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Sensory re-weighting for balance control and the effects of ankle foot orthoses and stance width: A comparison of people with diabetic peripheral neuropathy and healthy participants

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Sensory re-weighting for balance control and the effects of ankle foot orthoses and stance width: A comparison of people with diabetic peripheral neuropathy and healthy participants

By

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Abstract

Sensory re-weighting for balance control and the effects of ankle foot orthoses and stance width: A comparison of people with diabetic peripheral neuropathy and healthy participants

Samuel Glasser

Background: Diabetic peripheral neuropathy (DPN) is diagnosed clinically as a loss of sensation in the feet and affects over 2 million people in the UK. One of the functional effects of DPN is a decrease in standing stability giving rise to a risk of falls. In an attempt to stabilise in the mediolateral direction, people with DPN frequently walk with a wider base of support and stand with a larger stance width. This is often seen in the elderly and is not always beneficial for stability contributing to falls risk. Standing balance requires the integration of sensory information from somatosensory, vestibular and visual systems. Alterations in distal sensory input may result in a re-weighting of the effectiveness of remaining sensations in mediating a stabilising postural response; termed sensory re-weighting. Alterations in posture such as adopting a wider stance width and wearing Ankle Foot Orthoses (AFOs) may also affect sensory input as well as altering the mechanics of the ankle and hip joints. The impact of distal sensory loss on the sensory control of balance in people with DPN compared to the healthy population is unknown. Moreover, it is not known whether standing balance or the sensory control of balance is affected by the adoption of an increased stance width and wearing (AFOs) that restrict mediolateral ankle motion. A better understanding of the mechanisms underlying balance dysfunction in diabetic peripheral neuropathy and how it might be manipulated could inform the development of future interventions to improve balance.

Aim: To explore the effects of ankle foot orthoses and stance width on standing balance and the sensory control of mediolateral balance in people with DPN and healthy controls.

Objectives: To assess how mediolateral postural stability and the sensory control of balance is affected by (a) AFO use and alterations in stance width in healthy participants (study 1) (b) acute distal sensory loss in healthy participants (study 2) (c) chronic sensory loss in people with DPN and how this in turn is modulated by AFO use and alterations in stance width (study 3).

Methods: Postural stability and the response to selective muscle vibration that stimulates muscle spindle afferents was measured by 3D motion analysis. Study 1 investigated the effects of stance width and AFOs on postural sway and the response to selective hip proprioception stimulation induced by vibration of the hip abductors in healthy participants.

Study 2 investigated the effect of an acute reduction of somatosensory information induced by cooling in healthy participants on the response to ankle evertor and hip abductor vibration. This provided a model of the acute effects of sensory loss. Study 3 compared healthy people with people with chronic DPN. It investigated the impact on stance stability and whether there was a change in the postural response (gain) to ankle evertor and hip abductor vibration. It further explored the effect of altering the stance width and wearing an AFO on stability and the postural response to hip abductor vibration.

Results:

Study 1: In healthy controls postural sway was significantly reduced when wearing an ankle foot orthoses and when standing at wider stance widths. Whilst this was also seen during balance perturbation, trunk motion increased at larger stance widths. This could be the result of the AFO restricting ankle motion and affecting the interpretation of the hip vibratory input by the postural control system.

Study 2: Experimental reduction in distal sensation by cooling resulted in a reduction in postural responses to ankle evertor muscle vibration. Conversely postural responses at the level of the hip, to proximal (hip) muscle vibration, significantly increased.

Study 3: Baseline sway velocity was higher in people with DPN compared to healthy controls. Postural strategies were modified in the DPN group, with increased motion at more proximal segments of the shoulder and head. In both groups, AFO and stance width significantly reduced baseline sway velocity, and the size of postural responses (translations) to hip abductor muscle vibration.

Conclusion: Alterations in stance width and the use of AFOs can affect postural sway and the response to selective proprioceptive stimulation. Whilst acute reductions in distal sensory loss are associated with sensory re-weighting of distal and proximal proprioceptive information this is not seen in people with chronic DPN, possibly resulting from long term adaptive changes in the multi-sensory control of balance. Novel differences were found in postural strategies between healthy and DPN groups. The increase in head and trunk motion in people with DPN may have a negative impact on visual acuity and therefore a risk factor for falls.

In people with diabetic peripheral neuropathy AFOs and increased stance width led to a reduction in postural response size and postural sway. The effect of AFO on sway velocity was more pronounced in those with DPN at smaller stance widths. Clinically this suggests that an AFO could be used in those with diabetic peripheral neuropathy to slow down the velocity of sway and increase stability.

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Authors Declaration

At no time during the registration for the degree of Doctor of Philosophy has the author been registered for any other University award without prior agreement of the Graduate Sub-Committee.

I, Samuel Glasser, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Work submitted for this research degree at the Plymouth University has not formed part of any other degree either at Plymouth University or at another establishment.

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2. **Paton, J., Glasser, S., Collings, R., Marsden, J.** (2016). Getting the right balance: insole design alters the static balance of people with diabetes and neuropathy. Journal of Foot and Ankle Research. 2016;9:40. doi:10.1186/s13047-016-0172-3.
3. **Collings, R., Freeman, J., Latour, JM., Glasser, S., J Paton, J.** (2017). Footwear and insole design features to prevent foot ulceration in people with diabetes: a systematic review protocol. JBI Database System Rev Implement Rep2017; 15(0):1–12

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5. Rehabilitation research group, Plymouth University (Feb 2013)
6. Plymouth University, School research conference (June, 2014)
7. Plymouth PCT conference, Derriford Hospital (Oct 2014) (Poster presentation)
8. Society of Podiatrists and Chiropodists, Annual conference (Sept 2014) (Oral presentation)
9. Clinical Biomechanics, Staffordshire University, April 2015 (Oral presentation)
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Contents

List of figures

List of tables

List of abbreviations

ADC	Analogue to digital converter
AFO	Ankle foot orthoses
AMED	Allied and complimentary medicine database
APA	Anticipatory postural adjustment
A/P	Anterior-posterior
BOS	Base of support
BMI	Body mass index
CAI	Chronic ankle instability
CINAHL	Cumulative index to nursing and allied health literature
CNS	Central nervous system
COG	Centre of gravity
COM	Centre of mass
COP	Centre of pressure
deg	Degrees
DVA	Dynamic visual acuity
DPN	Diabetic peripheral neuropathy
EMG	Electromyography
GVS	Galvanic vestibular stimulation
g	grams
Hz	Hertz
LLR	Long latency responses
mA	Milliamps
MLR	Medium latency responses
mm/s	Millimetres per second
mm	Millimetres
ML	Mediolateral

MS	Multiple sclerosis
MVS	Moving visual stimuli
N	Newtons
NHS	National Health Service
PPI	Patient and public involvement
PPN	Pedunculopontine nucleus
PVD	Peripheral vascular disease
RPM	Revolutions per second
s	Seconds
SD	Standard deviation
SLR	Short latency responses
SOT	Sensory organisation test
SW	Stance width
TMS	Transcranial magnetic stimulation
U3A	University of the 3rd Age
Vib	Vibrator
V	Volts
3D	3-Dimentional

Chapter 1 . Introduction

Diabetes affects more than 422 million people worldwide[1], 6.9% of the adults in the UK[2]. Up to 30% of those people will experience Diabetic peripheral neuropathy (DPN)[3,4].

DPN is a type of peripheral nerve damage that can result in muscle weakness[5] and loss of sensation to the feet and lower limb[6–8]. This lack of sensation is known to have a devastating effect, by increasing the risk of foot ulceration and subsequent amputation[7,9]. The functional impact of DPN is a decrease in the ability to maintain postural stability[8,10], increasing the risk and incidence of falls[11,12] and falls related injury[13].

Diabetic peripheral neuropathy has been identified as an independent risk factor for falls[14]. People with DPN are at a greater risk of sustaining a fall when compared to the healthy elderly population[15]. The underlying reasons are multifactorial; in addition to the intrinsic risk factors for falls suffered by the elderly population including medication, history of falls, impaired mobility, visual impairment and foot problems[16], people with diabetes also have the added disease specific complications such as greater BMI, peripheral neuropathy and retinopathy[14,17].

Falls occur in 33 million people with DPN each year[18], and results in a reduction in quality of life for the patients experiencing pain, injury, distress, loss of confidence and a greater risk of death[19]. The associated financial cost in the care of those experiencing a fall also increases[20], with the cost of elderly fallers

estimated to be in the region of £2 billion per year and over 4 million inpatient bed days[21].

To date most time and attention have been dedicated to diabetic foot ulcer prevention. However, there is a growing recognition of the need to also address the problems associated with poor stability and falls considering these personal and financial burdens of diabetes related falls and falls related injury. This emphasises the need to further understand the pathophysiology of this balance dysfunction, if effective interventions are to be developed that can aid balance and reduce falls risk.

Understanding the mechanisms underlying balance dysfunction and its recovery in people with DPN will help to design and target interventions addressing these primary deficits. The research described in this thesis lies within Phase one of the Medical Research Council (MRC) framework (figure 1.1) which guides researchers in the design and development of complex interventions[22].

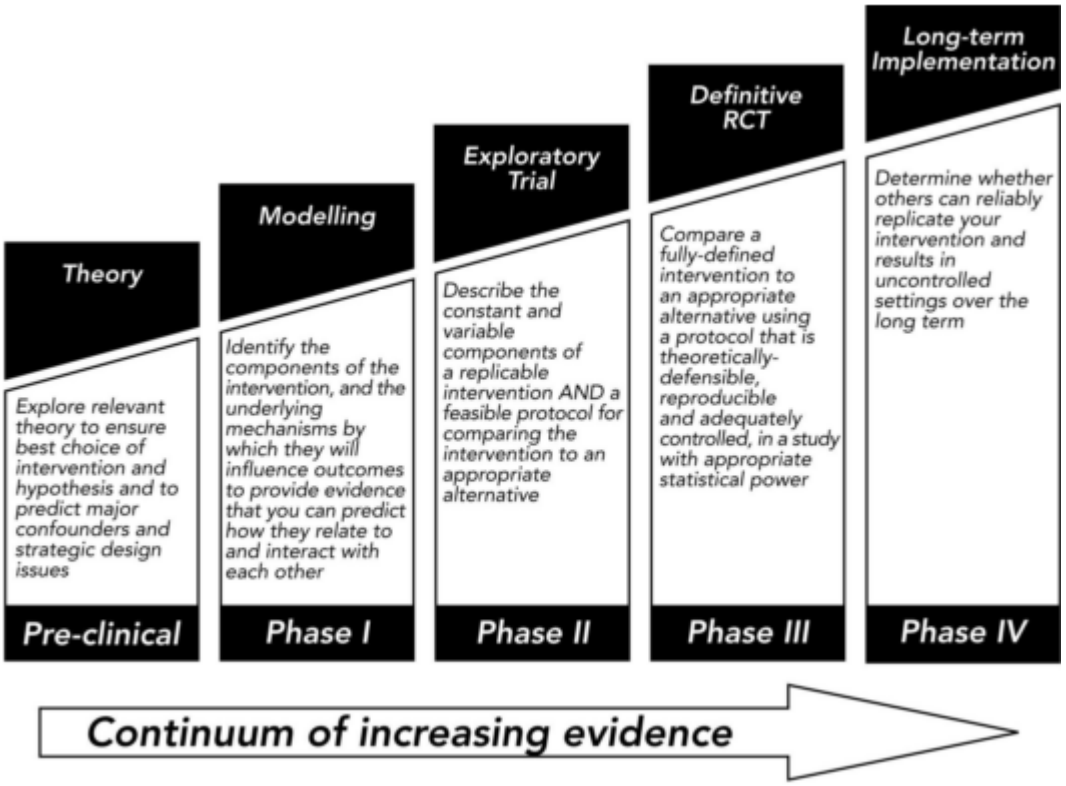


Figure 1.1. Medical Research Council framework for trials of complex interventions.

Sensory input can be modified by changes in movement patterns and environmental factors such as an alteration in stance width[23] or the addition of an Ankle Foot Orthosis (AFO)[24]. Whilst AFO use has been largely overlooked in the diabetic population, their stabilising effect has been demonstrated in people with stroke[25,26], multiple sclerosis[27], ankle instability[28] and the elderly[29]. AFO's by design can limit sagittal and/or frontal plane movements. The best foot and ankle device for enhancing stability in the diabetic peripheral neuropathic population is yet to be established. AFO's designed to restrict sagittal plane movement traditionally consist of a hard shaped plastic shell with a distal edge ending around the area of the plantar forefoot. This type of AFO worn in-shoe is contraindicated for use in the diabetic population because it may increase foot ulcer risk through the introduction of increased plantar pressure at the distal

edge. In addition, there is a clinical consideration to ensure that an AFO designed for use in the diabetic population can be used in conjunction with offloading insoles for foot ulcer prevention. The AFO designed for sagittal restriction would make it difficult to fit offloading insoles for foot ulcer prevention. In light of these clinical challenges an AFO designed to limit mediolateral movement at the rearfoot whilst still allowing the provision of an offloading insole may be considered clinically more appropriate for people with diabetes and neuropathy.

Understanding how the sensory control of balance changes with alterations in posture (altered stance width) and environmental factors (with an AFO) in healthy participants and how that compares to the response seen in the diabetic neuropathic population, will form an important basis into our understanding of normal and pathological mediolateral control of balance. In healthy participants the effect of acute distal sensory loss, induced by cooling, on hip proprioceptive control of mediolateral balance will be used as a method to provide insight into the adaptability of proprioceptive control and a potential proof of concept model of sensory re-weighting[30] (a process where sensory contributions to balance are adjusted depending on environmental conditions[31]), that may then be tested in those with diabetes and neuropathy.

1.1 Thesis summary

The investigations in this thesis were completed as three individual studies. The first repeated measures experimental study was designed to investigate in healthy participants the effects of 1) an ankle foot orthoses (AFO) offering mediolateral ankle support, 2) alterations in stance width, on postural responses to balance perturbation induced by stimulation of proximal hip proprioceptive afferents using muscle vibration.

The aim of the second study was to assess whether the distal and proximal proprioceptive control of balance was affected by experimental distal sensory loss in healthy participants; an example of sensory re-weighting. A repeated measures design was used to assess postural movements in the frontal plane before and after a reduction in distal sensation induced by cooling. Here, frontal plane motion was induced by stimulation of either hip proprioceptive or ankle proprioceptive channel. Whilst past work has investigated sagittal plane postural movement, this is the first study to place a focus on movement in the frontal plane. This study provides insight into the potential adaptability of the proprioceptive system.

The methods of study 2 were combined with those of study 1 to inform the protocol and design of study 3. This investigated people with diabetes and peripheral neuropathy. To add clarity, this study will be discussed in terms of Part 1 - the effect of sensory loss on postural responses to proximal proprioceptive balance perturbation and Part 2 - the effect of stance width and AFO on postural responses to balance perturbation.

This thesis therefore explores;

1. The impact of stance width and ankle-foot orthoses on the proximal proprioceptive control of mediolateral balance in healthy participants.

2. The effect of acute distal sensory loss on the distal and proximal proprioceptive control of mediolateral balance in healthy participants.

3. Re-weighting of proximal proprioceptive control of mediolateral balance in people with diabetic peripheral neuropathy.

4. How the proximal proprioceptive control of mediolateral balance is modulated by i) increased stance width, and ii) ankle foot orthoses which limit mediolateral ankle/foot motion in people with DPN.

This will:

- Provide further knowledge about the role of an AFO and alteration in stance width for balance improvement in healthy people (study 1) and in people with diabetic peripheral neuropathy (study 3).
- Highlight the role of proximal sensory information in compensating for acute (study 2) vs chronic (study 3) distal sensory loss.

1.2 Contribution to knowledge

It is well known that somatosensory information is reduced in people with diabetic peripheral neuropathy and can lead to instability and increased incidence of falls. The management of balance dysfunction in people with diabetic peripheral neuropathy is still open to discussion due to the lack of quality research indicating an effective intervention[32]. Studies of the control of mediolateral balance in health and disease will be reviewed in chapter 2 with chapter 3 critically appraising the evidence base for balance control on DPN and its management using ankle foot orthoses.

The experimental chapters of this thesis provide an improved understanding of the effect of using an AFO to provide mediolateral rearfoot stability on postural balance in people with diabetic peripheral neuropathy. The thesis also explores how people with diabetic peripheral neuropathy compensate for the reduced foot-ankle sensation using residual senses. Previous work in this area has highlighted compensatory mechanisms that may aid balance dysfunction particularly in the sagittal plane where the vestibular system increases its' sensitivity[33]. However, little is known about mediolateral compensations in people with diabetic peripheral neuropathy. Maki and McIlroy (1996)[34] have suggested that control of lateral movement should be the major focus in assessing balance and falls risk, particularly so as lateral falls are more likely to cause hip fractures[35,36]. This thesis will therefore add new evidence to a topic dominated by sagittal plane exploration, to give a better understanding of frontal plane sensori-motor control of balance.

This laboratory based investigation fits into Phase one, 'Exploratory work', of the (Medical Research Councils (MRC) framework)[22]. The results and conclusions drawn from this thesis will provide new knowledge about the role of an AFO for mediolateral stability and adaptability of postural control and strategies following acute and chronic distal sensory loss. It is intended that the findings from this thesis will be used to inform the development of an AFO suitable for clinical use and in the development of a multi-sensory balance re-training programme, both of which will be assessed in phase 3 - clinical trials, targeted at the neuropathic population.

Chapter 2 . The Control of mediolateral balance in health and disease

2.1. Introduction

Postural sway in standing in healthy participants is omnidirectional with 60% occurring in the anterior-posterior (AP) direction and 40% in the mediolateral (ML) direction; this is similar when the eyes are open or closed[37]. Although there are many similarities in AP and ML balance there are important differences necessitating an investigation of either component. Some pathologies such as cerebellar disease[38], vestibular dysfunction[39] and hemispheric stroke[40] lead to marked increases in the amount of ML sway. Further, ML instability is more associated with an increased risk of falls in the elderly compared to AP instability, and there are age-related increases in ML instability[41] (see section 2.3 - Effects of ageing and pathology).

Other differences include the effectors controlling AP and ML. AP sway is controlled by muscles acting in the sagittal plane especially the ankle plantar and dorsi-flexors[42], whilst ML sway is controlled by the ankle invertors and evertors and the hip abductors and adductors. Further, there may be differences in the accuracy and use of afferent feedback associated with motion in the two planes. Trunk positioning accuracy in the frontal plane, for example, is 16-45% more accurate than in the sagittal plane[43,44] (see section 2.2.5 - Control Mechanisms and section 2.2.8 - Sensation and sensory integration/re-weighting).

This thesis explores the proprioceptive control of ML balance in healthy participants and people with diabetic peripheral neuropathy. The control of balance in the ML plane has not been investigated in detail in people with diabetic peripheral neuropathy. Understanding frontal plane balance control, how it is affected by diabetic related pathology and potential mechanisms that underlie recovery from that pathology could provide new useful information to inform the rehabilitation of balance.

The following sections will therefore provide an overview of the control of ML motion while standing and walking in healthy participants and in selected patient groups. Chapter 3 will provide a critical overview of diabetic peripheral neuropathy and its impact on balance, walking and falls.

2.2. Mediolateral balance when standing and walking

Several approaches have been used to investigate balance in standing and during tasks such as walking.

2.2.1. Postural sway

Posturography, the measurement of postural sway has been used for decades to quantify stability[6,45–49]. Sway is typically measured using markers placed on the body, such as at the level of the C7 spinous process[50–53]. Motion of these markers are recorded using 3D motion analysis systems. Alternatively, motion of the centre of pressure (CoP) is recorded via a force plate during quiet standing[54–56]. The motion of the marker / CoP in the anterior-posterior (AP) or mediolateral (ML) direction is then measured (figure 2.1). Several measures

have been used to describe postural sway such as the total path length[57] covered in a set time; the average velocity or the area of an ellipse that covers 95% of the data[58]. Of the measures used, sway velocity has been shown to be more reliable and sensitive to detecting differences between patient groups and healthy participants and showing changes with interventions[59–61].

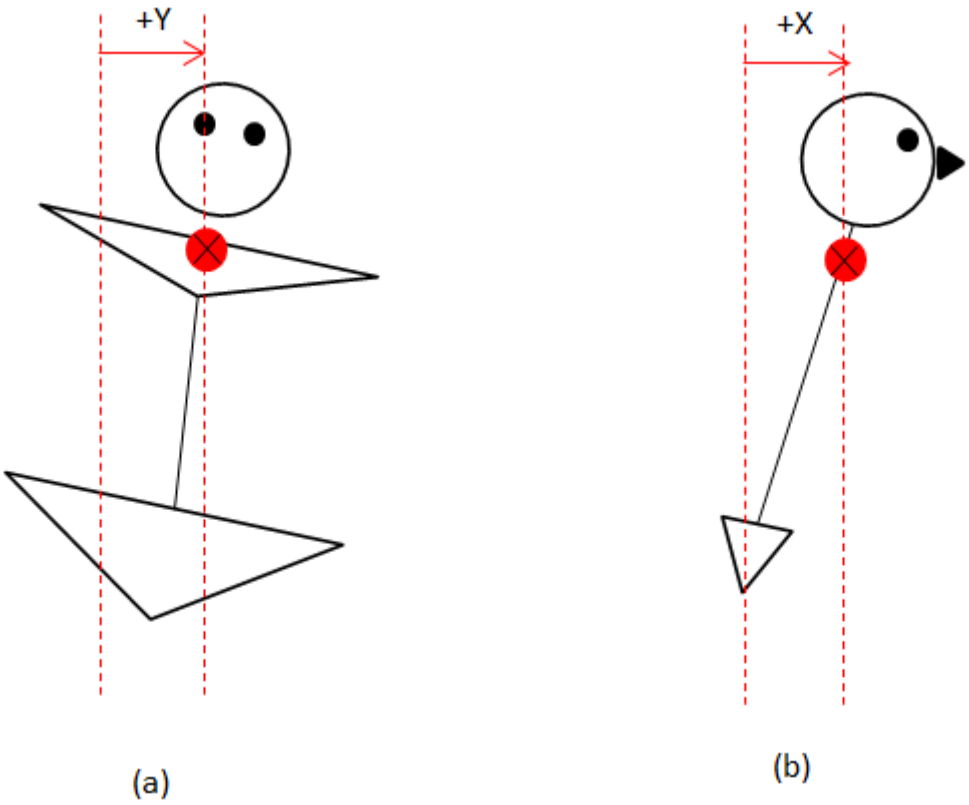


Figure 2.1 Graphical representation of motion (X and Y) of marker placed at C7 spinous process in a) mediolateral (Y) and b) anterior posterior (X) directions.

Postural sway has been criticised by some as being a gross, non-specific measure of balance. However, others have demonstrated that is sensitive enough to show differences between pathology with ageing and interventions[59–61]. Recent work has highlighted the complexities of controlling postural sway, most of this has focused on motion in the anterior-posterior direction[62]. In the

past it was assumed that the load of the body could be balanced, like an inverted pendulum, by setting the appropriate tension in the ankle plantarflexors, a so-called stiffness strategy[63]. However, this theory did not take into account the fact that the ankle plantarflexors lie in series with the tendo-achilles[64] whose compliance is too high (low stiffness) to permit the maintenance of balance solely using a stiffness strategy. Instead postural sway results from intermittent contractions[65] of the ankle plantarflexors[64] that control backward motion, contract prior to the body moving forward. This suggests that the contraction is generated in a feedforward manner i.e. it predicts the forward sway and acts to halt and reverse it[66–68]. Therefore, it can be postulated that postural sway reflects the control process that are used to maintain balance during more complex tasks such as voluntary movement.

2.2.2. Anticipatory postural adjustments

The anticipatory, feedforward control of balance can also be preceding or during volitional movement[69,70]. Contractions occur in postural muscles prior to or at the same time as contraction of the prime mover i.e. before a postural disturbance occurs (figure 2.2), thus serving to minimise any postural disturbance caused by the voluntary motion[71]. To measure these therefore requires measurement of motion of the body and the muscles associated with the anticipatory postural adjustment (APAs) using electromyography.

APAs that control ML stability are seen prior to a hip flexion or a step[72]. The aim of APAs during stepping is to propel the Centre of Mass (CoM) to the stance limb prior to lifting the swing limb thus effectively reducing the tendency of the CoM to fall to the swing limb side[73]. The APAs are flexible and can be changed

by task constraints, for example stepping up onto a step compared to stepping forwards, is associated with greater ML CoP motion and earlier gluteus medius activation suggesting this poses a greater challenge to ML stability requiring a larger APA[74].

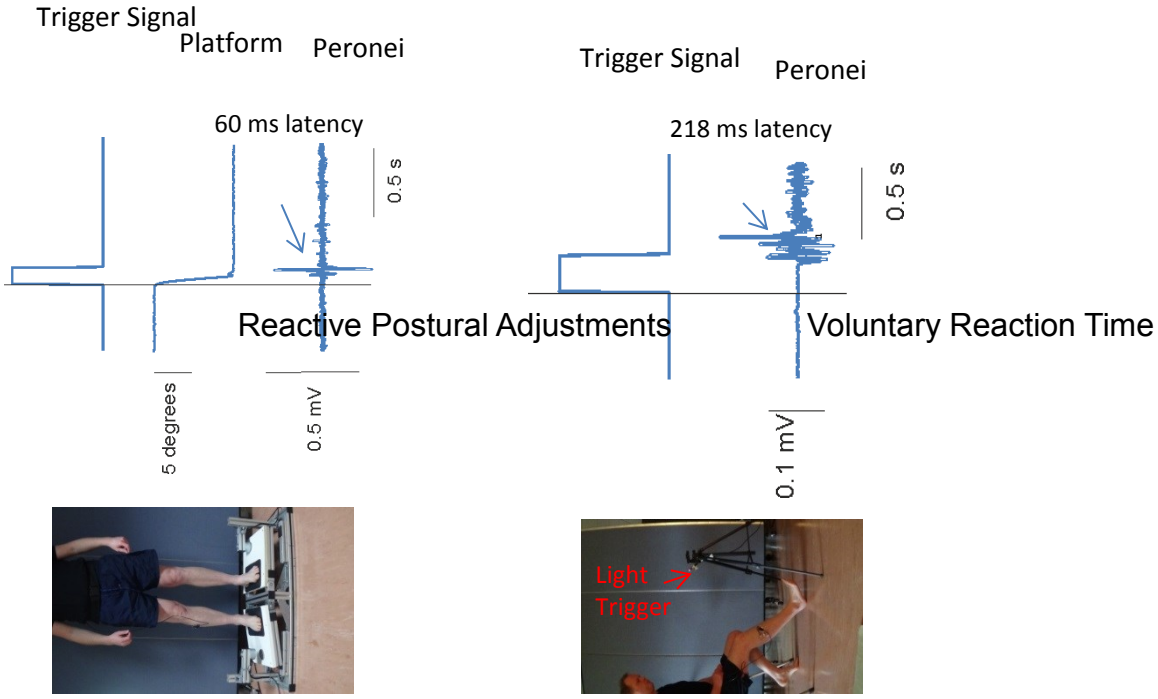
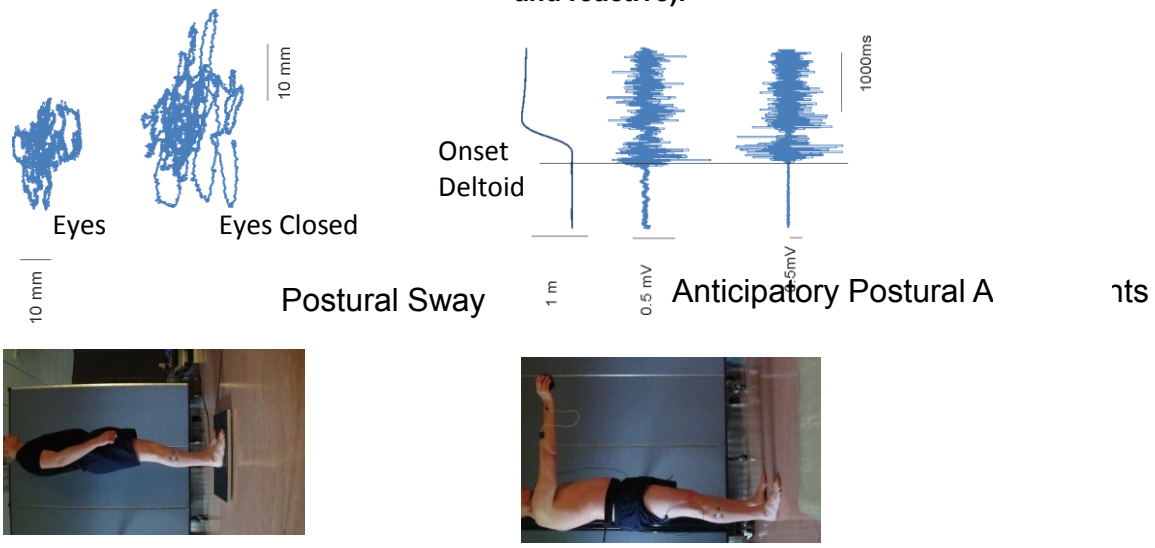


Figure 2.2 Examples of sway (unperturbed) and postural adjustme and reactive).



2.2.3. Reactive control of balance

Balance cannot always be predicted and often perturbations occur that unless corrected would lead to a fall. In this situation a whole body response is generated with a latency of less than 100 ms[75] (figure 2.2). This is well within a normal voluntary reaction time indicating that it is automatically generated[76]. Afferent feedback triggers a postural response that varies, depending on the type of perturbation[77]. Early work investigating the effects of platform perturbations on balance highlighted that stretch of distal ankle muscles activating muscle spindle (stretch) receptors were crucial to triggering the postural responses[76]. However, later work with more complex platform perturbations that included translatory and rotational components showed that proximal afferents (e.g. around the knee) could also trigger postural responses[78]. A further study, using water to influence gravity emphasised the importance of load related afferents, possibly golgi tendon organs, in triggering and modulating balance[79]. In contrast vestibular afferents seem to be more important in modulating the size of postural responses as with bilateral vestibular loss the responses appear at the right latency but the amplitude and timing of the response is altered[80].

ML perturbations when standing on one leg results in short, medium and long latency responses in distal and proximal leg muscles (SLR, MLR and LLR respectively)[81]. Generally regardless of perturbation direction the distal muscles lead to fast compensations via SLRs while proximal muscles contribute to LLRs[81]. It is hypothesised that distal muscles act to quickly regain equilibrium whilst the proximal muscles around the hip act as delayed stabilisers[81]. The short latency responses (30-60ms latency) are stretch reflexes mediated

through a spinal monosynaptic reflex pathway. The origin of the medium (60-85ms latency) and longer latency (85-120ms) reflexes remain less clear[82]. They may be mediated via spinal, polysynaptic pathways[83]. The pathways used and the afferents triggering the response differ depending on the pattern of perturbation and the task[84,85]. The ankle plantarflexors, for example, have been stretched in isolation during the stance and swing phase of walking[86–88]. The short latency response is mediated via a monosynaptic stretch reflex[87,89,90]. However, the medium latency stretch reflex is mediated via activation of group II muscle spindle afferents[83] and the longer latency stretch reflexes may be mediated via a transcortical route[91].

2.2.4. Dynamic balance

A body is in equilibrium when the projection of its CoM lies within the base of support[57]. Whole body analysis of movement allows the position of the CoM to be estimated. Measuring the CoM motion and the base of support using 3D motion analysis has allowed a quantification of balance during dynamic tasks[92].

Whole body analysis of movement during walking, for example, indicates that the CoM passes medially to the supporting foot while walking i.e. the body is not in equilibrium[93]. In this case a fall is prevented through the interaction of different moments acting on the body. There is, for example, a medial acceleration of the body that is caused by a gravitational moment about the foot. This is counteracted by an active hip abduction moment on the support (stance) leg and a passive acceleration moment due to the motion of the body towards the stance side. When walking and stepping the co-ordination between the

motion of the body and positioning of the foot is critical to maintain balance. The motion of the body has been measured when stepping onto different targets and has been modelled as an inverted cone[94] whose motion is captured by movement of the swing leg; a type of throw and catch[68]. In essence the body (or cone) is given an initial push and then falls with gravity. The size of the initial push, dictates how the body moves and this is scaled to the laterality of the step. If the push is too large the body will fall laterally away from the stepping leg. If the person steps laterally and the push is too small the person will fall medially[95]. Thus, it seems that the relative motion of the CoM to the base of support is critical. Dynamic balance is maintained while walking if stability limits are not exceeded[96,97]. The stability limits depend on the velocity of the CoM towards the supporting leg; too high and the swing leg must cross over and too low the swing leg must move to the side[98].

2.2.5. Control mechanisms

There are several mechanisms by which ML stability could be maintained. It could for example be that ML stability is maintained through anatomical constraints or through increased stiffness and viscosity of muscles and joints. This stiffness/viscosity in turn could be passive in nature (e.g. resulting from stretching connective tissue) or caused by a muscle contraction. The muscle contraction in turn could be broadly classified as being reflexive or volitional in nature. Elderly people, for example, may stabilise themselves by increasing stiffness in the ML direction through co-contraction of muscles[99]. These mechanisms will be discussed in detail in the following sections.

As people are normally passively unstable in the lateral direction when walking some form of active control is required[100]. Due to the longer latency of volitional responses, this control relies on automatic reflex activity[101].

Balance in standing and walking further requires the integration of sensations from different sources (vestibular, vision, proprioceptive and cutaneous)[102]. The relative importance of these sensations in maintaining balance can vary[103] (e.g. with a change of task condition and with ageing and pathology). The complex integration of sensory inputs and the relative contribution of each in the control of balance in standing and walking will also be introduced in the following sections.

2.2.6. Biomechanical considerations

There are some anatomical considerations in the control of ML balance. In females the neck-shaft femoral angle is proportional to the hip abductor strength , an important muscle in determining ML stability[104]. Stabilisation of the hip is not, however, just achieved through active contraction of the hip muscles, as the trunk moves to the contralateral side there is an increase iliotibial band stiffness that may act to stabilise the hip[105]. Distal changes in anatomy may also be important by altering the effectiveness of muscles by changing lever arms. In elderly people for example, foot deformity (e.g. changes in the longitudinal and transverse arch height and valgus deformity of the hallux) are associated with greater ML balance impairment[106].

The ML control of balance requires contributions from the whole multi-linked musculo-skeletal system from the trunk to the toes[107–109]. Trunk muscles such

as the external obliques; rectus abdominis and erector spinae muscles aid stability and compensate for weakness in other muscle groups[93,110]. A lean to the side of the stance leg, for example, leads to a reduction in hip abductor moments[111]. The hip abductors, a focus of this thesis, play a central role in stabilising the pelvis and leg in the frontal plane[107]. There is for example, a greater increase in ML instability following fatigue of the hip abductors compared to fatigue of the ankle evertors / invertors[112]. With isolated hip abductor fatigue there is also an increase in ankle evertor (peroneus longus) activation and earlier onset of activation when balancing on one leg; this may reflect a compensation for the proximal fatigue-induced weakness[113].

The knee although limited by anatomical constraints in the ML direction, contributes to ML balance, where knee flexion enables the tilting of the pelvis in the frontal plane[114,115], with an effective shortening of the leg on one side[116]. A 17% reduction in knee extensor strength in elderly leads to greater ML instability as measured by the lateral force required perturb participants[117]. Further, in cerebellar dysfunction locking of the knees can result in greater trunk postural sway following a platform perturbation as the normal knee flexion/extension coupled with pelvic motion is reduced[118].

2.2.7. Central control of balance and walking

The central control of balance and walking involves regions from the cortex to the spinal cord[33]. Spinal reflexes produce short and medium latency responses to a perturbation[82,83]. Brainstem areas are important in the control of balance, walking and postural tone[119]. In the decerebrate cat stimulation of the pedunculopontine nucleus (PPN) (also termed the mesencephalic locomotor region) induces rhythmic walking[120]. Its actions are mediated via reticulospinal pathways to the spinal cord[120,121]. The PPN receives a direct input from the substantia nigra part of the basal ganglia[122]. Degeneration of this pathway and the PPN itself is seen in Parkinson's disease and may underlie the deficits in walking (e.g. festinating gait and akinesia) and postural control (inflexible postural responses and excessive co-contraction) seen in this condition[123–126]. Direct stimulation of this nucleus in people with Parkinson's induces walking like activity and improves walking related symptoms[127].

Reticulospinal and vestibulospinal pathways running from the reticular formation and vestibular nuclei respectively also control balance. The vestibular system can be stimulated in humans either through head-related perturbations or electrically; a technique called galvanic vestibular stimulation (GVS). GVS leads to a stereotyped postural response in humans[128]. Recordings of spinal cord potentials following GVS highlight that the ventro-medial spinal cord is activated suggesting the signals run down to the spinal cord via the vestibulo-spinal tract[129]. However, the latency of postural response to stimulation much longer (~130 ms) than would be expected if the signal simply stimulated the vestibular nuclei neurons that gives rise to the vestibulospinal tract. What accounts for the longer latency is unclear although studies in people with a supertentorial stroke

suggest that fibres from the cortex to the brainstem (cortico-fugal fibres) at least modulate the response to GVS[130].

Postural responses can be modulated; with repeated presentations the size of the response scales appropriately to the size of the perturbation i.e. it is just large enough to stop a fall. Part of this modulation seems to arise from the interaction of brainstem postural centres with the cerebellum. With cerebellar damage people show higher postural responses that do not adapt with repeated perturbations[131,132] (See section 2.2.3 - Ataxia).

It is clear from human and animal studies that cortical areas play an important role in balance and walking. Although a decerebrate cat can walk and balance, a role of the motor cortex in the control of walking and balance is suggested by the modulation of neurones in the fore and hindlimb areas of the motor cortex with the stance width[133]. The timing of firing tends to be closer to the swing phase, where most instability occurs, suggesting a role in dynamic stability[134]. This is in agreement with the longer latency stretch reflexes seen after an ankle joint perturbation during walking in humans[91]. These are transcortical in nature[91]. Further, perturbation-evoked cortical responses are seen, for example, when balancing an inverted pendulum in sitting[135]. Here there are an early and late response maximal over frontal-central electrodes that may represent sensory processing and/or sensorimotor processing. These reflexes are adaptable and are abolished when there is a lesion to ascending (e.g. dorsal column) or descending (e.g. corticospinal tract) pathways as seen in multiple sclerosis[88,136]. The loss of such reflexes is felt to contribute to the balance impairment[82].

In summary spinal cord and brainstem circuits seem to be important for rapid responses to perturbations. However anticipatory postural adjustments and

dynamic balance may also rely on cortical and subcortical areas (e.g. basal ganglia and cerebellum). These areas provide the ability to adapt to changing task conditions. They may also play a critical role in improving balance with training in both healthy people and following pathologies such as diabetic peripheral neuropathy.

2.2.8. Sensation and sensory integration/re-weighting

The role of sensation in the control of balance has been explored using several paradigms. In healthy people sensation has been reduced/blocked, for example by closing the eyes, or distally through local ischaemic block[137], anaesthesia[83] or cooling of a body part[138–140]. Alternatively, sensory channels may be stimulated. For example moving visual stimuli can lead to perceived self-motion and a postural response[141]. Vibration of muscles or tendons can activate muscle spindle afferents to produce the sensation that a muscle is lengthened[142]. Cutaneous afferents on the plantar aspect of the feet can be directly stimulated[143]. The vestibular system can also be stimulated using a constant current delivered via electrodes placed on the mastoid processes[144]. An alternative way of exploring the sensory control of balance is to assess people with selective sensory loss. This can be particularly important in revealing how the relative effectiveness of other, remaining sensations can change, a phenomena called sensory re-weighting. The following sections will explore the role of different sensations in the control of balance particularly in the ML direction.

Proprioceptive and cutaneous sensation:

Stimulation of the plantar aspect of the foot causes a postural adjustment. The direction of the postural adjustment depends on the site of stimulation[145]. The direction of sway is opposite to the side/site of stimulation as if the body is responding to increased weight on that segment and acting to even out the load across the foot[143]. In keeping with this, blocking the cutaneous sural nerve can affect postural stability when standing on one leg[146].

Vibratory stimulation of muscles and tendons also results in a reproducible postural sway[124,129]. The stimulus is interpreted as muscle lengthening[77]; therefore the postural response is in the direction to decrease the perceived lengthening. For example vibration of the Achilles tendon leads to a posterior sway[149]. Vibration of hip abductors and vibration of the ankle evertors leads to sway in the frontal plane[142,149]. This stimulus will be used in this thesis to explore the proprioceptive control of balance.

Other proprioceptive inputs, for example from joint receptors / ligaments may not be as important as muscle spindle activation. Anaesthetic block of ankle ligament receptors leads to impaired passive position sense but normal active position sense and ankle peroneal reaction time to a perturbation is not affected[150].

Vision:

Reductions of vision (e.g. by closing the eyes) lead to an increase in postural sway in standing[151]. Blocking visual input can also led to a change in postural strategy[152]. When standing on one leg healthy participants change from a strategy of swaying about the ankle with vision present to a more proximal balance strategy involving trunk and upper limb motion when vision is obscured[153]. Viewing distance affects postural sway with reductions in sway being seen with near targets[154]. The increased instability when viewing far distance targets with both eyes is attributed to decreased sensitivity to binocular disparity cues and to visual motion in depth resulting from body sway although alterations in attention between monocular and binocular cues may be important[155]. The relative impact of altering sensory inputs on ML and AP sway may differ. Closing the eyes for example mainly affects muscles controlling AP sway whilst support surface changes affects muscles controlling ML sway[156].

Vestibular:

Stimulation of the vestibular system using galvanic vestibular stimulation (GVS) results in a stereotyped postural sway. With binaural stimulation with the head facing forwards people sway to the side of the anode. This is caused by the stimulus decreasing the vestibular nerve firing rate on the side of the anode and increasing the firing rate on the side of the cathode[128]. The direction of sway is not rigid. The same stimulus will produce different directions of sway depending on the position of the head in yaw[51]. This highlights that the postural response to GVS involves integration of multiple inputs not just vestibular but also from neck afferents. The response to GVS is also modulated by task and the availability of other sensory inputs. The size of the response, for example,

decreases in sitting compared to standing. The sway is also markedly reduced when eyes are open compared to closed or when 3-dimensional visual information and cues are available[144]. Other sensations modulate the vestibular response. Loading one leg leads to a larger response size on the loaded leg which is not simply explained by a larger activation of the muscles on that side. Unloading the legs also reduces response size[157,158]. This suggests that load-related afferent information (e.g. from golgi tendon organs) may also modulate response size.

Sensory integration and re-weighting:

The process of adjusting the sensory contributions to balance control depending on environmental and cognitive conditions is called sensory re-weighting and may underlie improvements in balance following different pathologies such as diabetic peripheral neuropathy[57]. This theory states that balance and postural sway varies depending on the weight given to each sensory input[31] (i.e. vestibular , visual and proprioceptive). Peterka et al (2002)[102], for example, showed that postural sway could be explained by a linear combination of appropriately weighted sensory cues. Other groups have suggested that the sensory weights were predicted by minimizing the variance of visual and proprioceptive estimates termed minimum variance integration[159].

These theories suggest that the gain of different sensori-motor channels can be modulated on a trial-by-trial basis. Factors such as the availability of sensory cues and even conscious effort lead to the re-weighting effect[31]. For example, closing the eyes or standing on a more compliant surface that alters the accuracy of support surface information leads to instantaneous changes in how

the body responses to a visual (e.g moving visual scene) or proprioceptive stimuli (e.g moving support surface)[102]. As the sensory re-weighting can vary on a trial by trial basis this implies that it is not resulting from structural plastic changes within the nervous system but presumably due to changes in the relative inhibitory/excitatory drives at key processing stages of sensory information such as the thalamus. More longer term changes in sensory re-weighting as the result of pathology where marked increase in the postural response to stimulating one sensory channel have been observed[33,160]. These may result from plastic changes including structural changes (e.g dendritic sprouting and synaptogenesis) within the nervous system[102].

GVS has been used to investigate the effects of sensory loss[40,130,161]. In a participant with proprioceptive loss below the neck the response to GVS was marked even in sitting highlighting that the gain of the vestibular system had increased[160,162]. This may be a compensatory strategy to use remaining sensory information to maximum effect to signal body motion and to maintain sway. Increases in the response to GVS are also seen with more restricted sensory loss such as diabetic peripheral neuropathy[163].

Changes in the size of response to different sensory manipulations can also be seen in healthy participants. The effects of vestibular (GVS) and visual (eyes open/closed) manipulations increase when sitting on an unstable as opposed to a stable surface suggesting an increase in the weighting of vestibular and visual information. In contrast there was a decrease in the response to proprioceptive (paraspinal vibration) and haptic (light touch) manipulations suggesting a relative reduction in the weighting of these sensations[164]. When standing

altering the stability of the support surface has similar effects with a reduction in people orientating to the support surface and an increase in people orienting to vertical[165]. This suggests a decreased reliance on proprioceptive cues (that oriented to the support surface) and increased reliance on visual / vestibular cues (that oriented to the vertical)[166,167]. It is hypothesised that head angular stabilisation provides the CNS with necessary visual and vestibular references for effective balance[166,167]. Changes in the balance strategy of people diabetic peripheral neuropathy will be investigated in this thesis.

2.3. Effects of ageing and pathology

2.3.1. Development of balance

The control of balance develops over time. Angular motion in the frontal plane, for example, decreases dramatically in the first 10-15 weeks of walking[168]. Interestingly in the first week of walking, stabilization of the hip in space appears preceding stabilization of the shoulder. This suggests an ascending progression of control; at first there is a correlation between head and shoulder motion consistent with an en-bloc operation of the head-trunk unit[169]. This resonates with the pattern of postural control found in the thesis in people with diabetic peripheral neuropathy.

The reliance on different sensations for balance also changes over time. Initially children are very reliant on vision as highlighted by falls, seen when the visual surround is moved; the classic swinging room experiments, in the 1970s[170]. Over time children learn to balance using multiple sensations[171].

2.3.2. Balance in the elderly

The majority of people with diabetic peripheral neuropathy are elderly[172]. The following section will firstly describe common deficits in balance seen with ageing, before exploring possible causes of this.

Mediolateral Balance when standing and walking and during falls:

ML balance decreases from the age of 40 years[173,174]. While walking or during clinical balance tests elderly people (>65 yrs) show a greater angular sway and velocity in roll and pitch[175] and a larger stance width and step width variability compared to young (15-25 yrs) and middle age participants (45-55 yrs)[176]. ML instability is associated with an increased risk of falls in the elderly[81]. This highlights the importance of studying balance in this plane. When taking a lateral step elderly people seem to prioritise regaining anterior-posterior balance and can take up to 30 seconds to regain ML balance[177]. When recovering ML balance following a perturbation, younger people typically use a side stepping strategy. In contrast elderly take multiple steps (55% Vs 9% of the time) or use the strategy seen with younger people but with a longer latency[178]. Further, when recovering from a lateral waist pull elderly people are more often closer to their limits of stability[179] and the legs more frequently collide with each other[180]. The need to take multiple steps following a lateral perturbation is predictive of falls[180]. As highlighted in the next section, changes in the control systems contribute to this decrease in ML stability.

Biomechanical and peripheral musculoskeletal changes:

Older people may increase hip abductor moments while stepping laterally to maintain frontal plane stability or descending stairs[181,182]. In keeping with this

weakness and reductions in the rate of force development in the hip abductors predicts the amount of sway in tandem stance and the incidence of falls in the elderly[180,183].

The strategy used to maintain ML stability seems to change in the elderly. Elderly participants show greater co-contraction of (agonist and antagonist) muscles leading to higher stiffness and damping[99,184]. Although potentially aiding stability increased stiffness due to co-contraction or reductions in joint range of motion will impede motion and may affect the ability to quickly prevent a fall. Reduction in trunk axial rotation, for example, is associated with a higher incidence of falls[180]. The increase stiffness may also lead to a reduction in the use of sensory feedback for the control of balance[185].

Sensation and control systems:

With ageing degeneration in sensory systems and in areas of the brain associated with sensory-motor integration such as the cerebellum occur with a subsequent increase in sensory thresholds[45,186,187]. Visual acuity and proprioceptive thresholds, for example, are strong predictors of sway in tandem stance in the elderly[41]. Elderly people become more reliant on vision and show greater ML motion with visual perturbations[188]. This may reflect a compensation for degrading somatosensory functions. The importance of vision in the control of ML balance was further assessed by exploring the response to graded galvanic Vestibular stimulation while walking with and without vision. Younger participants showed postural responses that were scaled to the size of the GVS stimulation. In contrast in the elderly when vision was available this scaling was absent, thus highlighting the dominance of vision[189].

2.3.3. Balance in pathology

This section will discuss pathologies that can affect ML balance and highlight conditions that support the importance of peripheral musculoskeletal and central nervous system mechanisms in the control of balance.

Stroke:

A specific deficit in frontal plane stability is seen in Wallenburg's syndrome, a stroke that affects the brainstem including the vestibular nuclei. Here people have increased ML sway termed latero-pulsion[190]. Interestingly the degree of lateropropulsion is proportional to people's perceived deficit in visual vertical, which is in turn related to the degree of ocular torsion associated with this condition. This is felt to arise through lesions to vestibular-oculomotor pathways[191].

Following a cortical stroke people have a hemiplegia with reduced weight bearing and transference while walking onto the paretic leg[192]. Anticipatory postural adjustments and reactive postural responses are usually reduced on the paretic side[193]. Compensatory increases in activity are seen on the unaffected side. Disruption of pathways from the motor cortical areas to the brainstem may underlie some of these changes[130]. However, the right parietal areas play an important role in polysensory integration and the representation of body and visual vertical[194–197]. Right sided parietal lobe lesions, for example, are associated with a higher incidence of balance deficits than left sided lesions[194,198]. People with lesions affecting the posterior parietal lobes and polymodal area such as the insula-cortex show deficits in the perception of verticality that is associated with deficits in balance[197]. This can lead to a pusher

syndrome that is characterised by an active push in the frontal plane towards the paretic side in sitting and standing. It is associated with multi-modal deficits in the representation of vertical and is a poor prognostic indicator for recovery[195].

Ataxia:

Cerebellar disease results in marked balance deficits. People show hypermetric postural responses to a platform perturbation that do not scale or adapt with repeated presentations[131,132]. Postural responses of the trunk and pelvis in the frontal plane may be excessive. This may be because people often lock their knees into extension; a strategy that may serve to decrease the degrees of freedom that need to be controlled[118].

The co-ordination between anticipatory postural adjustments and the voluntary movement can be disrupted by cerebellar dysfunction[199]. APAs can be absent or delayed in time resulting in the volitional movement perturbing the balance as the centre of mass of the body is altered and joint torques associated with a movement are not compensated for[200]. Deficits in leg co-ordination can also affect dynamic balance by altering the intended foot placement such that it is inappropriate for the trunk motion[201]. Recently the sensory control of balance in people with Spinocerebellar ataxia type 6, a relatively pure hereditary cerebellar degeneration, has been explored[141]. It was found that postural responses to moving visual stimuli were markedly increased and the size of response correlated positively with clinical measures of balance. This suggests an increase in the gain of the response to visual stimuli as has been described in the elderly and in people with stroke[40].

Vestibular:

Unilateral and bilateral vestibular dysfunction is associated with higher ML sway at low (0.1-0.2 Hz) frequencies[39,202]. Healthy controls use vestibular information to contribute to the perception of, and orientation to vertical[128,203]. In contrast following bilateral vestibular loss proprioceptive information seems instead to signal upper body orientation relative to the fixed lower body[202]. People with bilateral vestibular loss are unable to stand with absent / reduced visual and proprioceptive cues[204]. With unilateral vestibular loss there is often an increased reliance on visual motion. This can actually lead to difficulties with balance as visual cues in isolation do not distinguish between the motion of the environment or self-motion. Therefore, visually dominant people often become imbalanced or feel unstable when there are moving visual stimuli (e.g. when walking down shopping aisles)[205,206].

Chronic Ankle Instability:

Chronic ankle instability (CAI) is associated with marked instability in the frontal plane[207]. In some people this may result from mechanical disruption to the ligaments around the ankle joint or reductions in foot evertor strength[208].

Balance deficits may also be associated with poor proprioception and/or poor processing of proprioceptive information from the ankle[208,209]. As a joint moves impulses must arise from muscular, fascial, tendon, and articular receptors. Injury to any or all of these receptors can result in a sensory deficit[210] reducing joint position awareness.

2.4. Effects of intrinsic and environmental factors on balance

There are many factors that can influence balance and walking. This section shall review some of the more commonly investigated factors.

2.4.1. Dual task and attention

Undertaking two tasks at once, dividing ones attention often leads to deterioration in walking and balance[211]. Reductions in stability with dual tasking are more marked in the elderly or in the presence of pathology (e.g. basal ganglia disease)[212,213]. In the elderly verbal dual tasks induce more instability compared to visual or cognitive tasks[214].

2.4.2. Body Mass Index and weight

Changes in the body morphology can affect balance. Higher Body Mass Index (BMI) is associated with higher sway in the AP and ML directions[215]. Pregnancy is also associated with an increase in stance width and a worsening of AP balance that is correlated with perceived balance. This may be due to alterations in body morphology although changes in ligament laxity within the trunk / pelvic region may also be important. Interestingly ML sway varies little during pregnancy but is increased after delivery[216].

2.4.3. Stance width

An increase in stance width is commonly seen in pathology and in the elderly[217]. With an increase in stance width there is a reduction in postural sway[23]. This is

seen in diabetic peripheral neuropathy where the stabilising effects of stance width are more marked with eyes closed[218]. An increase in stance width is associated with a reduction in ML ankle motion[219–221]. The coupling between ankle and hip motion varies with stance width. With smaller stance width most motion occurs around the ankles, and the ankles and hips show uncoupled motion. With greater stance widths the ankles and hips are coupled, and due to the motion of more segments the overall structure is stiffer[221]. Changes in stance width may therefore lead to changes in the relative contribution of proprioceptive information from different proximal and distal joints[221]. The relative role of vestibular and visual cues in stabilising balance in the frontal plane may also vary with stance width. When standing on a surface, rotating in the frontal plane vestibular and visual cues seem important in keeping the lower body oriented to upright at small but not large stance widths[222]; this may support the hypothesis that proximal proprioceptive information may be relatively more important in maintaining balance with a large stance width.

2.4.4. Walking aids, orthoses and shoes

Walking aids such as walking sticks and crutches can improve stability and reduce postural sway. In part this is because stabilising moments or torques are additionally transmitted vertically through the arms[223]. However, improvements in ML stability are also seen in healthy participants, stroke and MS even when a light touch (e.g. ~2 Newton) is applied[224]. The light touch is thought to provide self-positional and spatial cues to aid ML stability[225]. The support of a hand from a person by the side may act in a similar way to reduce body sway and postural muscle activity[226]. For light touch to be maximally effective the support surface

touched should be stable. While walking, for example, light touch decreases ML step width variability when touching a static support surface but there is no effect when a dynamic object (stick that moves) is touched[227]. The effect of light touch and the use of a stick on reducing postural sway have been observed after unilateral vestibular loss[228] and after stroke[229].

