UNIVERSITY COLLEGE LONDON

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Sensory mechanisms of balance control in cerebellar disease

PhD Neuroscience

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DECLARATION

I, Lisa May Bunn, 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.

……

ABSTRACT

A wealth of evidence exists to suggest that the cerebellum has an important role in the integration of vestibular, proprioceptive and visual sensory signals. Human bipedal balance depends on sensory integration and balance impairment is a common feature of cerebellar disease. I test the hypothesis that disrupted sensori-motor processing is responsible for balance impairment in cerebellar disease. Balance control in subjects with pure cerebellar disease (SCA6) was compared with matched healthy subjects using a mix of traditional clinical and laboratory-based tests. Sensory processing was explored using a novel combination of tools designed to deliver single-sensory channel balance perturbations. The vestibular, proprioceptive and visual channels were stimulated with galvanic vestibular stimulation, vibration and visual scene motion respectively.

Standing balance was explored using 3D whole body motion analysis. Sway speed when standing quietly with eyes open was significantly increased in those with SCA6 and strongly correlated with disease severity scores.

Responses to isolated vestibular stimulation suggest largely normal vestibulo-motor processing in SCA6 subjects. Responses had normal latency and magnitude. Response direction followed head position in the normal way suggesting intact vestibulo-proprioceptive integration. Vision had a normal attenuating effect on response magnitude suggesting intact vestibulo-visual integration.

Responses to isolated vestibular, proprioceptive and visual stimuli responses were compared to investigate whether there might be a predominant deficit in any one channel. Vestibular and proprioceptive stimuli evoked largely normal responses. In contrast, visual stimuli consistently evoked abnormally large responses with significant timing delays.

Increases in SCA6 response magnitudes to moving visual stimuli strongly correlated with disease severity scores. This finding is the first to point to a specific change in sensori-motor processing in cerebellar disease. This finding could contribute to balance impairments but is unlikely to explain balance impairment observed with the eyes closed. Overall sensory processing for balance control in SCA6 is largely intact.

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ABBREVIATIONS

ADCA	Autosomal dominant cerebellar ataxia
AP	Antero-posterior
CMCT	Central motor conduction time
CoP	Centre-of-pressure
deg	degrees
deg/sec	degrees per second
Df	Dorsi-flexors
FBS	Functional balance scale, also known as the Berg balance scale
FIM	Functional independence measure
FN	Fastigial nuclei
FSO	Following stimulation onset
GVS	Galvanic vestibular stimulation
HC	Healthy control
Hz	Hertz
IRED	Infra-red light emitting diodes
ML	Mediolateral
mm	millimeters
mm/s	millimeters per second
ms	milli-seconds
MVS	Moving visual scenery
N	Newtons of force
ns	No stimulation
PET	Photon-emisson tomography
Pf	Plantar-flexors
SCA	Spino-cerebellar ataxia
SCA6	Type 6 SCA
SARA	Scale for assessment and rating of ataxia
SHP	Start head position
SW	Stance width
TMS	Trans-cranial magnetic stimulation
VI	Vision intact
VIB	Vibrators
VN	Vestibular nuclei
VO	Vision obscured

1 CHAPTER ONE: INTRODUCTION

1.1 BACKGROUND

SCA6 is one variant of the genetically inherited forms of ataxia. Ataxia is a diagnostic umbrella term for a wide range of conditions and literally means 'incoordination of movement'. Spino-cerebellar ataxia (SCA) describes a collection of genetically acquired diseases primarily affecting the cerebellum and spinal column which are known to clinically manifest with impaired balance, gait and limb ataxia. There are currently twenty-eight different types of clinically characterised spino-cerebellar ataxias of which the genes to sixteen of these diseases (namely SCA types 1-8, 10-14, 16-17 and dentro-rubral-pallidoluysian atrophy) have so far been mapped[100]. Prior to the availability of genetic mapping an autosomal dominant cerebellar ataxia (ADCA) classification system was described by Harding [327]. SCA type 6 (SCA6) would previously have been classified as a type 3 ADCA meaning it displayed a relatively 'pure cerebellar syndrome' with cerebellar degeneration and almost no extra-cerebellar pathology. Type I autosomal dominant cerebellar ataxias (ADCAs) have more complex presentations involving intra- and extra-cerebellar pathologies, such as parkinsonianism and peripheral neuropathy [144,145]. Type 2 ADCAs have cerebellar syndromes with additional retinal degeneration (such as SCA7) [144]. Even within Harding's classifications, individual SCA types and individuals within these types exhibit a great deal of variability of clinical presentation and pathology [344].

SCA6 affects approximately one in one-hundred thousand people worldwide and accounts for ten percent of the world's population of ADCAs [1,231]. SCA6 is the most common cause of ADCAs in northern Europe and the United Kingdom and is easily diagnosed with genetic analysis of blood samples [75]. Like many of the SCA types, the autosomal dominant mechanism of inheritance affects both male and female subjects equally [75,231].

Despite the prefix 'SCA' being allocated as part of the genetic label, SCA6 has cerebellar pathology but no spinal cord involvement [144,347]. The most commonly reported presenting symptom in SCA6 is impaired balance [125].

SCA6 is of late onset, with first symptoms typically reported at age 50 years (+/- 11 yrs, range 16-72 years). Despite this traditional 'late onset', knowledge of parental diagnoses and confirmation of inheritance with genetic tests may now lead to earlier natural detection of symptoms, an effect known as ascertainment bias [125,337]. In some types of SCA, the

disease becomes more severe as passed down through generations causing within-type variability. This effect is however rare in those with SCA6 due to the relatively shorter and more stable nature of the genetic mutation [125,201,344].

Despite past exploration of balance in subjects with ADCA III and more recent studies specifically targeting subjects with genetic variants of SCA, the question of how balance is impaired in cerebellar disease remains largely unanswered. The simplest way to address this question in the first instance is to selectively investigate subjects with the least variable presentation of a genetically determinable ataxia. The genetic assurance of condition type and pure cerebellar presentation makes individuals with SCA6 ideal candidates for this purpose. In turn, there is a great need for an improved understanding of mechanisms of balance impairment in SCA6 since there are no pharmacological treatments available and conventional physiotherapies do not appear to offer effective treatment.

I will now detail pertinent background information concerning SCA6 pathology and balance control which has been instrumental in generating hypotheses of how disease changes could affect sensory mechanisms of balance control. The interaction between possible regions of the brain which potentially have a role in balance control and SCA6 pathology is summarised in figure 1.1.

1.1.1 SCA6 DISEASE PATHOLOGY

1.1.1.1 Genetics

SCA6 is thought to be due to a gene mutation causing extra repeats of the CAG nucleotide on chromosome 19:p13, known as CACNL1A4 [406]. The expanded gene in SCA6 most likely causes a mutation in a membrane protein, known to be a building block of a voltage-gated calcium channel α-1A subunit. It is as yet unknown if this leads directly to calcium channel voltage dependent changes or rather has an indirect effect, possibly even by releasing polyglutamine-containing fragments that act in the nucleus in a similar fashion to the other polyQ diseases [193].

1.1.1.2 Structure

The neuropathological hallmark of SCA6 is widespread Purkinje cell loss in the cerebellum [315,347]. Autopsies have revealed that atrophy of the cerebellum is due to extensive Purkinje cell loss in the flocculus as well as the cerebellar vermis and hemispheres [129]. The vestibular and fastigial nucleus are additionally affected with mild to moderate gliosis [129]

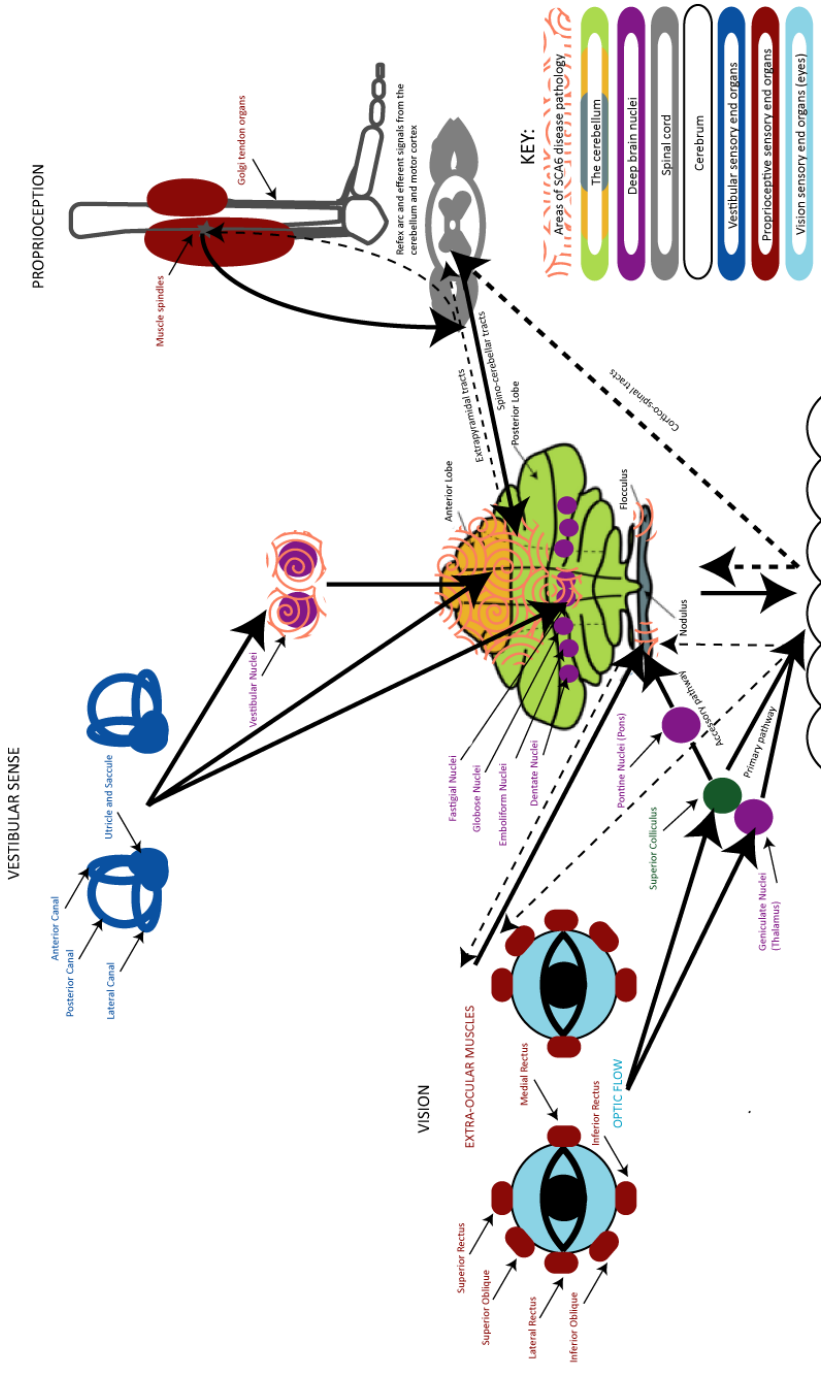


Figure 1.1: Schematic of sensory signal processing for balance control and distribution of SCA6 pathology.
Sensory end organs and their afferent projections illustrate the conceptual model of how sensory signals pass through central nervous system structures for balance control, with an emphasis on the cerebellum. Full black arrows illustrate the afferent projections and black dashed arrows illustrate efferent signals. Anatomical structures are colour coded and explained by the key. Orange patterned areas overlapping some cerebellar parts and some nuclei illustrate regions of Purkinje cell death or granule cell depletion. Projections of afferent sensory signals to these affected areas indicate the potential for disrupted signal processing to cause balance impairment in SCA6, forming the basis for the investigation.

and cerebellar peduncles, the pons and the red nucleus have been reported as mildly atrophied from MRI analysis of structureal sizes [259]. Brain imaging suggests an anatomical progression in cerebellar atrophy; antero-superior structures being most affected and postero-inferior structures least, with the superior cerebellar vermis appearing to be the most affected of all structures [75]. Further microscopic studies have revealed that, in addition to severe loss of cerebellar Purkinje cells, moderate loss of granule cells and dentate nucleus neurons as well as mild to moderate neuronal loss of inferior olive neurons occurs [319,406].

More recent imaging studies using single photon-emission tomography (PET) have revealed reduced glucose uptake (hypometabolism) in both the cerebellum and cerebral structures and in areas that are neurologically damaged as well as areas that appear to be structurally intact [345]. Specific areas of significant hypometabolism (in seven subjects with SCA 6 compared to a group of ten age matched healthy subjects) occurred in the cerebellar hemispheres, brainstem, basal ganglia and the frontal, temporal and occipital cortices. The authors interpret the latter findings as evidence for extra-cerebellar pathology in SCA6. They suggest this is either due to a direct action of the disease protein affecting cells throughout the brain, or possibly secondary to a damaged fastigial nucleus, which itself has been linked to carotid blood flow supplying all major brain structures. They further hypothesise that dysfunction of the fastigial nucleus could be due to the significantly damaged cerebellar vermis in SCA6, known to have abundant direct connections with the fastigial nucleus.

1.1.1.3 Electrophysiology

Electrophysiology studies have revealed controversial results regarding extracerebellar pathology in SCA 6. Typically SCA 6 is not thought to have any spinal or peripheral nerve abnormalities and studies support this with normal findings for both sensory and motor nerve conduction amplitudes, velocities and latencies [41,66,316]. However, compound muscle action potential amplitudes and sensory nerve action potentials have also been reported as reduced in others [196].

In addition to nerve conduction tests, investigations using trans-cranial magnetic stimulation (TMS) have further been able to reveal minimal gross electrophysiological changes in those with SCA6. In 2002, Schwenkreis and colleagues used TMS of the right

first dorsal interosseous muscle to evaluate motor thresholds, central motor conduction time, cortical silent periods, intracortical facilitation/inhibition in a group of nine subjects with SCA 6, compared against fourteen healthy control subjects and other SCA groups. It was found that, unlike the other SCA types, SCA6 pathologies did not elicit any abnormal electrophysiology measurement parameters [330]. In contrast to this, work by Chen and colleagues in 2003 [66] investigated the same parameters but this time stimulated the lower limb using TMS either over the motor cortex or the spinal cord (L5-S1 spinous processes). Their findings revealed significantly delayed latencies of motor evoked potentials to TMS when stimulated via the motor cortex and significantly prolonged central motor conduction times (CMCT) but normal responses to spinal generated activations and normal motor evoked potential amplitude sizes. In the absence of signs of axonal degeneration (using nerve conduction studies) the authors hypothesised that the delays in CMCT could be due to hypometabolism in the cerebral cortex (in agreement with recent PET studies), but equally these could be due to sub-cortical processing abnormalities.

1.1.2 Balance

In order to maintain any upright posture against gravity, external and internally generated forces acting upon the body, which can be continually changing in terms of magnitude and direction, must be opposed i.e. balanced. Balance control uses sensory information to monitor instability through constant feedback of postural and positional changes [86].

For control of balance to be successful the availability and correct processing of multi-sensory information is essential [84]. Vestibular, visual and proprioceptive (including proprioceptor and cutaneo-receptor) systems provide information regarding the body's position and motion in external space. If one of these sensory systems is compromised immediate increases in standing body sway are observed (such as when subjects suffer proprioceptive loss [109], loss of vision [79] or loss of vestibular function: [43]). In view of the multi-sensory control of balance, it seems logical that loss of one of the senses will lead to increased instability but in the longer term, instability tends to improve despite no improvement in the sensory loss. This is suggested to be due to compensatory use of the remaining sensory signals, (a) visual and vestibular in the case of those with chronic proprioceptive loss [71], (b) proprioceptive and vestibular in those with loss of vision [308] and (c) proprioceptive and visual in those with loss of vestibular function [275]). This

compensatory use of sensory signals has been suggested by Nashner *et al*. be due to a gradual reweighting of sensory signal contributions in the central nervous system [263]. This suggestion has accumulated a great deal of support over time from independent studies of balance [63,156,222,269,286]. A slightly different idea for the changes observed with sensory impairment is that instead of gradual re-weighting, a change in the 'number of votes' available from each sensory system occurs, i.e. when a 'vote' is unavailable from one sensory system, the remaining systems have a larger relative vote [84]. For postural sway under normal eyes open conditions, proprioceptive votes tend to have the most influence over standing balance conditions, with visual and vestibular contributions coming in a joint second [84]. For this voting system to result in reduced postural sway over time, this would require either learned improvement of a motor control of sway specific to the remaining sensory signals, or increased sensitivity of the remaining sensory channels informing the motor response. Either of these latter theories could be supported by work by Pavlou *et al*., where over-sensitivity to visual motion in patients with vestibular dysfunction was found to be reduced by visual stimuli training protocols [281,280,279]. The following sub-sections will briefly outline current knowledge of vestibular, proprioceptive and visual sensory systems and what is known of their role in control of balance within the cerebellum.

1.1.2.1 ***The vestibular system***

The vestibular system provides the sense of the head's orientation in space and how it is rotating and translating [85].

Vestibular end organs, the otoliths (including the utricle and saccule) and semicircular canals (anterior, posterior or lateral), contain hair cell receptors which are arranged to selectively activate during different directions of head referenced tilt and acceleration. Otolith receptors (the utricle and saccule) sense linear translational acceleration forces or changes in gravitational force relative to head tilt. Semicircular canals (anterior, posterior and horizontal canals) sense angular accelerations of the head in three directions (for a review see Day and Fitzpatrick [85] or Wardman and Fitzpatrick [384]).

Human and primate studies have determined that vestibular afferents within the eighth cranial nerve project to the vestibular nuclei[9,11,21].

Vestibular afferents integrate and selectively converge in the rostral vestibular nuclei [13,12,15,95] one fourth seemingly coding for otolith stimulation, one fourth coding semi-

circular canal stimulation and the remaining half coding for converged information from otolith and semicircular canal afferents [13].

Vestibular nerve afferents also project directly to the fastigial nuclei, the most medial deep cerebellar nuclei, where spatiotemporal convergence of otolith and semicircular canal signals has again been reported [335,405].

In addition to the deep cerebellar nuclei, some vestibular afferents make direct connections with the flocculonodular lobe in the posterior cerebellar vermis (lobules 9 and 10; nodulus and uvula), which is in turn heavily interconnected with the vestibular nuclei [401]. In this part of the cerebellum semicircular canal and otolith inputs converge on Purkinje cells which produce inertial (earth-centered) motion signals concerning overall head in world motion [401]. The functional consequence of convergence currently remains unknown but theoretically this signal could be used to inform novel balance motor responses or learned motor responses.

From the vestibular and fastigial nuclei, neurons interconnect with the anterior cerebellar vermis [18,194,292,377,379], the uvula and nodulus of the flocculonodular lobe of the cerebellum [380], the cortex [239] thalamus [141,239,346], and spinal cord [4,45,289,313,393].

1.1.2.2 The proprioceptive system

Proprioception provides a sense of 'position and motion of one's body segments, derived from central processing of efferent signals as well as afferent signals from muscles, tendons, joints and skin' [199]. Both the position of the body relative to the support surface and the relative configuration of the body need to be known for control of balance. The sense of the relative configuration of the body is known as the body schema [198].

Muscle spindles are found alongside muscle fibres in skeletal muscle, they respond to muscle length changes, where increasing stretch correlates with increasing firing [295]. Two types of muscle spindle endings synapse with afferent neurons, these are known as type 1 and type 2 receptors (or primary and secondary endings) [294]. Primary endings seem to respond to both the size of a muscle length change and the rate of change [236]. Secondary endings rather appear sensitive to change in length but not rate of change [236]. As well as sensory innervation, muscle spindles also receive their own motor supply [294]. Primary ending muscles spindles appear to be the most sensitive of all spindle and Golgi tendon organ endings to vibration [53,56,306]. Vibration of muscle spindles not only results in

perceived motion of the joint over which the muscles act but also results in a sway response when applied to a postural muscle in standing subjects [105]. The frequency of vibration behaves somewhat linearly with the speed of the sway response [261]. Muscle spindles are generally acknowledged as having the greatest influence over proprioceptive awareness of the body schema and body motion [295].

Golgi tendon organs are found alongside strands of tendon, which are situated next to muscle fibres [294]. As the muscle lengthens with stretch, the attached tendon is also put on stretch and this in turn stretches the attached nerve endings which then discharge [121]. They discharge at much higher thresholds than muscle spindles and are thought to be a measure of local muscle tension, rather than a measure of muscle rate of change of length [294]. They are almost as prevalent in skeletal muscle as muscle spindles [294].

Group 2 and 4 receptors in skeletal muscle have also been shown to be sensitive to mechanical stimulation and metabolic toxins released by exercise but they seem to act predominantly on the sympathetic nervous system or on alpha-motor neuron excitability. They do not appear to be related to a proprioceptive function which could inform balance [181].

Cutaneous mechanoreceptors, as the name suggests are located in the skin [177]. There are four different types of cutaneous mechanoreceptor: (1) Slowly adapting type 1 afferents that end in Merkel cells. (2) Rapidly adapting afferents that end in Meissner corpuscles. (3) Pacinian afferents that end in Pacian corpuscles. (4) Slowly adapting type 2 afferents ending in Ruffini corpuscles.

Most often investigation of these receptors has been undertaken in the hand, where there is a high density [177] but the same receptors are found in dense clusters on the sole of the foot [163]. Cooling of the foot sole, thought to reduce firing rate of these receptors, was found to have a destabilising effect on whole body sway during unperturbed and perturbed standing in humans, suggesting a role for these receptors in balance control [220,270]. Studies applying vibration to human foot soles provide further evidence for the role of these receptors in balance control, including determining both response size and orientation to balance perturbations [183,184,237,307].

SA type 1 receptors sit at the base of the epidermis and discharge when the skin is indented. They have a small receptor field and (2-3mm diameter) and therefore offer high spatial resolution, particularly good for identifying sharp edges, points and curves [177]. As

the name suggests, they adapt slowly, related to the indentation depth [177].

RA type 1 receptors lie just beneath the epidermis and are more densely arranged in the foot than SA1 receptors [163,177,184]. They are insensitive to static skin deformation but are highly sensitive to dynamic deformation [177]. They can detect slip between the skin and an object (such as the support surface), which clearly is of use to balance control and they are sensitive to low frequency vibration [177].

Pacian receptors are the most sensitive of the cutaneous mechanoreceptors to skin motion and vibration, even vibration transmitted from distant locations with as little as 3nm amplitude [177]. Traditional use of muscle vibration in the lower limb may therefore also act to stimulate these receptors.

SA2 receptors lie in the connective tissue of the dermis and, like Golgi tendon organs, are sensitive to stretch of this neighbouring structure [177]. They are less densely populated in the foot than SA1 and RA receptors but are more sensitive to skin stretch than SA1 receptors [177]. These receptors, coupled with Pacian receptors, may be important to balance in when light touch is employed as a method of stabilising balance [303].

Joint receptors were traditionally thought to be main contributors to proprioception but investigation of these receptors reveal that they have a relatively small contribution relative to muscle spindles [199,299].

The mono-synaptic stretch reflex, with the fastest conduction velocities and the simplest loop construction has long been thought to contribute towards the proprioceptive control of balance [320]. With electro-myographic (EMG) responses recorded between 20 and 50ms after whole body (platform) perturbations, it is thought that reflex activity from primary muscle spindle ending receptors and 1a afferent fibres is responsible for this short latency balance response [320]. Additionally, secondary muscle spindle endings combined with other group II afferents (of slower conduction velocities and involving spinal inter-neurones) are thought to further modulate the initial reflex response to produce a measureable medium latency response in EMG at ~80ms [320]. These short and medium latency responses are absent in those with total proprioceptive loss and neural conduction is delayed in subjects with diabetic peripheral neuropathy [5,83,156].

A longer latency response occurs and is thought to be governed by processing within the brain. Proprioceptive signals travel via the spino-thalamic and spino-cerebellar tracts in the spinal cord to terminate in the vestibular nuclei, cerebellum, cortex, thalamus and

brainstem [4,156,313,393]. The complexity of the system undoubtedly aids the synthesis of precise motor responses to balance perturbations at the level of the brain. Proprioceptive signals at this point must inform on perturbation magnitudes, direction relative to the base of support and body schema so that craniocentric perturbation signals (from vestibular and visual senses) can appropriately combine with proprioceptive signals to elicit whole body responses that are appropriately directed.

1.1.2.3 The visual system

'The visual system transforms transient light patterns on the retina into a coherent and stable interpretation of a three-dimensional world' [180].

Light enters the eye and is focussed on the retina by the cornea and lens. The iris contracts or relaxes to determine how much light to allow into the eye [368]. It travels through the vitreous humor (gelatinous medium of the eye cavity) and falls on the photoreceptors on the retina at the back of the eye [368]. The fovea is a central part of the retina which receives light in the least distorted form [368]. The eyes are moved in the socket to enable capture of the target image on the fovea to achieve the sharpest optical resolution [368]. This movement is provided by extra-ocular musculature using smooth motion to pursue an object (known as pursuit) or through a fast jerk movement to quickly reach a target known as a saccade [124]. The visual receptors in the retina (rods and cones) code for visual information in low lighting conditions (rods) and high lighting intensities (cones) [368]. Different wavelengths of light are absorbed by these receptors which cause polarisation changes relative to light intensity [368]. Photoreceptors synapse with bipolar cells which in turn synapse with the large ganglion cells which collect to form the optic nerve [73].

The primary visual pathway is also called the geniculostriate system, the secondary pathway is also called the tectopulvinar system. The primary visual pathway is traditionally thought to be concerned with object recognition (e.g. pattern, texture, colour), whereas the secondary pathway is thought to be concerned with object motion, localisation of objects in space and guidance of eye movements [73]. Signals from each eye travel via the optic nerve to cross over at the optic chasm and enter the lateral geniculate and pulvinar nuclei of the thalamus via the optic tracts [73]. Although some nerves supply these structures ipsilaterally, most cross over to make contra-lateral connections [73]. In the lateral

geniculate nucleus, structural layers comprise a form of visual map of the retina encoding both colour and motion properties of visual stimuli [73].

The primary visual pathway involves neuronal projections called optic radiations which spray out from the geniculate nucleus and synapse with the occipital lobe. The most abundant connections are made with the striate cortex, also known as the primary visual cortex [73]. Fewer but substantial connections are made with the extrastriate cortex, also known as the secondary visual cortex.

