 (0.10-0.70) respectively. The ICCs suggest that these measures of sway are reliable in healthy controls in test-retest (same day) conditions and do not have major systematic errors due to fatigue or practice. This is confirmed by the Pearson coefficients that show significant correlations and paired t-tests that do not demonstrate significant differences between phases 1 and 2 in any of these measures.

In the PD group, there was no evidence of major fatigue or practice effects in any of the sway tests as initial measures, with 14 subjects 'on' and 14 'off', were not significantly different to repeat measures, with 14 'off' and 14 'on', on paired t-tests (table 5.4).

Table 5.4 **Systematic error of sway measurements in PD subjects**

	Initial	**Repeat**	***p***
PD group 1 (n = 14)	On	Off	
PD group 2 (n = 14)	Off	On	
A-P sway (mm)			> 0.05
Eyes open/firm surface	21 (18-25)	21 (17-25)	> 0.05
Eyes closed/firm surface	28 (24-34)	26 (20-31)	> 0.05
Eyes open/compliant surface	31 (26-38)	29 (24-34)	> 0.05
Eyes closed/compliant surface	56 (46-68)	54 (44-68)	> 0.05
Maximal A-P range (mm)	112 (103-122)	111 (98-123)	> 0.05
A-P sway:range ratio (%)	19 (16-24)	20 (16-24)	> 0.05
Coordinated stability task			
Total score	14 (10-19)	12 (8-17)	> 0.05
Sides	6 (4-8)	5 (4-7)	> 0.05
Corners	2 (1-2)	1 (1-2)	> 0.05

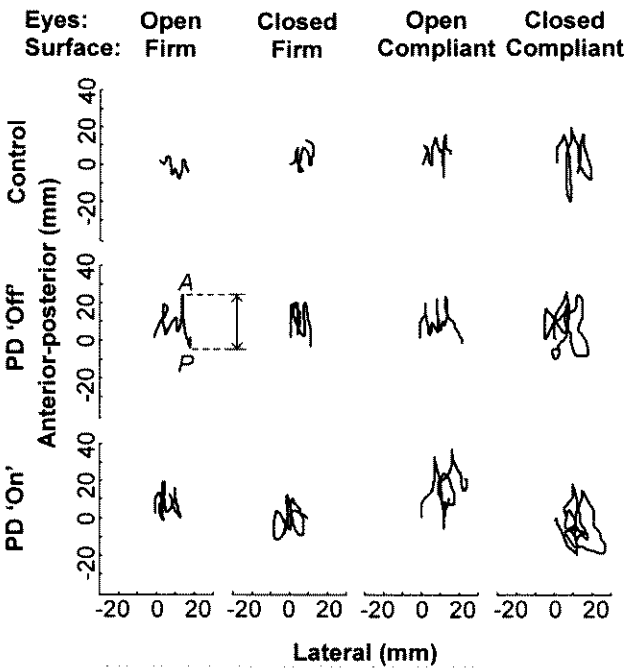
Table shows means (95% CI) for initial and repeat measurements in PD subjects divided randomly into two counterbalanced groups (group 1 having initial measurements in the 'on' phase and repeat measurements in the 'off' phase and group 2 having order of phases reversed) and results of paired t-tests examining differences between initial and repeat measurements.

5.3.4 Visual and support surface conditions

5.3.4.1 Univariate analyses

All subjects were able to perform all tests without falling. Trajectories of a typical PD subject and a control are presented in fig. 5.3.

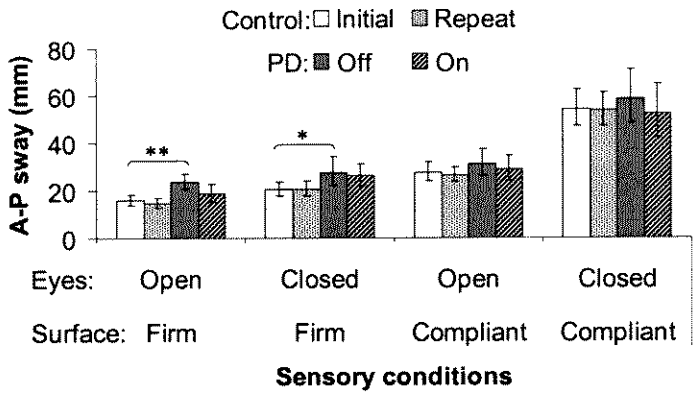
Figure 5.3 **Effects of vision and support surface on sway**



Center of gravity trajectories for a typical control and a typical PD subject in 'off' and 'on' states. Sway tests involved standing on a firm surface with eyes open or closed, or on a compliant surface with eyes open or closed. Sway was calculated as the distance (arrowed line) along the A-P axis between the most anterior (*A*) and posterior (*P*) points of the center of gravity trajectory.

In the 'off' phase, PD subjects had significantly greater A-P sway than controls on the firm support surface with the eyes open ($t_{54} = -3.6$, $p < 0.005$) or closed ($t_{54} = -2.7$, $p < 0.05$) (fig. 5.4).

Figure 5.4 **Anterior-posterior sway distances**



Anterior-posterior (A-P) sway distances in PD subjects and controls with eyes open and closed on firm and compliant surfaces. * $p < 0.05$, ** $p < 0.005$ for differences between initial measurements in controls and 'off' phase measurements in PD subjects and between repeat measurements in controls and 'on' phase measurements in PD subjects.

In the 'on' phase, there were no significant differences between PD subjects and controls in A-P sway in any of the visual input/support surface conditions (fig. 5.4). There were no differences between 'off' and 'on' phase measurements in PD subjects on paired t-tests (fig. 5.4).

5.3.4.2 Multivariate analyses

The 'off' phase/initial test Pearson coefficients demonstrated significant correlations between A-P sway on the firm surface with eyes open and leg strength ($p < 0.05$), reaction time ($p < 0.001$) and posture ($p < 0.05$) (table 5.5). Reaction time was the only variable on linear regression that was significantly associated with A-P sway ($t_{55} = 4.4$, $p < 0.001$) and was independent of subject group, leg strength and posture.

Table 5.5 **Correlation matrix, including 'off' phase measurements in PD subjects and initial measurements for controls**

	EO	EC	EO/C	EC/C	Range	Ratio	CST
EC	0.59***						
EO/C	0.34*	0.31*					
EC/C	0.28*	0.24	0.39**				
Range	-0.40**	-0.27*	-0.11	-0.14			
Ratio	0.85***	0.52***	0.29*	0.24	-0.82***		
CST	0.35**	0.25	0.06	0.06	-0.57***	0.54***	
Knee extension	-0.38**	-0.21	-0.24	-0.08	0.37**	-0.48***	-0.24
Knee flexion	-0.13	0.05	-0.15	-0.00	-0.07	-0.05	0.05
Ankle flexion	-0.28*	-0.06	-0.28	-0.09	0.13	-0.25	-0.08
Reaction Time	0.51***	0.39**	0.02	0.01	-0.54***	0.63***	0.37**
Proprio-ception	0.02	0.01	0.14	0.11	0.07	-0.01	-0.12
Leg length	0.08	-0.13	0.08	0.07	-0.12	0.10	0.13

Table shows anterior-posterior (A-P) sway with eyes open on the floor (EO), eyes closed on the floor (EC), eyes open on the compliant surface (EO/C) and eyes closed on the compliant surface (EC/C), maximal A-P range (Range), A-P sway : range ratio (Ratio), Coordinated Stability Task Score (CST), knee extension, knee flexion, ankle dorsiflexion, proprioception and leg length. * $p < 0.05$, ** $p < 0.005$, *** $p < 0.001$ for Pearson correlation coefficients.

In the 'off' phase in PD patients and initial test in healthy controls, A-P sway on the firm surface with eyes closed was significantly correlated with reaction time ($p < 0.005$) and leg rigidity ($p < 0.05$). Once again, linear regression analysis showed that A-P sway in this condition was associated with reaction time ($t_{55} = 3.1$, $p < 0.005$) but not subject group or leg rigidity.

There were no significant correlations between measures of sway on the complaint surface and leg strength, reaction time, proprioception.

Leg reaction time was used as a covariate in a GLM with visual input and support surface characteristics as within-subject factors, subject group as a between-subjects factor and A-P sway measures as outcome variables. Sway was not influenced by subject group ($F_{1,52}$ = 2.1, $p > 0.05$), visual input conditions ($F_{1,52}$ = 1.6, $p > 0.05$) or reaction time ($F_{1,52}$ = 0.7, $p > 0.05$), although it was effected by support surface changes ($F_{1,52}$ = 22.8, $p < 0.001$). There were no interactions between support surface ($F_{1,52}$ = 0.0, $p > 0.05$) or visual input conditions ($F_{1,52}$ = 1.6, $p > 0.05$) and subject group.

During the 'on' phase in PD patients and repeat tests in controls, sway was not correlated with leg strength, reaction time or proprioception (table 5.6).

Table 5.6 **Correlation matrix, including 'on' phase measurements in PD subjects and repeat measurements for controls**

	EO	EC	EO/C	EC/C	Range	Ratio	CST
EC	0.57***						
EO/C	0.38**	0.43**					
EC/C	-0.01	0.29*	0.31*				
Range	-0.14	-0.10	-0.08	0.07			
Ratio	0.85***	0.50**	0.34**	-0.05	-0.64**		
CST	0.29*	0.15	0.16	-0.04	-0.42**	0.45**	
Knee extension	-0.01	-0.03	-0.24	-0.06	0.18	-0.11	-0.14
Knee flexion	0.20	0.25	-0.07	0.05	-0.04	0.16	-0.09
Ankle flexion	0.13	0.16	-0.10	0.02	0.05	0.08	-0.05
Reaction Time	0.12	0.14	0.10	-0.06	-0.47***	0.35**	0.32*
Proprio-ception	-0.02	-0.08	0.13	0.04	0.09	-0.05	-0.16
Leg length	0.11	-0.03	0.09	-0.04	-0.09	0.13	-0.03

Table shows anterior-posterior (A-P) sway with eyes open on the floor (EO), eyes closed on the floor (EC), eyes open on the compliant surface (EO/C) and eyes closed on the compliant surface (EC/C), maximal A-P range (Range), A-P sway : range ratio (Ratio), Coordinated Stability Task Score (CST), knee extension, knee flexion, ankle dorsiflexion, proprioception and leg length. * $p < 0.05$, ** $p < 0.005$, *** $p < 0.001$ for Pearson correlation coefficients.

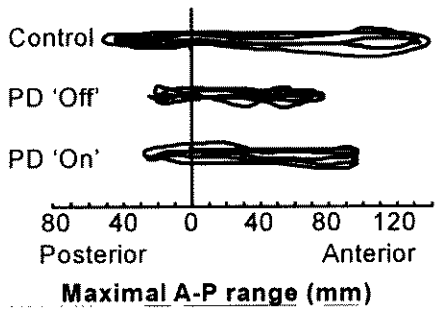
Using a repeated measures GLM, no differences in A-P sway measures between PD subjects in the 'on' phase and controls were found ($F_{1,52} = 2.8$, $p > 0.05$). Although support surface ($F_{1,52} = 120.5$, $p < 0.001$) and visual inputs ($F_{1,52} = 99.2$, $p < 0.001$) affected sway, there were no interactions between either of these variables and subject group.

5.3.5 Maximal A-P range

5.3.5.1 Univariate analyses

COG trajectories for a typical control and a PD subject in 'off' and 'on' conditions are shown in figure 5.5.

Figure 5.5 **Maximal anterior-posterior (A-P) range**



COG trajectories for a typical control subject and a typical PD subject in 'off' and 'on' phases.

PD patients had significantly lower maximal ranges in the anterior-posterior plane in both 'off' ($t_{54} = 15.3$, $p < 0.001$) and 'on' ($t_{54} = 10.5$, $p < 0.001$) phases than controls (fig. 5.6). In the group of PD subjects, A-P range was significantly greater in the 'on' phase than in the 'off' phase ($t_{27} = 6.8$, $p < 0.001$).

(t_{55} = -2.1, $p < 0.05$). This final model which explained 81% of the variance in maximal range in this sample. The presence of PD reduced maximal A-P range by 91 ± 13 mm on average.

In the 'on'/retest phase, maximal range was significantly correlated with reaction time ($p < 0.001$), posture ($p < 0.001$) and rigidity ($p < 0.001$) (table 5.6).

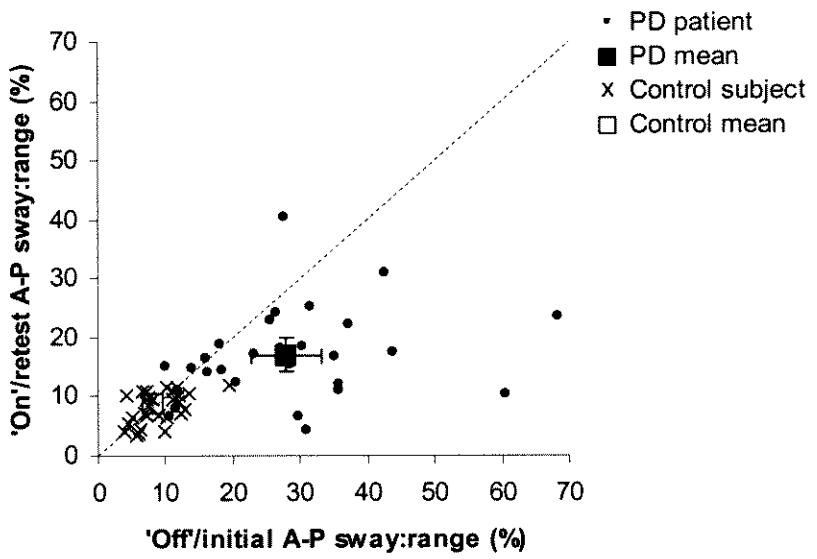
Subject group had a significant effect on maximal A-P range (t_{55} = -7.0, $p < 0.001$) after adjusting for reaction time (t_{55} = -1.5, $p > 0.05$), posture (t_{55} = -0.9, $p > 0.05$) and leg rigidity (t_{55} = -0.8, $p > 0.05$). Following sequential elimination of redundant variables, subject group alone remained in the model (t_{55} = -10.5, $p < 0.001$) and explained 67% of the variance in maximal A-P range and suggested that range was reduced on average by 71 ± 13.2 mm in PD subjects in the 'on' phase compared with controls (t_{55} = 10.5, $p < 0.001$).

5.3.6 A-P sway:range ratio

5.3.6.1 Univariate analyses

As a fraction of their maximal A-P range, PD patients swayed significantly more in 'off' (t_{54} = -9.1, $p < 0.001$) and 'on' (t_{54} = -6.0, $p < 0.001$) phases than healthy controls (fig. 5.7).

Figure 5. 7 **Ratio of A-P sway distance on the floor with eyes open to maximal A-P range**



A-P sway:range for PD subjects in 'on' and 'off' phases of their antiparkinsonian treatment cycle and controls on initial and repeat tests. Dashed line indicates points where values are equal on horizontal and vertical axes. 95% confidence interval bars are shown of the means of each group.

5.3.6.2 Multivariate analyses

In the 'off' phase, A-P sway:range ratio was significantly correlated with knee extension strength, reaction time, posture and leg rigidity ($p < 0.001$ for both) (table 5.5). The effect of subject group ($t_{55} = 4.0$, $p < 0.001$) was independent of reaction time ($t_{55} = 2.2$, $p < 0.05$), knee extension strength ($t_{55} = -0.7$, $p > 0.05$), posture ($t_{55} = 0.7$, $p > 0.05$) and leg rigidity ($t_{55} = 1.0$, $p > 0.05$). In the final linear regression model, A-P sway:range ratio was significantly greater in PD subjects ($t_{55} = 6.3$, $p < 0.001$) than controls after accounting for reaction time ($t_{55} = 2.5$, $p < 0.05$) (adjusted $R^2 = 0.65$).

In the 'on' phase, A-P sway:range ratio was correlated with reaction time ($p < 0.005$) and leg rigidity ($p < 0.05$) (table 5.6). A-P sway:range ratio remained significantly greater in PD subjects than in controls ($t_{55} = 4.9$, $p < 0.001$) after adjusting for reaction time ($t_{55} = 1.0$, $p > 0.05$) and leg rigidity ($t_{55} = 0.8$, $p > 0.05$). The final linear regression model containing subject group alone ($t_{55} = 6.0$, $p < 0.001$) accounted for 40% of the variance in sway:range ratio.

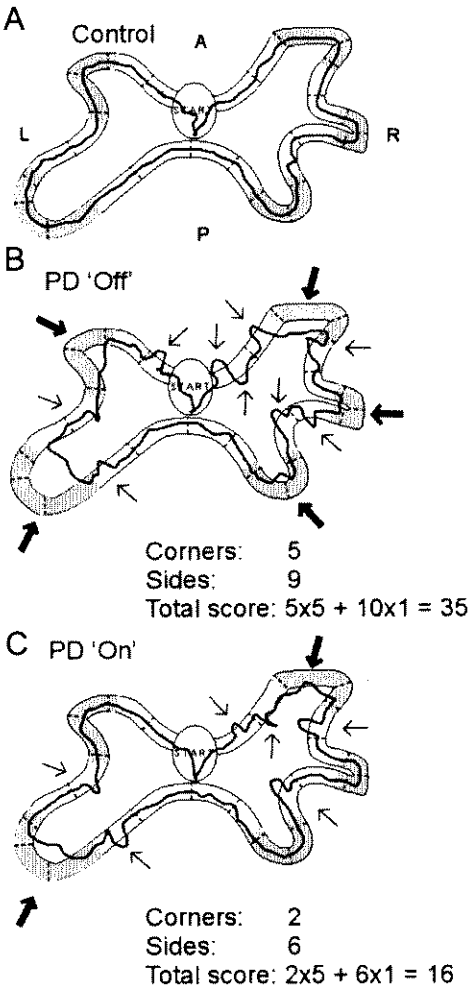
When the PD subjects were examined using paired t-tests, 'on' phase ratios were significantly lower than 'off' phase values ($t_{27} = -4.4$, $p < 0.001$).

5.3.7 Coordinated stability

5.3.7.1 Univariate analyses

Tracings of L2 movement during the coordinated stability task are shown for typical control (fig. 5.8A) and PD (figs. 5.8B and C) subjects.

Figure 5.8 **Coordinated stability task (CST) tests**

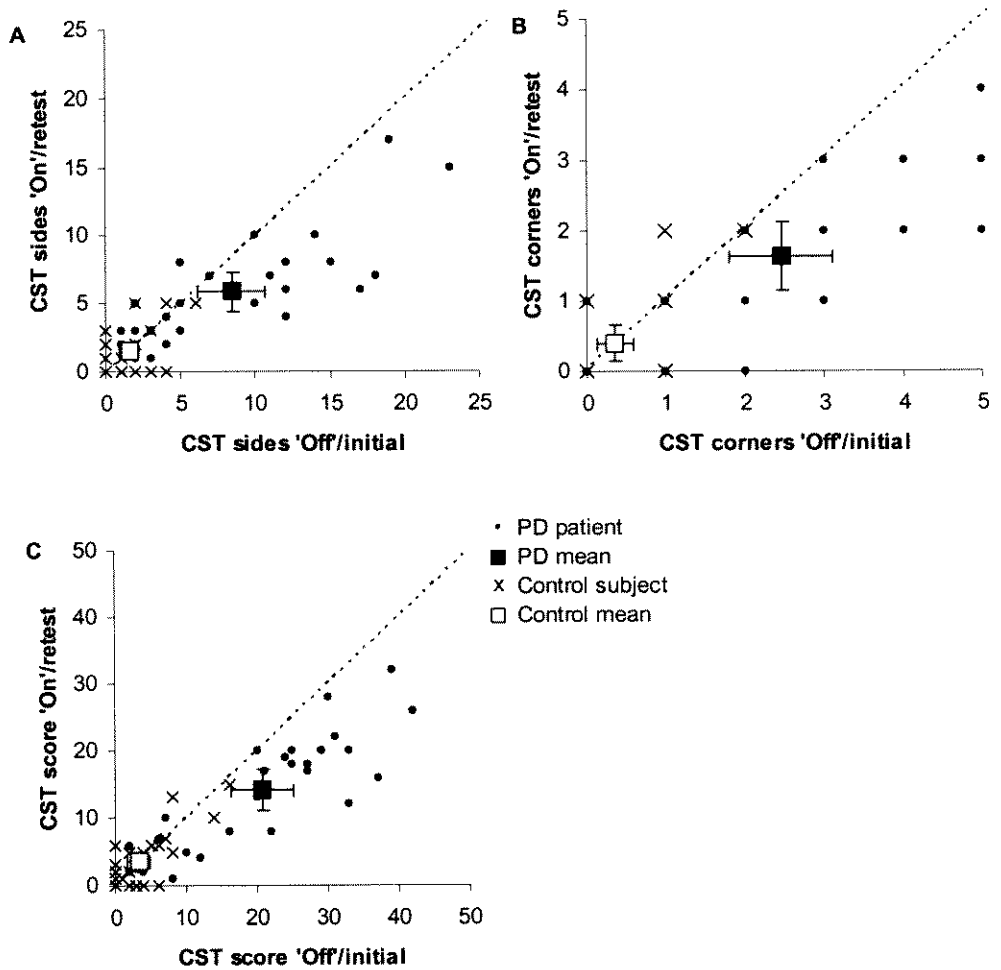


Tracings of the test for a typical control subject (A) and a typical PD subject in 'off' (B) and 'on' (C) phases. Errors made by the PD subject are indicated by thin arrows where a side of the track has been crossed and thick arrows where a corner has been cut.

PD subjects made significantly more errors, crossing sides ('off' $t_{54} = -5.2$, $p < 0.001$; 'on' $t_{54} = -4.7$, $p < 0.001$) and cutting corners ('off' $t_{54} = -5.2$, $p < 0.001$; 'on' $t_{54} = -4.1$, $p < 0.001$) more frequently than controls, leading to higher total scores in both 'off' ($t_{54} = -5.4$, $p < 0.001$) and 'on' ($t_{54} = -4.5$, $p < 0.001$) phases (fig.5.9). PD subjects had significantly better (lower) values in the 'on' phase than in the 'off' phase for total score ($t_{27} = -3.7$, $p < 0.001$) and number

of sides crossed (t_{27} = -2.2, $p < 0.001$). They cut fewer corners in the 'on' phase but this result was not statistically significant (t_{27} = -1.6, $p > 0.05$).

Figure 5.9 **Coordinated Stability Task in PD subjects and healthy controls**



Results for PD subjects in 'on' and 'off' phases of their antiparkinsonian treatment cycle and controls on initial and repeat tests. Dashed line indicates points where values are equal on horizontal and vertical axes. 95% confidence interval bars are shown of the means of each group.

5.3.7.2 Multivariate analyses

In the 'off'/initial phase, there were significant correlations between total score and sway with eyes open on the firm surface ($p < 0.005$), maximal A-P range ($p < 0.001$), knee extension strength ($p < 0.001$), reaction time ($p < 0.001$), posture ($p < 0.005$) and leg rigidity ($p < 0.005$). Linear regression arrived at a model containing only subject group as an independent predictor ($t_{55} = 5.4$, $p < 0.001$) which explained 34% of the variance in total score. On average, PD subjects scored 15 points (95% CI 8 to 28 points) more than controls in the 'off'/initial phase.

In the 'on'/retest phase, there were significant correlations between total score and sway ($p < 0.05$), range ($p < 0.005$) and reaction time ($p < 0.05$), posture ($p < 0.05$) and rigidity ($p < 0.005$). Once again, backward elimination of variables resulted in a model containing only PD group as an independent predictor of total score ($t_{55} = 4.5$, $p < 0.001$), explaining 26% of the variance. On average, PD subjects scored 10 points (95% CI 5 to 19 points) more than controls in the 'on'/retest phase.

5.4 DISCUSSION

This study demonstrated that postural sway can be significantly increased on a firm support surface in PD subjects when they are in the 'off' phase of levodopa therapy. Treatment with levodopa reduces sway so that these

significant differences between PD subjects and controls no longer exist. Altering visual input and support surface conditions does not exacerbate sway to any greater extent in PD subjects than in controls. PD subjects have difficulty with tasks requiring leaning postures, reflected by lower maximal A-P ranges and worse coordinated stability task scores. As a percentage of their maximal A-P range, PD subjects sway significantly more than controls. Levodopa led to significant improvements in maximal A-P range, A-P sway:range ratio and performance in the coordinated stability task in PD subjects even though these measures remained significantly worse than in controls.

5.4.1 How does PD affect postural stability?

In our study, there were significant differences between PD and control groups in leg strength, reaction time, posture and rigidity. Differences between PD and control groups in A-P sway on the floor, with eyes open or closed, could be explained by differences in reaction time between these groups. For all other tests of postural stability, reaction time, leg strength, posture and leg rigidity did not explain fully the differences observed between PD and control groups. These factors either did not correlate with the tests of postural stability or failed to exert an effect that was independent of PD.

Investigators have hypothesized that some of the abnormal postural reflexes observed in PD subjects might be attributable to their stooped posture and have demonstrated similar abnormalities in healthy controls who assumed equivalent degrees of stooping [Bloem, Van Dijk et al. 1992]. Differences in posture between PD subjects and controls and between 'off' and 'on' phases in PD subjects were perceptible in our study, the clinical significance of these differences appears uncertain as all but one PD subject had normal or only slightly stooped posture and all subjects were encouraged to stand as straight as possible when beginning maximal A-P range and coordinated stability tests. Any initial stooping of the subject does not affect the maximal A-P range, as any reduction in anterior range resulting from this posture would be equalled by an increase in posterior range. Furthermore, subject posture did not exert any effect upon the measures of postural stability that was independent of subject group.

Increased ankle stiffness has been postulated in PD [Dietz, Berger et al. 1988; Horak, Nutt et al. 1992] and may account for more frequent and less regular lateral displacements of the centre of foot pressure [Rocchi, Chiari et al. 2004]. Intrinsic musculoskeletal stiffness, however, can not account for the abnormal sway patterns observed in PD. As Maurer and colleagues suggest (2003) [Maurer, Mergner et al. 2003], increased stiffness should lead to a reduced sway amplitude, rather than the normal to slightly increased measures observed in our study across a range of visual and support surface conditions.

In addition, levodopa should reduce stiffness and increase sway rather than reduce it.

5.4.2 Can PD subjects maintain postural stability across a range of visual input/support surface conditions?

In our study, PD subjects were no more dependent upon visual inputs or somatosensory inputs from the legs than healthy controls. In the scientific literature, there is no consensus whether sway across a range of sensory/support surface conditions is normal in PD. Horak and colleagues (1992) [Horak, Nutt et al. 1992] also found that subjects with moderate to severe PD were able to maintain postural stability appropriately using visual, somatosensory and vestibular information but had significantly smaller sway than elderly controls in usual and altered sensory conditions. Their findings were supported by other investigators [Waterston, Hawken et al. 1993; Chong, Horak et al. 1999] who found that there were no significant differences in sway between PD and control groups, although PD subjects tended to fall more frequently, across a range of conditions. These studies modified sensory conditions using versions of the Sensory Organization Test (SOT) [Nashner, Black et al. 1982], in which subjects' vision can be eliminated by blindfolding, somatosensory inputs from the legs modified by standing on a support surface that rotates in the A-P plane and visual anchoring reduced by a visual field that moves in phase with support surface movement. In the SOT, angular sway is

measured in the A-P plane. Our protocol differed in several ways that could account for our finding of increased sway in PD subjects on the stable surface: we measured linear rather than angular sway and allowed PD subjects to take their usual morning dose of short-acting levodopa.

A disadvantage of measuring sway angle at the hips is the inherent assumption that the body is an inverted pendulum with movement only at the ankles and only in the A-P plane. When linear displacement of the COG is used as a measure of A-P sway the body can be treated as a multi-segmented structure with degrees of freedom at the hips and knees.

Previous investigators withheld all antiparkinsonian medications from the evening before the morning of the test [Horak, Nutt et al. 1992; Waterston, Hawken et al. 1993] or made no change to doses [Chong, Horak et al. 1999]. By allowing our PD subjects to take their usual morning dose of levodopa, we hoped to gain an impression of postural stability during typical 'on' and 'off' phases, optimize compliance and safety with the test protocol and avoid changes in test performance that might be caused by withdrawal effects of levodopa rather than PD per se. The random division of PD subjects into two counterbalanced groups was performed to prevent clouding of our results by fatigue or practice effects.

We tried to match PD and control subjects as closely as possible on a 1:1 basis for age and leg length. Although PD patients had legs 1 cm longer and were 2

years younger on average than control subjects, theses differences between the two groups were not statistically significant. Our group of PD subjects had relatively mild PD, in contrast with previous studies investigating patients with moderate and severe disease [Horak, Nutt et al. 1992; Waterston, Hawken et al. 1993].

Surprisingly, our study was unable to detect a significant difference between PD subjects and controls when standing with eyes open or closed on a compliant support surface. This implies that our PD subjects were able to integrate sensory information to some degree and adapt to the task of maintaining stability on an unstable surface. The sway measurements with eyes closed on the compliant surface suggest that PD subjects are able to utilize vestibular inputs and/or modify somatosensory inputs from the legs appropriately. This contrasts with a study by Bronte-Stewart and colleagues (2002) [Bronte-Stewart, Minn et al. 2002] involving 50 PD patients with advanced disease that found that 52% of patients exhibited greater postural sway than 95% of non-PD subjects when vision was eliminated and the support surface was unstable (condition 5 of the SOT). That study, however, involved PD subjects with quite advanced PD requiring unilateral pallidotomy.

Previous research suggests that PD patients may have more difficulty in responding to incongruent or misleading sensory inputs than in adjusting to the removal of normal inputs. Bronstein (1990) [Bronstein, Hood et al. 1990] found that changing the visual field laterally caused a greater increase in sway

in PD patients than in controls, suggesting that patients had problems suppressing incongruent visual inputs in order to maintain postural stability. Pastor and colleagues (1993) [Pastor, Day et al. 1993] found normal responses in ground reaction force to galvanic stimulation of the mastoid in PD patients. In that experiment, patients were able to reduce their reliance on 'misleading' vestibular inputs and maintain normal postural responses, probably due to visual fixation. These studies suggest PD patients experience more difficulty suppressing incongruent visual than incongruent vestibular inputs.

5.4.3 Do patients with PD perform appropriately in tasks that require leaning or inclining postures?

A number of studies have shown that postural responses to external perturbations, such as toe-up surface rotations or backward surface translations, are abnormal in PD, with poorly coordinated stabilizing responses [Dietz, Berger et al. 1988; Beckley, Bloem et al. 1991; Horak, Nutt et al. 1992]. In addition, it has been demonstrated that PD patients have difficulty changing postural set to adapt to anticipated external perturbations, such as toe-up surface rotations of an expected amplitude [Beckley, Bloem et al. 1991; Bloem, Beckley et al. 1995; Chong, Horak et al. 2000]. These abnormalities are thought to be secondary to defective basal ganglia that can not exercise appropriate control of spinal and supraspinal reflex centres and sequence motor programmes [Marsden 1984].

Postural stability during self-initiated leaning tasks has received little attention in PD. Our findings of a reduced maximal A-P range in PD conform to those of Schiepatti and colleagues (1994) who demonstrated that maximal anterior displacement of the centre of foot pressure (COP) during self-initiated forward leaning is significantly reduced in PD patients compared with healthy young and elderly controls. Some of this reduction in anterior range could be explained by the finding that the COP in patients with severe PD tends to lie more anterior than normal even when they attempt to stand upright [Schieppati and Nardone 1991].

The finding of a severely reduced A-P range becomes more confronting when examined in conjunction with A-P sway on the floor with eyes open. In our study, differences between the PD and control groups in A-P stability became more apparent when the A-P displacement is considered as a percentage of maximal A-P balance range, with PD patients swaying significantly more than controls ($p < 0.001$). We found that the COG of PD subjects tends to encroach upon their limits of stability to a much greater extent than healthy controls even when standing 'still' in normal sensory and support conditions. External and internal perturbations in these subjects are more likely to result in imbalance and a fall, like a bowling ball rolling off a narrow bar stool.

The coordinated stability task results show that PD patients have difficulty controlling movement of their COG at or near their limits of stability. This test

disadvantaged PD subjects who had significantly smaller maximal A-P balance ranges than healthy controls and may have been unable to reach the corners of the track comfortably. Nevertheless, PD patients still performed significantly worse than controls after adjusting for maximal A-P range or when corners were ignored in the comparison and only the number of times subjects crossed the sides of the track was considered. All subjects were able to reach the anterior, posterior and lateral lengths of the track, excluding the corners.

A problem with voluntary postural tasks such as maximal balance range and coordinated stability tests is that it is difficult to determine to what extent performance is limited by psychological factors such as fear of falling. To limit the influence of fear of falling, we excluded subjects who had a history of falling or experiencing near falls in the last 12 months. Nevertheless, it remains possible that performance in these tests was impaired just as much by psychological inhibition as by physical impairment in PD patients. If this were the case, however, it is improbable that performance in these tests would have been so much better when performed in the 'on' phase of treatment.

5.4.4 How does levodopa affect stability in usual standing conditions, situations where sensory inputs are modified and tasks requiring controlled movements of the COG?