Mechanically stabilising the ankle using an ankle foot orthosis can improve stability in healthy participants such as after jumping down from a height[230]. As such they have been used in the rehabilitation of people with chronic ankle instability (CAI)[231]. However, their effects may not be solely mechanical in nature as earlier described. Cutaneous stimulation on the plantar aspect of the foot may also aid stability in CAI and the elderly especially when there are alterations in the availability/reliability of other sensations (e.g. standing on foam or with eyes closed)[231–233].

Shoes can also aid ML stability[234]. The degree of stability depends on the shoe structure. 20mm lateral and medial polystyrene blocks on the heel, for example, can reduce stepping responses to lateral perturbation by up to 25% in older[235] and younger adults[236]. The role of ankle foot orthosis in the rehabilitation of people with diabetic peripheral neuropathy will be explored in Chapter 3.

2.4.5. Training and learning

Balance can adapt to changes in environmental conditions and improve with task related training[32,237,238], i.e. training on the balance task itself. This can be seen after a wide variety of conditions such as stroke, cerebellar ataxia,

vestibular dysfunction, sensory loss and in the elderly[237,239–241]. This observation emphasises that the postural control system is not static but adaptable even in the face of pathology.

Training may also involve targeting primary impairments such as weakness in the hip abductors[116,239]. Training can also lead to changes in the central control of balance and in how multi-sensory information is used. An example of this is vestibular compensation, which describes the processes in the central nervous system used to compensate (using other sensory inputs) for a peripheral vestibular lesion[242].

2.5. Summary and Conclusions

This review highlights the complexity of ML control of balance. ML stability in response to a perturbation and accompanying voluntary movement relies on biomechanical factors as well as the integration of multi-sensory information in multiple areas of the central nervous system. The control of balance is not static but can be affected by task conditions (e.g. stance width), training and pathology. The ability of the balance control system to adapt to differing conditions provides a potential mechanism whereby people may improve their balance during acute or chronic pathology. For people with damage to peripheral and central sensory pathways (i.e. visual, vestibular and somatosensory) one potentially important mechanism is the re-weighting of remaining sensory information. Understanding if and how sensation is re-weighted with pathology or with acute changes in sensory information (e.g.

following anaesthetic or cooling) may therefore inform rehabilitation approaches. Improvement in stability may also arise from alterations in people's biomechanics, for example, by adopting a different stance width or by stabilising the ankles using ankle foot orthoses. These approaches however may not only act biomechanically but they may also influence how different sensations are used to stabilise balance. To understand this it is firstly important to assess whether alterations in sensory processing for the control of ML balance varies in healthy participants with a change in stance width or when wearing an ankle foot orthoses. This will be explored in Chapter 5.

Chapter 3 . Diabetic Peripheral Neuropathy: Balance, Walking and Falls

3.1. Pathophysiology of diabetes

Diabetes is classed as both a genetic and autoimmune disease characterised by abnormally high levels of blood glucose[243]. This is due to a reduction in the body's capacity to modulate levels of glucose in order to prevent hyperglycaemia (elevated blood glucose levels). Two main types of diabetes exist; Type 1 and Type 2, previously known as insulin dependent diabetes mellitus (IDDM) and non-insulin dependent diabetes mellitus (NIDDM)[2,244].

Definitive causes of diabetes type 1 are unclear, although it may be due to hereditary, genetic or environmental factors such as foods or viruses[245]. Research has shown that the body's own immune system, which normally fights against viruses and harmful bacteria, mistakenly destroys the insulin-secreting beta cells within the pancreas which store and release insulin, required for reducing blood glucose concentration[243].

The cause of type 2 diabetes is also inconclusive, although risk factors such as poor diet, high blood pressure/cholesterol, obesity, and family history of diabetes are commonly reported. Type 2 diabetes is characterized by a combination of peripheral insulin resistance and inadequate insulin secretion by pancreatic beta cells[245].

Prolonged hyperglycaemia (excessive glucose levels) affects almost all tissues in the body. It can be monitored by measuring glycated haemoglobin (HbA1c) levels[246]. Blood vessels are particularly affected by hyperglycaemia and can

lead to vascular complications such as atherosclerosis, which is accelerated by diabetes[247]. Blood vessel complications are divided into two sub sections; 1) Macrovascular; including pathologies such as coronary artery disease, peripheral arterial disease, and stroke. 2) Microvascular complications; including nephropathy (kidney disease), retinopathy (damage to the retina of the eyes) and neuropathy (nerve damage)[57]. The pathways leading to macro- and micro-vascular complications are summarised in figure 3.1.

Microvascular complications, such as neuropathy are experienced as a result of decreased blood flow (e.g. to the vaso nervorum) supplying oxygen and nutrients[248]. This will affect the viability of the cutaneous tissues, sensory receptors and nerves[249], including both afferent and efferent nerves. Typically de-myelination of the large and small myelinated peripheral nerves occur and loss of peripheral sensation from tactile and proprioceptive receptors results[250], including sense of touch and pressure from the mechanoreceptors of Pacinian corpuscles, Merkel's cells, Ruffini endings, Meissner's corpuscles and the sense of muscle length, stretch and tension from muscle spindles and Golgi tendon organs[62].

The combination of macrovascular and microvascular i.e. reduced blood flow and neuropathy, can lead to further long term complication such as ulceration[7]. Ulceration can develop when mechanical trauma to the feet goes un-noticed due to the reduction in protective foot sensation[251]. With a poor vascular supply healing can be delayed[252]. Whilst the lack of sensation to the feet can have devastating effects, the resulting balance dysfunction also gives rise to the increased risk and incidence of falls[12,253]. Injurious falls are a major problem for people with diabetic peripheral neuropathy (DPN); often the underlying cause of

a reduced quality of life and life expectancy[19]. In recognition of the negative impact of falls on wellbeing, researchers have investigated the effect of DPN on balance and walking ability[6,14,254–256]. Such studies have revealed balance stability as a significant independent risk factor for falls[257]. However, there are a number of mechanisms which may attribute to this instability. The following sections firstly describe the deficits in balance, walking and falls reported in people with diabetic peripheral neuropathy before exploring potential causes of these functional deficits.

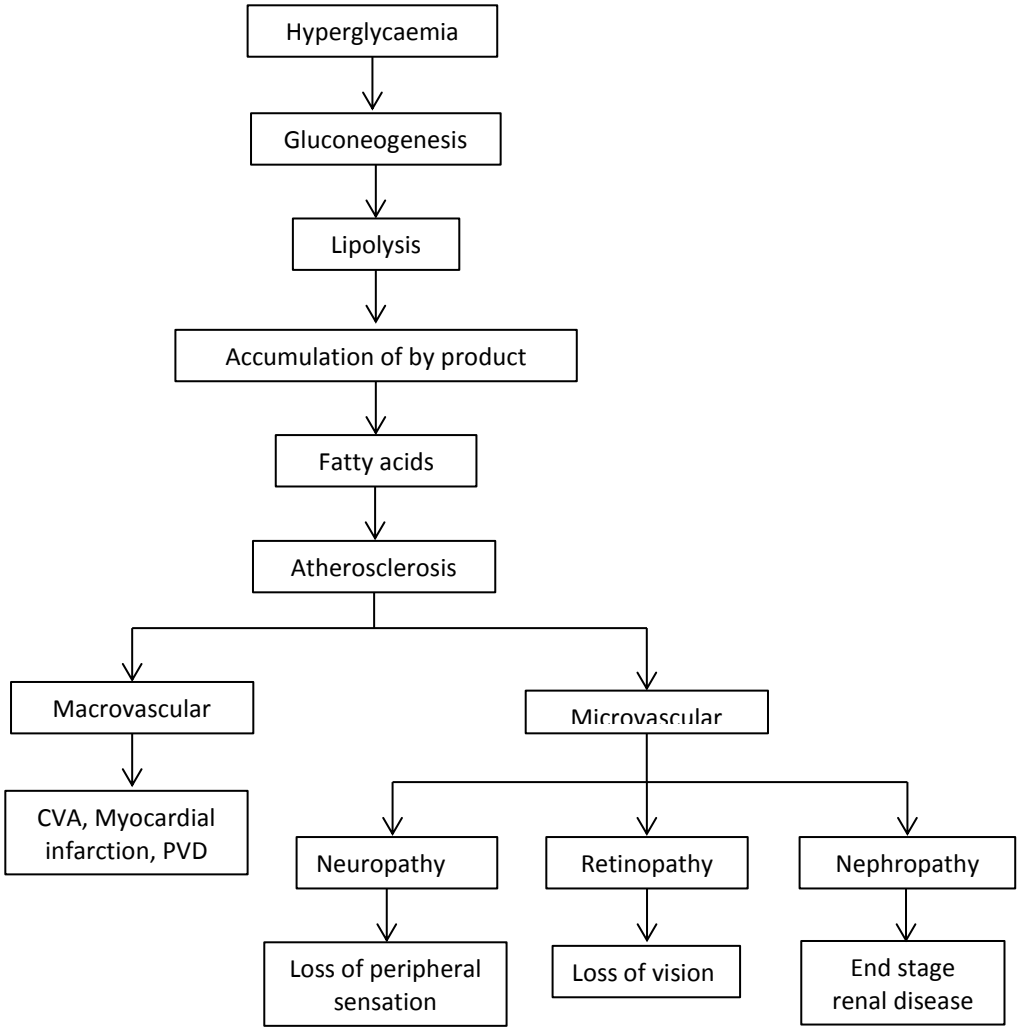


Figure 3.1 Summary of the pathogenesis of diabetes leading to macro- and micro-vascular complications.

3.2. Impact of DPN on balance, walking and falls

3.2.1. Falls

People with diabetes are particularly vulnerable to falls[5] often preceded by a loss of balance. Loss of balance in some instances maybe recoverable, but this requires rapid responses and adequate strength from the muscles in the lower limbs[258]. There are several risk factors predictive of falls such as older age and severity of DPN[259], muscle weakness[260], sensory loss[261], and visual impairement[262]. These risk factors are known to have a detrimental effect on balance[11,12,263]. A prospective cohort study in 2002, highlighted that postural instability in the presence of DPN was the factor most strongly associated with falls[13,264].

3.2.2. Balance

Postural instability is higher in people with diabetes[53,265] even more so in those with poor HbA1c control[266]. The additional presence of clinically detectable DPN further increases the degree of postural sway[267]. A reduction in nerve conduction velocity in DPN is associated with reductions in clinical scores (Timed Up and Go, Berg balance scale) of balance[268] and people with DPN have 66 to 117% more instability compared to people with diabetes without peripheral neuropathy[269].

Postural instability in people with DPN is greatest when visual or vestibular cues are absent[269] or changing such as when standing with eyes closed with a rotated head or while moving the head in yaw, altering vestibular inputs[270,271]. The increased amplitude of low frequency sway with head turning is able to

differentiate people with DPN from other conditions such as Parkinson's disease, head injury, whiplash and peripheral vestibular dysfunction that also show higher sway speeds[271]. This suggests that a stable head (with eyes closed) providing stable vestibular inputs may be important for balance control in the presence of distal sensory loss. Factors associated with increased postural sway in DPN include the severity of neuropathy and diabetes (as defined by HbA1c levels >9[272]), the presence of cataracts, the use of metformin (a medication to control type 2 diabetes) and increasing age[269].

3.2.3. Reactive balance control

People with DPN have slower reaction times[273], and exhibit a longer response latency to balance perturbation compared to what is commonly seen in healthy subjects[274]. With distal sensory loss toe up rotations of a platform result in delayed or absent short- and medium-latency responses in distal muscles (e.g. soleus)[138]. The Medium latency responses are felt to be mediated by Group II afferents[83], and these are affected in people with DPN as the condition affects both small and large diameter myelinated fibres[275]. The fact that Group II afferent conduction velocity (estimated via the Medium latency stretch reflex) correlates with postural sway area in people with DPN suggests that neuropathy affecting smaller fibres may significantly contribute to imbalance in DPN[276,277].

3.2.4. Anticipatory postural adjustments

As DPN does not affect the central nervous system directly it would be expected that anticipatory postural adjustments would be relatively unaffected. To date there have been limited studies directly exploring this. The functional reach test requires participants to stand with an outstretched arm and lean forwards[278]. The forward motion is initiated by activation of the tibialis anterior, a type of anticipatory postural adjustment, which is earlier and higher amplitude in people with DPN[279]. The cause of this is unclear; it was hypothesised to be related to delays in movement timing caused by the neuropathy[279]. However differences in biomechanical factors such as increased ankle stiffness in DPN (see next section) were not measured and could account for this.

3.2.5. Balance strategy

Changes in balance strategy have also been described in people with DPN[261]. Research suggests that people with DPN tend to shift postural control from ankle to hip strategy especially when vision was deprived[282]. This was not seen in healthy controls[256]. The change in strategy in DPN may reflect their instability[282] i.e. they are closer to their limits of stability. In DPN the correlation between the ankle and trunk is less than that seen in healthy participants. Thus the segment motion pattern at the hip observed when a hip strategy is employed by the two groups is quantitatively different. This may reflect differences in the availability of distal ankle motion or reduced ability to generate ankle torques. This is reflected in an association between the balance strategy used and the level of peripheral neuropathy and hip and ankle strength in

DPN[283]. A greater understanding of the role of proximal muscles in postural control after DPN and why some participants adopt this strategy and whether it is indeed useful to maintain balance is therefore required and will be explored in this thesis.

3.2.6. Gait

People with DPN walk with a slower walking speed, larger base of support and with an increased double support time i.e. when both feet are in contact with the ground compared to controls[284–286]. This has been shown to reduce accelerations of the pelvis and head, an indicator for whole body balance[14]. The parameters of walking are more variable from step to step and this variability increases when walking speed is reduced or vision is restricted. The altered spatiotemporal gait parameters in those with DPN are predicted by balance ability, ankle muscle strength[287,288] and duration of type II diabetes[289]. Step width and step length in turn predict of falls on un-even surfaces[290].

During functional tasks such as stair ascent / descent there is a greater separation of CoP and CoM in the frontal plane. This will result in the need for higher joint torques / muscle activation to control upright posture[258]. As discussed below this coupled with proximal weakness may explain why ML falls are common in DPN[258].

3.3. Factors impacting on balance, walking and falls in DPN

3.3.1. Muscle weakness

People with DPN, develop a distal muscle weakness[287] which is predictive of the spatiotemporal changes found in walking in DPN[287]. However, muscle weakness is not just limited to the distal muscle groups; proximal muscle weakness, indicated by trunk variability, has also been reported during functional tests (e.g. five sit to stand repetitions)[53]. The need to generate higher torques to maintain balance during functional tasks such walking, highlights the importance of muscle strength for balance. In keeping with this hip abductor strength is the single best predictor of unipedal stance time in people with DPN[291]. People with higher hip abductor strength showed longer unipedal stance times and it was hypothesised that those with greater strength were better able to compensate for increased ankle proprioceptive thresholds[291].

3.3.2. Biomechanical changes

In diabetes, the non-enzymatic oxidative reactions of proteins with glucose (glycation) leads to the formation of advanced glycation end-products (AGEs)[292]. These increase the formation of covalent cross-links within collagen fibres[293,294]. This observed alteration of collagen structure inhibits normal connective tissue gliding[295] and is manifested in diabetic people as limited joint mobility[293]. Limited joint mobility syndrome (LJMS) occurs in 30-40% of patients[296].The loss of tissue elasticity results in reductions of foot and ankle

segmental mobility, a thicker Achilles tendon and stiffer plantar soft tissues than is found healthy controls[297].

The relationship between changes in peripheral tissue stiffness and balance, has been investigated using the EQUITEST ®[297]. The EQUITEST ® is specially designed to measure postural sway under 6 different conditions that vary; visual input (eyes open / closed; fixed platform), somatosensory input (firm surface vs sway referencing the platform so ankle joint angle remains constant), or sway referencing the room with eyes open (fixed / tilted visual surround). Interestingly the study by Cheing et al (2012)[297] reported an increased ankle tendon stiffness which correlated with the ability to use vestibular inputs when somatosensory inputs were disrupted. Further, an increase in stiffness in the plantar soft tissue at the first metatarsal head was correlated with large differences in sway between the eyes open / closed conditions and between sway referencing the platform and standing on a stable platform. Although the results of their study, do not imply cause and effect, the correlation found may suggest that biomechanical changes alter how people with DPN use sensations to balance[297]. Such that reduced motion at distal joints seemed to increase reliance on vision, somatosensory information and vestibular information.

3.3.3. Morphology

Obesity is directly linked with the development of type II diabetes[243,248]. The presence of obesity, may further affect balance by requiring increased joint torque generation to stabilise movement of the heavier body part. This may explain why in other literature on obesity, sway is larger in people who are more

obese[298], who may not have the additional muscular power to generate the required torque. There has been a greater association reported between increased BMI and falls in women over men and has been inferred to as sex-based differences in typical fat distribution patterns i.e. men gather fat in a less-destabilizing mid-line location, and women in relatively more-destabilizing lateral hip and thigh locations[18].

3.3.4. Visual system

During the first two decades of the disease, nearly all patients with type 1 diabetes and >60% of patients with type 2 diabetes develop retinopathy[299]. Together with diabetic macular oedema they are leading causes of blindness in the working-age population of most developed countries[300]. Visual information from the eye has an integral role in maintaining balance whilst standing and during locomotion. The role is to provide a visual reference of self-position and the position of obstacles within an individual's surroundings[301]. Poor visual function has been related to an increased risk of falls[301–303]. In particular visual acuity and contrast sensitivity have been reported to be two of the strongest risk factors of falls[303]. Visual acuity is the acuteness or clearness of vision[304]. A loss of visual acuity is found to lead to postural instability[305]. Contrast sensitivity is the ability of the visual system to distinguish between an object and its background. A reduction in contrast sensitivity is also associated with increased sway and falls[306].

3.3.5. Vestibular system

The vestibular system supplies information about linear (including gravitational) and angular accelerations of the head in relation to inertial space[307]. The vestibular system is also affected by microvascular compromise in diabetes[308]. In recent years evidence has emerged about the effect of diabetes on the vestibular system[308] and its association with reduced balance[309] and falls[310–312]. However it is not yet clear which part of the vestibular system is most affected by diabetes[313]. As well as potential contribution to balance dysfunction, the vestibular system may also aid in balance recovery. In people with diabetic peripheral neuropathy there is an increase in the gain of the vestibular system (as measured using GVS) which may act to aid postural control in the presence of impaired distal leg somatosensation[33]. The tendency for more frequent use of a hip strategy to balance in people with DPN has been interpreted as reflecting reliance on the vestibular system[282].

3.3.6. Somatosensory system

Due to the extensive contribution of the somatosensory system in the control of balance, the impact of diabetic related sensory loss on postural instability has research attention. The consensus of evidence strongly suggests that reduced function through the loss of plantar cutaneous sensory feedback and distal proprioceptive information is the primary cause of postural instability[10,57]. Ankle inversion/eversion proprioceptive thresholds, for example, are higher in those with DPN and have been associated with an inability to maintain the mediolateral control to stand on one foot[314].

Somatosensory changes are however not restricted to distal lower limb joints. Increased thresholds for trunk re-positioning are seen in DPN and may contribute to impaired balance[315].

3.3.7. Medication and co-morbidities

A high number of medications have been associated with an increased risk of falls in the elderly[16], but this pattern was not found in people with DPN. Metformin use has not been reported to have direct links to falls and there are no trials linking Insulin to falls in those with DPN[316]. A comparison of medication usage pattern among fallers and non-fallers both with DPN were similar, suggesting that medication usage was not a risk factor for falls people with DPN[317]. The effects of co-morbidities on the incidence of falls have also been shown to be insignificant in those with peripheral neuropathy[18].

3.4. Ankle foot orthoses: A review of sensorimotor and mechanical effects on balance in people with diabetic peripheral neuropathy

3.4.1. Background

Ankle foot orthoses (AFO's) are a modifiable external factor with the potential to improve postural control in people with diabetes and peripheral neuropathy[318–322]. However the mechanism by which postural control is improved is not fully understood. In a non-pathological group of people diagnosed with ankle instability Douglas and Richie (2007)[323] proposed a number of possible mechanisms of action; 1) a reduction in range of motion of the ankle joint or subtalar joint (mechanical support), 2) maintenance of the alignments around the subtalar joint within a neutral position enhancing ligament mechanoreceptor function (sensory cues), 3) an improvement in tactile sensation on the plantar surface of the foot (sensory cues), and 4) a reduction in muscular strain about the ankle (mechanical support). AFO's may also provide auxiliary sensory cues (sensory cues)[24]. However, whilst plausible these hypotheses remain largely speculative.

The current literature suggests that AFO's have a positive effect on balance and postural control in people with Stroke[25,26] and multiple sclerosis (MS)[27]. Two systematic reviews have been published to provide evidence of an improvement in gait when people who have experienced a stroke wore an AFO[324,325]. They reported gait parameters to benefit from the addition of an AFO in this population, including gait velocity and cadence. Authors also reported benefits in improved self-confidence and postural control. In people with MS, AFO

reduced sway velocity of the head in static stance particularly in the mediolateral direction (25% reduction) compared to anterior posterior direction (18% reduction)[27].

There appears to be some evidence to suggest that AFOs can effect balance across a number of diseases, including neurological disease where sensory and proprioception dysfunction exists[326–328]. However, what is less clear is mechanism of action by which the AFO applies its effect, specifically in those with diabetic peripheral neuropathy. Therefore, a systematic review of the literature has been conducted to synthesis the current available evidence, to investigate the effect of an AFO on balance in people with diabetes and neuropathy, and to give insight into the mechanism of effect (in terms of mechanical stabilisation of the ankle or in the provision of auxiliary sensory cues to enhance stability).

3.4.2. Aim

The aim of this review is to evaluate the current evidence regarding the mechanism of effect on balance of AFOs for people with diabetic peripheral neuropathy.

3.4.3. Review methods

This review was carried out in accordance with the guidelines and recommendations set out by the Centre for reviews and dissemination[329] and the Cochrane handbook for systematic reviews of interventions[330].

3.4.4. Search strategy

To identify relevant publications concerning the effects of AFO's on balance a search was performed (December 2016), using the following databases: Medline (Ovid), AMED, CINAHL and PubMed. Each potentially relevant article found using search terms and groups of terms shown in table 3.1, was initially screened by SG and JM.

Population	Boolean operator	**I**ntervention	Boolean operator	**O**utcome
diabet*	AND	orthoses	AND	balance
		orthotic		postur*
neurop*		splint		sway
		brace		centre of pressure
		ankle-foot		cop
		afo		

Table 3.1 Search terms used in the literature search.

3.4.5. Selection process

3.4.5.1. Inclusion criteria

This review considered full-length articles published in English, and adhering to the following criteria:

- Types of Participants

  Adults with diabetes (type 1 or 2) and peripheral neuropathy, defined clinically as 1) being unable to detect a 10g monofilament at one or more sites on the plantar surface of the foot, or 2) a vibratory perception threshold of greater than 25V, test by neurothesiometer or similar.

- Types of Intervention

  This review considered studies investigating any type of external device designed to be worn upon the ankle. AFOs were defined as any device that crossed the ankle. Those that extended beyond the level of the knee joint were excluded from the review. Footwear including high toped boots were also excluded from the study.

- Comparison

  Studies were included in the review if they compared the effects of an ankle foot orthoses to another ankle foot orthoses or no intervention.

- Outcomes

  Studies that reported on any laboratory based assessment of static or dynamic standing balance. E.g. centre of pressure movement.

- Types of studies

All types of experimental and epidemiological study designs were included in this review including randomised controlled trials, non-randomised controlled trials, quasi-experimental, before and after studies, case control studies. Descriptive epidemiological study designs including case series, individual case reports were excluded from the review.

3.4.5.2. Exclusion criteria

Articles were excluded if they were conference abstracts, unpublished or grey literature. Studies involving participants with lower limb amputation, prosthetic devices or other pathologies which affect balance or co-ordination were also excluded.

3.4.6. Study selection

In total 273 articles were identified in the initial search. 243 articles with inappropriate titles were excluded by SG and JM, 20 duplications were then removed. This left 10 articles for initial screening (table 3.2).

Study, Title, Year
Aruin, A., Rao, N: Ankle-Foot Orthoses: Proprioceptive inputs and balance implications. 2010
Bigelow Edginton, K., Jackson, K: Immediate influence of carbon composite Ankle-Foot Orthoses on balance and gait in individuals with peripheral neuropathy: A pilot study. 2014
Deursen, R: Footwear for the neuropathic patient: offloading and stability. 2008
Rao, N., Aruin, A., Automatic postural responses in individuals with peripheral neuropathy and ankle-foot orthoses. 2006
Broglio, SP., Monk, A., Sopiarz, K.,Cooper, ER: The influence of ankle support on postural control.2009
Glasser, S., Paton, J., Collings, R., Marsden, J: The effects of ankle foot orthoses and stance width in people with diabetic peripheral neuropathy. 2016
Son, J., Ashton-Miller, J., Richardson, MD: Do Ankle orthoses improve proprioceptive thresholds or balance in older persons with peripheral neuropathy. 2010
Hijmans, J M., Geertzen, JHB., Dijkstra, PU., Postema, K: A systematic review of the effects of shoes and other ankle or foot appliances on balance in older people and people with peripheral nervous system disorders. 2007
Rao, N., Aruin, A: Auxiliary sensory cues improve automatic postural responses in individuals with diabetic peripheral neuropathy. 2011
Rao, N., Aruin, A: The Effect of Ankle-Foot Orthoses on balance impairment: Single-Case study. 1999

Table 3.2 Full list of potentially relevant articles for review.

6 articles were excluded, based on abstract or inclusion criteria. Four full text articles were assessed for eligibility by two independent reviewers SG and JM, based on the inclusion/exclusion criteria. Three articles were identified as articles eligible for review (table 3.3) and were scored for methodological quality using Downs and Black Quality Index tool[331] by SG and JM. Where agreement between reviewers could not be made through discussion, an adjudicator was in place to help resolve the disagreement (JP). Figure 3.2, presents the selection process.

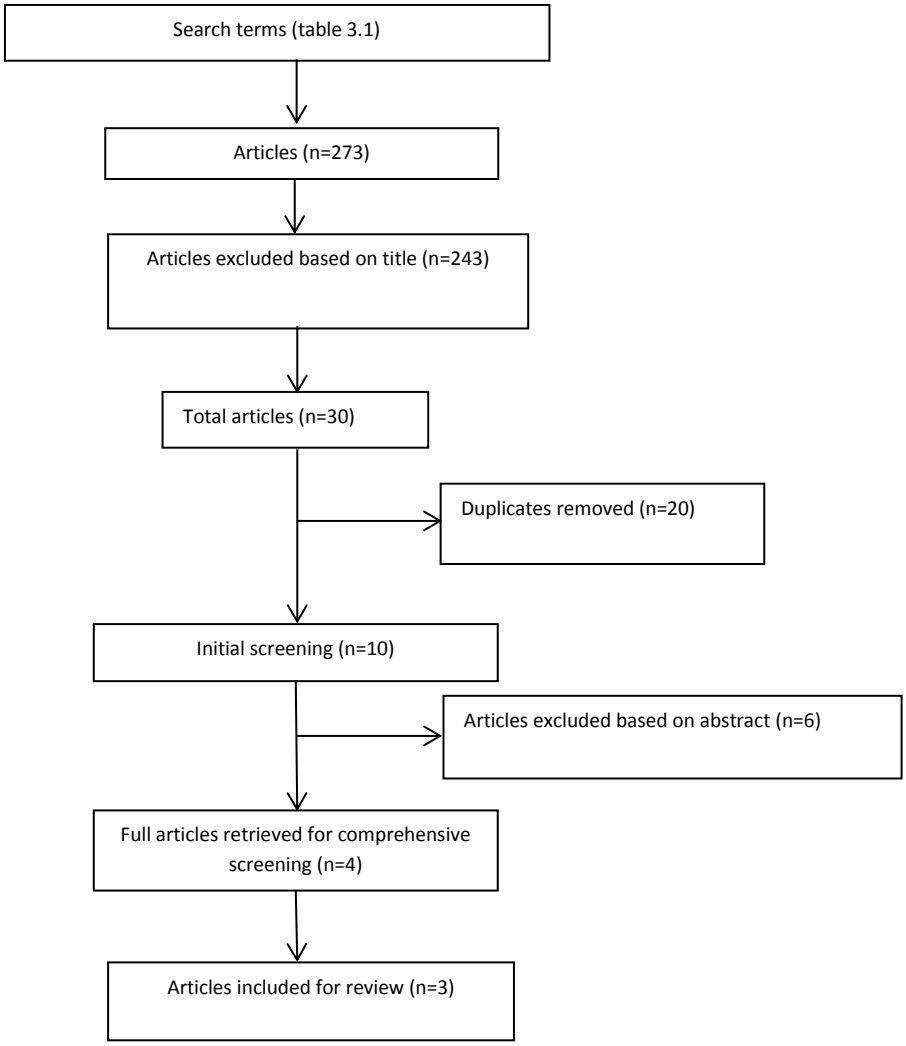


Figure 3.2. Flow diagram of selection process.

3.4.7. Details of included studies

The three papers which met the inclusion criteria were observational, repeated measures studies[24,320,332]. Each of the studies used different methods to assess the effect of AFO, therefore having dissimilar outcome measures. The sample size for each study was eleven[320,332] or twelve[24] participants. Rao et al's earlier study[320] included people with peripheral neuropathy, with just six of those being

due to diabetes. A separate set of eleven participants with confirmed diabetic peripheral neuropathy was also used[332]. A sample size of twelve participants with DPN was investigated in the remaining study[24]. DPN was confirmed by one or more clinical assessments of sensation using semmes-weinstein monofilaments (all studies), 128Hz tuning fork[24,332], stretch reflex tests[323], electrodiagnostic testing of peroneal and sural motor responses[332]. There was no inclusion of a control group in any of the included studies. The type of AFO and its mechanistic action for each of the studies were also different; two studies used an AFO that had minimal stabilising properties but provided proximal tactile proprioception[24,320]. One study investigated the effects of an AFO designed to provide mediolateral stabilisation[332]. Only one of the studies described what was worn on the feet during testing, where standardised footwear was reported but not fully described[25]. The Sensory Organisation Test was used to evaluate balance to evaluate the proprioceptive effects of an AFO[24,320]. Another study used an AFO designed to restrict mediolateral motion of the foot and ankle and measured proprioceptive thresholds to mediolateral foot rotations to assess proprioceptive change with AFO use[332].

Selected study details

Author/Year	Study design	Population and sample size	Intervention	Sensory/Mechanical property of AFO	Conditions	Outcome measures	Significant Findings	Conclusions
Rao, N et al, 2011[24]	Repeated measures; Observational	Convenience sample: 12- DPN 9/3:Male/Female Age:69.5(14.1)	Ankle foot orthoses that provided auxiliary sensory cues, not ankle stabilisation. Shank of brace connected with the foot bed via a semi rigid element .Velcro straps used to secure the shank of the brace to the leg	Sensory	Static stance: Eyes Open and Eyes Closed On Firm and sway referenced surface	Partial Sensory organization test scores (force displacement) and latency of responses to a platform perturbation SOT1:EO,Fixed platform SOT2:EC,Fixed platform SOT4:EO, Sway referenced SOT5:EC, Sway referenced	Decreased A/P sway (force displacement) Increased SOT scores in all conditions with AFO Changes in latency due to AFO not significant	Automatic postural responses improved by using AFOs, which allow sensory information to bypass the disrupted pathways in the lower legs
Rao, N et al, 2006[320]	Repeated measures; Observational	11-Peripheral neuropathy (including 6 with DPN) 6/5:Male/Female Age: 56 (7.7)	Flexible custom-moulded polypropylene AFO of 4.5 mm thickness ankle foot orthoses	Sensory and mechanical	Static stance: Eyes Open and Eyes Closed On Firm and sway referenced surface	Partial Sensory organization test scores (force displacement) and latency of responses to a platform perturbation SOT1:EO,Fixed platform SOT2:EC,Fixed platform SOT4:EO, Sway referenced SOT5:EC, Sway referenced	Increased SOT scores in all conditions with AFO Reduction in latency due to AFO significant	Potential sensory changes with AFO. However small sample size and previous use of AFO limit the validity of the study

Table 3.3 Data extraction of selected studies evaluating ankle foot orthoses in people with DPN.
Age, BMI is given as: Mean (SD).

Author/Year	Study design	Population and sample size	Intervention	Sensory/Mechanical property of AFO	Conditions	Outcome measures	Significant Findings	Conclusions
Son et al[332]	Repeated measures; Observational	DPN-11 8/3: Male/Female Age: 72 (7.1) BMI: 30.9 (5)	Ankle foot orthoses - designed to provide mediolateral support- semi-circular shaped shells lined with foam that lie on either side of the malleoli and extend proximally over the lower leg	Sensory	Static stance: Eyes open	Frontal plane (inversion/eversion) ankle proprioceptive threshold, Unipedal Stance time		No change in proprioceptive thresholds with AFO

Table 3.3 continued. Data extraction of selected studies evaluating ankle foot orthoses in people with DPN.
Age, BMI is given as: Mean (SD).

3.4.8. Assessment of study quality

To evaluate methodological quality of each article, the Quality Index Tool developed by Downs and Black[334] was used (table 3.4). This is a 27 point valid and reliable checklist, sub-divided into Quality of reporting, external validity, internal validity (bias and confounding) and power. The tool has high internal consistency, good test-retest and inter-rater reliability appropriate for assessing both randomised and non-randomised studies.

	Selected study		
	Rao et al (2011)[24]	Son et al (2010)[332]	Rao et al (2006)[320]
Reporting			
Is the hypothesis/aim/objective of the study clearly described?	1	1	0
Are the main outcomes to be measured clearly described in the Introduction or Methods section?	1	1	1
Are the characteristics of the patients included in the study clearly described?	1	0	1
Are the interventions of interest clearly described?	1	1	1
Are the distributions of principal confounders in each group of subjects to be compared clearly described?	0	0	0
Are the main findings of the study clearly described?	1	1	1
Does the study provide estimates of the random variability in the data for the main outcomes?	0	0	0
Have all important adverse events that may be a consequence of the intervention been reported?	0	0	0
Have the characteristics of patients lost to follow-up been described?	0	0	0
Have actual probability values been reported (e.g.0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?	0	1	0

Table 3.4 Table of scores for methodological quality.

External validity			
Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	0	0	0
Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	1	1	1
Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	1	1	1
Internal validity - bias			
Was an attempt made to blind those measuring the main outcomes of the intervention?	0	0	0
If any of the results of the study were based on "data dredging", was this made clear?	0	0	0
In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?	1	1	0
Were the statistical tests used to assess the main outcomes appropriate? The	1	1	1
Was compliance with the intervention/s reliable?	0	0	0
Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	1	1	1
Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	1	0	0
Were study subjects randomised to intervention groups?	0	0	0
Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	0	0	0
Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	0	0	0
Were losses of patients to follow-up taken into account?	0	0	0
Power			
Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?	0	0	0
Total score	11	10	8

Table 3.4 continued; Table of scores for methodological quality.

The methodological quality of the three studies was poor. One study did not report a clear objective[320], although the information provided in all papers was sufficient to allow the reader to make an unbiased assessment of the intervention, outcome measures and findings.

To make predictions about a population (i.e. the transferability of the results to the general population) study subjects should represent the entire population from which they were recruited. All of the studies used a convenience sampling strategy, and thus introduced a potential sampling/selection[335] bias that reduced the ability of the results to be generalised to the rest of the population, i.e. the external validity.

All studies were completed in the USA, two in Chicago[24,320] and one in Michigan[332]. Studies obtained participants from referrals from primary care physicians and neurologists[24], a rehabilitation hospital[320], from an Electrodiagnostic laboratory and an Orthotics and prosthetics centre[332]. The setting was not reported for any study.

Blinding of study subjects was impractical in all studies due inability to conceal the device. It may however, have been possible to blind the researcher completing the data analysis from the test condition; however this was not reported in any study. Randomisation of the intervention sequence is an important aspect in the design of repeated measure studies because it guards against bias being introduced by an intervention order effect or participant learning effect. Two of the studies incorporated this precaution into the study design[24,320], whilst it was not reported in one of the studies[332]. Both studies that

randomised the intervention sequence did not describe the method of randomisation used[24,320].

The main outcome measure was clearly described in each of the studies[24,320,332]. These included both static and dynamic measures of balance. Validity and reliability of these measures were detailed or referenced in only one study[25], which reported fair to good test-retest reliability of the sensory organisation test[336].

Although confounding factors such as age, BMI and muscle strength were recorded in all studies, statistical analysis of correlations on outcome measures were not reported in any study, making the pure effect of AFO difficult to ascertain.

All studies reported the statistical analysis used. However, missing from all studies was sample size analysis to indicate sufficient participant numbers to find a significant effect should one exist. One study reported a retrospective power analysis[332], all remaining studies did not report the power of the study to detect a significant effect of intervention[25,309].

3.4.9. Results of the review

The aim of this review was to evaluate the current evidence regarding the mechanism of effect (sensorimotor or mechanical) on balance of AFOs for people with diabetic peripheral neuropathy. All of the studies used AFO interventions that were in contact with the skin overlying the shin (table 3.3),

therefore having the potential to provide passive sensory cues to compensate for reductions in distal sensation. Just one of the studies described the AFO as a supportive device[332]. Two of the studies used an AFO, which was described by the authors to provide more proximal sensory cues[25,311], but by design only one[24] possibly two[320] of these used an AFO that could potentially provide solely sensory cues (table 3.3).

Within the following results the studies are discussed in terms of the AFO type under investigation, and the anticipated primary mechanism of effect associated with that type. Where the AFO by design was constructed from a ridged material, that crossed the ankle joint to provide ankle bracing, the intervention was considered to have a mechanical mechanism of effect and the results reported in that context. In contrast if the AFO used in the study was designed not to brace the ankle but rather to provide sensory information/cues proximal to the joint then the study was considered to be investigating the sensory mechanism of effect of an AFO on balance.

3.4.9.1. Mechanical effects of AFO

One Study used an AFO, which by design had potential to restrict foot/ankle anterior-posterior and mediolateral motion[320]. This did not measure or report changes in the available range of motion at the ankle joint with or without AFO, therefore the clinical effect of the AFO on joint motion is unknown.

One study which recruited 11 subjects with DPN[332] and assessed the only type of AFO designed to restrict joint motion in the mediolateral direction. The AFO used was an Active Ankle T2 (Active Ankle Systems, Louisville, KY) which are semi-circular shaped shells lined with foam that lie on either side of the malleoli

and extend proximally over the lower leg. They are held tightly to the lower leg and ankle by hook and loop straps that wrap circumferentially around the leg. The shells are connected inferiorly by a sling. No direct assessment of the mechanical properties of the AFO were carried out in this study, however they reported that ankle orthoses which provide mediolateral support did not change ankle inversion/eversion proprioceptive thresholds (1.06° ± 0.56° with AFO, 1.13° ± 0.39, P = 0.95), as measured by recording perceived ankle rotations mechanically imposed during standing. Unipedal stance time (UST), the time the participant could stand on one leg before the non-stance limb touched the ground, was also measured without (6.2 ± 5.4 sec) and with AFO (6.1 ± 6.5 sec) and no significant changes were found between conditions (P=0.92).

3.4.9.2. Sensory effects of AFO

Two studies by Rao and Aruin (2006, 2011)[24,320] used AFO's designed not to restrict joint motion but instead provide auxiliary sensory cues. Both studies assessed the effect of AFO on balance (CoP displacements), the latencies of responses to balance perturbations, muscle strength (hips, knees and ankles) and the contributions of sensory systems to postural control, as measured by centre of gravity body sway (sensory organisation test - SOT ,table 3.5). The first study[320] tested an AFO which provided minimal joint restriction in 11 people with DPN. The AFO was flexible, custom-moulded AFO, made of 4.5mm thick polypropylene. The study did not assess the mechanical stabilising effect on the ankle. The AFOs were made of a single, continuous piece of plastic, with flexible trim lines at the ankle, allowing the foot to dorsiflex and plantarflex. Measures of latency, defined as the onset of translation and the onset of the

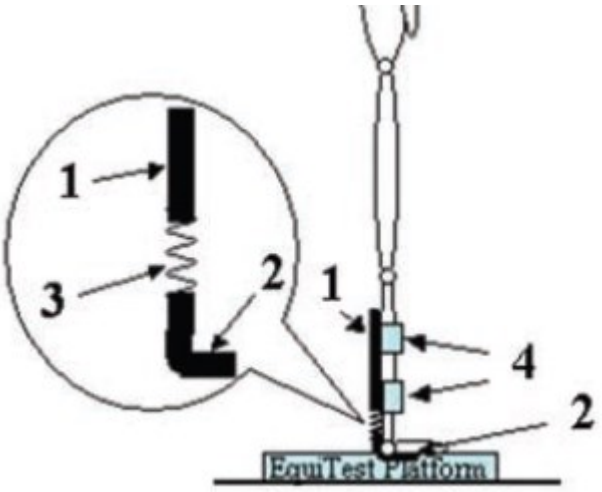
subject's active response to the support surface movement, was tested using medium and large forward and backward translations in the AP direction, with and without AFO. In all conditions the AFO reduced response latencies significantly (P<0.05) by 6.4ms and 2.4ms for medium and large platform translations in the backward direction. For forward translations an AFO also reduced latencies significantly (P<0.05) by 10.9ms and 4.7ms for medium and large platform translations. The displacement of CoP was not reported. Strength scores representing the amount of active force generated by each leg during the postural response to the translations of the platforms reduced but did not reach a level of significance. A partial SOT test was also performed without/with AFO (table 3.5); SOT1 (80.41 / 91.41), SOT2 (48.86 / 66.23), SOT4 (53.00 / 73.68), SOT5 (20.00 / 31.90). There was significant improvements in SOT scores due to the effect of AFO (P<0.0001). The effect of SOT condition was significant (P<0.001).

SOT 1	EO- Fixed platform
SOT 2	EC- Fixed platform
SOT 4	EO - Sway referenced
SOT 5	EC - Sway referenced

Table 3.5. Sensory Organisation test (SOT) conditions. EO/EC indicates eyes open or eyes closed. All tests were performed with ad without AFO.

Their second study[24] tested an AFO which was designed to solely provide auxiliary sensory cues in a separate set of 12 people with DPN, using the same battery of tests. The AFO in this study consisted of the shank of the brace

connected with the foot bed via a semi-rigid element. Velcro calf straps were used to secure the shank of the brace to the leg (figure 3.3).



1. Shank of foot brace
2. Foot bed
3. Semi rigid element
4. Velcro straps

Figure 3.3 AFO designed to provide auxiliary sensory cues only via semi regid element connecting shank of brace to foot bed[24]

The device provided sensory information to the calf via the shank of the brace and to the middle tibia via calf straps but at the same time did not provide any ankle stabilization as the connection of the shank of the brace with the foot bed was flexible. This was confirmed by measuring the horizontal force applied to the calf using a load cell. The force measured was 0.9N, enough to provide sensory cues, but less than that required to provide mechanical support to the joint[337]. Measures of latency were found to decrease but the difference when an AFO was worn did not reach a level of significance (P=0.20). The effect of AFO improved all SOT scores; SOT1 (92.37 / 93.99), SOT2 (85.29 / 86.80), Fixed platform, SOT4 (76.75 / 82.79), SOT5 (21.16 / 38.29) without and with AFO respectively. However in only SOT2 and SOT5 (eyes closed conditions) was the effect of AFO significant (P<0.005, P<0.03, respectively).

These two studies by Rao and Aruin[24,320] differed in the design of AFO used. Although both were reported to only provide sensory cues, only in their later study was this confirmed[24]. The AFO which had potential to stabilise the joint[320] reduced sway velocity and increased sensory organisation test score significantly in those with DPN. The AFO confirmed to solely provide sensory cues[24] did not significantly affect latencies, but did increase SOT scores. Therefore it may be possible that latencies are affected by the stabilising effect of AFO, whilst centre of gravity displacements and response latencies, as measured by sensory organisation tests are affected by the addition of sensory cues.

3.4.10. Discussion

The findings from this review suggest that AFO's have the potential to improve stability in people with diabetic peripheral newuropathy. However this must be interpreted with some caution as the methodological quality of all the studies was poor. AFO effects have been investigated using small sample sizes[24,320,332] although the significant results indicate that statistical power was reached, none were powered to assess the clinical significance[338]. There is a need to conduct similar studies using increased sample sizes estimated using sample size calculations. Not all studies used the same outcome measures of measure balance, making it difficult to make direct comparisons using meta-analysis; thus a narrative review of the results was undertaken. The interpretation of results would be more meaningful if researchers could come to a consensus as to the most valid and reliable outcome measures to assess changes in balance

following an intervention. With these criticisms notwithstanding, the findings do show a trend for improved balance when an AFO is worn by people with DPN. Moreover they provide insight into the underlying mechanisms by which the device imposes its affect. The two primary mechanisms of action tested using the AFO are mechanical stiffening of the ankles and providing passive sensory cues to compensate for reductions in distal sensation. This review set out to evaluate the current evidence to support the effectiveness of each.

One study[320] used an AFO design which had potentially stabilising effects on balance by means of both mechanical stiffening of the ankle and provision of auxiliary sensory cues. The study did not measure the physical restrictions imposed on the ankle by the AFO, thus the degree of mechanical support provided by the device cannot be estimated. Future studies would benefit from providing an indication of joint stiffness with and without the intervention. This could have been achieved for example using a Biodex system (dynamometer). This measure would have given important information about the AFO's mechanical effect.

This review has provided some evidence that an AFO which crosses the ankle joint may have not only have mechanical effect, but also a sensory mechanism of effect[24,320]. The findings suggest that the greatest benefit to balance is achieved when an AFO designed to provide both sensory cues and mechanical stabilisation is worn[320].

Son et al (2010)[332] used an AFO designed to stabilise/restrict ankle motion primarily in the ML direction. They found that there were no significant differences (AFO versus No AFO condition) in proprioceptive thresholds when

the AFO was worn. Although they did not complete any direct measure of the AFO's mechanical properties or balance per se, they concluded that any improvements in balance reported in previous literature, must be due to mechanical properties of the AFO. By assessing solely proprioceptive thresholds. it is difficult to make this assumption. It could reflect issues with the validity and reliability of the test of proprioception used. This was not reported, although the use of imposed ankle rotations in standing to measure ankle proprioceptive threshold show excellent test-re-test reliability in healthy participants (Intra class correlation coefficient >0.79)[339]. Its responsiveness to change/ intervention and its reliability in people with DPN however has not been reported.

Rao et al's first study[320] reported using an AFO which provided minimal joint motion stabilisation. Testing balance using the sensory organisation test they found significant improvements in all conditions when an AFO was worn. Latencies were also reduced. This may have been due to either mechanical or sensory changes with AFO use, as no direct evidence was provided to support the reported minimal restrictions on joint motion by the AFO. Although the design features suggest that gross restrictions in joint range was indeed minimal. However the AFO could have increased ankle stiffness in midrange. Previous work has found that increased ankle stiffness in people with DPN is associated with changes in how sensation is used to balance as measured by the SOT [297]. Thus, small changes in midrange stiffness could have an effect on balance through alterations in the pattern of sensory use.

Interestingly their second study[24], using an AFO evidenced to eliminate mechanical restrictions, found that the AFO only improved the scores significantly in eyes closed conditions; SOT2 (fixed platform) and SOT5 (sway

referenced platform). This may indicate that with eyes open sway was less (providing less force) than that required for the AFO to provide auxiliary sensory cues. However with eyes closed sway magnitudes were greater thus increasing the sensory cues from the AFO. The interpretation, that more movement is associated with greater auxiliary sensory feedback has not been confirmed and requires direct testing.

The difference between the two studies suggests that this was due to mechanistic properties of the different AFO's used[24,320]. It could be argued however that the availability of somatosensory sensory cues would not change when standing on a sway referenced platform which aims to minimise ankle motion. Therefore, the improvement in SOT5 score when there is sway referencing at the ankle and the eyes are closed, could reflect greater use of the vestibular system to maintain balance, which has been evidenced when somatosensory information is reduced[203].

A further finding from this review has highlighted that AFO's that provided some mechanical restriction of the ankle joint reduced latencies of the response to platform translations significantly[320]. Latencies to postural perturbations are delayed in people with somatosensory loss reflecting the reduction in distal sensory signals that normally trigger automatic postural adjustments[57,75]. With an increased latency of response to a perturbation the body would have moved further and attained a greater speed of movement before corrective stabilising muscle contractions are generated. This would require greater stabilising forces that often the person cannot generate leading to a fall. Thus, a reduction in response latency is potentially beneficial. In contrast response latency was not improved with the AFO that was designed to provide only auxiliary cues[24]. This may indicate that mechanical restrictions improve latencies by, 1) restricting

ankle motion, forcing proximal joints to move, 2) an increased force applied by the AFO during motion, increasing sensory input.

Therefore it can be concluded that AFOs designed to restrict ROM whilst also providing more proximal sensory cues are more effective because they appear to have a accumulative effect by combining the mechanical and sensory effect, although the relative contribution of each is unknown. An AFO with dual effect is therefore recommended for further investigation.

It should be emphasised that results observed and conclusions made from each of the studies in this review are based on studies with small sample sizes. This is highlighted when the two studies by Rao et al were compared[24,320]. For example the SOT scores in No AFO conditions showed large differences, where one would expect similar results if sample sizes were sufficient and participant characteristics were similar.

The AFO principles of action or mechanisms offered here will inevitably alter the information arising from the whole somatosensory system through mechanical restriction of distal motion and therefore potential alterations in proximal motion, or through direct sensory stimulation[24,320]. In people with DPN there is a reduction in distal sensory information[6,285,340], and as previously highlighted this leads to an increase in the gain of the response of the remaining sensations; termed sensory re-weighting[33,203]. In both healthy people and following pathology (e.g. sensory loss) the relative weighting placed on visual, vestibular and somatosensory information constantly varies according to intrinsic and extrinsic factors[33]. Therefore, it would be reasonable to suggest that such adaptions occur when whole body somatosensory information is altered with an AFO[297], although there is currently no direct evidence to support this. This

adaptation may occur over time and therefore require periods of training / use before the effects are optimised. Therefore, the effects of single use of an AFO, as measured in the studies reviewed, may vary from the effects of longer term use. In people with MS, for example, the immediate effects of an in-shoe orthotic were destabilising but with repeated use balance improved with and importantly without the orthotic[54] suggesting that some training /adaptation had occurred over time. Therefore, future work should also include a longer term evaluation of orthotic use.

3.4.11. Conclusion

There is limited evidence to suggest that AFOs can modify balance in people with diabetes and neuropathy by pure mechanical reduction of foot/ankle range of motion or sensory provision. Based on current evidence, AFOs that provide mechanical support by spanning across the ankle joint, whilst providing proximal sensory input (skin contact) appear to provide the most effective improvement in balance in those with DPN and justify the need for further study.

There is a lack of quality research that distinguishes between the AFO mechanisms of action. Understanding the mechanisms underlying AFO use will to help inform its clinical use. An AFO could be provided solely for its orthotic effect and its ability to mechanically stabilise the ankle. In contrast if its mechanism is through sensory stimulation / alterations in the use of more proximal sensory pathways this may require a period a training to optimise these effects.

Future research should be specific in terms of what the device aims to achieve (i.e which balance variable), the mechanisms by which this will be achieved (i.e. mechanical versus sensory mechanisms) and how this will occur (i.e. the orthotic design). Sample size analysis should be included to indicate sufficient participant numbers and include a healthy control group for reliable comparisons of balance data and responses to balance perturbations to those with DPN. Subject characteristics should also be more clearly defined, and their correlations with objective measures of balance reported.

To understand the mechanisms of an AFO, the mechanical properties of the AFO should be investigated, by measuring alterations in ankle stiffness throughout the range and restrictions in joint motion. To explore the effects of an AFO on sensation the impact of the device on sensory processing in distant sites (e.g. visual, vestibular and proximal somatosensory) should be explored. This thesis will explore how proximal somatosensory information is affected by AFO use as well as other conditions such as stance width and sensory loss.

In terms of outcome measures, the use of laboratory based measures such as posturography are ideal, due to the ability to measure postural stability and identify changes in postural strategies which as highlighted earlier can be affected in DPN. The outcome measures used in this thesis to measure balance will be outlined in the next chapter.

Chapter 4 . Outcome measures of balance

4.1. Clinical measures of balance

The use of objective balance measurement tools is an accepted part of evidence-based practice and recommended in clinical guidelines and core standards of physiotherapy practice for neurological conditions[341]. However, there is currently no standard measure for clinical balance assessment of patients with neurological disease in podiatric care. Clinical balance measures such as the functional reach test[342], Berg balance[343] scale and timed up and go[344], have an established role in screening a person's global balance abilities and predict falls risk. They have also been used to evaluate the effectiveness of interventions[326,345]. However clinical measures of balance only provide an overall measure of balance ability, and do not provide information concerning individual sensory system contributions to balance, or the movement pattern by which the tasks under assessment are achieved[346].

4.2. Laboratory measures of balance

Over the last decade additional measures have become available with the use of 3-dimensional motion capture systems such as CODAmotion (CODAmotion, Leicestershire, UK) which records multi-segmental postural movements at a high level of accuracy and test-retest variability [347]. Although motion detection is not generally used in a clinical setting due to cost and the time taken to

complete measures, they are used in laboratory based investigations under controlled environmental conditions. Motion detection systems have been used by a number of previous authors to assess gait[348] and sway parameters, during static[23,77,327,349] and dynamic balance[350,351].

Dynamic parameters such as stride time, stride length, and walking velocity are related to postural instability in the diabetic population[352], however these parameters can be variable[352]. Measures during quiet stance is therefore indicated as the consistency of the tonic postural activity in the lower limbs by removing the phasic firing of the muscles involved in walking[351]. A larger effect of a sensory perturbation could therefore be expected in quiet stance essentially increasing the signal to noise ratio.

Outcome measures using such systems have been reported widely, sway velocity (mm/s), excursions (mm) of centre of pressure[54–56] (CoP) and motion at the level of C7 spinous process[50–53] are typical measures of sway variability, with greater sway velocities indicating less postural control[175,353]. Angles (degree) of segmental movement are also used as primary outcome measures when exploring postural control[33,142,354]. For example Sartor et al (2007)[20] and Sawacha et al (2009)[350] compared multi segmental movement at the trunk, hip, knee and ankle in people with diabetes, with and without neuropathy against healthy controls and found significant reductions in joint kinematics (angles) between groups using 3-dimensional motion analysis. Assessing segmental movements as an outcome measure is particularly advantageous when assessing postural modifications with disease / different task conditions, as it

provides an accurate measure of postural contributions to balance responses (e.g. following a perturbation)[142].

4.3. Balance perturbation

To explore the use and contribution of individual sensory systems, individual sensory perturbations of the vestibular, visual and somatosensory systems have been used to stimulate sensory inputs individually whilst measuring whole body responses[152]. This has been made possible with the use of galvanic vestibular stimulation (GVS)[51,128], moving visual stimuli (MVS)[355,356] and a number of physical somatosensory perturbations[36,349,357–359]. These somatosensory perturbations include the use of moving platforms to generate postural response mechanisms. Although useful in determining the efficiency of the system globally the somatosensory system is a combination of multisensory inputs. Therefore stimulating global somatosensation is somewhat limited in the assessment of individual sensory contributions to balance control.