Within the primary visual cortex it has long been suggested that a dissociation of two visual processing streams of output exist [130,250]. These output streams are known as the ventral and dorsal streams. Ventral stream outputs are known to be associated with object vision, i.e. for defining characteristics such as pattern, colour and texture. Dorsal stream outputs are associated with spatial vision, i.e. object localisation and motion. These streams of outputs extend beyond the occipital lobe and into parietal and temporal zones of the brain [130]. Many studies have reported optic flow sensitive neurons in these output zones, some are reportedly selective to patterns resembling patterns of self-motion generated optic flow and some are reportedly modulated by vestibular inputs signalling head motion (for a review see Angelaki *et al*. [14]). For example, Wall and Smith [383] have recently used fMRI with human subjects experiencing optic flow stimuli (providing representations of self-motion) and have identified two areas which specifically respond to optic flow consistent with vestibular afferents signalling self-motion (the ventral intraparietal area and the cingulate sulcus visual area) [383]. This supports earlier reports of visual-vestibular combining in these areas using animal experimentation [47,321]. The primary visual cortex, the extra-striatum and the middle temporal area also respond to optic flow stimuli, which means that it is likely that these areas may contribute towards processing visual cues for balance control [14].

Although these cortical areas are likely candidates for making directional and speed computations of self-motion these pathways through the cortex would inherently add to response times to balance perturbation responses, which may limit the suitability of this pathway for a role in contributing towards fast reflex-type balance responses. This may not be a problem if visual contributions to balance operate on a feed-forward basis as suggested by Day *et al*. [86], meaning that optic flow prior to a balance perturbation may be used to weight fast automatic responses to vestibular or proprioceptive signalled

perturbations (such as the medium latency force response to GVS at 80ms) but responses to perturbations signalling optic flow may not become important until later. This idea would be consistent with the report of responses to isolated visual flow stimuli initiating at latencies of 250ms [49] and with Glasauer *et al*.'s findings of just a 80ms delay when using an oscillating LED to evoke oscillating sway responses [127]. The latter shorter latency could be explained by visual flow being predictable due to the oscillating nature of the stimuli although Glasauer *et al*. [127] propose that faster latency extra-ocular afferents from orbital eye muscles may contribute towards control of balance.

The secondary visual pathway is also known as the accessory pathway [376]. As part of the secondary pathway, neurons project directly from the optic tract to the superior colliculi of the brain stem [73]. The pathway then continues to the pulvinar and lateral posterior nuclei of the thalamus and finally projects up to the secondary visual areas of the extra-striatum and the temporal cortex [73].

In addition to projections to the superior colliculi, reports also suggest that the lateral geniculate nuclei also makes projections to the pontine nucleus as part of this 'accessory visual pathway'. From the pontine nucleus, large numbers of projections are seen with the deep cerebellar nuclei [132,153]. Authors of these papers propose that neurons coding retinal flow signals may have a descending sub-cortical pathway to the cerebellum via the pontine nuclei, which could be useful in order to generate short latency motor responses based on retinal flow information, such as for control of ocular movement following head movement. Perhaps this information could also be used in balance control.

Monosynaptic interconnections between the cerebellar nuclei and the superior colliculus have been reported [304]. These connections have been suggested to have a role in regulating eye and head movement [304]. However, signals from the superior colliculus to the cerebellum could also point to cerebellar use of retinal flow information for combining signals from other sensory systems (i.e. vestibular or proprioceptive signals).

In addition to retinal flow, an efference copy of eye movements or re-afferent signals from ocular muscles reportedly has a significant effect on the body's ability to use vision to stabilise the body [129]. Despite the compelling argument for this 'extraocular' contribution to balance, little is currently known of the neuronal pathways that could be concerned with this function. It is possible that cerebellar projections to the superior colliculus could be responsible for modulating visual information by eye movements to participate in fast motor

responses to balance perturbations before signals reach the visual cortices, where longer latency responses could be organised.

1.1.2.4 Cerebellar processing of sensory signals

Animal studies involving lesioning of the anterior cerebellar vermis report interesting findings of altered scaling of motor responses to vestibular perturbations following surgery [7,227]. By rotating cats around the axis of their body following lesioning of the anterior vermis (unilaterally, lobule V) with muscimol, Manzoni *et al*. reported decreased gain of ipsilateral triceps surae electromyography (EMG) compared with non-lesioned conditions [227]. Although it remains difficult to generalise findings to human cerebellar physiology, based on this work it seems reasonable to hypothesise that the human anterior cerebellar vermis could be concerned with scaling of response magnitudes to vestibular perturbations. Manzoni *et al*. also reported some spatial and temporal abnormalities of the response to body tilt after lesioning; the response was delayed and the overall direction of the response was different to that expected to counteract the direction of perturbing forces [227]. Earlier work by Andre *et al*. injected the unilateral anterior cerebellar vermis with a beta-adrenergic agonist designed to up-regulate adrenergic neurotransmission in the area [7]. After injection and tilt of the cats using a similar mechanism of tilt around the axis of the animal, bilateral triceps brachii EMG was discovered to increase in amplitude relative to non-injected conditions (particularly in the ipsi-lateral limb, relative to the side of the injection). Unlike Manzoni *et al*., this former study did not reveal any spatial or temporal changes. At least in cats, this reinforces the idea that this area of the cerebellum could be responsible for scaling of vestibulospinal reflexes. If these findings can be generalised to human cerebellar physiology, where cerebellar damage occurs in this area we may expect to find smaller than normal responses to vestibular perturbations due to reductions in vestibulo-spinal reflex gain. To date platform perturbations investigating balance in generic forms of cerebellar disease have reported increases in response gain [155,258,366]. This is inconsistent with the idea that damage would equal reduced response gain, but none-the-less still demonstrates a change in gain. There are a few reasons why the gain change could result in a positive rather than negative direction. The nature of cerebellar disease was largely unknown in the patient groups concerned, meaning that there is some uncertainty if the anterior vermis was an area of neuronal damage [155,258,366]. Platform

experimentation work cannot provide isolated vestibular perturbations and proprioceptive and visual inputs. Furthermore, chronicity of conditions could affect the relative contributions of proprioceptive and visual afferents, which could be compensating for vestibular processing deficits.

Alongside vestibular inputs a high degree of convergence of neck proprioceptive inputs has been found in the cat anterior cerebellar vermis [227,228,229]. As described, there is some association here with impaired response orientations to vestibular stimuli following lesioning of the area [227,228,229]. By simultaneously monitoring neural activity in the anterior cerebellar vermis during delivery of vestibular signalled whole body tilts and head on body positional changes, Manzoni *et al*. [228,229] were able to relate their two measures of neural activity and whole body responses to provide evidence for vestibulo-proprioceptive combining. However, lateral and inferior parts of the vestibular nuclei (VN) [6,45,310,312,393,392] and the fastigial nuclei (FN) [189,333,335,405] have also been reported to receive inputs from both vestibular and proprioceptive afferents, thus suggesting at least two additional locations where the two sensory inputs may interact. In addition to neural staining work, Roy and Cullen's investigation of vestibular neurons in the vestibular nuclei has determined that this population of neurons can be suppressed by proprioceptive neck afferents [309,312]. This suppression specifically occurs if the head on trunk position is actively moved by neck muscles but does not occur if this movement is performed passively on the primate animal. This work provides a clear argument for the combining of proprioceptive and vestibular signals concerned with the directional specificity of signals. More recent primate studies of the fastigial nuclei by Brooks and Cullen propose that proprioceptive and vestibular neuronal signals are brought together onto 'bimodal' neurons in the rostral FN which in turn signal head-on-body motion [52]. These bimodal neurons fire when the tuning of 'proprioceptive only' and 'vestibular only' neurons are similarly tuned, meaning that they signal vestibular changes brought about by active proprioceptive changes. Interestingly, the rostral FN is an area which receives output from the anterior vermis [379], which may provide some link between Manzoni *et al*. and Brooks and Cullen's findings. If we can generalise Manzoni *et al*.'s, Roy and Cullen's and Brooks and Cullen's findings based on animal (cat and monkey) cerebellar physiology with that of humans, it seems logical to hypothesise that cerebellar vermal, VN or FN damage may cause abnormalities in the directional orientation of responses to vestibular perturbations. In

these circumstances we may expect to see a constant response error to vestibular perturbations that is relative to the extent of damage in the cerebellar vermis and a function of the degree and direction of head turn.

In the flocculonodular lobe, visual and vestibular signals reportedly converge from VN and FN nuclei [17,164,165,274,403]. According to early investigation of these signals, they seem to relate both to visual stimuli associated with retinal slip (unwanted movement of the visual image on the retina) and to the direction of eye movements in their socket (thought to derive from orbital eye muscle proprioceptors). Based on animal studies, the retinal information could come from the sub-cortical accessory visual pathway (via one of the cerebellar nuclei) or via the primary visual pathway (from the visual cortex in the occipital cortical lobe). Visual and vestibular signals converge via climbing fibre input and have transitional properties between that of sensory and motor information, which has been suggested to be indicative of pre-processing of the sensory input in the brainstem [17]. According to the findings of animal and human investigations changes in vestibular-ocular reflex scaling (VOR) and pursuit speeds are reported following lesions of this part of the cerebellum [165,302]. In healthy subjects, vision is known to stabilise normal standing sway and additionally reduce magnitudes of responses to vestibular perturbations compared to conditions where subjects' eyes are closed or visual information is limited [86]. If the flocculus, VN and FN are damaged, it seems logical to hypothesise that impaired combining of retinal and eye-in-head signals may occur. Furthermore projections of vestibular and proprioceptive signals to these locations may further impair combining of visual information with head in space and body schema signals. If this were to occur in the sample of SCA6 subjects, we may expect to observe a reduced effect of vision on responses to balance perturbations driven via vestibular or proprioceptive stimuli, reduced response magnitudes to visual perturbations or more directional errors in the orientation of response to visual perturbations.

1.1.3 Perturbing balance

To investigate balance, many researchers have used platform rotations, translations or push-pull stimuli to deliver balance perturbations from which responses were measured. This approach incorporates perturbations which are similar to real world balance perturbations and for this reason can be instrumental in deciding if dysfunction with

physical tasks can be explained by balance dysfunction. These methods are however limited in their ability to provide information concerning individual sensory system contributions to balance control. To gain an understanding of the role of individual sensory systems in balance control, research has focussed on the use of single sensory perturbations, namely galvanic vestibular stimulation (GVS), muscle vibration and moving visual stimuli (MVS) to stimulate vestibular, proprioceptive and visual systems, respectively [84]. Although in the real world, all available sensory systems will most often participate in signalling a balance perturbation, it seems that application of any of these modalities in isolation is sufficient to generate whole body sway responses.

1.1.3.1 Galvanic vestibular stimulation

Galvanic vestibular stimulation is a well-described non-invasive modality which can be used to deliver isolated vestibular perturbations via delivery of current to vestibular nerves [48,70,82,113,264,265]. GVS involves delivery of a direct current by placement of electrodes on the skin overlying the mastoid process to target the underlying vestibular nerve. Current used is most commonly around 1mA (6v) and delivered binaurally so that one vestibular nerve receives cathodal current and the contra-lateral nerve receives anodal current [113]. This modulates the spontaneous firing frequency of vestibular nerve afferents but does not directly affect hair cell activity in the vestibular apparatus [128]. This is thought to be because the position of application is at the point of the synaptic trigger site [128]. Cathodal current delivered to the vestibular nerve current increases neural firing activity and anodal suppresses neural firing activity [74,113,128,215]. The orientation of the response to GVS is thought to be a vectorial sum of the imbalance between right and left vestibular polarisation [87,332], although the magnitude of the response does not appear to equate to a linear sum of what would otherwise result from left and right stimulation [87]. It has been suggested that Short-latency responses are mediated by otolith afferents and medium-latency responses by semi-circular canal afferent signals [60]. GVS can be applied unilaterally or bilaterally over mastoid processes [113,221]. The use of a single electrode over one mastoid process with a reference electrode elsewhere on the body is called monoaural GVS. Use of two electrodes of the same polarity over bilateral mastoid processes with a reference electrode elsewhere is called binaural monopolar GVS. Use of two electrodes of opposite polarity positioned bilaterally over the mastoid processes is called binaural bipolar

stimulation [113]. This method can allow switching between two GVS polarity conditions without movement of electrodes (condition 1: Right anodal, left cathodal stimulation, condition 2: Left anodal, right cathodal stimulation). Prior studies of GVS using standing subjects have revealed that GVS delivered in the binaural bipolar arrangement induces perceived sway in the direction of the cathodal ear [110,108,385] and physical whole body sway in the direction of the anodal ear [110,108,118,217,264,276]. Furthermore, as subjects turn their head in yaw over the position of their feet, the response direction re-orientates according to the head position, i.e. the response is always orientated in the direction of the anodal ear [118,179,217]. For this to occur, proprioceptive information concerning whole body posture needs to be integrated with craniocentric vestibular information [85,217]. Head-on-body position varied in yaw changes response direction, but head pitch also affects the response [60].

Numerous reports exist concerning the use of GVS with human subjects to investigate balance, and an increasing number of reports now involve the use of GVS to investigate disease pathophysiology in patient subjects (see appendix 1 for a bibliography). Some studies have employed current alternating in polarity in a sinusoidal pattern to look at changes in body position over time in standing subjects [25]. More recently, a stochastic form of delivery has been employed with EMG and ground reaction force measurements taken from standing subjects [77,246,273,278]. GVS has been used in sitting and lying subjects, though for the purpose of monitoring brain activation and measures of kinaesthetic perception of body parts and the visual vertical, rather than measuring balance responses [191,233,314,371,386]. GVS has been used during gait [185,205,326], stepping activities [33,240] and alongside muscle vibration, visual stimuli or support surface translations in an attempt to evaluate weighting of sensory signals for balance control [102,152,162,326]. The most common form of GVS involves binaural, bipolar delivery of a square-wave current used over a short duration of between 1 and 3 seconds with right anodal, left cathodal stimulation or vice-versa [113,118].

The form of standing balance responses to GVS vary according to the current used and placement choice of electrodes [291]. Initial reports by Popov *et al*. [291] described linear increases in response magnitudes (between 0.5mA and 6mA) when using monoaural cathodal GVS (with a distal reference electrode) but more recent work by Day *et al*. has challenged this idea suggesting instead that a non-linear relationship exists, well described

by a power law function . Day *et al*.'s study also reports that bipolar binaural stimulation is less than the sum of the monoaural responses [87]. Response magnitudes can also vary with age [172,389,390], sex [390], proprioceptive loss [83,108], stance width [80], posture [234], loading of the body [235], use of an external support [69,154], and support surface [162]. Stance width appears to have a particularly striking effect on whole body responses to GVS, since this not only alters response magnitudes but also inter-segmental motion associated with the response [80].

The availability and quality of visual information available during GVS delivery is also known to affect the magnitude of force and sway responses [86]. Specifically, response magnitudes are reduced for GVS conditions involving full availability of vision compared with eyes closed conditions, and as the environmental visual information increases from a single spot of light to a 2D grid or a 3D structure of lights in space [86].

Despite variability in response magnitude and direction, timings of responses to GVS are constant but dependent on the nature of the response measure. The shortest latency EMG responses in leg musculature occur at 55-65ms, and 40ms in the upper limb [48]. Medium latency EMG responses appear at 90ms [48]. However, some reports have quoted lower limb EMG responses to occur more in the region of 110-120ms and upper limb responses 20ms later [48,108,264,390]. Short-latency force responses are seen to follow EMG recordings but are small in magnitude and relatively difficult to measure. Oppositely directed medium-latency force responses, which drive a sway response, are reported to begin around 269ms and to be at their peak around 281ms [276].

Peak trunk sway responses generally appear around 1.5s following stimulation onset [118]. The plateau of the response, even prior to cessation of stimuli, is thought to be representative of a steady state realignment of the body, likely due to the sum of the vestibular signal and re-afferent signals from conflicting proprioceptive and visual afferents (where available) [60,80,162]. This plateau is known to be delayed when subjects are stood on a compliant surface, rendering proprioceptive signals unreliable [385] or absent in the case of a deafferented individual [83].

Whole-body response timings and magnitudes do not appear to be affected by expectation or knowledge of delivery of GVS [138] and it is generally accepted that habituation of sway responses to GVS does not occur [63,86,185]. Decreasing neural firing following GVS repeats delivered to rat vestibular nerves [74] and reports of GVS delivered in a repetitive non-

randomised method causing habituation of the magnitude responses in healthy subjects and gymnasts [24,25] do however exist to challenge this idea. Recent work by Reynolds *et al*. using a stochastic form of vestibular stimulation also highlights the ability of subjects to reduce postural sway amplitudes when asked to stand 'still' rather than 'relaxed' during stimulation [301].

1.1.3.2 Muscle vibration

Muscle vibrators were designed to deliver proprioceptive balance perturbations, as described in prior literature [105,133,148,152,168,182,183,305,365]. Muscle vibration excites muscle spindle stretch receptors in underlying muscle bellies [183]. Vibration of tendons further excites Golgi tendon organ receptors [72,306]. Stretch receptor activation following muscle belly and tendon vibration has been described by Cordo *et al.* [72] using single cell recordings under optimum control conditions. Muscle spindle receptors and Golgi tendon organ receptors have been shown to be sensitive to vibration ranging between 20 and 110Hz [306] and use of vibration bandwidths between 20 and 165Hz have been adopted for the purpose of balance perturbation delivery [105]. Vibration mainly activates primary (1a) afferents, but is also observed to have an effect on secondary muscle spindle afferents and tendon Golgi organs (1b afferents) [72,306,365]. Early studies of vibration reported illusions of movement in limbs [107] and involuntary whole body sway when subjects were standing [148], which can occur within seconds of delivery of the stimuli [198,306]. Increasing vibration frequency reportedly increases receptor firing rate and in turn whole body sway response magnitudes [72,105,296,370]. Although studies have suggested some linearity of this relationship, the frequency range for this appears to be dependent on receptor type analysed as well as variables such as force and amplitude of vibration [72,287]. When subjects are standing, activation of muscle receptors appears to be interpreted as a stretch, which naturally resembles proprioceptive signalling of a balance perturbation [64,105,131,148,182,287]. A whole body response occurs which appears organised across trunk, hips, knee and ankles to counteract proprioceptive signalling of a balance perturbation [105,148,169,287,306,365]. In the case that ankle dorsi- or plantar-flexors are stimulated by vibrators, the same muscles are observed contracting as response effectors [116,148,152]. However, contractions do not exclusively occur in the stimulated muscles but can be observed throughout a range of muscle groups in both legs and the trunk [360,364]. Therefore

whole body motion is unlikely to be a pure consequence of contractions of stimulated muscles but rather is the result of a synergy of contractions [360]. This response could be organised by spinal reflexes but evidence exists to suggest that higher level structures, such as the cerebellum, are also involved in the organisation of this response [105], such as to modulate the direction of the response with proprioceptive postural cues [166] or the magnitude of the response with visual cues [277,338].

Habituation effects have been reported to occur following repeated muscle vibration [62,340]. Knowledge of delivery of muscle vibration does not appear to necessarily prevent whole body responses from taking place in standing subjects [61,62] but early investigation of muscle vibration has reported that not all subjects naturally respond to this stimuli [106,142].

*1.1.3.3 **Moving visual scenery***

The use of moving visual scenes as a tool to provide visual balance perturbations was first described by Lee and Lishman [202] and has since become well-documented in the literature [38,49,51,108,139,136,137,206,222,285,343,372]. Subjects often perceive self-motion upon experiencing moving visual stimuli [108,139,202]. If subjects are standing during this experience, whole body responses are observed [38,49,51,108,139,136,137,202,206,222,285,343,372]. It seems that when an otherwise static visual display unexpectedly moves in one direction, the motion is mis-interpreted as self-motion ('ego-motion') information (mocking up the experience of the body having swayed in the opposite direction) rather than being correctly interpreted as object motion ('extero-motion') [93,108,139,150,202]. Optic flow patterns (retinal slip) have long been implicated as the trigger of whole body sway responses (see a review by Guerraz *et al.* [139]). Recent studies by Guerraz *et al.* further suggest that proprioceptive re-afferent signals from extra-ocular muscles, employed to generate eye movements to pursue moving visual information, also have a role in triggering these postural responses [139].

Early methods, first employed by Lee and Lishman [202] employed moving room scenery, which were 3D in design, encompassing total visual field with large bold circular targets in the central visual field and checkerboard designs to the periphery of vision. This approach is known as the moving room paradigm. This traditional moving room paradigm centrally positions subjects relative to three real screens onto which a display is fixed or projected [38,94,202,206,350]. Rooms are then moved via translation or tilt of the image either towards or

away from the subject in a push-pull fashion [38,94,202,350]. Subjects respond by swaying in the direction of the motion, i.e. backwards to displays pushed towards them and forwards to displays that are pulled away [38,94,202,206,222,350].

Simple single screen or projected 2D displays moved linearly [49,127,136,174,206,269] or rotated about a central fixation point [3,93,150,284,326] have also shown to be effective in evoking sway responses. These methods similarly elicit sway responses in the same direction as visual scene motion, and perceived sway in the opposite direction [206].

Using flat 2D surfaces or 3D 'room' designs optic flow information can be translated, expanded, rotated or moved linearly, all of which induce compelling perturbations and measurable whole body responses [192,372].

Whole body sway responses to MVS perturbations, as with all types of stimuli, can be measured using ground reaction forces, EMG of lower limb musculature or kinematics, most commonly focussing on upper trunk sway [50]. The reported latency of the whole body response to MVS is less well-defined than with GVS and vibratory stimuli. Early investigation of MVS responses by Bronstein *et al*. described force response latencies of 600ms preceding a measured whole body sway response [50]. Sundermier *et al*. reported a 600-800ms latency for centre-of-pressure response onsets, although this long latency could be due to human error involved with a researcher manually moving a MVS in time to a visual counter [357]. A later study investigating MVS motion parallax by Bronstein *et al*. reports much earlier force onset latencies of 250ms and head sway onsets detected at 300ms [49]. These latter timings seem to be more consistent with reports of perceptual thresholds to MVS stimulation of 330ms [108]. The time taken for subjects to accurately perceive MVS in standing (330ms) seems to be in the same order as the time taken to react to movement of a target at which subjects are pointing (365ms) [378]. If we assume that there are common mechanisms underlying detection of motion in each case, we could relate the pointing task study's findings to MVS response latencies; namely that response latencies were found to be dependent on visual attributes such as luminescence, colour and size affecting response latencies by up to 50ms. It seems reasonable that in view of possible variability in timing, lighting levels (potentially affecting display luminescence), and display object sizes and eye to target distance (in turn affecting object size) could affect response timings.

Magnitudes of responses to moving visual scenery vary according to stimuli speed and

duration of delivery [44,98,136,150,222,268,298,372]. Response magnitudes also reportedly vary with concurrent vestibular and proprioceptive signalling [3,269], the intensity of postural orientation cues in the display [206,222,372], the location of these cues in the visual field (peripheral field is said to be more sensitive to visual stimuli than central field area) [117,206,267,350], the size of the visual field area [139,150], eye to target distance [119], stance width [117] and the stability of the support surface on which subjects are stood [244,267]. Proprioceptive loss and aging, possibly associated with proprioceptive loss also appears to affect the response size to MVS, especially first trial experiences of unexpected perturbations [357]. Increased exposure to visual stimuli over time seems to reduce response magnitudes or even diminish the response completely [50,214,222,268]. Reduction in response magnitudes following repeated stimulation (habituation) is reported to particularly affect young healthy adults and older subjects with signs of proprioceptive loss [44,222,268,357]. Habituation to repeated stimuli seems appropriate given that responses are mis-interpretations of optic flow as ego-motion, rather than extero-motion. Conscious suppression of a response also seems appropriate if subjects have knowledge of the artificial nature of the stimuli and knowledge of when motion will occur [119,140,244]. Accurate prediction of the perturbation can be avoided with randomisation of perturbation condition. Online detection of the stimuli can be avoided if the full visual field is controlled to ensure that optic flow information is consistent throughout the visual field. Full visual field motion with no parallax cues should ensure delivery of a compelling and appropriately directed perturbation [49,127,136]. Where moving visual scenery is at risk of not encompassing the full visual field, a visual field restrictor, such as goggles, can be used to prevent subjects viewing earth-referenced orientation cues [372].

Perturbation directions and orientations of perceived sway and evoked sway responses depend on the direction of movement of the environment relative to the position of the subject and direction of gaze [167,328]. Where MVS do not encompass the full visual field, visual cues signalling motion parallax can act to inverse the typical direction of the response [49,135].

Response directions can further be modified by sensory afferents signalling incongruous balance perturbations or postural state. Proprioceptive perturbations delivered alongside incongruous visual perturbations have for example resulted in modifying the orientation of the resulting whole body sway response [3,339]. The presence of earth-referenced

background environments to moving visual scenes and parallax cues have also been shown to modify response directions [49,136,137].

1.2 The problem

Balance impairment negatively impacts on quality of life through activity-related dysfunction and risk of falling. Where falls do occur, this can exacerbate functional limitations caused by injury or fear of subsequent falls.

An improved understanding of mechanisms responsible for balance impairment in SCA6 needs to be achieved in order to effectively target development of future therapies and improve daily life for those with SCA6.

Mechanisms responsible for balance impairment in SCA6 are currently unknown.

1.3 Theories of SCA6 balance impairment

The results of all imaging and electrophysiology studies must be interpreted with caution in view of the relatively small samples involved and variability of age of onset and disease severity measures recorded in these studies. However, with knowledge of (a) how disease pathology affects central nervous system structures and (b) ideas concerning the function of these structures based on animal experimentation, the following theories for balance impairment can be generated:

1. **Responses to vestibular signalled balance perturbations could be insufficient in magnitude.** The anterior cerebellar vermis is known to diminish in numbers of Purkinje and granule cells with SCA6 disease pathology. Animal studies have determined that this area is associated with scaling of vestibular responses to whole body tilts. When lesioned, response sizes to vestibular perturbations are seen to reduce. It is therefore plausible that balance impairment in SCA6 could be due to vestibular scaling deficiencies.
2. **Responses to vestibular afferent information signalling balance perturbations could be temporally delayed.** Animal studies have also determined that the anterior cerebellar vermis is associated with determining the timing of responses to vestibular perturbations. When this area was lesioned, responses were found to be delayed. It is therefore plausible that balance impairment in SCA6 could be due to either delay in the motor response due to vestibular processing impairments.