We were unable to demonstrate an effect of levodopa on postural stability in a variety of sensory conditions. There were no significant differences between "on" and "off" phases in PD patients in sway with all sensory inputs, vision removed, somatosensory inputs modified or vision removed and somatosensory inputs modified. In contrast, Bronte-Stewart and colleagues (2002) [Bronte-Stewart, Minn et al. 2002] found that patients experienced increased sway in a similar range of sensory conditions after levodopa therapy. Other investigators have also found that levodopa increased the area of COP movement in PD patients who had deep brain stimulators [Rocchi, Chiari et al. 2002; Rocchi, Chiari et al. 2004]. When the patients were in the 'on' phase of levodopa treatment and their stimulators were turned off, they experienced significantly more movement of the COP than when they were 'off' both levodopa and stimulators. The increased COP movement following levodopa in these studies could be explained by the presence of dyskinesia which may not have been obvious clinically or a reduction in intrinsic stiffness without a concomitant improvement in COG control. In that study, patients had long- and short-acting dopaminergic agents ceased in advance of initial testing in the 'off' phase. Sway measurements in all patients were then repeated in the 'on' phase. Differences between 'on' and 'off' phases could have been accentuated by the long time abstaining from levodopa. We excluded patients with

moderate or severe dyskinesia to avoid artefact in sway measurements and did not alter the time between levodopa doses. In this setting, we could not demonstrate that levodopa influenced sensory integration in PD.

Our finding of improved postural responses to external perturbations is at odds with previous studies that suggest that postural instability responds poorly to treatment with antiparkinsonian medication [Bonnet, Loria et al. 1987; Koller, Glatt et al. 1989; Bloem, Beckley et al. 1996]. This discrepancy can be explained by differences in experimental design and focus. When clinical motor examinations were used to examine PD patients in cross-sectional studies, it was found that postural instability responded less to levodopa as the condition became more advanced [Bonnet, Loria et al. 1987] or did not respond at all [Koller, Glatt et al. 1989]. In our study, PD patients had significantly better scores in the retropulsion test following levodopa. However, the validity of this test in reflecting stability is questionable [Bloem, Beckley et al. 1998].

In response to toe-up rotational perturbations of the support surface, PD patients swayed slightly less in the posterior direction during the 'on' phase than during the 'off' phase [Bloem, Beckley et al. 1996]. Posterior displacement of the COG after two seconds was also slightly less during the 'on' phase. Destabilizing medium latency responses to stretch in the gastrocnemius did not change while stabilizing long latency responses in the tibialis anterior increased following levodopa administration. None of the

differences between the 'on' and 'off' phases was statistically significant. These results suggest minimal if any improvement in posterior sway and stabilizing reflexes following levodopa. Other studies have confirmed that postural reactions to external perturbations are not improved and may even be exacerbated by levodopa [Horak, Frank et al. 1996]. In addition, the ability to change postural set to adapt to different sensory and motor demands is unresponsive to levodopa [Horak, Nutt et al. 1992; Chong, Horak et al. 2000]. These studies examined postural stability in response to externally-generated perturbations. Our study investigated self-initiated movements of the COG during maximal balance range and coordinated stability tasks and concurs more closely with other studies dealing with self-initiated movements, which found some improvements in stability in PD patients following levodopa [Burleigh-Jacobs, Horak et al. 1997; Frank, Horak et al. 2000].

The possible explanations for the significant improvement in coordinated stability scores in the "on" phase in PD include an improvement in motor scaling in response to levodopa, increased force production in the legs, straighter posture, reduced rigidity in the legs, improved concentration and faster reaction times.

PD patients are able to scale their postural motor reactions to small but not large externally-generated anticipated perturbations, such as floor translations [Beckley, Bloem et al. 1993; Horak, Frank et al. 1996]. For centrally-initiated or self-generated perturbations, such as rise-to-toes movements, scaling is

essentially intact [Frank, Horak et al. 2000]. Levodopa does not appear to influence the degree of scaling in any of these situations. It does, however, increase the force of both voluntary and involuntary stabilizing motor responses during rise-to-toes tasks [Frank, Horak et al. 2000], although the magnitude is still substantially lower than in healthy controls. As our study did not use electromyography or force plates, the amount of muscle activity or torque generated by our patients in stability tests is unknown. It is plausible, however, that PD patients in the "off" phase were still able to scale motor responses to a certain extent but were unable to generate the torques required to incline the body in all directions in order to complete the coordinated stability task. Levodopa increased the amount of force patients were able to produce in their legs, improving their maximal A-P range and coordinated stability.

In this study, the subjects took their usual doses of levodopa. Differences in postural sway between 'on' and 'off' phases would depend substantially on each individual's dose of levodopa and his or her response to it. We were unable therefore to determine the effect of dose magnitude on postural sway.

5.5 CONCLUSION

In the 'off' phase, PD subjects sway more than healthy controls across a range of visual input/support surface conditions although differences between the groups were not statistically significant. Treatment with levodopa reduces A-P

sway in PD subjects to levels indistinguishable from healthy controls. PD subjects have severely reduced limits of stability and perform significantly worse in tasks involving self-initiated movements of the COG. As a percentage of their limits of stability, PD subjects sway significantly more than healthy controls. These features improve with levodopa therapy but remain significantly worse than in healthy controls.

CHAPTER 6

POSTURAL STABILITY AND SEVERITY OF PARKINSON'S DISEASE

6.1 INTRODUCTION

Many different tests have been used to examine postural stability in PD in both unperturbed and perturbed conditions. The Romberg test [Romberg 1853], where the patient stands with the feet touching side-by-side and the eyes closed, does not usually elicit differences between PD patients and healthy controls [Bronstein, Hood et al. 1990], although performance is more impaired in recurrent fallers with PD compared with patients who do not fall repeatedly [Bloem, Grimbergen et al. 2001]. A problem with this test is that it is highly subjective and dependent upon the experience of the observer. Other bedside tests include tandem stance and single-limb stance. These tests are able to detect differences between fallers and non-fallers with PD [Smithson, Morris et al. 1998; Morris, Iansek et al. 2000]. These tests, however, are limited in the clinical setting due to *floor* effects, where patients with postural instability are unable to assume the postures required for the tests. In addition, *ceiling* effects are apparent, where PD patients without postural instability can perform similarly to healthy controls.

Bedside tests of postural stability in PD include the shoulder-tug (retropulsion) test and the functional reach test. The retropulsion test involves pulling the standing patient by the shoulders from behind and observing the number of backward steps required and ability to correct posture. It has reasonable intra- and inter-rater reliability [Smithson, Morris et al. 1998] but is difficult to standardize for differences in patient height, weight and initial posture, is performed in several different ways according to the physician's preference and does not predict falls in daily life [Bloem, Grimbergen et al. 2001].

The functional reach test involves measuring how far a subject can reach forward with the arm positioned at 90 degrees of shoulder flexion [Duncan, Weiner et al. 1990]. Performance in this test can discriminate between fallers and non-fallers with PD [Behrman, Light et al. 2002] and between fallers with PD and healthy controls [Smithson, Morris et al. 1998] and improves in PD patients with rehabilitation [Schenkman, Cutson et al. 1998]. However, a recent study suggested that many strategies can be used to improve functional reach, such as extending the arm from the shoulder [Wernick-Robinson, Krebs et al. 1999].

Laboratory assessment of postural instability in PD is usually limited to the setting of an experimental trial, due to the complexity of the equipment. A variety of instruments have been used to provide accurate data pertaining directly or indirectly to postural sway. In the A-P plane, angular movement of

the COG has been observed directly with linear potentiometers [Bloem, Beckley et al. 1996]. Instruments using tilt sensors can provide direct information about A-P and medial-lateral sway but involve sensing modules, data converters, personal computers and power units [Viitasalo, Kampman et al. 2002]. Indirect information about sway can be obtained from force plates that record ground reaction forces and movement of the centre of foot pressure [Beckley, Bloem et al. 1993; Bloem, Beckley et al. 1996; Frank, Horak et al. 2000; Bronte-Stewart, Minn et al. 2002]. However, information about COG movement needs to be extrapolated from these measurements.

Some investigators have suggested that postural sway is reduced in both the early [Schieppati, Hugon et al. 1994] and late stages of PD [Horak, Nutt et al. 1992], possibly due to active co-contraction and increased body stiffness. Other investigators have found no differences between controls and PD patients in the late stages of the disease [Chong, Horak et al. 1999]. It is uncertain whether sway decreases [Schieppati, Hugon et al. 1994] or increases [Waterston, Hawken et al. 1993; Ashburn, Stack et al. 2001; Viitasalo, Kampman et al. 2002] as the condition worsens. It is also unclear what happens to stability in self-initiated movements as PD becomes more advanced. Despite the significance of falls in PD, few studies have compared measures of postural stability between fallers and non-fallers with PD [Smithson, Morris et al. 1998; Morris, Iansek et al. 2000; Ashburn, Stack et al. 2001; Behrman, Light et al. 2002].

In this study, we performed two related experiments. In the first experiment, we tested the hypotheses that postural sway increases and stability in tests of self-initiated movement worsens as the stage or severity of PD becomes more advanced. In the second experiment we hypothesized that: (1) there would be no differences in sway between fallers and non-fallers with PD in conditions with all sensory inputs present; (2) fallers would sway significantly more than non-fallers in the presence of incongruent sensory information; and (3) fallers would demonstrate significantly worse stability in tests of self-initiated movements.

6.2 METHODS

6.2.1 Subjects

In experiment 1 (table 6.1), 112 subjects with PD as defined by the United Kingdom Parkinson's Disease Brain Bank criteria [Hughes, Ben-Shlomo et al. 1992] (age 66, standard deviation – SD – 10 years, 56% male, height 171, SD 9 cm) and sixty-three healthy controls (age 71, SD 8 years, 52% male, height 166, SD 10 cm) were recruited.

Table 6.1 **Subjects in experiment 1**

	Parkinson Disease			
Factor	**HY I (n=36)**	**HY II (n=33)**	**HY III (n=43)**	**Control (n=63)**
Age (years)	63±11	64±9	70±8	71±8
Male (%)	61	55	54	53
Height (cm)	172±8	172±9	168±8	166±10
Weight (kg)	74±13	71±11	72±21	71±13
PD duration (years)	7(4-13)	11(4-13)	13(7-18)	
UPDRS**	78(44-107)	99(65-130)	113(85-137)	
motor subunit***	8(5-12)	15(12-21)	24(16-29)	
retropulsion item****	0(0-1)	0(0-1)	2(1-2)	
Number PD drugs	1(1-2)	1(1-3)	2(2-3)	
Frequency (per day)*	3(2-4)	4(3-6)	5(3-5)	
Total drugs*	4(2-6)	4(3-5)	5(4-6)	

Data are presented as mean ± standard deviation or median (interquartile range). HY: Hoehn and Yahr. PD: Parkinson's disease. UPDRS: Unified Parkinson's Disease Rating Scale. * $p < 0.05$, ** $p < 0.005$, *** $p < 0.001$ for overall differences across HY stages.

In experiment 2 (table 6.2), 50 PD subjects with a history of falls in the preceding year (age 66, SD 9 years, 56% male, height 171, SD 9 cm) were matched with 50 non-fallers with PD and 50 healthy controls for age, gender and height in a ratio of 1:1:1 from the database of volunteers. The protocol for this study was approved by the Human Studies Ethics Committees at the University of Sydney and the University of New South Wales. Informed consent was obtained from all subjects according to the declaration of Helsinki.

Table 6.2 **Subjects in experiment 2**

Factor	PD fallers (n=50)	PD non-fallers (n=50)	Control (n=50)
Age (years)	66±9	66±10	69±8
Male (%)	56	56	56
Height (cm)	171±9	171±9	169±9
Weight (kg)	70±11	74±9	70±14
PD duration (years)*	7(3-12)	4(2-7)	
Hoehn & Yahr***	3(2-3)	1(1-2)	
UPDRS*	114(71-134)	94 (72-113)	
UPDRS motor**	19(13-26)	12(8-18)	
UPDRS retropulsion item	1 (0-2)	1 (0-1)	
Number PD drugs (per day)	2(1-3)	2(1-3)	
Frequency (per day)	4(3-5)	3(3-5)	
Total drugs (per day)	5(3-6)	4(2-5)	
Postural hypotension (%)	32	38	
Diabetes (%)	2	8	
Angina (%)	14	6	
Myocardial infarct (%)	10	6	
Heart failure (%)	2	2	
Valvular heart disease (%)	2	6	
Hypertension (%)	34	18	
Atrial fibrillation (%)	2	6	
Pacemaker (%)	2	2	
Defibrillator (%)	0	0	
Urinary incontinence (%)	16	20	
Faecal incontinence (%)	4	6	
Hearing impairment (%)	22	22	
Osteoporosis (%)	22	8	
Osteoarthritis – back (%)	32	26	
Osteoarthritis – hip (%)	18	14	
Osteoarthritis – knee (%)	24	12	
Hip fracture (%)	8	2	
Depression (%)	24	22	
Cataract (%)	26	18	
Glaucoma (%)	8	2	
Macular degeneration (%)	4	2	
Myopia (%)	50	56	
Hypermetria (%)	60	52	
Astigmatism (%)	10	8	
Foot pain (%)	26	24	

Data are presented as mean ± standard deviation or median (interquartile range). HY Hoehn and Yahr, PD Parkinson's disease, UPDRS Unified Parkinson's Disease Rating Scale.
* $p < 0.05$, ** $p < 0.005$, *** $p < 0.001$ for differences between fallers and non-fallers with PD.

All subjects were interviewed and examined for medical problems by a geriatrician. Apart from PD, all patients were free of neurological conditions that could impair their balance. In addition, there was no evidence of leg

weakness, abnormal proprioception at the first metatarso-phalangeal joint, loss of sensation in the feet, nystagmus, abnormal vestibular ocular reflexes or a positive Unterberger's sign in any of the subjects. The severity and stage of PD were assessed by the Unified Parkinson's Disease Rating Scale (UPDRS) [Fahn, Elton et al. 1987] and the Hoehn and Yahr (HY) scale [Hoehn and Yahr 1967]. Postural sway was measured while patients were experiencing a typical "on" period in their anti-parkinsonian medication cycle. All patients were free of dyskinesia, leg tremor or substantial upper limb tremor at the time of sway measurements.

6.2.2 Procedure

Postural sway was measured while patients were experiencing a typical "on" period in their anti-parkinsonian medication cycle. The sway instrument used in this study have been described in detail in earlier chapters and previous studies [Lord, Clark et al. 1991; Lord, McLean et al. 1992; Lord, Caplan et al. 1993]. The following four tests of postural sway were performed: the subject stood initially on a non-compliant surface (the linoleum-covered floor) (i) with the eyes open and then (ii) with eyes blindfolded and secondly on a compliant surface (a 10 cm-high rectangle of foam, 40 x 40 cm wide) (iii) with the eyes open and then (iv) with eyes blindfolded. These four tests were used to assess the subject's postural stability with (i) all sensory inputs present, (ii) vision absent, (iii) leg sensation altered and (iv) vision absent and leg sensation

altered. Each test of postural sway was performed once and lasted for 30 s. Subjects were instructed to stand as still as possible, with feet shoulder width apart, looking at a point on the wall horizontally in front. For each of the tests, the investigator recorded the maximal distances swayed in the anterior-posterior and lateral planes and the total sway path distance (measured by counting the number of 1 mm squares through which pen moved).

Stability during self-initiated movements was assessed initially using the maximal A-P range test and secondly the coordinated stability task (CST).

6.2.3 Statistics

All analyses were performed using SPSS 10 for Windows. All measures of postural sway were examined for normality using stem-and-leaf plots and the Kolmogorov-Smirnov test statistic and were found to be non-parametric in distribution. Overall comparisons of sway distances, maximal A-P ranges and CST scores across the three H&Y stages of PD were made using Kruskal-Wallis tests. Comparisons between the H & Y stage I group and healthy controls, between fallers and non-fallers with PD and between non-fallers and healthy controls were made using Mann-Whitney-U tests. Non-parametric correlations between sway measures and UPDRS scores were made by calculating Spearman's rho coefficients.

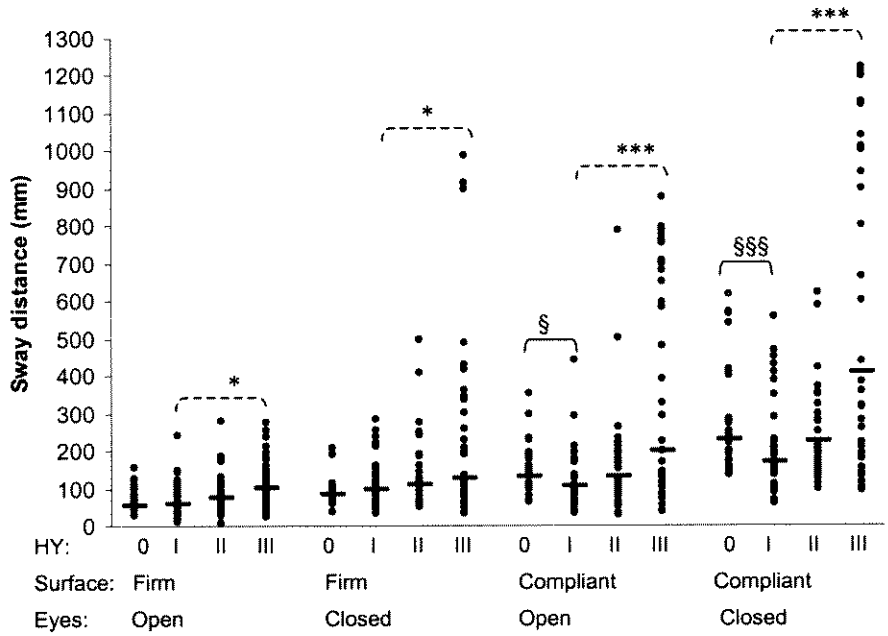
6.3 RESULTS

6.3.1 Experiment 1

6.3.1.1 Hoehn and Yahr stage I and healthy controls

There were no significant differences between HY stage I PD patients and healthy controls in sway distance on the firm surface with the eyes open or closed or maximal A-P range (fig. 6.2). PD patients had significantly less sway on the compliant surface with the eyes open ($p < 0.05$) and closed ($p < 0.001$) (fig. 6.1), smaller maximal A-P ranges ($p < 0.001$) and higher CST scores ($p < 0.005$) (fig. 6.2).

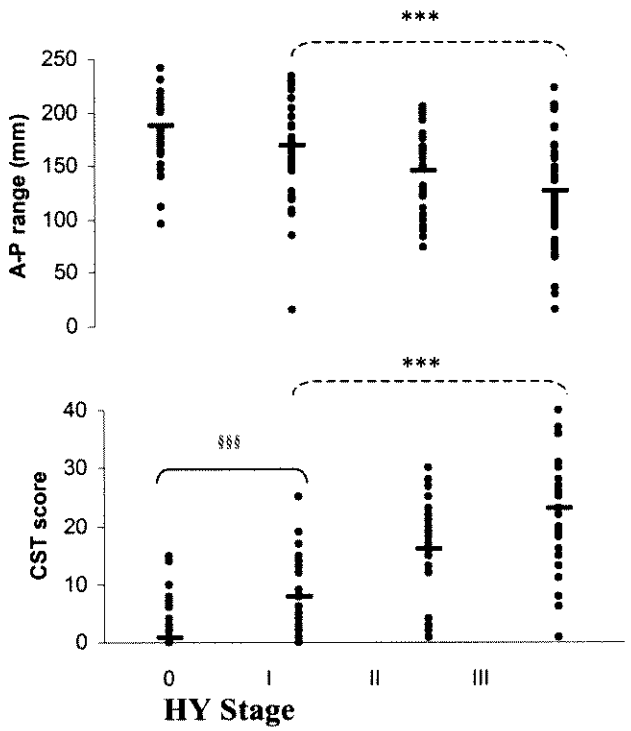
Figure 6.1 **Sway distances across a range of sensory conditions and Hoehn and Yahr (HY) stage in experiment 1**



HY stage 0 refers to the healthy control group. * $p < 0.05$, *** $p < 0.001$ for overall differences across HY stages. § $p < 0.05$, §§§ $p < 0.001$ for differences between healthy controls and HY stage I patients. Horizontal lines indicate medians.

Similarly, there were no significant differences between HY stage I patients and healthy controls in maximal A-P range (fig.6.2).

Figure 6.2 **Maximal anterior-posterior (A-P) range and coordinated stability task (CST) scores across the range of Hoehn and Yahr stages in experiment 1**



HY stage 0 refers to the healthy control group. * $p < 0.05$, *** $p < 0.001$ for overall differences across HY stages. § $p < 0.05$, §§§ $p < 0.001$ for differences between healthy controls and HY stage I patients. Horizontal lines indicate medians.

As the HY stage of PD increased from I to III, sway distances increased on the floor with the eyes open ($p < 0.05$) and closed ($p < 0.05$) and on the compliant surface with the eyes open ($p < 0.001$) and closed ($p < 0.001$) (fig. 6.1), maximal A-P ranges decreased ($p < 0.05$ and 0.005 respectively) and CST scores increased ($p < 0.001$) (fig. 6.2). There were significant correlations between HY stage and all measures of postural stability ($p < 0.05$ to $p < 0.001$) (table 6.3).

Table 6.3 **Spearman's coefficients**

	Eyes open (firm)	Eyes closed (firm)	Eyes open (compliant)	Eyes closed (compliant)	A-P Range	CST
HY	.30**	.23*	.38***	.42***	-.35***	.58***
UPDRS	.01	-.06	.13	.11	.04	.13
Motor	.19*	.16	.30**	.23*	-.40***	.48***
Retrop.	.14	.14	.25*	.23*	-.19*.	41***
Duration	.33**	.44***	.39***	.32**	-.27**	.40***

Correlations between measures of disease stage and severity and sway distances, maximal anterior-posterior (A-P) balance range and coordinated stability task (CST) scores.
* $p < 0.05$, ** $p < 0.005$, *** $p < 0.001$.

6.3.1.2 UPDRS scores, duration of PD and sway

Measures of postural stability were not significantly correlated with total UPDRS score (table 6.3). In contrast, the UPDRS motor subscale was significantly correlated with sway on the floor with eyes open ($p < 0.05$), on the compliant surface with eyes open ($p < 0.005$) and on the compliant surface with eyes closed ($p < 0.05$), maximal A-P balance range ($p < 0.001$) and performance in the CST ($p < 0.001$). The retropulsion item of the UPDRS was significantly correlated with sway of the compliant surface with eyes open ($p < 0.05$) and closed ($p < 0.05$), maximal A-P range ($p < 0.001$) and CST score ($p < 0.001$). The duration of PD since the onset of symptoms was significantly correlated with all measures of postural stability ($p < 0.001$ to $p < 0.005$).

6.3.2 Experiment 2

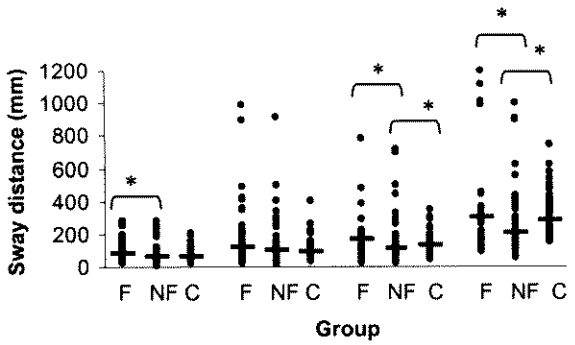
6.3.2.1 Falls and severity of PD

Compared with non-fallers with PD, fallers with PD had significantly higher stages of disease as assessed by the HY scale ($p < 0.001$) and worse symptoms and signs on the UPDRS scale ($p < 0.05$) and UPDRS motor subscale ($p < 0.005$) (table 6.2). There were no significant differences between the groups in past medical history or degree of retropulsion.

6.3.2.2 Sway distances

Fallers with PD had significantly greater sway distances than non-fallers on the firm surface with eyes open ($p < 0.05$) and on the compliant surface with eyes open ($p < 0.05$) and closed ($p < 0.05$) (fig.6.3).

Figure 6.3 **Sway distances across a range of sensory conditions**



Results in fallers with PD (F), non-fallers with PD (NF) and healthy controls (C) in experiment 2.
* $p < 0.05$, *** $p < 0.001$ for overall differences across HY stages. § $p < 0.05$, §§§ $p < 0.001$ for differences between healthy controls and HY stage I patients.

Although the group of fallers had a higher median value for sway on the firm surface with the eyes open than non-fallers, this difference was not statistically significant.

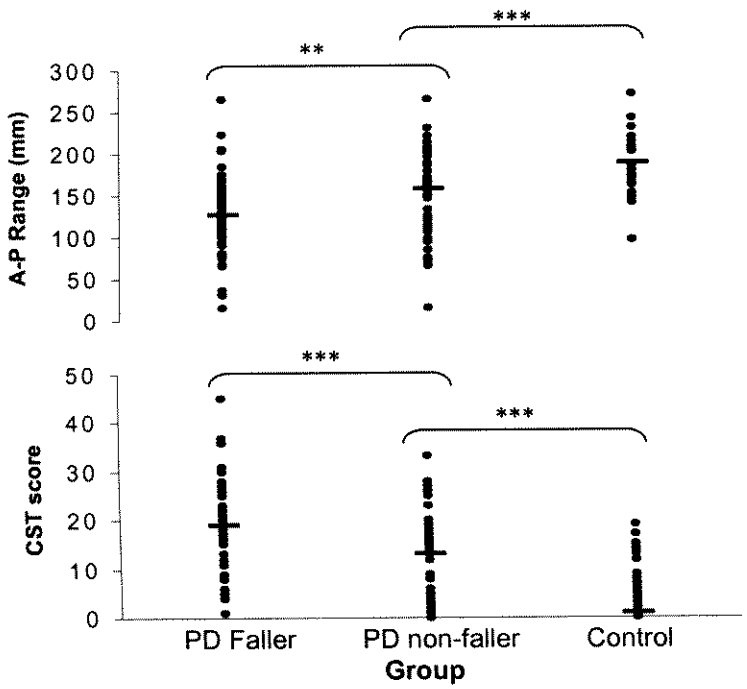
Non-fallers with PD had significantly less sway than healthy controls on the compliant surface with the eyes open ($p < 0.05$) and closed ($p < 0.05$). There were no significant differences between theses groups in sway on the firm surface with the eyes open or closed, although the group of non-fallers with PD had higher median values of sway distances.

Fallers with PD had significantly greater sway than healthy controls on the firm surface with eyes open ($p < 0.05$) and closed ($p < 0.005$). There were no significant differences between these groups on the compliant surface with eyes open or closed.

6.3.2.3 Maximal A-P range and CST score

Compared with non-fallers, fallers with PD had significantly smaller maximal A-P balance ranges ($p < 0.005$) and worse (higher) CST scores ($p < 0.001$) (fig. 6.4). Compared with healthy controls, non-fallers with PD had significantly smaller maximal A-P balance ranges ($p < 0.001$) and worse coordinated stability scores ($p < 0.001$).

Figure 6.4 **Maximal anterior-posterior (A-P) range and coordinated stability task (CST)**



Scores in fallers with PD (F), non-fallers with PD (NF) and healthy controls (C) in experiment 2.
*$p < 0.05$, *** $p < 0.001$ for overall differences across HY stages. § $p < 0.05$, §§§ $p < 0.001$ for differences between healthy controls and HY stage I patients.

6.4 DISCUSSION

These experiments demonstrated that measures of stability worsen as the stage, severity and duration of PD increases. In the early stage of PD, postural sway decreases or remains unchanged. Stability in tests requiring self-initiated movements, however, deteriorates even in the early stage of the disease.

Patients with PD who fall tend to have worse stability than PD patients who do not fall.

In experiment 1, the four groups of subjects were similar in age, male-to-female ratio, height or weight (table 6.1). In experiment 2, PD fallers, PD non-fallers and controls were matched as closely as possible for all these variables in a 1:1:1 ratio (table 6.2). Matching in this study was crucial as investigators have reported increases in postural sway after the age of 30 years [Overstall, Exton-Smith et al. 1977; Imms and Edholm 1981; Fernie, Gryfe et al. 1982; Maki, Holliday et al. 1990] and in women compared to men [Overstall, Exton-Smith et al. 1977]. It was similarly important to exclude patients and controls with evidence on history and clinical examination of other conditions that might influence performance on tests of balance.

All measurements of postural stability in this study were performed while patients were experiencing a typical "on" phase, when they felt that their parkinsonian symptoms were controlled to the usual degree when the medications were working, in order to optimize patients' comfort and compliance with the tests. Although levodopa may improve certain postural responses [Frank, Horak et al. 2000], postural stability generally responds poorly to antiparkinsonian medications [Bloem, Beckley et al. 1994; Bloem, Beckley et al. 1996] and PD patients may perform worse on tests of sensory organization and balance during the "on" phase of therapy [Bronte-Stewart, Minn et al. 2002]. It is possible that PD patients may have had different

amounts of sway if they were examined in the "off" phase or at random times in their treatment cycle. Previous investigations by our group, however, have found that levodopa therapy does not change sway significantly but improves stability during self-initiated movements.

Most studies dealing with sway in PD have used force platforms that measure centre of foot pressure motion as an approximation to COG motion [Beckley, Bloem et al. 1993; Bloem, Beckley et al. 1996; Frank, Horak et al. 2000; Bronte-Stewart, Minn et al. 2002]. In addition, they assume the body stands as an inverted pendulum with movement only about the ankles. In reality, the body is a multi-segmented structure with movement also at the knees and hips. In this study, we use a sway meter similar to the early instruments developed by Hinsdale (1887) [Hinsdale 1887; Lanska 2001]. Our instrument measures sway, or COG motion, directly at the level of the waist in the horizontal plane and takes movement at the ankles, knees and hips into account. In addition, it is inexpensive, readily portable to the outpatient clinic or patient's residence and simple to use. Its measures have been validated as predictors of falls in cohorts of elderly subjects [Lord, Clark et al. 1991; Lord, Clark et al. 1991; Lord, McLean et al. 1992; Lord, Ward et al. 1993; Lord, Sambrook et al. 1994; Lord and Ward 1994; Lord, Ward et al. 1994; Lord and Clark 1996]. As it produces objective measurements of sway distances, it does not have the floor or ceiling effects of most bedside tests of postural stability. Limitations of the sway meter include artefacts caused by rotation of the torso, tremor and hyperkinesia and underestimation of sway if pen markings overlap. These

problems were reduced by instructing subjects to stand as still as possible while focusing on a point on the wall directly in front and by limiting the duration of the tests to thirty seconds each. In this study, patient with "on" phase dyskinesia, leg tremor while standing and substantial upper limb tremor were excluded.

The physical burden of PD experienced by the patients was measured using clinician-based scales. The HY scale [Hoehn and Yahr 1967] was used to quantify the stage of the disease and the UPDRS motor subunit [Fahn, Elton et al. 1987] to measure severity of signs [Hobart, Lamping et al. 1996]. The duration of the disease from the time of onset of symptoms and a history of falls in the preceding year were additional measures of disease burden. HY stage and duration of disease were significantly correlated with all measures of stability. The motor subunit of the UPDRS was significantly correlated with all measures except sway on the firm surface with eyes closed.

We studied postural sway in a number of sensory conditions in order to examine how sensory integration changes with stage, severity and duration of PD. Altering sensory conditions, increased sway in all HY groups but did not alter this pattern. The greatest amount of sway was observed when vision was absent (with eyes closed), somatosensory inputs from the legs were modified (by standing on a compliant surface) and subjects were dependent upon vestibular inputs for maintaining stability. As expected, fallers swayed significantly more than non-fallers with PD in almost all sensory conditions.

There were no significant differences in sway between these groups when standing on the firm surface with vision removed, although fallers tended to sway more. The ability to integrate sensory information deteriorates with advancing disease, especially when somatosensory inputs from the legs are incongruous with the degree of movement perceived by the vestibular system. These findings concur with those of previous studies examining stability, stage [Waterston, Hawken et al. 1993], duration and severity [Ashburn, Stack et al. 2001; Viitasalo, Kampman et al. 2002] of PD.

Dynamic stability, which is required for coordinated, self-initiated movements, deteriorated as the stage of PD became more advanced. The maximal A-P balance range demonstrated how far subjects could move forwards or backwards without losing balance or moving their feet. Unlike the functional reach test, it is not influenced by strategies to improve reach by extending at the shoulders. A drawback of both tests is the difficulty in determining whether subjects are leaning to the limits of their stability or restraining themselves due to fear of falling. However, balance ranges decrease as PD becomes more advanced, suggesting that perturbations will be more likely to push the COG beyond the limits where it can be supported. It is not surprising that fallers with PD have significantly lower balance ranges than non-fallers and controls. The CST tested subjects' ability to move their COG in a controlled and stable manner near their limits of stability. The dimensions of the convoluted track used in this task were chosen a priori to reflect the range of linear and rotational movements the COG would make

during necessary activities of daily living, such as reaching for objects, turning and bending over [Lord, Lloyd et al. 1996]. As performance in this test depends upon maximal A-P and mediolateral ranges, it is not surprising that scores worsened with increasing HY stage and that fallers performed worse than non-fallers and controls.

In this study, scores in the retropulsion test item of the UPDRS correlated significantly with sway measures on the compliant surface, balance ranges and CST scores. No significant differences, however, were observed in this test between fallers and non-fallers with PD. Although it gives some impression of how patients may respond to external perturbations, it provides limited information of stability during self-initiated tasks. As PD patients are more likely to fall in response to self-generated rather than external perturbations the usefulness of the retropulsion test in the clinical context is limited.

Problems with dynamic stability in PD occurs as a result of muscle rigidity, ankle stiffness [Dietz, Berger et al. 1988], increased destabilizing responses to perturbations and poorly-sequenced compensatory responses [Beckley, Bloem et al. 1991; Beckley, Bloem et al. 1993; Bloem, Beckley et al. 1996]. Anticipatory postural responses cannot be scaled appropriately to match the magnitude of perturbations [Horak, Nutt et al. 1992; Bloem, Beckley et al. 1995; Latash, Aruin et al. 1995], even when perturbations are self-initiated [Frank, Horak et al. 2000]. As a result, patients are unable to generate forces strong enough to support their centre of gravity (COG) when it is perturbed.