Vibrating individual muscles/tendons provides a means of stimulating individual sensory modalities within the somatosensory system[360–363]. Muscle spindle primary endings are particularly sensitive to vibration, which creates an illusionary stretch of the muscle/tendon (perturbation)[364]. This results in a postural response that opposes the perceived stretch. For example, vibration of the calf muscles leads to a backward sway in response to the perceived lengthening of the muscle which is usually associated with forward sway[77,365–367]. Vibration of muscle/tendon in standing thus provides a standardised method of perturbing balance. By stimulating individual parts of the somatosensory

system and measuring whole body responses the contribution of proprioceptive information to balance and postural control during perturbation is therefore possible; measured in terms of response magnitude (distance and angle) and latency. The direction of sway response is unaffected by vibration frequency and amplitude, the magnitude of sway increases in approximate linearity with frequency range (40 to 100Hz)[148,368]. Vibration of the hip abductors (50-60Hz) leads to a lateral sway (≈3.5cm) with more motion occurring at the pelvis compared to more proximal segments[142]. Vibration (80Hz) of the dorsal neck muscles results in forward sway and CoP displacement (5.6 ±2.8 cm)[362]. The postural response observed can be directly attributed to the stimulation of these individual sensory modalities.

By stimulating particular sensory inputs (proprioceptive stimulation at the hips/ankles) to induce a perturbation of balance, the response differences between those with sensory deficits and healthy controls may be assessed. Using such selective sensory stimulation, differences in the sensory contributions to balance between groups can therefore be explored. Further by measuring postural responses over a number of experimental conditions; i.e. with/without intervention, the effect of intervention can be obtained using repeated measures study designs.

Chapter 5 .Study 1: Effect of ankle foot orthoses on balance and postural responses to balance perturbation in healthy adults

5.1 Background

Ankle-foot orthoses (AFO) are commonly prescribed for pathological conditions affecting joint stability, positioning, pressure distribution, and neuromuscular insufficiencies[369]. AFO's cross the ankle joint and act primarily to stabilise the ankle in the anterior-posterior (AP) or mediolateral direction (ML), depending on the direction of the support.

In healthy people AFO's are often used as a prophylactic measure to avoid ankle injuries or to stabilise the ankle joint after injury[369]. They are principally designed restrict ankle motion in the A/P or M/L direction[370] and are indicated to improve balance and postural stability by means of mechanical stabilisation and/or increasing sensory feedback[371–373]. The mechanisms whereby AFO's improve balance in people with sensory deficits were reviewed in chapter 3. In both healthy people and those with sensory loss an AFO mechanism of action is not fully understood.

Current literature indicates mainly positive effects of AFO on balance performance and proprioceptive enhancement in healthy people. Reductions in CoP deviations[371,372], sway magnitudes[374] time to stabilisation[373] and sway velocity[207] were indicative of the mechanical restrictions imposed by the AFO. In contrast one early study in 1994[375] found that postural control was reduced with AFO use. Here it was suggested that a postural shift from an ankle strategy to a

hip strategy may have occurred. A change in postural strategy has itself been previously described as an example of sensory re-weighting between somatosensory, visual or vestibular[30] information where a greater gain (importance) is placed on the proprioceptive information from more proximal body segments. This has been explored previously in healthy subjects by placing the feet at wider stance widths[23,219], commonly seen during gait in people with impaired balance[376]. With a wider stance width there is a reduction in the mediolateral angular motion about the ankles and feet[219–221]. This ankle motion is increasingly coupled with hip motion as stance width is increased[23,219], where motion at the ankle results in simultaneous motion at the hip, increasing hip proprioception in signalling lateral motion[23]. This coupling also results in increased overall stiffness of the pelvis and legs as the ankles and hips both contribute to the mechanical stiffness of the structure compared to the ankles alone at smaller stance widths[92].

The effect of restricting mediolateral ankle/foot motion with an AFO may therefore explain the postural shift earlier described by Bennell and Goldie (1994)[375], however this has not yet been tested. Understanding the effects of AFO's on balance and postural control in healthy people is of clinical importance considering their potential use in people with balance dysfunction.

It is possible to explore the contribution of proprioceptive information from the hip afferents to balance by assessing the postural response to vibration of the hip abductors. This vibratory stimulus of >80Hz stimulates muscle spindle afferents which is interpreted as the muscle lengthening[6,77,351,367,377] and results in a multi-segmented postural response. Vibration of the calf muscles, for example, leads to an initial backward sway in response to a perceived

lengthening of the muscle which is usually associated with forward sway[77,365–367]. Likewise vibration of the hip abductors leads to a lateral sway with more motion occurring at the hips/pelvis compared to more proximal segments[142]. Vibration of the hip abductors in standing thus provides a repeatable method of assessing the contribution of hip proprioceptive information to balance and postural control.

The vibratory stimulus is an artificial stimulus. It is delivered in addition to the natural afferent stimulation associated with balancing in standing. Therefore, if there is indeed increased proprioceptive afferent feedback from the hips with more afferents close to or above firing threshold when larger stance widths are adopted one may expect the vibratory stimulus would summate to produce a larger than normal afferent input. This in turn would result in a larger evoked postural response. With a large stance width however, other factors such as increased mechanical stiffening occur as discussed above, potentially reduce postural responses and improve overall stability[92]. With the addition of an AFO when normal ankle motion is restricted, it is hypothesised that this would further increase the reliance on, and activation of hip proprioceptive information. Therefore under these circumstances it is also hypothesised that the postural response to hip vibration would be greater with the AFO at wider stance width compared to the no AFO condition.

5.2 Aim

The primary aim of this study was to assess the effects of an ankle foot orthoses on balance, at different stance widths, in healthy adults.

Secondary aim was to assess the effects of an ankle foot orthosis, on postural control, at different stance widths, in healthy adults.

Objectives

- To explore the effect of an AFO on mediolateral postural sway (distance and velocity) at different three different stance widths (0cm 4cm and 16 cm) during a baseline period of quiet standing with eyes closed.

- To explore the effect of an AFO on the multi-segmental postural response to a mediolateral perturbation (hip) at three different stance widths (0cm 4cm and 16 cm).

5.3 Methods

5.3.1 Participants

Eighteen healthy participants (10 female, 8 male, aged 40 ±15yrs) volunteered to take part in the study after responding to email invitations (appendix 1) within the local University. Volunteers were included if they were over 18 years of age, able to stand unaided with eyes closed for 30 seconds, had no musculoskeletal injuries that affected their balance, and willing and able to give informed consent for participation in the study. Volunteers were excluded from the study if they were blind (or partially blind), they had self-reported musculoskeletal, neurological or vestibular complications such as stroke or labyrinthitis, which may have influenced balance or leg movement. Eligible participants gave informed written consent before taking part in the study. Ethical approval was granted by Plymouth University ethics committee (reference number: 12/13-116)

5.3.2 Sample size

Data taken from a study by Day and colleagues (1993)[23] showed that increasing the stance width from 0 to 4 cm resulted in a reduction of mediolateral sway velocity from 4.9 mm/s (+/- 2.5) to 3.4 mm/s (+/- 1), producing an effect size of 0.85. Due to the lack of available data investigating the effect of AFOs on mediolateral sway, an assumption was made that AFOs would produce a similar reduction in mediolateral sway velocity. Using this effect size it was estimated that a total of 15 participants (power =0.85, α=0.05) would be required to detect a similar reduction in mediolateral sway velocity in quiet standing with an AFO.

5.3.3 Experimental set-up

All participants were comfortably dressed wearing shorts, standardised socks and trainer footwear (Kappa, Italy). Purpose built vibration motor units (80mmm length, 22mm diameter, 118Hz ±6Hz, 14.3G, Precision Microdrives UK), were positioned over the left and right hip abductors; the gluteus medius muscles. These were palpated and the vibrator applied horizontally over the gluteus medius fibres at the midpoint between greater trochanter and superior point of the iliac crest. The vibrators were secured with hypoallergenic tape and an elasticated waist belt which applied approximately 31N of force perpendicular to the vibrator. Vibrators produced a repeatable 2 second (110Hz, 13.4G) vibration.

The onset of the vibration stimuli and collection of data were controlled remotely by Spike software and a 1401 analogue-digital converter (Cambridge Electronic

Design, UK) connected to a purpose built controller. Further information detailing the development and pilot testing of the vibrator motor units and control system can be found in appendix 2 and 3.

5.3.4 Intervention

The ankle foot orthoses were an Airform stirrup ankle brace (Ossur, USA) which have semi-circular shells lined with an air bladder that lie on either side of the malleoli and extend proximally over the lower leg (figure 5.1) secured in place with velcro straps that wrap around the ankle and lower leg. The AFO acts to minimise M/L movements of the foot and ankle, whilst allowing A/P movement.

Figure 5.1 Airform ankle foot orthoses (Ossur, USA).

5.3.5 Experimental procedure

Participants were asked to stand as still as possible with their arms in a crossed position, with eyes closed. After a two or three second baseline period,

(determined at random) a two second vibratory stimulus (Precision Microdrives, UK) was applied, by way of the vibrator motor unit, to an area overlying the hip abductor.

Participants were tested under two test conditions; 1. with the AFO and 2. without the AFO. Three trials were recorded for each test condition at three different stance widths. Three stance widths were adopted for each condition; 0cm, 4cm and 16cm. These were chosen based on previous work examining stance width and postural sway[23]. Each trial consisted of a total of twenty vibratory stimuli randomised equally between left and right sides. The test condition and stance width was presented to participants in a computer generated random order.

5.3.6 Data capture

Whole body motion

Whole body triplanar motion in quite stance during unperturbed and perturbed balance was captured using a 3-dimentional (3D) camera system (CODAMotion, Leicestershire, UK). The system consisted of 3 cameras placed on both sides and to the rear of the subject; aligned to a common co-ordinate frame (x, y and z axes). These cameras monitored the movement of individually addressed infra-red light emitting diodes which will be referred to as markers, placed over the body secured with double sided adhesive tape. Each marker was powered by a rechargeable battery pack capable of supplying 2 markers simultaneously. Markers were placed bilaterally (table 5.1) on a helmet securely attached to the head; shoulders (acromion process), and pelvis (figure 5.2) via a belt that

securely attached around the pelvis below the level of the anterior superior iliac spine.

Segment	Location
Head	Parietal bone via head piece
Shoulder	Acromion process
Pelvis	Below anterior superior iliac spine via bar secured to belt

Table 5.1 Location of motion detection markers.

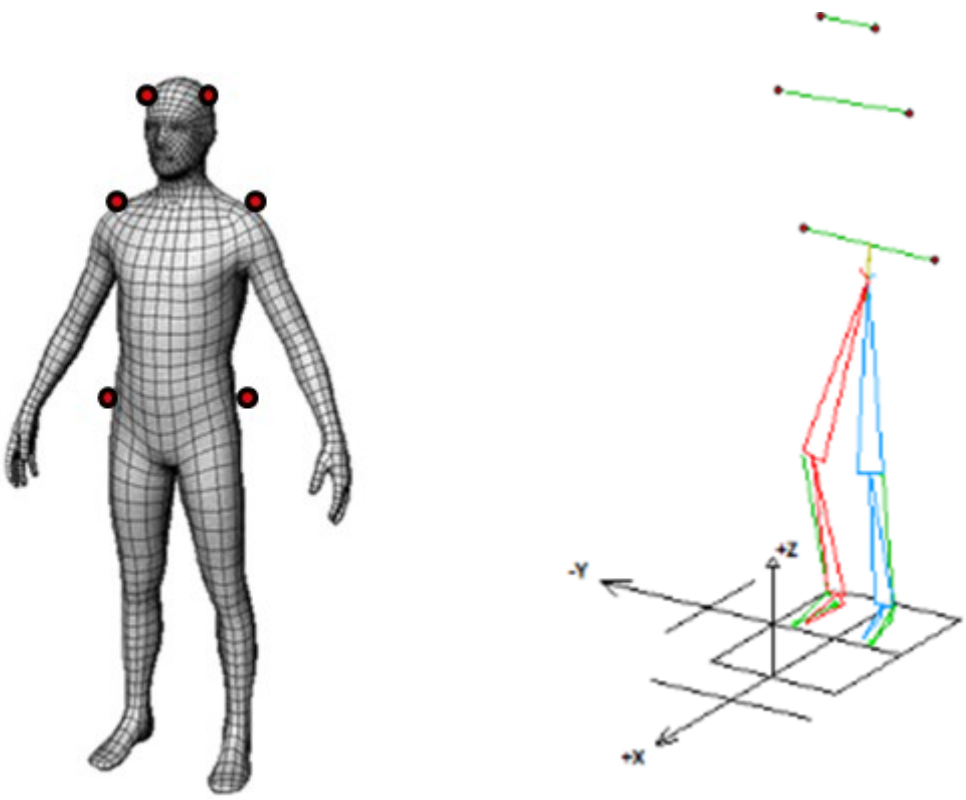


Figure 5.2 Graphical representations of Coda motion bilateral marker positions.

Integration of marker movement data by the CODA unit provided a precise 3D measurement of movement with a 0.002 degrees angular resolution and 0.05mm lateral resolution at the 3m recording distance[378]. A sampling rate of 200Hz (5ms inter-sample interval) was used. When markers were out of view for >10% of the data capture period, the measure was repeated to gain at least 90% of in view duration.

Motion was initialised and recorded after one second of quiet standing (eyes closed) had elapsed (figure 5.3), to allow for the stabilisation of postural sway. Postural responses to the vibratory balance perturbation were then recorded after a randomised one or two second period following initialisation of motion capture.

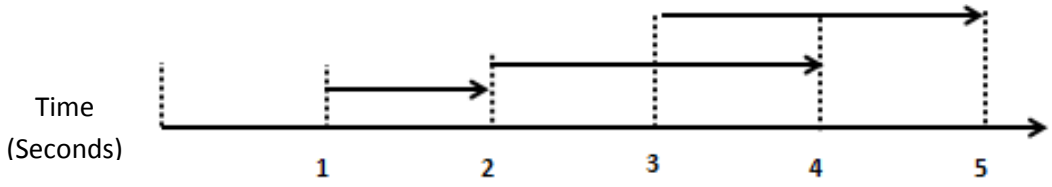


Figure 5.3. Time plot to show data capture periods during un-perturbed (1-2 seconds), and perturbed (2-4 seconds or 3 to 5 seconds) balance.

5.3.7 Data processing

MatLab (Mathworks, UK) programs written in-house by the author were used to process the raw data extracted from CODA text files. A program flow diagram is provided in figure 5.4, to give an overview of how the data was processed.

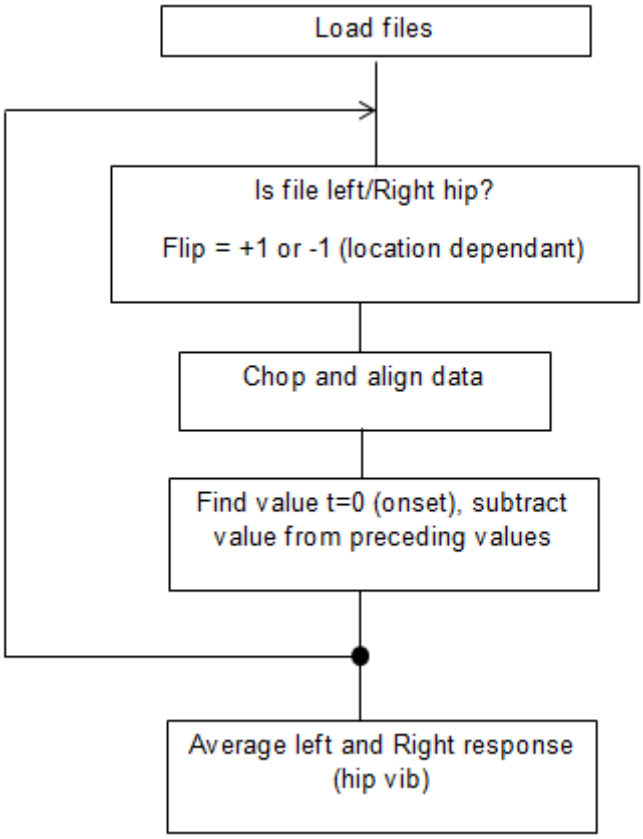


Figure 5.4 MatLab data processing flow diagram.

Movement was initially saved as subject specific CODA .mdf files (measurement data files) then converted to text files (.txt). These text files contained headed time-series data sampled at 200Hz for subsequent processing using MatLab (Mathworks, UK) programs written in-house. Each file contained movement data (X,Y,Z) from each marker at 5ms intervals (200Hz). Also included in these text files were signals from the control unit (1401 analogue-digital converter), used as an indicator for vibration location and onset of stimulation.

Files were sorted according to the condition, stance width and side of stimulus. Responses were aligned to stimulus onset and averaged. The responses to left

and right sided vibration were in opposite directions but did not significantly differ in absolute amplitude or latency. The responses to left and right vibration were subsequently averaged as performed previously[374], and displayed as if the stimulus was on the left side.

Sway velocity

Sway in the horizontal plane of a virtual marker situated midway between the acromion markers was calculated, from which sway velocity was determined. Sway velocity was selected as a suitable measure because it is sensitive enough to capture change before and after an intervention[379].

Motion data was filtered (Butterworth low-pass (20Hz, 1st order)) off line. Distance moved in the horizontal plane during each sampling period was calculated using Pythagoras' theorem:

Distance = $\sqrt{x^2 + y^2}$ (where x and y are the distances moved in the antero-posterior and mediolateral direction)

Segment Angles

Trigonometry was used to calculate frontal plane segmental movement in terms of angular deviations of the head, shoulders and pelvis.

Angles of pelvis, shoulder and head motion (in space) in the mediolateral plane were determined along with translation of the pelvis. Trunk movement was calculated by creating a virtual line between the mid points of shoulder and pelvis markers, to account for side to side translation of each segment. The

mean response 0.5 - 1s following stimulus onset relative to a 1s baseline pre-stimulus period were determined at all segments.

5.3.8 Statistical analyses

Data was normally distributed (Shapiro-Wilk test) and met all the assumptions for parametric testing. Results were analysed in SPSS (version 20) using a repeated measures ANOVA. Factors were “Stance width” (3 levels: 0, 4 and 16 cm) and “AFO” (2 levels: present / absent). Where main effects of the ANOVA were significant ($p<0.05$) post hoc ANOVAs were carried out as indicated.

A Greenhouse-Giesser correction for sphericity was made when required.

5.4 Results

5.4.1 Effect of stance width and AFO on baseline sway velocity

Mediolateral sway velocity was measured with and without AFOs at three stance widths in healthy adults whilst quiet standing (bare foot) with eyes closed (table 5.2, figure 5.5).

Stance width	**0 cm**	**4 cm**	**16 cm**
AFO [mm/s(SD)]	6.1(1.6)	5.7(1.5)	5.7(1.5)
No AFO [mm/s(SD)]	7.0(1.6)	6.4(1.5)	6.0(1.7)

Table 5.2. Sway velocity (mm/s) during baseline period. Mean (SD) indicated.

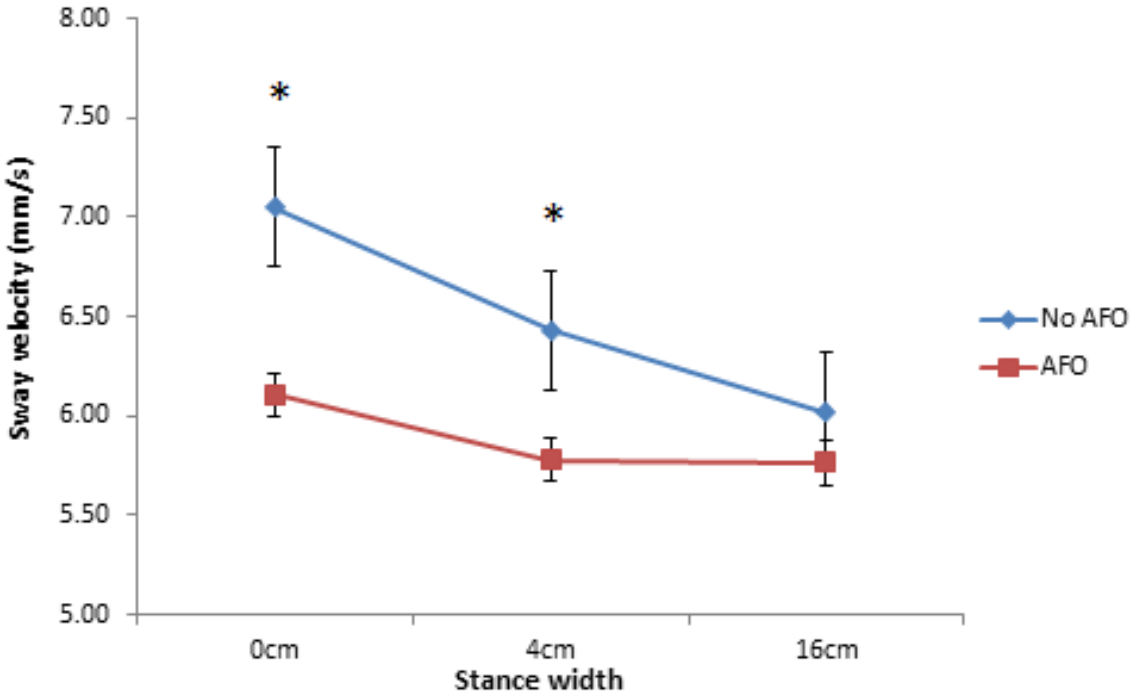


Figure 5.5. Line graph to show sway velocity with and without AFO in stance width conditions. * Indicates significant difference between AFO and NO AFO condition.

A repeated measure ANOVA was conducted to explore the impact of wearing an AFO and increasing stance width on horizontal sway velocity (table 5.3). The interaction effect between AFO and stance width was statistically significant F(2,34) = 3.5, P=0.04).

	Stance width (P)	AFO (P)	AFOxStance width (P)
Sway velocity	<0.001	0.004	0.04

Table 5.3. Results of repeated ANOVA, showing effects of stance width, AFO and the interaction of stance width and AFO on sway velocity.

5.4.2 Effect of AFO on sway velocity

Post hoc comparisons using ANOVA, showed that mean sway velocity significantly reduced when the AFO condition was compared with the no AFO condition and participants stood with a stance width of 0cm ($F(1,17) = 17.4$, $P= 0.01$) and 4cm ($F(1,17) = 5.1$, $P= 0.03$) respectively. There was a smaller reduction in the mediolateral sway velocity when the AFO was compared with the no AFO condition at a stance width of 16cm; this difference failed to reach a level of significance (figure 5.6).

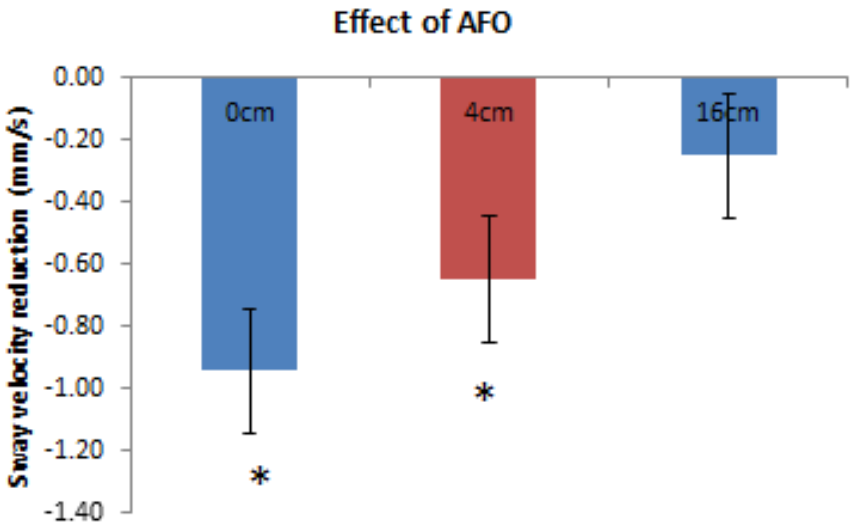


Figure 5.6. Graph to show the reductions in sway velocity with AFO, at stance widths of 0, 4 and 16cm. * Indicates significant effect of AFO. Error bars show standard error of mean.

5.4.3 Effect of stance width on sway velocity

Post hoc ANOVAs were performed on the difference in sway velocity as stance width increased under the No AFO conditions. This highlighted that without the AFO increasing stance width from 0cm to 4cm was associated with a significant reduction in sway velocity by 0.6mm/s ($F1, 17) = 7.2$, $P=0.01$) (figure 5.7); an effect size of 0.4. Increasing stance width from 4cm to 16cm (No AFO) also had a significant effect ($F1, 17) =5.8$, $P=0.03$) (figure 5.7) and reduced sway velocity

by 0.4mm/s, with an effect size of 0.2. There was no significant effect of stance width on sway velocity when the AFO was worn.

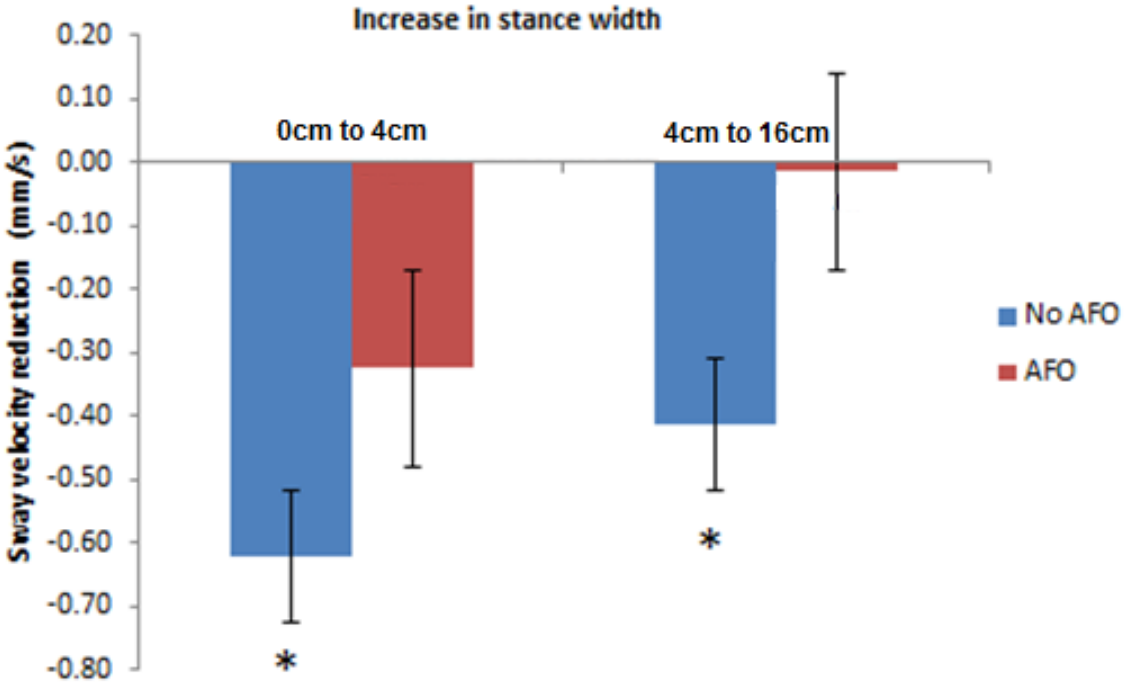


Figure 5.7. Graph to show reductions in sway velocity with a change in stance width (0cm to 4cm and 4cm to 16cm) in No AFO and AFO conditions. * Indicates significant effect of Stance width. Error bars show standard error of mean.

5.4.4 Effect of stance width and AFO on postural response to vibratory perturbation

In response to a unilateral vibration of the hip abductors with the feet 0 or 4cm apart participants translated their pelvis (>18mm) in the opposite direction to the stimulus at a latency of ~460ms (termed contralateral translation)(figure 5.8). There was an additional small tilt (angle) of the pelvis (>0.6°) at a latency of ~690ms such that the side opposite the stimulus tilted down (termed contralateral pelvic tilt)(figure 5.8). Movement of the pelvis was accompanied by a tilt of the shoulders and trunk towards the side of the stimulus; termed

ipsilateral trunk angle (figure 4-5). Grand average responses to hip vibration are seen in figures 5.9. The mean response magnitudes during 0.5 to 1 second of stimulus period is shown in table 5.4.

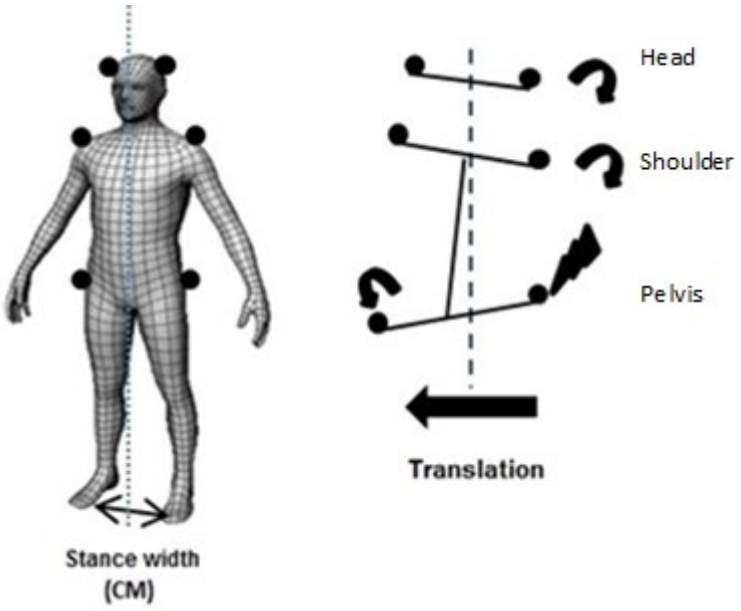


Figure 5.8. CODA motion marker locations and a graphical representation of the postural response direction to left hip vibration.

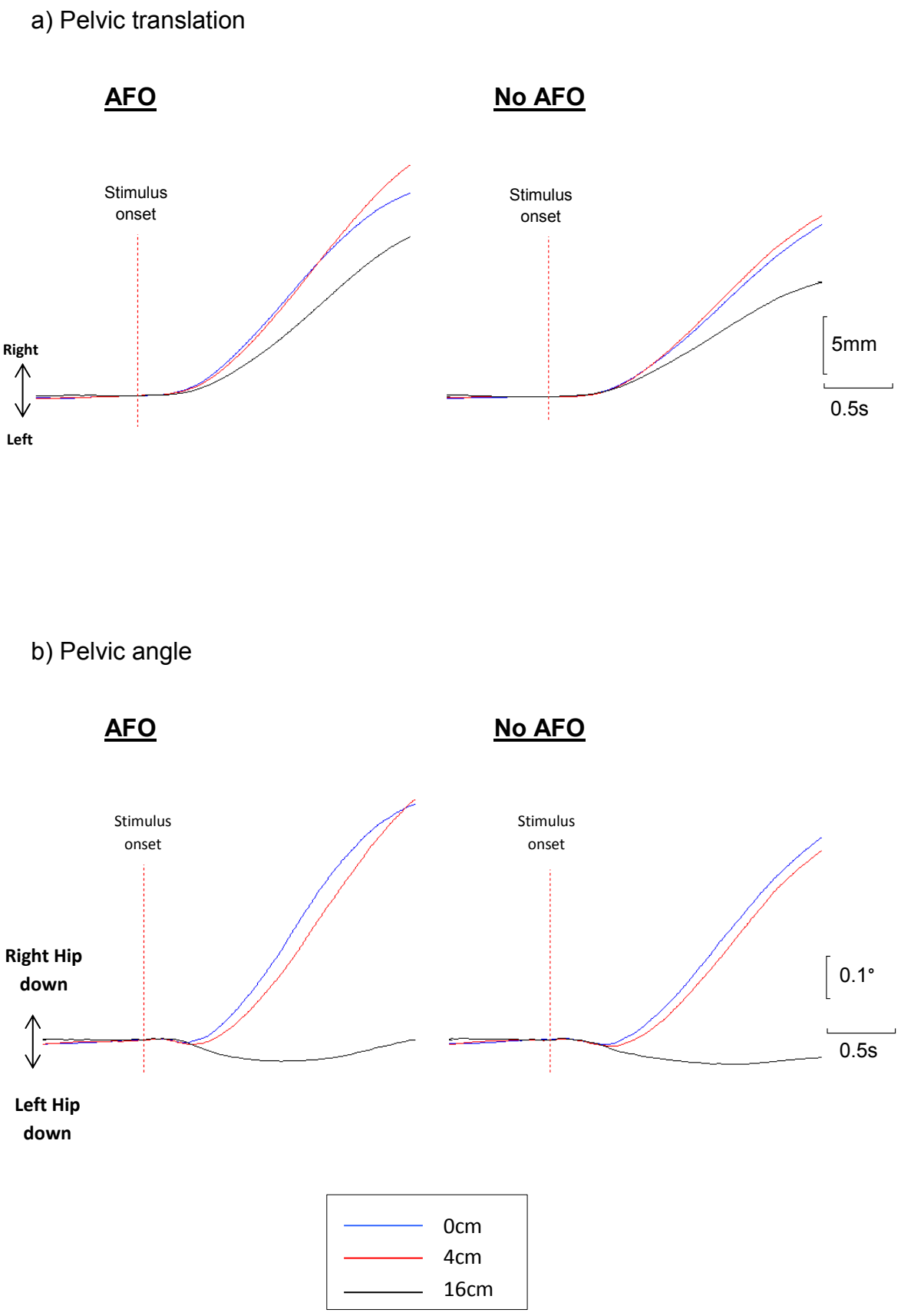
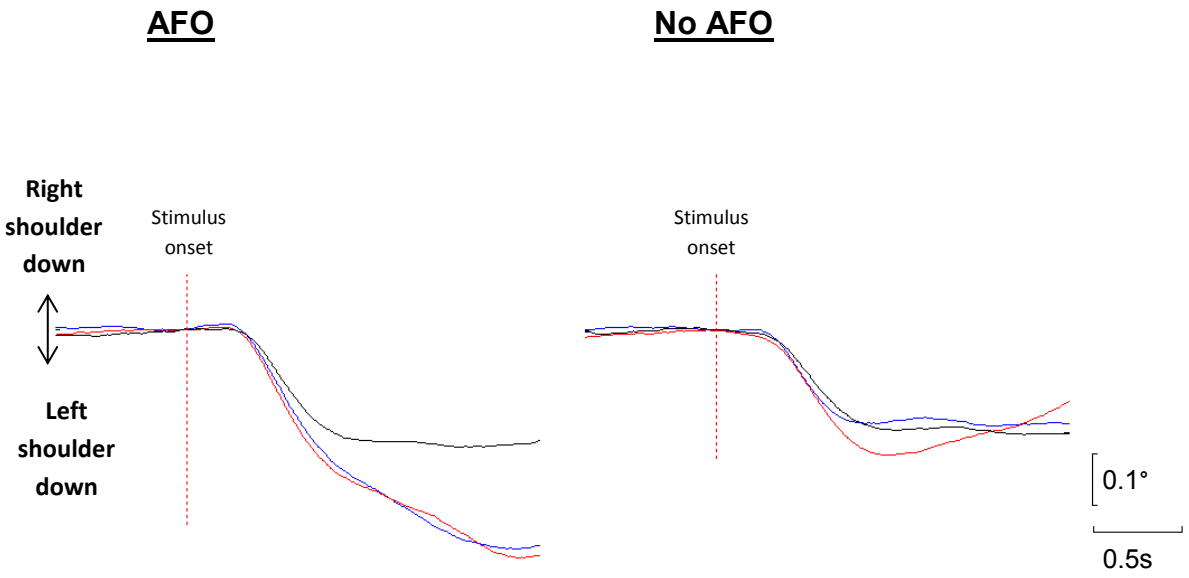


Figure 5.9. Grand average responses to hip abductor vibration; a)Pelvic translation b)Pelvic angle.

c) Shoulder angle



d) Trunk angle

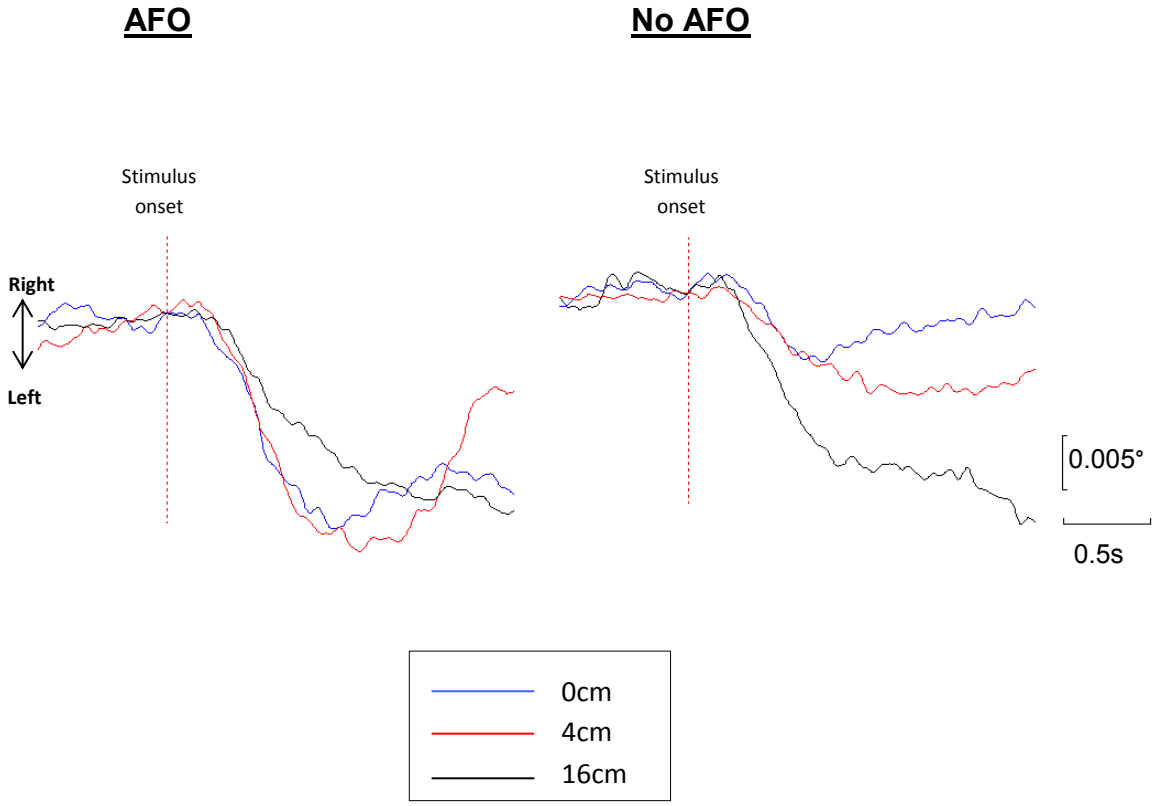


Figure 5.9 continued. Grand average responses to hip abductor vibration; c)Shoulder angle b)Trunk angle.

	Condition					
Segment	AFO 0cm	No AFO 0cm	AFO 4cm	No AFO 4cm	AFO 16cm	NO AFO 16cm
Pelvis translation (mm(SD))	-2.7 (1.3)	-4.1(2.1)	-2.8(2.0)	-3.7(2.5)	-2.1(1.8)	-2.5(2.3)
Pelvis angle (°(SD))	0.05(0.05)	0.10(0.07)	0.03(0.03)	0.06(0.03)	-0.04(0.04)	-0.04(0.07)
Shoulder angle (°(SD))	-0.16(0.17)	-0.22(0.26)	-0.20(0.17)	-0.23(0.23)	-0.16(0.11)	-0.17(0.15)
Trunk angle (°(SD))	-0.01(0.01)	-0.02(0.03)	-0.01(0.01)	-0.02(0.03)	-0.01(0.03)	-0.01(0.02)

Table 5.4. Mean response magnitudes during stimulation period (Translation: negative values = movement right, Angles: negative values = right side of segment up).

A comparison of the effect of the intervention (AFO and no AFO) at different stance widths (0cm, 4cm and 16cm) on measures of body segment motion (pelvic translation, pelvic angle, shoulder angle and trunk angle) in response to a hip perturbation (vibratory stimulus) was conducted on healthy adults standing with eyes closed. The results showed a statistically significant interaction effect between the AFO and stance width on pelvic and trunk motion (table 5.5). This finding indicates that the effect of wearing the AFO on body segment motion is dependent upon stance width.

Segment	Stance Width (P)	AFO (P)	Stance width x AFO (P)
Pelvic translation	<0.001	<0.001	0.025
Pelvic angle	<0.001	<0.001	0.042
Trunk angle	>0.05	>0.05	0.031
Shoulder angle	>0.05	>0.05	>0.05

Table 5.5. Table to show the effect of AFO, stance width and AFO x Stance width interactions.

There was a significant stance width x AFO interaction for pelvic translation and pelvic angle and trunk angle (translation: P<0.05; pelvic angle P<0.05 and trunk angle P<0.05). For both the pelvic translation and pelvic angle the reduction in response amplitude with an AFO was more marked at smaller stance widths (0cm>4cm>16 cm, figures 5.10 to 5.12).

Pelvic translation in response to hip vibration

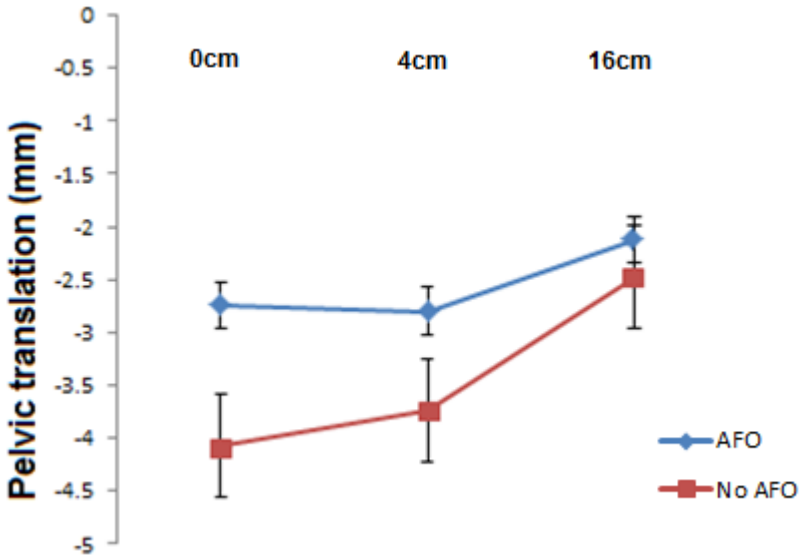


Figure 5.10. Line graph to show pelvic translation in response to hip vibration. Conditions of AFO and No AFO, in stance widths of 0cm, 4cm and 16cm are shown. Error bars indicate standard error of the mean.

Pelvic angle in response to hip vibration

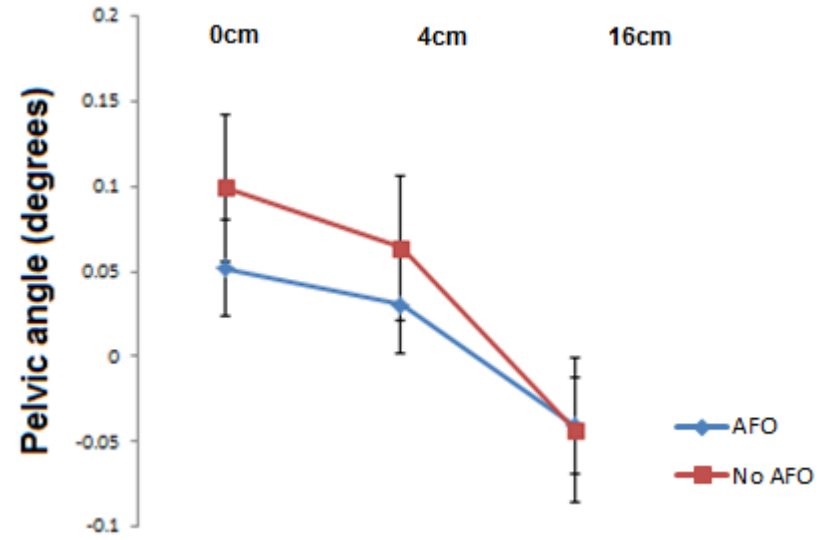


Figure 5.11. Line graph to show pelvic angle in response to hip vibration. Conditions of AFO and No AFO, in stance widths of 0cm, 4cm and 16cm are shown. Error bars indicate standard error of the mean.

Trunk response to hip vibration

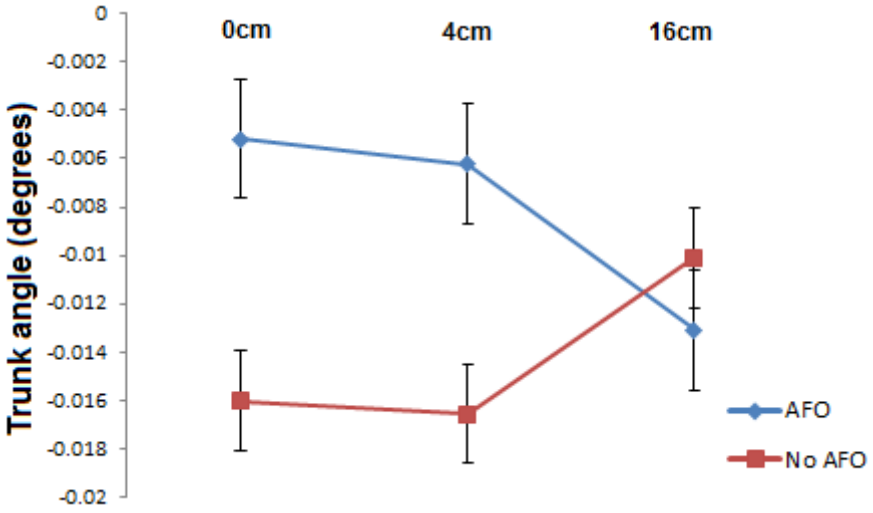


Figure 5.12. Line graph to show trunk angle in response to hip vibration. Conditions of AFO and No AFO, in stance widths of 0cm, 4cm and 16cm are shown. Error bars indicate standard error of the mean.

Post hoc ANOVAs showed that responses in pelvic translations (figure 5.13) were significantly less when in the AFO compared to the No AFO condition at a stance width of 0cm ($F(1,17)=12.6, P=0.002$) and 4cm ($F(1,17)=10.0, P=0.006$) with effect sizes (Cohen's d) of 1.05 and 0.46. Responses in pelvic angle (figure 5.14) were also significantly less in the AFO compared to the No AFO condition at stance widths of 0cm ($F(1,17)=6.2, P=0.02$) and 4cm ($F(1,17)=21.3, P<0.001$) with effect sizes of 1.04 and 1.07 respectively. However, when AFO and No AFO conditions were compared at a stance width of 16cm, there was little difference in the mean measures of body segment motion and a level of significance was not met.

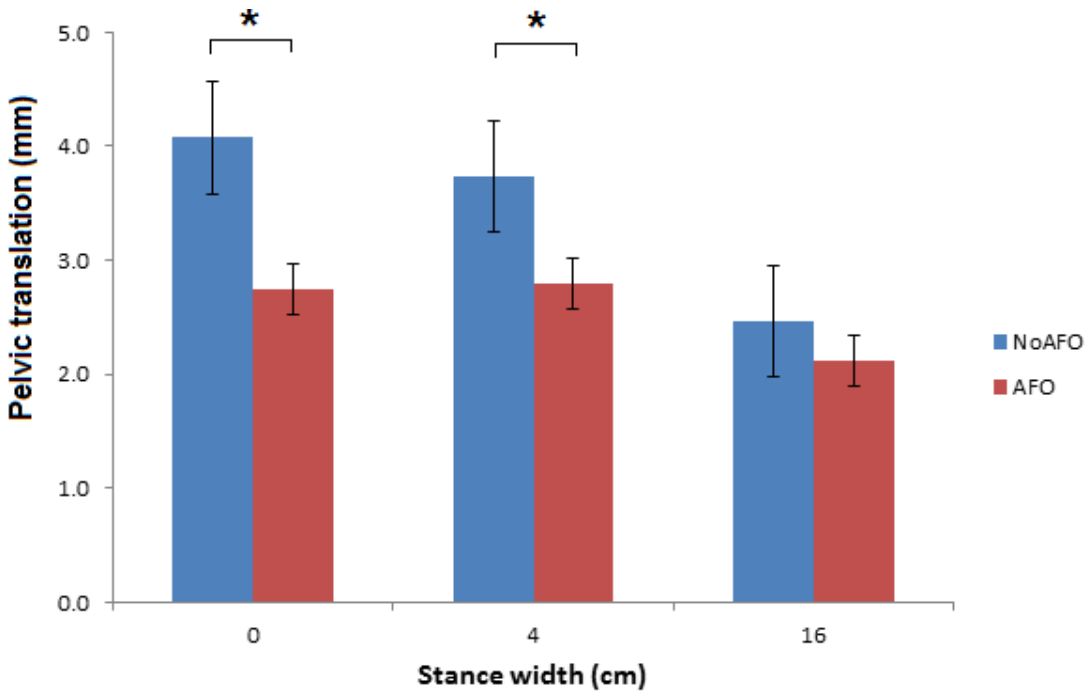


Figure 5.13. Bar chart to show mean Pelvic translation at stance widths of 0cm, 4cm and 16cm, in AFO and NO AFO conditions. *Indicates significant difference between No AFO and AFO conditions. Error bars indicate standard error of the mean.

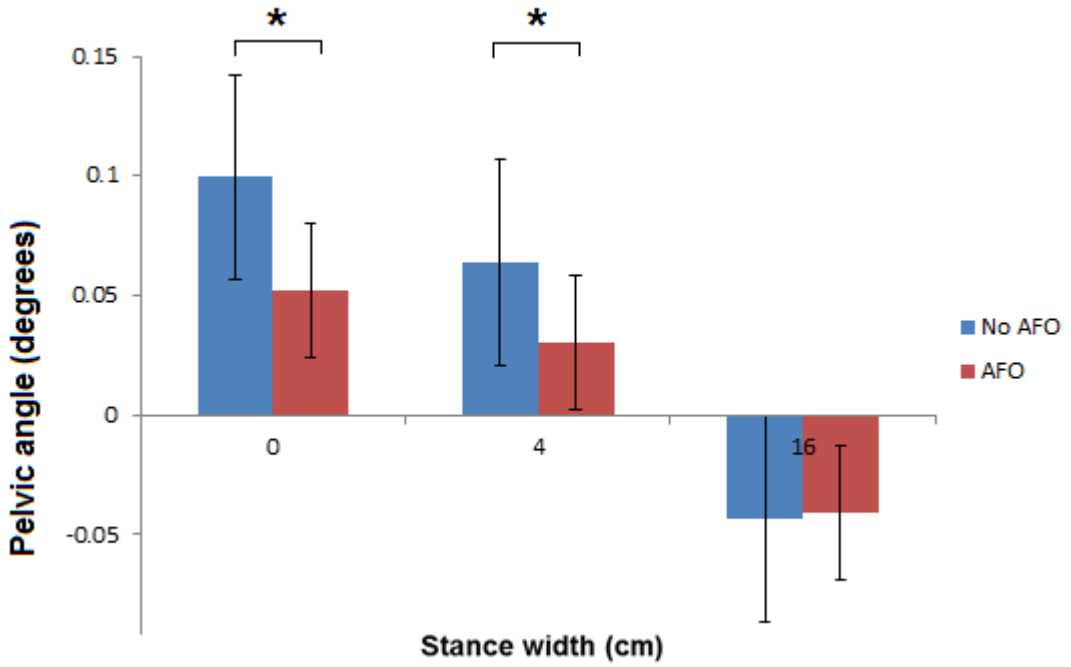


Figure 5.14. Bar chart to show mean Pelvic angle at stance widths of 0cm, 4cm and 16cm, in AFO and NO AFO conditions. *Indicates significant difference between No AFO and AFO conditions. Error bars indicate standard error of the mean.

Responses in pelvic angle were significantly less when stance width was increased from 0cm to 4cm compared in No AFO ($F(1,17)=6.2, P=0.023$) and AFO ($F(1,17)=4.1, P=0.05$) conditions with effect sizes of 0.53 and 0.47 respectively. When the stance width was 16cm the pelvic angle reversed in direction in both the AFO and No AFO conditions tilting to the side of the stimulus, an ipsilateral tilt (AFO_16cm and No AFO_16cm; figure 5.14). There was no significant effect of stance width on shoulder or trunk motion.

For the trunk angle the response amplitude reduced in AFO condition, when the stance width was 0cm or 4 cm. When wearing the AFO at 0cm and 4cm stance width responses were of similar amplitude. With an increase in stance width to 16cm, the trunk angle decreased in the No AFO condition whilst it increased in the AFO condition (figure 5.12 and 5.15).

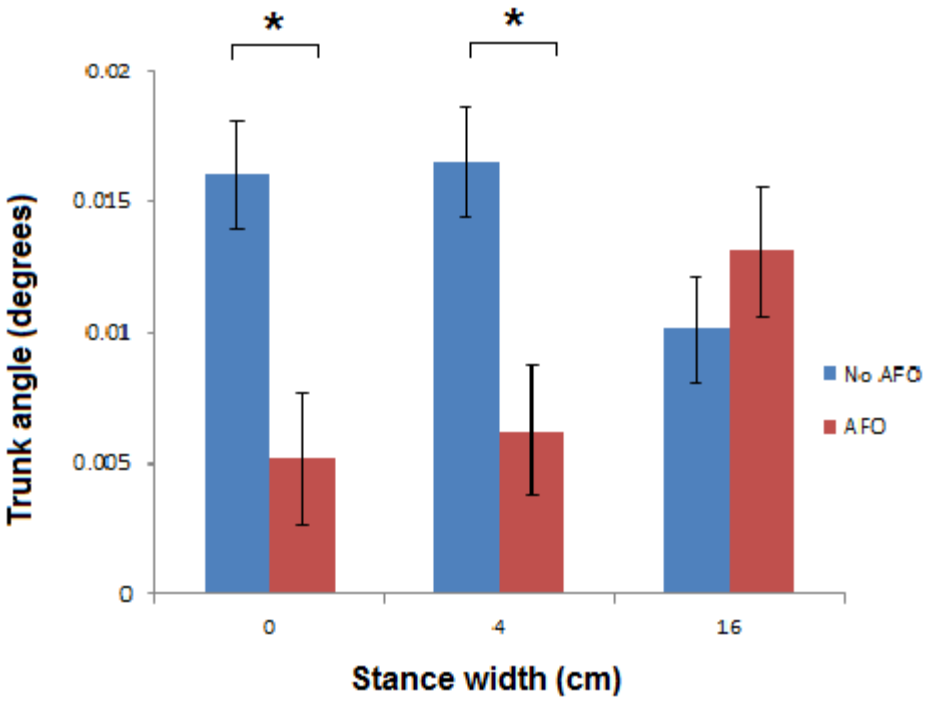


Figure 5.15. Bar chart to show mean trunk angle at stance widths of 0cm, 4cm and 16cm, in AFO and NO AFO conditions. Error bars indicate standard error of the mean. *Indicates significant difference between No AFO and AFO conditions. Error bars indicate standard error of the mean.