3. **Responses to vestibular afferent information signalling balance perturbations could be inappropriately spatially orientated.** Animal studies have infered that the anterior cerebellar vermis is associated with organising the spatial orientation of responses to vestibular perturbations. After vermal lesions, responses were found to be poorly orientated. It is therefore plausible that balance impairment in SCA6 could be due to vestibular processing impairments causing inappropriate directional orientations of the response to vestibular perturbations. This could be due to impaired combining of direct projections of vestibular afferents from different sensory end apparatus (originating from right and left saccules, utricles, anterior, posterior or horizontal semi-circular canals) or impaired combining of vestibular and proprioceptive afferents in the anterior vermis. Animal studies have also reported that vestibular and proprioceptive combining seem to occur in the fastigial and vestibular nuclei. Both of which are reportedly significantly atrophied in individuals with SCA6. Neuronal destruction of these areas could similarly affect the orientation of responses to vestibular perturbations.
4. **Responses to vestibular perturbations could be prolonged.** Animal study reports of vestibular and proprioceptive combining in the fastigial and vestibular nuclei have suggested that activity in this area is able to discern whether head motion is due to passive motion (external forces) or active motion (self-generated muscle activity). Actively generated proprioceptive signals likely to cause vestibular afferent signalling of head motion were seen to suppress vestibular signals within these nuclei. Both of these nuclei are reportedly significantly atrophied in individuals with SCA6. If this process is disrupted by neurological destruction of these nuclei, then the normal suppression of responses to vestibular perturbations by proprioceptive afferents may be impaired. This could lead to prolonged responses to vestibular perturbations.
5. **Responses to vestibular perturbations could be inappropriately scaled by vision.** Animal study reports of vestibular and visual combining in the fastigial nuclei, vestibular nuclei and flocculus have suggested that activity in this area is responsible for generating motor responses primarily used to drive eye movements. These are all areas significantly atrophied in SCA6. If vestibular and visual combining is impaired, the magnitude of responses to vestibular

perturbations with vision intact may be no different to that of responses with vision obscured.

6. **Motor response activity could incur global temporal delays.** Although unlikely given the wealth of evidence that suggests that motor conduction times are unaffected by SCA6 disease processes, Chen *et al*.'s [66] work reporting prolonged central motor conduction times could lead to delays in vestibular and visual responses and in the long latency response component of responses to proprioceptive stimuli.

1.4 Aim

The aim of this thesis is to identify abnormal features of balance in subjects with SCA6 which can be attributed to disrupted sensory control.

- In doing so, any new understanding of disrupted mechanisms of balance control will contribute towards the development of novel therapies.
- An improved understanding of mechanisms responsible for balance impairment in SCA6, a relatively uncomplicated variant of ataxia, will also provide a baseline against which future investigations of extra-cerebellar pathologies can be compared.

1.5 Experimental approach

The study will focus on describing balance impairments in subjects with relatively uncomplicated variant of cerebellar disease, SCA6.

Throughout this study, I examine a relatively uncomplicated form of balance involving subjects standing in an upright, bipedal posture. In this posture, external forces can be controlled by controlling the laboratory environment and support surface. Control of internal forces will be optimised by standardising subject's posture during trials and requesting no voluntary movement during trials.

Balance will be explored using isolated sensory channel perturbations. Due to the strength of reports concerning the cerebellum's role in vestibular processing in known areas of SCA6 damage the study begins with an investigation of vestibulo-proprioceptive combining. This will be achieved by using galvanic vestibular stimulation (GVS) to deliver

isolated vestibular signals, which induce a balance response by artificially replicating vestibular afferent signals generated when the head moves in space. Given that poor combining of vestibular and proprioceptive signals could result in inappropriately directed responses, head on trunk direction will be manipulated to explore the effect that whole body proprioception has on orientation of balance responses. This approach resembles that of Lund and Broberg's when initially investigating the effect of head turn on response direction to GVS [217]. Given that poor combining of visual and vestibular signals in damaged areas of the cerebellum (flocculus, fastigial and vestibular nuclei) could result in poorly scaled responses to vestibular perturbations, this investigation will also manipulate vision to assess the effect that this has on response scaling.

After initially targeting vestibular control of balance and the control of vestibular signals by proprioceptive and visual afferents, the study will investigate all responses to isolated sensory signals to gain a broader idea of all sensory contributions to balance control. Vibrators will be used to stimulate muscle spindle and Golgi tendon organ receptors. These receptors signal stretch. When used on ankle dorsi- or plantar-flexors in standing subjects, this is thought to artificially replicate the proprioceptive signalling of body sway in the opposite direction to the muscle action of the spindles being stimulated. A whole body response is expected in the same direction of the muscle action of the spindles being stimulated. A custom made moving visual scene (MVS) is used to deliver a controlled dose of optic flow and elicit saccades that mock up the experience of an individual swaying about their ankles upon movement of the scene. A whole body sway response is expected in the direction of motion of the MVS.

Responses will be measured using 3D whole body motion analysis. Markers will be fixed on each axial segment of each subject and their relative motion tracked throughout each trial. Ground reaction forces will also be collected from the contact that subjects feet make with the floor, where the floor consists of two embedded Kistler force plates.

In order to explore the above hypotheses, balance behaviour will be analysed in terms of timing, magnitude and direction of balance responses. Early measures of response will provide information concerning sensory processing of stimuli alongside baseline states of other sensory systems. Later timed sway responses (measured across the full duration of stimulation) will be analysed as measures of response incorporating re-afferent signals from other sensory systems.

Balance behaviour will be compared between a group of SCA6 subjects and age, sex, height and weight matched healthy controls.

Balance behaviour will not only be described in terms of average group measures but will relate response behaviour to individual disease severity (using the validated scale for the assessment and rating of ataxia, SARA [324]) and baseline measures of unperturbed balance (sway speeds).

1.6 Summary

- There is strong rationale to suggest that balance impairment in SCA6 could be due to disordered sensory processing in the diseased cerebellum and cerebellar nuclei.
- Isolated single sensory perturbations will be employed to test theories of disordered sensory processing in SCA6.
- The vestibular system will be targeted first as the majority of theories for balance impairment are concerned with vestibular processing and the combining of this signal with those of proprioceptive and visual afferents.
- Balance perturbations will be delivered to standing subjects using galvanic vestibular stimulation (GVS), vibration (VIB) and moving visual scenery (MVS), which are able to selectively target the vestibular, proprioceptive and visual systems, respectively.
- 3D whole body motion analysis will be used to collect measures of baseline balance and response to perturbation behaviour.
- SCA6 group responses will be compared with age, sex, height and weight matched healthy controls.
- Response characteristics will be compared against clinical assessments, validated disease severity measures and measures of unperturbed standing balance in order to establish any correlations between abnormal features of responses to sensory stimuli and disease-related changes.

2 CHAPTER TWO: GENERAL METHODS

2.1 INTRODUCTION

The investigations described within this thesis were organised to take place over three experimental sessions.

- The first session involved clinical assessment (described in chapter 3) and quantification of baseline balance (chapter 4).
- The second session was conducted on the same day as the first session but followed an extended break for subjects with cerebellar ataxia in accordance with the majority of subject's self-adopted pacing strategies designed to reduce daily fatigue. The latter part of the second session employed vestibular perturbations to investigate balance control.
- The third session took place a year later during which subjects with cerebellar ataxia once again underwent clinical assessment (described in chapter 3) and measurement of standing sway (longitudinal analysis of sway described in chapter 3). The latter part of the third session employed isolated proprioceptive, visual and vestibular perturbations to investigate balance control.

All investigations were funded by Ataxia UK and sponsored by UCL.

2.1.1 SUBJECTS

Subjects with spino-cerebellar ataxia were recruited from the Ataxia Centre at the National Hospital of Neurology and Neurosurgery over the full duration of the project.

Age-, sex- and height-matched healthy volunteer subjects (HVS) were recruited via advertisements on the Ataxia UK website and in a local adult education centre.

2.1.2 SELECTION CRITERIA

Only ataxic subjects with a confirmed genetic diagnosis of SCA6 were recruited to the study. Subjects who could not walk ten metres unaided or stand independently for 10 seconds with their eyes closed were excluded. Those who were blind, pregnant or had any current or history of neurological or orthopaedic conditions were excluded. Anyone presenting with acute or chronic musculo-skeletal injuries which were deemed by the researcher to potentially affect balance were also excluded. Individuals were only included if they were 18 or over and English speaking. Subjects who reported excessive tiredness

due to recent illness or insomnia were asked to reschedule to ensure optimal physical functioning during each testing day. Subjects who reported any past history of alcoholism or who those who had consumed alcohol in the past twelve hours were excluded. If subjects reported taking medication, the side effects of the medications were investigated and where involving high likelihood of dizziness, drowsiness or muscle weakness subjects were excluded. In the case of the latter two exclusion criteria, only two healthy subjects (no SCA6 subjects) were excluded for these reasons. The initial UK population of individuals with SCA6 comprised of 22 males and 20 females with a mean age of 67 years (ranging from 40-84 years). Successful recruitment of 17 subjects prior to testing day one was achieved from this population. Twenty-one members of the population responded to recruitment letters (50% response rate). Four were excluded due to a lack of independent mobility and one due to prior hip replacement surgery. Two of the recruited seventeen subjects were genetically diagnosed with SCA6 but did not complain of any impairments or functional problems and thus are referred to as 'pre-symptomatic subjects' within this thesis. During the total project duration of three years an overall SCA6 population growth of eleven occurred, this was due to twelve new diagnoses made and one death reported. Of the twelve newly diagnosed individuals, four agreed to participate in the second testing day of this study. Five participants from testing day one dropped out before the second testing day due to decreased independent mobility (two cases of which were associated with injurious falls).

2.1.3 Disease and anthropometric features

Over the course of the project some subjects with ataxia needed to cancel their involvement with the study due to physical deterioration and some newly diagnosed subjects were recruited. This resulted in slight differences in anthropometric and clinical features of groups between sessions one and two and three. Healthy controls were recruited throughout the duration of the study in order to ensure optimal case-matching of subjects and overall group matching.

Table 2.1 details the number of subjects per testing day, the ratio of males to females, mean values for age, height and weight of subjects (plus standard deviations) on which this matching process was based. Of the total number of SCA6 subjects in testing day 1, two were subjects who had genetic confirmation of SCA6 diagnoses prior to reporting any

ataxia symptoms. Testing day two included only one of these two subjects due to drop out. The anthropometric features of each subject and their healthy control matches are detailed in tables 2.2 and 2.3. Healthy controls generally participated in the study on a short term basis and for this reason many dropped out of participating in the final session.

Table 2.1: Overview of group characteristics for the first (1) and last assessment day (2)

Group	Number	Sex (M:F)	Mean age (S.D.)	Mean height (S.D.)	Mean weight (S.D.)
Healthy controls (1)	17	8:9	59.0 yrs (14.1)	1.68m (0.13)	71.3kg (10.8)
SCA6 (1)	17	7:11	59.8 yrs (12.0)	1.66m (0.09)	71.9kg (10.5)
Healthy controls (2)	16	7:9	60.3 yrs (11.6)	1.68 (0.11)	74.4kg (12.8)
SCA6 (2)	16	7:9	62.3 yrs (10.2)	1.67m (0.10)	68.5kg (9.8)

2.1.4 Ethical considerations

Research and development approval was gained from the Institute of Neurology, UCL scientific panel and University College London Hospitals NHS Trust with further approval gained from the Council of Research and Ethics Committees (U.K.) prior to undertaking any procedures outlined in this and the subsequent chapters.

Written informed consent was obtained from each participant according to the procedures set out by the Council of Research and Ethics Committees (U.K.) and in accordance with the declaration of Helsinki (2004).

Management of data complied with UCL's data protection procedures and those set out in the Data Protection Act 1998. Subject anonymity was assured with the use of individual subject codes. Actual subject codes relative to subject numbers used in this thesis are set out in appendix 2.

2.1.5 Instrumentation

In order to measure balance in both unperturbed and perturbed standing conditions throughout this investigation, whole body motion was recorded using a motion capture system and ground reaction forces were recorded from the contact made with subject's bare feet.

Details of session specific procedures will be described in the method section of the respective experimental chapter. It is worth noting that session one and two involved subjects standing with their feet pointing in the direction of the y+ laboratory axis, whereas session three involved subjects standing with their feet pointing in the x- laboratory axis. The reason for this change in position was to optimise visibility in each session (the moving visual scenery required for session three otherwise creating an obstruction to whole body

motion capture camaras). As a result, responses to antero-posteriorly directed perturbations in session one and two (discussed in chapters 4 and 5) are expected in the y-axis, whereas antero-posteriorly directed perturbations in session three (chapter 6) are expected in the x-axis.

2.1.5.1 3D whole body motion capture

3D whole body motion was captured using a CODA system (Charnwood Dynamics, Leicestershire, UK), which integrated two wall-mounted CX1 CODA camera units (each containing three independent cameras) sensitive to infra-red light emitting diodes (IRED), which will be referred to as markers, in the field of view.

These experimental protocols used twenty-four markers, organised into segmental clusters and sampled at 200Hz, to capture head, trunk, pelvis, shanks and feet 3D movements. These markers were powered and driven by control boxes that are able to power two markers per box (a total of 12 control boxes were used). In order to define segmental planes and to ensure visibility of markers, four markers were used at the head (aligned to Reid's plane), the upper thorax and the pelvis. CODA cameras were mounted 3 metres from the subjects and 40 degrees from their midline. Due to the oblique angle that the cameras made with the markers attached to lower landmarks of the body in experimental sessions one and two, it was necessary to re-orientate some using custom made mounts towards the cameras to optimise visibility. Mounting methods and a head set used to align markers to Reid's plane are illustrated in figure 2.1.

Session three marker configurations were slightly altered due to relocation of laboratory equipment (figure 2.2). A larger laboratory used for this session avoided acute viewing angles with lower limb markers and for this reason no lower limb marker mounts were required. Head markers were fitted to a newly constructed head band, the comfortable design of which was preferred by subjects. Back and pelvis markers were attached by fabrifoam nustim wrap during this session. This change in application methods was adopted because Fabrifoam more easily conformed to variable shapes of subjects, did not slip and was easy to apply.

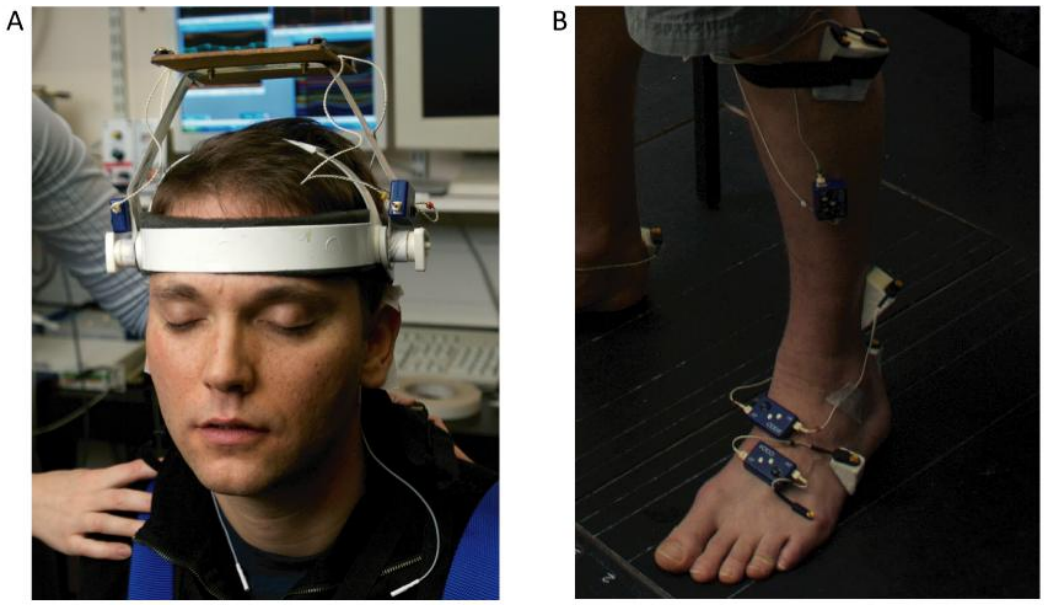


Figure 2.1: Custom made marker mounts.
A plate containing four markers was attached to subjects' heads via a size adustable headset to enable capture of 3D head motion (A). Visibility of leg and foot markers was optimised using wedge shaped marker mounts (B).

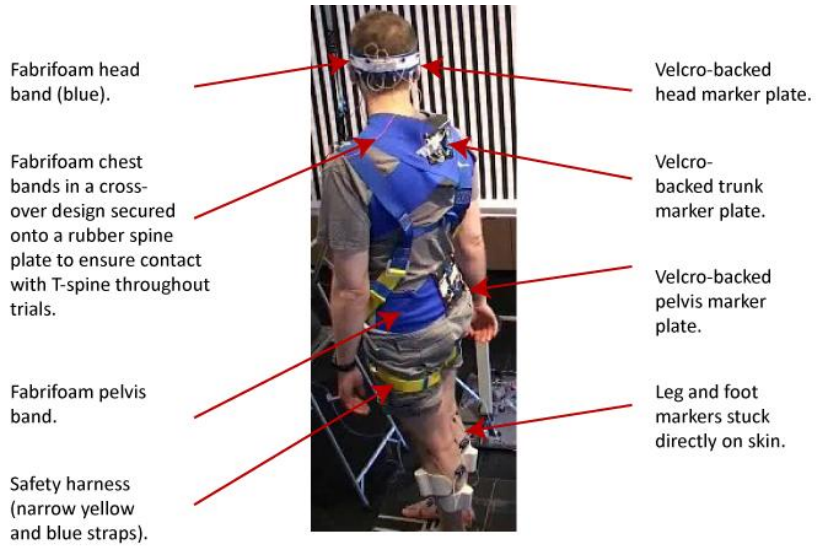


Figure 2.2: Session 3 marker attachments.
A plate containing four markers was attached to each subject's head via a fabrifoam headband to enable capture of 3D head motion. Fabrifoam bands also acted as attachment mediums for back and pelvis clusters of markers. Lower limb markers and boxes to power markers were stuck directly onto subjects via double-sided tape.

2.1.5.2 3D virtual body reconstruction

In addition to segmental motion captured by twenty-four active 'real' markers, a further twenty-eight 'virtual' markers were constructed to define the position of anatomical landmarks in space (illustrated in figure 2.3). This used five sixty second data collections

where subjects stood with all real markers visible to Coda cameras whilst a wand (itself made visible with four real markers) was used to point at each anatomical landmark in turn. When the wand was in the correct position, compression of the wand's shaft acted to tag the wands position in 3D laboratory coordinates. Offline processing of wand collections using Visual 3D software incorporated a calibration of the wand and static subject setup to translate tagged wand activity into virtual landmark definitions, each with an appropriate anatomical label. Visual 3D software was then used to build a model for each subject where the relative position of each 'virtual' marker anchored to clusters of 'real' LED over all forty second stance width collections (appendix 4). This also enabled further processing of virtual landmark data in the same manner as 'real' markers.

2.1.5.3 Ground reaction forces

In addition to tracking segmental motion and anatomical landmark position, ground reaction forces and centre of pressure movements were recorded from two Kistler 9286AA force plates at 400Hz; one under each foot of the subject. Each force plate senses x-, y- and z- forces from piezoelectric sensors in each of four corners of the plate. An initial configuration file was used to integrate the position of the two force plates relative to each other and to transform the output to ensure forces were relative to one origin and one coordinate system. Two perpendicular lines of real markers positioned along the x- and y- axes of the force plates, along with a marker over the origin, then enabled the force plates to become integrated and aligned with laboratory coordinates. In the Coda system, the six channels of force plate output were then converted into resultant x-, y- and z –forces and centre of pressure data per force plate.

The force plates were supplied with charge amplifiers. Additional anti-aliasing filters were fitted to restrict the bandwidth of the sample and help prevent aliasing of waveforms which can lead to erroneous sampling of sinusoidal phase or frequency. The anti-aliasing filters comprised of a seven section Butterworth, low pass filter with a cut-off frequency of 50Hz.The amplifiers are known to suffer from a small baseline drift and for this reason the plates were reset before every unperturbed standing balance collection and every block of perturbed standing balance collections.

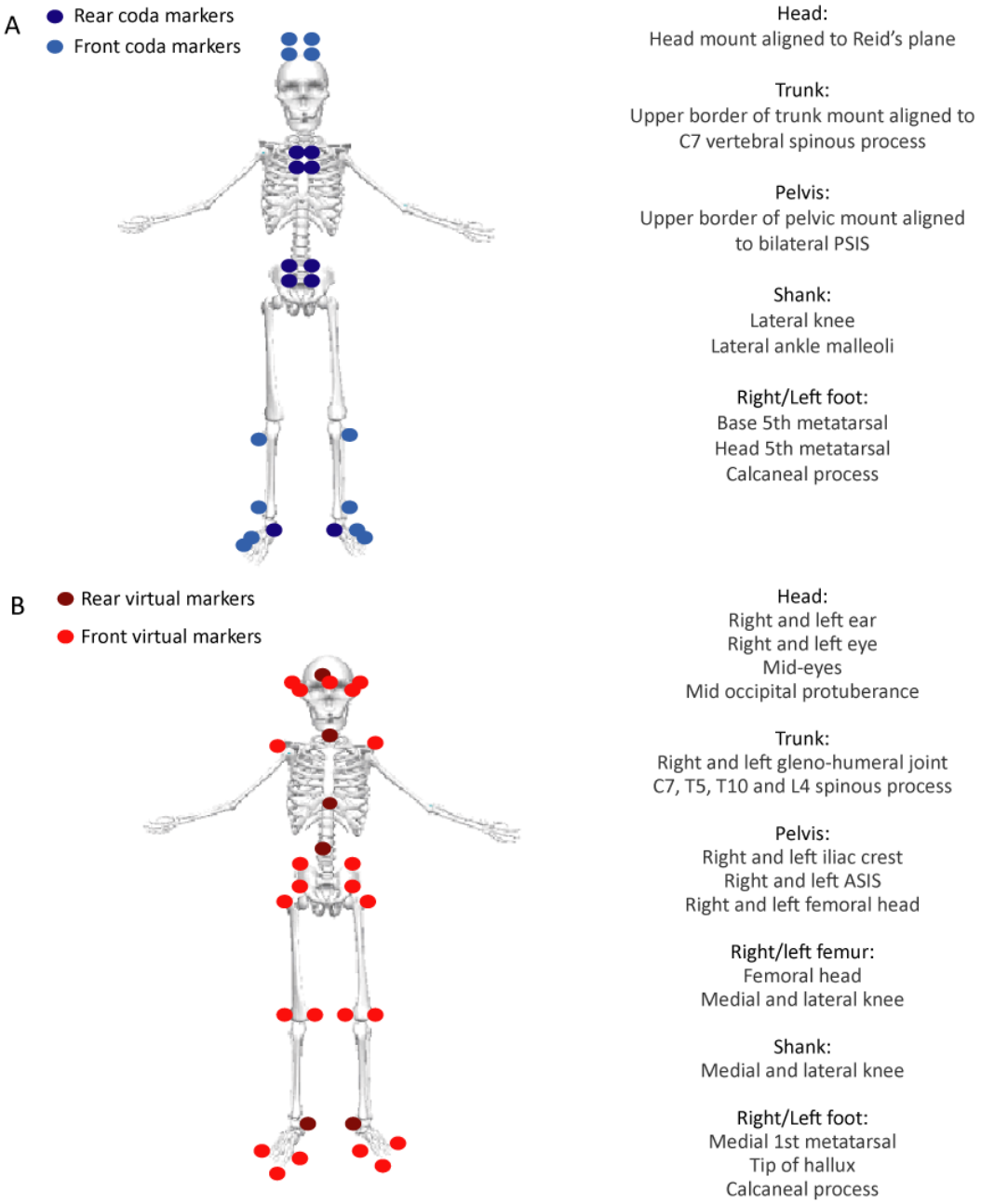


Figure 2.3: Real and virtual marker configurations.
Blue dots indicate the distribution of real infra-red emitting diodes attached to the subject via double-sided tape or custom made mounts (A). Red dots correspond to virtual markers created using techniques set out by Visual3D (B). Virtual markers are anchored to clusters of real markers sharing the same body segment. Descriptions to the left of the figures label the landmarks used. categoised according to the segment to which they attach.

2.1.6 SAFETY EQUIPMENT

A full body safety harness clipped at the chest to 5cm diameter straps from an overhead freely swivelling bar, itself secured to scaffolding, was installed to be able to take the weight of a subject should they drop more than 5cm due to a fall. This system could break a fall quickly yet still avoid any delivery of proprioceptive information from this system during normal upright stance.

2.1.7 DATA MANAGEMENT

Data collected into Coda was initially saved as .mdf (measurement data format) files under each subject code. Marker and force data was exported from Coda at 200Hz into text files for initial analysis in Matlab (Mathworks, Cambridgeshire, UK). For the purpose of analysing posture, .mdfs were also imported into Visual 3D, where they were saved as V3D files and .mat files for ongoing analysis in Matlab. The two main routines are as follows:

2.1.7.1 ***Matlab***

Matlab routines are provided in appendix 3. Exported marker data in text files comprised of position over time and velocity data in the x-, y- and z- axis and marker visibility (as in-view percentages). Exported force plate data included x-, y- and z- forces and CoP position data per plate. Extra channels exported include voltage signals issued from the control computer, which code for condition and onset/cessation of stimuli.

Matlab programmes were written to import text files. Trials were sorted according to condition using coding (voltages). Marker and CoP position time-series data were filtered using a low-pass second-order zero phase Butterworth filter (filt-filt) with a 20Hz cut-off to reduce erroneous interpretation of noise as physiological signal.

Inclusion of marker visibility levels enabled selection of in-view markers for the purpose of making average cluster calculations. Where markers dropped out more than 50% of total trial duration they were excluded from average cluster calculations. Marker positions in x and y laboratory coordinates were normalised to zero at stimulation onset before mean position of clusters were calculated.

Where dual force plates were initially used in sessions 1 and 2, force and CoP needed to be combined before further analysis ensued (see managing dual force plate data section below).

Managing dual force plate data

Experimental sessions one and two used two forces plates to collect ground reaction forces. Forces representing whole body responses were calculated simply by summing force plate 1 and 2 x,y and z outputs across all time series data-points.

CoP analysis required initial processing to calculate the resultant CoP, since subjects were stood across two force plates. This was achieved by taking the exported CoP values per force plate and combining them using z-forces to weight each force plates contribution to this resultant CoP position (see textbox: Definition 1).