Furthermore, PD patients have difficulty adapting their patterns of muscular activity in response to changes in environmental conditions [Chong, Jones et al. 1999].

This study produced some unexpected findings. HY stage I patients swayed significantly less than healthy controls when standing on a compliant surface. These patients tended to sway more than controls on the firm surface but the increase was not significant. In addition, there were no significant differences in sway on the compliant surface between fallers with PD and healthy controls. Non-fallers with PD swayed significantly less than controls on this surface. Patients with PD who have experienced falls perform just as well as healthy counterparts in this sensory condition.

There are several possible explanations for these findings. It is possible that PD patients have increased background postural muscle activity. This could result from co-contraction of antagonistic muscle groups secondary to fear of falling. Some investigators have found that PD patients of HY stages III and IV have reduced sway compared with controls across a range of sensory conditions [Horak, Nutt et al. 1992; Schieppati, Hugon et al. 1994] but have been unable to demonstrate any co-contraction or increase in background muscle activity to explain this. As surface electromyography was not performed in our study, we cannot exclude the possibility that HY stage I patients may have used this strategy in response to the increased fear of falling while standing on the compliant surface. This is unlikely to be the sole

explanation, as falls are more common in the latter stages of PD [Bloem, Grimbergen et al. 2001] and fear of falling and co-contraction should increase, and therefore sway decrease, as the disease becomes more advanced. We found, however, that sway increases as severity and stage of disease increases.

Another possible explanation is that the reduced sway early in the course of the disease is secondary to increased stiffness in the postural muscles and joints [Dietz, Berger et al. 1988]. If this were true, however, stiffness should increase and sway should decrease as PD becomes more advanced [Lauk, Chow et al. 1999]. These explanations rely on the ability of HY stage I patients to alter their postural strategies between standing on the firm surface and standing on the compliant one. PD patients, however, usually have difficulty changing postural set to adapt to different support conditions [Chong, Jones et al. 1999].

Although no significant differences in age across HY and control groups were observed in experiment 1, the HY I patients tended to be younger than their healthy counterparts. Similarly, both fallers and non-fallers with PD tended to be younger than healthy controls in experiment 2. These differences in age may have contributed to some of the unexpected findings. It is also possible that controls had medical conditions that were not picked up on baseline history and examination and could contribute to postural instability. A more serious issue is the validity of measures of sway as indicators of falling risk. There was a large overlap of all sway measures in all groups examined in this

study. To date, no prospective study has found that sway measures are independent predictors of falls in PD patients or other high-risk groups. This is not surprising as falls are the result of combinations of multiple intrinsic, extrinsic and environmental factors, most of which are not reflected in tests of sway.

6.5 CONCLUSION

In the early stages of PD, sway can be normal or reduced. As the stage and severity of the disease worsens, sway increases. Fallers with PD may have normal sway. Dynamic postural stability worsens as the stage and severity of PD increases, with fallers performing worse than non-fallers with PD. Even in the early stages of PD, patients may have worse dynamic stability than controls.

CHAPTER 7

THE USUAL GAIT SPEED, CADENCE AND STEP LENGTH OPTIMISE HEAD AND PELVIC RHYTHM

7.1 INTRODUCTION

Humans have a usual, comfortable gait speed that is the product of a preferred combination of step length and step frequency (cadence) [Murray, Kory et al. 1966]. When subjects are requested to walk at speeds slower or faster than their usual speed, the efficiency of energy consumption decreases [Cavagna, Saibene et al. 1963; Cavagna, Thys et al. 1976; Ralston 1976; Waters, Lunsford et al. 1988] and spatial variability [Brach, Berthold et al. 2001] and temporal irregularity [Menz, Lord et al. 2003] increase. This suggests that efficiency and rhythm are major determinants of an individual's locomotor pattern.

Control of balance is also an important factor underlying an individual's locomotor pattern, as a potential for imbalance when walking exists due to the inertia of the upper body and the times when only one foot is in contact with the ground. The 'cautious' locomotor pattern, characterized by reduced speed and step length and adopted by older people, is likely to be an adaptation to minimize perturbations to the body and reduce the risk of falls [Maki 1997].

On the other hand, adopting a lower than usual gait speed and step length may predispose to trips and slips [Guimaraes and Isaacs 1980; Wolfson, Judge et al. 1995]. It is therefore important to clarify the relationship between gait stability and temporo-spatial parameters, such as gait speed, cadence and step length.

It has been proposed that the measurement of accelerations of the head and pelvis provide useful indicators of gait rhythm and that rhythm is closely related to gait stability [Menz, Lord et al. 2003; Menz, Lord et al. 2003]. Head and pelvic accelerations were significantly less rhythmic in young subjects walking on an irregular, bumpy surface compared to a smooth, even surface [Menz, Lord et al. 2003], in elderly people with a high risk of falls compared to those at a low risk [Menz, Lord et al. 2003], and in subjects with diabetic peripheral neuropathy compared to healthy controls [Menz, Lord et al. 2004]. In each of these studies, we assessed subjects at their preferred or usual gait speed in order to obtain insights into stability in real life situations. Preliminary observations indicated that subjects' usual gait speed maximized the rhythm of acceleration signals [Menz, Lord et al. 2003]. The aim of this study was to examine the hypothesis that an individual's usual gait speed, cadence and step length optimize the rhythm of head and pelvis accelerations in vertical, A-P and lateral planes.

7.2 METHODS

7.2.1 Subjects

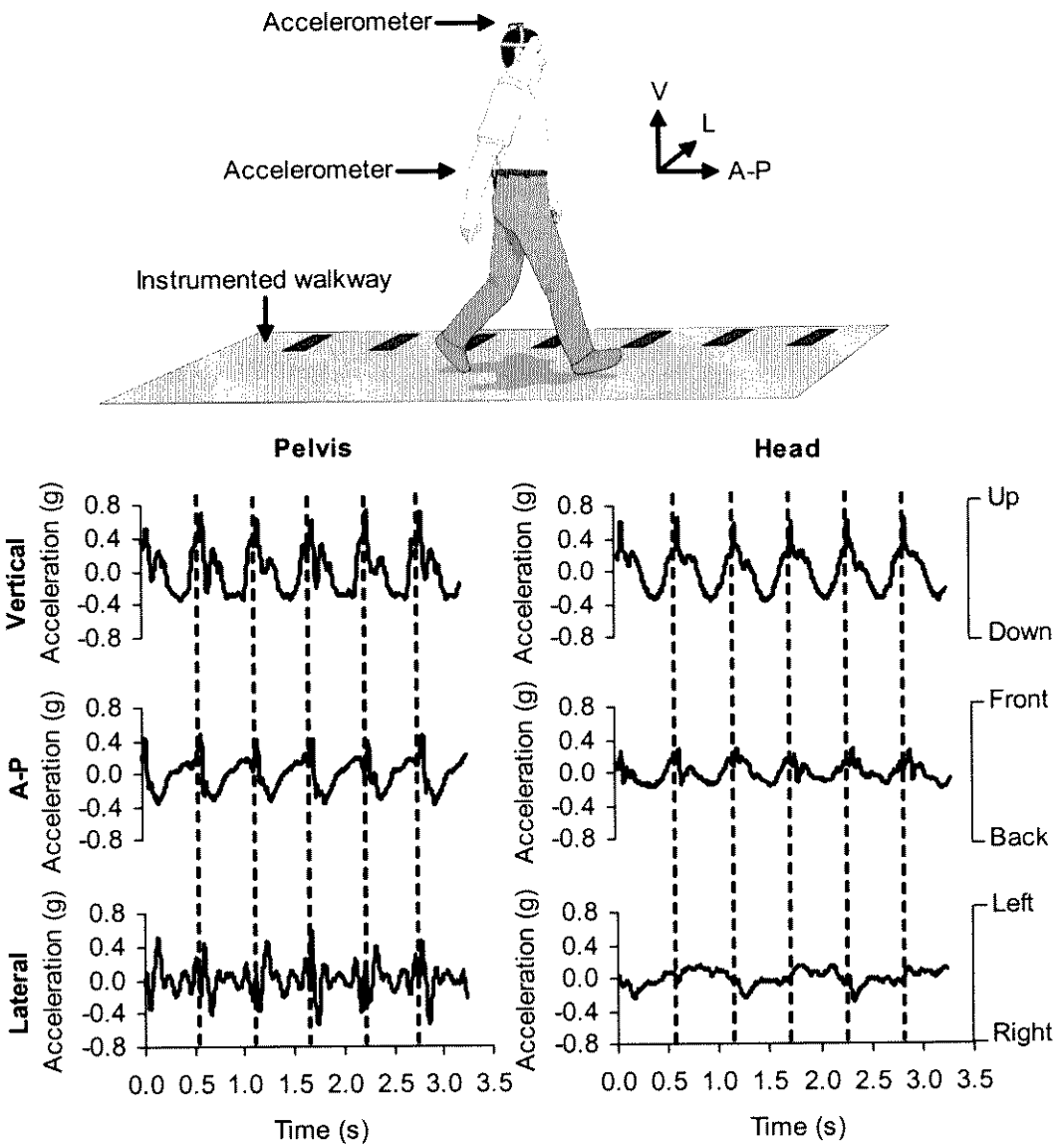
A sample of 10 healthy volunteers, 4 men and 6 women with ages ranging from 17 to 31 years (mean 26 ± standard error of the mean – SEM - 5.3 years), height 155 to 178 cm (mean 170 ± 3.1 cm) and weight 41 to 80 kg (mean 58 ± 4.2 kg), were recruited from the staff and student population of the Prince of Wales Medical Research Institute. All subjects were free of neurological, muscular and skeletal conditions affecting mobility and balance. The Human Studies Ethics Committee at the University of New South Wales gave approval for the study, and informed consent was obtained from all subjects according to the Declaration of Helsinki prior to participation.

7.2.2 Apparatus

Linear accelerations of the head and pelvis were measured along vertical, anterior-posterior (A-P) and lateral axes using piezoresistant accelerometers with ranges of -10 to +10 gravities and sampling frequencies of 200 Hz (fig. 7.1). The head accelerometer was attached firmly to the vertex using a light plastic frame. The pelvis accelerometer was attached to the back at the level of the second lumbar vertebral body using a Velcro™ belt. The accelerometers were wired to a light-weight laptop computer via a data acquisition card

interface. The computer was carried by an assistant walking behind the subject during gait trials. All subjects wore appropriately fitted, standardized walking shoes. In some trials, an electronic metronome was used to modify cadence and a one-meter ruler was used to give subjects an impression of the step lengths they needed to take for the trial. An instrumented walkway (the GAITRite® mat) was used to ensure as far as possible that subjects walked at the set cadence and step length when required and at a constant step width. The instrumented walkway was 460 cm long with an active area of 366 cm long by 61 cm wide, containing pressure sensors arranged in a grid pattern with a spatial resolution of 1.27 cm and a sampling frequency of 80 Hz. The test-retest reliability of the accelerometry equipment [Menz, Lord et al. 2003] and the instrumented walkway [Lord, Menz et al. 2003] are described in detail elsewhere.

Figure 7.1 **Accelerometers and tracings**



Top. Accelerometers measure linear acceleration in gravities (g) at the head and pelvis in vertical (V), anterior-posterior (A-P) and lateral (L) planes and the instrumented walkway (top). Bottom. Acceleration signals from a subject in vertical, A-P and lateral planes at the head and pelvis (bottom). Dashed lines indicate heel strike.

7.2.3 Protocol

Gait trials were conducted along a smooth, horizontal 15 m length of the laboratory. Data for the middle 10 m of each walking trial, when the subject was walking at a constant velocity, were analysed.

7.2.3.1 Experiment 1.

The aim of this experiment was to determine the effect of variations in gait speed on acceleration patterns of the head and pelvis. Subjects were asked to walk at five gait speeds: (i) much slower than usual, as though they were strolling in the park; (ii) slightly slower than usual; (iii) their usual gait speed; (iv) slightly faster than usual (as though they were in a hurry) and (v) as fast as possible without running (as though they were late for an appointment). Subjects performed three walking trials at each speed and the order of the speeds was randomized.

7.2.3.2 Experiment 2

The aim of this experiment was to determine the effect of variations in cadence on acceleration patterns of the head and pelvis. Each subject performed three walking trials at his or her usual gait speed. The average

cadence at this speed was recorded. Each subject was then asked to walk while stepping in time to a metronome set at the following cadences: (i) 33% of usual cadence; (ii) 67% of usual cadence; (iii) usual cadence; (iv) 133% of usual cadence and (iv) 166% of usual cadence. Three walking trials were made for each of the metronome-set cadences and the order of the cadences was randomized.

7.2.3.3 Experiment 3

The aim of this experiment was to determine the effect of variations in step length and cadence on acceleration patterns of the head and pelvis. Three walking trials were made for every subject at his or her usual self-selected gait speed. Both the average step length and cadence at this speed were recorded. Subjects were then asked to perform walking trials using each of the following step lengths in random order: (i) very small step lengths (approximately half the length of the foot); (ii) small step lengths (half the usual step length); (iii) usual step lengths; (iv) slightly longer than usual step lengths and (v) very long step lengths. The length of the step was indicated to the subject prior to the trials using the ruler and monitored during the trial using the instrumented walkway. For each of the step lengths, cadences were set at each of the following levels in a random order: (i) 67% of usual; (ii) usual cadence; and (iv) 125% of usual. Subjects were allowed four practice trials prior to three recorded trials for each combination of step length and cadence.

7.2.4 Data acquisition

Before each session, the accelerometers were calibrated statically against gravity to estimate ± 1 g values. Head and pelvis accelerations for each walking trial were recorded at 200 Hz. The mean vertical, A-P and lateral accelerations over the duration of each walking trial were assumed to be zero as the subjects were walking on a horizontal surface at a constant gait speed. The calculation of variables was discussed in the introduction.

7.2.5 Statistical analysis

Data for statistical analysis in this study was obtained by averaging the measurements of three walking trials for each gait speed (experiment 1), cadence (experiment 2) and step length/cadence combination (experiment 3) for each subject. All analyses were performed using SPSS 10 for Windows. In all experiments, values of HR in all orthogonal planes had parametric distributions when examined using box plots and the Shapiro-Wilks statistic. Within-subjects differences in HR across the five levels of gait speed (experiment 1) or cadence (experiment 2) were analyzed using one-way repeated measures analysis of variance (ANOVA). Two-way repeated measures ANOVA with step length (five levels) and cadence (three levels) as

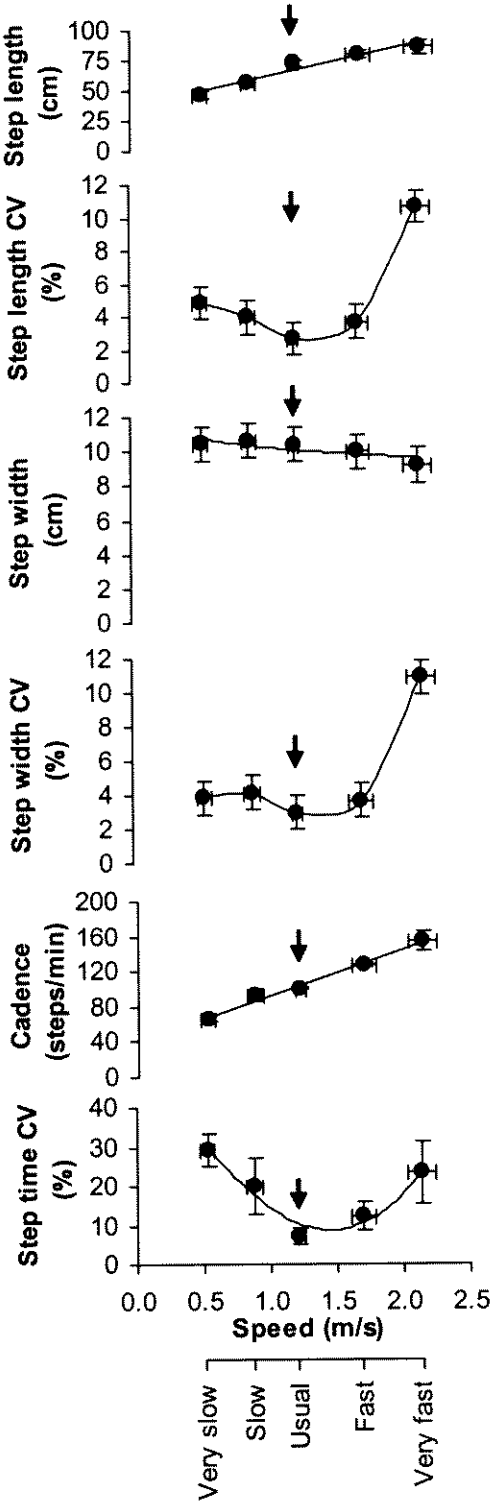
within-subject factors was used to examine the effect of step length on HR. Homogeneity of variances was assumed in all statistical analyses as F-max ratios were consistently less than 3. As Mauchly's test was not significant in any analysis, sphericity of the data was assumed.

7.3 RESULTS

7.3.1 Effect of variations in gait speed on step length, cadence and acceleration patterns

Gait speed increased linearly from very slow (0.5 ± 0.05 m/s) through to the very fast condition (2.1 ± 0.1 m/s) (fig. 7.2).

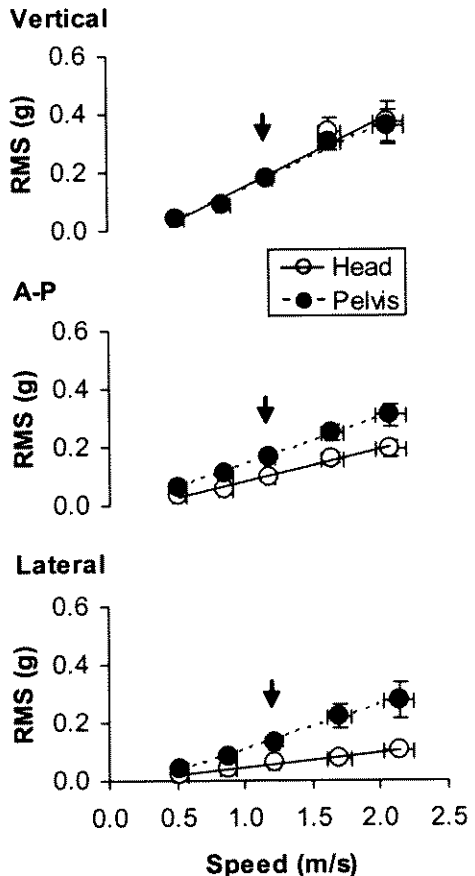
Figure 7.2 **The effect of gait speed on step length, cadence and step time CV in experiment 1**



Bars indicate SEM. Arrow indicates usual gait speed.

The preferred or usual gait speed was 1.2 ± 0.04 m/s. Step length was 73 ± 3 cm at the usual gait speed and varied from 47 ± 3 cm (very slow) to 86 ± 6 cm (very fast). Cadence increased from 67 ± 3 (very slow) to 154 ± 11 steps/minute (very fast) and was 100 ± 1 steps/minute at the usual speed. Step time CV was highest at the very slow speed, decreased to the trough at the usual speed and then increased as speed increased from usual to very fast. Acceleration RMS (fig. 7.3) increased in all planes at the head and pelvis as speed increased from very slow to very fast.

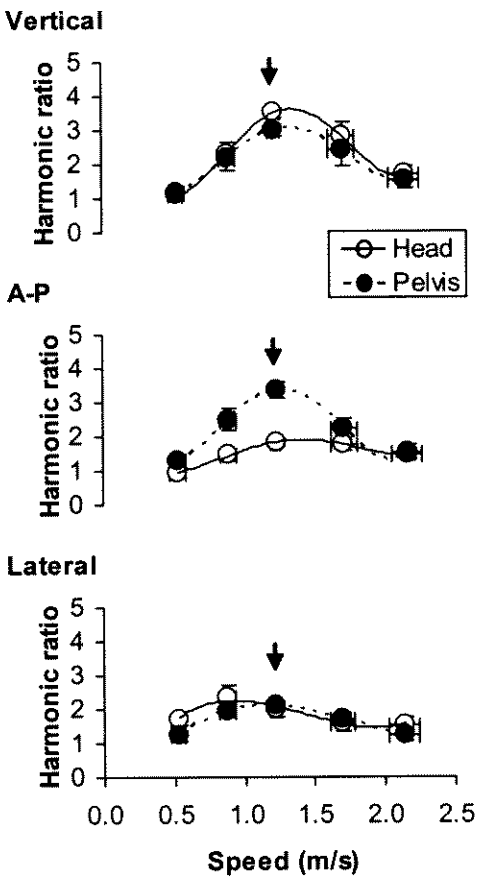
Figure 7.3 **The effect of gait speed on RMS, measured in gravities (g), in experiment 1**



Bars indicate SEM. Arrow indicates usual gait speed.

HRs (fig. 7.4) were highest at the usual gait speed and decreased as gait speed either increased or decreased from this level in both vertical (head $F_{4,36} = 18.2$, $p < 0.001$; pelvis $F_{4,36} = 13.8$, $p < 0.001$) and A-P planes (head $F_{4,36} = 7.1$, $p < 0.001$; pelvis $F_{4,36} = 11.3$, $p < 0.001$).

Figure 7.4 **The effect of gait speed on HR in experiment 1**



Bars indicate SEM. Arrow indicates usual gait speed.

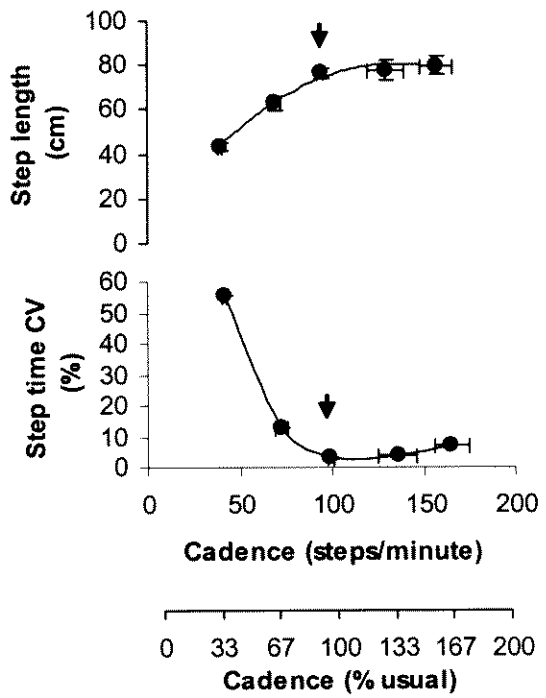
In the lateral plane, HRs at the head were highest at the slow speed while HRs at the pelvis were highest at the usual gait speed and tended to decrease as

speed varied from these levels (head $F_{4,36} = 3.7$, $p < 0.05$; pelvis $F_{4,36} = 5.2$, $p < 0.005$).

7.3.2 Effect of variations in cadence on acceleration patterns

Subjects walked in time to a metronome at a wide range of cadences (fig. 7.5) from 33% (41 ± 1 steps/minute) to 167% (159 ± 9 steps/minute) of preferred or usual cadence (99 ± 2 steps/minute).

Figure 7.5 **The effect of cadence on step length in experiment 2**

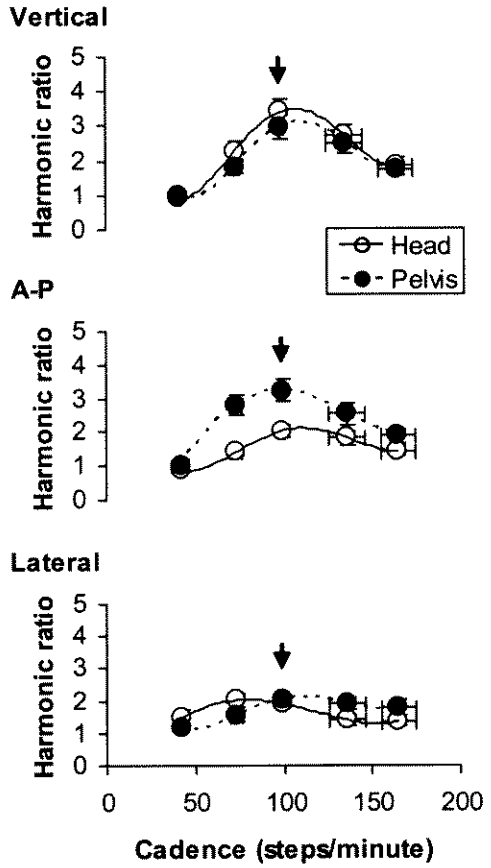


Bars indicate SEM. Arrow indicates 100% (usual) cadence.

Gait speeds corresponding to these cadences increased from 0.3 ± 0.01 to 2.1 ± 0.1 m/s. Step length increased as cadence increased from 33 % (43 ± 2 cm) to 100 % of usual (76 ± 4 cm) but appeared to plateau from 100 % to 167% of usual (79 ± 4 cm).

There were differences in HR across the five cadences in vertical (head $F_{4,36}$ = 14.7, $p < 0.001$; pelvis $F_{4,36} = 14.8$, $p < 0.001$), A-P (head $F_{4,36} = 9.8$, $p < 0.001$; pelvis $F_{4,36} = 11.7$, $p < 0.001$) and lateral planes (head $F_{4,36} = 4.1$, $p < 0.05$; $F_{4,36} = 2.4$, $p = 0.07$). In vertical and A-P planes, HRs were highest at 100% cadence and decreased as cadence increased or decreased from this point (fig. 7.6). In the lateral plane, HRs at the head were highest at 67% cadence and HRs at the pelvis were highest at 100% cadence.

Figure 7.6 **The effect of cadence on HR in experiment 2**

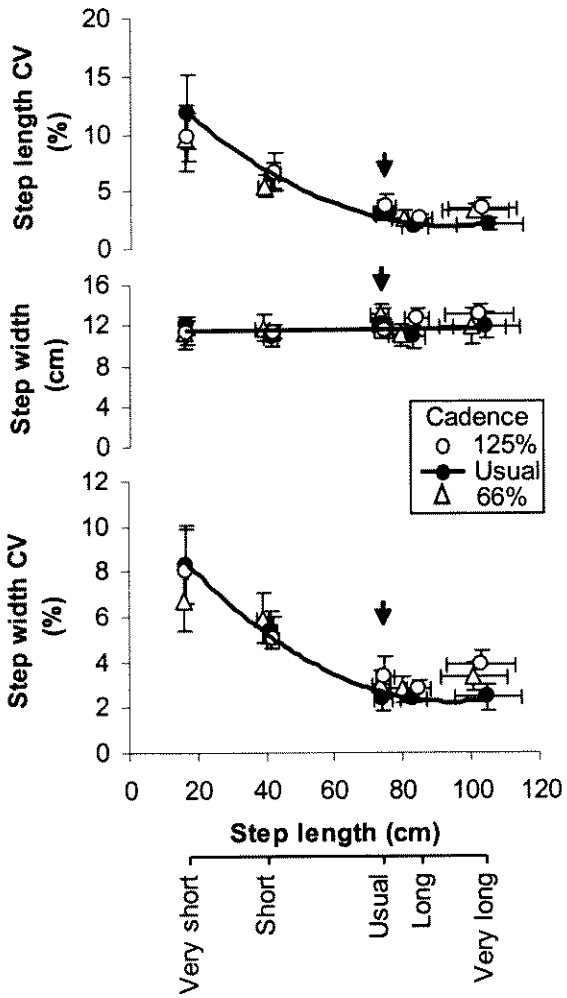


Bars indicate SEM. Arrow indicates 100% (usual) cadence.

7.3.3 Effect of step length variations on acceleration patterns

Subjects walked at five different step lengths, ranging from very short (16 ± 2 cm) to very long (105 ± 6 cm), for cadences 67% (70 ± 5 steps/minute), 100% (101 ± 2 steps/minute) and 125% (126 ± 5 steps/minute) of usual (fig. 7.7).

Figure 7.7 **Relationships between step length/cadence combinations and RMS**



Bars indicate SEM. Arrow indicates usual step length.

RMS increased as step length, cadence and hence gait speed increased. F-statistics for differences in harmonic ratio across the five levels of step length and three levels of cadence are presented in table 7.1.

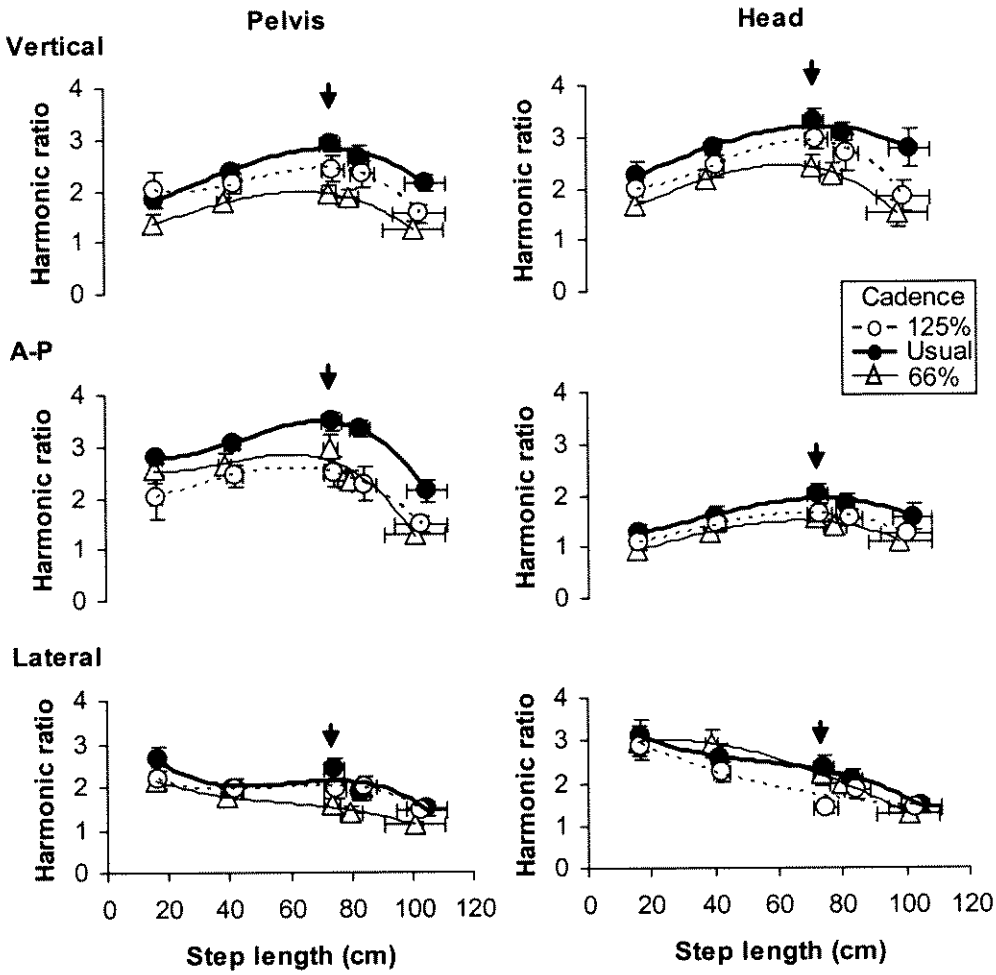
Table 7.1 **Within-subject differences in HR**

		Step length		Cadence	
Site	**Plane**	$F_{4,36}$	***P***	$F_{2,18}$	***p***
Head	Vertical	10.7	< 0.001	16.0	< 0.001
Pelvis	Vertical	8.1	< 0.001	17.7	< 0.001
Head	A-P	8.2	<0.001	3.0	NS
Pelvis	A-P	10.7	< 0.001	10.0	< 0.001
Head	Lateral	19.2	< 0.001	3.6	< 0.05
Pelvis	Lateral	10.1	< 0.001	6.8	< 0.05

F-statistic examining for differences in HR across five levels of step length (very short, short, usual, long and very long) and three levels of cadence (67%, 100% and 125%), NS not significant, A-P anterior-posterior

Highest HRs in vertical and A-P planes at the head and pelvis were observed at the usual step length and cadence (fig. 7.8) and tended to decrease as step length and cadence were varied from the usual levels.

Figure 7.8 **Relationships between step length/cadence combinations and HR**



Bars indicate SEM. Arrow indicates usual step length.

In these planes, there were quadratic trends between HR and step length and cadence (table 7.2). In the lateral plane, the highest HRs at the head and pelvis were observed at very small step lengths and the usual cadence and tended to decrease as step length increased or cadence increased or decreased (fig. 7.8). In this plane, there were linear trends between step length and HR but trends between cadence and HR were not significant (table 7.2).

Table 7.2 **Trends in HR**

		Step length		Cadence	
Site	**Plane**	$F_{1,9}$	***P***	$F_{1,9}$	***P***
Head	Vertical	73.1	$< 0.001^a$	17.6	$< 0.005^a$
Pelvis	Vertical	47.9	$< 0.001^a$	16.6	$< 0.005^a$
Head	A-P	18.9	$< 0.005^a$	1.4	NS
Pelvis	A-P	20.5	$< 0.001^a$	16.9	$< 0.005^a$
Head	Lateral	36.8	$< 0.001^b$	4.2	NS
Pelvis	Lateral	23.1	$< 0.001^b$	4.1	NS

F-statistic examining for trends in HR across five levels of step length (very short, short, usual, long and very long) and three levels of cadence (67%, 100% and 125%), NS not significant, A-P anterior-posterior, [a] quadratic trend, [b] linear trend.