5.5 Discussion

Previous studies have found that AFOs reduce CoP deviations[371,372], sway magnitudes[374] and sway velocity[207] in AP and ML directions, depending on their design, although these effects have not previously been tested over a range of stance widths. This study has also shown that wearing an AFO decreases sway velocity significantly in healthy people, at stance widths of 0cm and 4cm but not at 16cm.

By limiting foot and ankle motion with the use of an AFO, sway velocity was reduced at all stance widths with significant reductions at 0cm and 4cm. The AFO may have provided solely mechanical stabilisation of the joint that in turn led to a reduction in sway[371,372]. Any mechanical stabilisation was not absolute as the postural responses during vibrations of the hips did not show a

mechanical blockade which would have otherwise been observed if this was the case i.e. the potential for motion was still present. One proviso is that the sway caused by the vibration was small and mechanical blocking effects could have been seen with larger postural responses. Alternatively, the AFO may have increased the visco-elastic resistance of the ankle thus reducing sway at narrower stance widths. Ramdharry et al (2012)[380], for example, has found that AFOs which limit anterior-posterior motion, increase the visco-elastic resistance to motion about the ankle. Similarly, it can be assumed to occur for AFOs limiting mediolateral motion. In future this could be tested by determining the ankle stiffness and viscosity following stereotyped perturbations of the ankle when the participant is at rest or standing.

The magnitude of sway velocity was greater at smaller stance widths regardless of whether an AFO was worn. At smaller stance widths postural movement predominantly occurred about the ankle [23,220]. This movement pattern is defined as an ankle strategy[381]. At the wider stance width of 16cm, the sway velocity during quiet standing with eyes closed was less. The reduction in sway velocity in quiet standing at increased stance width could be explained by; 1) an increased coupling between the ankle and hip, where movement at the ankle is now matched with simultaneous increased movement at the pelvis. This movement pattern is defined as the hip strategy[381,382]. A change in balance strategy may therefore lead to an increase in the contribution of hip proprioceptive information to postural stability in addition to that derived from the ankle[23,222]. 2) an increased stiffness of the overall lower limb structure as now 4 joints (bi-lateral ankle and hip) contribute to the overall lower limb stiffness.

When a vibratory stimulus is applied to the hip vibrators a multi-segmented postural response was observed. A vibratory stimulus at the frequency used activates muscle spindle afferents providing an afferent signal that is normally associated with a muscle being lengthened[142,366,377]. Vibrating the hip abductors in this study therefore led to a hip abduction. At stance widths of 0cm and 4cm (No AFO condition), the response to the stimulus suggests that the perceived stimulus is mainly due to a translation of the pelvis to the ipsilateral side stretching the hip abductors; this leads to a response in the opposite direction (a translation away from stimulus).

The response direction and magnitude seen in this study is similar to that previously reported by Popov et al 1999[142], where vibrating the hip abductors in healthy subjects, led to a pelvic translation of 3.4cm (SD= 0.7) sway from the stimulus. Accompanying the pelvic translation is a tilt of the trunk in the opposite direction, that is, towards the side of the stimulus. This is felt to be an essential component in producing a perceived hip adduction with the stimulus i.e. the combination of pelvic translation and trunk tilt together produce a larger perceived hip adduction compared to hip translation alone. Alternatively, the tilt of the trunk could be due to the vibratory stimulus activating muscle spindles in adjacent trunk muscles which produced side flexion of the trunk, in particular quadratus lumborum. However, the modulation of the trunk by the combined effect of stance width and AFO, as discussed below, would suggest that the trunk response is more likely linked to vibration of the hip abductors. A final possibility is that the trunk motion is part of an overall co-ordinated postural response that is elicited by hip vibration and acts to help maintain the centre of mass over the base of support.

An increase in the stance width resulted in a significant reduction in response size at the pelvis. This could reflect several not mutually exclusive factors: (1) An increase in stance width is associated with a lowering of the centre of mass, and increased stability limits i.e. the distance the Centre of mass needs to move before it is outside of the base of support leading to imbalance. These factors could give rise to a reduction in response size to the same hip vibratory stimulus due to a change in central set or feedforward control. (2) An increase in the mechanical stability of the leg and pelvic structure occurs with increasing stance width. As highlighted by Day et al (1993)[23] at smaller stance widths (<8cm) mediolateral sway mainly occurs around the ankles whilst with greater stance widths ankle and hip movements become coupled resulting in 4 (bilateral hips and ankles) rather than 2 (bilateral ankles) joints contributing to stiffness in the mediolateral plane. Thus, the reduced response size with greater stance width could reflect increased stiffness and stability of the pelvis-leg structure. (3) With the addition of hip motion coupled to ankle motion at larger stance widths hip proprioceptive feedback may increase and supplement that arising from the ankle.

A significant reduction in pelvic response size was also seen when wearing the AFO. As discussed the AFO is felt to increase the visco-elastic stiffness of the ankle in the mediolateral direction. A significant effect of AFO is in keeping with the fact that mediolateral sway always involves some movement about the ankle.

The stance width x AFO interaction revealed that the largest reduction in response amplitude occurred at smaller stance widths. At larger stance widths the hips also contribute to the overall mediolateral stability[23] and thus minimize

the stabilising effects of the AFO. Clinically this suggests that the stabilising effect of an AFO may be increasingly limited as stance width is increased, for example in those with diabetic peripheral neuropathy who adopt wider step widths during gait[383].

For the trunk there was a significant stance width x AFO interaction. Increasing stance width from 4cm to 16cm whilst wearing an AFO resulted in an increased trunk angle, whilst in the No AFO condition the reverse was seen. The reduction in response size for the larger stance width with NO-AFO could be due to the factors described above for the effect of stance width on pelvic movement; that is a change in feedforward control[384] with a lowering of the COM and a widening of the BOS and/or a change in mechanical stability. The fact that potential trunk motion should not be affected directly by changes in ankle-hip coupling suggests that response size changes may be mainly due to changes in feedforward control.

The increase in trunk response when wearing the AFO (as appose to reduction without AFO) at a 16 cm stance width could be caused by several possibilities. One possibility is, as hypothesised by Day et al (1993)[23], that with larger stance widths there is an increased involvement of hip proprioceptive activity in postural stabilisation. Stimulation of these now more active and closer to threshold sensory pathways by an artificial vibratory stimulus could result in a larger afferent perturbation and thus a larger response. However, the trunk was the only segment to increase its motion whilst pelvic motion, for example, reduced its motion. One would have expected a larger overall response affecting several segments which was not observed. Therefore other explanations for the change in trunk strategy may be sought.

The increase in the trunk postural response when wearing the AFO at 16 cm stance width could be indirectly caused by the mechanical support offered by the AFO. With a larger stance width the ankles are closer to their end range and will be stiffer and the addition of the AFO will stiffen the ankles further. As the postural response seen to hip vibration normally involves combined ankle and hip/pelvic motion a mechanical block to ankle-pelvic motion may result in the vibration-evoked postural response being larger in the trunk to achieve a centrally-driven change in posture. If this were the case one may expect a reduction in pelvic motion as the postural response evolves accompanied by an increase in the trunk response. However, the grand average responses do not support this. The rate of pelvic translation is reduced when standing with the feet 16cm apart from the time the onset of the response (~500ms post stimulus onset), rather than being reduced later on in the response as may occur if a mechanical block were reached.

Another possibility is that the vibratory-evoked postural response in the trunk is normally terminated when there are sufficient sensory inputs from other sources informing the CNS that the illusory lengthening of the hip abductors and the perceived postural effects are not occurring. In the 16cm-AFO condition these competing sensory signals (e.g. from the ankles) may not be evoked as early as normal due to their restriction in motion leading to a prolonged trunk response. An assessment of the grand average trunk responses does suggest that when wearing the AFO and having a stance width of 16cm the response continues whilst it appears to stop in the other conditions.

The increase in trunk response size when wearing the AFO could also reflect the impact of the AFO on ankle-hip coupling and how the CNS interprets the

afferent input from hip vibration. The response to the stimulus seen at 0cm and 4cm involves a combined ipsilateral trunk tilt and contralateral pelvic translation. As discussed above this requires a combined movement of the ankle and hip.

The AFO impedes the rate and amplitude of ankle motion and this is more marked at larger stance widths with changes of whole body postural responses with an AFO at 16 cm. In figures 5.16A and 5.16B the illusory and actual responses to hip vibration respectively are shown when the stance width is <16 cm and not wearing an AFO. Here hip vibration leads to an illusory ipsilateral pelvic translation and minimal ipsilateral pelvic tilt. In figures 5.16C and 5.16D the illusory and actual responses to hip vibration respectively are shown when the stance width is 16 cm and wearing an AFO. Here pelvic translation is restricted by the AFO and hip vibration is felt to lead to an illusory contralateral pelvic tilt that is associated with a larger ipsilateral trunk tilt (angle x vs angle y – figures 5.16B and D). The larger trunk response may therefore reflect a change in how hip vibratory stimuli are interpreted in light of reduced ankle motion when the hips and ankles should normally be coupled.

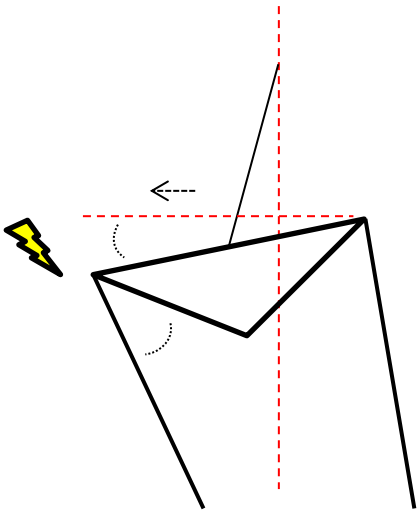


Figure 5.16A. Illusory effect with stance width <16 cm and no AFO - Hip adduction with ipsilateral translation and tilt of pelvis, and contralateral tilt of trunk.

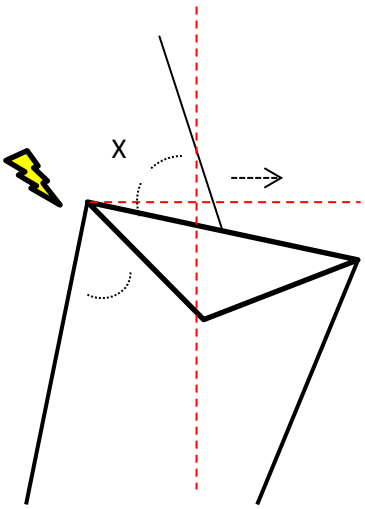


Figure 5.16B. Response with stance width <16 cm and no AFO - Hip abduction with contralateral translation and tilt of pelvis, and ipsilateral tilt of trunk.

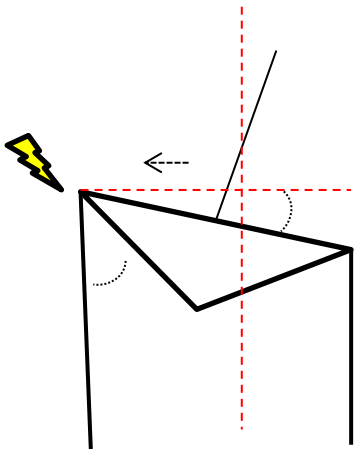


Figure 5.16C. Illusory effect with stance width 16cm and an AFO - Hip adduction with ipsilateral translation and contralateral tilt of pelvis, and contralateral tilt of trunk.

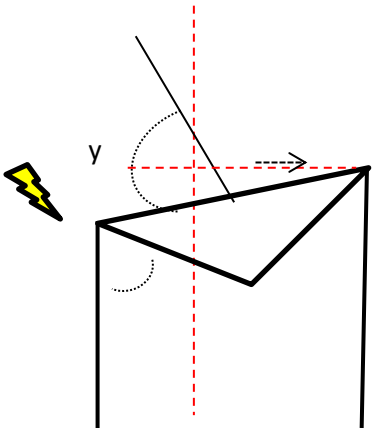


Figure 5.16D. Response with stance width 16cm and an AFO - Hip abduction with contralateral translation and ipsilateral tilt of the pelvis, and ipsilateral tilt of trunk.

Previous work has shown that an illusion can occur with muscle vibration. The pinnochio illusion[385] occurs when vibration of the elbow extensors is given while the person is touches their nose. Here people can erroneously perceive that the nose is lengthening. This is because the illusionary lengthening of the elbow extensors induced by the vibration dominates despite the nose being fixed in length. Thus, in the current study restricted ankle movement associated with unrestricted pelvic movement may cause a perceptual illusion to hip vibration that the pelvis has tilted rather than the pelvis translating. The finding that the response latency is long (~460ms) provides ample time for perceptual processes to interact with the central pathways mediating the postural response.

5.6 Conclusion

This study has provided exploratory findings about the effects of ankle foot orthoses and stance width on mediolateral control of balance in healthy subjects. Changes in stance width and the addition of ankle foot orthoses resulted in reductions in the size of hip vibration-evoked postural responses. Interactions between stance width and AFO use may be explained by alterations in the coupling between the ankles and hips at different stance widths that are affected by the differential contribution of the ankle and hip joints to the stability of the pelvic-leg segment and / or changes in how the CNS interprets the vibration-induced vibratory information. Practically this study suggests that the most benefit of AFOs in stabilising mediolateral sway occurs at smaller stance widths when the relative contribution of the ankle to stability is greatest. At larger stance widths overall stability is less but trunk motion may increase. This

could affect the usefulness of more proximal sensory information (e.g. vestibular information) in stabilising the body. From a clinical perspective restricting mediolateral motion about the ankle may therefore be beneficial particularly in people with balance dysfunction as a result of distal sensory loss. However, it may lead to an increase in more proximal movement when larger stance widths are adopted. Study 3 (chapter 7) tested this theory in people with diabetic peripheral neuropathy.

Important methodological findings were also obtained from this study. For example the magnitudes of postural response to stimulations provided by the in-house purpose built vibrators were large enough to show a significant effect of intervention (see also appendix 2). Further the study provided additional data for the study 3 (chapter 7) sample size calculation.

From this data it can also be concluded that the number of stimulations per location could be reduced without affecting the response size. This proved advantageous for study 3 because concerns were raised by a steering group (appendix 5) about the time participants were required to stand for data collection.

5.7 Limitations

A number of limitations should be highlighted and indicate where future studies could be improved. This study compared the effects of AFO at three stance widths (0cm, 4cm and 16cm), chosen based on previous findings[23] where the greatest effect of stance width on balance was seen. In hindsight the additional stance width of 8cm would have been advantageous in obtaining a complete

series of measures as stance width increased. However this would have meant a further twenty stimulation repeats and an increase in the occurrence of fatigue within the response trials.

Sway velocity was measured during a pre stimulus period of one second. Although the velocity measured in this study was comparable to previous investigations of healthy subjects[23,50,56] with >30second data capture periods, a longer baseline sway period may have strengthened the internal validity of the study.

Balance perturbations were achieved via a vibratory stimulus to the hip abductors. Further stimulus sites could have been included, for example at the hip adductors to enable a greater understanding of the ML responses to hip perturbations. Stimulation of the muscles that control AP motion could have also been included. The use of galvanic vestibular stimulation (GVS) and moving visual stimuli would have provided further insight to the use of other sensory systems, but again these additional sensory stimulations would have increased the number of stimulations required and increased the likelihood of fatigue.

The responses to vibratory stimuli seen in this study were small but larger than those found in pilot work using vibrator units with smaller amplitude. The response size therefore reflects the amplitude of the perturbation (vibration) being received. To gain greater responses, vibrations with even larger amplitudes could have been used; however this may have then led to vibrations being transmitted to adjacent muscles.

Chapter 6 .Study 2: Effect of experimentally reduced sensation on postural response to hip abductor/ankle evertor muscle vibration

6.1. Background

Successful Integration of vestibular, visual and somatosensory information is essential for the production of appropriate motor responses to maintain upright stance. When one or more of these senses have reduced efficacy, balance can be affected. Although all three sensory modalities play an important role in providing sensory feedback, the somatosensory system has been reported to carry the highest weighting of the integrated motor outputs[102,386].

Somatosensory information includes the sense of touch and pressure from the skin mechanoreceptors (tactile) and information on musculo-tendinous length changes and tension from muscle spindles and Golgi tendon organs (proprioception). Following a postural perturbation this information is relayed to the central nervous system where it is integrated with other sensory information eliciting a postural response appropriate to the direction, size and predictability of the perturbation.

Loss or reduced efficiency of somatosensory information is an important risk factor for increased falls[6,12,386]. When either tactile or proprioceptive information is reduced, as seen in a peripheral neuropathy, people show greater postural sway amplitudes[160], resulting in increased centre of pressure (CoP)

excursions[6,387–389]. To compensate for this, re-weighting of unaffected sensory modalities can occur[30,203]. Reduced somatosensory efficiency, for example, can result in an increased gain of the postural response to galvanic vestibular stimulation (GVS)[203]. Similarly an increased use of more proximal proprioceptive information may also occur following distal sensory loss[30].

In people with distal sensory loss, balance may depend on the ability to effectively re-weight remaining sensory information. In the sagittal plane, for example, people with distal sensory loss change from an ankle strategy, where sway is predominately around the ankle joints, to a hip strategy that involves combined ankle and hip motion[21,354]. Proprioceptive feedback around the hip is therefore increased as a result of movement around the joint. A similar increase in motion and feedback from around the hip and trunk may also exist in the mediolateral plane following distal sensory loss. However, to our knowledge this hypothesis has yet to be tested[282].

It is possible to explore the effects of acute distal sensory loss on balance by cooling the foot and ankle and measuring the change in postural stability. Previous studies have immersed the feet in iced water[391,392] (an established method for reducing plantar foot temperature/sensation), wrapped the foot/ankle in plastic tubing filled with cooled water[83], used anaesthesia[87] or applied an ischaemic block[83].

As highlighted in chapter 5, postural stability is improved with an increase in stance width. At narrower stance widths balance in the mediolateral plane is maintained by mainly ankle motion[23]. As highlighted in study 1 (Chapter 5), the stiffness of the overall structure is less with a stance width of 4 cm compared to that at 16cm. Therefore with a narrow stance width (4cm) the postural response

to stimulation of the ankle/hip would be less influenced by this structural stiffening and may therefore show a greater effect of cooling.

6.2. Aim

The primary aim of this study was to explore the effects of experimentally reducing distal sensory feedback from the foot in healthy people, on the postural responses to balance perturbation in the ML plane. The secondary aim was to determine that any change that occurred in postural response were due to the reduction in sensation loss rather than strength.

Objectives

- To compare the effect of distal sensory loss on mediolaterial postural responses to distal (ankle) and proximal (hip) sensory stimulation.
- To measure strength and sensation using clinical measures pre and post cooling of the foot.

6.3. Methods

6.3.1. Participants

Sixteen healthy participants (7 female, 9male, aged 40 ±17yrs), volunteered to take part in the study after responding to poster advertisements placed within

the university. Volunteers were excluded from the study if they self-reported musculoskeletal, neurological, visual or vestibular complications which may have influenced balance or leg movement. People with circulatory problems (e.g. Raynaud's disease) that could have been exacerbated by cooling were excluded. Eligible participants gave informed written consent before taking part in the study. Ethical approval was granted by Plymouth University ethics committee (*12/13-158*).

6.3.2. Sample size

Due to the limited number of similar studies, the sample size estimate was based on mediolateral sway using values sourced from Billot et al (2013)[140]. They previously found that decreasing plantar foot sensation, resulted in increased mediolateral sway from 1.29cm (±0.54cm) to 1.80cm (±1.44cm), producing an effect size of 0.94. A sample size of 12 participants gave 85% power at p=0.05.

6.3.3. Experimental set-up

All participants were comfortably dressed wearing shorts. Purpose built vibration motors (80mmm length, 22mm diameter, 118Hz ±6Hz, 14.3G) were positioned and secured with hypoallergenic tape over the left and right gluteus medius and peroneus longus muscles. Motion markers (CodaMotion, Leicestershire, UK) were placed bilaterally on a helmet securely attached to the head; shoulders (acromion process), pelvis via a belt that securely attached

around the pelvis below the level of the anterior superior iliac spine, thigh, shank, ankle and foot (figure 6.1). Movement of the markers following stimulation was measured using a 3D motion analysis system (CodaMotion, Leicestershire, UK) as described in chapter 5.

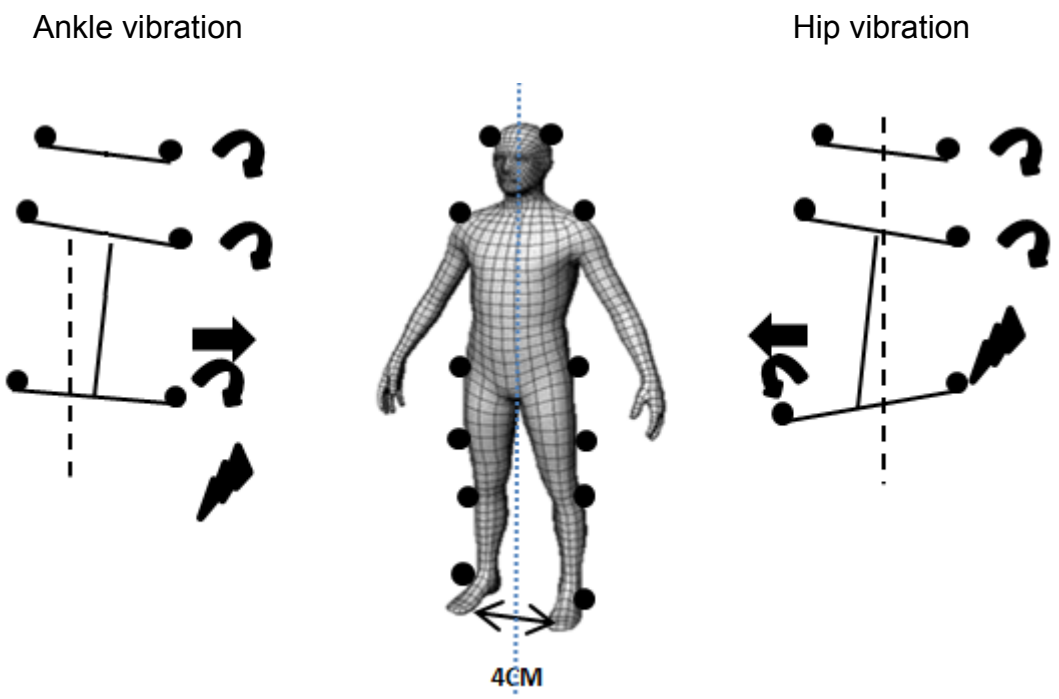


Figure 6.1 Frontal view of CODA motion marker locations and typical postural response to hip and ankle vibration; pre cooling.

6.3.4. Experimental procedure

Each foot was placed in a water cooled boot (PMT, USA) for 30 minutes (figure 6.2a). The boot reached up to 10-13 cm above the tip of the medial malleolus. Temperature of the water was maintained at 5°C using a water bath (Grant Instruments, UK) (figure 6.2b). Skin temperature was monitored throughout the cooling period via a temperature probe (Physitemp, USA) secured to the plantar

surface of the foot under the 2nd metatarsal phalangeal joint. Tests of sensation, strength and postural control were performed before and immediately after cooling.

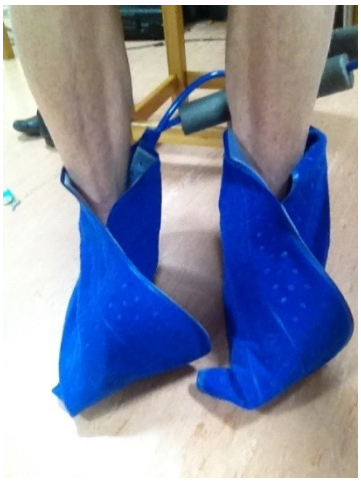


Figure 6.2a. Water cooled boots

Figure 6.2b. Water cooling system

Measures of sensation and strength: Tactile sensation was measured by assessing the ability to detect a 10g monofilament (Owen Mumford, UK)[393,394] used clinically to identify reduced cutaneous sensory perception in diabetic foot screening (NG19)[395]. Sensation perception was tested at 5 sites on the plantar aspect of foot; 1st and 3rd apices of the toes, overlying the 1st, 3rd and 5th metatarsalphalangeal joints[396].

Vibratory perception thresholds (VPTs) were also assessed to quantify the severity and extent of sensory loss[397],[398]. VPTs were tested (average of 3 repeats) using a neurothesiometer (Horwell, UK)[396], at the apex of the hallux, and medial malleolus. The device was rested on the tester's finger which acted

as a fulcrum, so that no additional pressure was applied to the head of the device[399], other than the weight of the device itself. The foot-ankle was rested on a chair and the neurothesiometer placed perpendicular to the medial malleolus.

Maximum isometric ankle evertor strength (Peroneus Longus) was measured using a strain gauge (Applied Weighing, UK). The effects on strength and sensation were clinically monitored to determine that significant changes only occurred in sensation rather than strength. Participants were asked to sit with the right leg extended, with the heel in contact with the floor. The foot was in a relaxed position. Subjects were then asked to apply their maximum eversion force to a padded strain gauge placed over the styloid process of the foot. The investigator resisted the movement whilst stabilising the heel with the opposite hand.

The output voltage of the strain gauge was A-D converted (Power 1401, CED, UK), to enable real-time data capture via Spike2 control software at 100Hz. Three tests were completed, after a 10 second rest period between efforts, recorded and later averaged for data analysis.

Measures of the sensory control of posture: Participants stood in bare feet with their eyes closed. The medial borders of their feet were positioned 4cm apart.

After a 1-2s random baseline period a 2s, 118Hz (±6Hz) 13.4G vibratory stimulus (Precision Microdrives, UK) was applied over the left or right hip abductors or ankle evertors.

The hip abductors were palpated and the vibrator motor unit applied horizontally over the gluteus medius fibres at the midpoint between greater trochanter and superior point of the iliac crest. The peronei were palpated and the vibrator motor unit attached in parallel with the peroneus longus muscle with the top of the motor vibrator unit vibrator placed 5cm distal to fibula head. The vibrator motor units were secured with hypoallergenic tape and an elasticated belt which applied approximately 31N of force perpendicular to the vibrator.

Vibration onset was controlled remotely by Spike software and a Power 1401 AD converter (Cambridge Electronic Design, UK), switched via an in-house, purpose built switching circuit. Ten stimuli per site and side were given with the order of presentation being randomised.

Motion analysis and was sampled at 200Hz and recorded for off-line processing using MatLab programs written in-house.

6.3.5. Data reduction

Files were sorted according to the condition and site of stimulus as described in chapter 5. All data was passed through a low-pass (20Hz) Butterworth filter, aligned to stimulus onset and averaged. The responses to left and right sided vibration were in opposite directions but did not significantly differ in absolute amplitude or latency; therefore the responses to left and right vibration were subsequently averaged and displayed as if the stimulus was on the left side for both hip abductor and ankle evertor vibration responses. Angles of ankle, pelvis, shoulder and head motion were determined along with translation of the pelvis in the mediolateral direction. Movement of the knee in the sagittal plane was

also assessed. The mean response 1.5- 2s following stimulus onset relative to a 1s baseline pre-stimulus period was determined at all segments.

6.3.6. Statistical analysis

Data was normally distributed (Shapiro-Wilks test) and met the other assumptions for parametric data. Results were analysed in SPSS (version 20) using a repeated measures ANOVA. Factors were pre/post cooling (2 levels) with significance set at $P \leqslant 0.05$.

6.4. Results

Baseline responses pre cooling*:* In response to unilateral vibration of the ankle evertors there was a whole body movement towards the side of the stimulus. Participants translated their pelvis (M = 22mm, SD=4.9) toward the side of the stimulus at a latency of ~770ms producing ipsilateral hip adduction. There was a small upward tilt of the contralateral pelvis (M=0.1°, SD=0.1) at a latency of ~1010ms and ipsilateral knee flexion and rearfoot eversion. There was an additional tilt of the shoulders and trunk toward the side of the stimulus; termed ipsilateral trunk tilt. The centre of pressure shifted toward the side of stimulus by ~0.5cm.

In response to a unilateral vibration of the hip abductor participants translated their pelvis (>15mm) in the opposite direction to the stimulus at a latency of ~420ms (termed contralateral pelvic translation). This was associated with ipsilateral hip abduction. There was an additional small tilt of the pelvis (>0.5°) at a latency of ~680ms such that the side opposite the stimulus tilted down

(termed contralateral pelvic tilt). This was accompanied by ipsilateral knee extension and ankle inversion. There was an additional ipsilateral tilt of the shoulders and trunk. The centre of pressure shifted away from the side of stimulus by 17mm. The mean (table 6.1) and grand average response (figure 6.3 to 6.5) to hip vibration at the pelvis and ankle are shown.

	Hip vibration			Ankle vibration		
Segment	**Pre cooling**	**Post cooling**	**(P)**	**Pre cooling**	**Post cooling**	**(P)**
Mean Pelvic translation (mm) (SD)	-14.1(9.3)	-16.0(9.7)	0.10	2.2(4.9)	-0.3(5.0)	0.03
Mean Pelvic angle (°)(SD)	0.4(0.3)	0.5(0.3)	<0.001	-0.09(0.2)	-0.09(0.2)	0.03
Mean Ankle angle (°)(SD)	0.3(0.5)	0.5(0.6)	>0.05	-0.2(0.3)	-0.07(0.3)	>0.05
Shoulder angle (°)(SD)	-0.1(0.5)	-0.2(0.7)	>0.05	-0.2(0.1)	-0.1(0.1)	>0.05

Table 6.1. Segmental responses to hip vibration/Ankle vibration, pre and post cooling. Negative values indicate pelvic translation to the right, a pelvic tilt - right pelvis down, left ankle inversion.

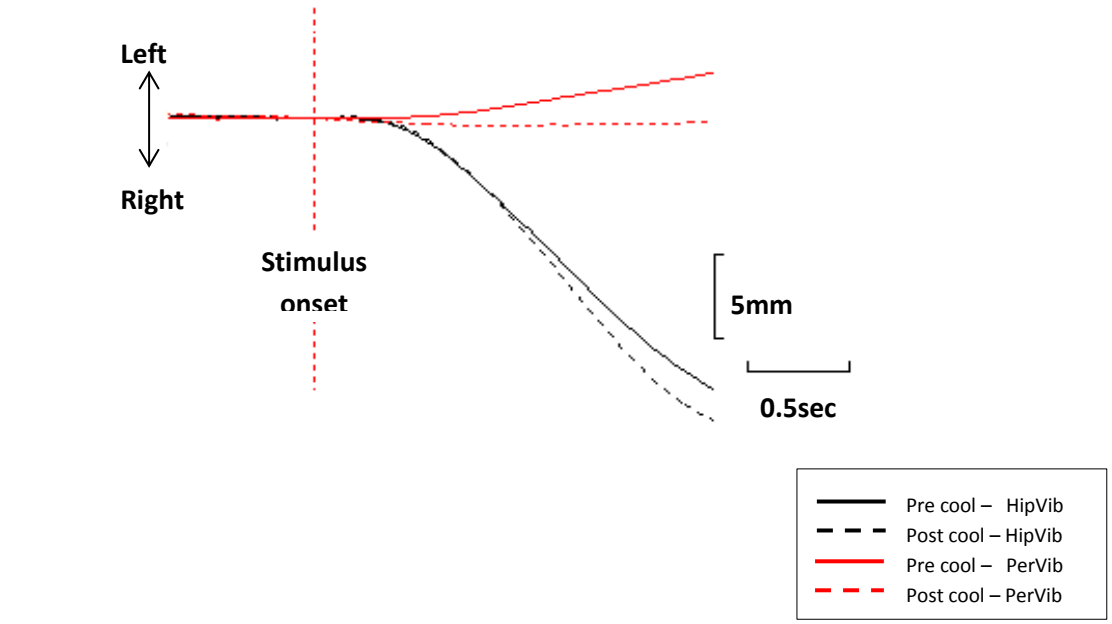


Figure 6.3 Grand average of pelvic translation in response to vibration of the hip/ ankle - pre and post cooling.

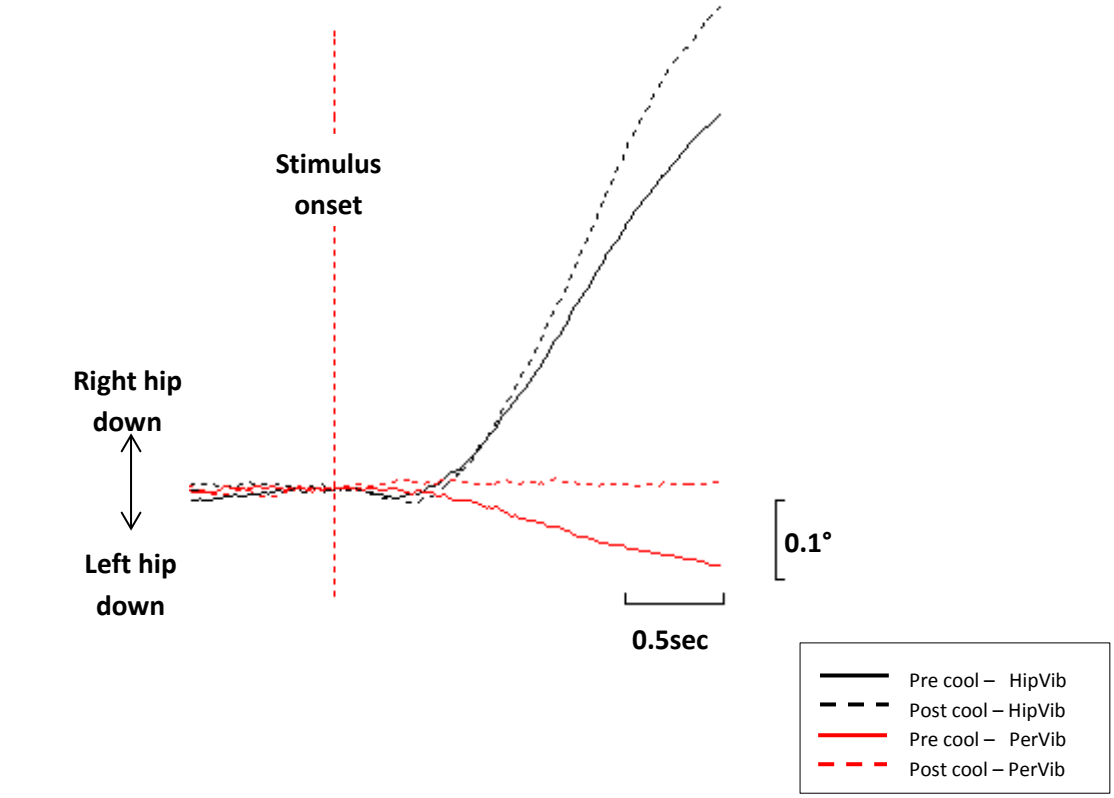


Figure 6.4 Grand average of pelvic angle in response to vibration of the hip/ ankle - pre and post cooling.

Left ankle (Degrees)

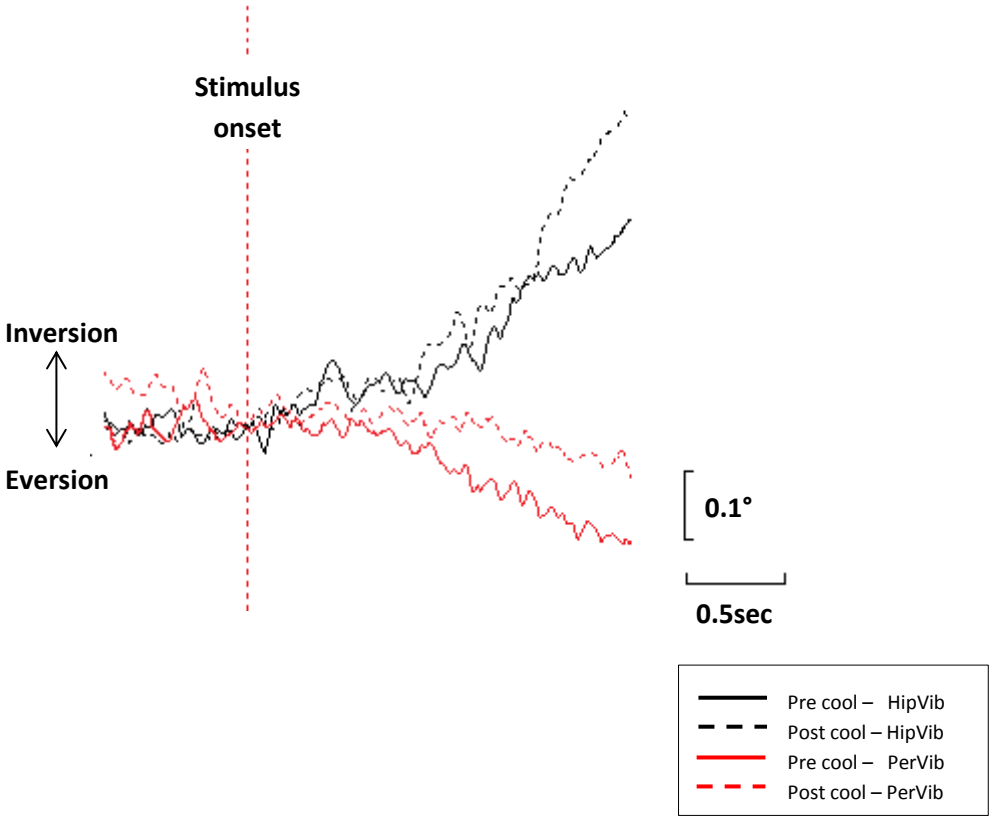


Figure 6.5 Grand average of ankle in response to vibration of the hip/ ankle - pre and post cooling.

Effects of Cooling*:* A skin temperature of 14.2°C ±1.4°C was achieved after cooling; a 12.3°C reduction. Tests post cooling took a maximum of 8 minutes during which skin temperature increased by ~6^{o}C. Cooling of the foot/ankle significantly reduced plantar foot sensation (Table 6.2). There was no significant change in ankle evertor (peroneus longus) strength.

Measure	Mean Pre-cool (Mean)(SD)	Mean Post-cool (Mean)(SD)	Significance (P)
Monofilament	7(0)	3.8(1.1)	0.001
Neurothesiometer (Volts) **Hallux** **Medial-Malleolus**	 6.5(2.4) 6.6(1.5)	 13.9(6.4) 12.7(4.1)	 <0.001 <0.001
Strength (ankle evertor) (Kg)	16.2(4.9)	16.8(5.4)	>0.05
Plantar skin temp(°C) **(2nd Metatarsal-Phalangeal joint)**	26.6(2.3)	14.3(1.4)	<0.001

Table 6.2 Table of baseline measures pre/post cooling. Significance between conditions is shown.

There was a significant effect of cooling on the response to hip abductor and ankle evertor vibration. Following cooling, in response to ankle evertor vibration there was a significant reduction in ipsilateral pelvic translation by 25.2mm ($F(1,15) = 5.77$, $P=0.03$; figure 6.6) and contralateral pelvic angle by 0.10° ($F(1,15) = 5.33$, $P=0.03$; figure 6.7). The response from other body segments did not show significant effects of cooling.

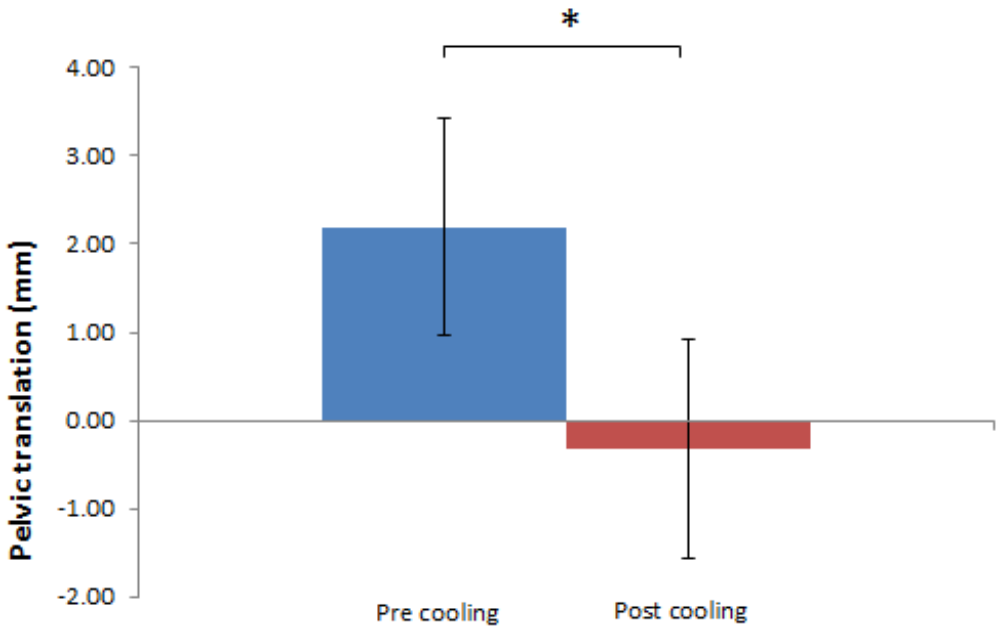


Figure 6.6 Bar chart to show the change in postural response (pelvic translation) to ankle vibration, following distal sensory reduction (cooling) . Error bars indicate standard error of the mean. *Indictes significant difference between pre and post cooling reponse.

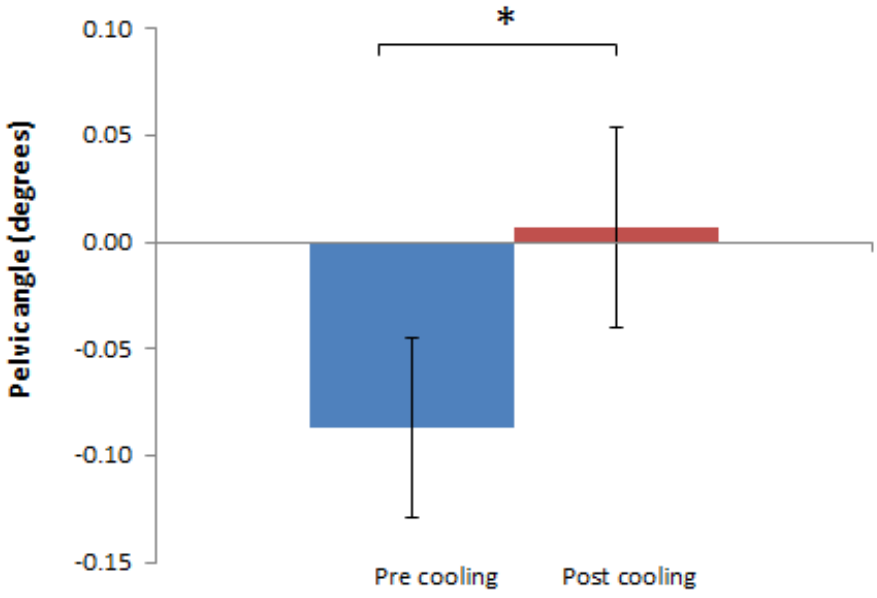


Figure 6.7 Bar chart to show the change in postural response (pelvic angle) to ankle vibration, following distal sensory reduction (cooling) . Error bars indicate standard error of the mean. *Indictes significant difference between pre and post cooling reponse.

Following cooling, in response to hip abductor vibration there was a significant increase in contralateral pelvic angle by 1.12° ($F(1,15) = 10.89$, $P=0.05$),figure 6.8). The response from other body segments did not show significant effects of cooling, ($P>0.05$).

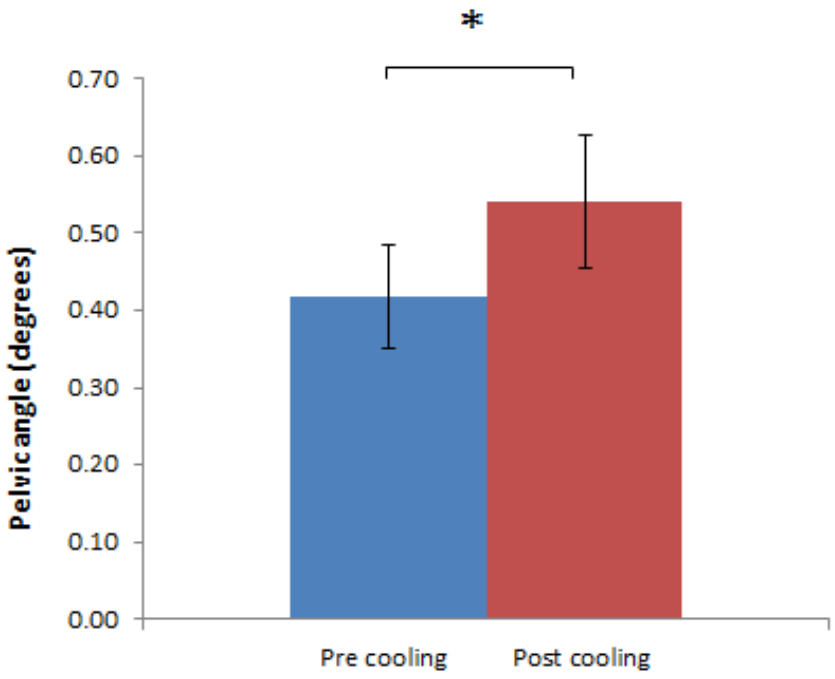


Figure 6.8 Bar chart to show the change in postural response (pelvic angle) to hip vibration, following distal sensory reduction (cooling) . Error bars indicate standard error 0f the mean. *Indictes significant difference between pre and post cooling reponse.

6.5. Discussion

Cooling of the foot and ankle resulted in a reduction in distal sensation to the extent that this would be categorised as neuropathy in the diabetic population. By experimentally reducing foot and ankle sensation this study has highlighted changes in postural response to both ankle and hip vibration in agreement with the proposed hypotheses. In the presence of experimentally induced distal sensory loss postural responses to ankle vibration were reduced significantly. However, postural responses to hip vibration increased significantly, indicating a change in the relative effectiveness of more proximal sensory feedback.

When a vibratory stimulus was applied to the ankle evertors or hip abductors a multi-segmented postural response was observed. The vibratory stimulus at the frequency used activates muscle spindle afferents providing an afferent signal that is normally associated with the muscle being lengthened[23,77,365,394]. When vibration is applied to other muscles (e.g. soleus) in standing, a postural response that counteracts the illusory muscle lengthening results (e.g. backward sway following vibration of the soleus). In keeping with this in the current study ankle evertor vibration resulted in an ankle eversion response. This motion was accompanied by translation of the pelvis toward the stimulus together with tilt of the trunk in the same direction. Similarly, vibration of the hip abductors led to ipsilateral hip abduction due to contralateral translation of the pelvis. Accompanying the pelvic translation was a tilt of the trunk in the opposite direction, that is, towards the side of the stimulus. This seems to be a co-ordinated postural response that produces minimal movement of the centre of pressure in the base of support. Another possibility is that following hip abductor

vibration, the tilt of the trunk is due to the vibratory stimulus activating muscle spindles in adjacent trunk muscles, in particular the quadratus lumborum, which produces side flexion of the trunk. However, the co-ordinated multi-segmented response seen following vibration of a distant site, the ankle evertors (peronei), makes this seem unlikely.

Cooling of the foot and ankle resulted in a decrease in tactile and vibratory sensibility. It is possible that the cooling also affected deeper tissues directly, for example, muscle spindle outputs in intrinsic foot muscles decreasing the observed response to local stimulation. Similar methods of cooling have previously been used and resulted in an increase in the onset of the medium latency stretch reflex response which is felt to be mediated by group II muscle spindle afferents[83,138].

Accompanying the sensory loss was a reduction in the postural response to ankle evertor (peronei) vibration. There are two, not mutually exclusive possibilities underlying this. Firstly, the cooling may have directly reduced 1a afferent conduction velocity[83,366,367] in the nerves supplying the peronei muscles leading to a reduced response to vibration. Although the boot used to cool the foot and ankle did not cover the bulk of the peronei muscle some parts may have been cooled producing local changes in blood flow that may have affected muscle temperature and slowed motor nerve conduction velocity. However, the strength of the ankle evertors did not change suggesting that the motor nerve conduction velocity within the mixed common peroneal nerve was not affected by cooling. A second possibility is that the reduced response to peronei vibration was due to a sensory re-weighting in response to reduced distal foot and ankle sensation[140]. The reductions in distal foot and ankle sensation may

have affected the reliability of the interpretation of muscle stretch signals induced by the vibratory stimulus. With reduced plantar cutaneous and ankle joint proprioceptive information, for example, it may be more difficult to interpret whether an illusory ankle inversion (induced by the peronei vibration) is due to a postural shift or isolated movement of the ankle relative to the shank.

In contrast, with distal cooling the postural response at the pelvis to hip abductor vibration increased. The hip muscles would not have been directly affected by the localised distal cooling. This change in response can therefore be interpreted as a being solely due to sensory re-weighting, where the gain in response to more proximal proprioceptive information increases[386]. When the hip proprioceptive channel is artificially stimulated, as in the current study, an increased response was seen reflecting change in response gain.

The observed changes in knee motion in the sagittal plane highlight that mediolateral postural control does not just rely on the movement of joints in the coronal plane. Knee flexion / extension allows for greater tilt of pelvis and motion of the hips in the coronal plane and suggests that the knee motion is essential for the motor effects of sensory re-weighting to be realised. The knee also plays an important role in sensory feedback[400], as is indicated by an increased postural instability in the presence of sensory loss above the knee level[23,30]. Early motion of the knee following a support surface postural perturbation can indicate sway onset and trigger further postural responses[78].

The increase in the gain of the postural response to hip proprioceptive afferent information seen in this study may not have occurred in isolation. Previous investigators have found increases in the gain of the vestibular system accompanying chronic distal sensory loss induced by a polyneuropathy or

diabetic peripheral neuropathy[203]. More effective stabilisation of more proximal head and trunk segments under the partial control of the vestibular system may explain why these segments did not show an increase in motion as seen around the hip and pelvis following hip abductor/ ankle evertor vibration. The testing of this hypothesis was outside the scope of this study.

The ability to use more proximal senses may be dependent on flexibility/strength in proximal segments such as the hip and knee as to obtain an abduction of the hip, flexion of the knee must occur[114]. Free movement of other joints may also play an important role in providing additional sensory positional feedback to facilitate the increased gain of hip proprioceptive and vestibular postural responses and indicates an area for rehabilitation of balance in those with pathological distal sensory loss.

6.6. Conclusion

Experimental cooling has enabled an insight to the sensory changes which may occur in the presence of distal sensory loss. Although the reduction in distal sensation was not to the extent seen in those with peripheral neuropathy, the experimental reduction in distal tactile sensation significantly reduced the amplitude of pelvic angle in response to ankle evertor vibration confirming that the cooling process reduced the weighting (gain) of sensory information from the foot/ankle. Conversely the amplitude of pelvic angle in response to hip vibration significantly increased following a reduction in sensation. This suggests that in the presence of distal sensory loss the body aims to maintain postural stability by re-weighting the relative importance of more proximal

sensory inputs. The next stage of this project is to assess the re-weighting of sensory information in the ML plane in people with pathological peripheral neuropathy.

6.7. Limitations

Cooling of the foot/ankle reduced plantar skin temperature significantly immediately after 30mintue cooling period. It is likely that the foot/ankle warmed during trials. To minimise this warming effect and the resulting responses to perturbations, stimulation repeats were reduced to decrease the time taken to complete data collection.

Similar to chapter 5 limitations, further stimulus sites could have been included, including those muscles that control AP motion. This would have added to the information gained on ML motion. Vestibular stimulation using GVS could have provided information about the sensory re-weighting previously seen in those with pathological distal sensory loss. Moving visual stimuli would have enabled exploration of the impact of distal sensory loss on the information gained from the visual system. But again adding these further stimulations would have led to more trials and therefore more time for the feet to return to normal temperature.

Chapter 7 .Study 3: Sensory re-weighting for balance control and the effects of ankle foot orthoses and stance width: A comparison of people with diabetic peripheral neuropathy and healthy controls

7.1. Background

People with Diabetic peripheral neuropathy (DPN) have a reduction in sensory feedback from the foot and ankle. This can induce static and dynamic balance instabilities and thus increase the risk of falling[284] when compared to diabetics without peripheral neuropathy and healthy controls. DPN has been identified as an independent risk factor for falls[14].

Instability occurs in both mediolateral and anterior-posterior directions although mediolateral instability is more associated with an increased risk of falls in the elderly[41,174] due to the importance of ankle torque generation in mediolateral balance control during walking[14]. Interventions for instability are therefore indicated for those who are particularly vulnerable to falls.

People with diabetes and neuropathy present with increased sensory[398,401,402] and proprioceptive thresholds[314,403]. Sensory control of balance is adaptable and can alter in response to pathological changes in the somatosensory system. This has been explored by reducing/blocking sensory feedback from somatosensory or visual systems and comparing postural responses to perturbations in healthy people. Sensory channels have also been stimulated to

assess sensitivity to sensory input and explore sensory re-weighting in pathology such as stroke[40] and vestibular deficit [102]. In those with DPN somatosensory information is reduced and leads to re-weighting of vestibular information to preserve stability[30].

Within the somatosensory system postural strategies are also modified in those with DPN, and this facilitates sensory re-weighting. For example, a shift from an ankle strategy to a hip strategy[30,256] in the sagittal plane, where there is increased motion in more proximal segments promotes the use of more proximal proprioception[23]. A similar increase in motion and feedback from around the hip and trunk may also exist in the mediolateral plane following distal sensory loss. However, to our knowledge this hypothesis has yet to be tested[282].

This study investigates the hypothesis that in the presence of DPN and the associated reduced distal proprioceptive feedback there is an increased reliance on more proximal proprioceptive feedback to maintain balance control in the mediolateral plane.

AFO's are a modifiable external factor with the potential to improve balance and postural stability by means of mechanical stabilisation and/or altering sensory feedback[371–373]. However, studies investigating the effect of AFO's on balance in people with diabetes and neuropathy are limited in number and of poor quality[24,274,332,333]. This study aims to build on the current evidence base by comparing the effect of an AFO on balance in people with DPN and healthy controls. AFO's designed to restrict joint motion about the ankle and or rear foot are likely to have a local mechanical mechanism of action[320,333]. In addition studies have shown that AFO's extending above the ankle also provide auxiliary sensory information believed to improve balance in people with DPN[24,320,332,333].

There are no known studies found in the review of English language studies that has investigated if wearing an AFO can artificially modify the contribution of proximal proprioceptive control of balance in the mediolateral plane; an aim of this study. Providing an understanding of the mechanisms underlying changes induced by an AFO could inform interventions to modify mediolateral postural responses in DPN.

People with diabetic peripheral neuropathy frequently increase their base of support (stance width) when walking[376] and standing[218]. Stance width (SW) is one factor shown to alter postural strategies in healthy people[23,404] where anterior-posterior postural strategies altered from a normal ankle strategy (associated with sway predominately about the ankle) to that of the hip strategy (associated with combined ankle and hip motion) increasing hip proprioceptive feedback. Increasing stance width may therefore have a positive effect on mediolateral stability[23] through improved sensory feedback; a possible advantage for people with distal sensory loss. It is not yet known if the change postural strategy at different stance widths is affected by DPN, or whether such changes are susceptible to manipulation by way of an AFO intervention.