Definition 1: Calculating resultant centre-of-pressure (CoP)

totCoP = whole body centre of pressure
CoP1 = centre of pressure data from force plate 1
CoP2 = centre of pressure data from force plate 2
FP1z = z forces from force plate number 1
FP2z = z forces from force plate number 2
x = x axis direction
y = y axis direction

- Individual force plate centre-of-pressures are weighted according to the % mass on each:

```
leftweighting = ((data(:,FP1z))./((data(:,FP1z)) + (data(:,FP2z))))
rightweighting = ((data(:,FP2z))./((data(:,FP1z)) + (data(:,FP2z))))
```

- Total centre-of-pressure is the sum of centre-of-pressures multiplied by the respective weighting:

```
totCoPx=sum(((data(:,CoP1x)).*(leftweighting))+((data(:,CoP2x)).*(rightweighting)),2)
totCoPy = sum(((data(:,CoP1y)).*(leftweighting))+((data(:,CoP2y)).*(rightweighting)),2)
```

*2.1.7.2 **Visual 3D***

Coda .mdf files were imported into Visual 3D for model building of body segments required for analysis of posture and angular joint motion over time. Angular joint excursion over time data was calculated from model building with virtual landmarks in Visual 3D (Visual 3D pipelines available in appendix 4).

3D joint data was calculated for all available joints per subject (head-on-trunk, trunk-on-pelvis, hips, knees and shanks-on-ground). Angles were taken from 3D joint data where local reference frames were calculated in order to define joint specific pitch and roll motion. For this purpose, convention dictated that the more distal segment acted as a local

reference frame. For each segment, the length of the axis pointing upwards (caudal to cephalad) was assigned a z+ coordinate. The right hand side of the body was assigned an x+ coordinate, where the right-left axis was defined using medial and lateral segment landmarks. The remaining y+ axis of each segment was fitted at 90 degrees to the x+ and z+ definitions. Figure 2.3 shows the virtual landmarks that were used to define proximal-distal and medial-lateral borders of each segment. In all cases, where real IRED markers lost visibility during trials, Visual 3D calculations assigned values of 'NaN' to the data and this contribution was ignored. Marker dropout was minimised by the use of four IREDs per cluster from which segmental motion could be anchored (since only three are required at any time this provided a backup should one dropout). Due to careful positioning of each subject in the laboratory, frontal plane joint angles crudely reflect joint angles in the laboratory x-axis and sagittal angles crudely project into the y-axis.

2.1.8 Data analysis

Descriptive analysis (calculation of subject means, within-subject measures of variability, group means and between-subject measures of variability) was principally accomplished using custom written Matlab scripts (appendix 3).

Analysis focuses on measures in x and y laboratory axis directions, assuming that total z forces will remain constant and z marker motion will be negligible. Data analysis throughout this study is principally concerned with rates of change of measures (forces, CoP and marker cluster positions) and the direction of this change in the two dimensional x-y plane (techniques explained in the following sub-sections).

Given the continuous nature of the data, parametric analysis was employed at all times, unless non-normal distributions or unequal variances within data were seen to occur. A wide range of statistical analysis techniques have been employed, including use of t-tests, repeated measure and correlation analyses. These will be explained within the relevant chapter method sections. Statistical analysis was accomplished using SPSS (PASW statistics 18). Graphics involved the use of Excel and Matlab. All figures employed Adobe Illustrator for stylising.

*2.1.8.1 **Rates of change***

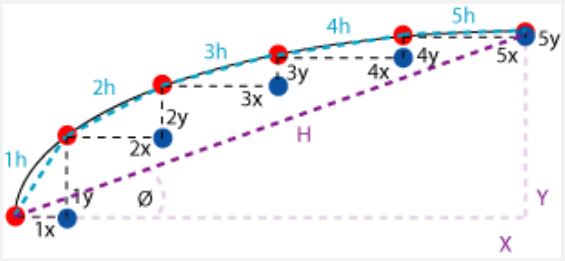
Force, CoP and cluster data in x and y laboratory axes sampled at 200Hz provide the basis for describing the measures of instability and the responses to balance perturbations.

Pythagoras' theorem is employed for this purpose (see textbox: Definition 2).

Calculation of the hypotenuse between two consecutive x and y direction data-points provides a vector measure over a two-hundredth of a second.

Summation of all hypotenuses across the total time series provides a total path for CoP and cluster motion. When divided by time this provides a measure of speed in the x-y plane (see textbox: Definition 2). Calculation of hypotenuse between two discrete time-points using the same method creates a vector from which magnitudes and directions can be calculated. This method has been employed to assess response magnitudes and directions in chapters 5 and 6 (see textbox: Definition 2. Note that time epochs sampled in the textbox example are considerably shorter than chapter 5 and 6 calculations).

Definition 2: Calculating rate of change measures



Key:
Black continuous line: Interpolated motion of CoP
Red markers: Data-points sampled at 200Hz plotted in x and y laboratory coordinates
Black dashed lines: x and y axis change in position in 1/200s
Blue dashed lines: Hypotenuse of change in 1/200s
Purple dashed line: Hypotenuse of change in 5/200s
Light purple dashed lines: x and y axis change in position in 5/200s

Using Pythagoras' theorem:
Transverse speed= $\sqrt{(1x^2+1y^2)}+\sqrt{(2x^2+2y^2)}+\sqrt{(3x^2+3y^2)}+\sqrt{(3x^2+4y^2)}+\sqrt{(5x^2+5y^2)}./(5/200)$
Discrete magnitude in 1/50s = $\sqrt{(X^2+Y^2)}$
Angle of motion during discrete period (1/50s) = $\tan^{-1}Ø(Y/A)$

2.1.8.2 Angles

Circular statistic techniques were employed in order to use descriptive analysis of angles according to the methods outlined by Batschelet [32]. Mean joint angles were calculated using this method to quantify posture and mean response directions to balance perturbations (see textbox: Definition 3). Angular deviations provide alternative measures of variability about the mean.

Definition 3: Calculating mean angles and angular deviations (AD) using circular statistics

- First angular data measured in degrees is converted into radians and the cosine and sine of these values are calculated.

ANGLE(degs)	Angle (rads)	COS (Angle)	SIN (Angle)
89	1.56	0.02	1.00
88	1.54	0.03	1.00
91	1.59	-0.02	1.00
92	1.61	-0.03	1.00
87	1.52	0.05	1.00
86	1.50	0.07	1.00

- The values are then used to calculate averages:

MeanCOS = sum(COS angles)/number
MeanSIN = sum(SIN angles)/number

- Averages are then used to calculate angular deviations:

MeanANGLE = atan2(MeanCOS, MeanSIN)
r = SQRT((MeanCOS)^2+(MeanSIN)^2)
AD = SQRT(2*(1-r))

	Radians:
MeanCOS	0.02
MeanSIN	1.00
MeanANGLE	1.55
r	1.00
AD	0.04

- Radians are converted back to degrees and final values for average angles and angular deviations (comparable to standard deviations) are reported and analysed.

MeanANGLE	**88.83**
AD	2.11

2.2 Conclusion

3D whole body motion kinematic measures and ground reaction forces provide measures of instability and enable quantification of characteristics of motor responses following sensory perturbations. These measures are of a continuous nature and parametric analyses may be used to help draw comparisons of these measures between matched groups.

3 CHAPTER THREE: CLINICAL CHARACTERISTICS AND LONGITUDINAL CHANGES

3.1 INTRODUCTION

Investigation of balance in SCA6 using clinical methods is important for three main reasons. First, in order to investigate sensori-motor control of balance in subjects with SCA6, it is critical to be aware of the degree of disease severity and any other non-ataxia signs in case these features have an effect on laboratory-derived measures of balance. In the absence of availability of more sophisticated electrophysiology tests, a clinical assessment battery was designed for this purpose based on the INAS [325]. This provides a standardised method for flagging any signs of central and peripheral nervous system or musculo-skeletal pathologies not related to ataxia which could affect balance. Second, valid clinical assessment methods need to be available for future evaluation of pharmacological and rehabilitation interventions. This investigation of balance will enable exploration of correlations between the already validated measure of disease severity (SARA) and other contemporary measures of balance (functional balance scores, sway speeds and fall frequencies). This may identify pre-existing measures of balance that have the potential to be useful outcome measures for monitoring disease progression and evaluating treatment effects. Third, knowledge of how these measures may change over time with disease progression is needed in order to properly evaluate future treatment effects. Correlations between already validated measures of disease severity (SARA score) and laboratory-derived measures of sway speed may serve to provide balance related outcome measures which are of a continuous nature. In turn, the continuous nature of such measures may even be more sensitive to treatment effects disease progression over shorter assessment timescales than the SARA.

3.1.1.1 What is currently known of SCA6 balance?

Individuals with SCA6 initially present with unsteady gait, stumbling, general imbalance and signs of slurred speech [75,337]. Despite a late onset and slow progressive nature of the condition, individuals in the UK on average reportedly use a stick within 5 years of diagnosis. Full-time wheelchair use is adopted on average within 14 years, which in turn is suggested to affect physical and social functioning [75]. Falls are common in SCA6

subjects. Falling is directionally unpredictable and thought to be caused by balance dysfunction and in-coordination of movement [115,373]. Visually busy environments have been proposed as risk factors for imbalance and falls [345]. Since balance control is multi-factorial and susceptible to extra-cerebellar pathological changes as well as cerebellar damage, knowledge of how SCA6 disease features may affect balance seems essential.

3.1.1.2 What is currently known of SCA6 disease characteristics?

Aside from gait and balance abnormalities, individuals can present with slurred speech, mild limb ataxia and oculo-motor abnormalities [75,337]. Recent studies of pre-symptomatic individuals have also highlighted early eye movement abnormalities [68]. These may be primary signs of disease onset in this patient group which were perhaps over-shadowed by more obvious balance and gait problems and historically un-noticed by patients before diagnosis [68]. As SCA6 disease progresses symptoms involve increasingly un-coordinated upper and lower limb movements (lower limb often being the more affected of the two), tremor and increasingly obvious eye movement abnormalities (including broken pursuit movements, dysmetric saccades, gaze evoked nystagmus, occasional downbeat nystagmus, diplopia and oscillopsia), tremor and dysarthria and eventually dysphagia [75]. Occurrences of double vision or visual disturbances as well as episodic symptoms (such as paroxysmal vertigo, dizziness and migraine; often evoked with head movements) are also reported to have occurred at some point in the course of the disease in approximately half of the population [1,337]. Dystonia and Parkinsonism, although not typical for the condition, have also been reported as unusual and isolated cases [126,331].

3.1.1.3 What measures of disease and balance are currently available?

Various measures of ataxia exist for the purpose of quantifying and monitoring disease severity, including the scale for assessment and rating of ataxia (SARA) [324], the international Cooperative Ataxia Rating Scale (ICARS) [353], self-rated health score [361], an inventory of non-ataxia symptoms (INAS) [325], and a composite functional score [99]. Perhaps due to the relatively rare prevalence of the genotype, these scores have not solely been evaluated for use with SCA6 subjects.

Of these scales, the efficacy of the ICARS and SARA for detecting longitudinal change over one year have both recently been evaluated using mixed groups of ataxic subjects, with encouraging findings [325,324,353]. Of the two, the SARA seems suited to ‘purer’

presentations of ataxia, such as SCA6, since it does not take into account non-ataxia signs. It is also shorter to undertake than the ICARS and for these reasons, seems worthy of further investigation for use with SCA6 subjects. However, given the discrepancies reported in electrophysiology literature concerned with non-ataxia signs in SCA6, it seems justified that investigation of non-ataxia signs should be undertaken alongside the SARA.

The composite functional score (CFS) has also been evaluated using mixed groups of ataxic subjects, providing support for its use particularly with SCA1 and SCA3 subjects [(99)]. However, the CFS focuses on upper limb activity and does not take into account functional balance.

Since balance impairment is a prominent feature of SCA6, it seems of considerable value to have a measure functional balance, such as Berg's Functional Balance Scale (FBS) [(36)]. A secondary measure, such as the Functional Independence Measure (FIM) [(342)], could then be used to then evaluate the effect that balance dysfunction may have on independence with activities of everyday living. A measure of falling may also help to understand the physical risk that balance impairments pose to everyday life for those with SCA6.

None of the currently available clinical scales with the potential to measure balance are validated for use with cerebellar disease patients but the SARA does contain three sub-scores which are related to balance (assessing stance, walking and sitting balance) [(324)]. These sub-scores will be collectively referred to as the Bal-SARA score. Although also relating to functional activity, I hypothesise that this score may provide a simple method of obtaining a measure of balance impairment in the clinical setting. To test this hypothesis, this score will be compared with measures of trunk and centre-of-pressure sway speeds, derived from same day laboratory tests (outlined in chapter 4).

3.1.2 Purpose

There is compelling evidence in the literature which suggests that cerebellar damage is the main feature of SCA6, but also evidence of irregularities in presentations. Rather than assume our sample is free from extra-cerebellar pathology which could affect balance, a battery of clinical tests have been designed to comprehensively describe the clinical characteristics of our sample.

The assumption that balance impairment is a primary consequence of cerebellar damage

will also begin to be tested by comparing measures of balance impairment and function with measures of disease severity.

Whilst assessing homogeneity, this study also provides the opportunity to describe dysfunction incurred by those with SCA6 and assess relationships between commonly used clinical measures and measures of disease severity. The results of which will act as a first step to assessing the validity of clinical tools for the purpose of measuring longitudinal change in condition and treatment effects.

3.1.3 Experimental aim

To understand how SCA6 clinical characteristics have the potential to affect balance.

In meeting the aim, this study will set out to provide answers to the following questions:

- What is the nature of the relationship between disease severity and balance?
- What are the functional consequences of balance impairment?
- Does our sample exhibit any significant non-ataxia signs and symptoms which could affect balance?
- How suitable are balance outcome measures as future measures of longitudinal change and treatment effects?

3.1.4 Approach

Assessment of disease and balance was undertaken with SCA6 subjects at the beginning of each testing day. Commonly used measures of disease severity (SARA score), non-ataxia symptoms, functional balance (FBS), functional independence (FIM) and falling behaviour were taken during the first session (see below).

Measures of severity of ataxia symptoms, functional independence and fall behaviour were repeated alongside laboratory based sway measures during the final testing day to look for indications of progression of impairment and disability. Functional balance scale assessment was not repeated due to the time cost of this measure (45 minutes per subject) and overlap in balance assessment forming part of motor assessment in other measures (FIM and SARA). All testing was undertaken by the author, a physiotherapist trained in the use of all assessment methods.

3.2 METHODS

3.2.1 DISEASE ASSESSMENT

3.2.1.1 The scale for assessment and rating of ataxia (SARA)

Although yearly impairment scores were available from subject's yearly clinical consultations, due to the progressive nature of neurological degeneration and the potential variability of the condition on a day-to-day basis, an assessment of physical impairment was carried out at the start of each testing day by the researcher using the Scale for the Assessment and Rating of Ataxia, SARA [(324)]. This measure has been validated as being able to provide a measure of disease severity and does so by rating eight activities categorised as gait, stance, sitting, speech disturbance (dysarthria), finger chase (dysmetria), nose to finger (tremor), fast alternating hand movements (dysdiadochokinesia) and heel-shin slide (incoordination). A wealth of literature exists which associates these clinical signs with cerebellar disease [(97,155,218,225,226,367)]. The SARA has been validated for use with individuals with SCA6 [(324)]. This produces a score between 0 and 40 points, where 0 indicates no ataxia symptoms and 40 the most severe ataxia symptoms. Any positive score indicates the presence of ataxia and subjects are then referred to as symptomatic. It is possible to achieve half points within this scale from taking averages from the left and right sides of the body in the latter four rated categories. A copy of the SARA can be downloaded for use from the appendix of the publication of Schmidt-Hubsch *et al*.[(324)].

3.2.1.2 Assessing non-ataxia signs and symptoms

Non-ataxia signs and symptoms affecting vision, proprioception or motor control, which could impact upon standing balance [(208,210,213,212)], were assessed during initial consultations in order to classify clinical features known to affect persons with SCA6 and to exclude potential SCA and healthy control subjects should unexpected signs and symptoms of an unrelated medical condition be present. These involved sensory and motor assessments similar to those set out by the inventory of non-ataxia symptoms (INAS) [(325)] and assessment as set out by a fall-predictor method as described by Lord *et al*. [(212)]. The resulting clinical assessment protocol is described in the following sub-sections.

Muscle strength

Assessment of ankle dorsi- and plantar-flexion through-range muscle strength was

undertaken using the MRC rating scale [243]. Muscle strength is scored out of 5 (5= Full range contraction maintained against maximal manual resistance, 4= Full range contraction maintained against gravity and additional resistance, 3= Full range contraction maintained against gravity but not with additional resistance, 2= Full range contraction maintained with gravity eliminated, 1= Muscle flicker observed, 0= No muscle flicker observed).

Range of movement

Ankle dorsi- and plantar-flexion was tested following muscle strength tests while supine. If full range of movement was not available, restrictions were measured using a goniometer as per methods set out by Moore and Norkin *et al*. [252,266].Subjects were sat on a plinth with the backrest elevated 80 degrees to the horizontal leg rest. A small 15cm lightweight plastic goniometer was stuck to the vertical length of the fibula and to the head and base of the 5th metatarsal to enable rotaion of the pivot point in line with the tibio-talar joint. Passive movement of each foot was performed by gripping the calcaneum. This allowed dorsi- and plantarflexion whilst laterally stabilizing to prevent inversion or eversion. Forefoot movement was prevented by splinting the plantar surface of the foot along the length of the testers forearm.

Tactile sensibility

Lack of tactile sensibility over the foot provides an indication of peripheral nerve damage [242]. Subjects were positioned in supine with their eyes closed and a microfilament was used to apply pressure at ten specified points over the plantar and dorsal aspects of the feet [40,242]. This provides a score for each subject per foot out of ten (averaged across three repeats). Eight points or less provides an indication of peripheral neuropathy when using this test.

Vibration sensibility

Signs of peripheral nerve damage can also be determined with the use of a biosthesiometer, a tool reviewed by the National Institute of Clinical Excellence and recommended for detecting peripheral neuropathy in patients with diabetes [39,242]. A biosthesiometer maintains constant frequency of vibration (100Hz) but a manually controlled level of amplitude. Testers are able to gradually increase and decrease amplitudes by turning a dial. A display provides an online measure of amplitude. Subjects

are asked to report when they can feel vibration as the researcher gradually increases the amplitude. Following this, vibration amplitude is turned up and then gradually decreased in order for the subject to report when they can no longer feel vibration. The measure of amplitude is noted at the point where the subject reports the change. This procedure is repeated three times per position in accordance with recent recommendations [101]. This tool was used not only to screen for proprioceptive receptor changes but also to contrast threshold measures against measures of responses to vibrator perturbations collected during the final testing day. In order to explore correlations between threshold and response magnitude measures, this test was conducted on both SCA6 and healthy control subjects prior to multi-sensory testing involving vibrator perturbations. Positions tested included the medial spine of the tibia (half-way down the shank recommended by the Bio-medical Instruments validation research), over the tibialis anterior muscle belly and over the junction between the tendo-achilles and gastrocnemius and soleus muscles on both legs. The latter two positions replicated the positioning of vibrators in session three and were therefore included in order to compare response characteristics to localized thresholds. Matched healthy controls were tested in order to compare average threshold results.

Kinesthesia

A crude measure of joint position sense (kinaesthesia) was obtained from a traditional neurological test recently described in a new assessment tool for subjects with ataxia, the inventory of non-ataxia symptoms [325]. Subjects were supine with their eyes closed. Researchers positioned the hallux longus into either a flexed, extended or neutral position. Subjects were asked to report whether the toes is ‘up’, ‘middle’ or ‘down’. Each position was tested three times using both feet and an average response scored.

Lower limb tone/identifying signs of spasticity

Spasticity has been defined by Stevenson as “disordered sensorimotor control, resulting from an upper motor neurone lesion, presenting as intermittent or sustained involuntary activation of muscles” [349]. The Ashworth scale (originally described by Ashworth, 1964 [19]) provides one way to rate muscle tone and identify signs of spasticity [78]. The resistance to passive movement of the ankle or tone of plantarflexors and dorsiflexors was assessed whilst subjects remained positioned in long sitting following assessment of range of

movement. This scale has been criticised for a lack of inter-rater reliability but is generally advocated as being an important tool. Since only one rater assessed all subjects using a standardised test procedure for the purpose of this study and all tests were conducted with subjects in a standardised position, this method satisfies the recommendations for use made by Stevenson *et al*. [348] and this scale should provide a simple and valid tool for flagging any signs of abnormal tone. According to the Ashworth scale, subjects were scored according to the definitions set out (0= No increase in muscle tone, 1=Slight increase in tone giving a catch when the limb is moved, 2=More marked increase in tone but limb easily moved, 3=Considerable increase in tone – passive movement difficult, 4=Limb is rigid in flexion or extension).

Spasms

According to the definition set out by Simons and Mense [336] a muscle spasm is "electromyographic (EMG) activity that is not under voluntary control and is not dependent upon posture. It may or may not be painful". The occurance of spasms in subjects with SCA6 is not well documented but spasms are known to affect the wider population of subjects with ataxia. Given that spasms could impact on balance measurements should they occur during testing, a measure of spasm frequency was taken in order to alert the researcher to this likelihood of this happening per experimental session. Prior attempts at quantifying spasms outlined by Simons and Mense are complicated and time-consuming and in order to merely screen for this factor within this study, use of the Penn spasm scale was deemed sufficient [282]. Before asking subjects about spasms, subjects were provided with a definition of a spasm based on previous scientific definitions [336] but translated into lay terms: "Spasms are an involuntary muscle contraction, which can sometimes be powerful and painful. Also called a cramp". Subjects were then asked to report if they had any spasms over (a) the last 24 hours and (b) the last week. For each timeframe they were asked to rate the frequency of spasms (0= No spasms, 1= Induced only by stimulation, 2= Occurring less than once an hour, 3= Occurring more than once per hour 4= Occurring more than ten times per hour). Subjects were asked to report spasms should they occur any time during testing and trials would be excluded from analysis.

Reflex activity

Patella tendon jerks were assessed in order to screen for reflex abnormalities prior to testing (methods described by Benz *et al*. [34]Subjects sat on the edge of a plinth supported only by their own upper limb activity. Subjects were asked to look at a picture on the wall in front of them and a queen square tendon hammer was used to tap right and left tendons three times each sequentially. The best response per side was rated as either (0=absent, 1=sluggish, 2=normal, 3=brisk). Any score not equal to 2 was said to flag abnormal reflex behaviour.

Visual acuity

Long distance visual acuity was tested using a three metre Keeler acuity chart and near vision acuity was tested using a modified ETDRS 40cm distance Lighthouse Near Vision Acuity chart, positioned 40cm from subject's eye level. The Lighthouse near vision acuity chart was designed to test right and left eyes individually whereas the Keeler 3m chart allowed subjects to use both eyes during testing. The last level in each test that subjects read without making any errors was recorded. During all tests of vision and eye movements, subjects remained sat with feet on the floor and the tester held subjects chin to prevent subjects from turning their head.

For all aspects of clinical assessment apart from acuity, subjects were asked to leave normal corrective lenses *in-situ*.

Contrast sensitivity

Impairment with contrast detection could affect the degree of visual information available to the central nervous system and thus available for use in balance control [86,209]. The Melbourne edge test, cited in Lord *et al*. [212], was undertaken in order to test subject's sensitivity to distinguishing contrast. Subjects were asked to trace a pointer along the dividing edge of two hemi-circles of contrasting grey intensities. The total number correctly traced out of twenty possibilities was recorded.

Visual field

A 30cm length of cord was used to define a starting forwards gaze position from each subject's mid eye level and the 30cm cord was then used to measure out positions left, right, up and down from the subjects. At these positions, the researcher would open and shut their hand. Upon opening the hand subjects were asked to look at the hand without

turning their head. This demonstrated appropriate peripheral field detection whilst subjects were looking forward, as well as allowing assessment of ocular movements generated for reaching the target (see eye movement section below: dysmetric saccades, pursuit, nystagmus)..Each up, down, left, right direction of jump to the target was assessed three times.

Eye movements: Rating of saccades, pursuit and fixation

Saccades are the ballistic movement of the eyes which ensures that the target image comes to rest on the fovea in one movement [(218)]. Saccadic movements need to be concerned with end point accuracy but also overcoming viscous drag from extra-ocular musculature. The faster the saccade, the more viscous drag will have to be overcome [(218)]. Assessment of saccade dysmetria was conducted by the researcher following the test for visual field. Saccades were rated as either dysmetric if they over or under shot a target fixation point.

The procedure described for visual field testing was repeated three times per direction to look for dysmetria of saccades since this is reportedly commonly affected in cerebellar disease [(218)]. The tester raised just one finger instead of opening their full hand and subjects eye movements on the ipsi-lateral side of the direction of the tester's finger was assessed for precision of gaze on the target. If square wave jerks were observed during testing at stationary gaze positions these were noted. Square wave jerks occur when fixation of a target cannot be maintained, the eye drifts away from the target and then is returned with a jerk like movement. Severe fixation difficulties have been observed following cerebellar ablation [(218)] but fixation difficulties do not appear to be a feature of SCA6 [(129)].

Pursuit describes the movement of the eyes to maintain an image of an object, itself moving in space, on the fovea [(218)]. A complete cerebellectomy in monkeys reportedly causes total loss of smooth pursuit [(218)]. Unilateral lesions to the cerebellar vermis and hemispheres cause micro-saccades to replace smooth pursuit in the direction of the movement of the object but contralateral movement is unaffected [(218,354)]. In the case of subjects with bilateral cerebellar lesions, or widespread cerebellar damage like that of SCA6, we could expect to see bilateral interruptions of smooth pursuit [(68)]. Intrusions of saccades during pursuit have been reported in older subjects and other patient populations

where pursuit has in some cases been found to be slower than normal [65,178,247]. In these cases, intrusions on smooth pursuit are said to act as 'catch up saccades', following slow and inadequate pursuit speeds, to ensure end eye-to-target accuracy [89,90,120]. Pursuit was assessed by asking subjects to follow a pen tip to left, right, up and down extremities of gaze directions. This movement was repeated three times per direction. The absolute speed of pursuit is difficult to assess objectively using this simple clinical method but any occurrences of saccadic intrusions during pursuit were noted.

End range eye in socket positions were held after assessing pursuit activity by keeping the position of the pen tip stationary for a couple of seconds to assess for signs of nystagmus during fixation. Where fixation is unable to be maintained, possibly due to tonic disinhibition, a centripetally beating movement, known as nystagmus, returns the eye to the primary position from where it has moved away from [204]. End range eye-in-socket positions are thought to most likely evoke signs of nystagmus following cerebellar damage since the elastic forces of extra-ocular musculature are at their highest at this position [218]. Where nystagmus was detected, this was noted according to the direction of the nystagmus jerk (i.e. horizontal or vertical). The direction of the rapid phase of the jerks was also assessed, e.g. if nystagmus jerks included a downbeat rapid phase component, the subject was said to have exhibited 'downbeat nystagmus'.