7.4 DISCUSSION

In this study, we evaluated the effect of speed/cadence/step length combinations on HRs at the head and pelvis. In vertical and A-P planes, HRs were highest at the usual or preferred gait speed, cadence and step length. In the lateral plane, the usual speed and cadence optimized HRs at the pelvis but not the head, where highest HRs were observed at the slow gait speed and at 67% of usual cadence. When step length and cadence (and therefore speed) were controlled in experiment 3 (fig. 7.7) HRs in the lateral plane tended to be highest when subjects walked with very small step lengths, at their usual cadence.

The maximization of vertical and A-P HRs by the usual locomotor pattern can be explained by variability in step time and acceleration. At slower than usual gait speeds, step time CV is increased (fig. 7.2). Although the accelerations experienced by the head and pelvis were small at slower speeds (fig. 7.3), the greater variability in step time caused irregularity in heel-strike, foot-flat and

toe-off accelerations. This led to more acceleration waveforms that were not resolved within each stride and to lower HRs (fig. 7.4). At faster than usual gait speeds, both acceleration RMS and Step time CV increased and created more high magnitude acceleration waveforms that were out of phase with heel-strike, foot-flat or toe-off. This led to lower HRs at faster speeds compared with the usual speed (fig. 7.4). Control of cadence (fig. 7.6) or step length and cadence (fig. 7.8) did not change the association between optimal HR and the usual gait pattern in vertical and A-P planes.

In contrast with vertical and A-P HRs, lateral HR was highest when extremely short step lengths were used and decreased linearly as step length increased (fig. 7.8). Lateral HR, however, remained above 2 at the subjects' usual step length and cadence, indicating that the preferred gait pattern still favored acceleration waveforms that were in phase with each stride over those that were out of phase, in a ratio of greater than 2:1. Previous studies did not encounter similar situations where the HR behaved differently in one plane compared to the other two in response to changes in gait pattern [Yack and Berger 1993; Menz, Lord et al. 2003]. Unlike our present study, these earlier studies modified gait speed within a relatively narrow range, without controlling for step length and cadence. Our findings, however, do not imply that optimal HR in one plane reflects optimal overall rhythm or stability, especially if HR in the other two planes is substantially reduced. The benefits of maximizing lateral HR remain doubtful, especially when the gait pattern involved (taking very small steps) is impractical and increases the risk of falls

[Guimaraes and Isaacs 1980; Wolfson, Judge et al. 1995]. Although the instrumented walkway was used to verify a constant step width, it is possible that step width variability worsened as step length increased and contributed to the irregularity of acceleration patterns in the lateral plane. We tried to limit artifacts caused by pelvic rotation and tilt by placing the accelerometers at the level of the second lumbar vertebra rather than on the pelvis per se.

In previous work by our group, we found that older people with a high risk of falling [Menz, Lord et al. 2003], and diabetic patients with peripheral neuropathy [Menz, Lord et al. 2004] demonstrated lower HRs at the head and pelvis than healthy young or elderly people with a low risk of falling. Therefore, the HR was used in the present study as a marker of head and pelvic rhythm and stability. Other parameters used more commonly to assess gait stability include step length, step width, speed and cadence. These variables, however, tend to increase in proportion to gait speed and may vary according to age, height and gender [Finley, Cody et al. 1969; Gabell and Nayak 1984; Moe-Nilssen, Helbostad et al. 2003]. Although, step-to-step variability in step width increases with age and does not appear to be associated with gait speed [Moe-Nilssen, Helbostad et al. 2003], no significant differences in step width variability between fit and frail elderly groups have been found [Moe-Nilssen and Helbostad in press]. A further limitation of all these measures is that they provide little direct information about head and pelvic stability.

The acceleration RMS is a parameter obtained from direct measurements of head and pelvic motion [Menz, Lord et al. 2003]. This variable, however, tends to increase with gait speed [Menz, Lord et al. 2003; Moe-Nilssen, Helbostad et al. 2003] and does not provide any additional information about stability. In experiments involving modulation of gait speed or cadence, its usefulness is limited as subjects will have higher RMSs when they walk faster. No significant differences in acceleration RMS between older people at a high risk of falling and those at a low risk have been reported.

The HR has advantages over these traditional parameters. Unlike step length, no relationship between HR and height or gender has been detected. The HR has the advantage of representing head and pelvic motion rather than the temporal and spatial relationships between footsteps. In addition, it appears to reflect gait stability independent of gait speed. This was demonstrated in a study where older people with a low risk of falling exhibited similar HRs to a healthy young control group, despite walking with reduced gait speeds [Menz, Lord et al. 2003]. Our results differ from those of Yack and Berger [Yack and Berger 1993] who found that HRs in vertical and A-P axes increase as gait speed increases from slow to normal and from normal to fast. This discrepancy can be explained by differences in experimental method. Yack and Berger's accelerometers were placed over the spinous process of the second thoracic vertebra rather than on the head or above the pelvis [Yack and Berger 1993] and may have detected different acceleration patterns that are not directly comparable to those in the present study. Their HRs tend to be

lower than those reported in this and other studies placing accelerometers lower on the trunk [Smidt, Deusinger et al. 1977; Menz, Lord et al. 2003; Menz, Lord et al. 2003; Menz, Lord et al. 2003]. In addition, Yack and Berger used only three self selected gait speeds and so it is not possible to determine from their study whether HR continues to increase as speed increases or whether a turning point is reached.

Optimization of head and pelvic rhythm facilitates the function of some compensatory mechanisms that maintain gait stability. Gait produces head and pelvis accelerations that perturb posture and disrupt gaze. In the presence of these perturbations, compensatory mechanism, such as the cervicocollic, vestibulo-ocular and vestibulocollic reflexes, are required to maintain stability. Stabilization of head and trunk movement is optimal at cadences of 1.2 to 2.2 Hz (72 to 132 steps/minute), corresponding to gait speeds of 1.2 to 1.8 m/s [Keshner, Cromwell et al. 1995; Hirasaki, Moore et al. 1999]. Not surprisingly, this range encompasses the preferred gait speed of most healthy adults [Finley and Cody 1970], the usual speed observed in our study that optimizes HRs and the speed where energy consumption is most efficient [Cavagna, Saibene et al. 1963; Cavagna, Thys et al. 1976; Ralston 1976; Waters, Lunsford et al. 1988].

7.5 CONCLUSION

Head and pelvic rhythm in vertical and A-P planes is best when the usual or preferred step length, cadence and gait speed are used. On the other hand, rhythm in the lateral plane is best when very short steps and usual cadence are used. The best overall stability, however, would be achieved with the usual step length, cadence and hence gait speed as this combination maximizes vertical and A-P rhythm while maintaining adequate lateral rhythm. As the purpose of human locomotion is to avoid falls and move efficiently from one point to another in the forward direction, it is possible that priority is given to vertical and A-P rhythm, rather than lateral rhythm in healthy young individuals. This study identified measures that could be used to distinguish the gait of PD patients from that of healthy subjects.

CHAPTER 8

LINEAR ACCELERATIONS OF THE HEAD AND PELVIS IN THE GAIT OF PARKINSON'S DISEASE

8.1 INTRODUCTION

Most studies of gait in Parkinson's disease have examined temporal and spatial relationships between footsteps while subjects walked at self-selected speeds. These studies have suggested that PD results in a lower gait speed and step length, a normal or reduced step time, higher double support time and stride-to-stride variability in stride length but no disturbance of regularity or rhythm of stepping [Knutsson 1972; Murray, Sepic et al. 1978; Blin, Ferrandez et al. 1990; Pedersen, Eriksson et al. 1991; McIntosh, Brown et al. 1997; Vieregge, Stolze et al. 1997; O'Sullivan, Said et al. 1998; Azulay, Mesure et al. 1999; Ebersbach, Sojer et al. 1999; Stolze, Kuhtz-Buschbeck et al. 2001]. Spatial and kinematic parameters, such as stride length and gait speed, are known to be sensitive to levodopa, whereas step time variability has proven levodopa resistant and may be caused through mechanisms other than dopamine deficiency [Blin, Ferrandez et al. 1991; Pedersen, Eriksson et al. 1991; O'Sullivan, Said et al. 1998; Stolze, Kuhtz-Buschbeck et al. 2001].

It is unclear in the literature how a reduced stride length and normal or near normal variability in step time affects head and trunk stability in PD as head and pelvic motion has not been investigated extensively in PD. This is an oversight as effective head stabilization is fundamental for processing visual, vestibular and somatosensory information about body position and movement and maintaining postural stability while walking [Grossman, Leigh et al. 1988; Grossman, Leigh et al. 1989; Amblard, Assaiante et al. 1997; Mesure, Azulay et al. 1999]. The few studies that have investigated head or torso motion in the gait of PD have observed reduced hip and knee excursions in the sagittal plane [Murray, Sepic et al. 1978; Zijlmans, Poels et al. 1996] and abnormal strategies of head stabilization leading to 'en bloc' movement of the head and upper torso [Mesure, Azulay et al. 1999]. The effects of levodopa on head and pelvic motion have not been investigated before. Furthermore, previous studies examining gait in PD have tended to compare PD subjects with healthy controls or patients with other diseases affecting gait stability. The second experiment in this study examines differences in accelerometric gait pattern between fallers and non-fallers with PD.

The aims of the present study was to determine how PD affects head and pelvic motion while walking, the extent to which motion abnormalities respond to levodopa therapy and the association between these abnormalities and falls.

8.2 EXPERIMENT 1 – EFFECTS OF LEVODOPA ON GAIT IN PD

8.2.1 Subjects

We recruited 43 subjects with PD (age 66 ± 95% confidence interval 2.5 years, 31 male, height 172 ± 2.66 cm and weight 71 ± 3.5 kg, 12 ± 1.9 years since the onset of symptoms and 10 ± 1.5 years since the diagnosis of PD) from a movement disorders clinic at a secondary referral hospital and metropolitan and rural PD support groups and matched them on a 1:1 basis for age and gender with healthy controls (table 8.1).

Table 8.1 **Controls and subjects with Parkinson's disease. Demographics, medical history and medications**

Factor	Controls N = 43	PD N = 43	*p*
Age (years)	68 ± 3.7	66 ± 2.5	NS
Male:female ratio	31:12	31:12	NS
Height (cm)	169 ± 2.5	171 ± 2.7	NS
Weight (kg)	72 ± 3.7	71 ± 3.5	NS
Events in last year			
Fall (number of subjects)	5	24	< 0.001
Near fall (number of subjects)	5	25	< 0.001
Injurious fall (number of subjects)	0	11	< 0.001
Duration of PD			
Since onset of symptoms (years)		12 ± 1.9	
Since diagnosis (years)		10 ± 1.5	
Medications			
Short–acting levodopa (mg/day)		500 ± 10 mg	
Long-acting levodopa (number of subjects)		12	
Dopamine agonists (number of subjects)		0	
Anticholinergics (number of subjects)		7	
COMT inhibitors[1] (number of subjects)		5	

Results presented as mean ± 95% confidence interval or number of subjects.
[1]Catechol-O-methyltransferase inhibitors
NS = not significant

PD subjects were eligible if they had a diagnosis of PD according to the UKPDBB criteria [Hughes, Ben-Shlomo et al. 1992], lived in the community, were able to walk unassisted with or without a walking aid and could perform activities of daily living (such as housework, grooming and dressing) independently (Hoehn and Yahr Stages I to III) [Hoehn and Yahr 1967]. All PD subjects were taking short-acting levodopa preparations with an average dose of 500 ± 10 mg per day. Twelve PD subjects were also on long-acting levodopa preparations but were only taking these in the evening before bedtime. Seven took anticholinergic drugs and five were on catechol-O-methyltransferase inhibitors in addition to levodopa. Subjects were excluded if they had a Folstein Mini-Mental State Examination (MMSE) score less than

24 [Folstein and Folstein 1981], clinical evidence of atypical parkinsonism, experienced freezing of gait or had dyskinesia that was obvious on examination during typical 'on' and 'off' phases. No subject had evidence on history, examination and review of the medical records of psychosis, neuroleptic use, vertigo, epilepsy, stroke, transient ischaemic attacks, syncope, uncompensated heart failure or moderate or severe valvular heart disease. In addition, all subjects had normal vestibular ocular reflexes and a negative Unterberger's sign on clinical examination. The protocol was approved by the Human Studies Ethics Committee at the University of Sydney and informed consent was obtained from all subjects according to the declaration of Helsinki. To optimize subject comfort and compliance, PD subjects were instructed to take their usual morning doses of levodopa prior to arriving at the laboratory for the tests. Neither PD nor control subjects were required to withhold any medications.

PD subjects were allocated at random into two counterbalanced groups: the first had clinical examinations and laboratory tests performed initially during a typical 'off' episode in the early to mid morning and repeated during a typical 'on' episode, usually 30 to 45 minutes following their next dose of short-acting levodopa; the second had initial measurements performed in the 'on' phase and repeated in the 'off' phase. The severity of PD was measured using the Unified Parkinson's Disease Rating Scale (UPDRS) [Fahn, Elton et al. 1987] and the stage of disease was measured using the Hoehn and Yahr (HY) scale [Hoehn and Yahr 1967].

The apparatus and data acquisition methods have been described in the introduction to this thesis. All subjects walked at their usual self-selected walking speed without the presence of external cues.

8.2.2 Statistics

All analyses were performed using SPSS 12 for Windows. Differences between controls and PD subjects in male:female ratio and events in the last year were examined using χ^2 and Fischer's exact tests. Differences between subjects and controls in age, height and weight were examined using independent samples t-tests. Measures of gait were examined for normality using stem-and-leaf plots and the Kolmogorov-Smirnov test statistic. Step length, cadence, gait speed, HR, RMS and step time coefficient of variation were normally distributed. Differences between controls and PD subjects (both 'on' and 'off' levodopa) were examined using independent samples t-tests. Differences between 'on' and 'off' phases in PD subjects were examined using paired t-tests.

The previous chapter demonstrated that HR is influenced by gait speed and step time CV. It was therefore necessary to adjust for these variables when calculating differences in HR between controls and PD subjects in the 'off' phase, between controls and PD subjects in the 'on' phase and between 'off'

and 'on' phases in PD subjects. To examine differences between controls and PD subjects in the 'off' phase, linear regression analyses were used with harmonic ratio (in controls and PD subjects in the 'off' phase) as the dependent variable, subject group (control and PD) as the independent variable of interest and gait speed and step time CV (in controls and PD subjects in the 'off' phase) as covariates. To examine differences between controls and PD subjects in 'on' state, 'on' phase measures of HR, gait speed and step time CV in PD subjects and control measures of these variables were included in the 'on' phase model.

Mixed linear regression models were used to analyse differences between 'off' and 'on' phases in PD subjects. These models used unstructured covariance matrices, HR as a repeated outcome variable, phase of treatment as a fixed effect and 'off' and 'on' gait speed and 'off' and 'on' step time coefficient of variation as repeated covariates exerting random effects.

8.2.3 Results

8.2.3.1 Subject characteristics

Compared with the control group, the group of PD subjects had a higher proportion of subjects who fell ($\chi^2 = 18.8$, 1 degree of freedom, df, $p < 0.001$), nearly fell ($\chi^2 = 21.3$, 1 df, $p < 0.001$) or injured themselves as a result of a fall

(χ^2 = 12.1, 1 df, p < 0.001) in the last year (table 8.1). In PD subjects, significantly better UPDRS total (t = -2.88, 42 df, p = 0.006) and UPDRS motor subscale (t = -6.02, 42 df, p < 0.001) scores were observed in the 'on' phase than in the 'off' phase of levodopa therapy (table 8.2). There were no differences between phases in HY stage or Schwab and England Scale.

Table 8.2. **'Off' and 'on' phase characteristics of subjects with Parkinson's disease**

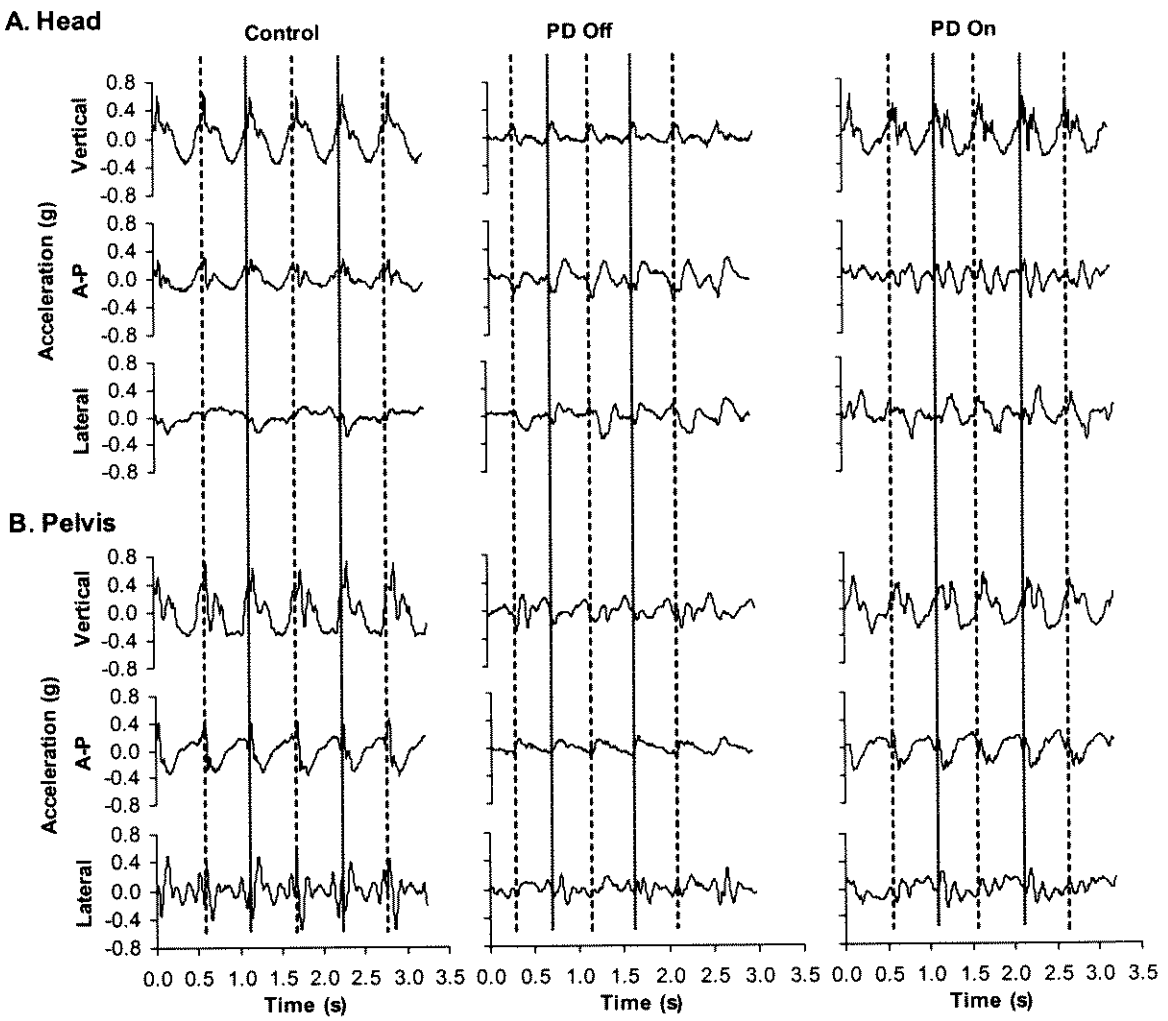
Factor	'Off' phase N = 43	'On' phase N = 43	*p*
UPDRS score	40 ± 4.6	35 ± 4.5	0.006[a]
UPDRS motor score	22 ± 3.3	16 ± 2.7	< 0.001[a]
Hoehn and Yahr stage	2 (1 – 3)	2 (1 – 3)	NS[b]
Schwab and England score	90 (70 – 100)	90 (70 – 100)	NS[b]

Results presented as mean ± 95% confidence interval or median (range).
[a] for paired samples t-tests
[b] for Wilcoxon signed ranks test
UPDRS = Unified Parkinson's Disease Rating Scale

8.2.3.2 Accelerometry patterns

Typical acceleration patterns obtained from the accelerometry system are shown in fig. 8.1. Acceleration patterns tended to be most regular in healthy controls and least regular in the 'off' phase in PD subjects, with 'on' phase patterns being somewhere between the two extremes.

Figure 8.1 **Typical acceleration patterns from the head (A) and pelvis (B) in a typical control and a typical PD subject 'on' and 'off' levodopa therapy**



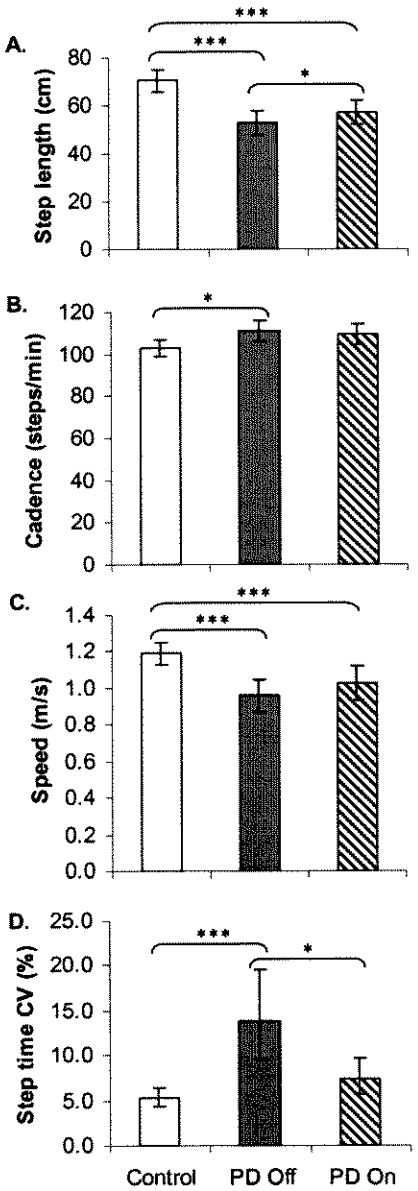
g = gravities
Dashed lines indicate right heel strike
Dotted lines indicate left heel strike

8.2.3.3 Step length, cadence, speed, step time CV and acceleration RMS

8.2.3.3.1 Controls and PD subjects

In the 'off' phase, PD subjects had significantly shorter step lengths ($t = 4.96$, 84 df, $p < 0.001$), higher cadences ($t = -2.36$, 84 df, $p = 0.021$), slower gait speeds ($t = 4.25$, 84 df, $p < 0.001$) and greater step time CVs ($t = -4.72$, 84 df, $p < 0.001$) than healthy controls (fig. 8.2).

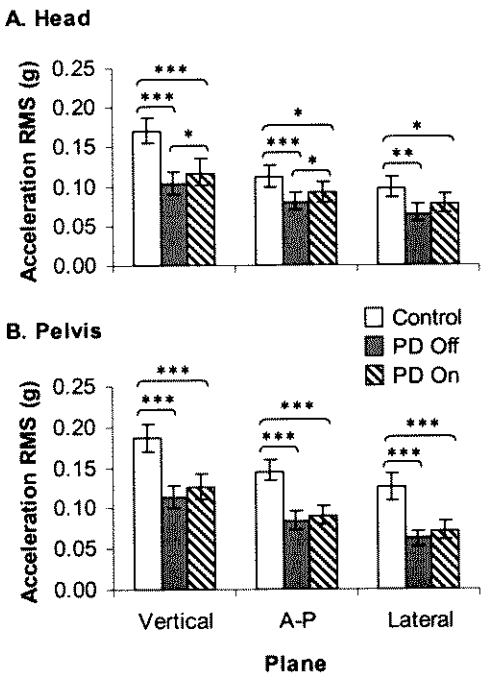
Figure 8.2 **Differences between controls and PD subjects ('off' and 'on') and between 'off' and 'on' phases in PD subjects**



Graphs show step length (A), cadence (B), gait speed (C) and step time coefficient of variation (CV) (D).
* $p < 0.05$, *** $p < 0.001$

PD subjects had significantly lower acceleration RMSs than healthy controls (fig. 8.3) at in vertical (head $t = 6.08$, 84 df, $p < 0.001$; pelvis $t = 6.29$, 84 df, $p < 0.001$), A-P (head $t = 3.64$, 84 df, $p < 0.001$; pelvis $t = 6.73$, 84 df, $p < 0.001$) and lateral (head $t = 3.58$, 84 df, $p = 0.001$; pelvis $t = 6.91$, 84 df, $p < 0.001$) planes.

Figure 8.3 **Differences between controls and PD subjects ('off' and 'on') and between 'off' and 'on' phases in PD subjects in acceleration root mean square (RMS)**



Graphs show RMS at the head (A) and pelvis (B).
g = gravities, * $p < 0.05$, *** $p < 0.001$

In the 'on' phase, PD subjects still had significantly shorter step lengths ($t = 3.71$, 84 df, $p < 0.001$) and slower gait speeds ($t = 2.98$, 84 df, $p = 0.004$). PD subjects had higher cadences ($t = -1.89$, 84 df, $p = 0.063$) and step time CVs (t

= -1.92, 84 df, p = 0.058) but these increases were no longer significant compared with the control group.

As in the 'off' state, PD subjects in the 'on' state had significantly lower RMSs than healthy controls (fig. 3) in vertical (head t = 4.25, 84 df, $p < 0.001$; pelvis t = 4.99, 84 df, $p < 0.001$), A-P (head t = 2.05, 84 df, p = 0.044; pelvis t = 6.03, 84 df, $p < 0.001$) and lateral (head t = 2.17, 84 df, p = 0.033; pelvis t = 5.42, 84 df, $p < 0.001$) planes.

8.2.3.3.2 'Off' and 'on' phases in PD subjects

PD subjects had significantly longer step lengths (t = -2.07, 42 df, p = 0.044) and greater step time CVs (t = 2.77, 42 df, p = 0.008) in the 'on' phase compared with the 'off' phase. PD subjects walked faster in the 'on' phase, but this increase was only of borderline significance (t = -2.01, 42 df, p = 0.051). There were no significant differences between the phases in cadence.

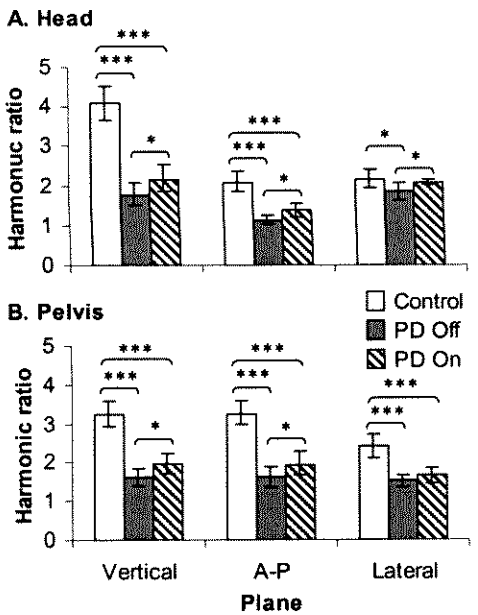
RMSs tended to be higher in the 'on' phase than in the 'off' phase in PD subjects but this difference was statistically significant only at the head in vertical (t = -2.09, 42 df, p = 0.043) and A-P planes (t = -2.11, 42 df, p = 0.040).

8.2.3.4 Acceleration HR

8.2.3.4.1 Controls and 'off' PD subjects

PD subjects in the 'off' state had significantly lower HRs than healthy controls (fig. 8.4) in vertical (head $t = 8.70$, 84 df, $p < 0.001$; pelvis $t = 8.07$, 84 df, $p < 0.001$) and A-P planes (head $t = 7.77$, 84 df, $p < 0.001$; pelvis $t = 7.19$, 84 df, $p < 0.001$). In the lateral plane, PD subjects had lower HRs than controls at the head ($t = 1.95$, 84 df, $p = 0.054$) and pelvis ($t = 5.60$, 84 df, $p < 0.001$).

Figure 8.4 **Differences between controls and PD subjects ('off' and 'on') and between 'off' and 'on' phases in PD subjects in acceleration harmonic ratio at the head (A) and pelvis (B)**



g = gravities, * $p < 0.05$, ** $p < 0.005$, *** $p < 0.001$

In linear regression analyses (table 8.3), subject group exerted a significant effects on vertical and A-P HRs ($p < 0.001$) that were independent of gait speed and step time CV.

Table 8.3 **The effect of subject group, gait speed and step time coefficient of variation on harmonic ratio**

		Control and PD 'Off'			Control and PD 'On'		
Site	**Parameter**	**Coefficient**	**t [a]**	**p**	**Coefficient**	**t [a]**	**P**
Vert.							
Head	**Group[1]**	-1.60 ± 0.62	-5.08	<0.001	-1.60 ± 0.61	-5.11	<0.001
	Speed (m/s)	1.32 ± 1.01	2.55	0.013	0.99 ± 1.14	1.70	0.092
	Step timeCV(%)	-0.03 ± 0.02	-2.70	0.008	-0.02 ± 0.04	-1.34	0.183
	Intercept	2.94 ± 1.28			3.31 ± 1.47		
Pelvis	**Group[1]**	-1.18 ± 0.50	-4.68	<0.001	-1.04 ± 0.47	-4.38	<0.001
	Speed (m/s)	1.03 ± 0.81	2.47	0.016	0.83 ± 0.87	1.88	0.064
	Step timeCV(%)	-0.02 ± 0.02	-2.04	0.044	-0.03 ± 0.02	-1.81	0.074
	Intercept	2.34 ± 1.03			2.63 ± 1.12		
A-P							
Head	**Group[1]**	-0.72 ± 0.36	-3.93	<0.001	-0.57 ± 0.35	-3.23	0.002
	Speed (m/s)	0.62 ± 0.59	2.06	0.042	0.42 ± 0.64	1.27	0.208
	Step timeCV(%)	-0.01 ± 0.01	-1.98	0.052	-0.02 ± 0.02	-2.22	0.029
	Intercept	1.59 ± 0.74			1.90 ± 0.83		
Pelvis	**Group[1]**	-1.15 ± 0.49	-4.60	<0.001	-1.01 ± 0.48	-4.09	<0.001
	Speed (m/s)	0.30 ± 0.80	0.72	0.474	-0.17 ± 0.90	-0.38	0.706
	Step timeCV(%)	-0.02 ± 0.01	-3.02	0.003	-0.04 ± 0.03	-2.90	0.005
	Intercept	3.21 ± 1.01			3.89 ± 1.16		
Lateral							
Head	**Group[1]**	0.09 ± 0.42	0.41	0.685	0.12 ± 0.46	0.50	0.616
	Speed (m/s)	0.15 ± 0.67	0.42	0.673	0.11 ± 0.74	0.29	0.745
	Step timeCV(%)	-0.02 ± 0.01	-3.45	0.001	-0.01 ± 0.01	-1.41	0.163
	Intercept	1.70 ± 0.26			2.24 ± 0.92		
Pelvis	**Group[1]**	-0.68 ± 0.45	-3.00	0.004	-0.65 ± 0.39	-3.26	0.002
	Speed (m/s)	0.18 ± 0.71	0.486	0.628	0.02 ± 0.37	-0.05	0.962
	Step timeCV	-0.02 ± 0.01	-2.35	0.021	-0.04 ± 0.02	-3.02	0.003
	Intercept	2.50 ± 0.89			2.81 ± 0.94		

Coefficients ± 95% confidence intervals obtained from linear regression analyses.
[1] PD group = 1, Control group = 2
[a] 82 degrees of freedom for independent t-tests
CV = coefficient of variation

In the lateral plane, the adjusted effect of subject group was significant at the pelvis ($p < 0.005$) but not the head. Compared with controls, the estimated mean HRs adjusted for gait speed and step time CV in 'off' phase PD subjects were significantly lower in vertical and A-P planes at both the head and pelvis and in the lateral plane at the pelvis (table 8.4). In the lateral plane, adjusted mean head HRs were higher in PD subjects but this difference was not statistically significant.

Table 8.4 **Adjusted mean harmonic ratios**

Models	Plane	Site	Control	PD Off	PD On	*p*
Control & PD Off	**Vertical**	**Head**	3.92	2.32 ± 0.62	-	< 0.001
		Pelvis	3.16	1.98 ± 0.50	-	< 0.001
	A-P	**Head**	2.11	1.39 ± 0.36	-	< 0.001
		Pelvis	3.24	2.09 ± 0.49	-	< 0.001
	Lateral	**Head**	1.57	1.66 ± 0.42	-	0.685
		Pelvis	2.40	1.72 ± 0.45	-	0.004
Control & PD On	**Vertical**	**Head**	4.20	-	2.60 ± 0.61	< 0.001
		Pelvis	3.33	-	2.29 ± 0.47	< 0.001
	A-P	**Head**	2.17	-	1.59 ± 0.35	0.002
		Pelvis	3.33	-	2.32 ± 0.48	< 0.001
	Lateral	**Head**	2.28	-	2.40 ± 0.46	0.616
		Pelvis	2.53	-	1.85 ± 0.44	0.002
PD Off & On	**Vertical**	**Head**	-	2.00 ± 0.29	2.46 ± 0.36	0.032
		Pelvis	-	1.78 ± 0.22	2.10 ± 0.25	0.041
	A-P	**Head**	-	1.12 ± 0.11	1.43 ± 0.20	0.009
		Pelvis	-	1.76 ± 0.29	2.19 ± 0.30	0.040
	Lateral	**Head**	-	2.08 ± 0.22	2.26 ± 0.25	0.166
		Pelvis	-	1.62 ± 0.17	1.78 ± 0.20	0.175

Table shows mean harmonic ratio ± 95% confidence interval adjusted for gait velocity and step time coefficient of variation.