A further aim of the study will therefore be to explore the effect of stance width on the mediolateral postural responses to balance perturbation in people with DPN compared to age matched healthy controls, and investigate if this effect could be modified using an AFO.

7.2. Aim

Part one of this study aimed to explore the effects of diabetic peripheral neuropathy on the mediolateral postural response to distal and proximal muscle vibration. Responses were compared to healthy matched controls to assess any differences in postural response pattern or magnitude.

Part two of this study aimed to investigate balance differences in people with DPN and aged matched controls, to determine the effects of diabetic peripheral neuropathy on;

a) the impact of stance width on postural control and the potential of an AFO to contribute to postural control; in terms of reducing sway velocity.
b) the impact of stance width on the mediolateral postural responses to proximal muscle vibration and the potential of an AFO to modulate those postural responses; in terms of changes in the magnitude and direction of body segment motion response.

7.3. Methods

7.3.1. Ethical considerations

A steering group that consisted of lay people with diabetic peripheral neuropathy was held to inform the feasibility and practicality of the methodology (appendix 5).

Approval of the Cornwall & Plymouth Research Ethics committee was obtained through the NHS Integrated Research Ethics application System (14/SW/0057, IRAS: 144959). In accordance with local procedure and, as Plymouth University acted as the study sponsor, approval was also gained from Plymouth University, Faculty Research ethics Committee (13/14-250).

Written informed consent from each subject was obtained prior to recruitment into the study as approved by the Research Ethics Committee. All potential participants were given the patient information sheet (appendix 6 and 7) to consider before deciding to take part. The study was conducted in full conformity with relevant regulations, with the ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) July 1996 and in accordance with the Declaration of Helsinki (2008).

7.3.2. Participants

Eight participants were recruited for the study by a third party whilst attending their routine Podiatry appointment. A further ten participants were recruited from participants enrolled on another study being conducted at Plymouth University.

7.3.2.1. Inclusion criteria

Participants with diabetic peripheral neuropathy were included into the study if ;

1. They had reduced foot and ankle sensation clinically diagnosed using a 10g monofilament as neuropathic by the podiatrist within Plymouth Primary Care Trust (see outcome measures).

2. They were community dwelling subjects able to follow simple instructions.
3. They were able to stand un-aided with eyes closed.

An age matched control (healthy) group of volunteers were recruited, five from friends and family of the participants with diabetes, seven from the students and staff responding to email invitation at the Peninsula Allied Health Centre, School of Health Professions, Plymouth University and a further six from University of the 3rd Age (U3A) volunteer group (Appendix 8).

7.3.2.2. Exclusion criteria (DPN and healthy groups)

Participants were excluded from joining the study if;

1. They were registered as partially sighted or blind.
2. They self-reported any other neurological or vestibular conditions, including episodes of dizziness.
3. They were prescribed medications known to affect balance such as amitriptyline were excluded.
4. They had conditions known to severely impair cognitive function (e.g. dementia).
5. They had active foot ulceration or had previously undergone an amputation of a lower limb.
6. They presented with charcot arthropathy.

7.3.3. Intervention

The ankle foot orthoses were an Airform stirrup ankle brace (Ossur, USA) which have semi-circular shells lined with an air bladder that lie on either side of the malleoli and extend proximally over the lower leg (figure 7.1a) secured in place with velcro straps that wrap around the ankle and lower leg. The AFO acts to minimise inversion and eversion movements of the foot and ankle, whilst allowing free movement of plantar flexion and dorsiflexion. These were worn in conjunction with a slipper (Pulman International) (figure 7.1b).

Figure 7.1a Airform ankle foot orthoses. (Pulman International).

Figure 7.1b Pulman slipper (Ossur, USA).

7.3.4. Sample size

Differences in the size of postural sway between healthy controls and people with DPN have found large effect sizes (>2) in previous studies[405] and it would therefore be possible to detect these differences with low sample sizes. Due to the lack of previous data investigating the effect of AFOs on postural response in people with diabetes and neuropathy the sample size calculation for this

study was based on data collected during the pilot work presented in this thesis. The calculation is therefore based on the results of an investigation into the effect of the AFO on postural control in healthy participants. In the study presented in chapter 5, the postural response to hip vibration at the pelvis (pelvis angle) when standing at a stance width of 4 cm, was modulated by wearing an AFO. When wearing an AFO the response was 0.03° (+/- 0.03) whilst in the No AFO condition, the response was 0.06° (+/-0.03). A sample size of 15 participants were therefore required for 95% power at p=0.05 (repeated measure ANOVA) to detect a similar change in response size.

7.3.5. Experimental set-up

Data was collected during a single visit to the laboratory for each participant.

As previously described all participants were comfortably dressed wearing shorts. Vibration motors (80mmm length, 22mm diameter, 118Hz ±6Hz, 13.4G) were positioned and secured with hypoallergenic tape over the left and right hip abductors and ankle evertors. The hip abductors were palpated and the vibrator applied horizontally over the gluteus medius fibres at the midpoint between greater trochanter and superior point of the iliac crest. The peronei were palpated and the vibrator attached in parallel with the peroneus longus muscle with the top of the vibrator placed 5cm distal to fibula head. The vibrators were secured with hypoallergenic tape and an elasticated belt which applied approximately 31N of force perpendicular to the vibrator.

Markers were place bilaterally on a helmet securely attached to the head; shoulders (acromion process), pelvis via a belt that securely attached around

the pelvis below the level of the anterior superior iliac spine (figure 7.2). Movement of the markers was measured using a 3D motion analysis system (CodaMotion, Leicestershire, UK). Motion analysis was sampled at 200Hz and recorded for off-line processing using MatLab programs written in-house.

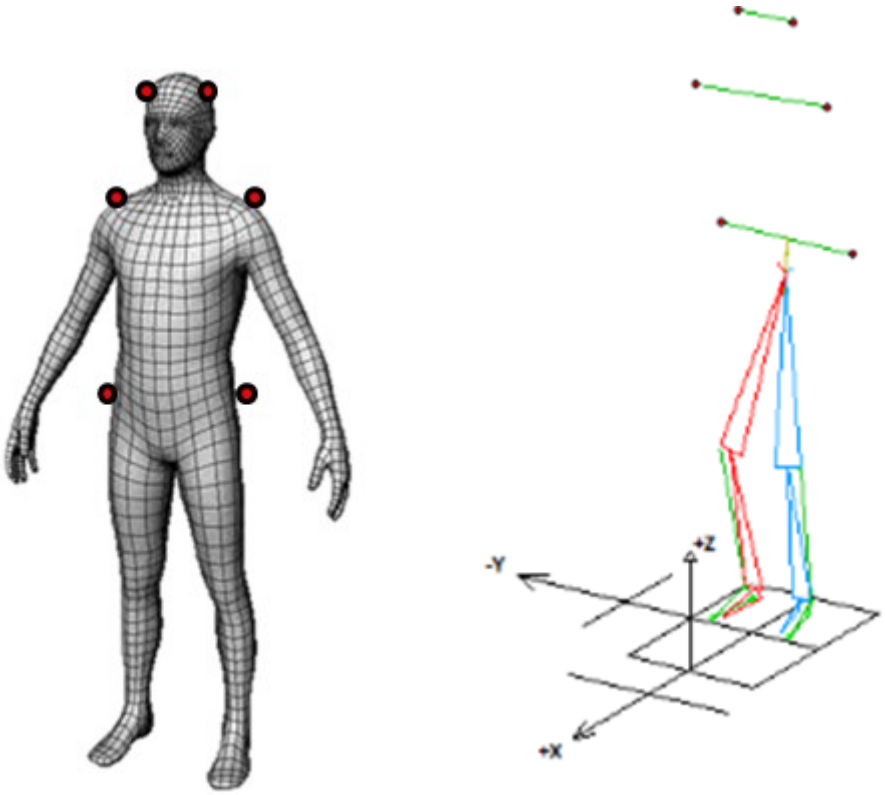


Figure 7.2 Graphical representations of Coda motion bilateral marker positions.

All participants wore a safety harness at all times which was attached to a purpose built overhead support. The harness was loose enough to allow the participant to respond to the stimulus but would prevent them from sustaining a fall. For people who were particularly unstable an additional researcher stood behind the participant to help correct excessive balance responses.

7.3.6. Baseline measures of foot sensation

Measures of plantar cutaneous sensory perception were measured using a 10gram monofilament[396]. The method used tested the ability of the participant to detect a 10g monofilament at 5 sites on each foot; the plantar aspect of the toes (1^{st}, 3^{rd}) and metatarsal phalangeal joints (1^{st}, 3^{rd} and 5^{th})(figure 7.3). Peripheral neuropathy was clinically defined as lack of sensation to one or more sites tested on either foot[406].

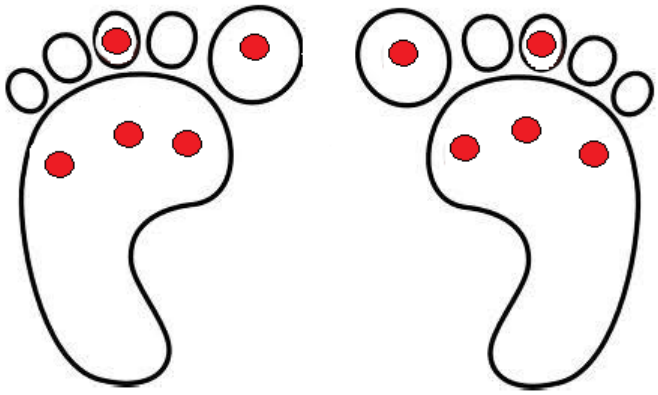


Figure 7.3 Testing sites for sensation using 10g Monofilament.

Although the monofilament is used worldwide as a tool to indicate the risk of ulceration in the diabetic population[407], Dros et al (2009) noted that it should not be used in isolation due to the accuracy of the test with sensitivity ranging from 41% to 93% and specificity ranging from 68% to 100%[407]. Therefore a neurothesiometer was used to measure vibratory perception thresholds (VPT) as a secondary measure of plantar cutaneous sensation, providing a means of testing with high discriminatory ability and an excellent balance between sensitivity (the ability to pick up all or most at risk of neuropathic foot ulceration), and specificity[408]. VPT was tested at the apex of the hallux, medial malleolus and knee (tibial tuberosity) using a neurothesiometer (Horwell, UK). Results

were recorded in hard copy format and later transferred to an excel spreadsheet. Peripheral neuropathy was clinically defined when vibration perception threshold was greater than 25 Volts.

7.3.7. Baseline measures of vision

Visual acuity and contrast sensitivity are commonly used tests in optometry practice[409,410] and have been reported to be two of the strongest risk factors for falls[303]. These were tested with participants wearing their usual visual corrections used for daily activities and walking. Although all studies were completed with eyes closed in this investigation, vision was tested to assess for correlations with measures of postural control.

To measure visual acuity a LogMar chart[411] was used (figure 7.4). The acuity is the smallest line of letters that can be identified from the chart from a distance of 3 meters. The acuity value is achieved if the subject can read 50% or more of the line. If they cannot, then the line above (of larger letters) is the grading given.

Figure 7.4 LogMar chart.

Contrast sensitivity was measured using the Pelli Robson chart[412] (figure 7.5). The chart ranges from 100% contrast to 0.6% contrast at the bottom. The letters are grouped into three with contrast decreasing in increments to the lowest contrast at the bottom. The subject is awarded the contrast sensitivity if they can read 2 out of three of the letters in the group of lowest contrast possible.

Figure 7.5 Pelli Robson chart.

7.3.8. Strength

Maximum isometric ankle evertor strength was measured using a strain gauge (Applied Weighing, UK).

Participants were asked to sit with the right leg extended, with the heel in contact with the floor. The foot was in a relaxed position. Subjects were then asked to apply their maximum eversion force to a padded strain gauge placed over the styloid process of the foot. The investigator resisted the movement whilst stabilising the heel with the opposite hand. The output voltage of the strain gauge was A-D converted (Power 1401, CED, UK), to enable real-time

data capture via Spike2 control software at 100Hz. Three tests were completed, after a 30second rest period between efforts, recorded and later averaged for data analysis.

7.3.9. Measures of sensory control of posture (Part 1)

Participants stood bare foot to eliminate any external mechanical or sensory input from a shoe. They stood with their eyes closed. The medial borders of their feet were positioned 4cm apart. After a 1-3s random baseline period a 2 s, 90Hz vibratory stimulus (13.4G Precision Microdrives, UK) was applied through the vibrator motor units, over the left or right hip abductors or ankle evertors (chapters 5 and 6). Five stimuli per site and side were given, with the order of presentation being randomised. Movement of the body was measured using 3D motion analysis (CodaMotion, UK) as previously described (chapter 5 and 6).

7.3.10. Measures of the effects of AFO and stance width (Part 2)

Participants stood in standardised footwear (Pulman International) with their eyes closed. Postural response data was collected whilst participants stood with the medial borders of their feet positioned (using spacers) at both 4 and 16cm apart. At each stance width postural response was recorded during 2 test conditions; No AFO and with an AFO. The order of the stance width and AFO use was randomised between participants using codes generated in MATLAB (randperm function). Participants rested in sitting between NoAFO/AFO conditions for 5 minutes.

Motion detection was initialised and baseline sway was recorded for 1 second (eyes closed). A 2 second vibratory stimulus (Precision Microdrives, UK) was then applied over the left or right hip abductors and the postural responses recorded. The onset of the data collection and hip vibration (randomised to the left and right side) were controlled remotely by Spike software and a Power 1401 analogue-digital converter (Cambridge Electronic Design, UK). Ten stimuli per side at each stance width and AFO condition were given. Motion analysis was sampled at 200Hz and recorded for off-line analysis.

7.3.11. Data reduction

Files were sorted according to the condition and site of stimulus. All data was passed through a low-pass (20Hz) Butterworth filter, aligned to stimulus onset and averaged. The responses to left and right sided vibration were in opposite directions but did not significantly differ in absolute amplitude or latency; therefore the responses to left and right vibration were subsequently averaged and displayed as if the stimulus was on the left side for both hip abductor and ankle evertor vibration responses. The centre point between shoulder markers was calculated in MatLab for subsequent calculation of sway velocity. The translation and roll angles of pelvis, shoulder and head motion in the mediolateral plane were also determined. Trunk motion was calculated by measuring the angular tilt to the vertical of a line joining the mid-point of the shoulder markers to the midpoint of the pelvic markers. The maximum response following stimulus onset relative to a 1sec baseline pre-stimulus period were determined at all segments.

7.3.12. Statistical analysis

Data was transferred to Excel for analysis in SPSS (version 20). From the grand average responses the overall gross response to vibration increased throughout the duration of stimulation. Therefore the maximal response at 2s post stimulus onset was analysed to enhance between group effects. Data was normally distributed (Shapiro-Wilk test) and met the other assumptions for parametric data.

Postural responses to hip vibration was analysed in SPSS (version 20) using between group repeated measures ANOVAs. Factors were Healthy/DPN (2 levels) with significance set at $P<0.05$. This analysis was repeated for the postural responses to ankle vibration. The effects of stance width and AFO on sway velocity and the response to hip vibration were compared using a between groups repeated measures ANOVA with factors being stance width (2 levels 4 cm vs 16 cm) and AFO (AFO vs No AFO) with significance set at $P<0.05$. A bonferroni correction was not performed for the 7 repeated measures ANOVA tests performed as it is felt that the motion of each segment was independent in terms of direction and magnitude of motion.

The effect size of both stance width and AFO was calculated using the equation shown below (Eq 6.1). Unpaired t-tests were used to compare the demographics and clinical measures between the two groups.

$$Effect\ size = \frac{Mean\ of\ intervention - Mean\ of\ control}{Standard\ deviation}$$

Equation 7.1 Effect size calculation.

To assess for the relationship between covariate such as age, BMI and visual acuity the grand average response across all conditions was calculated (i.e. 4cm stance width AFO, 4cm stance width No AFO, 16 cm stance width AFO, 16cm stance width No AFO). The relationship between each covariate and postural sway and segment motion (n=6) using a Pearson correlation. A Bonferroni correction was made for the multiple correlations made between each covariate and the postural sway / segment motion. In total there were 7 conditions (postural sway, 3 segmental angular motions and 3 segmental translatory motions). Therefore a significance level of 0.05/7=0.0071 was used.

7.4. Results

7.4.1. General participant characteristics

Group characteristics are summarised in table 7.1.

	Healthy controls	DPN
Participants	18	18 (type1=5, type2=13)
Age(Years)	67 (3.9)	69 (13.0)
Gender(M:F)	8/10	10/8
Height (cm)	166(8.3)	174(9.5)
Weight(Kg)	75±31	94±37*
BMI	27(5.3)	30(4.8)*
Diabetes type 1	N/A	5
Diabetes type 2	N/A	13
Strength (Kg)	11.9(3.5)	8.6(3.1)*
Monofilament		
Left(sites)	5(0)	1.7(1.7)*
Right (sites)	5(0)	2(1.8)*
Neurothesiometer		
Hallux(Volts)	10.6(2.9)	38.3(11.6)*
Medial mal (Volts)	12.9(3.2)	37.2(13.8)*
Knee (Volts)	11.9(2.4)	29.3(11.8)*
Visual acuity	-0.02(0.14)	0.06(0.26)*
Contrast sensitivity	1.9(0.21)	1.8(0.22)*

Table 7.1 Group characteristics/measures. Mean(SD) shown. * indicates significant between group differences(P<0.05).

An independent t-test was performed on group characteristics. There was no significant difference in age between the groups (t (30)= -0.8, p>0.05), Mean and Standard Deviation shown in table 7.1. People with DPN weighed significantly more than those in the control group (t (30)= -3.2, p=0.003). The Body mass index was also significantly higher in people with DPN (t (30)= -2.1, p=0.047).

There was a significant difference between groups for each clinical variable ($P<0.05$, Table 7.1). Monofilament and neurothesiometer measures confirmed distal sensation loss in the DPN group, whilst also showing reduced strength and inferior visual acuity and contrast sensitivity.

7.4.2. Part 1 – Comparison of group postural responses to distal and proximal sensory input

From the eighteen participants recruited, one healthy participant and one person with DPN had missing CODA motion data, resulting in 17 participants in each group.

A between group ANOVA was conducted to compare the impact of two different perturbations (hip abductor vibration and peronei (ankle) vibration) on the postural response (head translation and angle, shoulder translation and angle, pelvic translation and angle, trunk angle) between two participant groups (People with DPN and healthy controls). From the grand average responses (figure 7.8 to 7.14) the overall gross response to vibration increased throughout the duration of stimulation. Therefore the maximal response at 2s post stimulus onset was analysed to enhance between group effects.

Hip Vibration responses (Healthy Vs DPN)

The results showed that there was no significant difference between groups in direction of the postural response to hip abductor vibration, whilst participants stood with eyes closed and feet 4 cm apart. In both groups, in response to vibration of the left hip abductors the pelvis and shoulders translated away from the side of the stimulus (termed contralateral translation). This was accompanied by a tilt of the pelvis, shoulders and head in space where the right pelvis, shoulder and head tilted downwards (figure 7.6).

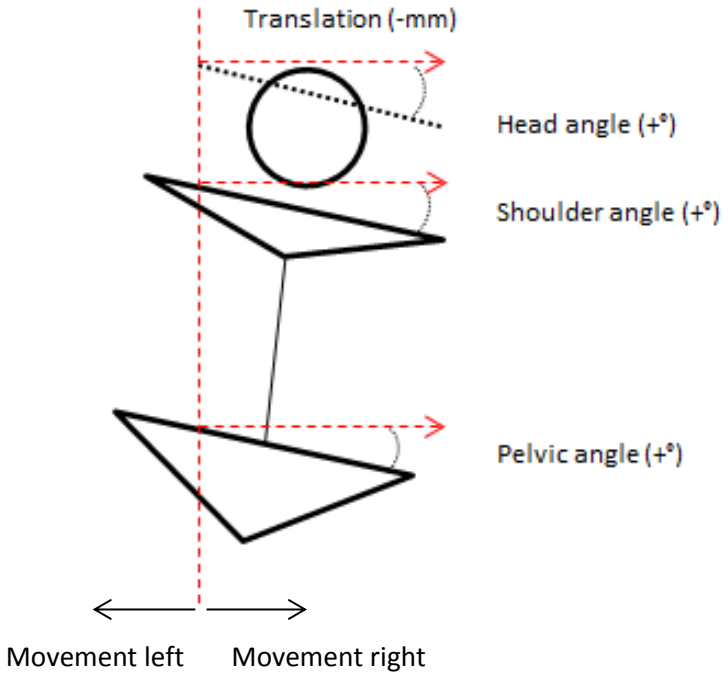


Figure 7.6 Graphical representation of the postural responses (rear view) to left hip vibration.

Comparing the magnitude of responses to vibration of hip, at the end point of stimulation (i.e. maximum response), there was no significant difference in pelvic translation or angle, shoulder translation, head translation or trunk angle

between the DPN and control groups (Table 7.2). However, the shoulder and head angle in space was significantly higher (by 0.12° in both segments) in the DPN group (shoulder F(1,16) = 5.2, P=0.036), head (F(1,16) = 5.1, P=0.038); Table 7.2).

	Hip vibration		
Segment	Healthy	DPN	Sig (P)
Max Pelvis translation (mm) (SD)	-6.11(4.3)	-6.24(4.1)	>0.05
Pelvis angle (°)(SD)	0.18(0.1)	0.17(0.1)	>0.05
Shoulder translation (mm)(SD)	-6.14(4.3)	-6.6(4.4)	>0.05
Shoulder angle (°)(SD)	0.10(0.1)	0.22(0.1)	**0.036**
Head translation (mm)(SD)	-6.27(4.02)	-7.18(4.45)	>0.05
Head angle (°)(SD)	0.12(0.1)	0.24(0.2)	**0.038**
Trunk angle (°)(SD)	0.005(0.01)	0.02(0.03)	>0.05

Table 7.2 Magnitudes of postural responses at end of stimulation period; Mean (standard deviation) shown, Translation: negative values = movement right, Angles: positive values = right side of segment down.

Ankle vibration responses (Healthy Vs DPN)

The results showed that there was no significant difference in direction of the postural response to peronei (ankle) vibration, whilst participants stood with eyes closed and feet 4 cm apart. In both groups in response to vibration of the

left peronei the pelvis and shoulders translated toward the side of the stimulus (ipsilateral translation). This was accompanied by a tilt of the pelvis, shoulders and head in space where the right pelvis, shoulder and head tilted upwards (figure 7.7).

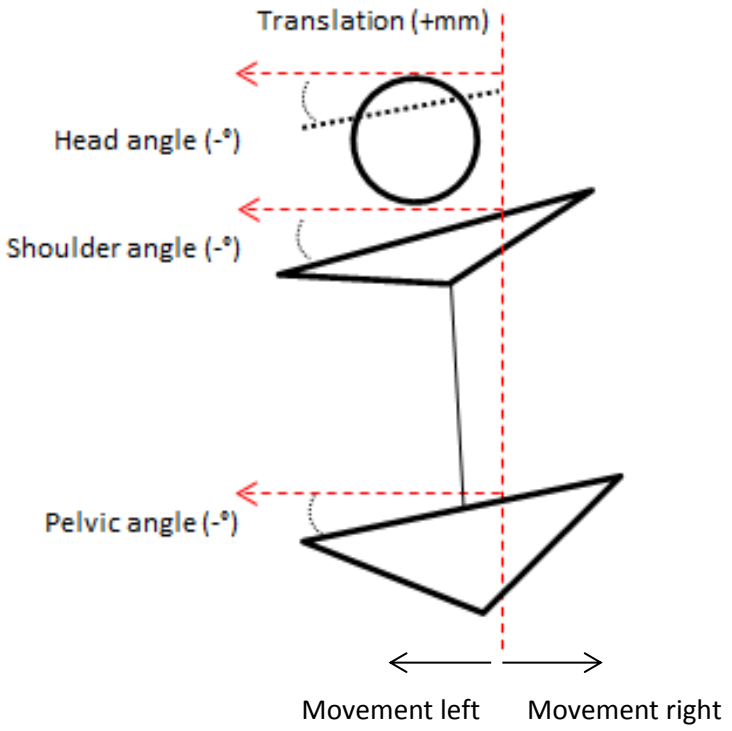


Figure 7.7 Graphical representation of the postural responses (rear view) to left ankle vibration.

The magnitude of responses, at the end point of stimulation (i.e. maximum response), at all body segments were compared. No significant differences between groups were found (Table 7.3), although head and shoulder angle was higher in the DPN group, similar to the response to hip abductor vibration.

	Per vibration		
Segment	Healthy	DPN	Sig (P)
Max Pelvis translation (mm) (SD)	4.42(3.2)	5.31(3.4)	>0.05
Pelvis angle (°)(SD)	-0.17(0.1)	-0.16(0.1)	>0.05
Shoulder translation (mm)(SD)	4.92(3.5)	6.1(4.0)	>0.05
Shoulder angle (°)(SD)	0.16(0.08)	-0.21(0.1)	>0.05
Head translation (mm)(SD)	5.36(3.48)	6.4(4.1)	>0.05
Head angle (°)(SD)	-0.16(0.1)	-0.24(0.2)	>0.05
Trunk angle (°)(SD)	-0.01(0.01)	-0.01(0.02)	>0.05

Table 7.3 **Magnitudes of postural responses at end of stimulation period; Mean (standard deviation) shown, Translation: negative values = movement right, Angles: positive values = right side of segment down.**

Grand average responses

A full graphical representation of the group comparison displaying the total recorded movement for each body segment during each test condition summarised as grand average responses are presented in figures 7.8 to 7.14. The graphs demonstrate the similarities in the postural response to hip abductor vibration and ankle vibration between the DPN and healthy control groups.

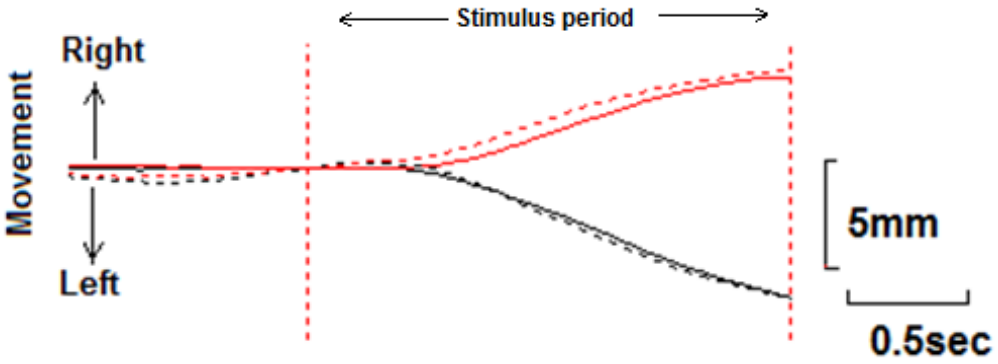


Figure 7.8 **Grand average of pelvic translation in response to hip (black) and ankle (red) vibration. Solid line represents Healthy group responses. Dotted line represents DPN group responses.**

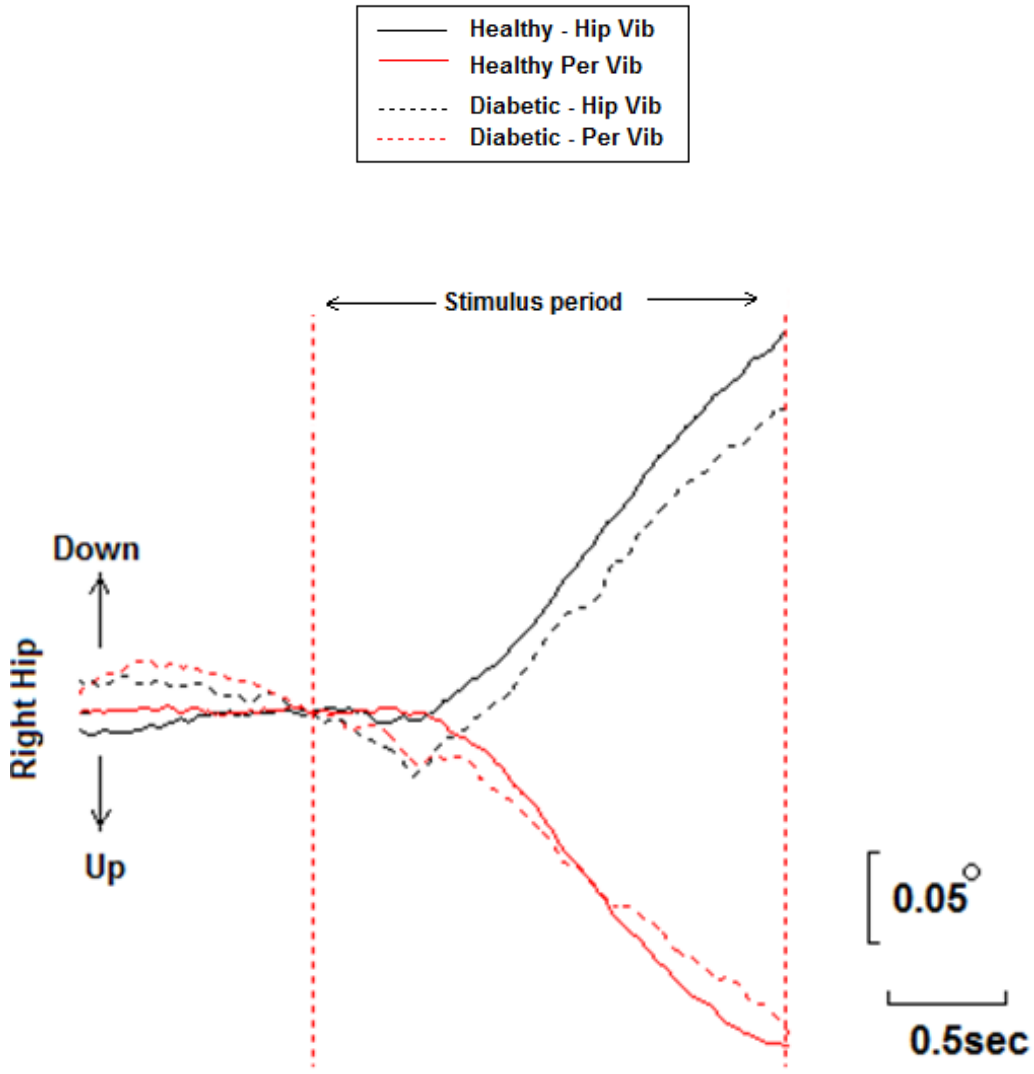


Figure 7.9. **Grand average of pelvic tilt in response to hip (black) and ankle (red) vibration. Solid line represents Healthy group responses. Dotted line represents DPN group responses.**

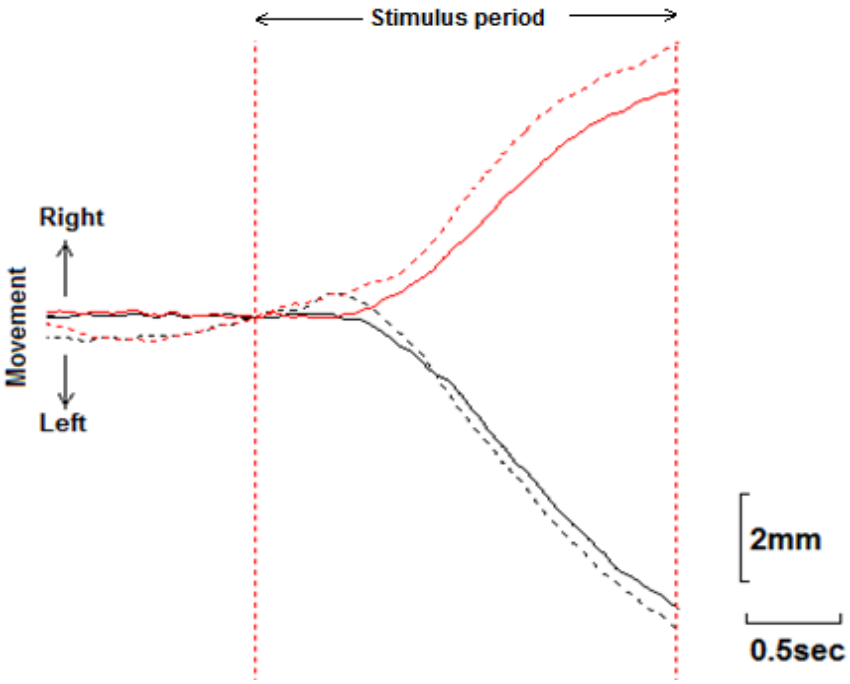


Figure 7.10. Grand average of shoulder translation in response to hip (black) and ankle (red) vibration. Solid line represents Healthy group responses. Dotted line represents DPN group responses.

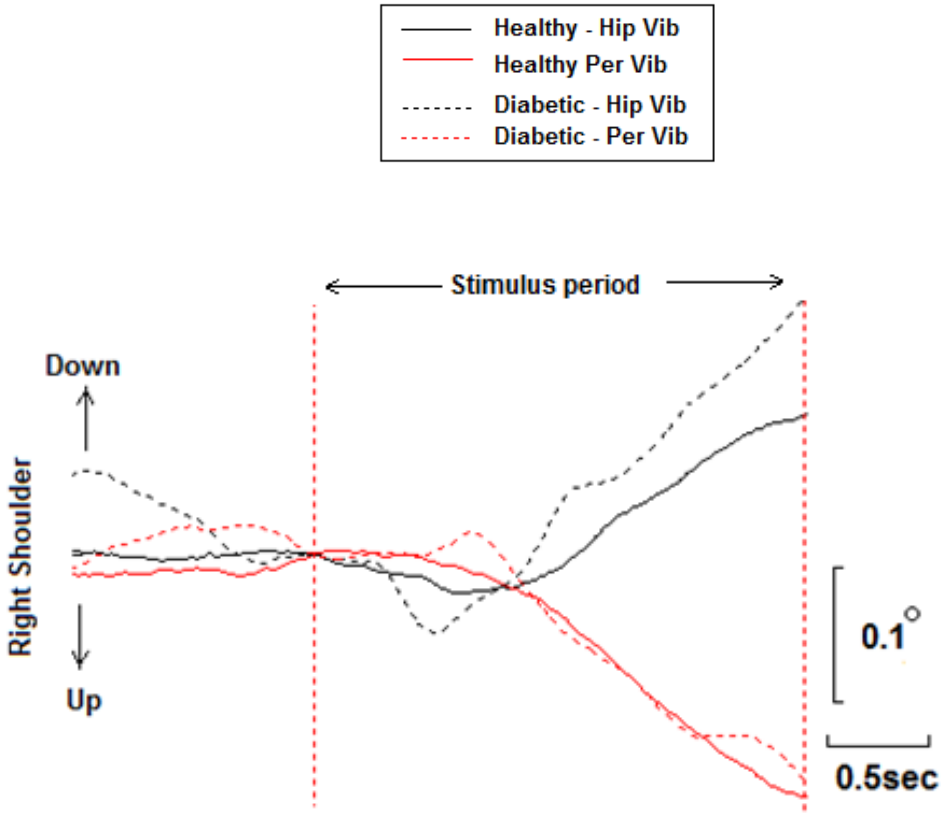


Figure 7.11. Grand average of shoulder angle in response to hip (black) and ankle (red) vibration. Solid line represents Healthy group responses. Dotted line represents DPN group responses.

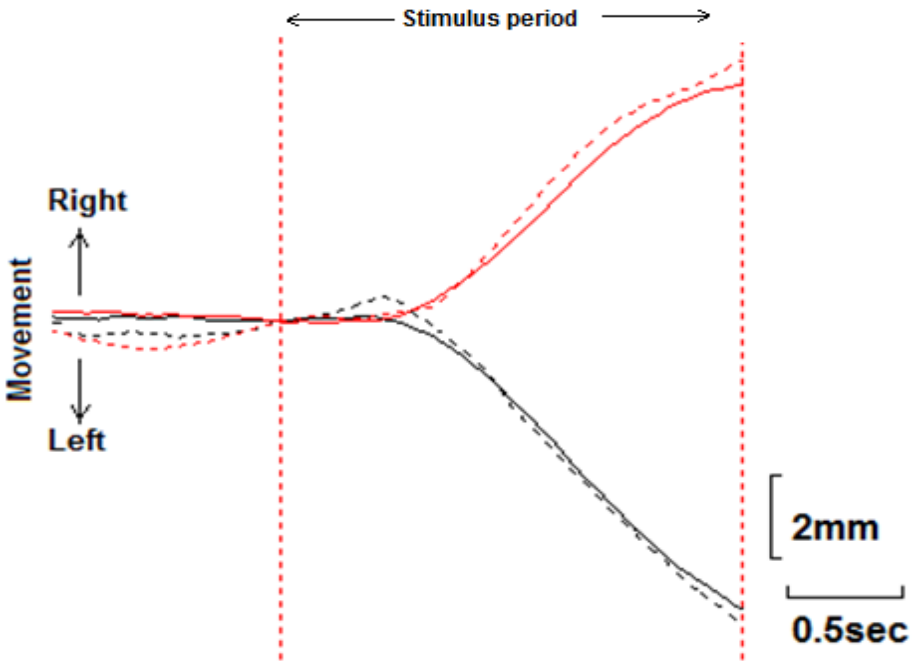
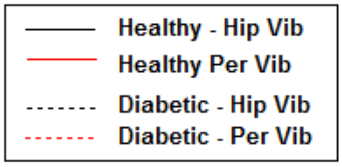


Figure 7.12 Grand average of head translation in response to hip (black) and ankle (red) vibration. Solid line represents Healthy group responses. Dotted line represents DPN group responses.



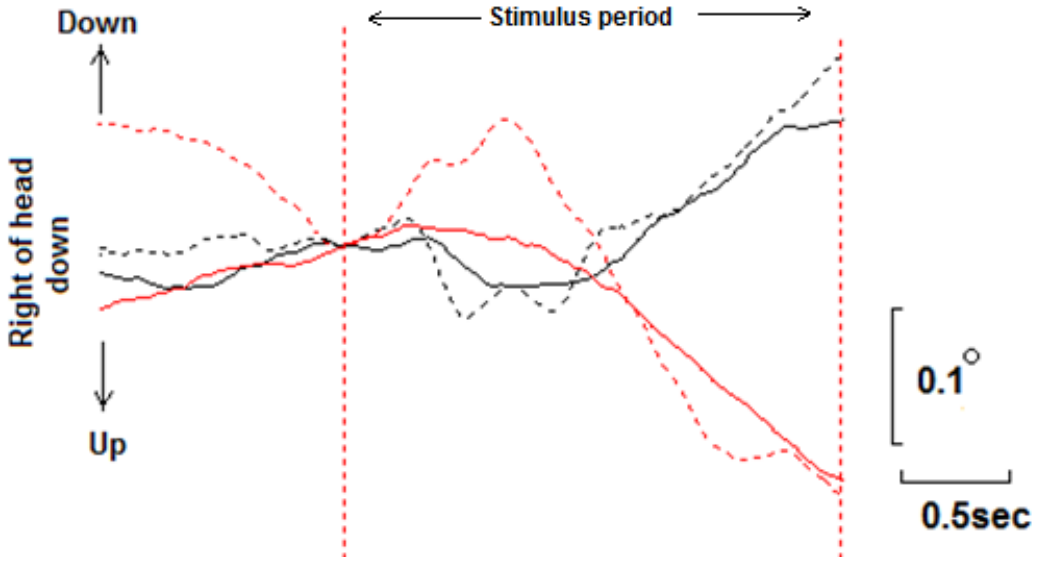


Figure 7.13. Grand average of head angle in response to hip (black) and ankle (red) vibration. Solid line represents Healthy group responses. Dotted line represents DPN group responses.

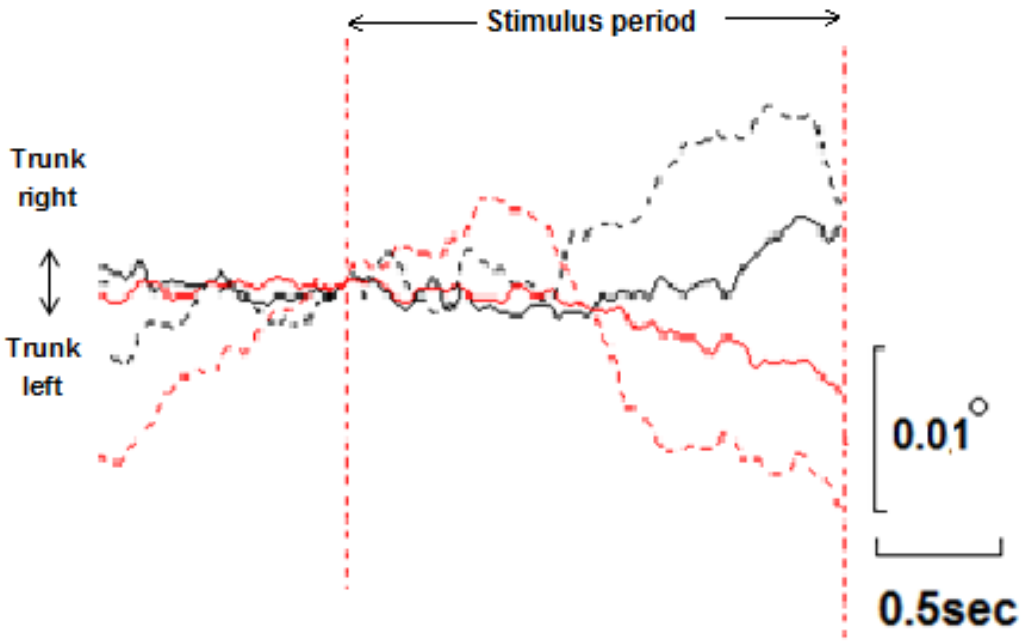
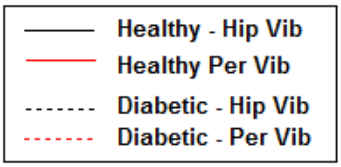


Figure 7.14. Grand average of trunk angle in response to hip (black) and ankle (red) vibration. Solid line represents Healthy group responses. Dotted line represents DPN group responses.



7.4.3. Part 2 – Effect of AFO and stance width on baseline sway velocity; a comparison of two groups

From the eighteen participants in each group recruited, two with DPN had missing CODA motion data. One further DPN participant failed to complete the test. This resulted in 18 healthy subjects and 15 DPN subjects.

Sway velocity was measured in both groups in conditions of stance width and AFO (figure 7.15).

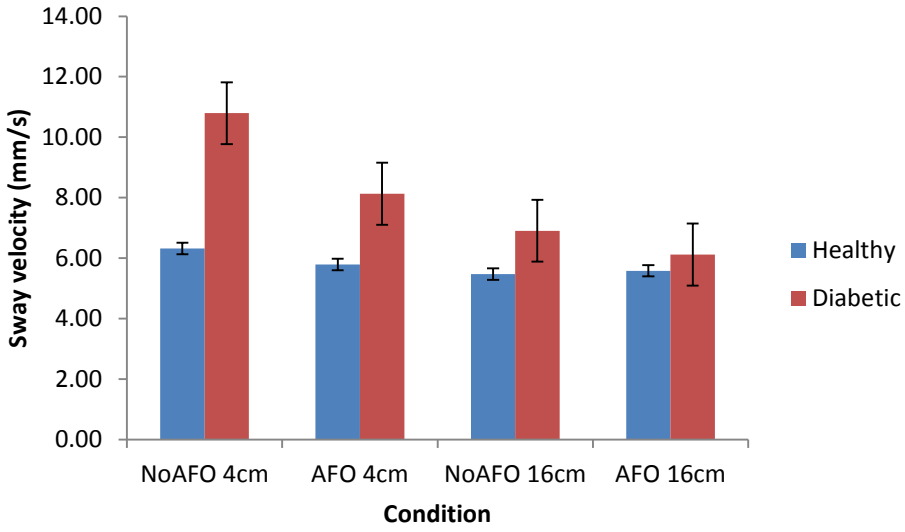


Figure 7.15. Bar chart to show sway velocity with/without AFO and in Stance width condtions; 4cm and 16cm. Error bars indicate standard error of the mean.

A between group ANOVA was conducted to assess the impact of two test conditions (with AFO, No AFO) on sway velocity in both groups (people with DPN and healthy controls) whilst standing at two different stance widths (4cm and 16cm). There was a significant interaction between stance width and AFO, stance width and group, and AFO and group (table 7.4).

	Group	SW	SW x Group	AFO	AFO x Group	SW x AFO	SW x AFO x Group
Sway Velocity (P)	0.02*	<0.001*	<0.001*	0.01*	0.04*	0.04*	>0.05

Table 7.4 Table of significance; Effect of AFO and stance width conditions on sway velocity across groups. * indicates signicant effect.

The stance width x group interaction suggests that the effect of stance width on sway velocity is dependent on group. Post hoc pairwise comparisons show in both groups sway velocity is significantly greater at a stance width of 4 cm when compared with a stance width of 16cm. Increasing stance width (No AFO condition) in the DPN group ($F(1,14)=11.5$, $P=0.004$) led to a reduction in sway velocity. This was greater than that seen in healthy controls ($F(1,17)=6.5$, $P=0.02$). This finding suggests that postural control is adversely affected by DPN and that the dysfunction is made worse at reduced stance widths.

The AFO x group interaction ($F1,31)=4.4$, $P=0.04$) (table 7.4) suggests that the effect of the AFO on sway velocity is dependent on group. Post hoc pairwise comparisons suggest that for both groups (DPN and control) wearing the AFO at a stance width of 4cm reduced sway velocity by 2.7mm/s (DPN) and 0.5mm/s (healthy) (table 7.5). This finding suggests that the AFO does have the potential to contribute to postural control and that the effect is more pronounced in those with DPN.

	Condition					
	NoAFO 4cm	AFO 4cm	NoAFO - AFO Sig (P)	NoAFO 16cm	AFO 16cm	NoAFO - AFO Sig (P)
Healthy Sway velocity mm/s(SD)	6.3(1.9)	5.8(1.9)	0.09	5.5(1.9)	5.6(1.9)	0.62
DPN Sway velocity mm/s(SD)	10.8(6.1)	8.1(3.0)	0.04	6.9(3.4)	6.1(2.7)	0.19

Table 7.5 Measures of sway velocity (mm/s [SD]) with/without AFO and in stance width conditions in Healthy and DPN groups. Post Hoc testing: Effects of stance width and AFO on sway velocity in healthy and DPN groups.

The stance width x AFO (F1, 31) = 4.7, P=0.04) interaction (table 7.4) suggests that the effect of AFO was dependant on stance width. Post hoc comparisons highlighted that the effect of the AFO on reducing sway velocity was greater at a stance width of 4cm compared to 16 cm stance width (table 7.5). This finding suggests that the contribution of the AFO to postural control is increased at smaller stance widths.

7.4.4. Effect of AFO and stance width on postural response to hip vibration

Postural responses to hip vibration were measured in both groups, in conditions of stance width and AFO (table 7.6). A between group ANOVA was conducted to assess the impact of two test conditions (with AFO, No AFO) on postural responses to hip vibration, in both groups (people with DPN and healthy controls) whilst standing at two different stance widths (4cm and 16cm) (table 7.6).

	Healthy				DPN			
Segment	A4	S4	A16	S16	A4	S4	A16	S16
Pelvic translation (mm)(SD)	-3.77(3.2)	-5.82(4.7)	-1.19(1.1)	-1.63(1.4)	-6.52(4.0)	-6.70(3.74)	-2.37(1.68)	-3.24(2.5)
Pelvis angle (°)(SD)	0.10 (0.09)	0.17(0.1)	0.02(0.02)	0.02(0.02)	0.19(0.14)	0.21(0.15)	0.08(0.11)	0.06(0.09)
Shoulder translation (mm)(SD)	-4.31(3.6)	-6.51(5.3)	-1.01(0.7)	-1.52 (1.1)	-7.68(4.9)	-8.20(4.8)	-2.10(1.3)	-3.34(2.5)
Shoulder angle (°)(SD)	0.13(0.1)	0.12(0.09)	0.04(0.05)	0.05(0.06)	0.26(0.1)	0.28(0.13)	0.09(0.1)	0.11(0.09)
Head translation (mm)(SD)	-4.56(3.9)	-6.70(5.5)	-0.96(0.7)	-1.37(1.0)	-8.22(5.1)	-8.65(4.8)	-2.14(1.2)	-3.35(2.3)
Head angle (°)(SD)	0.13(0.1)	0.12(0.08)	0.06(0.06)	0.07(0.08)	0.28(0.1)	0.27(0.19)	0.1(0.1)	0.15(0.19)
Trunk angle (°)(SD)	0.02(0.03)	0.02(0.03)	0.01(0.01)	1.1(0.01)	<0.001(0.01)	0.01(0.02)	<0.001(0.01)	>0.001(0.01)

Table7.6 Maximum magnitudes during stimulation period (translation: negative values = movement right, Angles: negative values = right side of segment down) A =AFO S =NO AFO (at 4 and 16cm stance widths).

Segment	Group	SW	AFO	SW x AFO	Group x SW	Group x AFO	Group x SW x AFO
Max Pelvic translation (P)	>0.05	<0.001	0.008	>0.05	>0.05	>0.05	0.05
Pelvic angle (P)	0.01	<0.001	>0.05	<0.001	>0.05	>0.05	>0.05
Shoulder translation (P)	0.03	<0.001	0.009	>0.05	>0.05	>0.05	>0.05
Shoulder angle (P)	<0.001	<0.001	>0.05	>0.05	0.01	>0.05	>0.05
Head translation (P)	0.02	<0.001	0.01	>0.05	>0.05	>0.05	>0.05
Head angle (P)	0.005	<0.001	>0.05	>0.05	0.02	>0.05	>0.05
Trunk angle (P)	>0.05	0.01	>0.05	>0.05	>0.05	>0.05	>0.05

Table 7.7 Table to show significance values across healthy and DPN groups. Effect of AFO, Stance width, AFO x Stance width interaction Group x Stance width interation, Group x AFO interaction and Group x Stance width x AFO interaction on segmental movements.

Effect of stance width on postural response to hip vibration

In both groups there was a significant effect of stance width on postural response in all body segments with response amplitude decreasing at the larger stance width (table 7.7). This finding suggests that stance width alters the postural response.

There was a significant group x stance width interaction for shoulder and head angle responses (table 7.7 and appendix 10). As in part 1, post hoc analysis indicated that in response to hip vibration at a stance width of 4cm the shoulder and head angle was higher ((F(1,14)=31.2, P<0.001), (F(1,14)=11.8, P=0.004) respectively) in the DPN group when compared to healthy controls. The effect of increasing stance width on shoulder and head angle was greater in the DPN group ((F(1,14)=19.5, P=0.001), F(1,14)=15.5, P=0.001) respectively) than in the control group ((F(1,14)=7.0, P=0.01), F(1,14)=7.0, P=0.01) respectively). This finding suggests that the effect of stance width on upper body postural response to hip vibration is amplified in the presence DPN.

Effect of AFO on Postural response to hip vibration

Across both groups (DPN and healthy controls) wearing the AFO reduced the magnitude of translations significantly at the pelvis(F(1,31)=8.06 ,P=0.008), shoulder(F(1,31)=7.81 ,P=0.009), and head(F(1,31)=6.58 ,P=0.01)(table 7.7); the decrease in the postural response when the AFO was worn was independent of stance width. There was no significant change in the angles of postural response at any of these segments when the AFO was worn at either

stance width. This finding suggests that wearing an AFO can consistently reduce upper body translational postural response, irrespective of stance width and even in the presence of distal sensory loss.

The grand average responses (figure 7.16 to 7.20) to hip vibration at the pelvis are shown. There was a significant Stance width and AFO interaction for the pelvic angle (table 7.7) but this interaction was not apparent for any other parameter. Both groups responded in a similar way. At 4 cm stance width pelvic angle was greater in the No-AFO compared to the AFO condition. In contrast at 16 cm stance width the pelvic angle was greater in the AFO compared to the No-AFO condition. In fact the healthy control group the pelvic angle reversed direction at 16cm stance width, which (as in study 1, chapter 5) can be seen in the grand averages (figure 7.17), i.e. the pelvis tilted to the side of the stimulation (ipsilateral tilt).

The comparison of postural response to the AFO between groups showed that there was no significant difference in the movement and magnitude of response for any of the parameters between the groups with the exception of pelvic translation. The results showed that for pelvic translation there was a significant group x stance width x AFO interaction. By wearing the AFO the reduction in pelvic translation whilst standing at 4cm was less in the DPN group compared to the control, but conversely when standing at the wider stance width (16cm) the reduction in pelvic translation in the AFO condition was greater in the DPN group. This finding suggests that whilst there is a trend for the AFO to reduce pelvic translation in both groups, the magnitude of the reduction is inconsistent and difficult to predict.

Pelvic translation

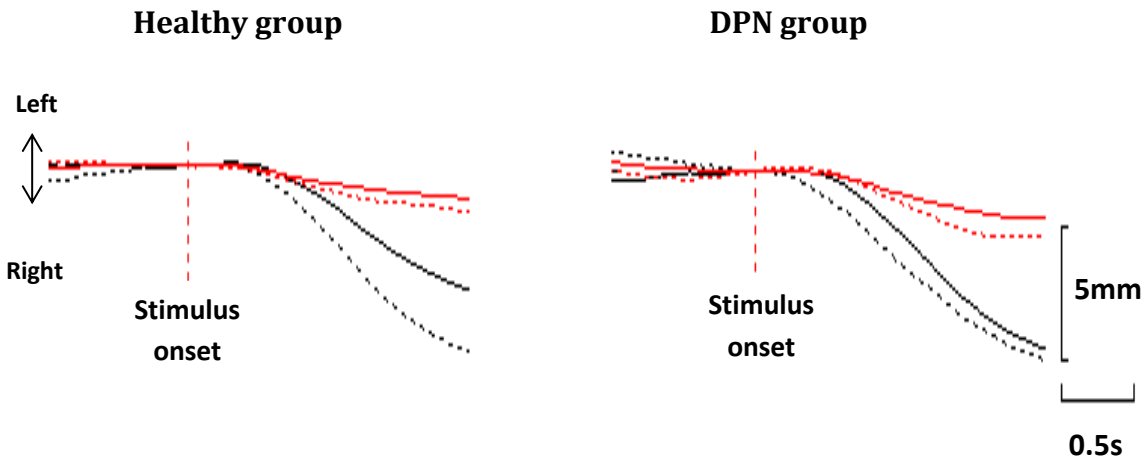
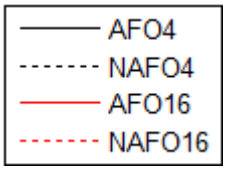


Figure 7.16. Grand average of pelvic translation in response to hip vibration (healthy vs DPN group) at stance widths of 4cm (black) and 16cm (red) in AFO/No AFO conditions.