Cognitive function

Severely impaired cognitive function could potentially affect balance control, fall prevention and ability to follow instructions, such as those involved in the study procedures. Individuals with SCA6 are not known to demonstrate signs of severe cognitive impairment but recent work has acted to question the assumption that cognitive functioning remains completely intact {Suenaga, 2008 265 /id;Klinke, 2010 819 /id}. The mini-mental state examination (MMSE) was therefore used to screen for signs of severe cognitive dysfunction prior to testing [46].

3.2.2 Balance assessment

3.2.2.1 The functional balance scale (FBS)

Functional assessment of balance was assessed by the researcher using the Functional Balance Scale (FBS), which standardises activities and provides a validated scoring method for use with older adults or those with known balance impairments [36,37]. Due to

the time required to undertake this measure with the SCA6 subjects (45 minutes), this was only undertaken once, during each subject's initial consultation. Healthy control subjects were assessed using this measure given that some were older adults with some risk of decreased functional balance.

3.2.2.2 The functional independence measure (FIM)

A measure of functional abilities was taken using a questionnaire delivery version of the functional independence measure [341]. This crudely assesses function by asking subjects to rate their level of independence against a series of functional activities listed. Scores range between zero and seven per category. Seven indicates no assistance with functional activities is required and zero indicates total dependence on others. This measure was conducted at the start of each testing day and was used to assess any change in functional independence over the project duration.

3.2.2.3 Fall frequency and fall behaviour

Frequent falling has been shown to be a feature of SCA6 [373]. In an attempt to quantify falling and compare fallers with their clinical features a fall questionnaire was incorporated from 'Falls in older people' by Lord *et al*. [212]. This involves a retrospective measure of fall behaviour. A retrospective timescale of one month was used in order to avoid recall problems. This provided a measure of fall frequency during the month prior to testing and provides further details of the location of falls, possible causes and any injuries that may have occurred following falls. This measure was taken at the start of each testing day and is therefore also available to assess change in fall frequency. Healthy control subjects were also assessed with this measure given that some were older adults, with some risk of falling.

3.2.2.4 Body sway

In addition to the already described clinical measures, laboratory-based measures of postural sway speeds collected during initial and final testing days are available for comparison. Sway speeds are popular choices of outcome measures when attempting to quantify balance [2,79,104,157,238,267] or an effect that an intervention may have on balance [161], with particular support for use of speed rather than acceleration or absolute position measures [175]. Although these measures are continuous and have the potential to be more sensitive to small changes in balance, they require specialist equipment and collection to

take place in a laboratory environment. Chapter 4 of this thesis outlines that SCA6 sway speeds were indeed increased relative to healthy control subjects and therefore these measures are thought to be have the potential to indicate impairment. Sway speeds in use are derived from trunk and centre-of-pressure speeds (calculated from trunk marker and centre-of-pressure motion in the x-y plane). These sway speed measures were averaged over a forty second data collection during which subjects stood with their eyes open, facing forward and with feet 4cm apart. Chapter 2 details the methods involved in collecting and calculating these measures. Chapter 4 presents these measures as part of a series collected from five different stance widths during the first testing day. Of this series, trunk and centre-of-pressure sway speeds from 4cm stance widths were found to best correlate with early SARA scores (see chapter 4 results) and for this reason are selected for further comparison with clinical measures of balance and function and longitudinal study. Here these scores are analysed for longitudinal change in the same way as clinical measures to provide information specifically regarding the progression of balance impairment in SCA6.

3.2.3 Analysis

Clinical assessment scores of an ordinal nature will be presented per subject. The nature of the distribution of scores from continuous scales, such as the SARA, FBS, FIM and sway speeds will be assessed using the Kolmongolov-Smirnov Test (KST). This test can be applied to non-parametric data, such as that of the total scores of the SARA, FBS, FIM and fall frequencies. If KST significance scores are less than p=0.05, scores are assumed to be not normally distributed and median measures of central tendency will be highlighted, otherwise mean scores will be used. Mode values are also available to inform the reader of plurality scores.

Longitudinal changes in score between the first and final assessment day will be normalised by the time period elapsed between the two days. Analysis of longitudinal change in score will incorporate paired t-tests for statistically significant differences between day-one scores and change per year scores.

Correlations will be explored between the already validated measures of disease severity (SARA scores) and all quantitative measures of balance (the FBS, FIM, fall frequencies, trunk and centre-of-pressure sway speeds). This will be repeated using the total score of just the sub-catagories of the SARA which directly relate to balance (stance, walking and

sitting), collectively known as the Bal-SARA score. This comparison will ascertain if correlations between measures are related to the severity of ataxia symptoms overall, or more specifically those related to balance.

Correlations will be explored for all longitudinal measures, including disease severity (SARA and Bal-SARA), FIM, fall frequencies, trunk and CoP sway. Due to the variability in absolute durations between each subject's first and last visit, change in score per year values will be calculated and used for the purpose of this correlation. Initial testing day scores will be compared to '[initial testing day scores + one year change in score value]'. Where significant correlations exist, the potential for these scores as future outcome measures will be discussed. Group mean change in score values will also be calculated for the purpose of evaluating whether change in scores could be clinically meaningful.

3.3 RESULTS

Seventeen subjects with SCA6 participated in the first experimental testing day (two of which were pre-symptomatic subjects). Sixteen subjects participated in the second experimental testing day (all of which by this point had signs of ataxia).

Twelve subjects with SCA6 participated in all testing sessions throughout the duration of the project. Longitudinal change in measures of disease severity, functional independence, fall frequency and sway measures are presented based on these twelve subjects.

Longitudinal measures of change in score per year for twelve subjects are presented in table 3.1. Following presentation of scores, columns indicating the nature of change in score have been added to simplify interpretation of scores. For each case, a change in score representing improvement in physical condition is indicated by an up arrow (↑), deterioration is represented by a down arrow (↓) and no change by sideways pointing arrows (↔). Kolmogorov-Smirnov one-sample tests determined that data from these subjects was normally distributed for all scores.

3.3.1 DISEASE RATINGS

3.3.1.1 The scale for assessment and rating of ataxia (SARA)

Subjects with SCA6 were found to have SARA scores ranging between 0 and 16.5 during the first testing session. Table 3.1 outlines the SARA score breakdown per subject, in descending order of SARA score. The group produced a mean SARA score of 8.8 and group mean sub-scores were highest for gait impairment ratings.

Table 3.2 outlines the SARA score breakdown per subject using the final assessment day scores. Final testing day mean group scores were larger than day one in all sub-categories and for total SARA score (12.0). Due to group changes, specifically drop out of five subjects and four new subjects recruited between the first and final testing days, average scores do not necessarily reflect a progression in disease severity but do highlight differences in disease severity between the two testing sessions. Gait impairments once again produced the highest average score for this group.

Table 3.1 reveals that one of the 'pre-symptomatic' SCA6 subjects (16) exhibited slight irregularities in repetitive hand turning on the initial testing day (this was noted when the subject was asked to undertake the task with their right hand). The same subject was unable to perform three consecutive heel-shin slides in either leg without slight deviation from the ideal path. This subject was unable to return for the final day testing session and therefore no final day clinical assessment data is available for comparison.

Longitudinal changes

SCA6 mean SARA scores increased from 9.2 (SD 5.4) on the initial testing day to 13.1 (SD 6.5) on the final testing day (table 3.2). Changes in SARA scores per year had a mean value of 1.9 points (SD 1.3). A significant difference between baseline and estimated change in score at one year was found ($t= 5.1$, $p<0.001$).

Mean Bal-SARA scores changed from 4.1 (SD 2.4) on the first testing day to 5.4 (SD 3.0) on the final testing day (table 3.3). Calculations of change in Bal-SARA score per year produced a mean value of 0.6 (SD 1.1). No statistically significant difference in Bal-SARA score was found between the baseline score and estimated score one year later ($t=1.8$, $p=0.093$).

Table 3.1: SARA scores for the first testing day

Subj. No.	Gait	Stance	Sitting	Speech	Finger chase	Nose to finger	Alternating hand movements	Heel-shin slide	Total SARA score	Bal-SARA score
1	5	2	0	2	2	0.5	2	3	16.5	7
2	3	4	0	2	3	1	3	1	15	5
3	3	2	0	1	2.5	1	2.5	2	14	5
4	5	0	0	3	0.5	0	3	2	13.5	5
5	3	2	2	1	1	1.5	1	2	13.5	7
6	4	2	0	2	1	1	1	2	13	6
7	3	2	1	1	3	0.5	0.5	0	11	6
8	1	3	0	1	2	0	2	1	10	4
9	5	1	0	0	1	0.5	1	1.5	9.5	6
10	3	2	0	1	0.5	0.5	1.5	1	9.5	5
11	2	0	0	1	0.5	1	1.5	1	7	2
12	3	1	0	1	0	0	0	0.5	5.5	4
13	2	0	0	1	0	0	1	1	5	2
14	1	1	0	0	0	0	0.5	1	3.5	2
15	1	0	0	0	0	0	0	0.5	1.5	1
16†	0	0	0	0	0	0	0.5	1	1.5	0
17†	0	0	0	0	0	0	0	0	0	0
Distribution (K.S.T. sig.)	Norm (0.582)	Norm (0.193)	NN (<0.001)	Norm (0.185)	Norm (0.465)	Norm (0.130)	Norm (0.623)	Norm (0.105)	Norm (0.877)	Norm (0.475)
Mean	2.59	1.18	0.18	1	1	0.44	1.24	1.18	8.79	3.94
SD	1.62	1.01	1.01	0.87	1.10	0.50	1.00	0.80	5.21	2.33
Mode	3	2	0	1	0	0	1	1	13.5	5
Median	3	1	0	1	0.5	0.5	1	1	9.5	5
Range	0:5	0:4	0:2	0:3	0:3	0:1.5	0:3	0:3	0:15.5	0:7

Key: Score of 0=Normal, top score dependent on category (Gait= /8; Stance= /6; Sitting= /4; Speech= /6; Finger chase= /4; Nose to finger= /4; Alternating hand movements= /4; Heel-shin slide= /4).
†=Pre-symptomatic subjects. Norm= Normal distribution, NN= Non- normal distribution.

Table 3.2: SARA scores for the final testing day

Subj. No.	Gait	Stance	Sitting	Speech	Finger chase	Nose to finger	Alternating hand movements	Heel-shin slide	Total SARA score	Bal-SARA score
1	6	2	1	4	3	1	2	3	22	9
2	5	3	2	3	1.5	1	3	2	20.5	10
3	5	3	2	2	1	1	1	2	17	10
11	4	2	0	2	2	1	3	3	17	6
5	4	2	0	2	2	1	3	3	17	6
6	3	1	0	1	2	1	3	3	14	4
9	3	2	0	3	2	0	2	1	13	5
8	2	2	0	3	3	0	2	1	13	4
18*	5	2	0	2	0	1	1	1	12	7
13	3	1	0	2	1	0	1	3	11	4
19*	2	1	0	1	0	0.5	2	3	9.5	3
12	2	2	0	3	0.5	0	1	1	9.5	4
20*	1	0	0	3	1	0	1	1	7	1
21*	1	0	0	2	1	1	1	0	6	1
15	2	1	0	0	0	0	0	0	3	3
17†	0	0	0	0	0	0	0	0	0	0
Distribution (K.S.T. sig.)	Norm (0.820)	Norm (0.229)	NN (0.001)	Norm (0.377)	Norm (0.810)	Norm (0.066)	Norm (0.371)	Norm (0.321)	Norm (0.991)	Norm (0.762)
Mean	3.00	1.50		2.06	1.25	0.53	1.63	1.69	12.00	4.81
SD	1.71	1.00		1.12	1.02	0.50	1.03	1.20	6.07	3.06
Mode	2	2	0	2	1	1	1	3	17	4
Median	3	2	0	2	1	0.75	1.5	1.5	12.5	4
Range	0:6	0:3	0:2	0:4	0:3	0:1	0:3	0:3	0:22	0:10

Key: Score of 0=Normal, top score dependent on category (Gait= /8; Stance= /6; Sitting= /4; Speech= /6; Finger chase= /4; Nose to finger= /4; Alternating hand movements= /4; Heel-shin slide= /4).
†=Pre-symptomatic subjects. *= Subjects who did not participate in the first session. Norm= Normal distribution, NN= Non-normal distribution

Table 3.3: Change in score per year (SARA, FIM, falls and laboratory-based measures of postural sway)

Subj No.	SARA change/ Year	Bal-SARA change/ Year	FIM change/ Year	Fall freq Change/ Year	Trunk sway change/ Year	CoP sway Change/ Year
1	2.8↓	1.0↓	2.6↑	-1.0↑	3.0↓	-2.5↑
2	2.2↓	2.0↓	0.0↔	-2.4↑	4.2↓	12.4↓
3	1.6↓	0.5↓	0.5↑	0.0↔	-6.2↑	-11.3↑
5	1.5↓	1.3↓	-1.3↓	0.4↓	-6.6↑	-7.6↑
6	0.8↓	-1.6↑	-6.4↓	2.4↓	-0.6↑	-4.4↑
8	1.5↓	0.0↔	1.5↑	-1.0↑	-3.3↑	-4.1↑
9	1.8↓	-0.5↑	-4.1↓	3.1↓	-3.1↑	-4.4↑
11	5.1↓	2.0↓	0.5↑	-0.5↑	10.6↓	12.7↓
12	2.1↓	0↔	0.5↑	0.5↓	-1.8↑	-5.9↑
13	3.0↓	1.0↓	-1.5↓	-0.5↑	0.3↓	-1.8↑
15	0.7↓	1.0↓	-0.5↓	0↔	2.0↓	1.6↓
17†	0.0↔	0.0↔	0.0↔	0↔	-0.4↑	-0.8↑
Distribution (K.S.T. sig.)	Norm (0.882)	Norm (0.961)	Norm (0.698)	Norm (0.613)	Norm (0.983)	Norm (0.617)
Mean	1.9↓	0.6↓	-0.7↑	0.1↓	-0.2↑	-1.4↑
S.D.	1.3	1.1	2.5	1.5	4.7	7.3
S.E.M.	0.4	0.3	0.7	0.4	1.4	2.1
95% C.I. Diff (Lower : Higher)	1.1 : 2.8	0.9 : 1.2	-2.3 : 0.9	-0.9 : 1.0	-3.2 : 2.9	-6.0 : 3.3
Paired Diff. t(p)	5.1 (<0.001)	1.8 (0.093)	-1.0 (0.360)	0.2 (0.848)	-1.1 (0.917)	-0.6 (0.534)

Key: SARA= Scale for the assessment and rating of ataxia total scores. FIM= Functional independence measure total scores. CoP= Centre of pressure. †= 'Pre-symptomatic' subjects. ↑= Improvement in physical/functional condition, ↔= no change, ↓= deterioration in physical/functional condition. Distribution (K.S.T. sig.) = Test of normality for each dataset using the Kolmogorov-Smirnov Test (significance value); Norm = Normal distribution. Correlation r(p) = Pearson's correlation coefficient (and p-value). Paired Diff. t(p) = Students paired t-test t-value (and p-value).

3.3.1.2 *Non-ataxia signs and symptoms*

Non-ataxia sensori-motor assessment is summarised in table 3.4. Three subjects with SCA6 (subjects 3, 10 and 12) could not detect two or more applications of the microfilament on one foot. Subject 3 also had absent patella tendon jerks and daily spasms. Subject 10 had normal reflex activity but experienced difficulties in perceiving joint position of the hallux. Subject 12 had unexpectedly larger average vibration threshold values in the right leg compared with the left, consistent with the side of light touch abnormalities, and bilaterally absent patella tendon jerks. Overall SCA6 average vibration thresholds (compared by averaging across positions and then right and left leg scores) were similar to those reported in the healthy control group (SCA6 [mean (s.d.)= 21.6 (6.8)], HC [mean (s.d.)=20.6 (7.9]). No significant statistical differences were reported by t-tests based on average vibration threshold scores (t(p)=-0.4(p=0.739)).

Three subjects (coded 6, 7 and 14) had brisk patella tendon jerks, an indication of upper motor neurone involvement. Subject 7 had accompanying increased tone in both ankle dorsi- and plantar-flexors. Subject 6 had no further signs of upper motor neurone involvement. Five subjects reported frequent spasms (subjects 2, 5, 9, 14 and 15) with no other sensory abnormalities.

A summary of visual assessment findings is provided in table 3.5. Visual assessment revealed that all subjects were free from visual field impairments. Visual acuities varied for both healthy and SCA6 subjects but where subjects were long/short sighted this was in all cases corrected with lenses prescribed by their optician. All following tests (clinical and laboratory-based) were performed with corrective lenses in situ to prevent visual acuity from affecting balance control.

Contrast sensitivity scores showed that all but nine SCA6 subjects could accurately detect relatively low contrasts (≤18) (table 3.5). All healthy control subjects were able to detect ≥18 contrasts.

Eighteen of twenty-one subjects with SCA6 were found to have visual pursuit of an object broken by multiple saccades. Of these, eleven subjects' saccades were rated as dysmetric, although on no occasion did eyeballs appear to be moving against resistance in the sockets (slow ++), as is sometimes the appearance of ocular movements in other types of SCA

(namely SCA2) [216]. Dysmetric eye movements generally involved initial overshooting of the target before re-focussing on the visual target of the researcher's open hand. Fifteen of twenty-one subjects were observed to have nystagmus and in fourteen of the fifteen cases, a downbeat component was detected. Healthy controls had no ocular movement abnormalities.

The pre-symptomatic subjects with SCA6 had relatively normal presentations of non-ataxia symptoms. On the initial testing day, subject 17 had only signs of mild muscle weakness. However, during the assessment in the final testing day, this subject was also found to have broken pursuit, dysmetric saccades and nystagmus with a downbeat component. Unfortunately subject 16 did not participate in the final testing session but had no non-ataxia signs or symptoms at the point of the initial testing day.

Table 3.4: Assessment of SCA6 group non-ataxia symptoms

Subj I.D.	Muscle power (TS)	Muscle power (TA)	ROM (R=L)	Light touch (R)	Light touch (L)	Vibration (R)	Vibration (L)	Joint position (R)	Joint position (L)	Tone (R=L)	Spasm	Reflex (R)	Reflex (L)	MMSE (/30)
1	5	5	FROM	10	10	19.7	20.3	1.0	1.0	1	0	1	1	26
2	5	5	-5˚D	10	10	13.6	11.7	1.0	1.0	1	3	2	2	29
3	5	5	FROM	8	10	26.9	37.1	1.0	1.0	1	2	0	0	30
4‡	5	5	-5˚D	10	10	n.t.	n.t.	1.0	1.0	1	0	2	2	29
5	5	5	FROM	10	10	13.9	15	1.0	1.0	1	2	2	2	27
6	5	4	-5˚D	10	10	13.1	17.8	1.0	1.0	2	0	3	3	26
7	5	5	-5˚D	10	10	15.2	22.2	0.3	1.0	1	0	3	3	30
8‡	5	5	-5˚D	10	10	n.t.	n.t.	1.0	1.0	1	0	2	2	26
9	4	4	FROM	10	10	19	27.2	1.0	1.0	2	0	1	1	27
10‡	5	4	-3˚D	7	10	n.t.	n.t.	0.7	0.7	1	0	1	1	28
11	5	5	FROM	10	10	26.9	37.1	1.0	1.0	2	0	2	2	30
12	5	5	-3˚D	7.5	10	20.2	11.3	1.0	1.0	1	1	0	0	30
13	4	4	FROM	10	10	8.5	8.1	1.0	1.0	1	0	1	1	29
14‡	5	5	-5˚D	10	10	n.t.	n.t.	0.8	0.8	1	2	3	3	30
15	5	5	FROM	10	10	31	30.5	1.0	1.0	1	2	2	2	30
16†‡	5	5	FROM	10	10	n.t.	n.t.	1.0	1.0	1	0	2	2	30
17†	4	4	FROM	10	10	13.6	12.8	1.0	1.0	1	0	2	2	30
18*	5	5	FROM	10	10	23	21	1.0	1.0	1	0	2	2	30
19*	5	5	FROM	10	10	20.2	18.9	1.0	1.0	1	0	2	2	30
20*	5	5	FROM	10	10	26.7	32.8	1.0	1.0	1	0	2	2	30
21*	5	5	FROM	10	10	19.2	18	1.0	1.0	1	0	2	2	30

Key: Muscle power TS = Rating triceps surae muscle power using the MRC scale; Muscle power TA = Rating tibialis anterior muscle power using MRC scale; ROM (R=L) = Assessing ankle range of movement (in all cases, right and left ankles were in all cases equal), FROM = Full range of movement, restrictions are indicated in degrees (D = dorsi-flexion); Light touch = Microfilament assessment, scored out of 10; Vibration = Biosthesiometer measures of vibration thresholds, averaged across all leg locations tested, re-tests and onset/off threshold readings; Joint position = Detection of hallux position, averaged across six position tests per toe; Tone = Rating of ankle tone using the Ashworth rating scale; Spasm = Rating of spasm frequency using the Penn spasm scales; Reflex = Rating of patella tendon reflex jerks; MMSE = Mini-mental State Examination total score. †='Pre-symptomatic' subjects. *= Subjects recruited for part two only. R = Right limb, L = Left limb. ‡= Subjects who did not participate in final session. n.t. = Not tested due to non-participation in final session.

Table 3.5: Assessment of SCA6 group visual non-ataxia symptoms

Subj I.D.	Visual field	Acuity (near R)	Acuity (near L)	Acuity (Keeler 3m)	Contrast	Saccade intrusions in pursuit	Slow ++ saccades	Saccade dysmetria	Hypermetric to target	Hypometric to target	Nystagmus	Downbeat
1	Full	3.2	3.2	0.33	15	Yes	No	Yes	Yes (rc)	No	Yes	Yes
2	Full	1.25	1	0.25	19	Yes	No	No	No	No	Yes	Yes
3	Full	1.25	1.25	0.67	18	Yes	No	No	No	No	Yes	Yes
4‡	Full	n.t.	n.t.	0.5	17	Yes	No	No	No	No	No	No
5	Full	0.4	0.4	0.33	18	Yes	No	Yes	Yes (rc)	No	Yes	Yes
6	Full	3.2	3.2	0.67	18	Yes	No	Yes	No	No	Yes	Yes
7	Full	1	2	0.25	17	Yes	No	Yes	Yes (rc)	No	No	No
8‡	Full	n.t.	n.t.	0.67	17	Yes	No	No	No	No	No	No
9	Full	2	3.2	0.67	18	Yes	No	Yes	Yes (rc)	No	Yes	Yes
10‡	Full	n.t.	n.t.	0.67	16	Yes	No	Yes	Yes (rc)	No	Yes	Yes
11	Full	1.25	1.25	1.00	19	Yes	No	Yes	Yes (rc)	No	Yes	Yes
12	Full	1.6	1.6	0.25	17	Yes	No	Yes	Yes (rc)	No	Yes	Yes
13	Full	1.25	1.25	0.67	17	No	No	No	No	No	No	No
14‡	Full	n.t.	n.t.	1.00	15	Yes	No	No	No	No	Yes	No
15	Full	0	0	0.25	17	Yes	No	Yes	Yes (rc)	No	Yes	Yes
16†‡	Full	n.t.	n.t.	0.67	19	No	No	No	No	No	No	No
17†	Full	0.5	0.4	0.67	18	No (Yes final day)	No	No	No (Yes final day)	No	No (Yes final day)	No (Yes final day)
18*	Full	2	2.5	0.67	18	Yes	No	Yes	Yes (rc)	No	Yes	Yes
19*	Full	2	1.6	0.25	18	Yes	No	Yes	Yes (rc)	No	Yes	Yes
20*	Full	6.3	6.3	0.33	19	No	No	No	No	No	No	No
21*	Full	3.2	4	0.25	18	Yes	No	No	No	No	Yes	Yes

Key: Visual field = Visual field assessment (full = no deficit); Acuity (near) = Rating of near vision acuity; Acuity (Keeler) = Rating of distance acuity; Contrast = Melbourne edge test score; Saccade intrusions in pursuit = Yes provided if pursuit is intruded by multiple saccades; Saccade dysmetria = Yes if eye movements are seen to over or undershoot a visual fixation target; Slow++ saccades = Yes if saccades are subjectively rated as extremely slow; Hypermetric saccade = Yes if subjects are observed over-shooting the target (r.c. indicates an observed fast recoil where subjects backtrack to reach the target); Hypometric saccade = Yes if subjects are observed undershooting the target. Nystagmus = Yes if observed. Downbeat = Yes if downbeat rapid phase jerk observed; †='Pre-symptomatic' subjects. *= Subjects recruited for part two only. R = Right limb, L = Left limb. ‡= Subjects who did not participate in final session. n.t. = Not tested due to non-participation in final session.

3.3.2 BALANCE SCORES

3.3.2.1 *The functional balance scale (FBS)*

Total functional balance scale scores revealed that the majority of SCA6 subjects encountered functional balance problems on testing (see table 3.6), unlike the HVS group where all subjects achieved a full score of 56/56. The SCA6 subjects' total FBS scores were reported as being normally distributed according to the one-sample Kolmogorov-Smirnov Test but sub-category ratings varied. The appropriate measure of group average and variance is reported according to sub-category in table 3.6.

Table 3.6 shows that as a group, subjects with SCA6 generally scored the lowest in the latter activities tested; standing on one leg (N), standing unsupported with one leg in front of the other (M), alternating placement of foot on step or stool while standing unsupported (L) and turning 360 degrees on the spot (K). More than half the subjects had some reduction in score with reaching (H) and head turning (J) activities s. The remaining activities were optimally scored by the majority of subjects (as represented by 4/4 mode values). However, sitting down remained the only functional activity which all subjects rated optimally (4/4).