8.2.3.4.2 Controls and 'on' phase PD subjects

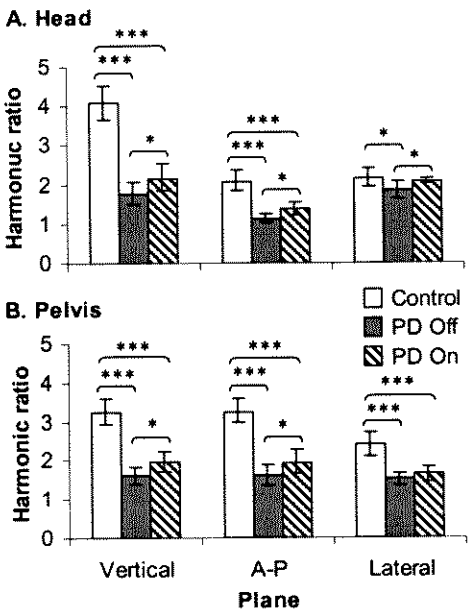
As in the 'off' state, PD subjects in the 'on' state had lower HRs than healthy controls (fig. 8.5) in vertical (head $t = 6.59$, 84 df, $p < 0.001$; pelvis $t = 5.88$, 84 df, $p < 0.001$), A-P planes (head $t = 4.51$, 84 df, $p < 0.001$; pelvis $t = 5.40$, 84 df, $p < 0.001$) and lateral planes (head $t = 0.47$, 84 df, $p = 0.637$; pelvis $t = 4.34$, 84 df, $p < 0.001$).

Using 'on' phase PD and control measures (table 8.3), subject group exerted a significant effects on vertical and A-P HRs at both the head and pelvis ($p < 0.001$ to 0.002) that were independent of gait speed and step time CV. In the lateral plane, the effect of subject group was highly significant at the pelvis ($p < 0.005$) but not the head. The estimated mean HRs were still lower in 'on' phase PD subjects compared with controls in vertical and A-P planes after adjusting for differences between groups in gait speed and step time CV. As in the 'off' phase, adjusted mean lateral HR at the head was higher in 'on' PD subjects than in controls although this difference was not significant (table 8.5). PD subjects had a significantly lower adjusted mean lateral HR at the pelvis than controls ($p < 0.002$).

8.2.3.4.3 'Off' and 'on' phases in PD subjects

Compared with the 'on' state, PD subjects in the 'off' state had significantly lower HRs at the head and pelvis in vertical (head t = -2.09, 43 df, p = 0.043; pelvis t = -2.28, 43 df, p = 0.028) and A-P planes (head t = -2.41, 43 df, p = 0.020; pelvis t = -2.10, 43 df, p = 0.042) (fig. 8.5). In the lateral plane, HR ratio was lower in the 'off' state but this difference was significant only at the head (head t = -2.50, 43 df, p = 0.017; pelvis t = -1.20, 43 df, p = 0.238).

Figure 8.5 **Differences between controls and PD subjects ('off' and 'on') and between 'off' and 'on' phases in PD subjects in acceleration harmonic ratio at the head (A) and pelvis (B)**



g = gravities, * p < 0.05, ** p < 0.005, *** p < 0.001

After adjusting for differences in gait speed and step time CV between the phases, HRs remained significantly lower in the 'off' than in the 'on' phase in

vertical (head p = 0.032; pelvis p = 0.041) and A-P planes (head p = 0.009; pelvis 0.040) (table 8.5). In the lateral plane, there were no significant differences in adjusted HRs, although HRs tended to be lower in the 'off' phase.

Table 8.5 **Differences in harmonic ratio between 'off' and 'on' phases in subjects with Parkinson's disease**

Plane	Site	Parameter	Estimate	t	df	*p*
Vertical	**Head**	**Off - On phase**	-0.45 ± 0.40	-2.23	39.8	0.032
		Intercept	2.46 ± 0.36	13.25	42.0	
	Pelvis	**Off - On phase**	-0.32 ± 0.29	-2.12	40.3	0.041
		Intercept	2.10 ± 0.25	16.74	8.80	
A-P	**Head**	**Off - On phase**	-0.30 ± 0.22	-2.74	37.2	0.009
		Intercept	1.43 ± 0.20	13.96	41.9	
	Pelvis	**Off - On phase**	-0.43 ± 0.32	-2.63	5.77	0.040
		Intercept	2.19 ± 0.30	14.20	65.2	
Lateral	**Head**	**Off - On phase**	-0.18 ± 0.18	-1.88	2.70	0.166
		Intercept	2.26 ± 0.25	17.96	42.5	
	Pelvis	**Off - On phase**	-0.16 ± 0.23	-1.38	39.0	0.175
		Intercept	1.78 ± 0.20	17.65	41.8	

Estimates ± 95% confidence intervals show differences in harmonic ratio (HR) between 'off' and 'on' phases. The estimates were obtained by mixed linear regression models with unstructured covariance matrices, HR as a repeated outcome variable, phase of treatment as a fixed effect and 'off' and 'on' gait speed and 'off' and 'on' step time coefficient of variation as covariates exerting random effects.

8.3 EXPERIMENT 2 – FALLERS AND NON-FALLERS WITH PD

8.3.1 Subjects

For this study, healthy controls, PD patients without a history of falls and PD patients with one or more falls in the previous year were matched on a 1:1:1 basis for age, male-to-female ratio, height and weight (table 8.6). Each group contained 33 subjects (15 male and 18 female). PD subjects were recruited from community-based PD support groups and healthy controls from a database of volunteers.

Table 8.6 **Experiment 2 subject data**

	Controls N = 33	**PD non-fallers** N = 33	**PD fallers** N = 33
Age (years)	67 ± 4	63 ± 4	67 ± 2
Male:female ratio	5:6	5:6	5:6
Height (cm)	168 ± 3	170 ± 3	169 ± 3
Weight (kg)	70 ± 4	73 ± 5	68 ± 5
Duration of PD			
Since onset of symptoms (years)		8 ± 2	10 ± 2
Since diagnosis (years)		7 ± 2	9 ± 2
UPDRS total score		25 ± 4	42 ± 5***
UPDRS motor score		12 ± 3	21 ± 3***
Hoehn and Yahr Stage		1 (1-1)	3 (3-4)***
Schwab and England Scale		100 (90 -100)	80 (60 – 90)***
Medications			
Short–acting levodopa (mg/day)		666 ± 133	958 ± 241*
Long-acting levodopa (subjects)		6	12
Dopamine agonists (subjects)		0	0
Anticholinergics (subjects)		3	4
COMT inhibitors[1] (subjects)		1	1

Results presented as mean ± 95% confidence interval, median (interquartile range) or number of subjects.

[1]Catechol-O-methyltransferase inhibitors

* $p < 0.05$, *** $p < 0.001$ for differences between PD fallers and non-fallers.

As per experiment 1, PD subjects were eligible if they had a diagnosis of PD according to the UKPDBB criteria [Hughes, Ben-Shlomo et al. 1992], lived in the community, were able to walk unassisted with or without a walking aid and could perform activities of daily living (such as housework, grooming and dressing) independently (Hoehn and Yahr Stages I to III) [Hoehn and Yahr 1967]. No subject had evidence on history, examination and review of the medical records of psychosis, neuroleptic use, vertigo, epilepsy, stroke, transient ischaemic attacks, syncope, uncompensated heart failure or moderate or severe valvular heart disease. In addition, all subjects had normal vestibular ocular reflexes and a negative Unterberger's sign on clinical examination. To optimize subject comfort and compliance, PD subjects were instructed to take their usual doses of levodopa and gait tests were performed during a typical 'on' phase.

8.3.2 Statistics

All analyses were performed using SPSS 12 for Windows. Measures of gait were examined for normality using stem-and-leaf plots and the Kolmogorov-Smirnov test statistic. Step length, cadence, gait speed, HR, RMS and step time CV were normally distributed in this sample. Differences between PD faller and non-faller groups and between PD non-faller and healthy control groups were examined using independent samples t-tests for normally-distributed variables and Mann-Whitney-U tests for non-parametric ones.

Significant differences across the three groups of subjects were examined using univariate analysis of variance (ANOVA) for parametric variables. It was necessary to adjust for step time CV and gait speed using multivariate analysis of variance when testing for differences in HR between subject groups and estimating marginal means. Bonferroni corrections were used for multiple comparisons between groups.

8.3.3 Results

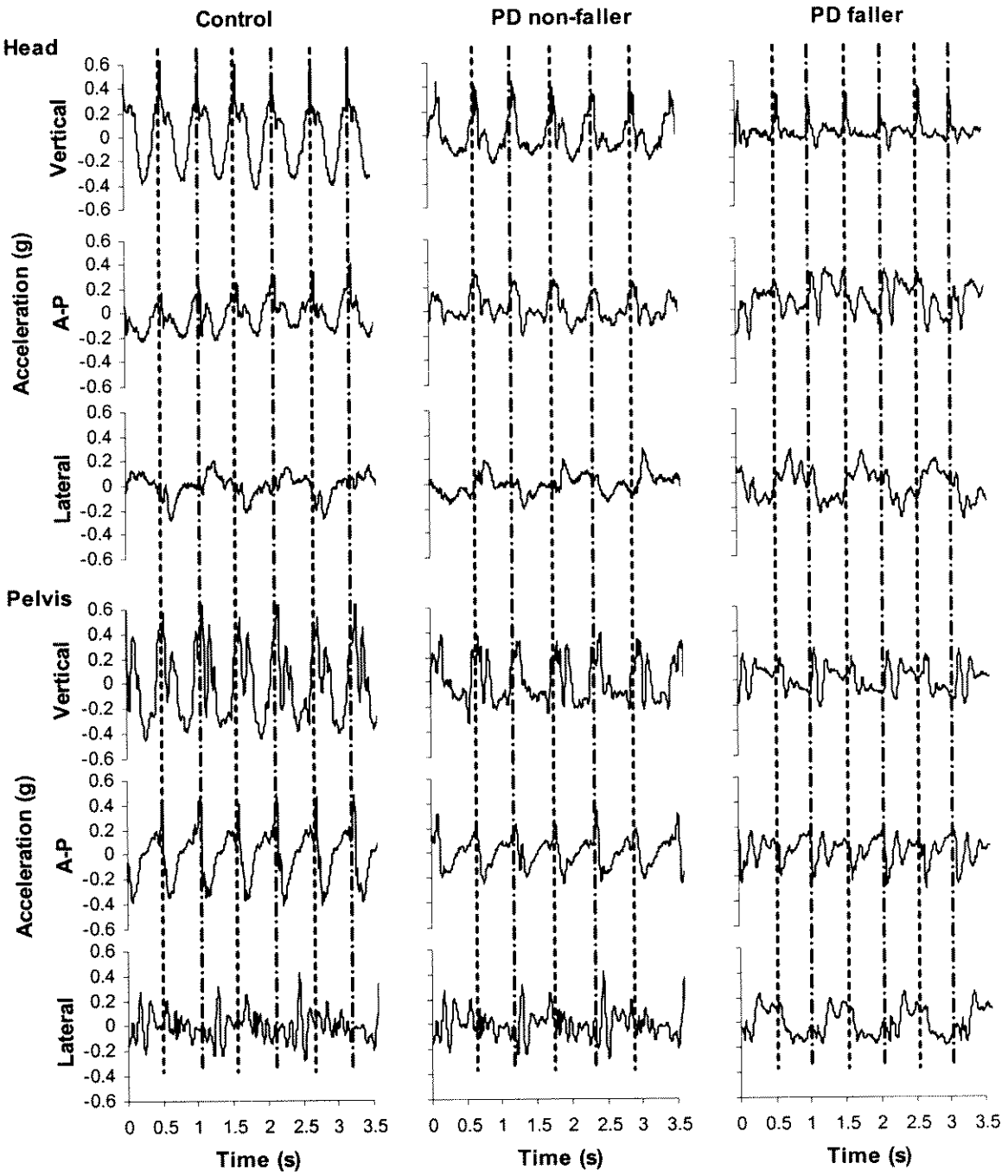
8.3.3.1 Subject characteristics

Fallers with PD had significantly worse UPDRS total and motor subscale scores, higher Schwab and England scores and more advanced HY stage than non-fallers with PD ($p < 0.001$) (table 8.6).

8.3.3.2 Accelerometry patterns

Typical acceleration patterns obtained from the accelerometry system are shown in fig. 8.6. Acceleration patterns tended to be most regular in healthy controls and least regular in the PD subjects with a history of falls in the last year.

Figure 8.6 **Typical acceleration patterns from the head (A) and pelvis (B) in a typical control, a typical PD subjects in the 'on' phase with and without a history of falls.**

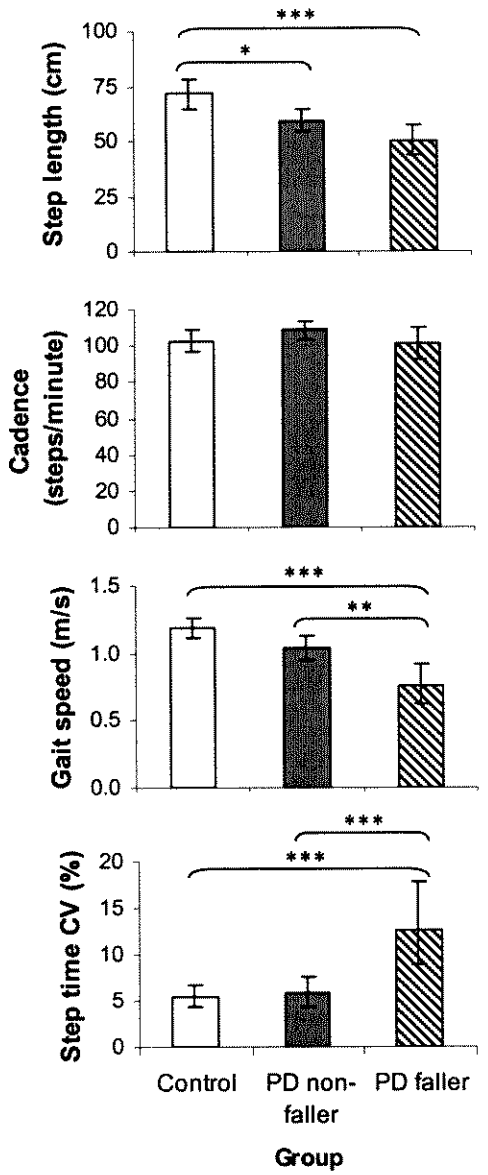


g = gravities
Dashed lines indicate right heel strike
Dotted lines indicate left heel strike

8.3.3.3 Step length, cadence, gait speed, step time CV, acceleration RMS and HR

Differences between the three groups are illustrated in fig. 8.7 below.

Figure 8.7 **Difference between groups in step length, cadence, gait speed and step time CV**

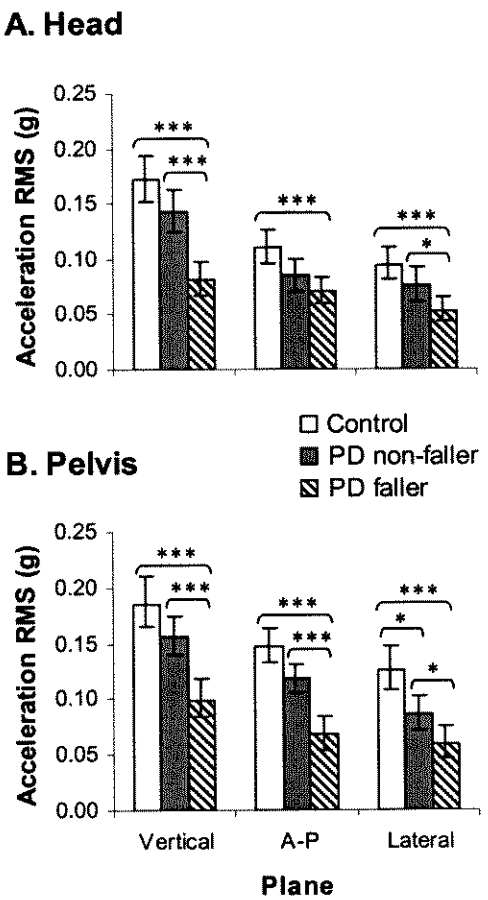


Error bars indicate 95% confidence intervals.
$p < 0.05$, ** $p < 0.005$ and *** $p < 0.001$ for difference between groups and across the three groups.

Fallers had significantly slower gait speeds and higher step time CVs than non-fallers with PD.

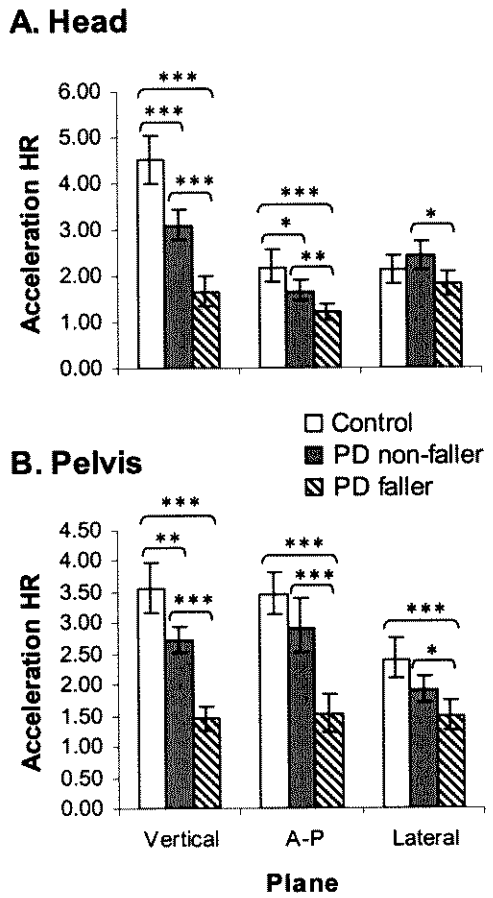
Significant difference between fallers and non-fallers in RMS and HR were observed (figs. 8.8 and 8.9).

Figure 8.8 **Acceleration RMS**



Error bars indicate 95% confidence intervals.
* $p < 0.05$, ** $p < 0.005$ and *** $p < 0.001$ for difference between groups and across the three groups.

Figure 8.9 **Acceleration HR**



Error bars indicate 95% confidence intervals.
* $p < 0.05$, ** $p < 0.005$ and *** $p < 0.001$ for difference between groups and across the three groups.

Even after adjusting for gait speed and step time CV, non-fallers with PD had significantly lower HRs at the head in all three planes and at the pelvis in vertical and lateral planes (table 8.7). Differences between fallers and non-fallers with PD were only apparent at the pelvis in vertical and A-P planes after adjusting for these variables.

Table 8.7 **Estimated marginal means for harmonic ratios, adjusted for gait speed and step time CV**

Models	Plane	Site	Controls	PD non-fallers	PD fallers
Control & PD Off	**Vertical**	**Head**	4.43 ± 0.42	3.09 ± 0.40***	2.38 ± 0.44
		Pelvis	3.54 ± 0.29	2.70 ± 0.28***	1.85 ± 0.31§§§
	A-P	**Head**	2.27 ± 0.26	1.72 ± 0.25*	1.47 ± 0.27
		Pelvis	3.39 ± 0.37	3.02 ± 0.35	2.10 ± 0.39§§§
	Lateral	**Head**	1.41 ± 0.33	2.50 ± 0.31***	2.14 ± 0.34
		Pelvis	1.44 ± 0.24	1.92 ± 0.22*	1.89 ± 0.25

* $p < 0.05$, ** $p < 0.05$, *** $p < 0.001$ with Bonferroni correction for differences between PD non-fallers and controls

§ $p < 0.05$, §§ $p < 0.05$, §§§ $p < 0.001$ with Bonferroni correction for differences between PD fallers and PD non-fallers

Comparisons between PD fallers and healthy controls are not clinically relevant and were not included in the table.

8.4 DISCUSSION

This study highlighted abnormalities in head and pelvic rhythm during gait in PD subjects, found that these abnormalities may respond to levodopa therapy and detected an association between these abnormalities and falls.

The effects of PD on gait extend beyond a shortening of step length, reduction in gait speed and increase in variability of temporal and spatial measures to involve a disruption of head and COG motion. In the 'off' phase, our PD subjects had significantly smaller step lengths ($p < 0.001$), higher cadences ($p < 0.05$), slower gait speeds ($p < 0.001$) and greater step-to-step variability in step time ($p < 0.001$). Treatment with levodopa improved these parameters although step length ($p < 0.001$) and gait speed ($p < 0.001$) remained significantly abnormal. In the PD group, levodopa treatment led to changes in

all measures with the increase in step length ($p < 0.05$) and reduction of step time CV ($p < 0.05$) reaching statistical significance. Compared with the control group, the PD group had significantly lower acceleration RMSs at the head ($p < 0.001$ to < 0.05) and pelvis ($p < 0.001$) in all planes both 'off' and 'on' levodopa. In the PD group, levodopa tended to increase acceleration RMS towards normal levels with the difference between 'on' and 'off' phases reaching significance at the head in vertical ($p < 0.05$) and A-P planes ($p < 0.05$).

In both 'off' and 'on' conditions, PD subjects had significantly lower acceleration HRs in vertical and A-P planes and higher HRs in the lateral plane at the head and pelvis compared with controls ($p < 0.005$ to < 0.001). In the PD group, levodopa treatment led to higher HRs in the 'on' than in the 'off' phase, with the differences being significant in all planes ($p < 0.05$) except the lateral plane at the pelvis.

Differences between controls and PD subjects in both 'off' and 'on' phases persisted after adjusting for gait speed and step time CV in linear regression models, although the lateral HRs were no longer significantly higher at the pelvis in the PD group. In the PD group, adjusted vertical and A-P HRs were significantly higher in the 'on' phase than in the 'off' phase of the levodopa treatment cycle. Adjusted lateral HRs were still higher in the 'on' phase but the differences between phases were not statistically significant.

In PD, fallers had significantly lower HRs than non-fallers in all three orthogonal planes at both the head and pelvis ($p < 0.001$ to < 0.05). Even after adjusting for step time CV and gait speed, these significant differences persisted at the pelvis in both A-P and vertical planes ($p < 0.001$).

Our study conforms with earlier ones in showing that step length and gait speed increase towards healthy control values in response to levodopa [Blin, Ferrandez et al. 1990; Bowes, Clark et al. 1990; Blin, Ferrandez et al. 1991; Morris, Iansek et al. 1994; Morris, Iansek et al. 1998]. While step length, cadence, gait speed and the CVs of these variables are useful descriptors of footstep movements, they provide little direct information about motion of higher segments of the body. Apart from the finding of an increased step time CV in PD subjects which improved partially with levodopa, our results do not conflict or add to previous work. We therefore used accelerometric methods to obtain information about head and pelvic motion. Like Mesure and colleagues [Mesure, Azulay et al. 1999], we found that linear accelerations at the head and pelvis were significantly lower in PD subjects in both 'off' and 'on' phases than in healthy controls. Levodopa therapy did not lead to substantial improvements in the PD group. Linear accelerations, however, tend to be highly correlated with speed. Therefore differences in RMS between controls and PD subjects or between 'off' and 'on' phases in the PD group could be explained by differences in preferred walking speed.

When making comparisons between subjects who walk at different preferred gait speeds, some investigators have used curvilinear interpolation to overcome the problem of speed-dependent gait variables [Moe-Nilssen, Helbostad et al. 2003]. In this method, the subject walks at several different self-selected speeds and a quadratic curve of best fit is drawn for each measured parameter versus the subject's gait speed. Comparisons between subjects and groups are then made at a selected reference speed, such as 1.0 m/s. Problems with this method include errors resulting from curve fitting and interpolation and the fact that the precise reference speed may not be one that the subject ever uses in real life.

We calculated the acceleration HR to obtain a measure of gait stability that was not influenced by gait speed in the same way as RMS. In previous studies, we proposed that acceleration HRs provide useful indicators of gait rhythm and that rhythm is closely related to gait stability [Menz, Lord et al. 2003; Menz, Lord et al. 2003]. Head and pelvic HRs were significantly less rhythmic in young subjects walking on an irregular, bumpy surface compared to a smooth, even surface [Menz, Lord et al. 2003], in elderly people with a high risk of falls compared to those at a low risk [Menz, Lord et al. 2003], and in subjects with diabetic peripheral neuropathy compared to healthy controls [Menz, Lord et al. 2004]. In addition, HRs reflect gait stability independent of gait speed. This was demonstrated in a study where older people with a low risk of falling exhibited similar HRs to a healthy young control group, despite walking with reduced gait speeds [Menz, Lord et al. 2003]. Finally, in healthy

young adults at least, HRs tend to be maximal when subjects walk at the preferred or usual gait speed and decreases as speed is varied from this level [Menz, Lord et al. 2003].

The HRs observed in PD suggest that people with this disorder experience irregular self-generated perturbations to the head and pelvis while walking in a straight line, at a constant speed and in undisturbed conditions. These perturbations exist even in the absence of gait freezing or clinically apparent dyskinesia and may reflect loss of automaticity. Treatment with levodopa improves but does not normalize the regularity of perturbations in these planes.

These differences in HR between healthy people and PD patients and between 'off' and 'on' phases in PD patients can be explained partially by differences between groups or phases in walking speed and temporal variability between one step and the next. The reduced step length characteristic of PD [Knutsson 1972; Murray, Sepic et al. 1978; Blin, Ferrandez et al. 1990; Pedersen, Eriksson et al. 1991; McIntosh, Brown et al. 1997; Vieregge, Stolze et al. 1997; O'Sullivan, Said et al. 1998; Azulay, Mesure et al. 1999; Ebersbach, Sojer et al. 1999; Stolze, Kuhtz-Buschbeck et al. 2001] is not accompanied by an adequate increase in cadence and results in a reduction of gait speed. At these lower speeds, there is lower variation about zero in perturbation amplitude, reflected by lower acceleration RMSs. However, step-to-step variability in step time is markedly increased, leads to perturbations that

appear at irregular intervals during the gait cycle and hence causes lower acceleration HRs.

Discrepancies between groups and between phases in step time CV and speed, however, can not account for all the differences observed in this study. Regression analyses were used to model the effect of subject group (or phase of levodopa treatment cycle in the PD group) on HR after adjusting for the influence of these covariates. It was found that PD subjects still had significantly reduced HRs compared with controls and in the 'off' phase compared with the 'on' phase at the head and pelvis in vertical and A-P planes even after accounting for differences between in gait speed and step time CV. In the lateral plane, reductions in HR in the PD group compared with the control group were less substantial but still significant at the pelvis. These results suggest that HRs tend to be lower in subjects that have lower preferred gait speeds and higher step time CVs but that the reductions observed in PD subjects can not be explained by gait speed and step time CV alone.

It is possible that PD subjects try to improve lateral stability by widening step width [Mesure, Azulay et al. 1999] and this might account for HRs in our PD group being more normal in the lateral plane than in vertical and A-P planes. Most previous studies, however, have not observed any differences between controls and PD subjects in step width [Vieregge, Stolze et al. 1997; Stolze, Kuhtz-Buschbeck et al. 2001] or detected them only in PD subjects with stages of disease more advanced than those of our subjects. In addition, step

width does not respond to levodopa [Mesure, Azulay et al. 1999] and could not therefore account for the increases in HR observed during the 'on' phase. It is also possible that step-to-step variability in step length influences HR, however this effect would be collinear with step time CV which already appears as a covariate in our models. It is more likely that the HR differences observed between PD and control groups reflect intrinsic differences in gait and postural control, such as axial rigidity [Van Emmerik, Wagenaar et al. 1999], adaptive responses designed to stabilize the head [Van Emmerik, Wagenaar et al. 1999], force production [Blin, Ferrandez et al. 1991; Ueno, Yanagisawa et al. 1993; Frank, Horak et al. 2000] and sensorimotor integration [Moore 1987; Schneider, Diamond et al. 1987; Lewis and Byblow 2002]. Some of these factors respond to levodopa (ie. force production [Frank, Horak et al. 2000]) and their effect on gait in PD require further investigation.

The connection between low HRs and falls detected in these experiments requires further explanation. Previous research has found that ranges of motion in the pelvis, thorax, and trunk tend to be larger at slower velocities in healthy subjects [van Emmerik and Wagenaar 1996]. At these slower than usual velocities, we observed reduced HRs in an earlier study of healthy young subjects (chapter 7). This suggests that the perturbations experienced by the body at slow speeds result not only in larger but also more irregular movements of the COG and head. This explanation corresponds with what we observed in our PD subjects who fell. Not surprisingly, a lot of the differences

between fallers and non-fallers in HR were lessened after adjusting statistically for step time CV and gait speed.

Even in normal gait, self-generated forces arise that perturb posture and disrupt gaze [Keshner, Cromwell et al. 1995; Hirasaki, Moore et al. 1999; Mesure, Azulay et al. 1999]. In the presence of these perturbations, compensatory mechanism, such as the cervicocollic, vestibulo-ocular and vestibulocollic reflexes, are required to maintain stability [Grossman, Leigh et al. 1989; Zangemeister, Bulgheroni et al. 1991; Hirasaki, Kubo et al. 1993; Bronstein and Guerraz 1999; Hirasaki, Moore et al. 1999]. Irregular perturbations would affect the head's ability to act as a postural reference point [Amblard, Assaiante et al. 1997]. This disruption of vestibular and visual inputs problems would exacerbate postural control in PD subjects who are already heavily dependent upon visual control for balance.

8.5 CONCLUSION

This study provides evidence that gait abnormalities in PD extend beyond traditional temporal and spatial parameters footstep parameters towards a disorder of head and COG control. Some aspects of these abnormalities are responsive to levodopa. The gait abnormalities are associated with falls.

CHAPTER 9

RISK FACTORS FOR FALLS IN PARKINSON'S DISEASE

9.1 INTRODUCTION

Three prospective studies have addressed risk factors for falls in people with PD [Ashburn, Stack et al. 2001; Bloem, Grimbergen et al. 2001; Wood, Bilclough et al. 2002]. However in each study, only a restricted range of potential variables was examined, and therefore these studies give only limited insight into the pathophysiology of falls. For example, many risk factors identified have been either non-causal indicators of increased risk, such as a history of falls, or measures of PD severity, such as loss of arm swing and duration of disease [Wood, Bilclough et al. 2002]. Such findings make it difficult to design specific interventions in order to reduce the risk of falling. Other studies have been either retrospective [Koller, Glatt et al. 1989] or used relatively small sample sizes of PD patients [Bloem, Grimbergen et al. 2001], precluding multivariate modeling. As a result, the predictive accuracy of identified risk factors has been modest.

A number of impairments specific to PD could hypothetically contribute to falls. These include abnormal postural reflexes [Beckley, Bloem et al. 1991; Beckley, Bloem et al. 1993], gait abnormalities [Morris, Iansek et al. 1994;

Ebersbach, Sojer et al. 1999; Stolze, Kuhtz-Buschbeck et al. 2001] or freezing of gait [Bloem, Hausdorff et al. 2004], and the poor response of postural instability to pharmacological treatment [Bloem, Beckley et al. 1996; Chong, Horak et al. 2000; Frank, Horak et al. 2000; Bronte-Stewart, Minn et al. 2002; Rocchi, Chiari et al. 2002]. In addition, concomitant age-related impairment such as poor vision, reduced peripheral sensation, lower limb weakness and slowed reaction time (exacerbated further by PD) might further increase the risk of falling, as they do in the elderly [Lord, Clark et al. 1991](31). Cognitive impairment occurs in PD [Gotham, Brown et al. 1988; Lange, Robbins et al. 1992; Owen, James et al. 1992] and a low score in the Mini-Mental State Examination (MMSE) [Folstein and Folstein 1975] in PD patients has been found to be associated with falls [Wood, Bilclough et al. 2002]. Clinical observations suggest that symptoms of impaired frontal lobe function such as impulsivity and lack of planning, cognitive functions poorly assessed by the MMSE, also contribute to falls in many patients with PD. However the relationship between frontal lobe impairment and falls in PD has not been studied.

We have studied prospectively risk factors for falls in a large sample of PD patients. Specific impairments in multiple physiological domains were assessed using detailed and validated clinical and objective measures. By using this approach, we have been able to construct clinically meaningful explanatory and predictive models for falls in PD, and identified risk factors that are amenable to specific therapeutic intervention.

9.2 METHODS

The selection, exclusion, response rates and follow-up of subjects and clinical and physiological measures have been described in the introduction to this thesis. No subjects had evidence on history or examination of psychosis, neuroleptic use, vertigo, epilepsy, stroke, transient ischaemic attacks, syncope, uncompensated heart failure or moderate or severe valvular heart disease.

All subjects had clinical and physiological assessments performed by the same researcher (ML), when their antiparkinsonian medications were providing maximum benefit (i.e. an 'on' state) typically in the mid morning. The clinical assessments usually took 25 minutes (range 20 to 52 minutes). No assessments caused discomfort or fatigue and all were completed before the effects of levodopa wore off.

The protocol was approved by the Human Studies Ethics Committees at the University of Sydney and the University of New South Wales and informed consent was obtained from all subjects according to the declaration of Helsinki.

9.2.1 Clinical assessment

1. the Unified Parkinson's Disease Rating Scale (UPDRS), including retropulsion, leg or axial rigidity, abnormal axial posture, bradykinesia, hypometria, dyskinesia and gait freezing [Fahn, Elton et al. 1987]
2. Hoehn and Yahr (HY) scale [Hoehn and Yahr 1967]
3. The "Timed Up and Go" test (TUAG) [Mathias, Nayak et al. 1986]
4. Number of steps taken to turn 180° from a standing position
5. Blood pressure and pulse supine, immediately rising to a standing position and after three minutes of standing still.