Pelvic angle

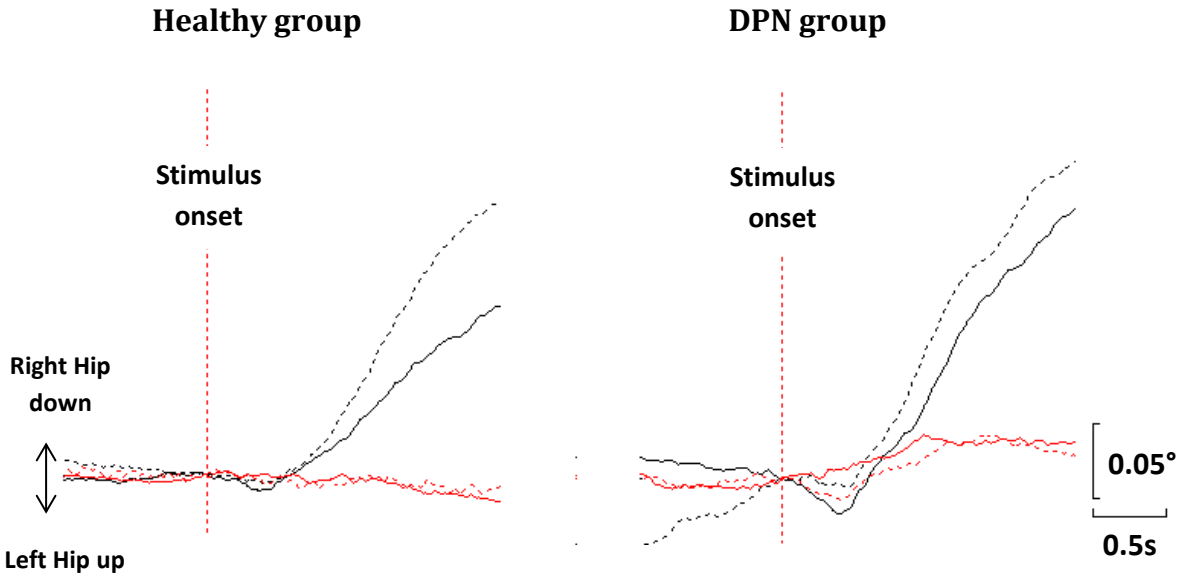


Figure 7.17. Grand average of pelvic tilt in response to hip vibration (healthy vs DPN group) at stance widths of 4cm (black) and 16cm (red) in AFO/No AFO conditions.

Shoulder angle

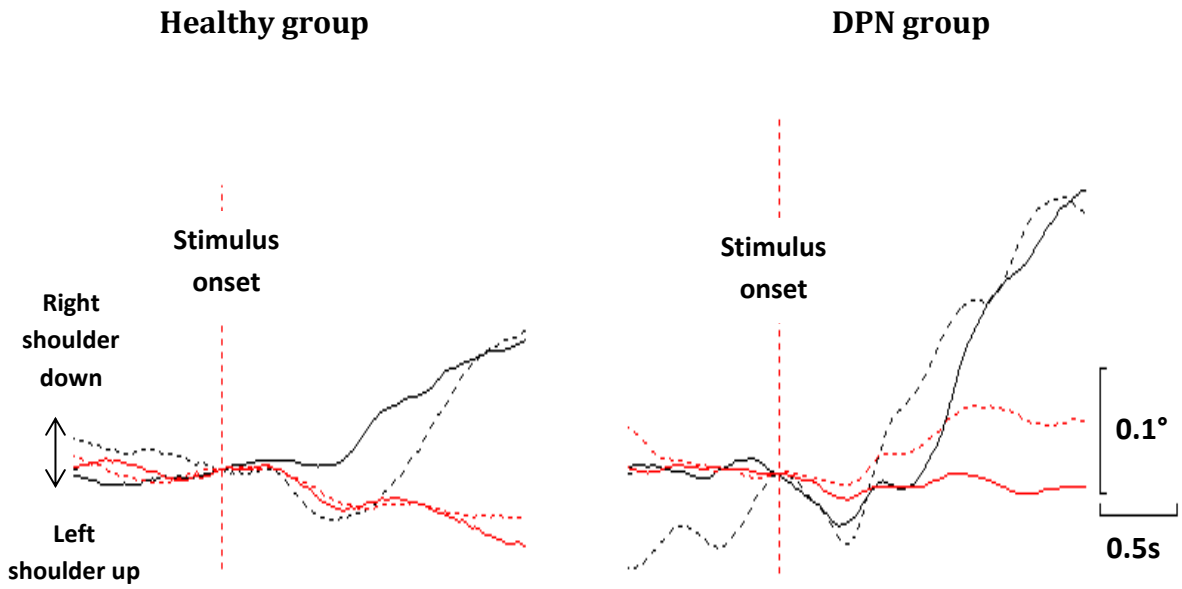
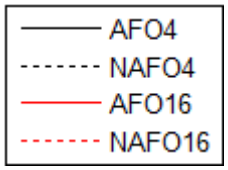


Figure 7.18 Grand average of shoulder angle in response to hip vibration (healthy vs DPN group) at stance widths of 4cm (black) and 16cm (red) in AFO/No AFO conditions.



Head angle

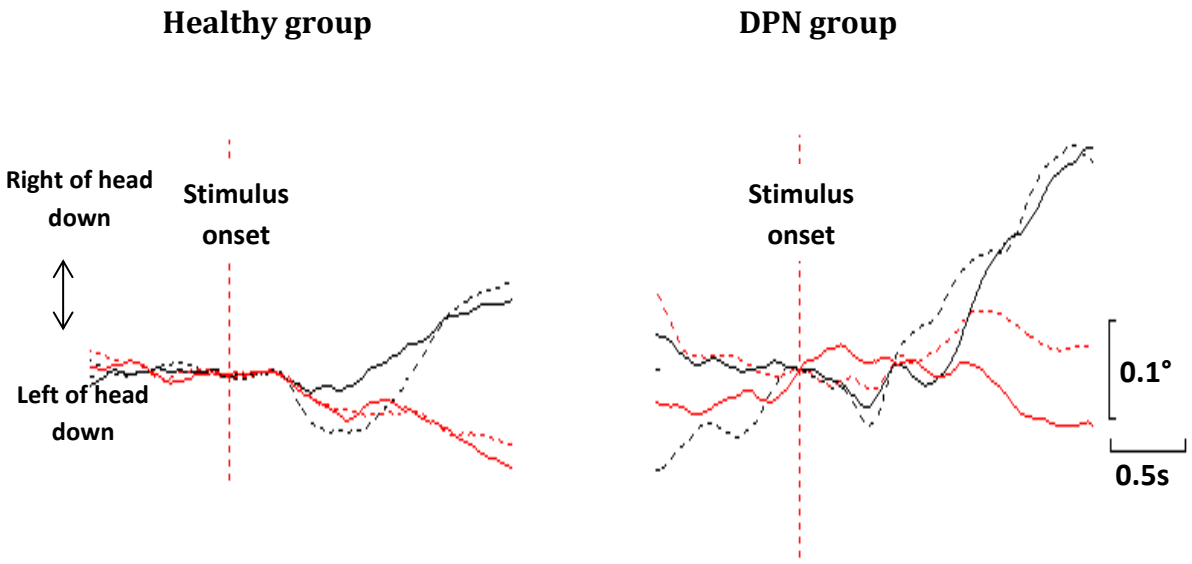


Figure 7.19 Grand average of head angle in response to hip vibration (healthy vs DPN group) at stance widths of 4cm (black) and 16cm (red) in AFO/No AFO conditions.

Trunk angle

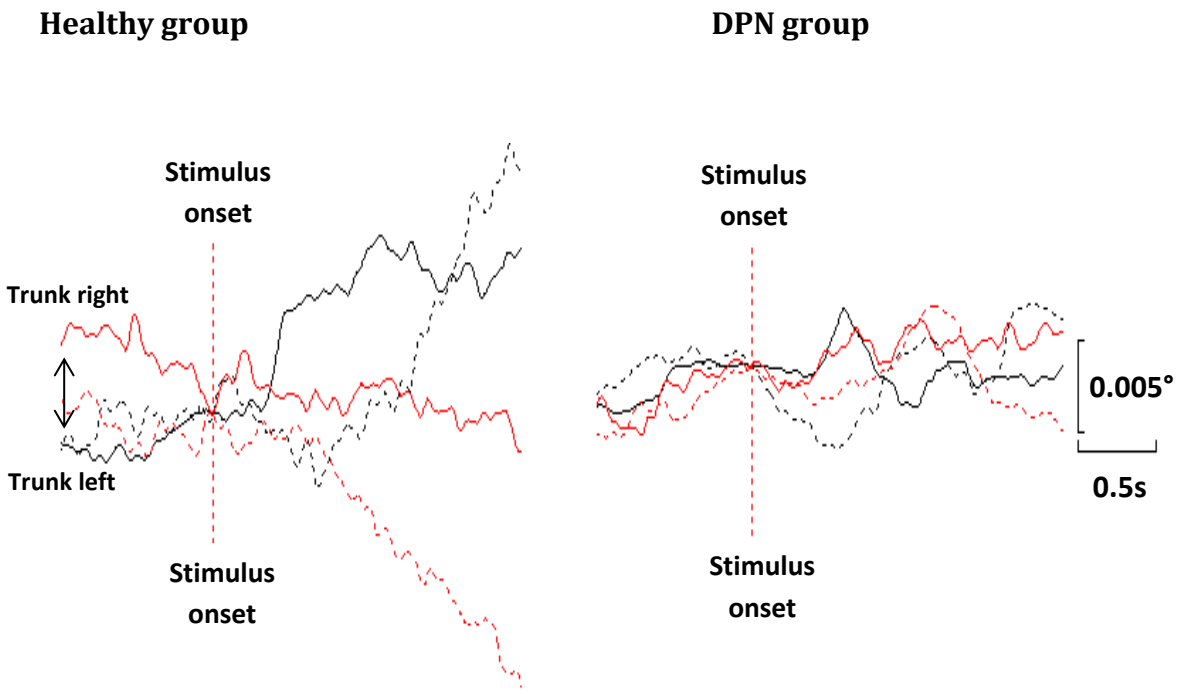


Figure 7.20 Grand average of trunk angle in response to hip vibration (healthy vs DPN group) at stance widths of 4cm (black) and 16cm (red) in AFO/No AFO conditions.

7.4.5. Relationship between participant demographics and postural sway/response in DPN

To assess for the relationship between covariate such as age, BMI and visual acuity the grand average response across all conditions was calculated (i.e 4cm stance width AFO, 4cm stance width No AFO, 16 cm stance width AFO, 16 cm AFO No stance width) and the relationship between each covariate and postural sway and segment motion (n=6) calculated. There was a significant positive correlation between visual acuity and postural sway and head, shoulder and hip translation. Here worse visual acuity (higher LogMar score) was associated with greater postural sway and greater segment translation following the hip vibration stimulus. There was no significant relationship between any other covariate and postural sway / segment motion after a Bonferroni correction was applied.

The relationship between visual acuity and head translation is shown in figure 7.21 (R^2=0.64). The healthy controls in contrast did not show any relationship (R^2=0.025).

	Visual Acuity	Age	BMI	Sensation	Strength	Duration
Sway	0.47*	0.07	0.15	0.04	0.14	0.07
Head Angle	0.16	0.02	0.39	0.00	0.01	0.03
Head Translation	0.64*	0.09	0.25	0.10	0.00	0.00
Shoulder Angle	0.06	0.01	0.03	0.04	0.11	0.05
Shoulder Translation	0.56*	0.08	0.25	0.08	0.02	0.00
Pelvic angle	0.13	0.09	0.41	0.00	0.10	0.00
Pelvic Translation	0.50*	0.05	0.20	0.09	0.02	0.00

Table 7.8 Correlation coefficients (R^2) between covariates and postural sway and the amplitude of segment angular and translatory movement following a hip vibration. * indicates p<0.0071 the significance level set after a bonferroni correction.

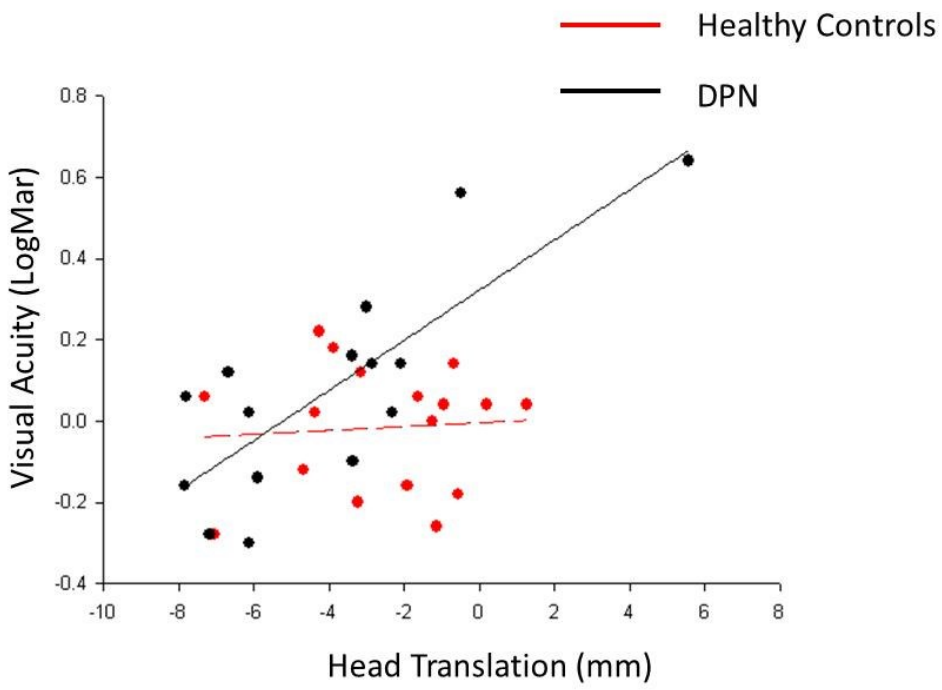


Figure 7.21 Relationship between head translation following hip vibration and visual acuity for healthy controls (red dots and line R^2=0.025) and people with DPN (black dots and line R^2=0.64)

7.5. Discussion

The effects of diabetic peripheral neuropathy on the mediolateral postural response to distal and proximal muscle vibration

This study aimed to test the hypothesis that people with diabetic peripheral neuropathy increase their reliance/weighting of proximal sensory information for balance control when compared to healthy controls. To do this a vibratory stimulation was used to provide an illusionary stretch of the hip abductor and ankle evertor which resulted in a measureable postural response.

This is the first study of its kind to investigate the effect of DPN on postural response to vibratory stimulation of the ankle (distal) and hip (proximal). The results suggest that people with DPN compensate for their distal sensory loss in a number of possible ways.

Postural responses to ankle vibration

Ankle evertor vibration resulted in a response similar in terms of direction in both healthy controls and the DPN group. This motion was a translation and tilt of the pelvis, shoulder and head toward the stimulus together with tilt of the trunk in the same direction. The similarity in response direction across groups highlights that the central processing of the vibratory stimuli are similar in the two groups which one may expect as the pathology affected the peripheral nervous system[413]. Sensory loss in the DPN group was impaired up to the level of the knee. Thus the size of the afferent input induced by ankle evertor vibration may have been reduced and yet the magnitude of response to evertor vibration was similar to that seen in healthy participants. This finding may reflect

an increase in the gain of the response, to the smaller sensory input. Over time the system may have compensated for the sensory loss such that a given input would lead to a larger output. A similar phenomenom was described by Wegampola (2002)[161] for the ageing vestibular system. The authors report that a standard galvanic vestibular stimulation led to a heightened oculomotor response in middle age and suggested that this finding is a reflection of upstream central nervous system compensations for the age-related decline in hair cell afferents[161]. It is difficult to determine with any accuracy the size of the incoming afferent stimulus received in response to a given applied vibration stimulus. Therefore it is difficult within the constraints of current knowledge and experimental techniques to explore this hypothesis further. It may be possible to use techniques such as common peroneal nerve conduction velocity or sensory evoked cortical potentials to help determine the integrity of the afferent pathways[414]. In future it could be useful to explore the effect of varying both the frequency and amplitude of the vibratory stimulus on the size of the postural response in healthy and neuropathic participants. Here stimulus-output curves could be used to determine changes in response gain in more detail.

Postural responses to hip vibration

Vibration of the hip abductor resulted in a similar postural response at the pelvis, shoulder and head in terms of direction in both groups. This was ipsilateral hip abduction due to contralateral translation of the pelvis. Accompanying the pelvic and shoulder translation was a tilt of the trunk in the opposite direction, that is, away from the side of the stimulus.

Analysing the magnitude of segmental movements exposed a change in postural strategies between groups. In the healthy control group in response to hip vibration, the pelvis in space tilts to a magnitude which is felt to be determined by the magnitude of the illusionary stretch of the muscle. More proximally the head and shoulder were stabilised in space with a significantly lower response (angle) to that seen at the pelvis. In the DPN group the pelvic tilt was similar in magnitude to that of the healthy controls. However, the tilt of the head and shoulder was greater, matching the angles seen at pelvis. The response in the DPN group is suggestive of a disease specific strategy whereby the pelvis, shoulder and head are fixed on one another resulting in similar, matched magnitudes of tilt at each segment. This could be a mediolateral equivalent of an increased hip strategy that is demonstrated in people with diabetes[281].

This disease specific strategy may be explained by a possible sensory re-weighting of sensory feedback, where due to unreliable information obtained from the foot/ankle, the DPN group increase the gain of the sensory information from the hips[23]. Whilst this explanation would provide a rationale for the greater shoulder and head movement observed in response to the same magnitude of pelvic tilt, it is at odds with the fact that the pelvis response did not increase in magnitude. If a gain of sensory information from the hips had occurred in the DPN group, there would be an expectation for an accompanying increase in the observed pelvic response. It may be that the increased trunk and head motion is associated with not only deficient distal sensory cues but also impaired visual input (the eyes were closed) and vestibular input as reported in diabetes[311,312]. For example if visual and vestibular information is distorted (e.g. by wearing

glasses that blur vision and receiving GVS) when walking young and elderly people show an increase in head and trunk roll when walking on a compliant surface or with a narrow base of support[165,415].

Alternatively, people with DPN may be preferentially aligned to the most stable sensory cues available. This is seen in healthy people, for example, when standing on an unstable surface there is a reduction in people orientating to the support surface and an increase in people orienting to vertical[166,167]. In, people with DPN with eyes closed the most reliable sensory information may come from around the trunk / pelvis rather than the distal legs. Here tilt of the pelvis in space is interpreted as a tilt of the support surface leading to head and trunk alignment with the pelvis. If this is the case one would expect people with DPN to align to the pelvis when tilted in sitting as well.

A final possible explanation is that there is a change in postural control strategy such that the greater magnitudes of motion at the shoulder and head result in an increased use of vestibular information to aid control of the whole body in space. An increase in the sensitivity to vestibular stimulation by means of GVS has previously highlighted that the vestibular system is more sensitive to stimulation in the presence of DPN[33,203]. The postural response to hip and ankle vibration is complex and develops over time during which multiple body segments move providing additional sensory input. Movement of the head elicited by hip vibration may in turn trigger vestibular-evoked responses that are larger in magnitude than healthy people because of the previously reported increased gain of the vestibular system[33,203]. Ultimately, increased shoulder and head movement seen in the DPN group result in the same outcome; increased

vestibular activity caused by greater head in space motion[416]. This is further supported by the fact that the covariate of visual acuity significantly affected the pattern of the postural response to hip vibration despite the eyes being closed. This suggests that there are long term adaptive changes in how multiple sensory inputs are used to control balance. As the changes can be seen without stimulation (e.g of the eyes) this suggests the changes occur in the areas of the brain dedicated to integrating multi-sensory inputs and producing a postural response rather than pathways dedicated to the initial processing of the sensory stimulus. That is the adaptive changes are downstream, of the areas of the brain involved in initial sensory processing. Currently based on the findings of this chapter and the supporting evidence from previous research[33,203] this is the primary theoretical explanation for the responses seen although further work exploring the responses to single and multi-channel sensory stimulation in people with DPN with / without support surface angle changes would be required to support or refute this theory.

In the healthy population the control of head position is achieved via a head in space strategy, such that the angle of the head remains relatively constant[417]. It can be hypothesised that healthy participants are orienting to the gravitational vertical , as described previously under different task conditions[166,167]. Fixation of the shoulder and head on pelvis as observed in the DPN group results in poor stabilization of the head in space. The difficulty with adoption of this strategy is that it is likely to result in a decrease visual acuity during functional task, because the eyes then move with the head and thus must be stabilised using gaze stabilising reflexes such as the vestibulo-ocular reflex[418]. This

compensatory balance strategy and its effect on the functional visual acuity of people with DPN, provides a line of enquiry that warrants further investigation.

Previous research has suggested that people with DPN adopt a slower walking speed as a compensatory strategy to slow down accelerations of body segments in an attempt to stabilise the visual field[14]. The results of this study indirectly agree with this finding. In this study the results suggest that when a stereotyped imposed sensory perturbation is applied to people with DPN, the head moves more in space than normal. When this finding is translated to a real world situation, it can be postulated that with eyes open (as opposed to the current study) this increased head motion would reduce visual acuity. Adopting a slower walking speed would counter this effect by reducing head motion. This functional gait adaption would increase gait stability and improve balance through maintenance of visual acuity. This compensatory method of balance control is of increased relevance to people with diabetes who often suffer primary deficits in visual acuity as a result of complications such as cataracts. The implications of this finding on motor control, and balance in people with DPN offers insight into how people with diabetic peripheral neuropathy use an additional compensatory postural strategy to slow down movement accelerations of the upper body which may threaten stability by interfering with the maintenance of a stable visual field[14]. This will be further explored in the final chapter.

The effect of DPN on the impact of stance with on postural control and the potential of an AFO to contribute to postural control.

The second group of hypotheses aimed to test the differences between people with DPN and aged matched controls in terms of the impact of stance width and the modulating effect of an AFO on; 1) baseline sway velocity and 2) postural responses to hip vibration. This study has shown that increased stance width and an AFO designed to reduce mediolateral motion of the foot/ankle (subtalar joint) decreases mediolateral sway velocity and postural translations to hip vibration by a significant amount in the diabetic population and healthy controls tested. These were more pronounced in those with DPN.

Sway velocity was measured over an initial 1 second baseline period. The DPN group had a greater sway magnitude compared to that of the healthy controls in both stance width positions (4cm and 16cm). The difference in velocity (DPN vs control group) was greater at smaller stance widths where the ankle contributes significantly to postural movement and sensory feedback about the ankle[222] where motion is described as an inverted pendulum[358]. People with reduced sensory feedback from the foot/ankle therefore show a greater sway velocity[256,284]. At the wider stance width of 16cm, the magnitude of sway was less in both groups. This could be explained by 1) an increased coupling between the ankle and hip, where movement at the ankle is matched with simultaneous movement at the pelvis as described in Chapter 5, 2) an increase in the limits of stability, the distance the centre of mass needs to move before it is outside of the base of support leading to imbalance[386]. Postural sway is predominately centrally generated. Higher stability limits could therefore lead to

a reduction in the amplitude of centrally generated postural responses; the reverse situation that occurs when one stands on an unstable surface or at the edge of a raised platform[419].

The use of an AFO induced reduction in sway velocity in both peripheral neuropathics and healthy control groups, in agreement with Bigelow and Jackson (2014)[333] who also found that AFO reduced sway velocity but unfortunately did not report on the stance width adopted during testing. In this study the effect of AFO was greatest in the DPN group at 4cm. The effect of AFO was therefore dependent on stance width.

The AFO may have provided solely mechanical stabilisation of the joint in the mediolateral direction and thus led to a reduction in sway. Whilst significant effects when wearing an AFO on segmental translations in response to vibrations were found, there were no significant changes in the pattern of body segment movement. As highlighted in study 2 angular motion of the pelvis in the frontal plane requires sagittal plane movements at the knee and ankle joints to allow for the change in functional leg length that must accompany angular pelvic tilt[114]. The lack of any change in the pattern of mediolateral angular motion may indicate that this type of AFO does not affect anterior-posterior movement of the ankle and thus the ankle and knee are still able to move to allow mediolateral motion at more proximal segments.

The mechanical effects of the AFO may be caused by an increase in joint stiffness and viscosity rather than blocking/preventing movement. Postural responses during vibrations did not show a mechanical blockade i.e. the

potential for motion was still present. One proviso is that the sway caused by the vibration was small and restriction of movement amplitude could have been seen with larger postural responses that may occur in functional movements. Chapter 3 highlighted that little is known about the mechanical effects of AFOs on balance in DPN. Future work could include the measurement of the visco-elastic properties of the AFO-ankle joint complex and if this affects balance in a linear manner.

It was previously hypothesised, that the effect of the AFO on postural responses to vibratory perturbation would be greater at 4cm when compared to that of the responses seen at a 16cm stance width. This was informed by the results from study 1 (Chapter 5), where this was observed. There, it was concluded that for healthy subjects the stabilising effect of AFO reduced as stance width increased. However, in this current study of people with diabetic peripheral neuropathy, the effects of AFO, particularly on hip translations, were significantly greater at 16cm as opposed to the responses seen when standing at 4cm. This may reflect that healthy participants are already very stable with a stance width of 16cm with no AFO and there is minimal stability to be gained when wearing an AFO. In contrast, people with DPN may still be relatively unstable with a stance width of 16 cm and can gain benefit from the stabilising effect of the AFO. This patient group are known to increase their base of support whilst standing[218] and walking[376], to aid stability. Therefore, investigations into the use of AFOs on stability in people with DPN when adopting different stance widths during functional tasks (e.g. walking in natural environments) maybe an area considered worthy of future research.

The significant AFO x Stance width interaction may be interpreted in a similar way to the pelvic / trunk changes seen in study 1. At larger stance widths when the ankles are constrained the brain interprets the hip vibration as arising from a tilt of the pelvis as translation is now affected by the restriction in mediolateral ankle motion. With greater restriction of ankle motion (i.e. when wearing the AFO) this behaviour is more marked. As there was no group interaction it can be concluded that the DPN do not show any greater response as hypothesised (hypothesis 3) although they still show this effect. The AFO x stance width interaction at the pelvis and trunk in fact seemed larger in the control group although this was not statistically significant.

As in study 1 the control participants showed a reversal in the direction of pelvic motion in keeping with a perceived change in the cause of vibration induced hip adduction (tilt Vs translation). The trunk showed a similar response although this was not significant. A reversal in trunk direction was seen in the trunk for the control group on the grand average. In contrast the DPN group showed minimal trunk motion (<0.005°) and no clear pattern of response under any condition. Although the DPN group showed an AFO x stance interaction at the pelvis a reversal of tilt did not occur. This may reflect the larger tilt of the shoulder and head dominating the overall postural response 2 s after stimulus onset as discussed previously.

The similarity in AFO x Stance Width interaction between groups for pelvic tilt adds to the evidence that people with DPN may not show an increase in the use of hip proprioceptive information to balance over that normally seen. Thus, in keeping with the findings following ankle evertor vibration, the effects of acute distal sensory loss compared to chronic sensory loss on both the processing of

distal and proximal vibratory stimuli is different. This will be explored further in the final chapter.

The relationship between covariates and postural sway/segment motion

Visual acuity showed a significant positive relationship between postural sway and segment translation following the hip vibratory stimulus). Higher scores on the logMAR scale (indicating worse visual acuity) were associated with greater postural sway velocity and high translation amplitude at the head, shoulders and pelvis in response to hip vibration. This association is seen despite the fact that postural sway and postural responses to hip vibration were recorded with the eyes closed. This suggests that visual loss leads to a long-term change in balance and posture control.

As visual stimulation is not required to see this association (i.e. it is seen when balance is measured with eyes closed) it suggests that any long-term changes occur downstream of the pathways conveying visual information and affects the central postural control areas that integrate information from multi-sensory channels and connect to descending pathways controlling postural control movements. Thus, it is felt that visual loss leads to a change in gain of the postural control system akin to that postulated for the vestibular system[33].

7.6. Conclusion

This study has given new insight into how the sensory control of balance changes with alterations in posture (altered stance width) and environmental factors (with an AFO) in healthy participants and how that compares to the response seen in the diabetic neuropathic population.

Firstly, this study has indicated that postural strategies exist in the mediolateral plane in response to sensory perturbation of the hip abductors. These strategies are modified in the presence of distal sensory loss, with increased motion at more proximal segments of the shoulder and head. Although potentially beneficial in one respect, as it results in a greater use of vestibular stimulation, the increase in motion of the head may have a negative impact on visual acuity which is required for balance maintanance[420] and therefore a risk factor for falls[301,303].

Secondly, the findings provide evidence that with increasing stance width the mediolateral postural response to hip vibration is reduced. In addition an AFO reduced the size of hip vibration-evoked mediolateral postural responses, even in those with peripheral sensory loss. Further, when assessing the pelvic motion elicited by hip vibration, the results indicate that there is an interaction between stance width and AFO use. In healthy participants the effect of an AFO on pelvic translation is less at 16cm compared to 4cm stance width. In contrast there is a larger effect of an AFO on pelvic translation at 16cm stance width in people with DPN.

Thirdly, this is the first study to demonstrate the beneficial effects of mediolateral stabilisation in people with DPN provided by ankle foot orthoses on postural control as measured by postural sway. Sway velocity, a commonly used outcome measure of stability, was found to be greater in those with diabetic peripheral neuropathy when compared to healthy controls particularly at a reduced stance width. The results showed that wearing the AFO can reduce sway velocity, and that the effect is more pronounced in those with DPN and at smaller stance widths compared to healthy controls.

These findings form an important basis into the understanding of normal and pathological mediolateral control of balance, and give an indication of how individuals with DPN may benefit from the use of AFOs for mediolateral postural stability.

7.7. Limitations

The interpretations of findings from this study are given with a note of caution. Postural sway is a measure of static balance, thus the findings from this study may not be a true reflection of the postural response occurring during dynamic gait or within the real word environment. In this study postural sway data was gathered over a 1 second baseline period. Other studies assessed sway over more prolonged periods of time (e.g. >20s)[55]. Collecting sway data over a greater period would have lengthened the data collection sessions and risked fatiguing participants. However, the duration of data collected may not have been sufficient to allow the body to achieve a steady state after closing the eyes.

This may have led to an overestimate of sway magnitude. This does not detract that there were group (Diabetic peripheral neuropathy vs healthy control) differences although this could reflect the fact that people with diabetic peripheral neuropathy were worse at stabilising in the first few seconds after closing their eyes as they are more visually dominant as a result of their distal sensory loss. The postural sway velocity measures with eyes closed in the healthy controls were of a similar magnitude to that previously reported[55] suggesting that this is a valid measure and comparable to previous work.

The use of a safety harness was necessary in this study due to the increased balance dysfunction in the DPN group. Although designed to provide support in the case of a fall during data collection, the harness would have inevitably provided sensory input at the level of the waist and shoulder. When safety measures are in place there may also be an increased confidence in one's stability leading to changes in one's normal movement pattern[419]. Alternatively to overcome the sensory implications of the harness, multiple spotters could be put in place to support the subject if required. The possible increase in confidence would be difficult to overcome as ethically participants need to be aware of their safety at all times.

This investigation is limited to the immediate effect of an AFO, any long term changes in balance responses cannot be assumed. Therefore a longitudinal study design could explore the effects of AFO use over time or after periods of use i.e. explore potential training effects on postural control and movement strategies. Studies in people with MS show that in-shoe orthoses can lead to improvements in balance when worn over prolonged (3 week) periods[54].

This investigation was a cross sectional design that explored balance in people with various durations of DPN. A longitudinal cross sectional observational study mapping stimulus response size over time from diabetes diagnosis to onset of diabetic peripheral neuropathy and onwards would have provided an insight into the adaptive process of people with diabetes.

The study would have also benefited from additional outcomes measures of balance. Force plate measures of centre of pressure were originally included; however pilot work showed that ankle vibrations used to induce postural responses were transmitted to the force plate from the limb or the AFO. This resulted in signal artefacts and poor signal to noise ratio. Currently there is no dampening solution to this vibratory noise. Electromyography (EMG) could have also provided an insight to the electrical activity of both distal and proximal muscles in response to the vibratory perturbations. However, measuring EMG responses to sensory perturbations requires averaging >15 stimuli per condition to improve signal to noise ratios[158]. These additional measures would therefore have placed greater burden on the participants, therefore, as guided by a PPI group they were not included in the study.

Chapter 8 . General discussion and conclusions

8.1 The problem revisited

The ability to maintain postural stability relies on reliable information from multiple sensory systems[151]. When feedback from one or more of these systems is reduced instability can occur[57], as demonstrated by those with DPN where peripheral somatosensory information is diminished. This increases the risk of falls and falls related injury in people with diabetic peripheral neuropathy[8]. Gaining a greater understanding of balance control in people with DPN and how that compares to healthy controls has the potential to inform the development of targeted interventions, where there is a lack in current evidence[32] as outlined in chapter 3. Improving the balance of people with diabetic peripheral neuropathy could reduce falls risk, improve quality of life and increase life expectancy[19]. In addition to this, the financial burden of falls related injuries on the National Health Service (NHS)[421] could be reduced.

Balance impairment can be identified through the measurement of increased sway during quiet standing in both sagittal and frontal plane motion[175]. Previous authors have explored changes in anterior-posterior balance strategies during quiet standing in people with DPN[30,33,256]. Changes in mediolateral balance strategies are yet to be fully explored. However with ageing, the control of mediolateral stability has been reported to be a major problem associated with increased risk of falling[34], due to impairments in the ability to generate rapid and

appropriately controlled muscular forces, joint torques, and postural movements involving mediolateral hip motion[41,174].

Although postural sway provides a measure of postural control it is a gross measure that does not provide information on specific aspects of postural control. As people with DPN have distal somatosensory loss, and there is previous evidence for sensory re-weighting after sensory loss[24], the proprioceptive control of balance was specifically investigated using ankle and hip muscle vibratory stimuli.

Postural control is not immutable but varies with the task and environmental conditions. Changes in conditions may affect balance in different ways by changing mechanical constraints or the availability or processing of sensory inputs. Therefore the effects of stance width alterations and AFO use were assessed. Both of these conditions provide information into the modulation of balance and are also potentially clinically useful strategies.

The thesis compared people with DPN and age matched healthy controls. However, people with DPN have a chronic condition. Therefore group differences could reflect both the effects of sensory loss and the effects of time as people adapt to the gradual onset of sensory loss. To investigate this further the effects of acute sensory loss in healthy people was explored.

8.2 The aims revisited

This investigation aimed to contribute to the current knowledge base by testing the following theories:

- Distal sensory loss (acute or chronic) will lead to a re-weighting of sensory information from proximal sources as measured by an alteration in the size of the postural response to a proprioceptive-induced balance perturbation.
- An AFO design to limit mediolateral motion of the foot/ankle will reduce sway velocity.
- Increases in stance width will reduce mediolateral sway velocity.

The investigation began by exploring the effects of AFO's, stance width (chapter five) and experimentally reduced distal sensation (chapter six) in healthy people. Results from this preliminary work informed the protocol of the main repeated measures observational study of people with diabetic peripheral neuropathy (chapter seven). Valuable information gained from a PPI group event (appendix 5) provided additional information to inform the data collection protocol and ensure acceptability for participants with diabetes and neuropathy.

8.3 Interpretation of main findings

The followings section will highlight some important points not covered in the discussion sections at the end of each experimental chapter.

8.3.1 Understanding balance in health and disease

This thesis focused on the control of standing balance. The studies measured balance through observation of postural sway and the measurement of postural responses to sensory perturbations. This approach gives insight into specific aspects of balance important for stability maintenance and prevention of falls. Balance is required to successfully perform the majority of day to day functional tasks. Postural muscle activity precedes voluntary movements such as lifting the arm or taking a step; these are termed anticipatory postural adjustments[70,422]. These are feedforward responses generated by the central nervous system (CNS). Postural muscle activity is also seen after a physical perturbation; termed a postural response or reaction[71,75]. Both feedforward and reactive responses require normal integration of the multiple senses that can contribute to balance. Sensation informs the CNS about the current state of the body (e.g. position, movement and inertia) that is used to plan forthcoming movements. Sensation is also used to signal a physical perturbation and thus trigger postural reactions[71,75].

It was not the intention of this study to look separately at the feedforward and feedback processes involved in balance control. Rather, as highlighted in chapter 2, postural sway consists of an interplay between feedforward and feedback processes[423] and was selected for use in this study as an accepted valid global measure of balance ability[66–68].

People with diabetic peripheral neuropathy have distal sensory loss and there is evidence that sensory re-weighting may occur[30,33] (e.g. increased gain in the vestibular system and changes from ankle to hip strategy). There are several methods to explore the sensory control of balance. 1) By systematically

removing remaining sensations and assessing the impact on balance (e.g. closing the eyes). Using this method increased sway would be considered an indication of importance of the removed sensation as seen when performing the Rhomberg's test. 2) By adding a sensory input such as a moving visual stimulus, galvanic vestibular stimulation or muscle vibration. Using this method a large postural response to a sensory perturbation may indicate that the gain of that sensory channel has increased[161]. By implication small imposed or self-generated movements occurring during everyday tasks would therefore result in a larger postural response than normal. The clinical interpretation of this observation is unclear from the literature. In one study a large response to Galvanic Vestibular Stimulation in people with diabetic peripheral neuropathy or sensory loss[33,160] was interpreted as an increased postural response gain that could lead to improved stability. Conversely in another study the increased size of response to moving visual stimuli in people with cerebellar disease was interpreted as a higher gain channel that could contribute to postural instability[38]. In the current thesis increases in the gain of the responses were seen to hip vibration following acute distal sensory loss but not following chronic sensory loss. Whilst the results of such studies are clear, further research is required to reveal the functional consequences. The differences in interpretation could reflect the relative ease that different sensations can distinguish between self-generated and external environmental motion. Proprioceptive and vestibular signals are more commonly associated with self-motion, whilst visual signals on their own cannot distinguish between self-generated and environmental motion. Therefore an increased proprioceptive and vestibular response gain may help with balance whilst an increased visual response gain could lead to instability if the cause is environmental rather than self-generated motion[38.] Future work

could explore the effects of environmentally imposed, artificially imposed and self-generated stimulation of different sensory channels on posture and balance. For example, one could compare the effects of a surface translation (environmentally imposed motion of the ankle) or an imposed perturbation at the hips with the effects of vibration of the ankle and/or hip muscles (artificially imposed sensory stimulation) and similar amplitude self-imposed movements.

The postural responses seen with muscle vibration were small but stereotyped. The pattern and latency of response was similar to that previously reported[142]. As demonstrated in appendix 2, a large vibrator produced a larger response but there is then a potential trade-off between the amplitude of the signal and the spread of the signal to adjacent muscles / receptors. It is possible to increase the response signal to noise ratio without the spread of the signal to adjacent muscles by simply increasing the number of trials; these varied from 3-10 in previous studies[30,33,51,142]. Informed by PPI feedback five trials for each test condition were chosen for the patient related studies to reduce the effects of fatigue in participants during data collection. However to maximise the signal to noise ratio it is recommended that for future work researchers consider minimising the number of conditions whilst maximising the number of trials per condition.

The postural response induced by the muscle vibration had a long latency with the response starting >500ms after stimulus onset. This is in contrast to the response to stimulation of the motor cortex using transcranial magnetic stimulation where motor evoked potentials are seen after 31ms in the leg[130]. The current responses were movements rather than electromyography responses (muscle activation) or measures from force plates. The latter would

occur at an earlier latency as changes in the ground reaction forces lead to the changes in movement that were measured in the current study. However, forces could not be recorded in this study as the ankle evertor vibration produced force plate artefacts. Whilst additional useful information about EMG responses for targeted key muscles in the pelvis and trunk could have been gathered, the additional number of trials per condition needed to average out background noise from the EMG data set were considered unacceptable for people with diabetic peripheral neuropathy due to the potential of inducing fatigue.

Regardless of the means of measurement there is still a large delay from stimulus onset to response. The delay is not particular to this thesis and has been reported elsewhere[142]. The delay may in part reflect that the stimulus is not a simultaneous electrical excitation of all the relevant nerves, as occurs with transcranial magnetic stimulation (TMS) or in nerve conduction studies. The vibratory stimulus used in the current study may need to build up and cross a threshold before a response is elicited. The long response time means that the neural pathways and structures that could contribute to the postural response could be numerous. Such long latency responses are also seen with even more discrete stimuli such as GVS where the latency is >150ms exceeding our voluntary reaction times[75]. There is ample time for the stimulus to elicit transcortical responses as well as excite areas in the brain stem / spinal cord. It is assumed that the stimulus is integrated in multiple sites within the CNS. In future looking at the interaction between different more discrete stimuli (e.g. GVS and motor cortical stimulation) and muscle vibration as well as looking at the effects of selective lesions (e.g. brain stem strokes) could help us to understand the pathways used to generate the postural response.

The timing of the response data collection is relevant to the interpretation of the findings. In studies 1-3 the response was measured 1 second after the vibration stimulus was received by the participant. This analysis window was determined using grand average data taken from pilot studies (appendix 2) that described the development of the response over time. The participant response to the stimulus tended to develop over time i.e. the movement started in one direction and then continued in that same direction until stimulus offset. Therefore the effect size between conditions essentially built up over time. Thus the chance of detecting a significant difference between conditions was increased by capturing data later in the response time course. However, a limitation of this approach is that the person has been moving for >1 second. Therefore the response will include sensory input from multiple systems as well as postural responses being elicited to respond to the effects of the initial sensory perturbation and movement. This means that the direct effects of vibration were not assessed but rather the data represents an amalgamation of these other effects. It may be that an analysis of the earlier postural responses is justified for future work but this would require more stimulation trials to overcome background noise which was not possible in this thesis. Therefore, this data should be interpreted as an initial evaluation of the proximal proprioceptive control of balance in diabetic peripheral neuropathy and healthy participants.

Movement usually requires multi-sensory information this avoids sensory information from one channel being misinterpreted. Vision alone for example will not tell you whether it is you or the environment that is moving; additional sensations are required to figure this out. Similarly vestibular signals (e.g. from the semicircular canals) alone do not tell you whether the head or the whole body is tilted in space; once again other information such as that arising from

neck afferents is required[424]. Interpreting muscle lengthening as induced by a vibratory stimulus can also be difficult and can give rise to illusions. The Pinnochio illusion[385] occurs where vibration of the elbow extensors is given while the person touches their nose. Here people can erroneously perceive that the nose is lengthening. This is because the illusionary lengthening of the elbow extensors induced by the vibration dominates. Given the hand is still touching the nose the interpretation is that the nose has lengthened. The large trunk response observed in study 1 when participants wore the AFO and adopted a large stance width may reflect a change in the interpretation of the same vibratory stimulus similar to the Pinnochio effect as discussed in chapter 4. Usually when applying sensory perturbations (eg GVS) response size invariably reduces when the base of support is increased[23,130]. The finding of a larger postural response to a sensory perturbation in a body segment when donning an AFO and adopting a large base of support is a novel finding in motor control literature. It has the important implication that constraining body parts to aid stability may in fact cause excessive motion at distant body segments. This could in turn lead to instability and falls and / or result in functional consequences such as large head / trunk motion that may affect visual acuity as discussed below (section 8.32). It would be interesting to explore the hypothesis that a rigid AFO would produce a larger trunk movement.

The functional significance of the trunk movements and the implications for people with diabetic peripheral neuropathy is unclear. No significant change in trunk motion was seen in study 3 when wearing an AFO and adopting a large stance width. This may reflect differences in the study paradigms (e.g. fewer stimulation trials; differences in the stimulus positioning, the influence of the

support harness) or a type II error (i.e. the study was underpowered to detect this).

8.3.2 Strategies: Implications for functional ability

One novel finding from study 3 was the difference in response pattern or strategy adopted by the DPN group. People in the DPN group moved their pelvis, trunk and head en-bloc whilst the healthy participants appeared to stabilise their head more in space so the pelvis translated/ tilted and the trunk tilted in opposite directions. The possible explanations for the diabetic peripheral neuropathy group response pattern were (a) changes in sensory re-weighting leading to a large proximal response to the vibratory stimulus (b) alignment to reliable somatosensory signals arising from the pelvis / hip area (c) co-contraction of the trunk and head (d) compensatory strategy to increase vestibular feedback to aid postural control. Changes in co-contraction could be assessed in future by recording surface EMG. Relating the change in response pattern strategy to the response amplitude to GVS stimulation may provide an indication whether this is at least linked to the vestibular system although it would not dissociate cause from effect.

It is not known if the increased head/trunk movement seen in the diabetic neuropathic group in response to the hip vibration perturbation is reflected during gait or if this phenomenon increases with walking speed. In the event of increased head motion during gait there would be an associated decrease in visual acuity (VA) as is seen when testing dynamic Vs static visual acuity[425]. Interpretations of changes in visual acuity however could be complicated by the fact that people with type I and II diabetes can show signs of vestibulopathy due

to pathology within central and peripheral pathways and the peripheral end-organ[309,313,426]. The implications of this will be explored further in section 8.5 (future research).

Models and modes of recovery

Study 2 and 3 produced different findings. In study 2 acute onset of sensory dysfunction led to a sensory re-weighting with reduced response amplitude driven by distal sensory information and an increase in response amplitude driven by proximal sensory information. This was interpreted as a response whereby the CNS ignored distal information that was less reliable and increased the importance (weighting) of more proximal information. Such immediate changes in postural responses are replicated in everyday life[102]. Postural sway and responses to physical perturbations change depending on whether a person is at ground level or standing on a platform high in the air[419] and will occur, for example, when walking on ice. Such adaptive changes maybe under the influence of the cerebellum which plays a crucial role in adaptation of postural responses[200] and it would be interesting to see whether similar adaptation to cooling occurs in people with isolated cerebellar lesions.

In contrast there was no direct evidence of sensory re-weighting in the people with diabetic peripheral neuropathy observed in study 3, despite having extensive distal sensory loss. This may reflect differences in the time of symptom onset. With a slowly progressing condition the CNS may adapt and make maximal use of the remaining distal sensation. Welgampola (2002)[161] found that the vestibular system adapts to the gradual decline in semicircular

canal hair cells with aging. In this case a GVS signal that bypassed the semicircular canals and stimulated the nerve directly led to a greater response i.e. an increased gain in the response[161,427]. This, however, was not apparent in the people with diabetic peripheral neuropathy with either distal or proximal sensory stimulation. This may be because distal muscle vibration used the end organs and peripheral pathways that were directly affected i.e. the actual input into the central nervous system was reduced and so not comparable with that of the healthy control group. The same cannot be said however for the proximal muscle vibration where sensory loss was not evident. Slow changes in postural control over time are also reported in people who have tumour growth (e.g. affecting the acoustic nerve -an acoustic neuroma[428]). People with slow progressive degenerative conditions have demonstrated adaption over time to the gradual nerve degeneration[354]. Parkinsonian symptoms, for example, only manifest themselves when the substantia nigra (highly affected by the pathology) has degenerated by up to 80%[429]. Clearly, with slow developing conditions adaptive changes are possible within the postural control system.

Understanding the adaptive process of people with diabetic peripheral neuropathy will help researchers optimise interventions to optimise these adaptive mechanisms and aid their maintenance over time. This may require future longitudinal studies following people as they develop sensory loss.

8.4 Limitations

Specific study limitations have been described at the end of each experimental chapter. This section explores limitations with the overall study approach.

1) Vibratory Stimulus: site and extent of stimulation.

Imposed sensory perturbations can result in illusory feelings of movement (e.g. spinning with GVS[430]).Vibration is perceived as a lengthening of a muscle due to activation of muscle spindles. However, vibration will also activate cutaneous receptors in particular Pacinian corpusles which have large receptive fields that can cover the whole of the limb[431]. Further, the vibratory stimulus was attached via a belt wound around the shank / waist. Therefore, the vibration may have affected distant receptors unaffected by the disease process as well as other adjacent muscle groups. This could have affected the observed postural response. Therefore, there is the possibility that the response seen and its interpretation are complicated by stimulation of distant effectors and different afferents. Regardless of this limitation the stimulus was standardised across conditions and groups and there were clear differences seen with changes in task and environmental conditions; acute sensory loss and in DPN compared to controls.

People with diabetes tended to have a higher BMI although this was not significant. Differences between people with DPN and the control group could therefore be attributed to differences in BMI. With higher BMI there could be less transmission of the vibratory stimulus to the underlying muscle. This may especially be the case for stimuli around the hips. Preliminary work using a pig hip joint model (appendix 9) suggested that the vibratory stimulus decreased its

amplitude dramatically at a depth of 4 cm. The pig hip was chosen due to similar anatomy to the human and similarities in skin and subcutaneous fat properties. However, the degree of subcutaneous fat was not systematically changed only the depth within the muscle. Subcutaneous fat may transmit the vibratory signal differently. However, this suggests that the effective vibratory stimulus may vary with interposing tissue between the vibrator and underlying muscle.

Group differences in study 3 (Chapter 7) were assessed using BMI as a covariate and this still produced group differences suggesting that this is not a major limitation. Future work should, however, aim to match for BMI more closely. However, this may result in many people in the control group having type II diabetes with no peripheral neuropathy which has also been shown to affect balance[284]. In addition calliper readings should be taken over the areas of stimulation to provide an estimate of subcutaneous fat and to allow a correction for this in the statistical analysis using an analysis of covariance.

2) Functional implications of postural measures.

Two measures of balance were used; postural sway and vibration-induced postural responses. The aim was to investigate the impact of sensory loss, task and environmental constraints on balance. Although the aim of the thesis was not to explore the functional consequences of balance dysfunction it is important to acknowledge the potential implications. Postural sway for example is a static measure of balance; if the person is balanced the centre of mass remains in the base of support. In contrast walking requires dynamic balance; as discussed in chapter 2 here the centre of mass is frequently outside the base of support. The control mechanisms underlying static and dynamic balance may

therefore vary. How much increased postural sway relates to balance dysfunction during functional tasks is therefore open to interpretation. Recent work suggests that postural sway is a result of centrally generated feedforward processes that presumably are also involved in the dynamic control of balance while walking[64,66–68]. Further, increased postural sway is a risk factor for falls and postural sway amplitudes correlate with walking speed in other patient groups[432,433]. This suggests that postural sway does indeed have functional significance.

Muscle vibration produces a reproducible postural response; this is an advantage of the method. However, the size of the response is small of the order of one degree or less. The relevance of these small responses to real life balance can be questioned. It is felt that the response is informing us about how the central nervous system uses proprioceptive inputs. In real life the sensory inputs are produced by movements due to external perturbations or internally generated movements. Although the movements seen in everyday life are much larger and faster than that produced with stimulation it is unclear whether the proprioceptive input would be similar to that seen with vibration. Further, the postural response with vibration seen is caused by the fact that the sensory input is unexpected. Normally sensory input that is expected to occur with movement is gated out centrally. Therefore, the postural response may not reflect how the brain processes sensory information during natural internally generated movement. The fact that the response to sensory stimulation correlates with clinical measures of balance and disease severity is people with cerebellar disease at least suggests that these measures have real world significance in some diseases[38].

3) The impact of multiple deficits on balance in diabetes.

This thesis has concentrated on mainly exploring the sensory control of balance with the main aim of understanding whether there are any changes in people with DPN that can be clinically targeted. By concentrating on balance and somatosensory information this thesis has ignored to a certain extent the role played by other potential co-existing impairments on balance and falls. These include muscle weakness, visual and vestibular dysfunction, biomechanical changes within soft tissues and cognitive decline[8]. All of these factors have been shown other patient groups (e.g. the elderly) to contribute to falls to a lesser or greater extent[434]. Therefore, the relative importance of the changes seen (e.g. the head / shoulder en-bloc movement strategy and the increase postural sway) to function and falls is unclear. As highlighted in the following section future work should address these issues.

8.5 Implications for rehabilitation/Future work

This section will focus on future work that has potential impact on function and participation.

1) Impact of AFOs on balance, walking and forefoot pressures.

One implication arising from the thesis for rehabilitation is the use of AFOs that restrict motion mediolaterally. These were shown to improve balance as indicated by a reduction in postural sway velocity and smaller postural responses to sensory perturbations. The mechanism of action may be predominantly a mechanical action; increasing the visco-elastic properties of the

ankle joint in a direction specific manner. In future it would be interesting to explore how the visco-elastic properties of different AFOs vary and how they affect ankle motion while standing and walking. Mechanical properties could be assessed by measuring the resistance to movement as the ankle is moved in/out of ankle eversion/inversion using a dynamometer. The resistive torque and the range of movement could be recorded and from this viscosity and elastic stiffness properties measured. A similar method was used to investigate AFOs mechanical properties in the sagittal plane for use in people with another peripheral neuropathy; Charcot Marie Tooth Disease[380].

One potential problem with using AFOs that restrict ankle motion in the sagittal plane is that this can contribute to people's already restricted ankle dorsiflexion range. This in turn will lead to an increase in forefoot pressures while walking, increasing the risk of ulceration[435–438]. Therefore any orthosis that aids balance should not lead to a significant increase in forefoot pressures in the diabetic group, particularly in people with diabetic peripheral neuropathy who due to reduced sensation and autonomic dysfunction, will already have poor foot health and high ulcer risk[439]. As well as forefoot pressures, shear forces also contribute to ulceration and skin breakdown. Recent developments have allowed the indirect measurement of shear forces[440]. Evaluating the impact of mediolateral AFO s on shear forces would therefore also be important. It could be that by improving stability while walking shear forces are actually decreased.

The next stage is therefore to evaluate a range of AFOs that restrict mediolateral motion. Assessment should look at the impact on balance during functional tasks and any changes in forefoot pressure and shear. Further, factors such as ability to "put on" and "take off" the AFO, and people's

subjective opinion should be sought. After initial pilot work and working with patient groups a long term evaluation of the clinical and cost effectiveness of limiting mediolateral ankle motion with an AFO on balance and forefoot pressures in people with diabetic peripheral neuropathy should be conducted. This will need to go through an initial feasibility stage to determine factors such as recruitment and attrition; adverse events; feasibility, suitability and percentage of outcome measures taken and to provide a sample size estimate for the larger randomised control trial.

Another mechanism of action of the AFO may be through enhanced cutaneous input around the ankle. This may be used in a feedforward manner to aid balance. Further, mediolateral movement of the shank in the AFO may provide sensory feedback about ankle motion. Mechanisms of improving sensory feedback for people with diabetic peripheral neuropathy, such as different textured insoles have also been investigated[441]. It could be that AFO's that do not restrict ankle motion but provide sensory feedback may be useful and could also be developed.

2) Determining the effects of altered postural strategies in DPN.

People with DPN showed an altered postural strategy to hip muscle vibration, moving their head and trunk en-bloc in line with the pelvis rather than stabilising the head in space. Future work should explore whether people with DPN show increased head and trunk movement while walking at different speeds / over different support surfaces and whether this causes a greater decrease in visual acuity as would normally be seen when walking. As recent work suggests that some people with DPN have signs of vestibulopathy, this as well as visual function should be quantified[309,313,425,426].

Future research in this area should work towards the development of a falls prevention intervention to address any change in dynamic visual acuity (DVA) resulting from postural control compensation strategies for diabetic peripheral neuropathy. Any change in DVA in a functional task should be compared to DVA when it is tested with the subject sitting to determine if the change in vestibular gain on the postural response for people with distal sensory loss also affects vestibular evoked ocular movements i.e. the vestibular ocular reflex. In addition it would be informative to assess people's subjective experiences i.e. whether there are difficulties in reading/assessing visual information when walking in the environment

If these strategies/patterns are seen in real life situations and impact on function, the next step would be to see whether improving head stability / postural strategy leads to an improvement in function. Re-training the en-bloc strategy and deficits in dynamic visual acuity could eventually include active balance and eye-head exercises under different environmental conditions using a similar model used to rehabilitate people with vestibular loss[442,443].