Table 3.6: Overview of group functional balance scale scores taken during the first testing day

Subj. No.	A	B	C	D	E	F	G	H	I	J	K	L	M	N	Tot.
1	2	3	2	4	3	4	1	3	3	2	0	0	0	0	27
2	2	4	1	4	3	3	3	4	1	2	0	1	0	0	28
3	4	4	4	4	3	4	4	2	3	3	2	2	1	0	40
4	3	4	4	4	4	4	4	2	4	2	2	0	1	0	38
5	3	4	2	4	3	4	3	4	4	3	2	0	0	1	37
6	2	3	2	4	3	0	0	3	3	4	0	0	0	0	24
7	4	4	4	4	4	4	4	3	3	4	4	3	0	0	45
8	4	4	4	4	4	4	4	3	4	3	2	0	2	1	43
9	4	4	4	4	4	4	4	3	4	2	2	3	3	2	47
10	4	4	4	4	4	4	1	3	3	2	1	0	0	1	35
11	4	4	4	4	4	4	4	4	4	3	2	3	4	3	51
12	4	4	4	4	4	4	4	4	4	4	2	1	4	2	49
13	4	4	4	4	4	4	4	4	4	4	2	4	4	4	54
14	4	4	4	4	4	4	4	3	3	4	2	3	0	1	44
15	4	4	4	4	4	4	4	3	4	4	4	0	0	0	43
16†	4	4	4	4	4	4	4	4	4	4	4	4	4	4	56
17†	4	4	4	4	4	4	4	4	4	4	4	4	4	4	56
Distribution (K.S.T. Sig.)	NN (0.004)	NN (<0.001)	NN (0.001)	NN	NN (0.003)	NN (<0.001)	NN (0.006)	Norm (0.201)	NN (0.045)	Norm (0.103)	Norm (0.133)	Norm (0.231)	Norm (0.136)	Norm (0.292)	Norm (0.963)
Mean	3.5	3.9	3.5	4.0	3.7	3.7	3.3	3.3	3.5	3.2	2.1	1.6	1.6	1.4	42.2
SD	0.8	0.3	1.0	0.0	0.5	1	1.3	0.7	0.8	0.9	1.3	1.7	1.8	1.5	9.8
Mode	4	4	4	4	4	4	4	3	4	4	2	0	0	0	43
Median	4	4	4	4	4	4	4	3	4	3	2	1	1	1	43
Range	2:4	3:4	1:4	4:4	3:4	0:4	0:4	n.a.	1:4	2:4	0:4	0:4	0:4	0:4	24:56

Key for FBS assessment sub-categories: A=Sit to stand; B=Standing; C=Sitting; D=Sitting down E=Transferring between chairs; F=Standing eyes closed; G=Standing feet together; H=Reaching; I=Picking up an object from the floor; J=Looking over shoulders; K=Turning through 360 degrees; L=Stepping; M=Standing in tandem; N=Standing on one leg. Maximal score per category is 4. Total=Total sum of sub-scores (56/56=best functional balance score). †='Pre-symptomatic' subjects. Norm= Normal distribution, NN= Non-Normal distribution.

3.3.2.2 *The functional independence measure (FIM)*

Subjects with SCA6 were assessed to have FIM scores ranging between 113 and 126 at the point of the first assessment day (table 3.7). Total FIM scores were reported as normally distributed according to the one-sample Kolmogorov-Smirnov Test. The majority of subjects with SCA6 reported some lack of independence with transferring out of their bath or shower (K), walking (L) and mobilising on the stairs (M). Additionally, three subjects reported some lack of independence with generally transferring between chairs (I), two subjects with bathing (C), one subject with management of bowel function (G) and one subject was unable to independently manage communication (reportedly due to hand-writing problems, O).

Functional independence measure scores for the group of SCA6 subjects ranged between 110 and 126 of a maximal 126 during the final testing day (see table 3.8). Similar to the results gained from the initial testing day group, the majority of subjects with SCA6 reported some lack of independence with transferring out of their bath or shower (K), walking (L) and mobilising on the stairs (M). Additional lack of independence with eating (A) was reported by one subject. Three subjects reported some loss of independence with bathing (C). One subject reported loss of independence with bowel management (G). Two subjects reported loss of independence with socialising (P) and one with communicating (O).

Longitudinal changes

Group mean functional independence scores dropped by one point between the first and final testing day ([first mean (SD): 122.2(3.1)], [final mean (SD):.121.2(5.0)], table 3.3). Calculations of change in FIM score per year gave a mean value of -0.7 (SD 2.5) but confidence limits (low= -2.3: high= 0.9) of the mean change in score spanned zero suggesting that this measure could represent no change. No significant difference was reported between scores at baseline and one year later (t=-1.0, p=0.360).

Table 3.7: Overview of group functional independence measure scores for the initial testing day

Subj. No.	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	Total score
1	7	7	5	7	7	7	7	7	5	7	5	4	5	7	7	7	7	7	115
2	7	7	7	7	7	7	7	7	6	7	6	6	6	7	7	7	7	7	122
3	7	7	7	7	7	7	7	7	7	6	6	6	6	7	7	7	7	7	122
4	7	7	4	7	7	7	7	7	7	7	2	6	6	7	4	7	7	7	113
5	7	7	7	7	7	7	7	7	7	7	7	6	6	7	7	7	7	7	124
6	7	7	7	7	7	7	6	7	7	7	6	5	6	7	7	7	7	7	121
7	7	7	7	7	7	7	7	7	7	7	7	6	6	7	7	7	7	7	124
8	7	7	7	7	7	7	7	7	7	7	6	6	6	7	7	7	7	7	123
9	7	7	7	7	7	7	7	7	7	7	7	4	2	7	7	7	7	7	118
10	7	7	7	7	7	7	7	7	7	7	7	6	6	7	7	7	7	7	124
11	7	7	6	7	7	7	7	7	6	7	7	6	6	7	7	7	7	7	122
12	7	7	7	7	7	7	7	7	7	7	6	7	6	7	7	7	7	7	124
13	7	7	7	7	7	7	7	7	7	7	6	6	6	7	7	7	7	7	123
14	7	7	7	7	7	7	7	7	7	7	7	4	6	7	7	7	7	7	122
15	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	126
16†	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	126
17†	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	126
Distribution (K.S.T. sig)	NN	NN	NN (0.001)	NN	NN	NN	NN (<0.001)	NN	NN (0.001)	NN (<0.001)	Norm (0.080)	NN (0.045)	NN (0.004)	NN	NN (<0.001)	NN	NN	NN	Norm (0.207)
Mean	7	7	6.6	7	7	7	6.9	7	6.8	6.9	6.2	5.8	5.9	7	6.8	7	7	7	122.1
SD	0	0	0.9	0	0	0	0.2	0	0.6	0.2	1.3	1.3	1.1	0	0.7	0	0	0	3.6
Mode	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	122
Median	7	7	7	7	7	7	7	7	7	7	7	6	6	7	7	7	7	7	123
Range	7:7	7:7	4:7	7:7	7:7	7:7	6:7	7:7	5:7	6:7	2:7	4:7	2:7	7:7	4:7	7:7	7:7	7:7	113:126

Key for FIM assessment sub-categories: A=Eating; B=Grooming; C=Bathing; D=Dressing upper body; E=Dressing lower body; F=Toileting; G=Management of bowel function; H=Management of bladder function; I=Transferring; J=Transferring on/off toilet; K=Transferring in/out bath/shower; L=Walking; M=Mobilising on the stairs; N=Understanding communication; O=Communicating; P=Socialising; Q=Problem-solving; R=Memory; Total=Total sum of sub-scores (126/126=best functional independence rating). †='Pre-symptomatic' subjects. Norm= Normal distribution, NN= Non-normal distribution.

Table 3.8: Overview of group functional independence measure scores for the final testing day

Subj. No.	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	Total score
1	7	7	6	7	7	7	7	7	7	7	6	6	4	7	7	7	7	7	120
2	7	7	7	7	7	7	7	7	7	6	6	6	6	7	7	7	7	7	122
3	7	7	7	7	7	7	7	7	7	7	7	3	6	7	7	7	7	7	121
11	7	7	7	7	7	7	7	7	7	7	6	6	6	7	7	7	7	7	123
5	7	7	7	7	7	7	7	7	7	7	6	6	6	7	7	7	7	7	123
6	6	7	7	7	7	7	6	7	7	7	6	4	6	7	7	1	7	7	113
9	7	7	5	7	7	7	7	7	7	7	5	2	6	7	4	4	7	7	110
8	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	126
18*	7	7	7	7	7	7	7	7	7	7	7	6	6	7	7	7	7	7	124
13	7	7	6	7	7	7	7	7	7	7	6	4	6	7	7	7	7	7	120
19*	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	126
12	7	7	7	7	7	7	7	7	7	7	7	6	7	7	7	7	7	7	125
20*	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	126
21*	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	126
15	7	7	7	7	7	7	7	7	7	7	7	7	6	7	7	7	7	7	125
17†	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	126
Distribution (K.S.T. sig.)	NN (<0.001)	NN	NN (0.001)	NN	NN	NN	NN (<0.001)	NN	NN	NN (<0.001)	NN (<0.042)	Norm (0.063)	Norm (0.091)	NN	NN (<0.001)	NN (<0.001)	NN	NN	Norm (0.454)
Mean	6.9	7	6.8	7	7	7	6.9	7	7	7	7	5.7	6.3	7	6.8	6.4	7	7	122.3
SD	0.3	0	0.6	0	0	0	0.3	0	0	0	0	1.6	0.8	0	0.8	1.6	0	0	4.7
Mode	7	7	7	7	7	7	7	7	7	7	7	6	6	7	7	7	7	7	126
Median	7	7	7	7	7	7	7	7	7	7	7	6	6	7	7	7	7	7	123.5
Range	6:7	7:7	5:7	7:7	7:7	7:7	6:7	7:7	7:7	6:7	5:9	3:7	4:7	7:7	4:7	1:7	7:7	7:7	110:126

Key for FIM assessment sub-categories: A=Eating; B=Grooming; C=Bathing; D=Dressing upper body; E=Dressing lower body; F=Toileting; G=Management of bowel function; H=Management of bladder function; I=Transferring; J=Transferring on/off toilet; K=Transferring in/out bath/shower; L=Walking; M=Mobilising on the stairs; N=Understanding communication; O=Communicating; P=Socialising; Q=Problem-solving; R=Memory; Total=Total sum of sub-scores (126/126=best functional independence rating). †='Pre-symptomatic' subjects. *= Newly recruited subjects (did not participate in testing session 1. Norm= Normal distribution, NN= Non-normal distribution.

3.3.2.3 *Fall frequency and fall behaviour*

Healthy control subjects had not incurred any falls prior to either testing day but seven of seventeen subjects with SCA6 fell over the course of one month prior to the initial testing day (table 3.9). Fall frequency data was reported to be normally distributed according to the Kolmogorov-Smirnov Test (sig. 0.077, mean 1.2, SD 2.5).

The seven different subjects collectively reported twenty-one falls. All falls took place within subjects' own homes; seven took place on level ground in subject's homes, six as a result of attempting to get up and out of a chair, three trying to get on or off of the toilet and five in the garden (not associated with curbs or tripping over obstacles). Subjects reported that on most occasions falls were caused by loss of balance but on isolated occasions they were also due to slips, trips and "not coordinating their legs and body upon turning too quickly". Of these falls, six were injurious causing bruises and a skin laceration in one case. Of the fallers, all reported using flat shoes indoors and outdoors to help prevent falling. Although all subjects independently walked ten metres in order to be included in the study, seven fallers preferred to use mobility aids in the home, ranging between use of furniture to use of one or two walking sticks. Outdoors, all but one faller used walking aids ranging between one walking stick, two walking sticks, two crutches and a wheeled rollator. Of the sub-group of fallers, six of seven were taking medication for problems not related to ataxia, including high blood pressure, depression and urinary incontinence. Two of the seven subjects were taking four or more different medications, a known predictor of falls in the elderly [(212)].

Table 3.10 summarises fall behaviour over the month prior to the final testing day. From this questionnaire it was possible to see that nine of sixteen subjects with SCA6 fell over the course of one month prior to the initial testing day. According to the One-Sample Kolmogorov-Smirnov Test, fall frequency data is normally distributed (sig.= 0.587) with a mean subject fall frequency of 1.9 and a standard deviation of 2.1.

In comparing group totals between the first and last assessment days (totals in tables 3.5 and 6), it is possible to see that the final assessment day included more fallers, a larger total number of falls but decreased incidence of injuries following falls. There is also an increased use of indoor and outdoor mobility aids reported by subjects. In comparing individual subject responses between initial and final testing days, it is interesting to note

that three previous fallers from the initial testing day did not report falls on the subsequent day, although one previous faller had dropped out. Five subjects with SCA6 who had dropped out were replaced with four new subjects, of which three reported falls (new subjects are marked with asterisks against their subject I.D. in table 3.6 to ensure clarity of group changes).

Of the thirty falls reported by nine subjects during final testing days, twenty-five took place within subjects' own homes; fourteen took place on level ground indoors, two as a result of attempting to get up and out of a chair, two walking up and down stairs, five over level ground in the garden, one going down a garden step and one in a garage (not associated with tripping over obstacles). Falls also occurred outside of the home; twice on level ground in another person's home, by the poolside on holiday, getting out of a car and on an underground train. The majority of known causes of falls were reported as loss of balance. Subjects also reported one fall caused by a slip of crutches and one due to loss of balance following visual distraction. Three falls were reportedly due to trips on carpet and a curb and two falls were reported by two subjects as due to "not coordinating their legs and body…" "when setting off walking" and "when getting up from a chair".

Of the thirty falls reported in the second session, only four were injurious. All four involved bruises and one a cut to the head, which required hospital treatment. Of the fallers, all reported using flat shoes indoors and outdoors to help prevent falling. Five of the nine fallers preferred to use mobility aids in the home, ranging from furniture to 1-2 walking sticks. Outdoors, seven fallers used walking aids ranging from one walking stick to a wheeled rollator. Six of nine fallers reported regularly taking medications, two of which took more than four different types of medication. All fallers wore flat shoes indoors and out in an attempt to prevent falling. All subjects questioned believed that they would fall more frequently if they did not take care to avoid falling whilst mobilising.

Three fallers had undertaken physiotherapy within the last year involving stretching (subject 2) and balance exercise (subjects 6 and 9). One faller had independently started to attend an exercise class at the local gym. No other fallers or non-fallers had undertaken any form of balance exercise or physiotherapy between the first or final testing day.

Longitudinal changes

Mean fall frequencies did not change between the first testing day (mean 1.8, SD 2.8) and the final testing day (mean 1.8, SD 2.3). Calculations of change in fall frequencies over time produced a statistically mean value of 0.1 (SD 1.5) (baseline vs 1 year t=2.3, p=0.046). No significant correlation was however reported between subject's initial testing day fall frequency and one year equivalent change in fall frequency scores (r=-0.438, p=0.155).

*3.3.2.4 **Body sway***

Mean measures of trunk and centre-of-pressure sway speeds (mm/s) derived from forty-second collections, involving subjects standing face forward with their feet spaced 4cm apart and vision available, remained of a similar magnitude between testing days one and two ([trunk sway: TD1 mean= 12.6, SD= 6.6; TD2 mean=12.4, SD=7.5], [CoP sway: TD1 mean= 20.0, SD= 9.7; TD2 mean= 18.2, SD= 13.9], table 3.3). Calculations of change in sway speeds (mm/s) over time produced a mean value of -0.2 (SD 4.7) for trunk sway and -1.3 (SD 7.3) for CoP sway. Despite small changes in mean values, t-test results report no significant statistical differences between initial testing day sway speeds and one year later ([trunk sway: t= -1.1, p= 0.917], [CoP sway: t= -0.6, p= 0.534]).

Table 3.9: Overview of initial testing day fall frequencies and behaviour

Subj. No.	SARA score	Fallen	Freq	Injurious	Indoor mobility aid	Outdoor mobility aid	Taking meds	Taking ≥4 Meds
1	16.5	Yes	2	Yes	Yes	Yes	Yes	No
2	15	Yes	10	Yes	No	Yes	Yes	Yes
3	14	No	0	No	No	No	No	No
4	13.5	No	0	No	No	No	No	No
5	13.5	Yes	1	Yes	Yes	Yes	No	No
6	13	Yes	3	Yes	No	No	Yes	No
7	11	Yes	1	No	Yes	Yes	Yes	No
8	10	No	0	No	No	No	No	No
9	9.5	No	0	No	No	No	No	No
10	9.5	No	0	No	No	No	No	No
11	7	Yes	1	Yes	Yes	Yes	Yes	Yes
12	5.5	No	0	No	No	No	No	No
13	5	Yes	3	Yes	No	Yes	Yes	No
14	3.5	No	0	No	No	No	No	No
15	1.5	No	0	No	No	No	No	No
16†	1.5	No	0	No	No	No	No	No
17†	0	No	0	No	No	No	No	No
Total 'yes' or no. of falls:		7	21	6	4	6	5	2

Key: †= 'Pre-symptomatic' subjects.

Table 3.10: Overview of final testing day fall frequencies and behaviour

Subj. No.	SARA score	Fallen	Freq	Injurious	Indoor mobility aid	Outdoor mobility aid	Taking meds	Taking ≥4 Meds
1	22	No	0	No	Yes	Yes	No	No
2	20.5	Yes	4	Yes	Yes	Yes	No	No
3	17	Yes	2	No	Yes	Yes	No	No
11	17	No	0	No	No	No	No	No
5	17	No	0	No	No	No	No	No
6	14	Yes	6	Yes	No	No	Yes	No
9	13	Yes	6	Yes	Yes	Yes	Yes	Yes
8	13	No	2	Yes	No	No	No	No
18*	12	Yes	1	No	Yes	Yes	Yes	No
13	11	Yes	2	No	Yes	Yes	Yes	Yes
19*	9.5	Yes	3	No	No	Yes	Yes	No
12	9.5	Yes	1	No	No	Yes	No	No
20*	7	No	0	No	No	No	No	No
21*	6	Yes	3	No	No	No	Yes	No
15	3	No	0	No	No	No	Yes	No
17†	0	No	0	No	No	No	No	No
Total 'yes' or no. of falls:		9	30	4	6	8	6	2

Key: †= 'Pre-symptomatic' subjects. *= Subjects recruited only for testing day 2.

3.3.3 Correlations

The scale for assessment and rating of ataxia provides an already validated measure of disease severity against which it is possible to contrast functional and balance impairment scores. Pearson's correlation coefficients calculated between SARA scores and clinical scores (from the functional balance scale, functional independence measure, fall frequency and sway measures) are displayed in table 3.11. Correlations between Bal-SARA and clinical scores were also explored in order to investigate whether the Bal-SARA could be a simple indicator of balance dysfunction. Correlations have been explored by averaging across scores from the first and final testing days for the twelve subjects who participated in both days, and using the single values obtained from the nine subjects who were tested on a single occasion.

Table 3.11: Correlations between clinical and sway measures

Measure	Bal-SARA	FBS	FIM	Fall frequency	Trunk sway	CoP sway
SARA	0.888 (<0.001)	-0.796 (<0.001)	-0.471 (0.006)	0.321 (0.068)	0.686 (<0.001)	0.750 (<0.001)
Bal-SARA	1	-0.731 (0.001)	-0.393 (0.024)	0.170 (0.345)	0.746 (<0.001)	0.614 (<0.001)

Key: Above entries show Pearson's correlation coefficients and corresponding p-values in brackets.

As outlined in table 3.11 and visually presented in figure 3.1 scatter plots with lines of best fit, strong correlations were reported between total SARA scores and functional balance scale scores as well as trunk and centre-of-pressure sway measures (figure 3.1a,d,e, left column).

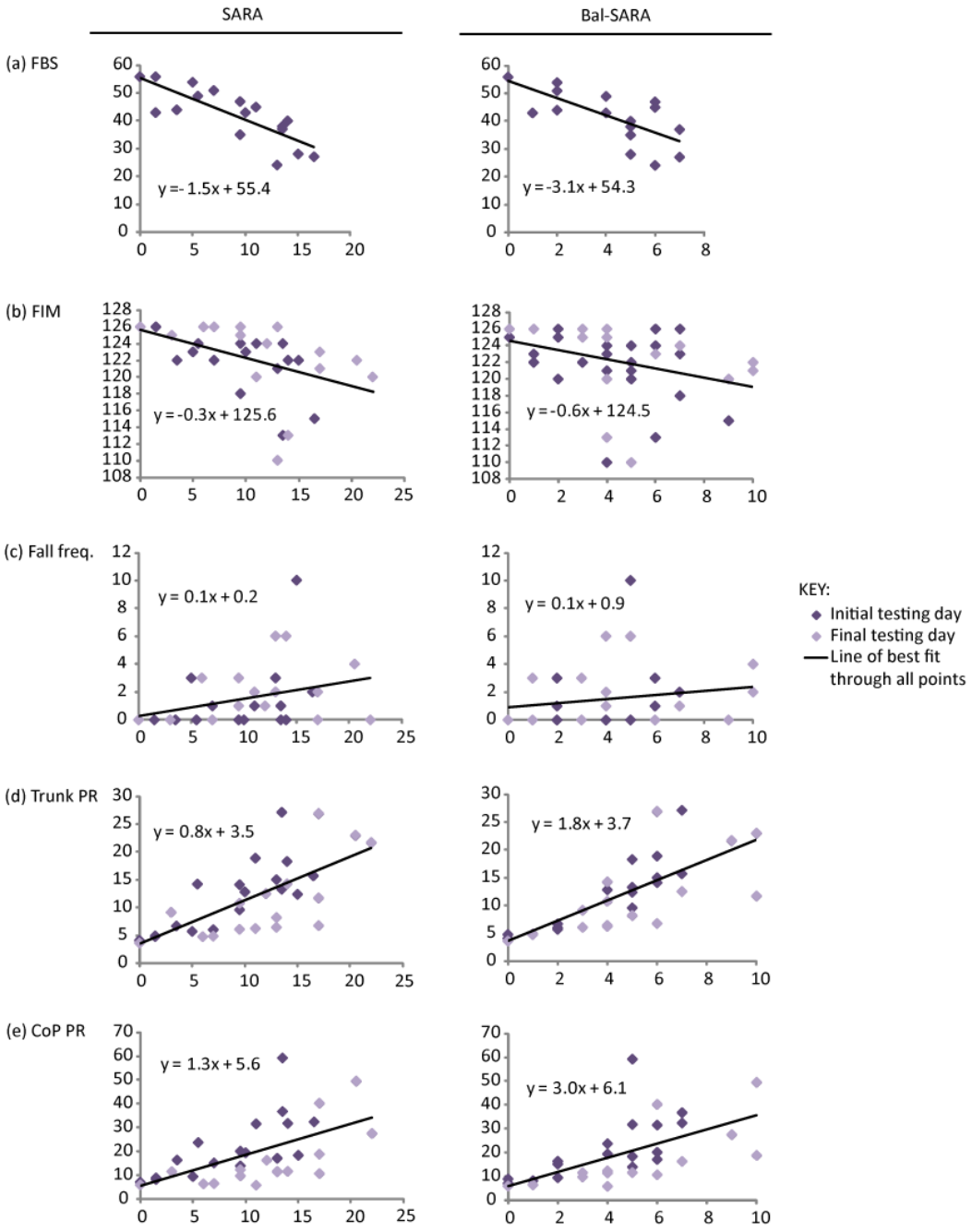


Figure 3.1: Relationships between ataxia severity scores and balance assessment scores.
The left column compares all assessment scores against total SARA scores. The right column compares assessment scores against just balance related sub-scores of the SARA; the 'Bal-SARA' score. Non-ataxia assessment score types are ordered into rows and labelled to the left (a-e). The colour intensity of the markers in each plot refers to which testing day individual scores were derived from, described in the key. Equations of the line of best fit have been added to indicate the average rate of decline in score relative to ataxia severity decline.

Similar strong correlations were reported when using just balance related sub-scores of the SARA (figure 3.1a,d,e, right column). Measures of functional independence also weakly correlated with SARA and Bal-SARA scores (figure 3.1b).

Visual inspection of fall frequency scores scatter-plotted against SARA or Bal-SARA scores appears to show a trend for fall frequency to increase with increasing SARA score (outlined by the positive gradient of the line of best fit in scatter plots (figure 3.1c).

However, fall frequency measures did not significantly correlate with SARA or Bal-SARA scores. In order to determine if the inclusion of non-fallers in the analysis could affect correlation strength, this was repeated using only nine fallers. Correlations between disease severity scores and fall frequencies for fallers only remained weak and statistically not significant (SARA: r= 0.278, p=0.280).

3.4 Discussion

This chapter set out to describe the relationship between disease characteristics and balance impairment.

In doing so it has contributed to the body of knowledge of SCA6 physical and functional impairments. In addition to describing disease and balance characteristics this study provides new knowledge concerning disease progression from a longitudinal examination of disease severity, balance impairment, function and falling behaviour.

The structure of this discussion will be organised around the questions set out in the introduction:

- **What is the nature of the relationship between disease severity and balance?**
- **What are the functional consequences of balance impairment?**
- **Does our sample exhibit any significant non-ataxia signs and symptoms which could affect balance?**
- **How suitable are balance outcome measures as future measures of longitudinal change and treatment effects?**

3.4.1 What is the nature of the relationship between disease severity and balance?

In agreement with prior reports, positive scores for the SARA revealed widespread signs of balance impairment in SCA6. These findings support previous reports describing gait and balance difficulties as common features of SCA6 [99,115,160].

A linear relationship was found to exist between total SARA and Bal-SARA (balance only SARA ratings) scores, suggesting that balance impairment increases with an increase in overall measures of ataxia.

Since balance impairment is often reported as the main clinical feature of those with SCA6 it seems logical that such a relationship between disease severity and balance scores would be observed. Therefore the correlation and linearity between SARA and Bal-SARA scores may not be observed for other SCA types and transferability of this finding

potentially limited.

SARA scores also correlated with functional balance scale scores (FBS), functional independence measure (FIM) scores, trunk sway and centre-of-pressure (CoP) speeds. Collectively these correlations suggest a close relationship between balance and disease severity, which acts to support the assumption that SCA6 disease pathology causes balance impairment.

Bal-SARA scores were also correlated with other clinical scores in order to determine if this score could provide a better measure of balance impairment than total SARA scores. If so, the Bal-SARA would provide clinicians with a fast, convenient method of assessing balance which could advise the need for physiotherapy referrals or perhaps even the risk of falls.

Correlations between Bal-SARA, FBS scores and sway measures were moderately strong and statistically significant but generally weaker than total SARA score correlations. Correlations between Bal-SARA and FIM scores or fall frequencies did not reach the level of statistical significance. Trunk sway speeds were the sole balance measure which produced a stronger correlation with Bal-SARA than total SARA scores.