9.2.2 Cognitive Assessment

Two bedside tests of cognitive function were used:

1. Mini-Mental State Examination (MMSE) [Folstein and Folstein 1975]
2. Frontal Assessment Battery (FAB) [Dubois, Slachevsky et al. 2000]

9.2.3 Measures of physiological function

1. High-contrast visual acuity
2. Low-contrast visual acuity [Verbaken and Johnston 1986]
3. Visual contrast sensitivity [Verbaken and Johnston 1986]

4. Proprioception at the knee [De Domenico and McCloskey 1987]
5. Tactile sensitivity [Semmes, Weinstein et al. 1960].
6. Average maximal voluntary isometric strength of the knee extensor, knee flexor and ankle dorsiflexor muscle groups in the subjects' stronger and weaker legs
7. Simple reaction time
8. Postural sway on the floor and on a foam rubber mat (60cm x 60cm x 15cm thick) with eyes open and eyes closed [Lord, Clark et al. 1991]
9. Leaning balance (coordinated stability test - CST) [Lord, Ward et al. 1996]
10. Average step length
11. Cadence
12. Gait speed
13. Step time coefficient of variation (CV) [Menz, Lord et al. 2003]

9.2.4 Follow-up

Subjects were asked to document the number or falls (defined as 'any event which resulted in you unintentionally coming to the ground or other lower level' [Gibson 1987]) on a daily basis in standardized diaries for twelve months. Subjects were asked to return the completed diaries by mail each month. To increase the accuracy of follow-up data, all subjects were also

contacted by telephone each month for a structured interview to obtain or verify the above information [Lamb, Jorstad-Stein et al. 2005].

Subjects were classified as non-fallers if they had no falls during the twelve-month follow-up period and fallers if they experienced one or more falls in this period.

9.2.5 Statistical analysis

In univariate analyses, relationships between explanatory variables and faller status were examined using χ^2 test statistics, odds ratios and t-tests for two independent samples. Sway values, number of steps to turn 180 degrees and step time CV were logged transformed to the base of 10 to normalise their distributions.

Multivariate logistic regression analysis was then undertaken to identify the best set of independent and significant risk factors for one or more falls (compared with no falls) in the twelve-month follow-up period. Three multivariate models were created from corresponding baseline models.

1. A 'clinical' model was created using only those variables that could be obtained entirely from clinical history and bedside examination, such as symptoms, signs and treatment of PD and other conditions, HY stage, UPDRS, blood pressure, pulse rate and MMSE score (tables 8.1

to 8.3). We wished to determine the feasibility of estimating risk of falling in a typical outpatient clinic, doctor's surgery or patient's home.

2. An explanatory model was created using only variables that could potentially explain how or why falls occurred. These variables included specific signs and symptoms (such as retropulsion, rigidity, bradykinesia, freezing of gait and dyskinesia), and measures of cognition (MMSE and FAB) (8.1 to 8.3) and physiological function (leg strength, reaction time, somatosensory function, postural stability and gait characteristics) (table 8.4). Measures that did not offer insights into the mechanisms of falls (e.g. history of falls, UPDRS and HY) were excluded.
3. A 'combined' predictive model was created using all variables as candidates, irrespective of whether they explained the pathophysiology of falls. We hoped to improve on the sensitivity, specificity and goodness and strength of fit of the final clinical and explanatory models.

Variables were selected for possible inclusion in the multivariate logistic regression model if they were associated with falls in univariate analyses ($p < 0.10$), and there was no evidence of collinearity with other variables (a major methodological consideration in studies of falls in PD due to high correlations among rating scales of disease stage or severity, items quantifying physical signs and symptoms, duration of disease and medication use). To minimise the problem of collinearity, only the variable most strongly associated with falls

from each of the following domains were included in the models: PD severity or stage (HY stage, UPDRS or UPDRS motor subscale), cardiovascular function (blood pressure, pulse or postural change in blood pressure or pulse), strength (knee flexion, knee extension or ankle dorsiflexion), postural stability (Coordinated Stability Task score or postural sway across a range of visual and somatosensory conditions) and cognition (MMSE or FAB). Restricting the number of possible predictor variables in this way also permitted modelling to conform with the suggested minimum ratio of 10 cases for every out come event (i.e. faller) [Concato, Feinstein et al. 1993]. According to these considerations, a minimum of 50 subjects was required for the study.

The Nagelkerke R^2 statistic was used to examine the amount of variability in the data explained by the model. The adequacy of fit of the model was examined using the Hosmer-Lemeshow (H-L) χ^2 statistic. In addition, the sensitivity, specificity and overall predictive accuracy of the model were calculated. The data were analyzed using SPSS v12 for Windows.

9.3 RESULTS

9.3.1 Univariate analysis

In the twelve months follow-up, 51 subjects (45%) suffered one or more falls while 62 subjects (55%) experienced no falls. Tables 9.1 to 9.3 compare

general medical and PD specific measures in fallers and non-fallers using univariate analysis.

Fallers were significantly more likely to have had a history of falls in the last year, be taking multiple medications and have evidence of general cognitive impairment and frontal lobe impairment (table 891). The variable that had the strongest association with falls in the twelve-month follow-up was a past history of a fall in the previous year.

Table 9.1 **Differences between fallers and non-fallers in clinical**

Factor	**Non-fallers N = 62**	**Fallers N = 51**	**OR (95% CL)**
Male gender	35	29	1.02 (0.48 – 2.15)
Fell last year	21	40	7.10 (3.04 – 16.60)***
Hip fracture	2	4	2.55 (0.45 – 14.54)
Dizziness	22	21	1.27 (0.59 – 2.73)
Angina or heart attack	5	6	1.52 (0.44 – 5.30)
Osteoarthritis	21	17	0.84 (0.36 – 1.93)
Urinary incontinence	11	14	1.75 (0.72 – 4.30)
Faecal incontinence	3	5	2.14 (0.49 – 9.41)
Medications			
Antihypertensive	18	12	0.75 (0.32 – 1.76)
Antiarrhythmic	4	1	0.29 (0.03 – 2.68)
Antidepressant	3	4	0.60 (0.13 –2.80)
Benzodiazepine	15	15	1.31 (0.57 – 3.02)
Number of drugs			
< 4	28	14	1.00**
4	16	5	0.63 (0.19 – 2.06)
5	5	14	5.60 (1.68 – 18.70)
> 5	13	18	2.77 (1.06 – 7.23)
MMSE score ≤27/30[1]	8	17	3.38 (1.31 – 8.67)*
FAB score ≤17/18[2]	14	33	6.29 (2.75 – 14.4)***

Results presented as a univariate odds ratio (95% confidence limit).
* $p < 0.05$,
** $p < 0.005$,
*** $p < 0.001$, for change in -2 log likelihood ratio χ^2 test statistic.
[1]LowerFolstein Mini Mental State Examination scores reflect worse cognition.
[2]Lower Frontal Assessment Battery scores reflect worse frontal lobe cognition.

As indicated in Table 9.2, fallers were older than non-fallers, had greater blood pressure drops at 3 minutes after rising from a supine rest period, had slower TUAG times and took more steps to turn 180 degrees.

Table 9.2 **Continuous clinical variables**

Factor	Non-fallers N = 62	Fallers N = 51	OR (95% CL)
Age (years)	64.4 ± 2.7	68.3 ± 2.1	1.05 (1.00 – 1.09)*
Height (cm)	171.6 ± 2.2	170.1 ± 2.5	0.98 (0.94 – 1.02)
Weight (kg)	73.0 ± 3.1	71.9 ± 5.5	1.00 (0.97 – 1.02)
Blood pressure[1] (mmHg)			
Supine	128 ± 5	127 ± 5	1.00 (0.98 – 1.02)
Standing 0 mins	126 ± 5	122 ± 6	0.91 (0.61 – 1.27)
Change 0 mins	-3 ± 2	-6 ± 4	1.30 (0.86 – 1.99)
Standing 3 mins	127 ± 5	121 ± 6	0.79 (0.54 – 1.16)
Change 3 mins	-1 ± 3	-6 ± 3	1.05 (1.01 – 1.09)*
Pulse[1] (beats/minute)			
Supine	74 ± 2	75 ± 3	1.01 (0.97 – 1.05)
Stand 0 mins	75 ± 2	75 ± 3	1.00 (0.96 – 1.04)
Change 0 mins	1 ± 2	0 ± 2	1.00 (0.96 – 1.04)
Standing 3 mins	76 ± 2	77 ± 3	1.01 (0.97 – 1.05)
Change 3 mins	1 ± 3	2 ± 2	0.99 (0.95 – 1.03)
Timed Up And Go (s)	9 ± 1	12 ± 3	1.09 (1.01 – 1.19)*

Results presented as mean ± 95% confidence interval, mean (95% confidence limit) and univariate odds ratio (95% confidence limit).
* $p < 0.05$, ** $p < 0.005$.
[1]Blood pressure and pulse measurements were taken initially with the subject supine, then immediately after standing and finally after standing for three minutes. *Change 0 mins* equals measurement immediately after standing minus supine measurement. *Change 3 mins* equals measurement after three minutes of standing minus supine measurement.

Univariate analysis also identified PD-specific risk factors for fall (table 9.3).

Table 9.3 **PD-specific differences between fallers and non-fallers.**

Factor	Non-fallers N = 62	Fallers N = 51	OR (95% CL)
Years since diagnosis[1]			
< 2	33	18	1.00
2 – 4	15	13	1.59 (0.62 – 4.06)
5 – 7	9	12	2.44 (0.87 – 6.90)
>7	5	8	2.93 (0.84 – 10.30)
UPDRS[2]			
< 20	21	5	1.00**
20 – 29	21	12	2.40 (0.72 – 8.02)
30 – 39	10	14	5.88 (1.65 – 20.91)
> 39	10	20	8.40 (2.44 – 28.91)
UPDRS[2] motor subscale			
< 10	26	11	1.00*
10 – 19	23	20	2.06 (0.82 – 5.19)
> 19	13	20	3.64 (1.35 – 9.81)
Retropulsion	29	33	2.09 (0.98 – 4.46)
Leg/axial rigidity	47	34	0.64 (0.28 – 1.45)
Axial posture			
Normal	26	5	1.00***
Slightly stooped	29	28	5.02 (1.69 – 14.9)
Severely stooped	7	18	13.4 (3.66 – 48.8)
Bradykinesia			
None	16	5	1.00***
Minimal slowness	43	28	2.08 (0.69 – 6.33)
Slowness	3	18	19.2 (3.95 – 93.39)
Dyskinesia	17	15	1.10 (0.49 – 2.51)
Freezing of gait	13	31	5.84 (2.55 – 13.41)***
Hoehn and Yahr stage			
I	32	7	1.00***
II	22	11	2.29 (0.77 – 6.81)
III	8	33	18.86 (6.12 – 58.1)
Levodopa dose (mg/day)			
< 500	16	8	1.00*
500 – 750	33	18	1.09 (0.39 – 3.04)
> 750	13	25	3.85 (1.30 – 11.34)
Other dopamine agonist[3]	11	8	0.86 (0.32 – 2.34)
Anticholinergic drug[4]	3	5	2.14 (0.49 – 9.41)
COMT inhibitor[5]	7	6	1.05 (0.33 – 3.34)

Results presented as a univariate odds ratio (95% confidence limit).
* $p < 0.05$, ** $p < 0.005$, *** $p < 0.001$, for change in -2 log likelihood ratio χ^2 test statistic.

[1]Years since diagnosis refers to the time elapsed since the diagnosis of PD by a doctor.
[2]UPDRS denotes the Unified Parkinson's Disease Rating Scale, where higher scores reflect greater disease severity.
[3]Other dopamine agonists include non-levodopa drugs with dopaminergic activity (eg. bromocriptine, cabergoline, pergolide, pramipexole, ropinirole)
[4]Anticholinergic drugs include benztropine, procyclidine and trihexyphenidyl.
[5]Catechol-O-methyltransferase inhibitor (eg. entacapone)

Fallers had significantly worse general measures of the clinical and functional impact of PD, with worse UPDRS scores and UPDRS motor subscale scores, higher HY stage and greater total doses of levodopa each day. Specific PD-specific impairments that increased risk of falling were axial posture, bradykinesia (both measured by the relevant items in the UPDRS) and freezing of gait (derived from a combination of the UPDRS item and structured interview of the subject]. Although retropulsion was more common in fallers than non-fallers, this difference was not statistically significant ($p = 0.058$).

Table 9.4 shows differences in physiological measures between fallers and non-fallers. Impairment in leg strength, visual contrast sensitivity, postural sway, the coordinated stability test and gait cadence (steps/min) significantly increased the risk of falls.

Table 9.4 **Differences between fallers and non-fallers in tests of physiological function.**

Factor	Non-fallers N = 62	Fallers N = 51	OR (95%CL)[†]
Isometric strength (kg)			
Knee extension weaker leg	24.0 ± 2.8	15.9 ± 1.7	0.19 (0.09 – 0.41)***
Knee extension stronger leg	24.8 ±2.8	22.1 ±2.8	0.77 (0.52 – 1.13)
Knee flexion weaker leg	13.8 ±1.8	10.9 ±1.6	0.63 (0.42 – 0.94)*
Knee flexion stronger leg	14.7 ±1.8	14.4 ± 3.7	0.97 (0.67 – 1.41)
Ankle dorsiflexion weaker leg	11.6 ± 1.5	9.5 ± 1.4	0.68 (0.46 – 1.00)*
Ankle dorsiflexion stronger leg	13.2 ±1.4	11.0 ± 1.5	0.67 (0.45 – 0.99)*
Simple reaction time (ms)			
Hand slower side	327 ± 22	366 ± 41	1.20 (0.81 – 1.79)
Hand faster side	285 ± 18	301 ± 33	1.19 (0.80 – 1.78)
Foot slower side	403 ± 33	444 ± 37	1.18 (0.81 – 1.72)
Foot faster side	351 ± 32	371 ± 28	1.38 (0.93 – 2.04)
Proprioception[1] (°error)	2.0 (1.5 – 2.5)	2.5 (1.5 – 4.3)	1.06 (0.87 – 1.29)
Light touch[2] (g)	4.5 (4.4 – 4.6)	4.5 (4.4 – 4.6)	0.93 (0.64 – 1.35)
Vision			
Contrast sensitivity score[3]	20.0 (19.4 – 20.5)	19.0 (18.0 – 20.1)	0.66 (0.45 – 0.98)*
High contrast[4] (MAR)	1.5 (1.4 – 1.7)	1.6 (1.4-1.8)	1.06 (0.73 – 1.53)
Low contrast[5] (MAR)	2.6 (2.3 – 2.9)	3.2 (2.6-3.8)	2.36 (0.70 – 7.94)
Postural Sway[6] (mm)			
Firm surface/eyes open	67 (56 – 79)	96 (80-115)	2.12 (1.06 – 4.25)*
Firm surface/eyes closed	113 (96 – 132)	143 (115-177)	1.52 (0.97 – 2.39)*
Compliant surface/eyes open	121 (99 – 148)	230 (172-309)	2.06 (1.32 – 3.21)***
Compliant surface/eyes closed	225 (191 – 266)	396 (316-497)	2.26 (1.47 – 3.49)***
Coordinated stability (score)	5 (3 – 10)	18 (15-23)	3.16 (1.91 – 5.22)***
Mobility			
Step length (cm)	57.2 ± 3.8	54.8 ± 5.4	0.87 (0.60 – 1.26)
Cadence (steps/min)	111.4 ± 4.3	104.3 ± 4.8	0.62 (0.40 – 0.97)*
Gait speed (m/s)	1.05 ± 0.07	0.94 ± 0.09	0.30 (0.08 – 1.09)
Step time CV[8] (%)	9.5 (7.4 – 12.2)	9.9 (7.6 – 12.9)	1.03 (0.71 – 1.49)

Results presented as mean ± 95% confidence interval, mean (95% confidence limit).
[†]Univariate odds ratios (95% confidence limit) were calculated with measures converted into t-scores, or standard deviations for the sample. For example, each 1 SD increase in knee extension strength of the weaker leg reduced the odds of falling are reduced by 0.19 times.
* $p < 0.05$, ** $p < 0.005$, *** $p < 0.001$, for change in -2 log likelihood ratio χ^2 test statistic.
[1]Proprioception refers to the discrepancy in knee flexion angle between the referent and the tested legs measured during position-matching tasks of the limbs.[De Domenico and McCloskey 1987]
[2]Light touch at the ankle was measured using Semmes-Weinstein filaments (higher scores reflect worse sensation).[Semmes, Weinstein et al. 1960]
[3]Visual contrast sensitivity was tested using the Melbourne Edge Test (lower scores reflect worse contrast sensitivity).[Verbaken and Johnston 1986]

[4]High contrast sensitivity was measured using standard eye charts.
[5]Low contrast sensitivity was measured by eye charts using lettering that is paler than on standard eye charts.[Verbaken and Johnston 1986]
[6]Sway refers to movement (total sway distance) of the COG as estimated by a dorsal sway rod and was measured on firm and then compliant surfaces with eyes open and then closed on each surface.
[7]Higher Coordinated Stability Task scores imply worse postural stability during self-initiated tasks.
[8]Step time CV (coefficient of variation) refers to the standard deviation of the step time expressed as a percentage of the mean step time

9.3.2 Clinical model

Multivariate logistic regression analysis arrived at a 'clinical' model that identified five variables that were significant independent predictors of falls: a fall in the preceding year ($p < 0.001$), freezing of gait ($p = 0.012$), MMSE score $\leq$27/30 ($p = 0.027$) and abnormal axial posture ($p = 0.019$) (table 9.5).

Table 9.5 **Multivariate logistic regression models predicting or explaining falls.**

Factor	Clinical OR (95% CL)	Explanatory OR (95% CL)	Predictive OR (95% CL)
Fell in the last year			
No	Referent	NA	Referent
Yes	6.40 (2.37 – 17.33)*		5.36 (1.91– 15.08)***
Freezing of gait[1]			
No	Referent	Referent	Referent
Yes	3.54 (1.30 – 9.47)*	4.28 (1.5 - 12.95)**	3.59 (1.31 – 9.82)**
MMSE score ≤27/30[2]			
No	Referent	NS	NS
Yes	3.94 (1.11 – 14.03)		
FAB ≤17/18[3]			
No	NA	Referent	NS
Yes		3.41 (1.15 – 10.13)*	
Axial posture[4]			
Normal	Referent	Referent	NS
Slightly stooped	5.32 (1.50 – 18.96)	4.34 (1.13 – 16.74)	
Severely stooped	4.33 (0.97 – 19.30)*	1.73 (0.32 – 9.23)*	
Coordinated Stability		2.04 (1.13 – 3.68) †*	2.01 (1.14 – 3.52) †*
Knee extension		0.34 (0.14 – 0.82) †*	0.28 (0.11 – 0.68) †**

Results presented as the multivariate odds ratio (95% confidence limit).
†Multivariate odds ratios (95% confidence limit) were calculated with measures of strength and coordinated stability converted into t-scores, or standard deviations for the sample.
* $p < 0.05$, ** $p < 0.005$ and *** $p < 0.001$, for change in -2 log likelihood ratio χ^2 test statistic.
NA denotes not appropriate for baseline model in multiple logistic regression analyses, NS not significant.
[1]Freezing of gait refers to both difficulty starting to walk (start hesitation) and difficulty taking a further step while walking (freezing).
[2]The Folstein Mini Mental State Examination is a bedside test where lower scores reflect worse cognition.[Folstein and Folstein 1981]
[3]The Frontal Assessment Battery is a bedside test where lower scores reflect worse frontal lobe cognition.[Dubois, Slachevsky et al. 2000]
[4]Higher Coordianted Stability Task scores reflect worse postural stability in self-initiated tasks.
[6]Isometric knee extension strength of the weaker leg

There were no significant interactions among these predictor measures. The final model fitted the data adequately ($p = 0.821$) and explained 46% of the

variability between fallers and non-fallers, correctly classifying 40/51 fallers (78%) and 47/62 non-fallers (76%).

9.3.3 Explanatory model

In the explanatory model including both clinical and physiological variables, freezing of gait ($p = 0.004$), FAB score $\leq 17/18$ ($p = 0.025$), abnormal axial posture ($p = 0.050$), CST score ($p = 0.015$) and knee extension strength of the weaker side ($p = 0.009$) were independently associated with falls (table 9.5). In this model, MMSE score was eliminated from the model by the backward stepwise approach. In contrast, FAB score retained it independent association with falls. CST score and knee extension strength had linear relationships to the logit of the probability of falling in the multivariate baseline model and could therefore be used in the model as continuous variables. This model fitted the data adequately ($p = 0.875$), and was the most accurate in distinguishing fallers from non-fallers. It correctly classified 39/51 fallers (77%) and 51/62 non-fallers (82%), and accounted for 54% of the variability between fallers and non-fallers.

9.3.4 Combined clinical and physiological model

In the 'combined' model using both clinical and physiological variables, history of one or more falls in the previous year ($p < 0.001$), freezing of gait ($p = 0.004$), CST score ($p = 0.012$) and knee extension strength ($p = 0.002$) were independent predictors of falls. This model correctly classified 39/51 fallers (77%) and 50/62 non-fallers (81%), accounted for 54% of the variability between fallers and non-fallers and fitted the data satisfactorily ($p = 0.817$).

9.4 DISCUSSION

The present study of falls in PD has a number of strengths. First, prospective follow-up with monthly assessments was likely to result in an accurate estimate of falls risk over the course of a year. Second, detailed clinical and physiological assessments across multiple PD and non-PD domains of function were performed at baseline, avoiding any assumptions about pathophysiology of falls in PD. Third, approximately equal proportions of patients with mild-moderate PD (HY stages 1-3) were studied, and two thirds of the study population were from a community based sample. This means that our data are likely to be applicable to a wide range of patients with PD. We found that 45% of our subjects had one or more falls over a year. Previous prospective studies of falls have reported slightly higher annual incidence rates of between 51 and 68%, but drew their samples from hospital or neurological

outpatient clinics [Ashburn, Stack et al. 2001; Bloem, Grimbergen et al. 2001; Wood, Bilclough et al. 2002].

9.4.1 Clinical predictive model

We identified several symptoms and signs that could be used at the 'bedside' to predict PD patients who will fall in the subsequent twelve months. Using only measures obtainable using routine clinical history taking and examination, and bedside tests of cognitive function, a model was obtained which can correctly identify the majority of fallers (75%) and non-fallers (73%). Independent predictors of experiencing one or more falls were: a fall in the preceding year, freezing of gait, MMSE score $\leq$27/30 and abnormal axial posture. These measures can be obtained quickly by standard clinical history, neurological examinations and assessments of cognition in the doctor's surgery, hospital outpatient clinic or patient's home, and can be used to identify high and low risk patients.

Previous studies [Bloem, Grimbergen et al. 2001; Wood, Bilclough et al. 2002] have also identified a fall in the preceding year as a strong predictor of falls during follow-up. On its own, we found that this risk factor had the highest sensitivity (78%) but lower specificity (66%). Table 9.1 demonstrates that relying solely on a past history of falls, which relies upon subjects' memory, would miss 22% of subjects who will fall and falsely predict a fall in

34% of patients in the subsequent year. In other words, a past history of falls immediately puts a PD patient at a high risk of falling in the next year however a negative past history of falls does not exclude the possibility of future falls. Furthermore, a past history of falls neither explains why a subject will continue to fall nor suggests a rational treatment strategy.

These results also suggest that 34% of people who recalled falling during the year before enrolment reported no falls falling during the follow-up year. The reasons for this are unclear but may be related to subject memory, adaptation to past experience or changes in physiological activity. It is also possible that medications were modified during the follow-up period. It is probable that a substantial number of falls and perhaps fallers were missed in the follow-up period due to the limitations of monthly self- and or carer-reporting.

The two PD-specific impairments identified as being associated with an increased risk of falls were gait freezing and abnormal axial posture. While an association between freezing of gait and falling has been hypothesized [Bloem, Hausdorff et al. 2004], this assumption has not been proven previously in a prospective study. Freezing of gait is a late complication in PD patients receiving antiparkinsonian treatment [Giladi, McDermott et al. 2001], and could potentially directly cause falls as a result of the resulting sudden perturbation to gait stability. As the presence of freezing of gait was determined using the relevant historical item of the UPDRS, it is likely that the prevalence of this problem was underestimated in this study. There might have

been other subjects who later developed freezing of gait during the follow-up period. Abnormal axial posture could potentially increased the risk of falls due to the secondary reduction in the limits of stability [Schieppati, Hugon et al. 1994]. In addition, it has been postulated that the abnormal righting reflexes observed in PD are exacerbated and may to some extent be caused by the stooped posture [Bloem, Van Dijk et al. 1992].

Previous studies have found significant differences between fallers and non-fallers in performance in the MMSE [Bloem, Grimbergen et al. 2001]. As it is commonly utilised in clinical practice to assess general cognitive function, the MMSE was chosen as a candidate variable for our clinical multivariate model instead of the FAB, which tests frontal lobe function more specifically. In the explanatory model we used both the MMSE and the FAB, a test of cognition that specifically assesses frontal lobe function.

We were unable to demonstrate a relationship between orthostatic hypotension and falls, even though this relationship has been described in past studies [Wood, Bilclough et al. 2002] and observed in clinical practice. This was surprising as orthostatic hypotension is prevalent in PD and may be due to the disease itself or its treatments. In our study, blood pressure was measured manually using a mercury sphygmomanometer. Continuous blood pressure monitoring and the use of a postural tilt table would have been preferable and may have detected postural blood pressure changes missed by manual

measurements of the subject lying supine, immediately on standing and after three minutes of standing.

The subjects recruited for this study did not report syncope or have a history of this problem reported by their friends or relatives or documented in their medical records. We found no significant relationships between a history of dizziness or lightness in the head and falls. Nevertheless, it remains possible that a not insubstantial proportion of the falls observed in this study were related to syncope that was not remembered or reported by the subjects.

9.4.2 Explanatory model

This study builds on previous research into causes of falls in people with PD, by including additional sensorimotor, balance and mobility measures found to be risk factors for falls in the general population of older people and other patient subgroups [Lord, Clark et al. 1991]. We were able to make accurate and reliable measurements of vision, sensation, strength, reaction time, balance and gait without causing fatigue or discomfort in our PD population. These physiological measures were included with clinical variables in logistic regression analyses to develop an explanatory multivariate model. We found that freezing of gait, FAB $\leq$ 17/18, abnormal axial posture, impaired coordinated stability (higher CST score) and lower knee extension strength were independent predictors of falls. This model identified risk factors (ie. leg weakness and dynamic postural instability) that are not assessed adequately in

routine clinical tests and may be significant in the pathophysiology of falling. Importantly, only two simple tests of strength and balance are required in addition to routine clinical assessment measures to not only provide greater predictive accuracy, but also identify factors that may be amenable to intervention. Both the knee extension strength and coordinated stability tests can be conducted within a few minutes and require only inexpensive, portable equipment.

After accounting for other variables in the explanatory model, the MMSE score was no longer significantly associated with falls. In contrast, the FAB score, a more specific measure of frontal lobe function, was identified as an independent risk factor. The quadrupling of falls risk with a suboptimal FAB suggests that frontal lobe impairment, perhaps through increased impulsivity and lack of planning, is a major cause of falls in PD and a better predictor than general cognitive impairment. This novel finding has escaped previous attention in PD.

9.4.3 Combined clinical and physiological predictive model

In the 'combined' predictive model, a history of falls in the previous year, freezing of gait, impaired coordinated stability (higher CST score) and weaker knee extension were independent risk factors for future falls. This model did not improve on the sensitivity, specificity of the explanatory model however it

suggested ways to identify de novo fallers. In other words, patients with gait freezing, postural instability and leg weakness have a high risk of future falls even if they do not have a past history of a fall.

A consistent finding in both explanatory and predictive models is the independent association between lower limb strength and falling. Although strength has been recognised as an important risk factor for falls in the elderly [Lord, Clark et al. 1991], its importance in the PD population has been understated. We found that the odds of falling in general tended to decrease as knee extension strength increased. Previous studies did not include quantitative assessments of strength and this may explain their failure to demonstrate the link between leg weakness and falls. Although several measures of lower limb strength were linked to falls on univariate analyses, knee extension strength of the weaker side showed the strongest relationship. This is not surprising as knee extension from contraction of the quadriceps femoris is responsible for knee stability during standing and walking.

Although strength has been recognised as an important risk factor for falls in the elderly [Lord, Clark et al. 1991; Lord, McLean et al. 1992; Lord, Caplan et al. 1993; Lord and Clark 1996; Lord, Allen et al. 2002], its importance in the PD population has been understated. Previous studies employed clinical assessment of strength rather than quantitative assessment and this may explain their failure to demonstrate the link between leg weakness and falling. Although several measures of lower limb strength were associated with falls in

univariate analyses, knee extension strength of the weaker side showed the strongest relationship. This is not surprising as knee extension from contraction of the quadriceps femoris is responsible for knee stability during standing and walking. Unilateral weakness would increase the risk of falls in situations where total body weight need to be placed on one leg only, i.e. when undertaking everyday activities like stepping up a step.

Previous studies have not found impaired balance to be an independent risk factor for falls in PD patients. These studies have used postural sway during 'quiet' standing [Ashburn, Stack et al. 2001; Ashburn, Stack et al. 2001], clinical examinations such as the Functional Reach [Ashburn, Stack et al. 2001] and Romberg tests [Bloem, Grimbergen et al. 2001] or the more global Tinetti balance score [Bloem, Grimbergen et al. 2001]. The CST was used in our study to quantify how well subjects could adjust their balance in a controlled manner when near the limits of their base of support. This aspect of postural stability is likely to be the most crucial as most falls in PD occur as a result of impaired balance control during daily tasks [Bloem, Grimbergen et al. 2001]. Our findings suggest that impaired "dynamic" balance may be more important than impaired standing balance as a risk factor for falls.

This study raises the possibility that strength and balance training may prevent falls in PD patients. Such interventions could be adapted from studies of exercise in the elderly [Robertson, Devlin et al. 2001; Robertson, Gardner et

al. 2001] and could be tested in a PD population in randomised controlled trials.

9.5 CONCLUSIONS

We have prospectively examined differences between fallers and non-fallers with PD. Fallers can be predicted with a high degree of sensitivity and specificity using information obtained through routine clinical history and examination and a bedside test of cognitive function. Detailed assessment of clinical and physiological measures in multiple physiological domains has identified a number of independent risk factors for falls: abnormal axial posture, freezing of gait, frontal impairment, impaired coordinated stability and leg weakness. Even after accounting for a past history of falls, impaired coordinated stability and leg weakness were independent predictors of future falls. These findings suggest that a few items on clinical history and examination can be used to screen for falls risk. In those people thus found to be at high risk of falling, diagnostic accuracy can be improved efficiently by adding measures of coordinated stability and leg strength. These measures can also be used to assess risk of de novo falls in PD patients who have never fallen.

Thus falls in patients with PD are multifactorial in origin, with different factors likely to play more or less significant roles in individual subjects.

Many of the novel risk factors proven to be associated with falls in the present study are likely to contribute directly to the pathophysiology of falls and amenable to specific therapeutic intervention.

CHAPTER 10

WHY DO PEOPLE WITH PARKINSON'S DISEASE FALL? - DISCUSSION AND CONCLUSION

10.1 OVERVIEW OF MAJOR FINDINGS

The aim of this project was to detect factors associated with falls in PD and to develop models that explain why falls occurred and identify PD patients at greatest risk of falling. Factors that are consistently associated with falling in PD include a past history of falling, frontal cognitive impairment, leg weakness, freezing of gait and impaired coordinated stability. Patients with PD should be screened for these risk factors as they are independent predictors of future falls.

10.1.1 Clinical history and examination

Older age, use of four or more medications of any type, cognitive impairment (MMSE score $\leq$27/30 or FAB $\leq$17/18), greater postural drop in blood pressure and slower mobility (TUAG test) were associated with falling. It is not surprising that the variable with the strongest association with future falls was a history of one or more falls in the previous year. The same factors

causing previous falls will predispose to future falls if they are not recognized or amenable to treatment. Asking one question, "Have you had any falls in the last year?" may be an efficient and reasonably accurate means of screening PD patients for those at high risk of falls. Exclusive reliance on a past history of falls, however, misses 22% of subjects who proceed to fall, ignores reasons for falling and fails to suggest a rational treatment strategy.

A number of PD-specific factors could contribute to falls. These include worse disease severity (higher UPDRS total and motor subscale scores), more advanced disease stage (higher HY stage), abnormal axial posture, bradykinesia and gait freezing. These factors suggest that falls are associated more with severity rather than duration of PD. It should be considered, however, that the risk of falling might decrease as PD advances to HY stages 4 and 5. Patients with advanced PD may have such limited mobility that they are wheelchair bound or unable to walk without considerable assistance and therefore spend less time mobilising.

10.1.2 Leg strength

Falls are associated with weaker isometric leg strength and impaired visual contrast sensitivity. Where isometric strength is concerned, the risk of falling is determined by the patient's weaker leg. As the signs of PD are often asymmetrical, it is therefore important to assess strength, especially knee

flexion strength, in both legs and recognise that *the patient's mobility is only as good as his or her weaker leg*. Strength has been examined in this thesis as a continuous rather than a discrete or categorical variable as it signifies a continuum of risk. In other words, the risk of falling appears to decrease as strength increases.

10.1.3 Visual contrast sensitivity

Poor visual contrast sensitivity impairs patients' ability to discriminate between shades of grey and detect irregularities in the contour, changes in the level and inconsistencies in the surface of the footpath. Combined with their propensity to shuffle and festinate, impaired visual contrast sensitivity could increase PD patients' risk of tripping over cracks or steps in their path.