Changes in co-contraction could be assessed by recording surface EMG. Relating the change in response pattern strategy to the response amplitude to GVS stimulation may provide an indication whether this is at least linked to the vestibular system although it would not dissociate cause from effect.

As discussed in Chapter 7 looking at the response to different amplitudes of vibration could help determine whether there are any changes in gain in the response to distal stimulation. A longitudinal cross sectional observational study mapping stimulus response size over time from diabetes diagnosis to onset of

diabetic peripheral neuropathy would provide insight into the adaptive process of people with diabetes.

3) Exploring the effects of multiple impairments on balance.

People with DPN fall more than age matched controls[281]. To date there have limited studies exploring factors that predict falls in people with diabetes. People with peripheral neuropathy fall more and fallers show higher vibration thresholds[444] and lower distal leg muscle strength. Neuropathy severity scores and dorsiflexion strength predict 75% of falls[445]. Other groups have suggested that the effects of ankle weakness could be compensated by increasing hip adductor strength as those with higher hip / ankle strength ratio fell less[260]. However, in these studies the impact of vestibular and visual function was not measured and biomechanical changes in the joints (e.g. bony deformity and stiffness associated with glycosylation of collagen[370]) were not quantified. Therefore, future work should measure multiple factors (e.g. visual acuity/ contrast, vestibular and somatosensory function and neuropathy, proximal and distal muscle strength, biomechanical changes, fear of falling) and assess whether these can predict falls rates as defined by prospective falls. This could be accompanied by an assessment of when and how people report they fall, for example whether it is inside or outside or when they are moving in reduced sensory conditions (e.g. with the light off or on thick piled carpets)

Understanding how the multiple impairments as well as potential environmental factors (e.g. trip hazards in the home) influence falls would allow clinicians to target therapies to the main deficit. In other populations balance (as measured by postural sway) is often the main predictor of falls[434], so the current findings and the future studies (1) and (2) outlined above will be relevant. Experience in

the field of elderly falls prevention has progressed from assessing interventions targeting one impairment, to whole care packages targeting multiple impairments as well as environmental factors. Randomised controlled trials highlight that these combinatorial approaches are more effective[446] and so it may be useful to adopt the lessons learnt from this patient group.

8.4 Overall conclusion

The findings of this PhD study offer new insight into how people with diabetic peripheral neuropathy compensate for distal sensory loss using residual sensory modalities.

This PhD study is the first to identify frontal plane postural balance strategies in those with diabetic peripheral neuropathy. More specifically it was discovered that balance strategies are modified in the presence of distal sensory loss, to increase motion at more proximal segments of the shoulder and head.

In addition the results of this investigation indicate that ankle foot orthoses designed to limit mediolateral motion decrease sway velocity and the postural response to perturbation whereby increasing postural stability.

The result of this exploratory study provides new evidence to support the concept that ankle foot orthoses may be used as a means of increasing static postural control.

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APPENDICES

Appendix 1. Email invitation

Dear Staff and Students

I am a 2nd year PhD student here at Plymouth University, looking into balance problems in people with Diabetes.

A common complication of Diabetes is nerve damage affecting the feet. People with diabetes and nerve damage are more likely to feel unstable on their feet and are at greater risk of having a fall or a trip. People may compensate for the nerve damage around the feet by relying more on sensory information coming from the hips. People's balance may be affected by the use of ankle supports and how far the feet are apart.

The aim of the study is therefore to test if

(a) people respond differently to mild vibratory stimuli that are applied at the ankles or the hips
(b) wearing a specially selected ankle support and varying the distance the feet are apart affects balance.

We are comparing the responses seen in people with diabetes and a loss of sensation to the feet to healthy people without diabetes of the same gender and a similar age. I am therefore hoping to recruit potential participants form the University of the 3rd age and staff here at Plymouth University.

Attached is an information sheet detailing the study and what would be required of you if you would be willing to participate.

If you feel you would like to be included in the study or would like to know any more details before making that decision, please contact me and we can discuss any further details.

Many thanks

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Appendix 2. Development and testing of 2 vibrators

The use of vibratory stimulations to perturb balance has been used for over forty years to stimulate individual parts of the somatosensory system. Vibration of a muscle/tendon creates an illusionary stretch at the location of the applied stimulus and results in a postural response that opposes the perceived stretch. By measuring this postural response over a number of experimental conditions i.e. with/without intervention, the effect of intervention can be obtained.

Vibrators for this purpose are selected for their vibration properties; frequency and amplitude. This is how fast they vibrate, and the strength of vibration. This chapter tests the theory that the elicited postural response to vibrations increase with vibration amplitude. Two vibrator units were tested. The first, a ready-made unit which produced an amplitude of 6G. The second, an in-house, purpose built unit which produced a greater amplitude of 14.3G. This following sections detail how a vibrator capable of being remotely controlled was developed. The complete control system used in all studies in this investigation will also be described.

Aim

To compare the magnitude of postural response to stimulations produced by two vibrators with differing levels of vibration; frequency and amplitude). The hypothesis being that a greater frequency and amplitude produces an increased postural response magnitude greater than that of baseline sway.

Vibrator 1

Vibrator 1 consisted of an encapsulated motor unit within a 25mm vibrator shown in figure A2.1 The advantage of this particular unit was that it was supplied as a ready-made vibrator requiring a small drive current (Table A2.1) to power the motors. The Digital to analogue converter used in the thesis (Power 1401 Cambridge Electronic Design, UK) was capable of producing the voltage required for vibrator start-up and operating current outlined in table A2.1

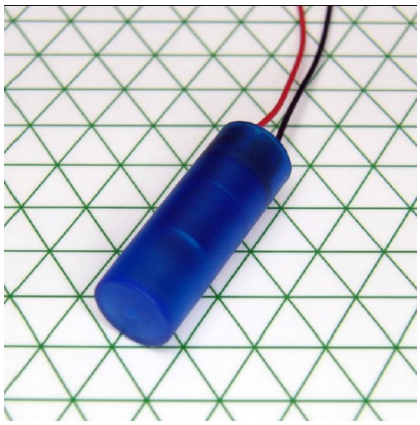

Figure A2.1 Vibrator 1 (Precision microdrivesUK).

Vibrator 2

The second vibrator unit was an in-house purpose built 60mm vibrator unit comprising of a motor with rotating mass (figure A2.2) and bespoke enclosure. At amplitudes above 6G, vibrators are not available as complete encapsulated units, only as a motor and attached mass.

Importantly the electrical characteristics of the motors within the vibrators also differ (table A2.1), with a larger operating current being required by vibrator 2.

This was outside of the capabilities of the DAC (150mA) used for direct switching/powering of vibrator 1. A system was therefore designed to control these new vibrators and will also be discussed later in this section.

Parameter	Vibrator 1 Motor specifications	Vibrator 2 Motor specifications
Typical operating current	130mA	250mA
Typical power consumption	390mW	750mW
Typical start up current	430mA	600mA
Typical normalised amplitude	6G	14.3G
Rated voltage	3V	3V

Table A2.1. Comparison of vibrator characteristics

FigureA2.2. Motor and attached rotating mass

Enclosure design

Due to the physical size of the attached mass and the position of the axel, the mass rotates outside of the motor body circumference, it was therefore necessary to build an enclosure which braced the motor body yet allowed free rotation of the attached mass.

Two enclosure designs were considered. The first was a cylindrical wooden housing constructed from wooden doweling (figure A2.3 and A2.4). This design proved difficult to construct due to the inaccuracy in boring the wood centrally to allow central rotation of the mass. Further, wood being a porous material was considered unsuitable for skin contact and could not be wiped clean after use for infection control purposes.

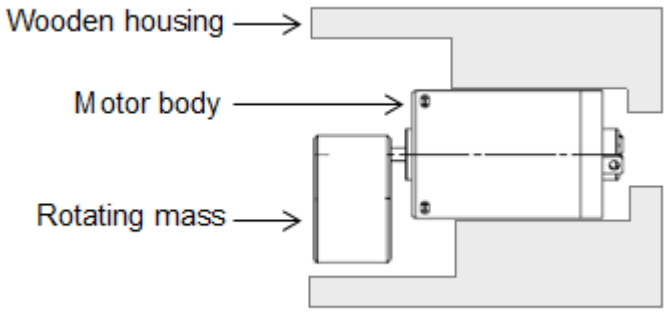

Figure A2.3. Wooden doweling enclosure design

Figure A2.4. Wooden doweling prototype

An alternative to wooden housing was UPvc plastic tubing (22mm) which had the advantage of being non-porous and could be wiped clean between uses. An internal wooden bush (22mm) was therefore required to secure the motor (figure A2.5). This proved advantageous as only a single cavity was required for the motor body to be positioned.

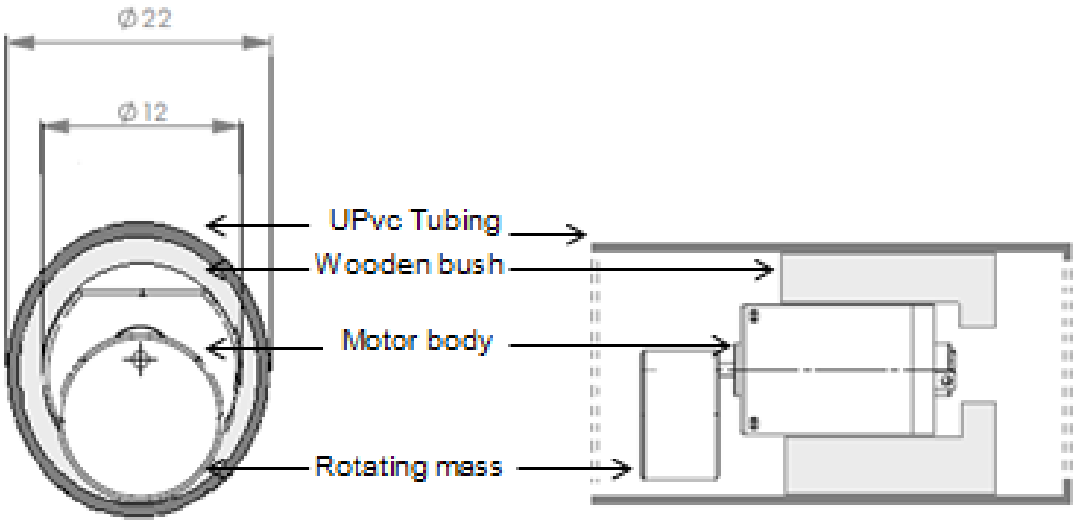

Figure A2.5. Enclosure design 2

For accurate drilling of the cavity in the wooden bush, a lathe was used for its accuracy in drilling. The precise cavity then held the motor body tightly allowing perpendicular rotation of the mass (figure A2.6a and 6b). Manufacturing the bush with same diameter as the UPvc housing (figure A2.6c and 6d) meant that the bush would be held tightly once in position within.

(A2.6a)

(A2.6b)

(A2.6e)

(A2.6f)

Figure A2.6. Vibrator construction (a) UPvc tubular housing (b) Motor inserted to wooden bush ce) motor and wooden bush insertion (d) completed device.

Power supply

A drive current of up to 300mA (600mA start current) was required to power each motor. A single stand-alone power supply capable of such drive current was therefore selected. A system was then designed to switch the power supply between up to four vibrators under the control of the low level DAC outputs used as a trigger signal (figure A2.7).

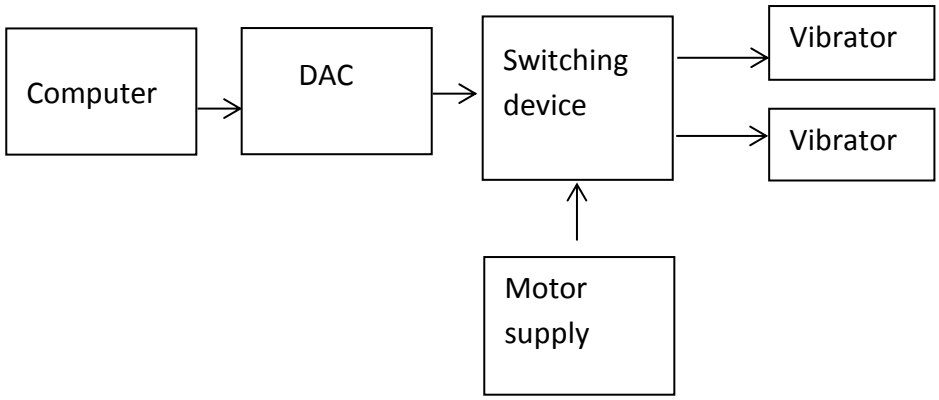

Figure A2.7. Vibrator 2 control system.

Switching device

The switching unit essentially comprised of four 'normally open' (NO) relays to act as switches. 'Normally open' means that the switch is only closed when a trigger voltage is supplied to the input. The trigger input was set at typical TTL logic voltage levels (0-2Volts) and could therefore be supplied by DAC outputs.

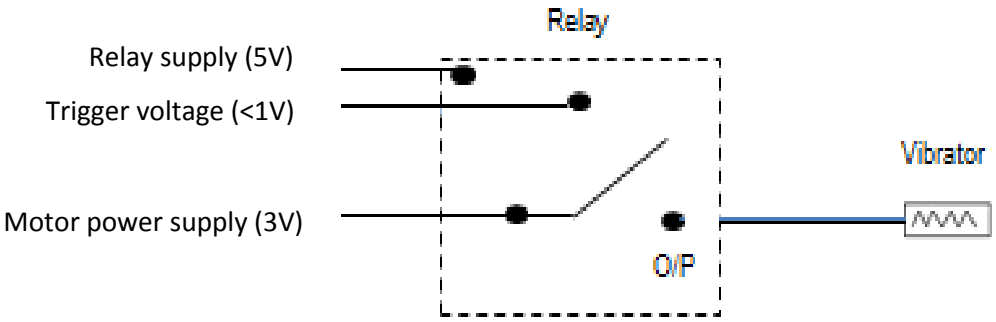

Figure A2.8. Single channel relay (switch).

When a trigger voltage is applied to the relay (figure A2.8) the contact arm closes and conects the power supply to the output (vibrator). For multiple outputs this single relay circuit can be reproduced creating a multi channel switching device (Figure A2.9). The advantage of this system was that it required no manual switching; only spike software (CED, UK) sequence initialisation. This reduced the subject participation time and removed the possibility of operator error in selecting which vibrator would be activated.

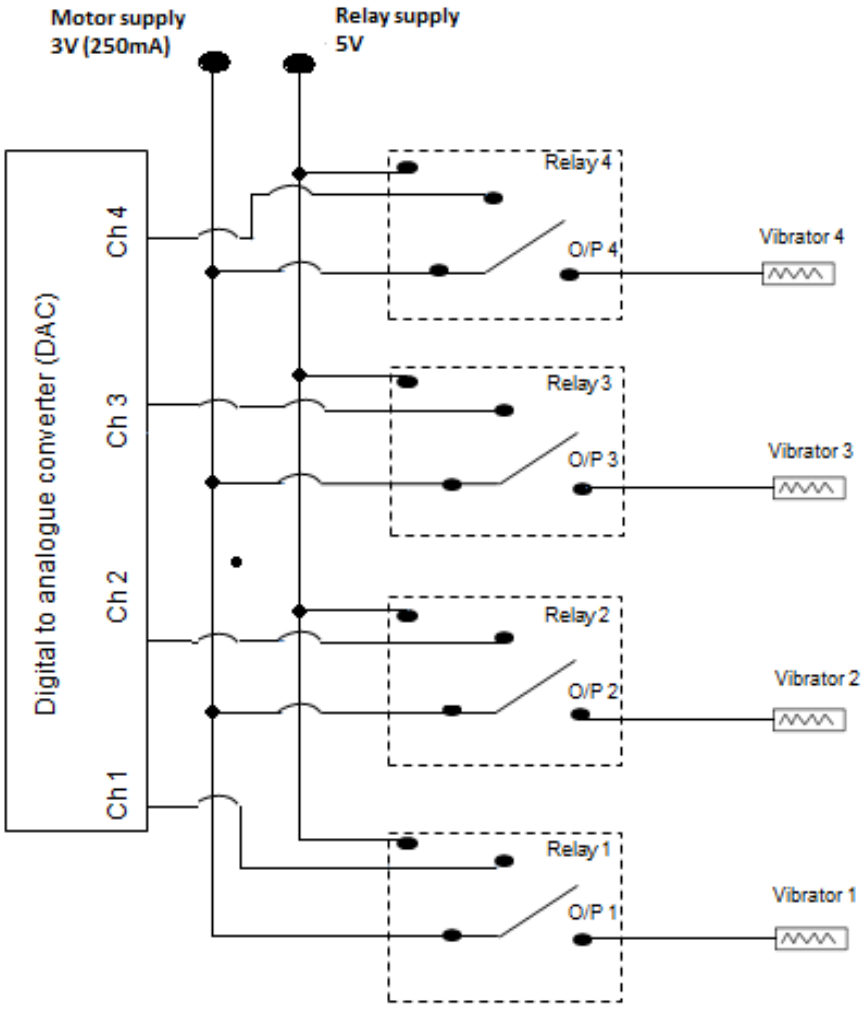

Figure A2.9. Four channel switching.

The 4-channel switching circuit was housed in a 150mm x 80mm plastic enclosure, with 4x male BNC connectors providing input from the DAC 1401 output, and 4x male BNC output connections supplying power to the vibrator units.

Comparison of Vibrator 1 and 2 on response amplitude

Methods

Eighteen healthy participants (10 female, 8 male, aged 40 ±15yrs), volunteered to take part in the study after responding to email to local university students. Volunteers were excluded from the study if they self-reported musculoskeletal, neurological, visual or vestibular complications which may have influenced balance or leg movement. Eligible participants gave informed written consent before taking part in the study. Ethical approval was granted by Plymouth University ethics committee.

Responses to hip vibration were assessed on two occasions with vibrator 1 and 2. Methods of application of the vibrator and measurement and analysis of the responses are given in Chapter 5.

Results

With an increase in vibration amplitude, the postural responses was similar in terms of direction and latency. The magnitude of the response increased with vibration amplitude (Figures A2.10 and A2.11, Table A2.2)

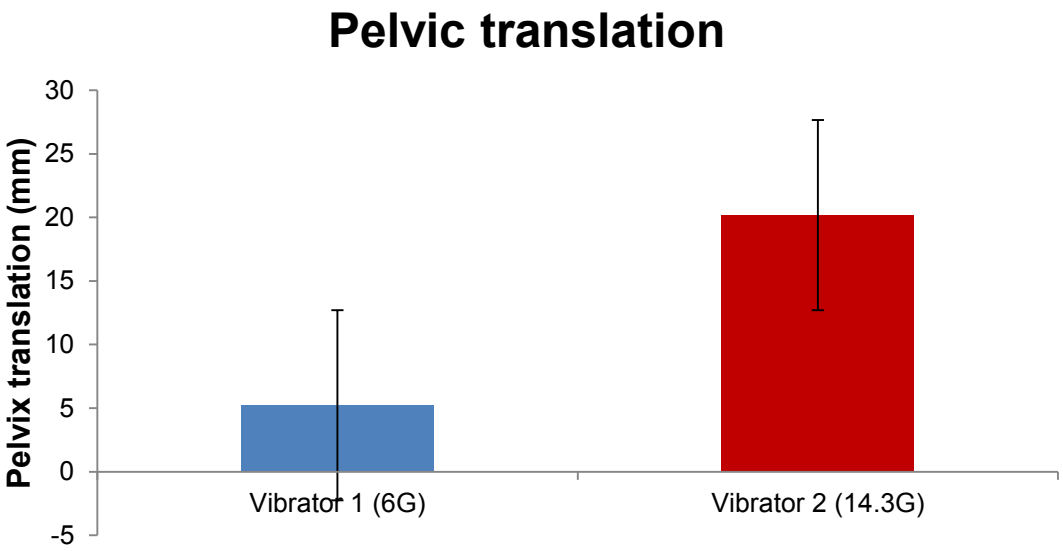

Figure A2.10. Bar chart to show response magnitudes of Pelvic translation to vibrators 1and 2.

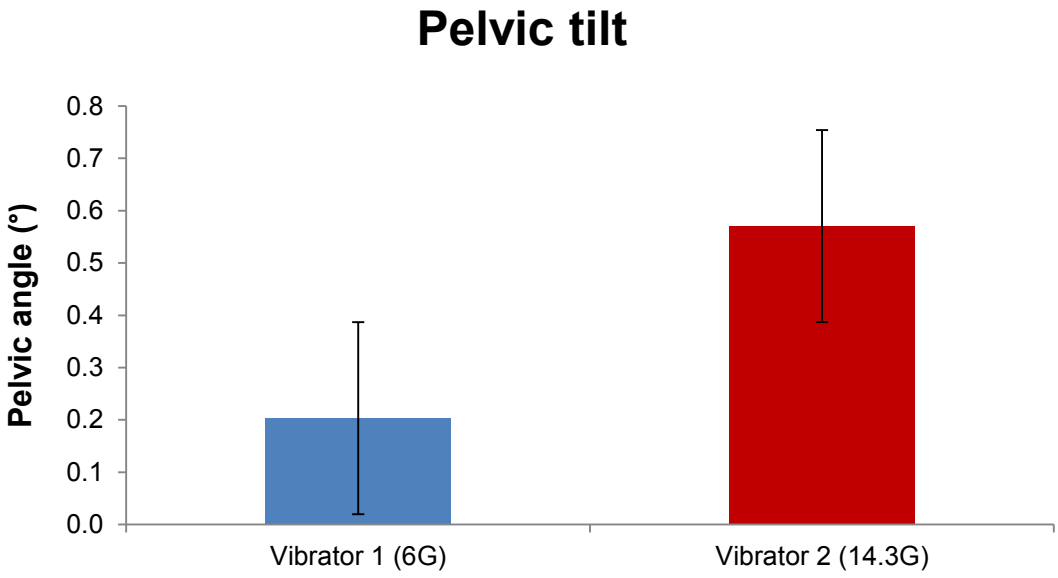

Figure A2.11. Bar chart to show response magnitudes of Pelvic translation to vibrators 1and 2.

	Pelvic Translation (mm)		Pelvic angle (deg)	
	Vib 1	Vib 2	Vib 1	Vib 2
Mean	5.2	35.3	0.2	0.6
SD	5.9	19.3	0.2	0.5
t-crit	2.1		2.1	
df	34		34	
p	<0.001		<0.05	

Table A2.2. Comparison between responses with vibrator 1 and vibrator 2. Results show paired T-Tests in pevic translation and tilt in response to vibrator 1 and 2

Conclusion

A higher amplitude vibration resulted in a larger postural response. Therefore vibrator 2 was used in studies 1-3 (Chapters 5-7)

Appendix 3. Vibration characteristics

Introduction

Using up to four vibrators in this investigation it was essential that each vibrator produced repeatable vibration frequencies so that postural responses to stimulations could be compared according to location. This section tests the purpose built vibrators for frequency and repeatability.

Methods

Four vibrators were measured individually for analysis of frequency response and repeatability. The set up for each vibrator is shown in Figure A3.1. Each vibrator was strapped to an accelerometer using an elastic band fixing. The band was placed at the mid-point of the accelerometer and 25mm from the end of the vibrator enclosure. Using the Spike software (CED, UK) sequences similar to those earlier described each vibrator was activated for a 5 second period for five consecutive samples following approximate 5 second rest periods. The accelerometer output was recorded via an analogue-to-digital converter (Cambridge Electronic Design, UK) and recorded in Spike2 software for later analysis.

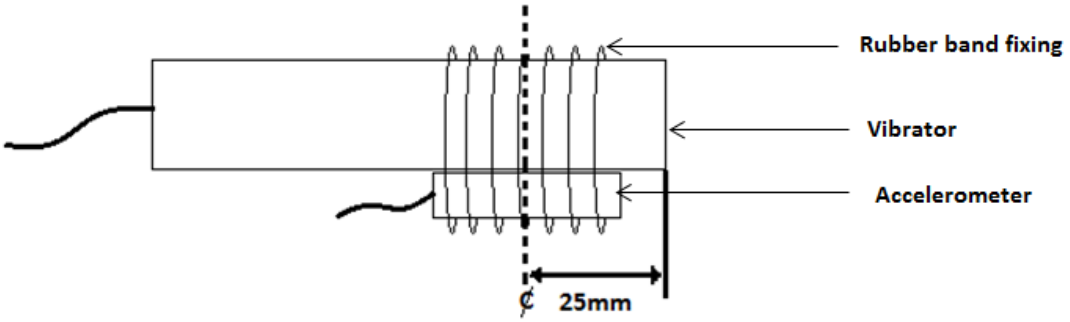

Figure A3.1. Frequency analysis set up

Results

Frequency responses, measured from a power spectrum calculated using a Fourier transform, were 118Hz ±6Hz and are shown in Table A3.1. This was similar to the 120Hz stated in the motor specifications (Precision Microdrives, UK). The small difference may have been due to a required warm-up period for the motors to reach a consistant operating temperature.

Vibrator	Sample 1 (Hz)	Sample 2 (Hz)	Sample 3 (Hz)	Sample 4 (Hz)	Sample 5 (Hz)	Frequency Range (Hz)
1	119	119	119	119	119	119
2	112	112	115	115	115	113.5 ±1.5
3	119	119	123	123	123	121 ±2
4	115	115	119	119	119	117 ±2
					Total	118 ±6

Table A3.1. Frequency analysis

Conclusion

This frequency analysis confirmed that each of the vibrators designed for the investigation operated at a similar frequency. The small variation in frequency although small was accounted for in the study methods by rotating the location of the vibrators between subjects. Rotating the location and averaging postural responses therefore cancelled these small variations in frequency. The frequency repeatability was also tested and it was found that a warm up period prior to use was required to stabilise the operating temperature of the motors. A warm-up period of 10 activations for each motor was therefore put in place, to allow motors to reach a steady state, before use on each subject in all studies.

Appendix 4. MatLab programs

Program 1 –Study 1 and 3

This program loads data for each condition, sorts into responses to left or right hip vibration, averages the data and saves the data according to condition.

```
clear               %close all % close all graphs
clear global
clc                 %clear the screen



%set number of rows,columns,conditions of data
ro = 1000;    %rows
co = 48;      %columns

%create vector for data location arguments in
later DLMREAD function
loc(1,1)=5; % row onset number -1
loc(1,2)=0;
loc(1,3)=loc(1,1) + ro - 1;
loc(1,4)=loc(1,2) + co - 1;

%work through files
[files, path]= uigetfile('*.txt','select multiple
files','MultiSelect','on');

sz = size(files);

for i=1:sz(2)

ifile1= strcat(path, files(i));
  ifile=char(ifile1);
 cond(i).data =
dlmread(ifile,'\t',loc(1,1),loc(1,2),loc);

names(1:(co*4)+1)=textread(ifile,'%s',(co*4)+1,'de
limiter','\t');
names2=names((co*1)+2:(co*2)+1)'

 cond(i).head =names2; %create list of column
names
```

```
cond(i).in(1,:)=files{i}; % save file name
end


% sort the data part1

sortnum=0;

for i=1:sz(2)
rmax=max(cond(i).data(:,44))    % this is right vib
indicator
lmax=max(cond(i).data:45);      % this is left vib
indicator

        if rmax>lmax
             sort=1;
             collook=44;
             flip=1;
        elseif lmax>rmax
             sort=2;
             collook=45;
             flip=-1;
        end

% align data
 on = find(cond(i).data(:,collook)>10);
 onset = on(1);

 clear on

%chop up & align
cond(i).data2=cond(i).data(onset-150:onset+750,:)


wn=[0.10];
b,a]=butter(1,wn,'low');% Butterworth Low pass
filter (10Hz)

cond(i).data2f=filtfilt(b,a,cond(i).data2);

all(:,1:48,i)=cond(i).data2f;

 %%%%%%%% Hip angles %%%%%%%%%%%%%%%%%
 %Right tilt
rhipy=all(:,18,i); %Hip Right Y
rhipz=all(:,19,i);  %Hip Right Z
```

```
lhipy=all(:,15,i);  % Hip Left Y
lhipz=all(:,16,i); %Hip Left Z

all(:,49,i) = atand((lhipz-rhipz)./(lhipy-
rhipy)); % Hip in degreees


%%%%%%%%%%%%%%%% shoulder angle %%%%%%%%%%

rshy=all(:,6,i);
rshz=all(:,7,i);
lshy=all(:,9,i);
lshz=all(:,10,i);

all(:,50,i) = atand((lshz-rshz)./(lshy-rshy)); %
Shoulder in degreees

%%%%%%%%%%%%%% head angle %%%%%%%%%%%%%%%%%%

 %Right tilt
rheady=all(:,3,i);
rheadz=all(:,4,i);
lheady=all(:,12,i);
lheadz=all(:,13,i);

all (:,51,i)= atand((lheadz-rheadz)./(lheady-
rheady)); % Head in degreees

%%%% Trunk angle %%%%%%%%%%%

hip_y1(:,1) = rhipy;
hip_y1(:,2) = lhipy;
hip_centre_y = mean(hip_y1,2)%Centre point between
hip markers (y)

hip_z1(:,1) = rhipz;
hip_z1(:,2) = lhipz;
hip_centre_z = mean(hip_z1,2) ; %Centre point
between hip markers (z)

sh_y1(:,1)= rshy;
sh_y1(:,2)=lshy;
sh_centre_y = mean(sh_y1,2);%Centre point between
shoulder markers (y)

sh_z1(:,1)= rshz;
sh_z1(:,2)= lshz;
```

```
sh_centre_z = mean(sh_z1,2);


all(:,52,i) = atand(hip_centre_y -
sh_centre_y)./(sh_centre_z - hip_centre_z)


all2(:,1:52,i)=all(:,:,i)*flip;

%%%%%%%%%%%%%%%%%%VELOCITY%%%%%%%%%%%%%%%%


left_sh_y= all(:,9,i)%LEFT SHOULER Y
right_sh_y=all(:,6,i)%RIGHT SHOULDER Y
sh_y(:,1)=left_sh_y
sh_y(:,2)=right_sh_y
centre_y = mean(sh_y,2)
left_sh_z=all(:,10,i)%LEFT SHOULDER Z
right_sh_z=all(:,7,i)%RIGHT SHOULDER Z
sh_z(:,1)=left_sh_z
sh_z(:,2)=right_sh_z
centre_z = mean(sh_z,2)

for n=1:201

    dist_y = centre_y(n+1,:)- centre_y(n,:);
    dist_y2(n,:,i) = dist_y;
    dist_z = centre_z(n+1,:)-centre_z(n,:);
     dist_z2(n,:,i) = dist_z;

end

   y_squared= dist_y2.*dist_y2
   z_squared=dist_z2.*dist_z2
   yz=y_squared + z_squared
   sqrt_yz = sqrt(yz)

   total_pathl= sum(sqrt_yz)
   vel = total_pathl./1
   vel_av= mean(vel)

end

%zero data
sall=size(all2);

for j=1:sall(3)
```

```
zero1=all2(151,:,j);
zero=repmat(zero1,[901,1,1]);
all3(:,:,j)=all2(:,:,j)-zero;
end


% average everything

gav_alli = mean(all3,3);      %sets out matrix one
infront of other
velo_av=vel_av;



t2=[-0.75:1/200:3.75]';


%%%%%%%%% Plot results %%%%%%%%%%%%%%%

figure(1)

plot (t2,gav_alli(:,18),'g'),  %grid
xlabel('Time (Secs)')
ylabel('HIP Y(mm)')
vline(0/200)
vline(400/200)
title('Hip Translation (right)')

figure(2)
plot
(t2,gav_alli(:,49),'g',t2,gav_alli(:,50),'r',t2,ga
v_alli(:,51),'k',t2,gav_alli(:,52),'b'),
xlabel('Time (Secs)')
ylabel('Hip/Shouder/Head angle/ Trunk (deg)')
legend ('hip','Sh','Head','Trunk');
vline(0/200)
vline(400/200)
title('Angles')


figure(3)

plot (t2,gav_alli(:,47),'g'),
xlabel('Time (Secs)')
ylabel('Med-Lat sway (mm)')
vline(0/200)
vline(400/200)
```

```
title('Force Y')

figure(4)
plot (t2,gav_alli(:,52),'b'),
xlabel('Time (Secs)')
ylabel('Hip/Shouder/Head angle/ Trunk (deg)')
legend ('hip','Sh','Head','Trunk');
vline(0/200)
vline(400/200)
title('Angles')


 %%Save the data

[name, path]=uiputfile('*.mat','save workspace');
outfile = [path name];
save(outfile,'gav_alli','velo_av') ;
```

Program 2 – Study 2

```
clear           %close all % close all graphs
clear global
clc             %clear the screen

j=0;
k=0;
ch_1_count=0;
ch_2_count=0;
ch_3_count=0;
ch_4_count=0;
hip_count=1;
per_count=1;

%set number of rows,columns,conditions of data
ro = 1001;%rows
co = 105;%
```

```
%create vector for data location arguments in
later DLMREAD function
loc(1,1)=5; % row onset number -1
loc(1,2)=0;
loc(1,3)=loc(1,1) + ro - 1;
loc(1,4)=loc(1,2) + co - 1;

%work through files
[files, path]= uigetfile('*.txt','select multiple
files','MultiSelect','on');

sz = size(files);

for i=1:sz(2)


ifile1= strcat(path, files(i));
  ifile=char(ifile1);
 cond(i).data =
dlmread(ifile,'\t',loc(1,1),loc(1,2),loc);


names(1:(co*4)+1)=textread(ifile,'%s',(co*4)+1,'de
limiter','\t');
names2=names((co*1)+2:(co*2)+1)'

 cond(i).head =names2; %create list of column
names

cond(i).in(1,:)=files{i}; % save file name
end

sortnum=0;
countr = 0;
countl = 0;


for i=1:sz(2)

 collook = 44;   %look at digital output for
trigger signal


% align data
 on = find(cond(i).data(:,collook)>10);
 onset = on(1);
 mean_digout= mean(on);
```

```
% clear on

%chop up & align
cond(i).data2=cond(i).data(onset-
150:onset+750,:) %-0.75s to 3.75

% %filter
           wn=[0.20]; % 20Hz filter
           [b,a]=butter(1,wn,'low');


 cond(i).data2f=filtfilt(b,a,cond(i).data2);

  % this is vib indicator %

        if mean_digout <180   % mean of ch1
digital pulse (98.63) - vib 1
             ch=1;
             flip=1;
             ch_1_count = ch_1_count+1

        elseif mean_digout <200 &&
mean_digout >180 % 1xdigital pulse ch2 digital
pulse (197.93)- vib 2
             ch=2;
             flip=-1;
              ch_2_count = ch_2_count+1
        elseif mean_digout <225 &&
mean_digout >200 % 1xdigital pulse ch3 digital
pulse (297.31)- vib 3
            ch=3;
            flip=-1;
             ch_3_count = ch_3_count+1
        elseif mean_digout  >225 % 1xdigital pulse
ch4 digital pulse (396.23) - vib 4
            ch=4;
            flip=1;
             ch_4_count = ch_4_count+1
        end


     if ch <2.9


         j= hip_count;
```

```
all_hips(:,1:105,j)=cond(i).data2f;      %Creates
all: 1 to 105

 %%%%%%%%%%%%%%% Add in angle to
'all_hips' %%%%%%%%%%%%%%%%

 %%%%%%%% Hip angles %%%%%%%%%%%%%%%%
rhipy=all_hips(:,18,j);  %Hip Right Y
rhipz=all_hips(:,19,j);  %Hip Right Z
lhipy=all_hips(:,15,j);  %Hip Left Y
lhipz=all_hips(:,16,j);  %Hip Left Z


all_hips(:,106,j) = atand((lhipz-rhipz)./(lhipy-
rhipy)); % puts hip in degreees into all col 106

%%%%%%%%%%%%%%% shoulder angle %%%%%%%%%%
rshy=all_hips(:,6,j);
rshz=all_hips(:,7,j);
lshy=all_hips(:,9,j);
lshz=all_hips(:,10,j);


all_hips(:,107,j) = atand((lshz-rshz)./(lshy-
rshy)); % puts shoulder angle into all col 107

%%%%%%%%%%%%%% headangle %%%%%%%%%%%%%%%%%%
rheady=all_hips(:,3,j);   %Right head Y
rheadz=all_hips(:,4,j);   %Right head Z
lheady=all_hips(:,12,j);  %Left head Y
lheadz=all_hips(:,13,j);  %Left head Z


all_hips (:,108,j)= atand((lheadz-
rheadz)./(lheady-rheady)); % Head in degreees

%%%%%%%%%%%%%%% Trunk angle %%%%%%%%%%%%%

hip_y1(:,1) = rhipy;
hip_y1(:,2) = lhipy;
hip_centre_y = mean(hip_y1,2)%Centre point between
hip markers (y)

hip_z1(:,1) = rhipz;
hip_z1(:,2) = lhipz;
```

```
hip_centre_z = mean(hip_z1,2) ; %Centre point
between hip markers (z)

sh_y1(:,1)= rshy;
sh_y1(:,2)=lshy;
sh_centre_y = mean(sh_y1,2);%Centre point between
shoulder markers (y)

sh_z1(:,1)= rshz;
sh_z1(:,2)= lshz;
sh_centre_z = mean(sh_z1,2);


all_hips(:,109,j) = atand(hip_centre_y -
sh_centre_y)./(sh_centre_z - hip_centre_z)

all2_hips(:,1:109,j) = all_hips(:,:,j)*flip;


hip_count = hip_count+1;

     elseif ch>2.1
         k= per_count
         all_pers(:,1:105,k)=cond(i).data2f;

%%%%%%%%%%%%%%% Add in angles to
'all_pers' %%%%%%%%%%%%%%%%%

 %%%%%%%% Hip angles %%%%%%%%%%%%%%%%
 %Right tilt
rhipy=all_pers(:,18,k);  %Hip Right Y
rhipz=all_pers(:,19,k);  %Hip Right Z
lhipy=all_pers(:,15,k);  %Hip Left Y
lhipz=all_pers(:,16,k);  %Hip Left Z
hip_centre_y = rhipy-lhipy; %Centre point between
shoulder markers
hip_centre_z = rhipz-lhipz; %Centre point between
hip markers

all_pers(:,106,k) = atand((lhipz-rhipz)./(lhipy-
rhipy)); % puts hip in degreees into all col 106

%%%%%%%%%%%%%%% shoulder angle %%%%%%%%%%
rshy=all_pers(:,6,k);
rshz=all_pers(:,7,k);
lshy=all_pers(:,9,k);
lshz=all_pers(:,10,k);
```

```
all_pers(:,107,k) = atand((lshz-rshz)./(lshy-
rshy)); % puts shoulder angle into all col 107


%%%%%%%%%%%%%% head angle %%%%%%%%%%%%%%%%%%

 %Right tilt
rheady=all_pers(:,3,k);    %Right head Y
rheadz=all_pers(:,4,k);    %Right head Z
lheady=all_pers(:,12,k);   %Left head Y
lheadz=all_pers(:,13,k);   %Left head Z

all_pers (:,108,k)= atand((lheadz-
rheadz)./(lheady-rheady)); % Head in degreees

%%%%%%%%%%%%%%%% Trunk angle %%%%%%%%%%%%%%

hip_y1(:,1) = rhipy;
hip_y1(:,2) = lhipy;
hip_centre_y = mean(hip_y1,2)%Centre point between
hip markers (y)

hip_z1(:,1) = rhipz;
hip_z1(:,2) = lhipz;
hip_centre_z = mean(hip_z1,2) ; %Centre point
between hip markers (z)

sh_y1(:,1)= rshy;
sh_y1(:,2)=lshy;
sh_centre_y = mean(sh_y1,2);%Centre point between
shoulder markers (y)

sh_z1(:,1)= rshz;
sh_z1(:,2)= lshz;
sh_centre_z = mean(sh_z1,2);


all_pers(:,109,k) = atand(hip_centre_y -
sh_centre_y)./(sh_centre_z - hip_centre_z)


all2_pers(:,1:109,k) = all_pers(:,:,k)*flip;


per_count = per_count+1;
     end
```

```
%%%%% Keep a record of the file/channel/av value
of peak(secs)
rec((i),1)= (i);
rec((i),2)= mean(on);
rec((i),3)= ch;

%%%%% Keep a record of channel occurance %%%%%%%%%%
ch_count(1,1:4) =  1:4;
ch_count(2,1) =  ch_1_count;
ch_count(2,2) =  ch_2_count;
ch_count(2,3) =  ch_3_count;
ch_count(2,4) =  ch_4_count;
end


%%%%%%%%%%  set x axis  %%%%%%%%%%
t2=[-0.75:1/200:3.75]';

%zero data
sall_hips=size(all2_hips);

for j=1:sall_hips(3)

zero1=all2_hips(151,:,j);
zero=repmat(zero1,[901,1,1]);
all3_hips(:,:,j)=all2_hips(:,:,j)-zero;

end

sall_pers=size(all2_pers);
for k=1:sall_pers(3)

zero1=all2_pers(151,:,k);
zero=repmat(zero1,[901,1,1]);
all3_pers(:,:,k)=all2_pers(:,:,k)-zero;

end


% average everything
gavalli_hips = mean(all3_hips,3);       %sets out
matrix one infront of other
gavalli_pers = mean(all3_pers,3);

per_leftstim = gavalli_pers(:,66);
per_rightstim = gavalli_pers(:,102);
```

```
gavalli_pers(:,110) = per_leftstim;    % Was this
repeated measures analysis??
gavalli_pers(:,111) = per_rightstim;


%%%%%%%%% Plot results %%%%%%%%%%%%%%%
figure(1)

plot
(t2,gavalli_hips(:,18),'g',t2,gavalli_pers(:,18),'
r');
xlabel('Time (Secs)');
ylabel('Hip Tx');
legend ('Hip Vib','Per Vib');
vline(0/200);
vline(400/200);
axis([-0.75 3.5 -30 5])
title('Hip Y');

figure(2)
plot
(t2,gavalli_hips(:,106),'g',t2,gavalli_pers(:,106)
,'r');
xlabel('Time (Secs)');
ylabel('Degrees');
legend ('Hip Vib','Per Vib');
vline(0/200);
vline(400/200);
axis([-0.75 3.5 -0.2 2])
title('Hip Angle');

figure(3)
plot
(t2,gavalli_hips(:,109),'g',t2,gavalli_pers(:,109)
,'r');
xlabel('Time (Secs)');
ylabel('Degrees');
legend ('Hip Vib','Per Vib');
vline(0/200);
vline(400/200);
axis([-0.75 3.5 -1 0.4])
title('Trunk Angle');


figure(4)
```

```
plot (t2,gavalli_hips(:,106),'g',t2,
gavalli_hips(:,107),'r',t2,
gavalli_hips(:,108),'k',t2,
gavalli_hips(:,109),'b');  %grid
xlabel('Time (Secs)');
ylabel('Degrees');
legend('Hip','Shoulder','Head','Trunk');
vline(0/200);
vline(400/200);
axis([-0.75 3.5 -1 2])
title('Angles HipVib');

figure(5)
plot (t2,gavalli_pers(:,106),'g',t2,
gavalli_pers(:,107),'r',t2,
gavalli_pers(:,108),'k',t2,
gavalli_pers(:,109),'b');  %grid
xlabel('Time (Secs)');
ylabel('Degrees');
legend('Hip','Shoulder','Head','Trunk');
vline(0/200);
vline(400/200);
axis([-0.75 3.5 -0.3 1])
title('Angles PerVib');

figure(6)
plot (t2,gavalli_hips(:,74),'g',t2,
gavalli_pers(:,74),'r');  %grid
xlabel('Time (Secs)');
ylabel('PoA (mm)');
legend('Response to Hip Vib', 'Response to Per
Vib');
vline(0/200);
vline(400/200);
axis([-0.75 3.5 -5 35])
title('Hip stim Vs Per Stim responses');

figure(7)
plot (t2,gavalli_hips(:,6),'g',t2,
gavalli_pers(:,6),'r');  %grid
xlabel('Time (Secs)');
ylabel('Shoulder Tx (mm)');
legend('Response to Hip Vib', 'Response to Per
Vib');
vline(0/200);
vline(400/200);
```

```
axis([-0.75 3.5 -20 5])
title('Shouder translation');


figure(8)
plot(t2, gavalli_hips(:,85),'r',t2,
gavalli_hips(:,97),'g');
xlabel('Time (Secs)');
ylabel('movement');
legend('Left Knee_x','Right Ankle_x');
vline(0/200);
vline(400/200);
title('Knee A/P Angle');

figure(9)
plot(t2, gavalli_hips(:,88),'r',t2,
gavalli_hips(:,100),'g');
xlabel('Time (Secs)');
ylabel('movement');
legend('Left Ankle_x','Right Ankle_x');
vline(0/200);
vline(400/200);
title('Ankle A/P angle');


%Save the data

[name, path]=uiputfile('*.mat','save workspace');
outfile = [path name];
save(outfile,'gavalli_hips','gavalli_pers') ;
```

Program 3 – Group files

```
clear
close all % close all graphs
clear global
clc %clear the screen



for x=1:6
    switch(x)
        case{1}
        o='a0';
        case{2}
        o='s0';
        case{3}
        o='a4';
        case{4}
        o='s4';
        case{5}
        o='a16';
        case{6}
        o='s16';
    end

[files, path]= uigetfile('*.mat',o,'MultiSelect',
'off');


   ifile= [path files];                %curly braces
required to index files

  % load in data
    eval(['load ', ifile,';']);

    gav_alli2(:,:,x)=gav_alli;
    velocity_av(:,:,x)=velo_av;



end


%
[name, path]=uiputfile('*.mat','save
workspace');        % Save 1x6 matrix as .mat file
outfile = [path name];
```

```
save(outfile,'gav_alli2','velocity_av' );
```

Program 4 – grand average output (study 3_part a)

```
clear
close all % close all graphs
clear global
clc %clear the screen

   for x=1
    switch(x)
        case{1}
        o='Healthy';

    end
   end

[files, path]= uigetfile('*.mat',o,'MultiSelect',
'on');


   ifile= [path files];


  sz = size(files);
for i=1:sz(2)

   ifile= [path files{i}];
  % load in data
       eval(['load ',ifile,';']);
       cond(i).names =ifile; %create list of
column names


 for x=1

h_total_hip1(:,x,i)=gavalli_hip_group(:,18,x);
  %Data during hip vib only

h_total_hip2(:,x,i)=gavalli_per_group(:,18,x);
  %Data during per vib


h_total_force1(:,x,i)=gavalli_hip_group(:,74,x);
```

```
h_total_force2(:,x,i)=gavalli_per_group(:,74,x);

h_total_hipang1(:,x,i)=gavalli_hip_group(:,106,x);

h_total_hipang2(:,x,i)=gavalli_per_group(:,106,x);

h_total_shang1(:,x,i)=gavalli_hip_group(:,107,x);

h_total_shang2(:,x,i)=gavalli_per_group(:,107,x);

h_total_sh_tx1(:,x,i)=gavalli_hip_group(:,6,x);

h_total_sh_tx2(:,x,i)=gavalli_per_group(:,6,x);

h_total_headang1(:,x,i)=gavalli_hip_group(:,108,x);

h_total_headang2(:,x,i)=gavalli_per_group(:,108,x);

h_total_headtx1(:,x,i)=gavalli_hip_group(:,3,x);

h_total_headtx2(:,x,i)=gavalli_per_group(:,3,x);

h_total_trunk1(:,x,i)=gavalli_hip_group(:,109,x);

h_total_trunk2(:,x,i)=gavalli_per_group(:,109,x);

h_total_kneeang1(:,x,i)=gavalli_hip_group(:,112,x);

h_total_kneeang2(:,x,i)=gavalli_per_group(:,112,x);

h_total_opp_kneeang1(:,x,i)=gavalli_hip_group(:,11
3,x);

h_total_opp_kneeang2(:,x,i)=gavalli_per_group(:,11
3,x);

h_total_ankleang1(:,x,i)=gavalli_hip_group(:,110,x
);

h_total_ankleang2(:,x,i)=gavalli_per_group(:,110,x
);

h_total_opp_ankleang1(:,x,i)=gavalli_hip_group(:,1
11,x);
```

```
h_total_opp_ankleang2(:,x,i)=gavalli_per_group(:,1
11,x);

h_total_hipad1(:,x,i)=gavalli_hip_group(:,114,x);

h_total_hipad2(:,x,i)=gavalli_per_group(:,114,x);

     %%%%%%Get Data for plotting later

h_total_hip_hip=mean(h_total_hip1,3);      %Data
during hip vib

h_total_hip_per=mean(h_total_hip2,3);      %Data
during per vib

h_total_force_hip=mean(h_total_force1,3);

h_total_force_per=mean(h_total_force2,3);

h_total_hipang_hip=mean(h_total_hipang1,3);

h_total_hipang_per=mean(h_total_hipang2,3);

h_total_shang_hip=mean(h_total_shang1,3);

h_total_shang_per=mean(h_total_shang2,3);
           h_total_shtx_hip=mean(h_total_sh_tx1,3);
           h_total_shtx_per=mean(h_total_sh_tx2,3);

h_total_headang_hip=mean(h_total_headang1,3);

h_total_headang_per=mean(h_total_headang2,3);

h_total_headtx_hip=mean(h_total_headtx1,3);

h_total_headtx_per=mean(h_total_headtx2,3);
           h_trunk_hip=mean(h_total_trunk1,3);
           h_trunk_per=mean(h_total_trunk2,3);
           h_total_kneeang_hip =
mean(h_total_kneeang1,3);
           h_total_kneeang_per =
mean(h_total_kneeang2,3);
           h_total_opp_kneeang_hip =
mean(h_total_opp_kneeang1,3);
```

```
            h_total_opp_kneeang_per =
mean(h_total_opp_kneeang2,3);
            h_total_ankleang_hip =
mean(h_total_ankleang1,3);
            h_total_ankleang_per =
mean(h_total_ankleang2,3);
            h_total_opp_ankleang_hip =
mean(h_total_opp_ankleang1,3);
            h_total_opp_ankleang_per =
mean(h_total_opp_ankleang2,3);
            h_total_hipad_hip =
mean(h_total_hipad1,3);
            h_total_hipad_per =
mean(h_total_hipad2,3);


end

end

%************************************************
********

    for x=1
     switch(x)
         case{1}
         o='Diabetic';

     end
    end


    [files, path]=
uigetfile('*.mat',o,'MultiSelect', 'on');


    ifile= [path files];
  sz = size(files);
for i=1:sz(2)

    ifile= [path files{i}];
  % load in data
        eval(['load ',ifile,';']);
        cond(i).names =ifile; %create list of
column names
```

```
 for x=1

d_total_hip1(:,x,i)=gavalli_hip_group(:,18,x);
  %Data during hip vib

d_total_hip2(:,x,i)=gavalli_per_group(:,18,x);
  %Data during per vib

d_total_force1(:,x,i)=gavalli_hip_group(:,74,x);

d_total_force2(:,x,i)=gavalli_per_group(:,74,x);

d_total_hipang1(:,x,i)=gavalli_hip_group(:,106,x);

d_total_hipang2(:,x,i)=gavalli_per_group(:,106,x);

d_total_shang1(:,x,i)=gavalli_hip_group(:,107,x);

d_total_shang2(:,x,i)=gavalli_per_group(:,107,x);

d_total_sh_tx1(:,x,i)=gavalli_hip_group(:,6,x);

d_total_sh_tx2(:,x,i)=gavalli_per_group(:,6,x);

d_total_headang1(:,x,i)=gavalli_hip_group(:,108,x);

d_total_headang2(:,x,i)=gavalli_per_group(:,108,x);

d_total_headtx1(:,x,i)=gavalli_hip_group(:,3,x);

d_total_headtx2(:,x,i)=gavalli_per_group(:,3,x);

d_total_trunk1(:,x,i)=gavalli_hip_group(:,109,x);

d_total_trunk2(:,x,i)=gavalli_per_group(:,109,x);

d_total_kneeang1(:,x,i)=gavalli_hip_group(:,112,x)
; %Sagital plane

d_total_kneeang2(:,x,i)=gavalli_per_group(:,112,x)
;   %Sagital plane

d_total_opp_kneeang1(:,x,i)=gavalli_hip_group(:,11
3,x);
```

```
d_total_opp_kneeang2(:,x,i)=gavalli_per_group(:,11
3,x);

d_total_ankleang1(:,x,i)=gavalli_hip_group(:,110,x
); %frontal plane

d_total_ankleang2(:,x,i)=gavalli_per_group(:,110,x
); %left ankle angkle in Y (Inv/ever)

d_total_opp_ankleang1(:,x,i)=gavalli_hip_group(:,1
11,x); %frontal plane

d_total_opp_ankleang2(:,x,i)=gavalli_per_group(:,1
11,x);

d_total_hipad1(:,x,i)=gavalli_hip_group(:,114,x);

d_total_hipad2(:,x,i)=gavalli_per_group(:,114,x);

     %%%%%%Get Data for plotting later

d_total_hip_hip=mean(d_total_hip1,3);      %Data
during hip vib

d_total_hip_per=mean(d_total_hip2,3);      %Data
during per vib

     d_total_force_hip=mean(d_total_force1,3);
     d_total_force_per=mean(d_total_force2,3);
     d_total_hipang_hip=mean(d_total_hipang1,3);
     d_total_hipang_per=mean(d_total_hipang2,3);
     d_total_shang_hip=mean(d_total_shang1,3);
     d_total_shang_per=mean(d_total_shang2,3);
     d_total_shtx_hip=mean(d_total_sh_tx1,3);
     d_total_shtx_per=mean(d_total_sh_tx2,3);
     d_total_headang_hip=mean(d_total_headang1,3);
     d_total_headang_per=mean(d_total_headang2,3);
     d_total_headtx_hip=mean(d_total_headtx1,3);
     d_total_headtx_per=mean(d_total_headtx2,3);
     d_trunk_hip=mean(d_total_trunk1,3);
     d_trunk_per=mean(d_total_trunk2,3);
     d_total_kneeang_hip =
mean(d_total_kneeang1,3);
```

```
     d_total_kneeang_per =
mean(d_total_kneeang2,3);
     d_total_opp_kneeang_hip =
mean(d_total_opp_kneeang1,3);
     d_total_opp_kneeang_per =
mean(d_total_opp_kneeang2,3);
     d_total_ankleang_hip =
mean(d_total_ankleang1,3);
     d_total_ankleang_per =
mean(d_total_ankleang2,3);
     d_total_opp_ankleang_hip =
mean(d_total_opp_ankleang1,3);
     d_total_opp_ankleang_per =
mean(d_total_opp_ankleang2,3);
     d_total_hipad_hip = mean(d_total_hipad1,3);
     d_total_hipad_per = mean(d_total_hipad2,3);


end


end


t2=[-1:1/200:3.5]';


figure(1)
plot(t2,h_total_hip_hip (:,1),'k', t2,
h_total_hip_per(:,1),'r', t2,
d_total_hip_hip(:,1),'k:',
t2,d_total_hip_per(:,1),'r:');
legend('HipVib(H)','PerVib(H)','HipVib(D)','PerVib
(D)' );
title('total hip translate')
vline(0/200)
vline(400/200)
v=axis;
axis([-1 3.5 -30 10])
hold off

figure(2)
plot(t2,h_total_hipang_hip (:,1),'k', t2,
h_total_hipang_per(:,1),'r', t2,d_total_hipang_hip
(:,1),'k:', t2, d_total_hipang_per(:,1),'r:');
```

```
legend('HipVib(H)','PerVib(H)','HipVib(D)',
'PerVib(D)');
title('total hip angle')
vline(0/200)
vline(400/200)
v=axis;
axis([-1 3.5 v(3) v(4)])
hold off


figure(3)
plot(t2,h_total_shang_hip (:,1),'k', t2,
h_total_shang_per(:,1),'r',t2,d_total_shang_hip
(:,1),'k:', t2, d_total_shang_per(:,1),'r:');
legend('HipVib(H)','PerVib(H)','HipVib(D)',
'PerVib(D)');
title('total sh angle')
vline(0/200)
vline(400/200)
v=axis;
axis([-1 3.5 v(3) v(4)])

figure(4)
plot(t2,h_total_headang_hip (:,1),'k', t2,
h_total_headang_per(:,1),'r',t2,d_total_headang_hi
p (:,1),'k:', t2, d_total_headang_per(:,1),'r:');
legend('HipVib(H)','PerVib(H)','HipVib(D)',
'PerVib(D)');
title('total head angle')
vline(0/200)
vline(400/200)
v=axis;
axis([-1 3.5 v(3) v(4)])

figure(5)
plot(t2,h_trunk_hip (:,1),'k', t2,
h_trunk_per(:,1),'r',t2,d_trunk_hip (:,1),'k:', t2,
d_trunk_per(:,1),'r:');
legend('HipVib(H)','PerVib(H)','HipVib(D)',
'PerVib(D)');
title('total Trunk angle')
vline(0/200)
vline(400/200)
v=axis;
axis([-1 3.5 -0.025 0.1 ])
```

```
figure(6)
plot(t2,h_total_shtx_hip(:,1),'k', t2,
h_total_shtx_per(:,1),'r',t2,d_total_shtx_hip(:,1)
,'k:', t2, d_total_shtx_per(:,1),'r:');
legend('HipVib(H)','PerVib(H)','HipVib(D)',
'PerVib(D)');
title('Right shoulder Translation')
vline(0/200)
vline(400/200)
v=axis;
axis([-1 3.5 v(3) v(4)])

figure(7)
plot(t2,h_total_headang_hip(:,1),'k', t2,
h_total_headang_per(:,1),'r',t2,d_total_headang_hi
p(:,1),'k:', t2, d_total_headang_per(:,1),'r:');
legend('HipVib(H)','PerVib(H)','HipVib(D)',
'PerVib(D)');
title('Head Angle')
vline(0/200)
vline(400/200)
v=axis;
axis([-1 3.5 v(3) v(4)])

figure(8)
plot(t2,h_total_headtx_hip(:,1),'k', t2,
h_total_headtx_per(:,1),'r',t2,d_total_headtx_hip(
:,1),'k:', t2, d_total_headtx_per(:,1),'r:');
legend('HipVib(H)','PerVib(H)','HipVib(D)',
'PerVib(D)');
title('Head Tx')
vline(0/200)
vline(400/200)
v=axis;
axis([-1 3.5 v(3) v(4)])

figure(8)
plot(t2,h_total_ankleang_hip,'k',  t2,
h_total_ankleang_per,'r',t2, d_total_ankleang_hip,
'k:', t2, d_total_ankleang_per,'r:');
legend('HipVib(H)','PerVib(H)','HipVib(D)',
'PerVib(D)');
title('Ankle angle(left)')
ylabel('Ever / Inv');
vline(0/200)
vline(400/200)
```

```
v=axis;
axis([-1 3.5 v(3) v(4)])
hold off


cond.names % this file order
```