These findings support the use of the Bal-SARA as an indicator of balance impairment but not general function. Bal-SARA scores do not appear to predict fall frequency but given that faller subjects possessed Bal-SARA scores upwards of 1, we could infer that a positive Bal-SARA score could be used as an indicator of increased risk of falling. These findings also pose three main questions, which could be addressed in future studies: Firstly, could the inclusion of more 'coordination' related ratings in total SARA scores produce stronger correlations with balance measures and thus point to a coordination rather than sensory control problem affecting balance? Secondly, could the limited range in scoring for the Bal-SARA (maximum score: 18) relative to the total SARA score (maximum score: 40) be responsible for the majority of weaker correlations observed? Thirdly, why would Bal-SARA scores correlate more closely with trunk sway but total SARA score more closely correlate with centre-of-pressure equivalents?

3.4.2 What are the functional consequences of the disease?

Scores obtained using the Functional Balance Scale (FBS), the Functional Independence Measure (FIM) and a fall questionnaire provide new information with regards to how SCA6

cerebellar disease affects function.

In agreement with prior reports, positive scores for the FBS and FIM revealed widespread signs of balance impairment and dysfunction in SCA6 subjects. The SARA is also instrumental in rating some functional activity (standing, sitting, walking).

Global functional balance scores calculated from FBS ratings are reduced for all SCA6 subjects rated as ataxic (defined by any SARA score above zero). For this reason the FBS could be a useful outcome measure for therapists in the clinical setting. According to the FBS, SCA6 subjects pointed to difficulties with all tested functional activities reliant on balance with the exception of sitting down.

Given the relationship between SARA and FBS scores, the SARA may provide an indication of functional balance in SCA6 but the FBS has the potential to have greater specificity. Assessments of standing balance as part of the Scale for the Assessment and Rating of Ataxia revealed that all but eight subjects had some degree of standing balance impairment. FBS assessment of standing with the eyes open or closed detected fewer subjects with standing balance difficulties than the SARA (three subjects). The main difference between the two scales rating criteria being that the SARA uses different specified feet positions to determine the overall score, whereas the FBS takes an overall measure of standing balance where the subjects may stand with their feet in any position. The FBS goes on to rate balance with the feet together and in tandem as separate categories. Subjects were said to have experienced difficulties if they could not fully satisfy the requirements of the task. In this case, subjects would produce a reduction in score according to the definition of scoring criteria per category. Assessment of feet-together standing identified five subjects (of seventeen) who experienced difficulties. Eleven subjects were rated as experiencing difficulties with tandem standing and fifteen of seventeen were unable to independently stand on one leg for more than three seconds. These findings suggest that stance width may be a critical factor in determining the severity of balance impairment, which will be investigated alongside quantification of standing balance in chapter 4.

Assessment of gait impairment contributed the highest group mean rating of all SARA sub-categories (where increasing positive scores for this scale indicate increasing impairment). According to the SARA, all but the two ‘pre-symptomatic’ subjects were found to have some difficulty with gait, ranging from not being able to walk and turn in tandem to

requiring strong assistance to mobilise during a ten-metre walk. Gait abnormalities in ataxia have been well described and attempts have been made to quantify them, although these attempts have not yet specifically targeted those with SCA6 [104,160,254,256,255,351]. Despite these studies the cause of gait impairments remains undetermined. Like balance, they could be a consequence of poor processing of sensory signals or of movement in-coordination due to problems with joint torque control [160,161]. The FBS does not directly rate gait but does rate subjects turning through 360˚ on the spot and stepping, which could be said are both important activities involved with walking. According to FBS ratings, thirteen out of seventeen SCA6 subjects had problems turning through 360˚. Fourteen of seventeen subjects were rated as experiencing problems with stepping (eight steps up and down with alternate foot placement using a small step). FBS ratings also indicated problems with dynamic forms of functional balance such as picking up an object from the floor, reaching, looking over shoulders and transferring between chairs.

Difficulties maintaining sitting balance contributed towards the lowest SARA and highest FBS scores (i.e. appeared to be the least difficult tasks of both assessment tools). Only the three most severely affected subjects (according to total SARA score) were rated as having impaired sitting balance, ranging from involving intermittent sway to constant sway present when subjects were unsupported. The functional balance scale once again uses slightly different rating criteria to that of the SARA, namely it asks subjects to fold their arms rather than have them outstretched and assesses safety and independence with the task over a maximum of two minutes. Using these criteria, four rather than three subjects were assessed as having sitting balance impairments.

In addition to ratings of activity from SARA and FBS assessments, dysfunction can also be inferred from self-reported falling and decreased functional independence scores. From fall questionnaire responses we are able to learn that more than half of SCA6 group subjects (with symptoms of ataxia) fell in the month prior to either testing day. This suggests that even individuals with mild ataxia are at risk of falling in line with recent findings from other fall studies [115]. Furthermore, according to the functional independence measure, the majority of subjects reported requiring help with mobility. Fall questionnaires provided further information regarding the nature of this help, which ranged from furniture and sticks to wheeled rollators.

Reductions in other FIM scores include loss of independence with transferring between

chairs, on and off a toilet and in and out of a bath or shower, all of which could be consequences of balance dysfunction. After walking, the next most severe loss of independence was reported with mobilising on the stairs. Loss of independence with stair mobility could be due to balance dysfunction, but could also be due to subject's avoiding independent use of stairs due to loss of confidence and fear of falling.

Collectively these findings suggest that balance is clearly impaired in subjects with SCA6, with direct impacts on physical and social functioning. These findings support a plethora of studies which have reported balance dysfunction for a wider population of types of ataxia [22,23,51,103,160,197,251,255,272,351,374]. This knowledge of dysfunction in SCA6 may significantly contribute to the design of future targeted balance therapies.

3.4.3 Does our sample exhibit any significant non-ataxia signs and symptoms which could independently affect balance?

In agreement with prior reports of clinical features of SCA6, our sample had few non-ataxia symptoms [75,115,158,325,375].

Measures of muscle weakness and range of movement revealed only mild impairments in less than half the sample. Signs of reduced sensation to light touch and joint position sense were present in three of twenty-one subjects and scores remained only mildly deviated from normal. Work by Butler *et al.* [57] has previously linked muscle weakness with proprioceptive loss but the incidence of just three subjects with both signs here is not sufficient to contribute further support for this finding.

Central nervous system signs of increases in tone and reflex gain were equally scarce (affecting 3 of 21 subjects). Despite widespread reports of associations between increased tone and cerebral cortex lesions, numerous other pathologies, emotion, pharmaceuticals or even external cutaneous stimuli can alter reflex gains or change muscle and connective tissue visco-elasticity to ultimately affect tone [200,288]. Without more sophisticated electrophysiological tests, the causative nature of these signs remains largely unknown. However, the mere existence of these signs using relatively crude clinical tests point to the presence of extra-cerebellar pathology with the potential to affect balance.

Increases in tone, for example has the potential to impair balance through altered reflex gains or changes in intrinsic properties of joints. Support exists for the idea that increased imbalance can result from intrinsic stiffness in musculature controlling joints such as the ankles [395]. Yet ankle stiffness alone is not sufficient to control ankle torque for upright

standing [207], which in turn implies support for ideas that reflex mechanisms of control or ballistic activity at joints such as the ankle or hips have the potential to affect balance [111,123,207]. Further support for the idea that changes in tone could affect balance in those with ataxia comes from the study by Oude Nijhuis *et al*. where correlations were found between measures of knee stiffness and impaired measures of balance. This study did use subjects with SCA6 but they formed only part of a mixed group of subjects with SCA. As a consequence some uncertainty regarding the nature of these changes (i.e. intrinsic or reflex) and their physiological cause (i.e. cerebellar or extra-cerebellar disease pathologies) remains [271].

Balance behaviour may also be directly affected by intrusion of spasms [336]. Electro-myography studies certainly support the theory that spasms can cause disrupted lower limb muscle contractions, which in turn could affect balance if subjects are standing [336]. Although spasms are generally felt by individuals, they can also go un-noticed, meaning that measures of sway speeds derived from experimental methods may unknowingly incur bias from spasm [336].The Penn spasm scale proved to be a quick and simple tool which allowed easy identification of those subjects who are affected by spasms, of which there were five subjects. In all subsequent testing of balance, these subjects were asked to let the researcher know if they experience any spasms. However, subjects did not report spasms at any point during testing. Subjects experiencing spasms were not those with either the highest disease severity or most severe measures of impaired balance or function.

Disrupted afferent proprioceptive signals from cutaneous receptors (due to peripheral nerve or spinal cord damage) could also impair balance. This could be due to disrupted propagation of initial sensory afferents encoding balance perturbations or re-afferent signals providing feedback with regards to whole body balance responses [83,109,112,147,156,211]. The most extreme consequence of proprioceptive loss on balance control can be seen in a paper by Day *et al*. studying balance in a subject with almost total proprioceptive loss [83].

If changes in intrinsic tone, reflex behaviour or cutaneous sensation for these subjects were to affect balance behaviour, we can expect to see a difference in whole body responses following balance perturbations between these sub-samples of subjects and the remainder of the group in chapters 4 and 5. However, differences may not be obvious

given the relatively mild nature of the extra-cerebellar signs. Differences in sub-groups of SCA6 subjects will be explored further after analysing group static and perturbed standing balance behaviour if between-subject variability is particularly high (chapters 4-6).

Vision and oculo-motor abnormalities

Visual abnormalities were consistent with prior reports from studies investigating vision in those with SCA6 [75,129]. Nystagmus and impairment of pursuit were present for the majority of subjects [58,68,129,203,232,402]. Nystagmus was most prominent at end-range lateral eye positions ("gaze-evoked nystagmus"). According to the theory proposed by Mackay and Murphy, end range eye in socket position is most likely to reveal signs of fixation control problems because extra-ocular musculature is involved in countering the highest visco-elastic forces caused by antagonist muscle and soft-tissue stretch [218]. The nature of the nystagmus was primarily horizontal and downbeat. This finding seems consistent with the literature, which suggests that downbeat nystagmus may be a characteristic oculomotor feature of SCA6 [400,402]. Since all but three subjects exhibited signs of nystagmus and there was no way of quantifying this finding, it is not possible to meaningfully correlate these findings with laboratory derived or clinical balance measures. However, given that vision has a major role in balance control and a recent study has suggested an association between nystagmus and balance impairments [171], this may be an interesting area to explore in future investigations of oculo-motor control of balance.

Saccade speed appeared grossly normal but saccades hypermetric. This is another result in support of the existing literature [58] althoughsome prior investigations of subjects with SCA6 have reported slow saccades [68,129,203,232] this would not have been possible to rate to the assessors naked eye. Use of an eye tracking device would have been preferable but this was not available for this purpose. Pursuit of an object was seen to be slowed in a clear majority of subjects (eighteen of twenty-one). Pursuit is also difficult to rate clinically but in the case of these subjects, visible catch-up saccades (broken pursuit) were present acting as clear signs of compensatory activity for initial slow pursuit speeds [89,90,91]. Findings of slowed pursuit provides further support for the emerging evidence base for this being not only a common feature of cerebellar disease [124] and a characteristic feature SCA6 [68]. Object pursuit is clearly of importance for recognition of moving objects [218] but pursuit also plays an important role in informing individuals of self-motion relative to

moving objects [387,391]. Given these findings and prior reports that SCA6 subjects report difficulties with visually busy environments [345], it may be interesting to investigate this sign further relative to balance control. Chapter six of this thesis will explore the effects that a moving visual scene has on upright standing. In healthy controls pursuit of moving scenery causes a perceived balance perturbation to which whole body responses occur. The moving visual scene will deliver optic flow to the retina and it is assumed that ocular pursuit of the display will occur as a result. Given that pursuit is slowed, responses elicited in SCA6 subjects MVS may also be slowed as a consequence. Perhaps whole body motion will also involve a 'catch-up' latter response, as is the case with the ocular scenario of catch up saccades. These ideas will be discussed in more detail in chapter 6.

Contrast sensitivity was in eight cases very slightly reduced compared to the predicted normal score of ≥18. Impairments in contrast sensitivity have not been reported in those with SCA6 to date. However, since impaired contrast sensitivity has been linked to decreased balance [399]and increased risk of falling in the elderly[208,209], this finding may warrant future investigation. Theoretically, reduced contrast sensitivity could reduce the quality of information available to provide visual awareness of self-motion for balance thus increasing sway. Although reduced contrast sensitivity is traditionally associated with age-related changes in pathology [208] and conditions such as cataracts or diabetic retinopathy [88,300], this finding could be explained by the oculo-motor impairments observed in our sample. By testing subjects sitting on a plinth, natural sway could require subjects to make multiple eye movements during their attempts to detect contrast lines of shaded semi-circles. If oculo-motor impairments are unable to optimally maintain gaze on target due to sway, perhaps this could cause problems with detection of subtle information such as contrast. Until further information is gained regarding the nature of reduced contrast sensitivity in SCA6, investigations of the role of vision in balance control should involve high contrast and moving visual environments.

Despite the significant oculo-motor impairments affecting the majority of the sample, all subjects had full visual fields and a normal range of visual acuity, which was in all cases corrected with lenses. If self-sway motion was responsible for contrast abnormalities we may expect the same abnormalities to exhibit in measures of acuity, which was not the case. This may refute the idea that sway could affect contrast sensitivity, or the different nature of the tasks (object recognition versus identifying contrast) could be responsible for

the discrepancy and could perhaps point to underlying visual processing impairments in SCA6.

Could non-balance related measures of ataxia impact on balance control?

Activities such as walking, transferring, reaching, picking up an object from the floor and stepping form significant parts of the functional balance scale. However, the problems observed with these activities could be caused by un-coordinated movements rather than balance dysfunction [103,160,254,255,363]. 'Ataxia' is derived from the Greek *'a'+'tassein'* literally meaning an inability to put in order or un-coordinated [29,249]. Mechanisms underpinning in-coordination of movement has long been investigated in subjects with ataxia. These investigations are well described in a review by Bastian [29] and a more recent review with a focus on locomotion by Morton and Bastian [256]. These reviews highlight two potential different causes of ataxia which can manifest with in-coordinated movement; 'sensory ataxia' and 'cerebellar ataxia' [29]. Regardless of whether sensory system damage or cerebellar damage is responsible for ataxia, Morton and Bastian report that in-coordinated movement results from mis-timing of muscle activity and unbalanced joint torques across multiple joints contributing towards a movement. When movement then becomes function, i.e. walking, a subject is seen to have short, irregular strides that are unequal in length and timing [256]. In some cases subjects are seen to widen their stance width or decompose movement (limit the number of joints actively involved in the movement) [22,103,160,256,318], which are thought to be compensatory strategies designed to optimise coordination [22,256].

Lower limb coordination was specifically assessed in the SARA using a heel-shin slide, which was found to be abnormal in all but four subjects tested. Ratings ranged from foot-shin contact being slightly irregular to being clearly irregular through four losses of contact in three attempts. Despite a range of SARA ratings indicating lower limb in-coordination, self-rated functional independence scores for dressing the lower half of the body indicated no loss of independence. On face value it could be interpreted that subjects with SCA6 experience no difficulties with this task but equally it could be due to subjects adopting different methods of dressing, perhaps involving less standing but no assistance or use of aids.

Upper limb in-coordination is not specifically assessed as part of the SARA but measures taken of rapid hand turn movements (assessing dysdiadochokinesia) and pointing to a

target (assessing dysmetria) both require coordination of movement to undertake the task [29]. Dysdiadochokinesia scores ranged between zero, indicating normal rhythmic hand turning, to three indicating that the task required more than 10 seconds to be completed and involved clearly irregular hand turns with single movements hard to distinguish. The majority of subjects, however, were able to complete the task with just mild signs of irregularity of movement. Similarly, most subjects had only mild difficulties with finger-chase activities, where subjects attempt to point to a target quickly moved from a common start point to an unknown end point (a measure of dysmetria). Group scores ranged between normal behaviour to overshooting by over 15cm.

These findings of dysmetria of upper limb movement are consistent with under and over-shooting observed when previously investigating upper limb torque control and visually guided movement in subjects with ataxia [30,81]. Upper limb assessments also revealed relatively few signs of tremor in the sample, which, where present, was low in amplitude.

Functionally, if upper limb coordination impairments were present in our sample, we may expect to observe reports of loss of independence in the FIM for activities such as eating, grooming, dressing the upper body, bathing and toileting. Findings involved relatively few reports of loss of independence with these activities during either testing day. One subject reported loss of independence with eating and five subjects reported loss of independence with bathing. No other losses of independence were reported.

Overall, upper limb assessment of this group appears consistent with prior reports suggesting that upper limb ataxia is relatively mild in those with SCA6 [325]. However, although upper and lower limb coordination is tested within the SARA, there is not a common test for arms and legs that can provide a true comparison between them. If sparing of upper limb coordination is a feature of SCA6, as previously suggested [325], perhaps the rating of a common activity between upper and lower limbs may facilitate future diagnosis or help to target therapeutic strategies.

The theory that in-coordination of movement is responsible for balance impairments has moderate support [160,254] but is also strongly contested by theories that sensory abnormalities cause balance impairments [155,367]. If balance is a consequence of uncoordinated movement across joints and not due to sensory abnormalities we may expect to see strong correlations between lower limb scores of coordination and laboratory derived measures of sway. However, since the SARA only has one category devoted to

assessment of lower limb coordination (an ordinal scale of 0 to 4 points), this is deemed insufficient to assess for correlations. For this purpose, design of a quantified measure of lower limb coordination could be of benefit to future investigations of balance.

Coordination of movement has already formed the basis for targeted therapy in subjects with SCA, with positive outcomes reported in both disease severity and balance outcome measures [161]. This approach to measurement along with the inclusion of balance exercises alongside coordination exercises in the treatment regime has created some confusion regarding the true nature of processes targeted by the therapy [161]. In order to clarify whether improvements in balance are a direct result of coordination training or an epiphenomenon of this, a more systematic approach to intervention and measurement must be encouraged. However, it remains encouraging that improvements in disease severity and balance have been reported following the use of exercise in subjects with SCA.

Speech impairment

Speech as rated by the SARA was found to be in some way impaired in fifteen of twenty-one subjects assessed, ranging between a mere suggestion of a speech disturbance to occasional words being difficult to understand. According to a study of patients in the Northeast region of England, slurred speech is the second most common presenting complaint [75], but little investigation of the cause of speech disturbance has yet been undertaken. Combined results of the SARA and the FIM suggest that speech and communication difficulties are incurred by SCA6 subjects, but since this is unlikely to be of significance to balance, this finding will not be discussed further in this thesis.

3.4.4 How suitable are balance outcome measures as future measures of longitudinal change and treatment effects?

Changes in total SARA score show that subjects are on average almost 2 points (mean 1.9, SD1.3) more severely rated per year. This is in a similar range to the recently published mean of 1.6 points per year for a European mixed sample of SCA types (SCA1,2,3 and 6) by Schmitz-Hubsch *et al*. [325]. The Bal-SARA also deteriorated in the majority of cases (mean 0.6, SD 1.1) but the change in scores was not statistically significant. The reported change in SARA score is likely to be clinically relevant since assessment of disease severity in those with SCA6 is recommended to take place on a yearly basis [20] and this tool is sensitive enough to measure change in disease severity to

0.5 of a point. The clinical relevance of change in Bal-SARA score is on the other hand questionable due to the lack of statistical support for detection of a yearly change in score.

Conversely, sway measures could provide a more continuous and potentially sensitive measure of overall progression of disease severity, which may be useful when evaluating new treatments despite being a potentially more costly outcome measure.

FIM scores do not clearly signal deterioration of functional independence over time. A lack of significant difference in scores between the first and normalised change per year scores suggests that this score may not be sensitive enough to detect yearly changes in function which would coincide with known increases in disease severity.

A lack of statistically significant differences in scores between baseline and normalised change over one year was also found for fall frequency, trunk and centre-of-pressure sway measures. This poses questions concerning the reliability of using such measures for the purpose of monitoring disease progression or effects of therapeutic interventions.

Since fall frequency scores were not found to correlate significantly with SARA scores, a lack of sensitivity to change over time was not unexpected for this measure. However, contrasting findings with regards to correlations with disease severity measures in Fonteyn *et al*.'s recent study [115] could question the validity and reliability of the fall questionnaire used in our study.

In contrast to fall frequency measures, sway measures, were found to initially strongly correlate with SARA scores and for that reason were expected to deteriorate relative to deterioration in SARA score. By using the gradient of line of best fit derived from SARA correlations in figure 3.1 (e-f), we would expect to see a significant increase in trunk and centre of pressure scores of 5.02 and 8.07mm/s, respectively, following an increase in SARA score of 1.9 (our average measure of group SARA change in one year) but this was not the case.

However, if trunk and CoP sway can be assumed to be a valid, sensitive and reliable measure of instability, then despite overall increases in ataxia signs, perhaps we should entertain the idea that balance may not have deteriorated over the two year period. Some support for this theory may come from lack of significant change in the other balance-related measures; the Bal-SARA score and fall frequencies. It is also interesting to note from questionnaire responses that three of nine initial fallers received physiotherapy targeting falls prevention and balance improvement between the baseline and final

assessments for this study. These programmes varied in terms of design, duration and intensity of training. One subject undertook only daily stretches (subject 2) and no improvement in fall frequency or sway measures was observed between testing days. The two other subjects undertook a series of exercises for at least an hour a week and both showed improvements in fall frequency and sway measures between testing days. One further subject (3) reported independently starting gym and exercise sessions (not directed by a physiotherapist) and also showed improvements in fall frequency and sway measures. As yet the effect of outpatient physiotherapy or gym programmes for those with SCA6 has not been evaluated by research, so the effect of this uncontrolled intervention on the fall and balance measures collected here remains largely unknown. However, results from a controlled programme of coordination and balance training exercises suggest that improvement in balance may be possible [161]. If this was indeed the case for all three of the subjects in question, then it is feasible that this could be responsible for a dilution in deterioration observed in group mean measures.

Regardless of theories for either *no change* or *some change over time* in sway measures, the predicted change in these measures derived from correlation analysis remains very small and it is possible that a lack of differences reported could be due to high levels of within-subject variability. Other methodological explanations for the no change reported could include the small sample of subjects studied or variability of environment in which data was collected between testing days. Human or environmental variables particularly had the potential to affect sway measures for the following reasons.

Firstly, measurements of trunk and centre-of-pressure speeds were collected and averaged over forty seconds. For healthy volunteers this tended to involve near constant sway speeds over this total time-span. Subjects with SCA6, however, did not appear to maintain constant sway speeds. Rather sway speeds appeared to wax and wane and in some cases evidence of 2-3Hz tremor was also detected, which would also affect the overall measure of speed (illustrated in chapter 4). Perhaps the sampling duration needed to be longer in view of the nature of this behaviour, or multiple collections taken from which more reliable averages could be calculated.

Secondly, the unexpected findings could involve variability of the experimental environment. During the first testing session, subjects were positioned in a small environment facing a blank beige wall at a distance of 1.5 metres which contained few

defining visual features. The final testing day was in contrast, spacious, walking aids were able to be positioned close by and the visual environment was more informative with wood textured sliding doors and laboratory objects such as chairs and a table positioned directly in-front of the subject. In both cases subjects were stood with their eyes open and corrective lenses *in-situ* but the final testing day provided subjects with the benefit of experience with the task and more visual information which could be used to improve overall stability [86]. Given these findings, further investigation of the visual contribution to balance control in SCA6 seems necessary. Accordingly, chapters 5 and 6 will present new findings with regards to how the availability of vision can affect response sizes to vestibular balance perturbations and how moving visual cues are used to control balance in subjects with SCA6.

This finding remains of importance, not only because it highlights the need for further investigation of visual control of balance in SCA6, but because it potentially identifies a source of bias on sway speeds which could have otherwise been assumed to have a negligible effect and ignored. Further investigation into the repeatability of measuring sway using better controlled visual environments is therefore indicated before recommendations for or against its use as an outcome measure can be made.

Targeted therapies are urgently needed to optimise function and ultimately arrest progression of disease severity. There are no pharmacological treatments currently recommended for this type of ataxia but recent studies involving oral administered doses of gabapentin [262] and acetozolamide [158] have reported improvements measures of postural sway and disease severity. Likewise, some rehabilitation based strategies have reported improvements in SCA6 disease severity and balance related outcome measures [161]. However, little is currently known about the validity of the tools used by these studies to track changes in ataxia symptoms. Similarly, little is known of the association between postural sway and disease severity measures or the nature of longitudinal change due to disease progression. Assessment of the SARA, Bal-SARA, FBS, FIM and sway speeds in this study begins to provide support for and against these tools as potential outcome measures.

By comparing total SARA scores with FBS, FIM, fall and sway measurements, strong correlations were found for all but FIM and fall frequency comparisons. Correlation coefficients indicated that functional balance and standing balance sway speeds both

deteriorate with increasing disease severity in a linear fashion. These correlations point to these measures being of potential use for the purpose of measuring longitudinal change in impairment and function or as outcome measures for evaluating the effect of an intervention. However, before these measures can be recommended, an investigation of validity and reliability would be advisable for the following reasons.

First, no data exists regarding balance dysfunction for more severely rated ataxia excluded for the purpose of this study.

Second, since FBS scoring was conducted during testing on day one only, correlation analysis was based on assessment of only seventeen subjects with SCA6 (fifteen confirmed symptomatic subjects and two 'pre-symptomatic' subjects). All other correlation analyses are based on thirty-three assessment scores (derived from twenty-one different subjects) collapsed across the first and final testing days. Twelve subjects participated in both testing days and therefore may have exerted some bias over nine single day participants' scores.

Despite a lack of correlation with SARA or the lack of sensitivity to change in one year, the range of scores produced by the FIM suggest that the FIM may remain as an appropriate outcome measure to monitor functional independence in those with SCA6. No change in FIM over one year could reflect the slow progressive nature of the condition or good current management of disease resulting in optimised function. Improvement in functional independence is often the goal of treatment and for this reason the FIM may also offer an appropriate outcome measure for measurement of effects of therapy. However, further investigation of reliability of the FIM would be recommended before use is advocated as an outcome measure. It should also be stressed that this score should not be used to infer disease severity.

Fall frequency measures may also remain potentially useful as outcome measures despite a lack of correlation or significant change in measure in one year. Although fall frequencies were available from thirty-three assessment sessions, only seventeen of these involved at least one fall. The lack of significant correlations suggests that on face value SARA (or Bal-SARA) score does not predict falling but this is a somewhat unexpected finding given that falls have long been reported as a feature of ataxia [115,373]. Recent results of a longitudinal study of falls involving 56 subjects with SCA6 (part of a total sample of 228 subjects with SCA1,2,3 and 6) were found to correlate with disease severity [115]. The major difference

between the two studies was that here fall frequency is based on retrospective reports over the duration of one month, whereas subjects in Fonteyn *et al.'s* (2009) study were asked to report average fall frequency over the past year by selecting one of the following options: (a) Never, (b) Once a year, (c) At least every month, but not every week, (d) At least every week, but not every day (e) Every day [115]. The difference in design, number of subjects used, inclusion criteria affecting the range of group SARA scores and the overall sampling timeframe could all act as possible explanations for the differences reported between studies.