10.1.4 Postural sway

PD patients sway more than healthy controls across a range of support surface and visual conditions. In the early stages of PD, sway can be normal or reduced. As the stage and severity of the disease worsens, sway increases. Treatment with levodopa reduces sway to the level seen in healthy controls.

PD subjects have severely reduced limits of stability and perform significantly worse in tasks involving self-initiated movements of the COG. Dynamic

postural stability worsens as the stage and severity of PD increases, with fallers performing worse than non-fallers with PD. Even in the early stages of PD, patients may have worse dynamic stability than controls. These features improve with levodopa therapy but remain significantly worse than in healthy controls.

The combination of increased postural sway and reduced limits of stability in PD could increase the risk of falling in a number of ways. If the COG encroaches upon the limits of stability even in unperturbed, 'static' conditions, the risk that it will exceed these limits is greater with any self-initiated movement or external perturbation. When the COG exceeds the limits of stability, a fall will ensue. In PD, the margin of error between postural sway and limits of stability is significantly reduced.

10.1.5 Gait rhythm

PD patients have significantly smaller step lengths, higher cadences, slower gait speeds and greater step-to-step variability in step time than healthy people. Treatment with levodopa improves these features although step length and gait speed may remain significantly abnormal.

Gait abnormalities in PD, however, extend beyond changes in step length and time towards a deranged control of head and COG motion, evinced by lower

acceleration harmonic ratios (HRs). PD subjects have significantly lower HRs at the head and pelvis compared with controls. These differences persist even after adjusting for gait speed and step time CV. In PD, fallers have significantly lower HRs than non-fallers in all three orthogonal planes at both the head and pelvis. Even after adjusting for step time CV and gait speed, these significant differences persist at the pelvis in both A-P and vertical planes. These findings suggest that changes in head and pelvic rhythm during gait are not simply the result of increased step-to-step variability in step time or reduced gait speed, may point towards are more fundamental disorder of body control and may predispose to falls.

10.1.6 Explanatory and predictive models of falls in PD

In PD, a patient at risk of falling may be identified through clinical history, physical examination and a bedside test of cognitive function. The presence of a fall in the preceding year, freezing of gait, MMSE score $\leq 27/30$ and abnormal axial posture can be used to screen for falls risk.

To determine potential causes for falls, a specific test of 'frontal' cognitive impairment and physiological measures could be performed. Frontal impairment, impaired coordinated stability and leg weakness are independent risk factors for falls after adjusting for abnormal axial posture and freezing of gait. Even after accounting for a past history of falls, impaired coordinated

stability and leg weakness remained independent risk factors for future falls. These findings suggest that diagnostic accuracy can be improved efficiently by measuring coordinated stability and leg strength in those PD patients found to be at high risk of falling on simple clinical screening tests.

This project highlights the multifactorial nature of falls in PD, with different constellations of risk factors predisposing to falls in different subjects. Many of the risk factors documented in this thesis are likely to contribute directly in pathophysiology of falls and may be amenable to specific therapeutic intervention.

10.2 LIMITATIONS OF THE PROJECT

While case-control and prospective cohort studies can investigate associations between risk factors and falls, they cannot prove conclusively that these factors were pathophysiological causes of falls rather than merely epiphenomena. Establishing causation of postural instability and falls requires a double-blinded randomized controlled trial (RCT) or meta-analysis of such trials examining whether modification of potential risk factors reduces the incidence of falls. Level IA evidence of this nature does not exist in the area of falls in PD. Case-control and prospective cohort studies are therefore necessary to determine which risk factors (eg. leg strength, impaired dynamic stability etc.) may need to be modified in future RCTs.

A lack of power is a valid criticism of this project. As the prospective cohort study contained only 113 subjects, the number of putative risk factors had to be limited. The number of variables for baseline logistic regression models was restricted by selecting one variable from each major clinical, physiological and cognitive domain. This helped to avoid the inclusion of collinear variables in the baseline models. Nevertheless, it is possible that this study failed to detect a significant association between falls and measures of vision and reaction time (and perhaps proprioception and peripheral sensation) due to a lack of power.

A lack of power also limited the number of comparisons we were able to perform in the case-control studies to those that were specified before recruitment, measurement and analysis of the studies. Wherever possible, we examined significant differences between PD patient groups and between patients and controls (eg .in acceleration harmonic ratios) after adjusting for known confounders (ie. gait speed and step time CV).

In the prospective study, we tried to minimize sample bias by selecting a study population that was reflective of PD across the entire community. Subjects were recruited from both hospital outpatient and community settings. To examine the risk of falling in independently mobile PD patients, we excluded

those with HY stages higher than 3, evidence of cognitive impairment and other diseases (such as stroke and syncope) that affect mobility and postural stability. Sample bias may also be a problem of the case-control studies in this thesis. We tried to reduce this by matching patients and controls on a 1:1 basis for age, gender, height, weight and, where feasible, comorbidities.

The circumstances surrounding the subjects' falls were not included in the studies described in this thesis due to difficulties collecting and quantifying this data. For example, it is unknown what activities of daily living occupied individual subjects just prior to falling. For these activities of daily living to be included in the multivariate models as predictors of falling, they would need to be recorded by some means in both fallers and non-fallers during the follow-up period. It is acknowledged, however, that this information would be beneficial in understanding and preventing falls in individual patients.

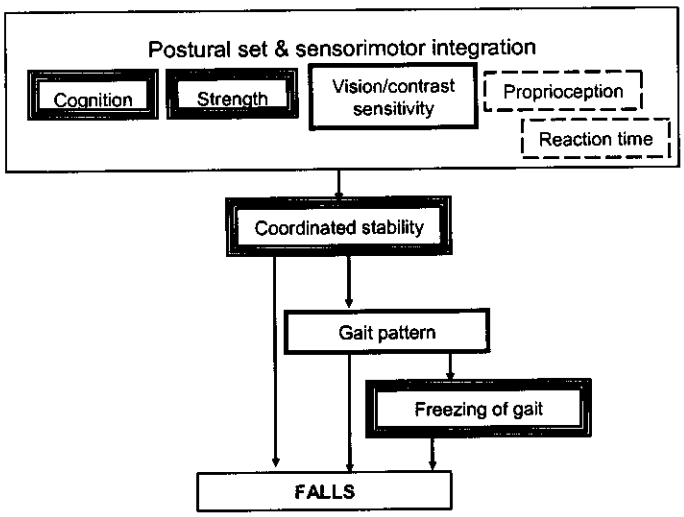
10.3 STRENGTHS OF THE PROJECT

This project adds to the existing literature on PD and falls by using both physiological and clinical measures. The main advantage of this approach is that possible explanations for falls, as well as associations with falls, could be examined. While the sample size is small, it is larger than those of previous prospective studies in this area.

10.4 HYPOTHESES FOR FUTURE RESEARCH

From our findings, a hierarchical model of falls in PD can be hypothesized (fig. 10.1).

Figure 10.1 **Hypothesized hierarchical model of falls in PD**



Framed text boxes denote independent predictors of falls, lined boxes predictors on univariate analyses and dashed boxes possible predictors.

In this model, physiological and cognitive functions underlie the abnormalities observed in coordinated stability, gait pattern and FOG. These abnormalities predispose to falls in PD. This model raises further hypotheses that could be tested in intervention trials. It could be reasoned that improvements in leg strength, visual contrast sensitivity and coordinated stability would reduce the risk of falling. Interventions to improve cognition and reduce impulsivity may be developed in the future and may have potential to reduce falling.

10.5 CONCLUSION

Falls in people with Parkinson's disease result from the effects of a combination of factors:

1. reduced leg strength,
2. impaired postural stability during tasks involving coordinated movement of the COG,
3. cognitive impairment, particularly that of 'frontal' or executive function and
4. PD-specific problems such as freezing of gait and abnormal axial posture.

The risk of falling may be increased by:

1. impaired visual contrast sensitivity,
2. increased postural sway as a proportion of the limits of stability and
3. abnormalities in the control of head and COG motion during gait.

REFERENCES

Kellogg International Working Group. The prevention of falls in later life. Danish Medical Bulletin 1987; 34(4): 1-24.

Amblard B, Assaiante C, et al. Voluntary head stabilization in space during oscillatory trunk movements in the frontal plane performed in weightlessness. Experimental Brain Research. 1997; 114(2): 214-25.

Anstey KJ, Smith GA, et al. Test-retest reliability of a battery of sensory, motor and physiological measures of aging. Perceptual & Motor Skills. 1997; 84.(831-834.

Ashburn A, Stack E, et al. A community-dwelling sample of people with Parkinson's disease: characteristics of fallers and non-fallers. Age & Ageing 2001; 30(1): 47-52.

Ashburn A, Stack E, et al. Predicting fallers in a community-based sample of people with Parkinson's disease. Gerontology. 2001; 47(5): 277-81.

Azulay JP, Mesure S, et al. Visual control of locomotion in Parkinson's disease. Brain 1999; 122(Pt 1): 111-20.

Balash Y, Peretz C, et al. Falls in outpatients with Parkinson's disease: frequency, impact and identifying factors. Journal of Neurology 2005; 252(11): 1310-5.

Beckley DJ, Bloem BR, et al. Impaired scaling of long latency postural reflexes in patients with Parkinson's disease. Electroencephalography & Clinical Neurophysiology 1993; 89(1): 22-8.

Beckley DJ, Bloem BR, et al. Long latency postural responses are functionally modified by cognitive set. Electroencephalography & Clinical Neurophysiology 1991; 81(5): 353-8.

Beckley DJ, Bloem BR, et al. Electrophysiological correlates of postural instability in Parkinson's disease. Electroencephalography and Clinical Neurophysiology 1991; 81(4): 263-8.

Beckley DJ, Panzer VP, et al. Clinical correlates of motor performance during paced postural tasks in Parkinson's disease. Journal of the Neurological Sciences 1995; 132(2): 133-8.

Behrman AL, Light KE, et al. Is the functional reach test useful for identifying falls risk among individuals with Parkinson's disease? Archives of Physical Medicine & Rehabilitation. 2002; 83(4): 538-42.

Bennett DA, Beckett LA, et al. Prevalence of parkinsonian signs and associated mortality in a community population of older people. New England Journal of Medicine 1996; 334(2): 71-6.

Birkmayer W and Hornykiewicz O. Der L-3,4-dioxyphenylalanin (= DOPA)-Effekt bei der Parkinson-Akinese. Wien Klin Wschr 1961; 73(787-788.

Bland JM and Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet. 1986; 1(8476): 307-10.

Blin O, Ferrandez AM, et al. Dopa-sensitive and dopa-resistant gait parameters in Parkinson's disease. Journal of the Neurological Sciences 1991; 103(1): 51-4.

Blin O, Ferrandez AM, et al. Quantitative analysis of gait in Parkinson patients: increased variability of stride length. Journal of the Neurological Sciences 1990; 98(1): 91-7.

Bloem BR, Beckley DJ, et al. Postural reflexes in Parkinson's disease during 'resist' and 'yield' tasks. Journal of the Neurological Sciences 1995; 129(2): 109-19.

Bloem BR, Beckley DJ, et al. Are automatic postural responses in patients with Parkinson's disease abnormal due to their stooped posture? Experimental Brain Research 1999; 124(4): 481-8.

Bloem BR, Beckley DJ, et al. Medium latency stretch reflexes in young-onset Parkinson's disease and MPTP-induced parkinsonism. Journal of the Neurological Sciences 1994; 123(1-2): 52-8.

Bloem BR, Beckley DJ, et al. Influence of dopaminergic medication on automatic postural responses and balance impairment in Parkinson's disease. Movement Disorders 1996; 11(5): 509-21.

Bloem BR, Beckley DJ, et al. Clinimetrics of postural instability in Parkinson's disease. Journal of Neurology 1998; 245(10): 669-73.

Bloem BR, Beckley DJ, et al. Long latency postural reflexes are under supraspinal dopaminergic control. Movement Disorders 1995; 10(5): 580-8.

Bloem BR, Grimbergen YA, et al. Prospective assessment of falls in Parkinson's disease. Journal of Neurology 2001; 248(11): 950-8.

Bloem BR, Hausdorff JM, et al. Falls and freezing of gait in Parkinson's disease: a review of two interconnected, episodic phenomena. Movement Disorders 2004; 19(8): 871-84.

Bloem BR, Valkenburg VV, et al. The Multiple Tasks Test: development and normal strategies. Gait & Posture 2001; 14(3): 191-202.

Bloem BR, Van Dijk JG, et al. Altered postural reflexes in Parkinson's disease: a reverse hypothesis. Medical Hypotheses 1992; 39(3): 243-7.

Bloem BR, van Vugt JP, et al. Postural instability and falls in Parkinson's disease. Advances in Neurology 2001; 87(209-23.

Bonnet AM, Loria Y, et al. Does long-term aggravation of Parkinson's disease result from nondopaminergic lesions? Neurology 1987; 37(9): 1539-42.

Bowes SG, Charlett A, et al. Gait in relation to ageing and idiopathic parkinsonism. Scandinavian Journal of Rehabilitation Medicine 1992; 24(4): 181-6.

Bowes SG, Clark PK, et al. Determinants of gait in the elderly parkinsonian on maintenance levodopa/carbidopa therapy. British Journal of Clinical Pharmacology. 1990; 30(1): 13-24.

Brach JS, Berthold R, et al. Gait variability in community-dwelling older adults. Journal of the American Geriatrics Society. 2001; 49(12): 1646-50.

Bronstein AM and Guerraz M. Visual-vestibular control of posture and gait: physiological mechanisms and disorders. Current Opinion in Neurology 1999; 12(1): 5-11.

Bronstein AM, Hood JD, et al. Visual control of balance in cerebellar and parkinsonian syndromes. Brain 1990; 113(Pt 3): 767-79.

Bronte-Stewart HM, Minn AY, et al. Postural instability in idiopathic Parkinson's disease: the role of medication and unilateral pallidotomy. Brain. 2002; 125(Pt 9): 2100-14.

Burleigh-Jacobs A, Horak FB, et al. Step initiation in Parkinson's disease: influence of levodopa and external sensory triggers. Movement Disorders 1997; 12(2): 206-15.

Campbell AJ, Borrie MJ, et al. Risk factors for falls in a community-based prospective study of people 70 years and older. Journal of Gerontology 1989; 44(4): M112-7.

Campbell AJ, Robertson MC, et al. Randomised controlled trial of a general practice programme of home based exercise to prevent falls in elderly women. British Medical Journal 1997; 315(7115): 1065-9.

Canter CJ, de la Torre R, et al. A method of evaluating disability in patients with parkinson's disease. J Nerv Ment Dis 1961; 133(143-147.

Cavagna GA, Saibene FP, et al. External work in walking. Journal of Applied Physiology. 1963; 18(1): 1-9.

Cavagna GA, Thys H, et al. The sources of external work in level walking and running. Journal of Physiology. 1976; 262(3): 639-57.

Chong RK, Horak FB, et al. Sensory organization for balance: specific deficits in Alzheimer's but not in Parkinson's disease. Journals of Gerontology Series A-Biological Sciences & Medical Sciences 1999; 54(3): M122-8.

Chong RK, Horak FB, et al. Parkinson's disease impairs the ability to change set quickly. Journal of the Neurological Sciences 2000; 175(1): 57-70.

Chong RK, Jones CL, et al. Postural set for balance control is normal in Alzheimer's but not in Parkinson's disease. Journals of Gerontology Series A-Biological Sciences & Medical Sciences 1999; 54(3): M129-35.

Clarke CE Parkinson's disease: experience with large multicentre trials. Clinical trials in neurology. R. J. Guiloff. London, Springer: 325-337.

Close J, Ellis M, et al. Prevention of falls in the elderly trial (PROFET): a randomised controlled trial.[see comment]. Lancet 1999; 353(9147): 93-7.

Concato J, Feinstein AR, et al. The risk of determining risk with multivariable models. Annals of Internal Medicine 1993; 118(3): 201-10.

Cotzias GC, van Woert MH, et al. Aromatic amino acids and modification of Parkinsonism. New England Journal of Medicine 1967; 276(374-379.

Cummings SR, Nevitt MC, et al. Forgetting falls. The limited accuracy of recall of falls in the elderly. Journal of the American Geriatrics Society. 1988; 36(7): 613-6.

De Domenico G and McCloskey DI. Accuracy of voluntary movements at the thumb and elbow joints. Experimental Brain Research 1987; 65(2): 471-8.

Dietz V, Berger W, et al. Posture in Parkinson's disease: impairment of reflexes and programming. Annals of Neurology 1988; 24(5): 660-9.

Dubois B, Slachevsky A, et al. The FAB: a Frontal Assessment Battery at bedside. Neurology 2000; 55(11): 1621-1626.

Duncan PW, Weiner DK, et al. Functional reach: a new clinical measure of balance. Journal of Gerontology. 1990; 45(6): M192-7.

Duvoisin RC (1971). The evaluation of extrapyramidal disease. Monoamines noyaux gris centraux et syndrome de Parkinson. J. De Ajuriaguerra and G. Gauthier. Geneva: 313-325.

Ebersbach G, Sojer M, et al. Comparative analysis of gait in Parkinson's disease, cerebellar ataxia and subcortical arteriosclerotic encephalopathy. Brain. 1999; 122(Pt 7): 1349-55.

Ehringer H and Hornykiewicz O. Verteilung von Noradrenalin + und Dopamine (3-hydroxytyramin) im Gehirn des Menschen und ihr

Verhalten bei Erkrankungen des extrapyra-midalen Systems. Klin Wschr 1960; 38(1236-1239.

England AC and Schwab RS. Post-operative evaluation of 26 selected patients with Parkinson's disease. Journal of the American Geriatrics Society 1956; 4(1219-1232.

Fagius J and Wahren LK. Variability of sensory threshold determination in clinical use. Journal of the Neurological Sciences. 1981; 51(1): 11-27.

Fahn S, Elton RL, et al. (1987). Unified Parkinson's disease rating scale. Recent developments in parkinson's disease. S. Fahn, C. D. Marsden, M. Goldstein and D. B. Calne. New Jersey, Macmillan Healthcare Information. 2: 153-163.

Feder G, Cryer C, et al. Guidelines for the prevention of falls in people over 65. The Guidelines' Development Group. BMJ 2000; 321(7267): 1007-11.

Fernie GR, Gryfe CI, et al. The relationship of postural sway in standing to the incidence of falls in geriatric subjects. Age & Ageing. 1982; 11(1): 11-6.

Ferrandez AM and Blin O. A comparison between the effect of intentional modulations and the action of L-dopa on gait in Parkinson's disease. Behavioural Brain Research 1991; 45(2): 177-83.

Ferrandez AM, Pailhous J, et al. Slowness in elderly gait. Experimental Aging Research. 1990; 16(1-2): 79-89.

Fink HA, Kuskowski MA, et al. Association between Parkinson's disease and low bone density and falls in older men: the osteoporotic fractures in men study. Journal of the American Geriatrics Society 2005; 53(9): 1559-64.

Finley FR and Cody KA. Locomotive characteristics of urban pedestrians. Archives of Physical Medicine & Rehabilitation. 1970; 51(7): 423-6.

Finley FR, Cody KA, et al. Locomotion patterns in elderly women. Archives of Physical Medicine & Rehabilitation. 1969; 50(3): 140-6.

Folstein M and Folstein S. Mini-Mental State: a practical method for grading the cognitive state of patients for the clinician. Journal of Psychiatric Research 1975; 12(189-198):

Folstein S and Folstein M. Diagnosis and treatment of Huntington's disease. Comprehensive Therapy 1981; 7(4): 60-6.

Frank JS, Horak FB, et al. Centrally initiated postural adjustments in parkinsonian patients on and off levodopa. Journal of Neurophysiology 2000; 84(5): 2440-8.

Gabell A and Nayak US. The effect of age on variability in gait. Journal of Gerontology. 1984; 39(6): 662-6.

Gardner MM, Buchner DM, et al. Practical implementation of an exercise-based falls prevention programme. Age & Ageing. 2001; 30(1): 77-83.

Gardner MM, Phty M, et al. Application of a falls prevention program for older people to primary health care practice. Preventive Medicine. 2002; 34(5): 546-53.

Gardner MM, Robertson MC, et al. Exercise in preventing falls and fall related injuries in older people: a review of randomised controlled trials. British Journal of Sports Medicine. 2000; 34(1): 7-17.

Gibson. The prevention of falls in later life. A report of the Kellogg International Work Group on the Prevention of Falls by the Elderly. Danish Medical Bulletin 1987; 34(Suppl 4): 1-24.

Giladi N, McDermott MP, et al. Freezing of gait in PD: prospective assessment in the DATATOP cohort. Neurology 2001; 56(12): 1712-21.

Gotham AM, Brown RG, et al. 'Frontal' cognitive function in patients with Parkinson's disease 'on' and 'off' levodopa. Brain 1988; 111(Pt 2): 299-321.

Grey CP and Yap M. Edge contrast sensitivity in optometric practice: an assessment of its efficacy in detecting visual dysfunction. American Journal of Optometry & Physiological Optics. 1987; 64(12): 925-8.

Grossman GE, Leigh RJ, et al. Frequency and velocity of rotational head perturbations during locomotion. Experimental Brain Research. 1988; 70(3): 470-6.

Grossman GE, Leigh RJ, et al. Performance of the human vestibuloocular reflex during locomotion. Journal of Neurophysiology. 1989; 62(1): 264-72.

Guimaraes RM and Isaacs B. Characteristics of the gait in old people who fall. International Rehabilitation Medicine. 1980; 2(4): 177-80.

Guy W (1976). ECDEU Assessment Manual for Psychopharmacology, revised ed. Washington, DC., US Department of Health, Education and Welfare.

Hausdorff JM, Cudkowicz ME, et al. Gait variability and basal ganglia disorders: stride-to-stride variations of gait cycle timing in Parkinson's disease and Huntington's disease. Movement Disorders. 1998; 13(3): 428-37.

Hayashi R, Tokuda T, et al. Impaired modulation of tonic muscle activities and H-reflexes in the soleus muscle during standing in patients with Parkinson's disease. Journal of the Neurological Sciences 1997; 153(1): 61-7.

Haymes SA, Johnston AW, et al. A weighted version of the Melbourne Low-Vision ADL Index: a measure of disability impact. Optometry & Vision Science. 2001 Aug;78(8):565-79

Hinsdale G. The station of man, considered physiologically and clinically. American Journal of the Medical Sciences. 1887; 93(478-485.

Hirasaki E, Kubo T, et al. Analysis of head and body movements of elderly people during locomotion. Acta Oto-Laryngologica Supplement. 1993; 501(25-30.

Hirasaki E, Moore ST, et al. Effects of walking velocity on vertical head and body movements during locomotion. Experimental Brain Research. 1999; 127(2): 117-30.

Hobart JC, Lamping DL, et al. Evaluating neurological outcome measures: the bare essentials. Journal of Neurology, Neurosurgery & Psychiatry. 1996; 60(2): 127-30.

Hoehn MM and Yahr MD. Parkinsonism: onset, progression, and mortality. Neurology 1967; 17(427-442.

Horak FB, Frank J, et al. Effects of dopamine on postural control in parkinsonian subjects: scaling, set, and tone. Journal of Neurophysiology 1996; 75(6): 2380-96.

Horak FB, Nutt JG, et al. Postural inflexibility in parkinsonian subjects. Journal of the Neurological Sciences 1992; 111(1): 46-58.

Hughes AJ, Ben-Shlomo Y, et al. What features improve the accuracy of clinical diagnosis in Parkinson's disease: a clinicopathologic study. Neurology 1992; 42(6): 1142-6.

Imms FJ and Edholm OG. Studies of gait and mobility in the elderly. Age & Ageing 1981; 10(3): 147-56.

Jankovic J, McDermott M, et al. Variable expression of Parkinson's disease: a base-line analysis of the DATATOP cohort. The Parkinson Study Group. Neurology 1990; 40(10): 1529-34.

Jorm L, Astbury L, et al. (1995). New South Wales Health Department Falls Prevention in Older People Campaign.

Report on the Baseline Survey, NSW Health Department.

Kannus P, Parkkari J, et al. Fall-induced injuries and deaths among older adults. Jama 1999; 281(20): 1895-9.

Keshner EA, Cromwell RL, et al. Mechanisms controlling human head stabilization. II. Head-neck characteristics during random rotations in the vertical plane. Journal of Neurophysiology 1995; 73(2302-12.

Knutsson E. An analysis of Parkinsonian gait. Brain. 1972; 95(3): 475-86.

Knutsson E and Martensson A. Quantitative effects of L-dopa on different types of movements and muscle tone in Parkinsonian patients. Scandinavian Journal of Rehabilitation Medicine. 1971; 3(3): 121-30.

Koller WC, Glatt S, et al. Falls and Parkinson's disease. Clinical Neuropharmacology 1989; 12(2): 98-105.

Kumar S, Fernando DJ, et al. Semmes-Weinstein monofilaments: a simple, effective and inexpensive screening device for identifying diabetic patients at risk of foot ulceration. Diabetes Research & Clinical Practice. 1991 Aug;13(1-2):63-7

Lamb SE, Jorstad-Stein EC, et al. Development of a common outcome data set for fall injury prevention trials: the Prevention of Falls Network Europe Consensus. Journal of the American Geriatrics Society 2005; 53(1618-1622.

Lange KW, Robbins TW, et al. L-dopa withdrawal in Parkinson's disease selectively impairs cognitive performance in tests sensitive to frontal lobe dysfunction. Psychopharmacology 1992; 107(2-3): 394-404.

Lanska DJ. Nineteenth-century contributions to the mechanical recording of postural sway. Archives of Neurology. 2001; 58(7): 1147-50.

Latash ML, Aruin AS, et al. Anticipatory postural adjustments during self inflicted and predictable perturbations in Parkinson's disease. Journal of Neurology, Neurosurgery & Psychiatry 1995; 58(3): 326-34.

Lauk M, Chow CC, et al. Assessing muscle stiffness from quiet stance in Parkinson's disease. Muscle & Nerve 1999; 22(5): 635-9.

Lewis GN and Byblow WD. Altered sensorimotor integration in Parkinson's disease. Brain. 2002; 125(Pt 9): 2089-99.

Lewis GN, Byblow WD, et al. Stride length regulation in Parkinson's disease: the use of extrinsic, visual cues. Brain. 2000; 123(Pt 10): 2077-90.

Lord SR, Allen GM, et al. Risk of falling: predictors based on reduced strength in persons previously affected by polio. Archives of Physical Medicine and Rehabilitation 2002; 83(6): 757-63.

Lord SR, Anstey KJ, et al. Psychoactive medication use, sensori-motor function and falls in older women. British Journal of Clinical Pharmacology 1995; 39(3): 227-34.

Lord SR, Caplan GA, et al. Sensori-motor function in older persons with diabetes. Diabetic Medicine 1993; 10(7): 614-8.

Lord SR, Caplan GA, et al. Balance, reaction time, and muscle strength in exercising and nonexercising older women: a pilot study. Archives of Physical Medicine & Rehabilitation 1993; 74(8): 837-9.

Lord SR and Clark RD. Simple physiological and clinical tests for the accurate prediction of falling in older people. Gerontology 1996; 42(4): 199-203.

Lord SR, Clark RD, et al. Physiological factors associated with falls in an elderly population. Journal of the American Geriatrics Society 1991; 39(12): 1194-200.

Lord SR, Clark RD, et al. Postural stability and associated physiological factors in a population of aged persons. Journal of Gerontology 1991; 46(3): M69-76.

Lord SR, Clark RD, et al. Visual acuity and contrast sensitivity in relation to falls in an elderly population. Age and Ageing 1991; 20(3): 175-81.

Lord SR, Lloyd DG, et al. The effect of exercise on gait patterns in older women: a randomized controlled trial. Journals of Gerontology. Series A, Biological Sciences and Medical Sciences 1996; 51(2): M64-70.

Lord SR, McLean D, et al. Physiological factors associated with injurious falls in older people living in the community. Gerontology 1992; 38(6): 338-46.

Lord SR, Menz HB, et al. A physiological profile approach to falls risk assessment and prevention. Physical Therapy 2003; 83(3): 237-52.

Lord SR, Sambrook PN, et al. Postural stability, falls and fractures in the elderly: results from the Dubbo Osteoporosis Epidemiology Study. Medical Journal of Australia 1994; 160(11): 684-5, 688-91.

Lord SR, Sherrington C, et al. (2001). Epidemiology of falls and fall-related injuries. Falls in older people. Cambridge, Cambridge University Press: 3-16.

Lord SR and Ward JA. Age-associated differences in sensori-motor function and balance in community dwelling women. Age and Ageing 1994; 23(6): 452-60.

Lord SR, Ward JA, et al. Exercise effect on dynamic stability in older women: a randomized controlled trial. Archives of Physical Medicine and Rehabilitation 1996; 77(3): 232-6.

Lord SR, Ward JA, et al. An epidemiological study of falls in older community-dwelling women: the Randwick falls and fractures study. Australian Journal of Public Health 1993; 17(3): 240-5.

Lord SR, Ward JA, et al. Physiological factors associated with falls in older community-dwelling women. Journal of the American Geriatrics Society 1994; 42(10): 1110-7.

Louis ED, Lynch T, et al. Reliability of patient completion of the historical section of the Unified Parkinson's Disease Rating Scale. Movement Disorders. 1996; 11(2): 185-92.

Maki BE. Gait changes in older adults: predictors of falls or indicators of fear. Journal of the American Geriatrics Society 1997; 45(3): 313-20.

Maki BE, Holliday PJ, et al. Aging and postural control. A comparison of spontaneous- and induced-sway balance tests. Journal of the American Geriatrics Society 1990; 38(1): 1-9.

Marsden CD. Motor disorders in basal ganglia disease. Human Neurobiology 1984; 2(4): 245-50.

Martinez-Martin P, Gil-Nagel A, et al. Unified Parkinson's Disease Rating Scale characteristics and structure. The Cooperative Multicentric Group. Movement Disorders. 1994; 9(1): 76-83.

Mathias S, Nayak US, et al. Balance in elderly patients: the "get-up and go" test. Archives of Physical Medicine and Rehabilitation 1986; 67(6): 387-9.

Maurer C, Mergner T, et al. Effect of chronic bilateral subthalamic nucleus (STN) stimulation on postural control in Parkinson's disease. Brain. 2003; 126(Pt 5): 1146-63.

McIntosh GC, Brown SH, et al. Rhythmic auditory-motor facilitation of gait patterns in patients with Parkinson's disease. Journal of Neurology, Neurosurgery & Psychiatry. 1997; 62(1): 22-6.

McRae C, Diem G, et al. Reliability of measurements of patient health status: a comparison of physician, patient, and caregiver ratings. Parkinsonism & Related Disorders. 2002; 8(3): 187-92.

Menz HB, Lord SR, et al. Acceleration patterns of the head and pelvis when walking are associated with risk of falling in community-dwelling older people. Journals of Gerontology Series A-Biological Sciences & Medical Sciences. 2003; 58(5): M446-52.

Menz HB, Lord SR, et al. Acceleration patterns of the head and pelvis when walking on level and irregular surfaces. Gait & Posture 2003; 18): 35-46.

Menz HB, Lord SR, et al. Age-related differences in walking stability. Age & Ageing. 2003; 32(2): 137-42.

Menz HB, Lord SR, et al. Walking stability and sensorimotor function in older people with diabetic peripheral neuropathy. Archives of Physical Medicine & Rehabilitation. 2004; 85(2): 245-52.

Mesure S, Azulay JP, et al. Strategies of segmental stabilization during gait in Parkinson's disease. Experimental Brain Research 1999; 129(4): 573-81.

Mitoma H. [Kinematic and EMG pattern of parkinsonian gait]. Nippon Rinsho - Japanese Journal of Clinical Medicine. 1997; 55(1): 163-7.

Mitoma H. [A physiological study on instability in Parkinson's disease]. Nippon Rinsho - Japanese Journal of Clinical Medicine 1997; 55(1): 168-72.

Moe-Nilssen R and Helbostad JL. Interstride trunk acceleration variability but not step width variability can differentiate between fit and frail older adults. Gait & Posture in press;

Moe-Nilssen R, Helbostad JL, et al. Balance and gait in children with dyslexia. Experimental Brain Research. 2003; 150(2): 237-44.

Moller J (1998). Estimated cost of injury ($ millions) by Cause 1995-1996.

Moller J (2000). Changing resource demands relating to fall injury in an ageing population.

Moore AP. Impaired sensorimotor integration in parkinsonism and dyskinesia: a role for corollary discharges? Journal of Neurology, Neurosurgery & Psychiatry 1987; 50(5): 544-52.

Morens DM, Davis JW, et al. Epidemiologic observations on Parkinson's disease: incidence and mortality in a prospective study of middle-aged men. Neurology 1996; 46(4): 1044-50.

Morgan RF and Fevens SK. Reliability of the adult growth examination: a standardized test of individual aging. Perceptual & Motor Skills. 1972.; 34.(415-419.

Morris M, Iansek R, et al. Abnormalities in the stride length-cadence relation in parkinsonian gait. Movement Disorders. 1998; 13(1): 61-9.

Morris M, Iansek R, et al. Postural instability in Parkinson's disease: a comparison with and without a concurrent task. Gait & Posture 2000; 12(3): 205-16.

Morris ME, Iansek R, et al. Ability to modulate walking cadence remains intact in Parkinson's disease. Journal of Neurology, Neurosurgery & Psychiatry. 1994; 57(12): 1532-4.

Morris ME, Iansek R, et al. The pathogenesis of gait hypokinesia in Parkinson's disease. Brain. 1994; 117(Pt 5): 1169-81.