Program 4 - Study 3_part b

```
clear
close all % close all graphs
clear global
clc %clear the screen


%work through files
[files, path]= uigetfile('*.mat','select multiple
files','MultiSelect','on');

sz = size(files);


for i=1:sz(2)

   ifile= [path files{i}];     %curly braces
required to index files

  % load in data

    eval(['load ',ifile,';']);

     cond(i).names =ifile; %create list of column
names

    for x=1:4
```

```
total_hip1(:,x,i)=gavalli_hip_group(:,18,x);
%Data during hip vib

total_force1(:,x,i)=gavalli_hip_group(:,74,x);

total_hipang1(:,x,i)=gavalli_hip_group(:,106,x);

total_shang1(:,x,i)=gavalli_hip_group(:,107,x);

total_sh_tx1(:,x,i)=gavalli_hip_group(:,6,x);

total_headang1(:,x,i)=gavalli_hip_group(:,108,x);

total_headtx1(:,x,i)=gavalli_hip_group(:,3,x);

total_trunk1(:,x,i)=gavalli_hip_group(:,109,x);

total_kneeang1(:,x,i)=gavalli_hip_group(:,112,x);
%Sagital plane
                        total_vel(:,x,i) =
velocity_av(:,1,x);


     %%%%%%Get Data for plotting later

total_hip_hip=mean(total_hip1,3);      %Data
during hip vib
             total_force_hip=mean(total_force1,3);

total_hipang_hip=mean(total_hipang1,3);

total_shang_hip=mean(total_shang1,3);

total_shtx_hip=mean(total_sh_tx1,3);

total_headang_hip=mean(total_headang1,3);

total_headtx1_hip=mean(total_headtx1,3);

trunk_hip=mean(total_trunk1,3);
                                    total_kneeang_hip
= mean(total_kneeang1,3);
                                        total_vel_hip
= mean(total_vel,3)
```

```
        %%%%%%%%%%%%%%%%%%  HIP
TRANSLATION  %%%%%%%%%%%%

         [a,b]
=min(gavalli_hip_group(150:550,18,x));
          hipstim_ht(i,x)=a; % max hip trans
          hipstim_ht(i,x+4)=(b)/200; % time of max
hip trans

hipstim_ht(i,x+8)=gavalli_hip_group(550,18,x); %
hip at end

hipstim_ht(i,x+12)=mean(gavalli_hip_group(250:350,
18,x)); % mean 0.5 to 1 sec

hipstim_ht(i,x+16)=mean(gavalli_hip_group(350:450,
18,x)); % mean 1 to 1.5 sec

hipstim_ht(i,x+20)=mean(gavalli_hip_group(450:550,
18,x)); % mean 1.5 to 2 sec



          %%%%%%%%%%%%%%%%%
FORCE  %%%%%%%%%%%%%%%%%%%

          [a,b]
=max(gavalli_hip_group(150:550,74,x));
          hipstim_force(i,x)=a; % max force    x=
i=
          hipstim_force(i,x+4)=(b)/200; % time of
max force

hipstim_force(i,x+8)=gavalli_hip_group(550,74,x);  %
force at end

hipstim_force(i,x+12)=mean(gavalli_hip_group(250:3
50,74,x)); % mean 0.5 to 1 sec

hipstim_force(i,x+16)=mean(gavalli_hip_group(350:4
50,74,x)); % mean 1 to 1.5 sec

hipstim_force(i,x+20)=mean(gavalli_hip_group(450:5
50,74,x)); % mean 1.5 to 2 sec
```

```
        %%%%%%%%%%%%%%%%%%  HIP
ANGLE  %%%%%%%%%%%%%%

           [a,b]
=max(gavalli_hip_group(150:550,106,x));
          hipstim_ha(i,x)=a; % max
          hipstim_ha(i,x+4)=(b)/200; % time of max
hipang

hipstim_ha(i,x+8)=gavalli_hip_group(550,106,x); %
hip ang at 2seconds

hipstim_ha(i,x+12)=mean(gavalli_hip_group(250:350,
106,x)); % mean 0.5 to 1 sec

hipstim_ha(i,x+16)=mean(gavalli_hip_group(350:450,
106,x)); % mean 1 to 1.5 sec

hipstim_ha(i,x+20)=mean(gavalli_hip_group(450:550,
106,x)); % mean 1.5 to 2 sec


          %%%%%%%%%%%%%%%%%%%%%%  SHOULDER
ANGLE  %%%%%%%%%%%%%%

          [a,b]
=max(gavalli_hip_group(150:550,107,x));
          hipstim_sa(i,x)=a; % max
          hipstim_sa(i,x+4)=(b)/200; %

hipstim_sa(i,x+8)=gavalli_hip_group(550,107,x); %
2 seconds

hipstim_sa(i,x+12)=mean(gavalli_hip_group(250:350,
107,x)); % mean 0.5 to 1 sec

hipstim_sa(i,x+16)=mean(gavalli_hip_group(350:450,
107,x)); % mean 1 to 1.5 sec

hipstim_sa(i,x+20)=mean(gavalli_hip_group(450:550,
107,x)); % mean 1.5 to 2 sec

          %%%%%%%%%%%%%%%%%%%%%%Shoulder
Tx%%%%%%%%%%%%%%%%%%%%%%%%
```

```
            [a,b]
=min(gavalli_hip_group(150:550,6,x));
            hipstim_stx(i,x)=a; % max
            hipstim_stx(i,x+4)=(b)/200; %

hipstim_stx(i,x+8)=gavalli_hip_group(550,6,x); % 2
seconds

hipstim_stx(i,x+12)=mean(gavalli_hip_group(250:350
,6,x)); % mean 0.5 to 1 sec

hipstim_stx(i,x+16)=mean(gavalli_hip_group(350:450
,6,x)); % mean 1 to 1.5 sec

hipstim_stx(i,x+20)=mean(gavalli_hip_group(450:550
,6,x)); % mean 1.5 to 2 sec



            %%%%%%%%%%%%%%%%%%  HEAD
ANGLE  %%%%%%%%%%%%%%%%%%%%%

            [a,b]
=max(gavalli_hip_group(150:550,108,x));
            hipstim_heda(i,x)=a; % max
            hipstim_heda(i,x+4)=(b)/200; %

hipstim_heda(i,x+8)=gavalli_hip_group(550,108,x);  %
2 seconds

hipstim_heda(i,x+12)=mean(gavalli_hip_group(250:35
0,108,x)); % mean 0.5 to 1 sec

hipstim_heda(i,x+16)=mean(gavalli_hip_group(350:45
0,108,x)); % mean 1 to 1.5 sec

hipstim_heda(i,x+20)=mean(gavalli_hip_group(450:55
0,108,x)); % mean 1.5 to 2 sec

            %%%%%%%%%%%%%%%%%%%%%%HEAD
TX %%%%%%%%%%%%%%%%%%%%%%

             [a,b]
=min(gavalli_hip_group(150:550,3,x));
            hipstim_hedtx(i,x)=a; % max
            hipstim_hedtx(i,x+4)=(b)/200; %
```

```
hipstim_hedtx(i,x+8)=gavalli_hip_group(550,3,x); %
2 seconds

hipstim_hedtx(i,x+12)=mean(gavalli_hip_group(250:3
50,3,x)); % mean 0.5 to 1 sec

hipstim_hedtx(i,x+16)=mean(gavalli_hip_group(350:4
50,3,x)); % mean 1 to 1.5 sec

hipstim_hedtx(i,x+20)=mean(gavalli_hip_group(450:5
50,3,x)); % mean 1.5 to 2 sec

          %%%%%%%%%%%%%%%%%%%% TRUNK
ANGLE  %%%%%%%%%%%%%%%%

          [a,b]
=max(gavalli_hip_group(150:550,109,x));
          hipstim_ta(i,x)=a; % max
          hipstim_ta(i,x+4)=(b)/200; %
          hipstim_ta(i,x+8)=
gavalli_hip_group(550,109,x); % 2 seconds

hipstim_ta(i,x+12)=mean(gavalli_hip_group(250:350,
109,x)); % mean 0.5 to 1 sec

hipstim_ta(i,x+16)=mean(gavalli_hip_group(350:450,
109,x)); % mean 1 to 1.5 sec

hipstim_ta(i,x+20)=mean(gavalli_hip_group(550:550,
109,x)); % mean 1.5 to 2 sec


          %%%%% Ankle side of hip stim %%%%%%%%

         [a,b]
=min(gavalli_hip_group(150:550,110,x));
          hipstim_ank_side(i,x)=a; % max
          hipstim_ank_side(i,x+4)=(b)/200; %
          hipstim_ank_side(i,x+8)=
gavalli_hip_group(550,110,x); % 2 seconds

hipstim_ank_side(i,x+8)=mean(gavalli_hip_group(250
:350,110,x)); % mean 0.5 to 1 sec
```

```
hipstim_ank_side(i,x+12)=mean(gavalli_hip_group(35
0:450,110,x)); % mean 1 to 1.5 sec

hipstim_ank_side(i,x+20)=mean(gavalli_hip_group(55
0:550,110,x)); % mean 1.5 to 2 sec


          %%%%%%%%%%%%%%Velocity%%%%%%%%%%%%%%%%%%%
%%%%

           hipstim_vel(i,x) = velocity_av(:,1,x);

           %%%%% Ankle opposite hip
stim %%%%%%%%%%%%%%


          [a,b]
=min(gavalli_hip_group(150:550,111,x));
           hipstim_ank_opp(i,x)=a; % max
           hipstim_ank_opp(i,x+4)=(b)/200; %
           hipstim_ank_opp(i,x+8)=
gavalli_hip_group(550,111,x); % 2 seconds

hipstim_ank_opp(i,x+12)=mean(gavalli_hip_group(250
:350,111,x)); % mean 0.5 to 1 sec

hipstim_ank_opp(i,x+16)=mean(gavalli_hip_group(350
:450,111,x)); % mean 1 to 1.5 sec

hipstim_ank_opp(i,x+20)=mean(gavalli_hip_group(550
:550,111,x)); % mean 1.5 to 2 sec


    end % end of x loop


end


t2=[-1:1/200:3.5]';


figure(1)
```

```
plot(t2,total_hip_hip (:,1),'k', t2,total_hip_hip
(:,2),'k:',t2,total_hip_hip
(:,3),'r',t2,total_hip_hip (:,4),'r:');

legend('AFO4', 'NAFO4', 'AFO16','NAFO16');
title('total hip translate')
vline(0/200)
vline(400/200)
v=axis;
axis([-1 3.5 -30 10])
hold off

figure(2)

plot(t2,total_hipang_hip (:,1),'k',
t2,total_hipang_hip (:,2),'k:',t2,total_hipang_hip
(:,3),'r',t2,total_hipang_hip (:,4),'r:');

legend('AFO4', 'NAFO4', 'AFO16','NAFO16');
title('total hip angle')
vline(0/200)
vline(400/200)
v=axis;
axis([-1 3.5 v(3) v(4)])
hold off


figure(3)

plot(t2,total_shang_hip (:,1),'k',
t2,total_shang_hip (:,2),'k:',t2,total_shang_hip
(:,3),'r',t2,total_shang_hip (:,4),'r:');

legend('AFO4', 'NAFO4', 'AFO16','NAFO16');
title('total sh angle')
vline(0/200)
vline(400/200)
v=axis;
axis([-1 3.5 v(3) v(4)])

figure(4)
plot(t2,total_headang_hip (:,1),'k',
t2,total_headang_hip (:,2),'k:',
t2,total_headang_hip (:,3),'r',
t2,total_headang_hip (:,4),'r:');
legend('AFO4', 'NAFO4', 'AFO16','NAFO16');
```

```
title('total head angle')
vline(0/200)
vline(400/200)
v=axis;
axis([-1 3.5 v(3) v(4)])

figure(5)
plot(t2,trunk_hip (:,1),'k', t2,trunk_hip
(:,2),'k:', t2,trunk_hip (:,3),'r', t2,trunk_hip
(:,4),'r:');
legend('AFO4', 'NAFO4', 'AFO16','NAFO16');
title('total Trunk angle')
vline(0/200)
vline(400/200)
v=axis;
axis([-1 3.5 v(3) v(4)])



figure(6)
plot(t2,total_force_hip (:,1),'k',
t2,total_force_hip (:,2),'k:',t2,total_force_hip
(:,3),'r', t2,total_force_hip (:,4),'r:');
legend('AFO4', 'NAFO4', 'AFO16','NAFO16');
title('CoP -Y')
vline(0/200)
%vline(400/200)
v=axis;
axis([-1 3.5 v(3) v(4)])



figure(9)
plot(t2,total_shtx_hip(:,1),'k',
t2,total_shtx_hip(:,2),'k:',t2,total_shtx_hip(:,3)
,'r', t2,total_shtx_hip(:,4),'r:');
legend('AFO4', 'NAFO4', 'AFO16','NAFO16');
title('Right shoulder Translation')
vline(0/200)
%vline(400/200)
v=axis;
axis([-1 3.5 v(3) v(4)])

figure(10)
```

```
plot(t2,total_headang_hip(:,1),'k',
t2,total_headang_hip(:,2),'k:',t2,total_headang_hi
p(:,3),'r', t2,total_headang_hip(:,4),'r:');
legend('AFO4', 'NAFO4', 'AFO16','NAFO16');
title('Head Angle')
vline(0/200)
vline(400/200)
v=axis;
axis([-1 3.5 v(3) v(4)])


[name, path]=uiputfile('*.mat','save workspace');
outfile = [path name];
save(outfile,'hipstim_ha','hipstim_ht','hipstim_sa
','hipstim_heda','hipstim_ta','cond' );

fileout=['C:\dpn\study3\partb\',name,'hipstim_hipt
rans','.txt'];    e
eval(['save ',fileout,' hipstim_ht -ascii']);

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,'.txt'];
```

```
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x','.txt'];
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cond.names %  file order
```

Appendix 5. Patient and public involvement

Patient and public involvement (PPI) is important when designing research studies to make them more relevant to patient needs (NIHR, 2015). A steering group that consisted of lay people with diabetic peripheral neuropathy was therefore held to inform the feasibility and practicality of the methodology use in study 3. The Patient information sheet (Appendix 4) and Healthy control information sheet (Appendix 5) was given to each group member and time was allowed for individuals to read and feedback on their understanding of the study from this information. All individuals agreed that the patient information sheet was clear and well understood, and that it would provide sufficient information to make an informed decision on about whether to participate in the study. A verbal explanation was also presented to the group explaining further the theories behind the study, why it was being done and how it was going to be achieved. A demonstration of the measurement techniques proposed was also presented in the laboratory to the group. Here they raised a number of questions and issues that could have been potentially difficult or worrying for participants. These included:

1. Changing into shorts may have been challenging.
2. Having eyes closed was felt to be a safety worry.
3. Time standing may have been an issue.

In response to these points a number of changes were made to the study. Firstly, I had overlooked the difficulties participants may have had in changing into lycra style shorts. These were used in healthy subject studies 1 and 2 so that markers would not be obscured by clothing. The PPI group suggested

using bigger/baggier shorts that could be rolled up/taped away from marker viewing angles. Extra safety measures were also suggested so that participants were made to feel safe and were indeed safe if they lost their balance during balance measures. This led to the construction of an in-house purpose built harness. The harness was loose enough to not interfere with the participant responding to the stimulus but was able to prevent them from falling down. Further, an aluminium frame around the area they would be standing in was added to act as an extra support surface if required. In addition I provided participants with a seat to rest upon between measurement sets or if they became fatigued at any time. To reduce the time participants were required to stand and the overall the duration of the study, the number of stimulations were reduced in study 3. The measurement order was re-designed to incorporate rest periods where subjects could sit for any desired period.

Appendix 6. Patient information sheet

Patient information sheet

Plymouth University
Faculty of Health and Human Sciences

(version 3- 28/04/14)

Project title: Sensory re-weighting for balance control and the effects of ankle foot orthoses and stance width: A comparison of people with diabetic peripheral neuropathy and healthy participants

Principle investigator: Mr S. Glasser

We would like to invite you to participate in a new research study. Before you decide whether or not to participate, it is important for you to understand why the research is being done and what it will involve. This information sheet explains the background and aims of the study. Please take time to read it carefully and discuss it with others if you wish. If there is anything that is unclear, or if you would like more information, please contact us on the number below and we will be happy to explain. Your participation in this study is entirely voluntary.

What is the aim of the project?

A common complication of Diabetes is nerve damage affecting the feet. People with diabetes and nerve damage are more likely to feel unstable on their feet and are at greater risk of having a fall or a trip. People may compensate for the nerve damage around the feet by relying more on sensory information coming from the hips. People's balance may be affected by the use of ankle supports and how far the feet are apart.

The aim of this study is to test if

(a) people move differently in response to a mild vibration (a small vibrator unit, see figure 1) applied to the ankles or the hips
(b) wearing a specially selected ankle support and varying the distance the feet are apart affects balance.

We hope that the results of this study will inform the development of future treatments for people with diabetes and balance problems

Why have I been invited?

You have been asked to participate because you have diabetes and a loss of sensation to your feet. We are comparing the responses seen in people with diabetes and a loss of sensation to the feet, to healthy people without diabetes of the same gender and a similar age.

What would I have to do?

Take time to read this information sheet and discuss it with your friends and family if you wish.

Participation in the study would require you to visit the measurements laboratory at the Peninsula Allied Health Centre, Marjon Campus, PL6 8BH. We will send you directions if you volunteer for the study. Parking is available on-site. You are more than welcome to bring someone along for support.

Your visit will take approximately 2 hours. During the session we will test:

1. Vision, using charts with different sized letters for you to read.
2. Strength of your feet, measured by monitoring the amount of force you can apply to a small device positioned on the side of the foot.
3. Foot sensation, by recording your awareness to small amounts of pressure and vibration applied to the bottom of your foot using a thin nylon thread called a monofilament, and a variable vibration called a neurothesiometer.
4. General balance, by measuring the distance you can reach forward whilst standing.
5. You will then be required to stand for short periods of time (10 seconds at a time) adding up to no more than 25 minutes in total. You will have the

opportunity to sit down for a rest at any time. We will firstly apply a small vibration to your skin over the side of your hips (fig 1) and ankles when you stand in barefoot and with your eyes closed. The vibrator unit sits just below the trouser line. The vibration will result in a small sway to the side. We will measure this sway by placing small lights on your head shoulders, hips and legs (fig 2) which are monitored on a camera system and by recording the forces that you apply with your legs using a plate that you stand on.

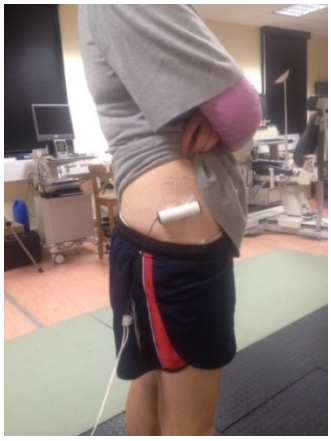

Figure 1

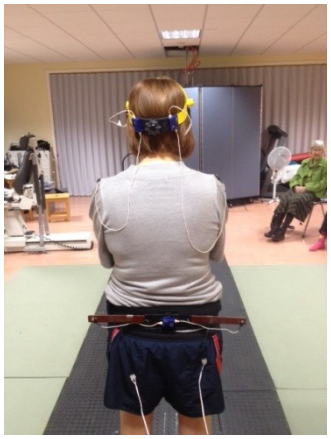

Figure 2

Figure 3

After a rest we will repeat the same test. But this time we will vary the width your feet are apart, and ask you to wear an ankle support (fig 3) whilst wearing special slippers specifically for people with diabetes.

Do I have to take part?

No. It is entirely up to you whether or not to take part. If you decide to take part you may choose to withdraw at any time without giving any reason. If you decide not to take part your usual healthcare will not be affected in any way.

If you decide to take part you will be asked to sign a consent form. You will be given a signed copy of the consent form and an information sheet for your own records.

Will my records be confidential?

All information collected about you during the course of this research will be kept strictly confidential. All information will be stored electronically on a computer which is password protected, in a document file that is also password protected. All information will be handled in compliance with the Data Protection Act (1998).

Your name and address (which we need in order to contact you) will be stored separately from the other information you supply during the project. You will be assigned a unique code under which all the data collected is stored, so that you cannot be identified from your study data.

What are the potential risks or benefits of taking part?

Risks

The risks of taking part in this study are minimal. There is a slight risk that the ankle support or footwear could rub your skin during the short time you are wearing them. We will take care to check your feet during the appointment to ensure no damage is done.

As described the vibration may cause you to sway slightly. Although the amount of sway is unlikely to cause you to fall, you will wear a harness at all times attached to an overhead support as a precaution.

Benefits

There is unlikely to be any benefit to you taking part in this study. However some people gain satisfaction from knowing that the information provided will enable us to further our knowledge on the effect diabetes has on balance.

Participating in this study should not have any effect on any of your insurance policies (for example critical illness, mortgage repayment, health and private medical insurance). However, please consider that if we do identify a health concern during the course of this study this may affect your future health / medical insurance policies, please seek advice if you wish.

Who is organising the study?

The organiser of the study is Mr S. Glasser, PhD student, Plymouth University.

Who has reviewed this study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by the South West Research Ethics Committee, the Research and Development team at Plymouth community Healthcare trust and the Plymouth University, Faculty of Health and medicine Research Ethics Committee.

What will happen to the results of the research study?

The results of the study form the focus of a PhD project. We will aim to talk about the work at meetings in this country and abroad and we will aim to publish the findings widely in medical journals.

We will provide you with a summary of the results.

Your rights

Your participation in this study is entirely voluntary. You may withdraw at any time without giving a reason for withdrawal or without it affecting your current or future health care treatment in any way.

What if I have any further questions or require further information?

If you have any questions about our project, either now or in the future, please feel free to contact Mr Sam.Glasser on:

Tel: 01752 587541
Email: sam.glasser@plymouth.ac.uk

What if I have a complaint?

Should you have reason to complain about the way you have been treated at any stage during the study you can access the NHS patient advisory liaison service (PALS) who will be able to advise and help you (plh-tr.PALS@nhs.net or tel. 0845 1558123/01752 439884).

Alternatively, you can make your complaint directly the Chief Investigator involved in this study (contact details as above).

Thank you for taking the time to read this information sheet.

Lead Researcher:

_____ _____

Mr S.Glasser *Date*

Contact: Faculty of Health, Education and Society
Plymouth University
Peninsula Allied Health Centre
Derriford Rd
Plymouth
PL6 8BH

Telephone: 01752 587541

Email: sam.glasser@plymouth.ac.uk

Appendix 7. Healthy control information sheet

Healthy control information sheet
(version 3- 28/04/14)

Plymouth University
Faculty of Health and Human Sciences

Project title: Sensory re-weighting for balance control and the effects of ankle foot orthoses and stance width: A comparison of people with diabetic peripheral neuropathy and healthy participants

Principle investigator: Mr S. Glasser

We would like to invite you to participate in a new research study. Before you decide whether or not to participate, it is important for you to understand why the research is being done and what it will involve. This information sheet explains the background and aims of the study. Please take time to read it carefully and discuss it with others if you wish. If there is anything that is unclear, or if you would like more information, please contact us on the number below, and we will be happy to explain. Your participation in this study is entirely voluntary.

What is the aim of the project?

A common complication of Diabetes is nerve damage affecting the feet. People with diabetes and nerve damage are more likely to feel unstable on their feet and are at greater risk of having a fall or a trip. People may compensate for the nerve damage around the feet by using more on sensory information coming from the hips. People's balance may be affected by the use of ankle supports and how far the feet are apart.

The aim of this study is to test if

(a) people respond differently to a mild vibration (a small vibrator unit, see figure 1) applied to the ankles or the hips

(b) wearing a specially selected ankle support and varying the distance the feet are apart affects balance.

We hope that the results of this study will inform the development of future treatments for people with diabetes and balance problems

Why have I been invited?

We are comparing the responses seen in people with diabetes and a loss of sensation to the feet, to healthy people without diabetes of the same gender and a similar age. You have been asked to participate as you may act as a healthy control in this study. You should not have any conditions that would affect your balance such as previous neurological conditions (e.g. a stroke), rheumatological conditions (e.g. rheumatoid arthritis) or current sprains and pain affecting the legs

What would I have to do?

Take time to read this information sheet and discuss it with your friends and family if you wish.

Participation in the study would require you to visit the measurements laboratory at the Peninsula Allied Health Centre, Marjon Campus, PL6 8BH. We will send you directions if you volunteer for the study. You are more than welcome to bring someone along for support.

Your visit will take approximately 2 hours. During the session we will test:

1. Vision, using charts with different sized letters for you to read.
2. Strength of your feet, measured by monitoring the amount of force you can apply to a small device positioned on the side of the foot.
3. Foot sensation, by recording your awareness to small amounts of pressure and vibration applied to the bottom of your foot using a thin nylon thread called a monofilament, and a variable vibration called a neurothesiometer.
4. General balance, by measuring the distance you can reach forward whilst standing.
5. You will then be required to stand for short periods of time (10 seconds at a time) adding up to no more than 25 minutes in total. You will have the

opportunity to sit down for a rest at any time. We will firstly apply a small vibration to your skin over the side of your hips (fig 1) and ankles when you stand in barefoot and with your eyes closed. The vibrator unit sits just below the trouser line. The vibration will result in a small sway to the side. We will measure this sway by placing small lights on your head shoulders, hips and legs (fig 2) which are monitored on a camera system and by recording the forces that you apply with your legs using a plate that you stand on.

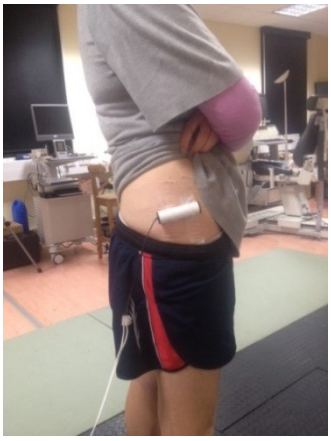

Figure 1

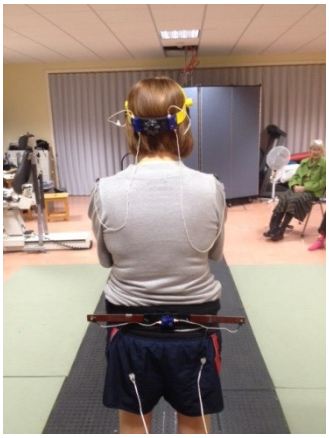

Figure .2

Figure .3

After a rest we will repeat the same test. But this time we will vary the width your feet are apart, and ask you to wear an ankle support (fig 2) whilst wearing special slippers specifically for people with diabetes.

Do I have to take part?

No. It is entirely up to you whether or not to take part. If you decide to take part you may choose to withdraw at any time without giving any reason. If you decide not to take part your usual healthcare will not be affected in any way.

If you decide to take part you will be asked to sign a consent form. You will be given a signed copy of the consent form and an information sheet for your own records.

Will my records be confidential?

Figure 1

All information collected about you during the course of this research will be kept strictly confidential. All information will be stored electronically on a computer which is password protected, in a document file that is also password protected. All information will be handled in compliance with the Data Protection Act (1998).

Your name and address (which we need in order to contact you) will be stored separately from the other information you supply during the project. You will be assigned a unique code under which all the data collected is stored, so that you cannot be identified from your study data.

What are the potential risks or benefits of taking part?

Risks

The risks of taking part in this study are minimal. There is a slight risk that the ankle support or footwear could rub your skin during the short time you are wearing them. We will take care to check your feet during the appointment to ensure no damage is done.

As described the vibration may cause you to sway slightly. Although the amount of sway is unlikely to cause you to fall, you will wear a harness at all times attached to an overhead support as a precaution.

Benefits

There is unlikely to be any benefit to you taking part in this study. However some people gain satisfaction from knowing that the information provided will enable us to further our knowledge on the effect diabetes has on balance.

Participating in this study should not have any effect on any of your insurance policies (for example critical illness, mortgage repayment, health and private medical insurance). However, please consider that if we do identify a health concern during the course of this study this may affect your future health / medical insurance policies, please seek advice if you wish.

Who is organising the study?

The organisers of the study is Mr S. Glasser, PhD student, Plymouth University.

Who has reviewed this study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by the South West Research Ethics Committee, the Research and Development team at Plymouth community Healthcare trust and the Plymouth University, Faculty of Health and medicine Research Ethics Committee.

What will happen to the results of the research study?

The results of the study form the focus of a PhD project. We will aim to talk about the work at meetings in this country and abroad and we will aim to publish the findings widely in medical journals.

We will provide you with a summary of the results.

Your rights

Your participation in this study is entirely voluntary. You may withdraw at any time without giving a reason for withdrawal or without it affecting your current or future health care treatment in any way.

What if I have any further questions or require further information?

If you have any questions about our project, either now or in the future, please feel free to contact Mr Sam.Glasser on:

Tel: 01752 587541
Email: sam.glasser@plymouth.ac.uk

What if I have a complaint?

Should you have reason to complain about the way you have been treated at any stage during the study you can access the NHS patient advisory liaison service (PALS) who will be able to advise and help you (plh-tr.PALS@nhs.net or tel. 0845 1558123/01752 439884).

Alternatively, you can make your complaint directly the Chief Investigator involved in this study (contact details as above).

Thank you for taking the time to read this information sheet.

Lead Researcher:

_____ _____

Mr S.Glasser *Date*

Contact: Faculty of Health, Education and Society
Plymouth University
Peninsula Allied Health Centre
Derriford Rd
Plymouth
PL6 8BH

Telephone: 01752 587541

Email: sam.glasser@plymouth.ac.uk

Appendix 8. University of the 3rd Age invitation

Dear University of the 3rd Age

I am a 2nd year PhD student here at Plymouth University, looking into balance problems in people with Diabetes.

A common complication of Diabetes is nerve damage affecting the feet. People with diabetes and nerve damage are more likely to feel unstable on their feet and are at greater risk of having a fall or a trip. People may compensate for the nerve damage around the feet by relying more on sensory information coming from the hips. People's balance may be affected by the use of ankle supports and how far the feet are apart.

The aim of the study is therefore to test if:

(a) people respond differently to mild vibratory stimuli that are applied at the ankles or the hips
(b) wearing a specially selected ankle support and varying the distance the feet are apart affects balance.

We are comparing the responses seen in people with diabetes and a loss of sensation to the feet to healthy people without diabetes of the same gender and a similar age. I am therefore hoping to recruit potential participants form the University of the 3rd age and staff here at Plymouth University.

Attached is an information sheet detailing the study and what would be required of you if you would be willing to participate.

If you feel you would like to be included in the study or would like to know any more details before making that decision, please contact me and we can discuss any further details.

Many thanks
Sam

Sam Glasser
Plymouth Universtiy
Plymouth Allied Health Centre
Marjon Campus
Derriford Road
Plymouth
PL6 8BH
Email: sam.glasser@plymouth.ac.uk Tel: 01752 587541

Appendix 9. Vibration penetration

Introduction

Although vibratory stimuli have been used previously to investigate balance the stimuli have usually been applied to tendons or muscles with little subcutaneous fat. Little is known about how much of the vibration is actually received by the muscle/tendon in locations that have a thicker layer of subcutaneous tissue, for example the gluteus medius. To assess this, the received vibration amplitudes at levels of sub-cutaneous tissue were measured.

Methods

For the purpose of this investigation a section of pig hip was sourced and dissected by butcher, in an attempt to replicate that of human tissue at the pelvis. The meat was refrigerated overnight and allowed to reach room temperature before measurements were completed.

The vibrator was positioned on the cutaneous tissue above an accelerometer (figure A9.1) which was inserted at depths of 0, 2, 4 and 8cm. At each depth, the vibration of 5 sets of 10 second stimulations were recorded and exported to excel spreadsheet (table A9.1). The root mean square amplitude and frequency was recorded.

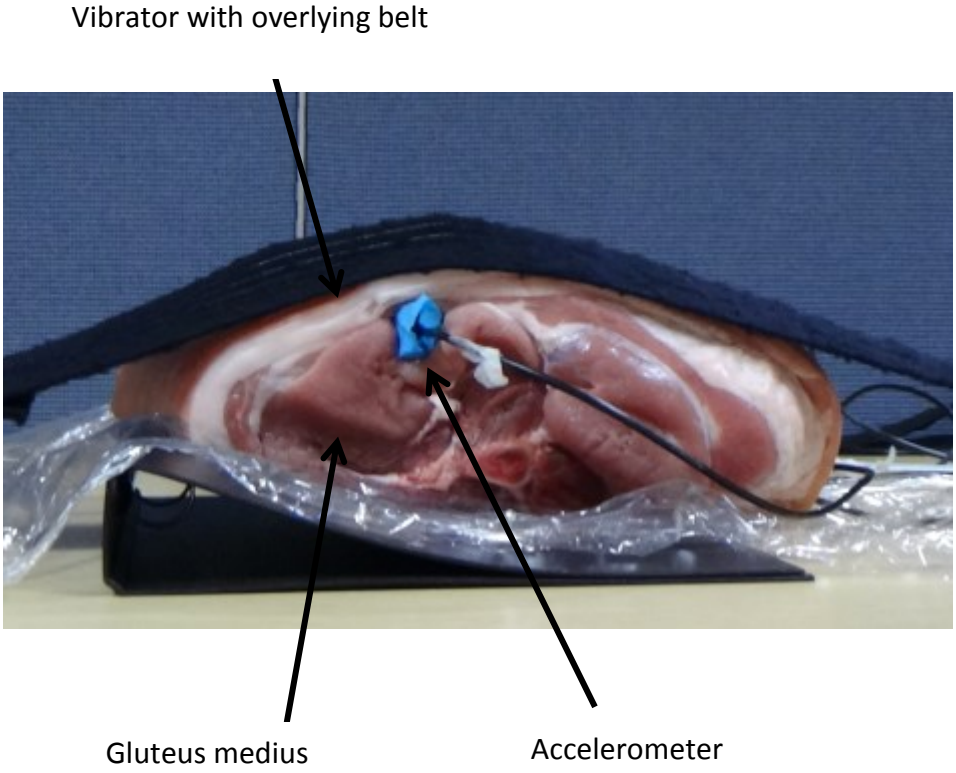

Figure A09.1 Measurement set up.

Results

	Vibration amplitude			
Depth	0 cm (G)	2cm (G)	4cm (G)	8cm (G)
Trial 1	2.17	1.12	0.13	0.15
Trial 2	2.25	1.12	0.15	0.15
Trial 3	2.24	1.13	0.17	0.14
Trial 4	2.25	1.13	0.19	0.15
Trial 5	2.22	1.13	0.22	0.15
Average	2.226	1.126	0.172	0.148

Table A9.1 Vibration amplitudes at levels of subcutaneous tissue.

Results showed that by increasing the depth of sub cutaneous tissue the resulting vibration amplitude is reduced significantly ($P<0.05$) up to a depth of

4cm (A9.2). At depths greater than 4cm the received amplitude was insignificant (P>0.05)

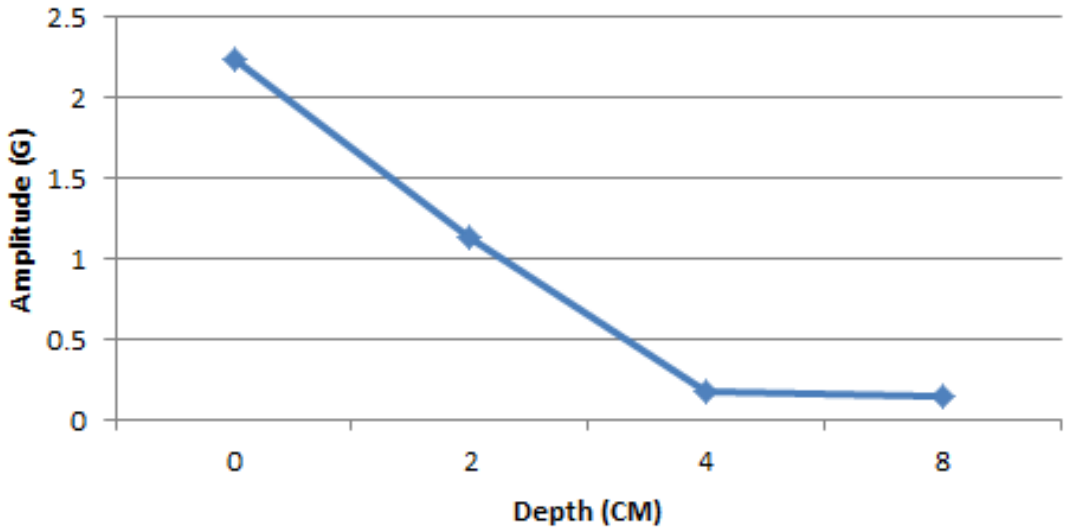

Figure A9.2 Plot to show vibration amplitude Vs subcutaneous tissue depth.

Analysing the frequency of vibration at the same depths revealed that frequency was not affected by the depth of subcutaneous tissue (Table A9.3).

	Depth (cm)		
	0cm (Hz)	2cm (Hz)	8cm (Hz)
Sample 1	62	61	61
Sample 2	62	61	61
Sample 3	62	61	61
Sample 4	62	61	61
Sample 5	62	61	61
Average	62	61	61

Table A9.3 Vibration frequency at levels of subcutaneous tissue.

Conclusion

Findings from these pre-clinical tests indicate that although the frequency is unaffected by subcutaneous tissue thickness (i.e. the gluteus medius), peak to peak amplitudes are affected. Amplitude is dependent on the attached mass and therefore supports our findings that increased subcutaneous tissue reduces vibration amplitudes. This is therefore a finding that should be considered when comparing different groups of people.

Appendix 10. SPPS data output

SPSS outputs related to table 7.7 – Between groups repeated measures ANOVA for head angle

General Linear Model

Within-Subjects Factors

Measure: MEASURE_1

StanceWidth	AFO	Dependent Variable
1	1	AFO_4
	2	NAFO_4
2	1	AFO_16
	2	NOAFO_16

Between-Subjects Factors

		N
Group	1.00	18
	2.00	15

Multivariate Tests[a]

Effect		Value	F	Hypothesis df	Error df	Sig.
StanceWidth	Pillai's Trace	.541	36.466[b]	1.000	31.000	.000
	Wilks' Lambda	.459	36.466[b]	1.000	31.000	.000
	Hotelling's Trace	1.176	36.466[b]	1.000	31.000	.000
	Roy's Largest Root	1.176	36.466[b]	1.000	31.000	.000
StanceWidth * Group	Pillai's Trace	.162	6.010[b]	1.000	31.000	.020
	Wilks' Lambda	.838	6.010[b]	1.000	31.000	.020
	Hotelling's Trace	.194	6.010[b]	1.000	31.000	.020
	Roy's Largest Root	.194	6.010[b]	1.000	31.000	.020
AFO	Pillai's Trace	.006	.175[b]	1.000	31.000	.678
	Wilks' Lambda	.994	.175[b]	1.000	31.000	.678
	Hotelling's Trace	.006	.175[b]	1.000	31.000	.678
	Roy's Largest Root	.006	.175[b]	1.000	31.000	.678
AFO * Group	Pillai's Trace	.006	.189[b]	1.000	31.000	.667
	Wilks' Lambda	.994	.189[b]	1.000	31.000	.667
	Hotelling's Trace	.006	.189[b]	1.000	31.000	.667
	Roy's Largest Root	.006	.189[b]	1.000	31.000	.667
StanceWidth * AFO	Pillai's Trace	.054	1.763[b]	1.000	31.000	.194
	Wilks' Lambda	.946	1.763[b]	1.000	31.000	.194
	Hotelling's Trace	.057	1.763[b]	1.000	31.000	.194
	Roy's Largest Root	.057	1.763[b]	1.000	31.000	.194
StanceWidth * AFO * Group	Pillai's Trace	.006	.178[b]	1.000	31.000	.676
	Wilks' Lambda	.994	.178[b]	1.000	31.000	.676
	Hotelling's Trace	.006	.178[b]	1.000	31.000	.676
	Roy's Largest Root	.006	.178[b]	1.000	31.000	.676

a. Design: Intercept + Group

Within Subjects Design: StanceWidth + AFO + StanceWidth * AFO

b. Exact statistic

Mauchly's Test of Sphericity[a]

Measure: MEASURE_1

Within Subjects Effect	Mauchly's W	Approx. Chi-Square	df	Sig.	Epsilon[b]		
					Greenhouse-Geisser	Huynh-Feldt	Lower-bound
StanceWidth	1.000	.000	0	.	1.000	1.000	1.000
AFO	1.000	.000	0	.	1.000	1.000	1.000
StanceWidth * AFO	1.000	.000	0	.	1.000	1.000	1.000

Tests the null hypothesis that the error covariance matrix of the orthonormalized transformed dependent variables is proportional to an identity matrix.

a. Design: Intercept + Group

Within Subjects Design: StanceWidth + AFO + StanceWidth * AFO

b. May be used to adjust the degrees of freedom for the averaged tests of significance. Corrected tests are displayed in the Tests of Within-Subjects Effects table.

Tests of Within-Subjects Effects

Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
StanceWidth	Sphericity Assumed	.337	1	.337	36.466	.000
	Greenhouse-Geisser	.337	1.000	.337	36.466	.000
	Huynh-Feldt	.337	1.000	.337	36.466	.000
	Lower-bound	.337	1.000	.337	36.466	.000
StanceWidth * Group	Sphericity Assumed	.056	1	.056	6.010	.020
	Greenhouse-Geisser	.056	1.000	.056	6.010	.020
	Huynh-Feldt	.056	1.000	.056	6.010	.020
	Lower-bound	.056	1.000	.056	6.010	.020
Error(StanceWidth)	Sphericity Assumed	.286	31	.009		
	Greenhouse-Geisser	.286	31.000	.009		
	Huynh-Feldt	.286	31.000	.009		
	Lower-bound	.286	31.000	.009		

AFO	Sphericity Assumed	.002	1	.002	.175	.678
	Greenhouse-Geisser	.002	1.000	.002	.175	.678
	Huynh-Feldt	.002	1.000	.002	.175	.678
	Lower-bound	.002	1.000	.002	.175	.678
AFO * Group	Sphericity Assumed	.002	1	.002	.189	.667
	Greenhouse-Geisser	.002	1.000	.002	.189	.667
	Huynh-Feldt	.002	1.000	.002	.189	.667
	Lower-bound	.002	1.000	.002	.189	.667
Error(AFO)	Sphericity Assumed	.328	31	.011		
	Greenhouse-Geisser	.328	31.000	.011		
	Huynh-Feldt	.328	31.000	.011		
	Lower-bound	.328	31.000	.011		
StanceWidth * AFO	Sphericity Assumed	.009	1	.009	1.763	.194
	Greenhouse-Geisser	.009	1.000	.009	1.763	.194
	Huynh-Feldt	.009	1.000	.009	1.763	.194
	Lower-bound	.009	1.000	.009	1.763	.194
StanceWidth * AFO * Group	Sphericity Assumed	.001	1	.001	.178	.676
	Greenhouse-Geisser	.001	1.000	.001	.178	.676
	Huynh-Feldt	.001	1.000	.001	.178	.676
	Lower-bound	.001	1.000	.001	.178	.676
Error(StanceWidth*AFO)	Sphericity Assumed	.160	31	.005		
	Greenhouse-Geisser	.160	31.000	.005		
	Huynh-Feldt	.160	31.000	.005		
	Lower-bound	.160	31.000	.005		

Tests of Within-Subjects Contrasts

Measure: MEASURE_1

Source	StanceWidth	AFO	Type III Sum of Squares	df	Mean Square	F	Sig.
StanceWidth	Linear		.337	1	.337	36.466	.000
StanceWidth * Group	Linear		.056	1	.056	6.010	.020
Error(StanceWidth)	Linear		.286	31	.009		
AFO		Linear	.002	1	.002	.175	.678
AFO * Group		Linear	.002	1	.002	.189	.667
Error(AFO)		Linear	.328	31	.011		
StanceWidth * AFO	Linear	Linear	.009	1	.009	1.763	.194
StanceWidth * AFO * Group	Linear	Linear	.001	1	.001	.178	.676
Error(StanceWidth*AFO)	Linear	Linear	.160	31	.005		

Tests of Between-Subjects Effects

Measure: MEASURE_1

Transformed Variable: Average

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Intercept	2.787	1	2.787	68.230	.000
Group	.383	1	.383	9.380	.005
Error	1.266	31	.041		

SPSS outputs related to table 7.7 – Between groups repeated measures ANOVA for shoulder angle

General Linear Model

Within-Subjects Factors

Measure: MEASURE_1

StanceWidth	AFO	Dependent Variable
1	1	AFO_4
	2	NAFO_4
2	1	AFO_16
	2	NOAFO_16

Between-Subjects Factors

		N
Group	1.00	18
	2.00	15

Multivariate Tests[a]

Effect		Value	F	Hypothesis df	Error df	Sig.
StanceWidth	Pillai's Trace	.609	48.368[b]	1.000	31.000	.000
	Wilks' Lambda	.391	48.368[b]	1.000	31.000	.000
	Hotelling's Trace	1.560	48.368[b]	1.000	31.000	.000
	Roy's Largest Root	1.560	48.368[b]	1.000	31.000	.000
StanceWidth * Group	Pillai's Trace	.191	7.300[b]	1.000	31.000	.011
	Wilks' Lambda	.809	7.300[b]	1.000	31.000	.011
	Hotelling's Trace	.235	7.300[b]	1.000	31.000	.011
	Roy's Largest Root	.235	7.300[b]	1.000	31.000	.011
AFO	Pillai's Trace	.024	.747[b]	1.000	31.000	.394
	Wilks' Lambda	.976	.747[b]	1.000	31.000	.394
	Hotelling's Trace	.024	.747[b]	1.000	31.000	.394
	Roy's Largest Root	.024	.747[b]	1.000	31.000	.394

AFO * Group	Pillai's Trace	.016	.515[b]	1.000	31.000	.478
	Wilks' Lambda	.984	.515[b]	1.000	31.000	.478
	Hotelling's Trace	.017	.515[b]	1.000	31.000	.478
	Roy's Largest Root	.017	.515[b]	1.000	31.000	.478
StanceWidth * AFO	Pillai's Trace	.004	.115[b]	1.000	31.000	.737
	Wilks' Lambda	.996	.115[b]	1.000	31.000	.737
	Hotelling's Trace	.004	.115[b]	1.000	31.000	.737
	Roy's Largest Root	.004	.115[b]	1.000	31.000	.737
StanceWidth * AFO * Group	Pillai's Trace	.004	.135[b]	1.000	31.000	.716
	Wilks' Lambda	.996	.135[b]	1.000	31.000	.716
	Hotelling's Trace	.004	.135[b]	1.000	31.000	.716
	Roy's Largest Root	.004	.135[b]	1.000	31.000	.716

a. Design: Intercept + Group

Within Subjects Design: StanceWidth + AFO + StanceWidth * AFO

b. Exact statistic

Mauchly's Test of Sphericity[a]

Measure: MEASURE_1

Within Subjects Effect	Mauchly's W	Approx. Chi-Square	df	Sig.	Epsilon[b]		
					Greenhouse-Geisser	Huynh-Feldt	Lower-bound
StanceWidth	1.000	.000	0	.	1.000	1.000	1.000
AFO	1.000	.000	0	.	1.000	1.000	1.000
StanceWidth * AFO	1.000	.000	0	.	1.000	1.000	1.000

Tests the null hypothesis that the error covariance matrix of the orthonormalized transformed dependent variables is proportional to an identity matrix.

a. Design: Intercept + Group

Within Subjects Design: StanceWidth + AFO + StanceWidth * AFO

b. May be used to adjust the degrees of freedom for the averaged tests of significance. Corrected tests are displayed in the Tests of Within-Subjects Effects table.

Tests of Within-Subjects Effects

Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
StanceWidth	Sphericity Assumed	.489	1	.489	48.368	.000
	Greenhouse-Geisser	.489	1.000	.489	48.368	.000
	Huynh-Feldt	.489	1.000	.489	48.368	.000
	Lower-bound	.489	1.000	.489	48.368	.000
StanceWidth * Group	Sphericity Assumed	.074	1	.074	7.300	.011
	Greenhouse-Geisser	.074	1.000	.074	7.300	.011
	Huynh-Feldt	.074	1.000	.074	7.300	.011
	Lower-bound	.074	1.000	.074	7.300	.011
Error(StanceWidth)	Sphericity Assumed	.313	31	.010		
	Greenhouse-Geisser	.313	31.000	.010		
	Huynh-Feldt	.313	31.000	.010		
	Lower-bound	.313	31.000	.010		
AFO	Sphericity Assumed	.004	1	.004	.747	.394
	Greenhouse-Geisser	.004	1.000	.004	.747	.394
	Huynh-Feldt	.004	1.000	.004	.747	.394
	Lower-bound	.004	1.000	.004	.747	.394
AFO * Group	Sphericity Assumed	.003	1	.003	.515	.478
	Greenhouse-Geisser	.003	1.000	.003	.515	.478
	Huynh-Feldt	.003	1.000	.003	.515	.478
	Lower-bound	.003	1.000	.003	.515	.478
Error(AFO)	Sphericity Assumed	.179	31	.006		
	Greenhouse-Geisser	.179	31.000	.006		
	Huynh-Feldt	.179	31.000	.006		
	Lower-bound	.179	31.000	.006		
StanceWidth * AFO	Sphericity Assumed	.001	1	.001	.115	.737

	Greenhouse-Geisser	.001	1.000	.001	.115	.737
	Huynh-Feldt	.001	1.000	.001	.115	.737
	Lower-bound	.001	1.000	.001	.115	.737
StanceWidth * AFO * Group	Sphericity Assumed	.001	1	.001	.135	.716
	Greenhouse-Geisser	.001	1.000	.001	.135	.716
	Huynh-Feldt	.001	1.000	.001	.135	.716
	Lower-bound	.001	1.000	.001	.135	.716
Error(StanceWidth*AFO)	Sphericity Assumed	.151	31	.005		
	Greenhouse-Geisser	.151	31.000	.005		
	Huynh-Feldt	.151	31.000	.005		
	Lower-bound	.151	31.000	.005		

Tests of Within-Subjects Contrasts

Measure: MEASURE_1

Source	StanceWidth	AFO	Type III Sum of Squares	df	Mean Square	F	Sig.
StanceWidth	Linear		.489	1	.489	48.368	.000
StanceWidth * Group	Linear		.074	1	.074	7.300	.011
Error(StanceWidth)	Linear		.313	31	.010		
AFO		Linear	.004	1	.004	.747	.394
AFO * Group		Linear	.003	1	.003	.515	.478
Error(AFO)		Linear	.179	31	.006		
StanceWidth * AFO	Linear	Linear	.001	1	.001	.115	.737
StanceWidth * AFO * Group	Linear	Linear	.001	1	.001	.135	.716
Error(StanceWidth*AFO)	Linear	Linear	.151	31	.005		

Tests of Between-Subjects Effects

Measure: MEASURE_1

Transformed Variable: Average

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Intercept	2.349	1	2.349	126.493	.000
Group	.308	1	.308	16.609	.000
Error	.576	31	.019		

Appendix 11. Publication

Glasser S, Collings R, Paton J, Marsden J (2016). Effect of experimentally reduced distal sensation on postural response to hip abductor/ankle evertor muscle vibration. 2015. Gait and Posture; DOI: 10.1016/j.gaitpost.2015.05.009