Morris ME, Iansek R, et al. Stride length regulation in Parkinson's disease. Normalization strategies and underlying mechanisms. Brain. 1996; 119(Pt 2): 551-68.

Morris ME, McGinley J, et al. Constraints on the kinetic, kinematic and spatiotemporal parameters of gait in Parkinson's disease. Human Movement Science 1999; 18(461-83.

Murray MP, Drought B, et al. Walking patterns of normal men. The Journal of Bone and Joint Surgery 1964; 46-A(2): 335-348.

Murray MP, Kory RC, et al. Comparison of free and fast speed walking patterns of normal men. American Journal of Physical Medicine. 1966; 45(1): 8-23.

Murray MP, Kory RC, et al. Walking patterns of normal women. Archives of Physical Medicine & Rehabilitation. 1970; 51(11): 637-50.

Murray MP, Sepic SB, et al. Walking patterns of men with parkinsonism. American Journal of Physical Medicine. 1978; 57(6): 278-94.

Nakazumi Y and Hamasaki M. Electrophysiological studies and physical examinations in entrapment neuropathy: sensory and motor functions compensation for the central nervous system in cases with peripheral nerve damage. Electromyography & Clinical Neurophysiology. 2001 Sep;41(6):345-8

Nashner LM, Black FO, et al. Adaptation to altered support and visual conditions during stance: patients with vestibular deficits. Journal of Neuroscience 1982; 2(5): 536-44.

Nevitt MC, Cummings SR, et al. Risk factors for recurrent nonsyncopal falls. A prospective study. Jama. 1989; 261(18): 2663-8.

Nieuwboer A, Dom R, et al. Abnormalities of the spatiotemporal characteristics of gait at the onset of freezing in Parkinson's disease. Movement Disorders. 2001; 16(6): 1066-75.

O'Loughlin JL, Robitaille Y, et al. Incidence of and risk factors for falls and injurious falls among the community-dwelling elderly. American Journal of Epidemiology. 1993; 137(3): 342-54.

O'Sullivan JD, Said CM, et al. Gait analysis in patients with Parkinson's disease and motor fluctuations: influence of levodopa and comparison with other measures of motor function. Movement Disorders. 1998; 13(6): 900-6.

Olmos PR, Cataland S, et al. The Semmes-Weinstein monofilament as a potential predictor of foot ulceration in patients with noninsulin-dependent diabetes. American Journal of the Medical Sciences. 1995 Feb;309(2):76-82

Overstall PW, Exton-Smith AN, et al. Falls in the elderly related to postural imbalance. British Medical Journal. 1977; 1(6056): 261-4.

Owen AM, James M, et al. Fronto-striatal cognitive deficits at different stages of Parkinson's disease. Brain 1992; 115(Pt 6): 1727-51.

Parkes JD, Calver DM, et al. Controlled trial of amantadine hydrochloride in Parkinson's disease. Lancet. 1970; 1(7641): 259-62.

Parkinson J (1817). An Essay on the Shaking Palsy. London, Sherwood, Neely and Jones Paternoster Row.

Pastor MA, Day BL, et al. Vestibular induced postural responses in Parkinson's disease. Brain 1993; 116(Pt 5): 1177-90.

Pedersen SW, Eriksson T, et al. Effects of withdrawal of antiparkinson medication on gait and clinical score in the Parkinson patient. Acta Neurologica Scandinavica. 1991; 84(1): 7-13.

Perkins BA, Olaleye D, et al. Simple screening tests for peripheral neuropathy in the diabetes clinic. Diabetes Care. 2001 Feb;24(2):250-6

Pratorius B, Kimmeskamp S, et al. The sensitivity of the sole of the foot in patients with Morbus Parkinson. Neuroscience Letters 2003; 346(3): 173-6.

Ralston HJ (1976). Energetics of human walking. Neural control of locomotion. R. M. Herman, S. Grillner, P. S. G. Stein and D. G. Stuart. New York, Plenum: 77-98.

Richards M, Marder K, et al. Interrater reliability of the Unified Parkinson's Disease Rating Scale motor examination. Movement Disorders. 1994; 9(1): 89-91.

Robertson MC, Devlin N, et al. Effectiveness and economic evaluation of a nurse delivered home exercise programme to prevent falls. 1: Randomised controlled trial. British Medical Journal 2001; 322(7288): 697-701.

Robertson MC, Devlin N, et al. Economic evaluation of a community based exercise programme to prevent falls. Journal of Epidemiology & Community Health. 2001; 55(8): 600-6.

Robertson MC, Gardner MM, et al. Effectiveness and economic evaluation of a nurse delivered home exercise programme to prevent falls. 2:

Controlled trial in multiple centres. British Medical Journal 2001; 322(7288): 701-4.

Robinson K, Dennison A, et al. Falling risk factors in Parkinson's disease. Neurorehabilitation 2005; 20(3): 169-82.

Rocchi L, Chiari L, et al. Comparison between subthalamic nucleus and globus pallidus internus stimulation for postural performance in Parkinson's disease. Gait and Posture 2004; 19(2): 172-83.

Rocchi L, Chiari L, et al. Effects of deep brain stimulation and levodopa on postural sway in Parkinson's disease.[comment]. Journal of Neurology, Neurosurgery and Psychiatry 2002; 73(3): 267-74.

Rogers MW. Disorders of posture, balance, and gait in Parkinson's disease. Clinics in Geriatric Medicine 1996; 12(4): 825-45.

Romberg MH (1853). A Manual of the Nervous Diseases of Man. London, Sydenham Society.

Salgado R, Lord SR, et al. Factors associated with falling in elderly hospital patients. Gerontology 1994; 40(6): 325-31.

Salkeld G, Cumming RG, et al. The cost effectiveness of a home hazard reduction program to reduce falls among older persons. Australian & New Zealand Journal of Public Health 2000; 24(3): 265-71.

Sato Y, Kaji M, et al. Risk factors for hip fracture among elderly patients with Parkinson's disease. Journal of the Neurological Sciences. 2001; 182(2): 89-93.

Schenkman M, Cutson TM, et al. Exercise to improve spinal flexibility and function for people with Parkinson's disease: a randomized, controlled

trial. Journal of the American Geriatrics Society. 1998; 46(10): 1207-16.

Schieppati M, Hugon M, et al. The limits of equilibrium in young and elderly normal subjects and in parkinsonians. Electroencephalography and Clinical Neurophysiology 1994; 93(4): 286-98.

Schieppati M and Nardone A. Free and supported stance in Parkinson's disease. The effect of posture and 'postural set' on leg muscle responses to perturbation, and its relation to the severity of the disease. Brain 1991; 114(Pt 3): 1227-44.

Schneider JS, Diamond SG, et al. Parkinson's disease: sensory and motor problems in arms and hands. Neurology 1987; 37(6): 951-6.

Schrag A, Ben-Shlomo Y, et al. How common are complications of Parkinson's disease? Journal of Neurology. 2002; 249(4): 419-23.

Schwab RS and England AC (1969). Projection technique for evaluating surgery in Parkinson's disease. Third symposium on Parkinson's disease. F. J. Gillingham and I. M. L. Donaldson. Edinburgh, E & S Livingstone: 152-157.

Semmes J, Weinstein S, et al. (1960). Somatosensory changes after penetrating brain wounds in man. Cambridge Mass., Harvard University Press.

Smidt GL, Arora JS, et al. Accelerographic analysis of several types of walking. American Journal of Physical Medicine. 1971; 50(6): 285-300.

Smidt GL, Deusinger RH, et al. An automated accelerometry system for gait analysis. Journal of Biomechanics. 1977; 10(5-6): 367-75.

Smithson F, Morris ME, et al. Performance on clinical tests of balance in Parkinson's disease. Physical Therapy 1998; 78(6): 577-92.

Sosenko JM, Sparling YH, et al. Use of the Semmes-Weinstein monofilament in the strong heart study. Risk factors for clinical neuropathy. Diabetes Care. 1999; 22(10): 1715-21.

Stolze H, Kuhtz-Buschbeck JP, et al. Comparative analysis of the gait disorder of normal pressure hydrocephalus and Parkinson's disease. Journal of Neurology, Neurosurgery & Psychiatry. 2001; 70(3): 289-97.

Tanner CM. Epidemiology of Parkinson's disease. Neurologic Clinics 1992; 10(2): 317-29.

Tinetti ME. Performance-oriented assessment of mobility problems in elderly patients. Journal of the American Geriatrics Society. 1986; 34(2): 119-26.

Tinetti ME, Baker DI, et al. A multifactorial intervention to reduce the risk of falling among elderly people living in the community. New England Journal of Medicine. 1994; 331(13): 821-7.

Tinetti ME, Speechley M, et al. Risk factors for falls among elderly persons living in the community. New England Journal of Medicine. 1988; 319(26): 1701-7.

Ueno E, Yanagisawa N, et al. Gait disorders in parkinsonism. A study with floor reaction forces and EMG. Advances in Neurology 1993; 60(414-8.

van Emmerik RE and Wagenaar RC. Effects of walking velocity on relative phase dynamics in the trunk in human walking. Journal of Biomechanics. 1996; 29(9): 1175-84.

Van Emmerik RE, Wagenaar RC, et al. Identification of axial rigidity during locomotion in Parkinson disease. Archives of Physical Medicine & Rehabilitation 1999; 80(2): 186-91.

Verbaken JH and Johnston AW. Clinical contrast sensitivity testing; the current status. Clinical and Experimental Optometry. 1986; 69(204-212.

Verbaken JH and Johnston AW. Population norms for edge contrast sensitivity. American Journal of Optometry and Physiological Optics 1986; 63(9): 724-32.

Vieregge P, Stolze H, et al. Gait quantitation in Parkinson's disease--locomotor disability and correlation to clinical rating scales. Journal of Neural Transmission - General Section. 1997; 104(2-3): 237-48.

Viitasalo MK, Kampman V, et al. Analysis of sway in Parkinson's disease using a new inclinometry-based method. Movement Disorders. 2002; 17(4): 663-9.

Waters RL, Lunsford BR, et al. Energy-speed relationship of walking: standard tables. Journal of Orthopaedic Research. 1988; 6(2): 215-22.

Waterston JA, Hawken MB, et al. Influence of sensory manipulation on postural control in Parkinson's disease. Journal of Neurology, Neurosurgery & Psychiatry 1993; 56(12): 1276-81.

Webster DD. Critical analysis of the disability in Parkinson's disease. Modern Treatment. 1968; 5(2): 257-82.

Wernick-Robinson M, Krebs DE, et al. Functional reach: does it really measure dynamic balance? Archives of Physical Medicine & Rehabilitation. 1999; 80(3): 262-9.

Wielinski CL, Erickson-Davis C, et al. Falls and injuries resulting from falls among patients with Parkinson's disease and other parkinsonian syndromes. Movement Disorders 2005; 20(4): 410-415.

Wildsoet C, Wood J, et al. The effect of different forms of monocular occlusion on measures of central visual function. Ophthalmic & Physiological Optics. 1998; 18(3): 263-8.

Winter DA. Changes in gait with aging. Canadian Journal of Sport Sciences. 1991; 16(3): 165-7.

Winter DA, Patla AE, et al. Biomechanical walking pattern changes in the fit and healthy elderly. Physical Therapy. 1990; 70(6): 340-7.

Wolffsohn JS and Cochrane AL. The practical near acuity chart (PNAC) and prediction of visual ability at near. Ophthalmic & Physiological Optics. 2000; 20(2): 90-7.

Wolfson L, Judge J, et al. Strength is a major factor in balance, gait, and the occurrence of falls. Journals of Gerontology Series A-Biological Sciences & Medical Sciences 1995; 50(Spec No): 64-7.

Wood BH, Bilclough JA, et al. Incidence and prediction of falls in Parkinson's disease: a prospective multidisciplinary study. Journal of Neurology, Neurosurgery and Psychiatry 2002; 72(6): 721-5.

Wood JM and Lovie-Kitchin JE. Evaluation of the efficacy of contrast sensitivity measures for the detection of early primary open-angle glaucoma. Optometry & Vision Science. 1992; 69(3): 175-81.

Yack HJ and Berger RC. Dynamic stability in the elderly: identifying a possible measure. Journal of Gerontology. 1993; 48(5): M225-30.

Zangemeister WH, Bulgheroni MV, et al. Normal gait is differentially influenced by the otoliths. Journal of Biomedical Engineering. 1991; 13(6): 451-8.

Zijlmans JC, Poels PJ, et al. Quantitative gait analysis in patients with vascular parkinsonism. Movement Disorders. 1996; 11(5): 501-8.

APPENDIX A

United Kingdom Parkinson's Disease Society brain bank diagnostic criteria for Parkinson's disease [Hughes, Ben-Shlomo et al. 1992]

Step 1: Diagnosis of Parkinsonism

Bradykinesia **and** at least one of the following:

- Muscular rigidity
- 4–6 Hz resting tremor
- postural instability not caused by primary visual, vestibular, cerebellar or proprioceptive dysfunction

Step 2: Features tending to exclude Parkinson's disease as the cause of Parkinsonism

- History of repeated strokes with stepwise progression of parkinsonian features
- History of repeated head injury
- History of definite encephalitis
- Neuroleptic treatment at onset of symptoms
- >1 affected relatives
- Sustained remission
- Strictly unilateral features after 3 years
- Supranuclear gaze palsy
- Cerebellar signs
- Early severe autonomic involvement
- Early severe dementia with disturbances of memory, language and praxis
- Babinski's sign
- Presence of a cerebral tumour or communicating hydrocephalus on computed tomography scan
- Negative response to large doses of levodopa (if malabsorption excluded)
- MPTP exposure

Step 3: Features that support a diagnosis of Parkinson's disease (three or more required for diagnosis of definite Parkinson's disease)

- Unilateral onset
- Rest tremor present
- Progressive disorder
- Persistent asymmetry affecting the side of onset most
- Excellent (70–100%) response to levodopa
- Severe levodopa-induced chorea
- Levodopa response for ≥5 years
- Clinical course of ≥10 years

APPENDIX B

ID NUMBER _____ INITIALS _____

THE PRINCE OF WALES MEDICAL RESEARCH INSTITUTE

PREDICTORS OF INJURY IN OLDER PEOPLE- QUESTIONNAIRE

NAME _____

ADDRESS _____

_____

PHONE _____ ALTERNATIVE CONTACT ._____

1. What is your age? _____
2. What is your date of birth? _____
3. What is your gender? Male / Female

HEALTH – Disease

Have you ever been treated or told you have had any of the following conditions?

VERTIGO/ DIZZINESS.....	Yes	[ ]	No	[ ]
EPILEPSY.....	Yes	[ ]	No	[ ]
VASCULAR DISEASE/LEG ULCERS....	Yes	[ ]	No	[ ]
DIABETES.....	Yes	[ ]	No	[ ]
STROKE/TIAS.....	Yes	[ ]	No	[ ]
HEART ATTACK.....	Yes	[ ]	No	[ ]
ATRIAL FIBRILLATION.....	Yes	[ ]	No	[ ]
PERMENENT PACEMAKER	Yes	[ ]	No	[ ]
DEFIBRILLATION.....	Yes	[ ]	No	[ ]
SUDDEN LOSS OF CONSCIOUSNESS...	Yes	[ ]	No	[ ]
ANGINA.....	Yes	[ ]	No	[ ]
HEART FAILURE.....	Yes	[ ]	No	[ ]
HEART VALVE DISEASE OR MURMUR	Yes	[ ]	No	[ ]
LOW BLOOD PRESSURE.....	Yes	[ ]	No	[ ]
HIGH BLOOD PRESSURE.....	Yes	[ ]	No	[ ]
PARKINSON'S DISEASE.....	Yes	[ ]	No	[ ]
INCONTINENCE – URINARY.....	Yes	[ ]	No	[ ]
INCONTINENCE – FAECAL	Yes	[ ]	No	[ ]
HEARING IMPAIRMENT.....	Yes	[ ]	No	[ ]
OSTEOPOROSIS.....	Yes	[ ]	No	[ ]
OSTEOARTHRITIS – BACK/ NECK	Yes	[ ]	No	[ ]
OSTEOARTHRITIS – HIP.....	Yes	[ ]	No	[ ]
OSTEOARTHRITIS – KNEE.....	Yes	[ ]	No	[ ]
BROKEN HIP.....	Yes	[ ]	No	[ ]
CANCER.....	Yes	[ ]	No	[ ]
RHEUMATOID ARTHRITIS.....	Yes	[ ]	No	[ ]
DEPRESSION.....	Yes	[ ]	No	[ ]
PAINFUL FEET.....	Yes	[ ]	No	[ ]
LIGHT HEADEDNESS WHEN STANDING UP FROM SEAT or BED.....	Yes	[ ]	No	[ ]

APPENDIX C

Hoehn and Yahr Staging of Parkinson's Disease [Hoehn and Yahr 1967]

1. Stage One
    1. Signs and symptoms on one side only
    2. Symptoms mild
    3. Symptoms inconvenient but not disabling
    4. Usually presents with tremor of one limb
    5. Friends have noticed changes in posture, locomotion and facial expression

2. Stage Two
    1. Symptoms are bilateral
    2. Minimal disability
    3. Posture and gait affected

3. Stage Three
    1. Significant slowing of body movements
    2. Early impairment of equilibrium on walking or standing
    3. Generalized dysfunction that is moderately severe

4. Stage Four
    1. Severe symptoms
    2. Can still walk to a limited extent
    3. Rigidity and bradykinesia
    4. No longer able to live alone
    5. Tremor may be less than earlier stages

5. Stage Five
    1. Cachectic stage
    2. Invalidism complete
    3. Cannot stand or walk
    4. Requires constant nursing care

APPENDIX D

Unified Parkinson Disease Rating Scale (UPDRS) [Fahn, Elton et al. 1987]

I. Mentation, Behavior, Mood

Intellectual Impairment
0 = none
1 = mild (consistent forgetfulness with partial recollection of events with no other difficulties)
2 = moderate memory loss with disorientation and moderate difficulty handling complex problems
3 = severe memory loss with disorientation to time and often place, severe impairment with problems
4 = severe memory loss with orientation only to person, unable to make judgments or solve problems

Thought Disorder
0 = none
1 = vivid dreaming
2 = "benign" hallucination with insight retained
3 = occasional to frequent hallucination or delusions without insight, could interfere with daily activities
4 = persistent hallucination, delusions, or florid psychosis.

Depression
0 = not present
1 = periods of sadness or guilt greater than normal, never sustained for more than a few days or a week
2 = sustained depression for >1 week
3 = vegetative symptoms (insomnia, anorexia, abulia, weight loss)
4 = vegetative symptoms with suicidality

Motivation/Initiative
0 = normal
1 = less assertive, more passive
2 = loss of initiative or disinterest in elective activities
3 = loss of initiative or disinterest in day to say (routine) activities
4 = withdrawn, complete loss of motivation

II. Activities of Daily Living

Speech
0 = normal
1 = mildly affected, no difficulty being understood
2 = moderately affected, may be asked to repeat
3 = severely affected, frequently asked to repeat
4 = unintelligible most of time

Salivation
0 = normal
1 = slight but noticeable increase, may have nighttime drooling
2 = moderately excessive saliva, hay minimal drooling
3 = marked drooling

Swallowing
0 = normal
1 = rare choking
2 = occasional choking
3 = requires soft food
4 = requires nasogastric tube

Handwriting
0 = normal
1 = slightly small or slow
2 = all words small but legible
3 = severely affected, not all words legible
4 = majority illegible

Cutting Food/Handing Utensils
0 = normal
1 = somewhat slow and clumsy but no help needed
2 = can cut most foods, some help needed
3 = food must be cut, but can feed self
4 = needs to be fed

Dressing
0 = normal
1 = somewhat slow, no help needed
2 = occasional help with buttons or arms in sleeves
3 = considerable help required but can do something alone
4 = helpless

Hygiene
0 = normal
1 = somewhat slow but no help needed
2 = needs help with shower or bath or very slow in hygienic care
3 = requires assistance for washing, brushing teeth, going to bathroom
4 = helpless

Turning in Bed/ Adjusting Bed Clothes
0 = normal
1 = somewhat slow no help needed
2 = can turn alone or adjust sheets but with great difficulty
3 = can initiate but not turn or adjust alone
4 = helpless

Falling-Unrelated to Freezing
0 = none
1 = rare falls
2 = occasional, less than one per day
3 = average of once per day
4 = >1 per day

Freezing When Walking
0 = normal
1 = rare, may have start hesitation
2 = occasional falls from freezing
3 = frequent freezing, occasional falls
4 = frequent falls from freezing

Walking
0 = normal
1 = mild difficulty, day drag legs or decrease arm swing
2 = moderate difficultly requires no assist
3 = severe disturbance requires assistance
4 = cannot walk at all even with assist

Tremor
0 = absent
1 = slight and infrequent, not bothersome to patient
2 = moderate, bothersome to patient
3 = severe, interfere with many activities
4 = marked, interferes with many activities

Sensory Complaints Related to Parkinsonism
0 = none
1 = occasionally has numbness, tingling, and mild aching
2 = frequent, but not distressing
3 = frequent painful sensation
4 = excruciating pain

III. Motor Exam

Speech
0 = normal
1 = slight loss of expression, diction,volume
2 = monotone, slurred but understandable, mod. impaired
3 = marked impairment, difficult to understand
4 = unintelligible

Facial Expression
0 = Normal
1 = slight hypomymia, could be poker face
2 = slight but definite abnormal diminution in expression
3 = mod. hypomimia, lips parted some of time
4 = masked or fixed face, lips parted 1/4 of inch or more with complete loss of expression

Tremor at Rest
Face
0 = absent
1 = slight and infrequent
2 = mild and present most of time
3 = moderate and present most of time
4 = marked and present most of time

Right Upper Extremity
0 = absent
1 = slight and infrequent
2 = mild and present most of time
3 = moderate and present most of time
4 = marked and present most of time

Left Upper Extremity
0 = absent
1 = slight and infrequent
2 = mild and present most of time
3 = moderate and present most of time
4 = marked and present most of time

Right Lower Extremity
0 = absent
1 = slight and infrequent
2 = mild and present most of time
3 = moderate and present most of time
4 = marked and present most of time

Left Lower Extremity
0 = absent
1 = slight and infrequent
2 = mild and present most of time
3 = moderate and present most of time
4 = marked and present most of time

Action or Postural Tremor

Right Upper Extremity
0 = absent
1 = slight, present with action
2 = moderate, present with action
3 = moderate present with action and posture holding
4 = marked, interferes with feeding

Left Upper Extremity
0 = absent
1 = slight, present with action
2 = moderate, present with action
3 = moderate present with action and posture holding
4 = marked, interferes with feeding

Rigidity

Neck
0 = absent
1 = slight or only with activation
2 = mild/moderate
3 = marked, full range of motion
4 = severe

Right Upper Extremity
0 = absent
1 = slight or only with activation
2 = mild/moderate
3 = marked, full range of motion
4 = severe

Left Upper Extremity
0 = absent
1 = slight or only with activation
2 = mild/moderate
3 = marked, full range of motion
4 = severe

Right Lower Extremity
0 = absent
1 = slight or only with activation
2 = mild/moderate
3 = marked, full range of motion
4 = severe

Left Lower Extremity
0 = absent
1 = slight or only with activation
2 = mild/moderate
3 = marked, full range of motion
4 = severe

Finger taps

Right
0 = normal
1 = mild slowing, and/or reduction in amplitude
2 = moderate impaired. Definite and early fatiguing, may have occasional arrests
3 = severely impaired. Frequent hesitations and arrests
4 = can barely perform

Left
0 = normal
1 = mild slowing, and/or reduction in amplitude
2 = moderate impaired. Definite and early fatiguing, may have occasional arrests
3 = severely impaired. Frequent hesitations and arrests
4 = can barely perform

Hand Movements (open and close hands in rapid succession)

Right
0 = normal
1 = mild slowing, and/or reduction in amplitude
2 = moderate impaired. Definite and early fatiguing, may have occasional arrests
3 = severely impaired. Frequent hesitations and arrests
4 = can barely perform

Left
0 = normal
1 = mild slowing, and/or reduction in amplitude
2 = moderate impaired. Definite and early fatiguing, may have occasional arrests
3 = severely impaired. Frequent hesitations and arrests
4 = can barely perform

Rapid Alternating Movements (pronate and supinate hands)

Right
0 = normal
1 = mild slowing, and/or reduction in amplitude
2 = moderate impaired. Definite and early fatiguing, may have occasional arrests
3 = severely impaired. Frequent hesitations and arrests
4 = can barely perform

Left
0 = normal
1 = mild slowing, and/or reduction in amplitude
2 = moderate impaired. Definite and early fatiguing, may have occasional arrests
3 = severely impaired. Frequent hesitations and arrests
4 = can barely perform

Leg Agility (tap heel on ground, amplitude should be 3 inches)
Right
0 = normal
1 = mild slowing, and/or reduction in amplitude
2 = moderate impaired. Definite and early fatiguing, may have occasional arrests
3 = severely impaired. Frequent hesitations and arrests
4 = can barely perform

Left
0 = normal
1 = mild slowing, and/or reduction in amplitude
2 = moderate impaired. Definite and early fatiguing, may have occasional arrests
3 = severely impaired. Frequent hesitations and arrests
4 = can barely perform

Rising From Chair (patient rises with arms folded across chest)
0 = normal
1 = slow, may need more than one attempt
2 = pushes self up from arms or seat
3 = tends to fall back, may need multiple tries but can rise without assistance
4 = unable to rise without help

Posture
0 = normal erect
1 = slightly stooped, could be normal for older person
2 = definitely abnormal, moderately stooped, may lean to one side
3 = severely stooped with kyphosis
4 = marked flexion with extreme abnormality of posture

Gait
0 = normal
1 = walks slowly, may shuffle with short steps, no festination or propulsion
2 = walks with difficulty, little or no assistance, some festination, short steps or propulsion
3 = severe disturbance, frequent assistance
4 = cannot walk

Postural Stability (retropulsion test)
0 = normal
1 = recovers unaided
2 = would fall if not caught
3 = falls spontaneously
4 = unable to stand

Body Bradykinesia/ Hypokinesia
0 = none
1 = minimal slowness, could be normal, deliberate character
2 = mild slowness and poverty of movement, definitely abnormal, or decreased amplitude of movement
3 = moderate slowness, poverty, or small amplitude
4 = marked slowness, poverty, or amplitude

APPENDIX E

Schwab and England Activities of Daily Living [England and Schwab 1956; Schwab and England 1969]

* 100% - Completely independent. Able to do all chores without slowness, difficulty, or impairment.

* 90% - Completely independent. Able to do all chores with some slowness, difficulty, or impairment. May take twice as long.

* 80% - Independent in most chores. Takes twice as long. Conscious of difficulty and slowing

* 70% - Not completely independent. More difficulty with chores. Three to four times as long on chores for some. May take large part of day for chores.

* 60% - Some dependency. Can do most chores, but very slowly and with much effort.

* 50% - More dependant. Help with 1/2 of chores. Difficulty with everything. Errors, some impossible.

* 40% - Very dependant. Can assist with all chores but few alone

* 30% - With effort, now and then does a few chores alone of begins alone. Much help needed

* 20% - Nothing alone. Can do some slight help with some chores. Severe invalid

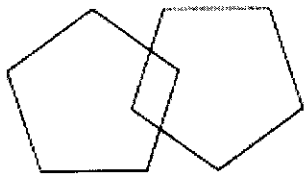
* 10% - Totally dependant, helpless

* 0% - Vegetative functions such as swallowing, bladder and bowel function are not functioning. Bedridden.

APPENDIX F

The Mini-Mental State Exam [Folstein and Folstein 1975]

Max.	Score	
Orientation		
5	( )	What is the (year) (season) (date) (day) (month)?
5	( )	Where are we (state) (country) (town) (hospital) (floor)?
Registration		
3	( )	Name 3 objects: 1 second to say each. Then ask the patient all 3 after you have said them. Give 1 point for each correct answer. Then repeat them until he/she learns all 3. Count trials and record. Trials _____
Attention and Calculation		
5	( )	Serial 7's. 1 point for each correct answer. Stop after 5 answers. Alternatively spell "world" backward.
Recall		
3	( )	Ask for the 3 objects repeated above. Give 1 point for each correct answer.
Language		
2	( )	Name a pencil and watch.
1	( )	Repeat the following "No ifs, ands, or buts"
3	( )	Follow a 3-stage command: "Take a paper in your hand, fold it in half, and put it on the floor."
1	( )	Read and obey the following: CLOSE YOUR EYES
1	( )	Write a sentence.
1	( )	Copy the design shown.



___ Total Score

ASSESS level of consciousness along a continuum _____
Alert Drowsy Stupor Coma

APPENDIX G

Frontal Assessment Battery [Dubois, Slachevsky et al. 2000]

1. Similarities (conceptualization)
"In what way are they alike?"
A banana and an orange (In the event of total failure: "they are not alike" or partial failure: "both have peel," help the patient by saying: "both a banana and an orange are..."; but credit 0 for the item; do not help the patient for the two following items)
A table and a chair
A tulip, a rose and a daisy

Score (only category responses [fruits, furniture, flowers] are considered correct)
Three correct: 3
Two correct: 2
One correct: 1
None correct: 0

2. Lexical fluency (mental flexibility)
"Say as many words as you can beginning with the letter 'S,' any words except surnames or proper nouns."
If the patient gives no response during the first 5 seconds, say: "for instance, snake." If the patient pauses 10 seconds, stimulate him by saying: "any word beginning with the letter 'S.' The time allowed is 60 seconds.

Score (word repetitions or variations [shoe, shoemaker], surnames, or proper nouns are not counted as correct responses)
More than nine words: 3
Six to nine words: 2
Three to five words: 1
Less than three words: 0

3. Motor series (programming)
"Look carefully at what I'm doing."
The examiner, seated in front of the patient, performs alone three times with his left hand the series of Luria "fist–edge–palm." "Now, with your right hand do the same series, first with me, then alone." The examiner performs the series three times with the patient, then says to him/her: "Now, do it on your own."

Score
Patient performs six correct consecutive series alone: 3
Patient performs at least three correct consecutive series alone: 2
Patient fails alone, but performs three correct consecutive series with the examiner: 1
Patient cannot perform three correct consecutive series even with the examiner: 0

4. Conflicting instructions (sensitivity to interference)
"Tap twice when I tap once." To be sure that the patient has understood the instruction, a series of three trials is run: 1-1-1.
"Tap once when I tap twice." To be sure that the patient has understood the instruction, a series of three trials is run: 2-2-2.

The examiner performs the following series: **1-1-2-1-2-2-2-1-1-2.**

Score
No error: 3
One or two errors: 2
More than two errors: 1
Patient taps like the examiner at least four consecutive times: 0

5. Go–No Go (inhibitory control)
"Tap once when I tap once." To be sure that the patient has understood the instruction, a series of three trials is run: 1-1-1.
"Do not tap when I tap twice." To be sure that the patient has understood the instruction, a series of three trials is run: 2-2-2.

The examiner performs the following series: **1-1-2-1-2-2-2-1-1-2.**

Score
No error: 3
One or two errors: 2
More than two errors: 1
Patient taps like the examiner at least four consecutive times: 0

6. Prehension behavior (environmental autonomy)
"Do not take my hands."
The examiner is seated in front of the patient. Place the patient's hands palm up on his/her knees. Without saying anything or looking at the patient, the examiner brings his/her hands close to the patient's hands and touches the palms of both the patient's hands, to see if he/she will spontaneously take them. If the patient takes the hands, the examiner will try again after asking him/her: "Now, do not take my hands."

Score
Patient does not take the examiner's hands: 3
Patient hesitates and asks what he/she has to do: 2
Patient takes the hands without hesitation: 1
Patient takes the examiner's hand even after he/she has been told not to do so: 0

APPENDIX H

ABNORMAL INVOLUNTARY MOVEMENT SCALE (AIMS)

Rate highest severity observed.

Code:
1 None
2 Minimal, may be extreme normal
3 Mild
4 Moderate
5 Severe

Facial and Oral Movements

1. Muscles of facial Expression (e.g. movement of forehead, eyebrows, periorbital area, cheeks; include frowning, blinking, smiling, grimacing)
1 2 3 4 5

2. Lips and Perioral Area (e.g. puckering, pouting, smacking)
1 2 3 4 5

3. Jaws (e.g. biting, clenching, chewing, mouth opening, lateral movement)
1 2 3 4 5

4. Tongue (Rate only increase in movement both in and out of mouth, NOT inability to sustain movement.)
1 2 3 4 5

Extremity Movements

5. Upper (arms, wrists, hands, fingers). Include choreic movements (i.e. rapid, objectively purposeless, irregular, spontaneous), athetoid movements (i.e. slow, irregular, complex, serpentine). Do NOT include tremor (i.e. repetitive, regular, rhythmic).
1 2 3 4 5

6. Lower (legs, knees, ankles, toes). (e.g. lateral knee movement, foot taping, heel dropping, foot squirming, inversion and eversion of foot.)
1 2 3 4 5

Trunk Movements

7. Neck, shoulders, hips (e.g. rocking, twisting, squirming, pelvic gyrations)
1 2 3 4 5

Global judgments

8. Severity of abnormal movements:
1. None, normal
2. Minimal
3. Mild
4. Moderate
5. Severe

9. Incapacitation due to abnormal movements:
1. None, normal
2. Minimal
3. Mild
4. Moderate
5. Severe

10. Patient's awareness of abnormal movements (Rate only patient's report)
1. No awareness
2. Aware, no distress
3. Aware, mild distress
4. Aware, moderate distress
5. Aware, severe distress

Dental Status
11. Current problems with teeth and/or dentures
1. No
2. Yes

12. Does patient usually wear dentures?
1. No
2. Yes