The use of retrospective and self reporting fall questionnaires is not always encouraged due to problems such as forgetting and telescoping [212,219]. Forgetting bias the results as falls will be under-reported and telescoping bias the results as subjects expand the recall period to include falls that should not have been reported within the timeframe specified and as a result falls are over-reported [212,219]. However, retrospective questionnaires are advocated for their convenience and lack of labour intensity for subjects and researcher and timeframes of one month is generally thought to avoid forgetting, even in older subjects [212,219]. For this reason, it could be argued that our fall frequency results are valid but that the sampling duration of one month is just not sensitive enough to fuel correlations with disease severity of balance measures. Another theory for the lack of correlations is that SCA6 subjects do not fall because they are afraid of falling and put measures in place in order to prevent this risk. A recent study by Wirz *et al*. investigated falls in subjects with incomplete spinal cord injury and correlated their findings with FBS (Berg) and fear of falling measures [396]. Similar to our group of SCA6 subjects, these subjects had no cognitive impairment and were conscious of the risk of falling. Wirz *et al*. discovered strong correlations between measures of functional balance measures and fear of falling but no correlations between these measures and fall frequencies (measured over five months).

These findings clearly have implications regarding the validity and reliability of our tool selected to measure falls and for the use of fall frequency as a measure of disease progression or to evaluate the effect of therapy. Until further investigation can take place concerning fall frequency parameters and the use of fear of falling as an outcome measure for SCA6 subjects, caution regarding use of falls as outcome measures should be encouraged.

3.5 Conclusion

This chapter has defined the sample of subjects with SCA6 in terms of anthropometric, ataxia and non-ataxia features. It acts to assure the reader that the sample is 'typical', relative to contemporary reports of clinical and functional measures of ataxia in those with SCA6.

This chapter suggests that balance dysfunction is likely a consequence of cerebellar disease and reinforces the idea that balance impairment is a characteristic feature of SCA6.

All measures investigated appear to have potential in providing clinicians with unique and important information regarding impairment, function, falls and independence. However, use of all but the SARA as an outcome measure must be regarded with caution until further investigation of validity and reliability can be undertaken with larger samples under controlled experimental conditions. Total SARA scores appear to offer the best indication of disease progression over time and remain the currently singularly validated measure of longitudinal change. Laboratory based measures of sway show some potential as providing continuous quantitative measures available to track the progression of disease or therapy related improvements. However, further investigations of validity and repeatability must be undertaken before this measure can be recommended as an outcome measure.

Investigation of clinical tests has highlighted scope for future research in many areas related to balance, such as physical and psycho-social functioning as a consequence of progressive balance impairment. However, this thesis will continue to focus on mechanisms underpinning balance impairment by investigating sensory control of balance in SCA6. An understanding of the mechanism underpinning balance impairment seems fundamental to ensuring optimal future management of the condition and development of novel therapies.

4 CHAPTER FOUR: UNPERTURBED STANDING BEHAVIOUR

4.1 INTRODUCTION

Despite a lack of information concerning balance behaviour specifically within individual types of spino-cerebellar ataxia, numerous studies have evaluated balance using subjects with other types of cerebellar disease [22,238,253,255,257,374], some of which have even included mixed samples of individuals with SCA [155,271,374]. These studies not only provide important information about the general nature of balance impairments in cerebellar disease but have also set conventions for how these impairments can be measured and described. Some have chosen to focus on falls as indicators of balance [115,352,373], some have used postural perturbations to assess the nature of balance responses [22,155,366,367] and others have addressed balance during gait [104,146,160,256,255,318,351]. Regardless of the approach selected, what underpins all balance behaviour is how the body is able to behave at baseline, i.e. when standing on firm ground, free from additional support, in equilibrium before any external sources of postural perturbation are applied. By understanding this baseline balance activity in those with SCA, it not only improves knowledge of balance impairment, but it may also better inform future findings that involve more dynamic balance responses from postural or sensory perturbations.

Such a simple approach was indeed the method of choice for Mauritz *et al.* who investigated different types of cerebellar disease using postural sway and electromyography as measures of instability [238]. This study was not only one of the first to demonstrate quantitative measures of increased postural instability in those with cerebellar disease but also began to quantify the directional characteristics of sway and the frequency of postural tremor that accompanied balance impairments in some cerebellar lesion types. Potentially of special interest to those investigating subjects with SCA6 include this study's group of subjects with anterior lobe cerebellar atrophy, since the nature of the anatomical distribution of the atrophy remains similar to that caused by the death of Purkinje cells in SCA6. For this cerebellar group Mauritz *et al.* reported that subjects were unstable in multiple directions but that they swayed significantly more than healthy individuals in the antero-posterior direction and possessed a significant 3 hertz (Hz) postural tremor, which was also most prevalent in antero-posterior components of postural sway. Although subjects with 3Hz tremor had anterior lobe cerebellar atrophy, resulting

from chronic alcoholism, the similarities in both lesion location and clinical presentation between this group and those with SCA6 could lead one to hypothesise that such measures of balance behaviour would be of a similar nature within the two populations.

More recently, studies have re-visited the directional nature of instability in those with different types of cerebellar disease and have explored different methods that involve postural perturbations and analysis of gait [22,96,155]. These studies have all supported the conclusion that individuals with cerebellar disease are more unstable multi-directionally than healthy controls but some disagreement remains regarding the directional bias of this instability. Specifically, work by van de Warrenburg *et al.* has acted to support Mauritz *et al.*'s findings that instability mainly occurs in an antero-posterior direction, whereas others have suggested that a medio-lateral and backwards instability exists [22]. One explanation for these conflicting findings may involve consideration of subjects' stance width between the protocols used. Using healthy individuals, Day *et al.* found that stance width had a significant effect on both the directional components of sway and the segmental composition of motion throughout the body in healthy individuals [79]. It therefore seems reasonable to suggest that the different stance widths adopted in pre-existing investigations of cerebellar subjects may be responsible for the conflicting findings.

Although not involving investigation of stance width, Oude *et al.* have further explored whole-body segmental composition of postural motion during platform perturbations to find out if there is a distinct distribution of segmental instability which contributes to global imbalance [271]. This study analysed joint motion and EMG responses from lower limb muscles to underpin theories that decreased joint excursion at the knee and pelvis in those with SCA could be responsible for whole-body over-responses to directional perturbations. The authors postulated that this decreased joint excursion was due to a stiffening strategy adopted to compensate for joint instability and suggested that balance impairment was more likely due to biomechanical constraints rather than centrally driven changes in response characteristics. If this is the case then it may be reasonable to further hypothesise that similar distributions of reduced joint excursions would be observed during unperturbed stance.

In addition to stance width and methodological differences, the specific nature of cerebellar lesions and any pathological co-morbidities could be responsible for different directional biases of instability reported in the literature. For instance, within diagnoses of spino-

cerebellar ataxia, different SCA types are known to involve a variety of molecular pathologies as well as patterns of lesion location and clinical presentations [55,226,323,325]. It has been recognised in previous evaluations of research that these factors in turn have the potential to affect physiological processes involved with balance control in different and as yet largely unknown ways. Studies by Mauritz *et al.* and Diener and Dichgans have begun to explore such factors by studying different groups of subjects with known cerebellar lesions and minimal extra-cerebellar disease pathologies [97,238]. In these studies, they outline how different anatomical lesions, associated with different functional regions of the cerebellum, produce differences in the directional preponderance of instability and postural tremor. They reported that anterior lobe cerebellar lesions produce 3Hz tremor and predominantly pitch plane instability, whereas posterior lobe lesions produce increased 1-2Hz oscillatory sway motion and a greater amount of roll plane instability.

4.1.1 Purpose

Features of unperturbed standing balance vary with different varieties of cerebellar disease and remain unquantified for those with SCA6. This investigation is therefore designed to quantify freestanding, unperturbed balance behaviour in a homogeneous sample of subjects with SCA6. Since SCA6 patients are known to adopt a wide base-of-support and stance width naturally varies conventional measures of standing sway in healthy subjects, this investigation will also determine the effect of stance width on sway measures.

4.1.2 Experimental aim

To provide quantified measures of posture and standing balance and to describe the effect of stance width on these measures.

4.1.3 Hypotheses

Taking into consideration the range of conclusions and hypotheses generated from other studies of balance in cerebellar disease to date, the following hypotheses will be tested:

1. **Whole body posture is largely unchanged in those with SCA6 but may differ as subjects adopt walking aids.**
2. **Whole body instability is increased across all stance widths.**
3. **Instability is increased multi-directionally with increasing antero-posterior preponderances with widening stance widths.**

4. **Due to in-coordination of movement being a feature of ataxia, joint instability is a widespread feature in standing subjects.**
5. **Due to damage to anterior parts of the cerebellum, postural tremor will be observed.**

4.1.4 Approach

This investigation will concentrate on six main features in order to comprehensively describe standing balance behaviour in SCA6:

- **Whole body posture**
- **Quantification of whole body instability**
- **Directional preponderance of instability**
- **Distribution of instability throughout the body**
- **Frequency components of postural sway**

In this study the homogeneity of our sample of subjects with SCA6 has been assured with genetic testing.

Whole body motion analysis will be employed to record body motion in three dimensional space. Traditional motion capture of markers placed over anatomical landmarks will be supplemented by improved model building of subjects in Visual 3D incorporating trials which define joint locations and segmental boundaries.

In order to assess how the severity of the disease may impact on balance behaviour, scores from the scale for the assessment and rating of ataxia (SARA), validated for use with individuals with SCA6, are available to compare disease severity scores with laboratory derived measures of postural sway [(324)].

4.2 Methods

4.2.1 Subjects

Seventeen subjects with SCA6 and seventeen age-, sex- and height-matched healthy control subjects (HC) were recruited for participation in this study (session 1), described in chapter 2.

4.2.2 Procedures

Subjects stood in the middle of the laboratory facing away from Coda cameras and computer monitors. This ensured that subjects could not see LEDs on Coda cameras

signalling data collection periods or potentially gain feedback from computer displays of force and body motion activity. Subjects donned kinematic measurement equipment and safety gear, which are explained in detail in chapter 2 (General Methods).

To quantify standing balance subjects were stood in the middle of the laboratory. Each foot was placed symmetrically over two abutting force plates.

To standardise stance widths, ten parallel lines were drawn on the floor (over two force plates) which were spaced 32, 16, 8, 4 and 0cm apart. The medial borders of each subject's feet were positioned along these lines and in doing so each subject was positioned symmetrically over the two hidden force plates. Although this method did not encompass the recommended 14 degree preferred foot splay angle [223] the use of parallel lines as feet alignment cues was a quick and simple way to set stance width and maintain subjects' foot angle throughout all data collections.

Measures of spontaneous body sway were taken continuously for 40 seconds per stance width using the kinematic measurement tools extensively described in chapter 2. Every subject started the first trial with their feet positioned along the widest (32cm) lines, which was an easy task for all subjects. Once familiar with the task, subjects were asked to repeat the trial with progressively narrower stance. This strategy optimised confidence with the task and therefore reduced the likelihood that fear of falling may affect the measures collected. Subjects were able to keep their eyes open throughout the trials and were asked to wear spectacles should they require them. Before onset of data collection, subjects were instructed to stand upright, relax their arms by their side, look ahead and avoid turning their head to the side during the trial. When the subject was correctly positioned and ready to begin, the researcher started the data collection period with a button press. A wireless microphone headset worn by the researcher was blown into any point at which the researcher made contact with the subject (in order to prevent a fall). This marked the data with an analogue signal to allow data before a fall to be analysed and data during and after the fall to be excluded. Where falls did take place, the stance width condition was repeated no more than two additional times in an attempt to achieve a full forty seconds of sway data.

4.2.3 Data analysis

Stance width text files were numbered according to the stance width condition and read into Matlab sequentially. Within the workspace, they were assigned a condition code of 1 to 5 (1 being 32cm stance width and five being 0cm stance width data).

4.2.3.1 Posture analysis

In order to analyse posture, angular joint excursion over time data was calculated from model building with virtual landmarks in Visual 3D (Visual 3D pipelines available in appendix 3).

Angles sometimes representing composite joint data were calculated for head-on-trunk, trunk-on-pelvis, hips, knees and shanks-on-ground per subject. Angles were taken from 3D joint data where local reference frames were calculated in order to define joint specific pitch and roll motion.

Circular statistics were used in order to calculate mean and angular deviations of joint angles according to the methods outlined by Batschelet [32] and described in chapter 2. Mean joint angles from 40 second data collection periods were used to quantify posture. Exported individual subject .mat files from Visual3D were used in Matlab in order to undertake these calculations and perform graphical display functions. The same circular statistic method was used to calculate group mean and angular deviation measures.

ANOVAs were employed to assess for *group* differences and analyse the effect of stance *width* on posture (within-subject factor: *stance width* (0, 4, 8, 16, 32 cm)); between subject factor: *group* (HC, SCA6)).

4.2.3.2 Instability analysis

Sway speeds

CoP and trunk cluster sway motion in the x-y plane were used to calculate postural sway speeds. CoP and the trunk cluster motion speeds act as primary measures of unperturbed postural sway, essentially a measure of whole body instability.

Sway speeds were calculated by taking every data point in a time series and subtracting the subsequent data point in the time series (for both x and y laboratory axis values). Using these x and y path-lengths it was then possible to employ Pythagorus' Theorum to calculate a 2-dimensional (x-y) vector length. Speed measures were then obtained by summating all vectors across the time series and dividing by the total time sampled.

Separate calculations of x and y direction velocities were achieved by dividing x and y path-lengths by the total sampling time. This method assumes that motion in the vertical is negligible and refers only to speed in the horizontal plane. In view of the careful positioning within the laboratory environment, x axis motion corresponds with mediolateral motion and y with antero-posterior motion.

Despite being a useful global measure of whole body instability, sway speeds do not provide information as to whether the degree of instability measured was due to (a) small amplitude but repetitive movements or (b) larger amplitude movements. In order to provide information regarding this behaviour, medio-lateral (ML) and antero-posterior (AP) components of displacement and velocities were calculated and their standard deviations about the mean used to define position and velocity specific measures of instability in the two cardinal directions. These methods of measurement have previously been described and used by Day *et al*. for the purpose of quantifying instability during unperturbed standing [(79)].

In order to provide information about the directional nature of balance behaviour, medio-lateral (ML) and antero-posterior (AP) components of displacement and velocities were obtained and their standard deviations about the mean were calculated and used to define position and velocity instability in the two cardinal directions (Day *et al.,* [(79)]). To investigate directional preponderances of instability, ratios of anteroposterior to mediolateral sway measures were calculated according to the following equation: (AP-ML)/(ML+AP). Positive values (+1 ≤ 0) indicate an antero-posterior preponderance to instability and negative values (0 ≥ -1) a mediolateral preponderance.

Initial statistical comparisons included analysing for the effect of stance width, group and interactions between these factors (ANOVAs: within-subject factor: *stance width* (0, 4, 8, 16, 32 cm)); between subject factor: *group* (HC, SCA6)). Where significant interactions were present, post-hoc comparisons using independent t-tests were used to further explain the effect of *group* per stance width condition. In order to better understand the effect of *stance width* on the relative increase of each subject's instability measures, individual measures of stability were plotted against stance width and a power-law curve was fitted to the points. The exponent of the power law was taken as a single-value descriptor of the relationship for each individual and was compared between groups using independent t-tests in SPSS.

Joint instability

Angular deviations were calculated alongside mean angles when initially assessing posture. These provide a measure of joint excursion variability, which could represent joint instability (where larger angular deviations were taken to represent greater joint instabilities).

ANOVAs were employed to assess the distribution of joint instability per joint, per subject. ANOVAs were employed to assess for *group* differences and analyse the effect of stance *width* on posture (within-subject factor: *stance width* (0, 4, 8, 16, 32 cm)); between subject factor: *group* (HC, SCA6)).

Postural tremor

To analyse for postural tremor individual subject measures of segment position and angle over time were used to calculate periodograms. Matlab scripts were written to calculate average power of the signal in roll and pitch for bandwidths of 0-1, 1-2, 2-3, 3-4 and 4-5Hz. The relative power of each bandwidth, per stance width, was compared across subjects and between groups. Statistical comparisons included analysing for the effect of stance width, frequency band, group and interactions between these factors (ANOVAs: within-subject factors: *stance width* (0, 4, 8, 16, 32 cm) and frequency (0-1, 1-2, 2-3, 3-4 and 4-5Hz)); between subject factor: *group* (HC, SCA6)).

Correlations

Pearson's correlation coefficients calculated in SPSS were used to explore whether postural measures of instability would correlate with subjective clinical measures commonly used in clinicians and physiotherapists; namely the scale for assessment and rating of ataxia (SARA), the functional balance scale (FBS) and the functional independence measure (FIM). These clinical measures were available from the clinical assessment undertaken prior to postural stability testing, described in chapter 3.

Of a total of eight different rated physical activities in SARA, three have the potential to be directly affected by whole-body instability; gait, stance and sitting balance. These have been collectively referred to as Bal-SARA components for the purpose of correlation analysis with quantitative measures of balance. Where outcome measures were significantly correlated with the total SARA score we used a post-hoc comparison with just Bal-SARA scores to further explore the strength of correlation coefficients

4.3 Results

4.3.1 Posture

Figure 4.3 illustrates group mean postures over 40s per stance width. For illustration purposes joint positions have been projected into laboratory x and y axes to illustrate frontal and sagittal plane postures respectively.

Mean values and standard deviations plus summaries of statistical analysis are described in tables (4.1-4.4). Analysis of mean joint position data showed no main effect of *group* in either sagittal or frontal planes. No effect of *stance width* was found for sagittal plane angles but in the frontal plane effects of *stance width* were observed at the hip ($p<0.001$) and ankle ($p=0.019$). There were no significant interactions between *group* and *stance width*.

Table 4.1: Group mean joint angles in the frontal plane (standard deviations)

Stance-width:	Group:	Head on Thorax:	Thorax on Pelvis:	Hip:	Knee:	Ankle:	Feet:
0cm	HC	3.6 (8.8)	1.7 (11.8)	5.7 (9.2)	4.8 (13.3)	-11.2 (8.6)	1.5 (11.6)
	SCA6	-0.7 (11.5)	-2.9 (10.5)	6.5 (6.4)	5.7 (3.8)	-9.3 (5.8)	4.8 (6.8)
4cm	HC	-4.1 (10.1)	1.8 (11.8)	4.7 (8.9)	5.4 (11.4)	-11.5 (7.9)	4.1 (2.7)
	SCA6	1.1 (12.1)	-3.1 (9.2)	5.0 (10.9)	6.9 (7.2)	-10.2 (5.9)	3.9 (6.6)
8cm	HC	-5.0 (10.6)	1.2 (11.6)	6.4 (7.7)	4.0 (8.6)	-10.8 (5.6)	1.2 (9.0)
	SCA6	1.3 (12.9)	-3.2 (9.8)	5.6 (13.0)	8.1 (7.6)	-10.8 (3.9)	3.0 (6.5)
16cm	HC	-3.3 (7.9)	1.1 (10.8)	8.1 (7.5)	2.1 (8.7)	-9.3 (5.2)	0.9 (8.4)
	SCA6	2.1 (9.7)	-3.0 (9.3)	6.9 (10.3)	8.2 (7.0)	-10.9 (4.2)	2.3 (7.0)
32cm	HC	-3.3 (9.4)	1.3 (9.9)	10.9 (6.1)	3.3 (10.0)	-7.0 (10.6)	1.2 (8.7)
	SCA6	2.3 (9.1)	-4.1 (10.1)	8.6 (10.7)	6.3 (6.4)	-8.7 (4.2)	2.6 (6.3)

Table 4.2: Statistical analysis of mean frontal plane joint angles.

ANOVA factors:	Head on Thorax:	Thorax on Pelvis:	Hip:	Knee:	Ankle:	Feet:
SW	F(3.2,82.3)=0.4, p=0.753	F(2.5,68.5)=2.1, p=0.122	F(3.2,54.9)=11.9, p<0.001	F(2.5,42.9)=2.0, p=0.141	F(2.6,44.6)=3.4, p=0.030	F(2.7,70.3)=2.6, p=0.068
Group	F(1.0,26.0)=2.2, p=0.153	F(1.0.27.0)-2.0, p=0.173	F(1.0,17.0)=0.3, p=0.613	F(1.0,17.0)=1.1, p=0.305	F(1.0,17.0)=0.3, p=0.564	F(1.0,26.0)=0.1, p=0.857
Interaction (*SW*Group*)	F(1.0,26.0)=0.2, p=0.622	F(2.5.68.5)=0.2, p=0.872	F(3.2,54.9)=1.2, p=0.302	F(2.5,42.9)=1.2, p=0.316	F(2.6,44.6)=1.0, p=415	F(2.7,70.3)=0.2, p=0.879

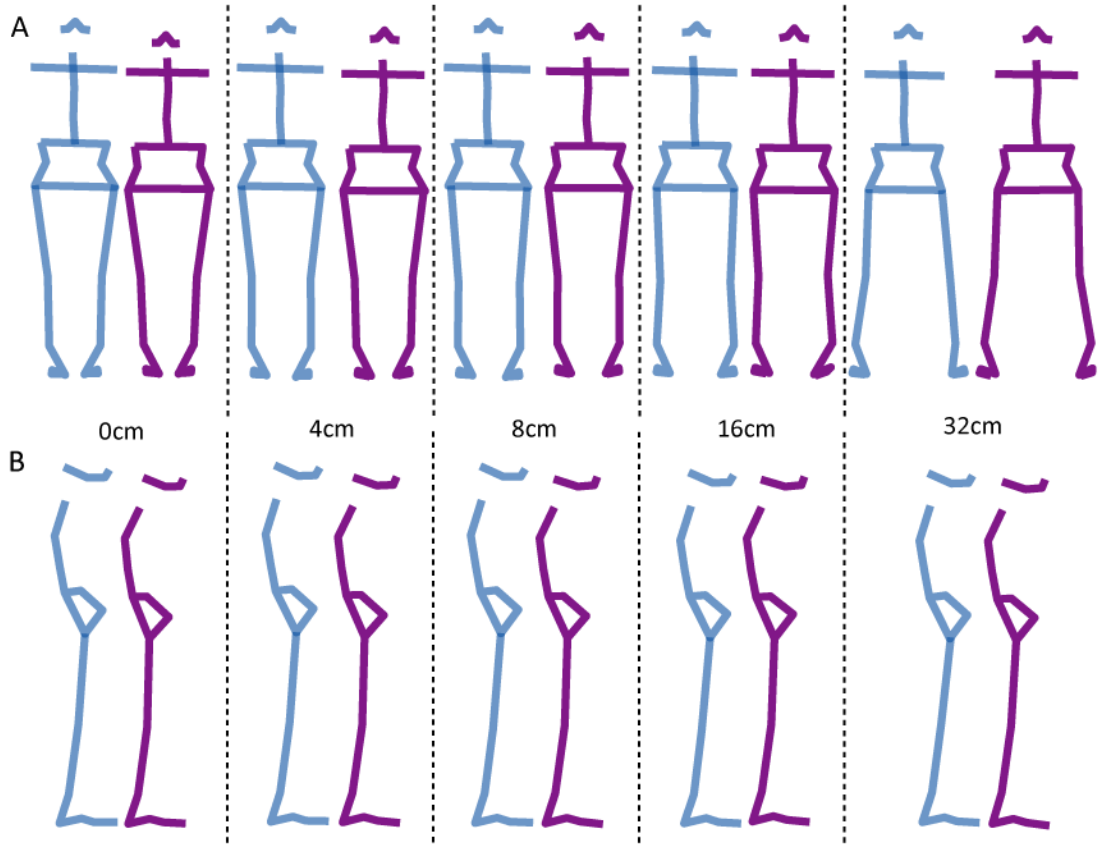


Figure 4.1: Group mean postures
Stick figures represent group average frontal (A) and sagittal (B) plane postures per stance width. Stance width is in ascending order left to right (0, 4, 8, 16 and 32). Blue figures correspond to healthy control group average angles and purple to that of the SCA6 group.

Table 4.3: Group mean joint angles in the sagittal plane (standard deviations)

Stance-width:	Group:	Head on Thorax:	Thorax on Pelvis:	Hip:	Knee:	Ankle:	Feet:
0cm	HC	2.0 (4.1)	-0.5 (4.8)	-0.6 (6.5)	-0.3 (4.0)	3.2 (6.9)	-0.2 (10.4)
	SCA6	2.4 (6.2)	-1.0 (5.4)	2.0 (6.1)	-1.0 (0.2)	-3.9 (12.9)	-3.1 (12.4)
4cm	HC	1.5 (4.0)	-0.3 (5.1)	-1.3 (5.5)	0.2 (3.6)	2.7 (9.0)	-2.8 (6.9)
	SCA6	2.9 (5.2)	-1.3 (4.9)	1.3 (6.0)	0.1 (2.5)	1.2 (13.6)	-3.8 (9.2)
8cm	HC	1.8 (4.0)	0.1 (5.1)	-2.2 (5.1)	-0.3 (3.8)	0.3 (6.8)	-2.5 (3.7)
	SCA6	3.4 (4.1)	-1.5 (4.8)	0.8 (5.4)	0.1 (2.3)	2.6 (6.8)	-2.2 (5.8)
16cm	HC	2.9 (4.0)	0.3 (5.2)	-2.0 (5.2)	-0.7 (3.3)	-1.3 (8.2)	-1.2 (5.1)
	SCA6	4.2 (6.6)	-1.1 (5.5)	0.1 (6.2)	-0.1 (1.9)	6.3 (8.0)	-3.6 (5.6)
32cm	HC	1.8 (2.8)	0.2 (5.1)	-0.9 (5.9)	-0.1 (1.7)	-2.8 (9.4)	-2.8 (5.8)
	SCA6	2.8 (7.0)	-0.4 (5.4)	2.1 (7.4)	-1.3 (2.2)	3.1 (11.0)	-2.5 (4.7)

Table 4.4: Statistical analysis of mean sagittal plane joint angles.

ANOVA factors:	Head on Thorax:	Thorax on Pelvis:	Hip:	Knee:	Ankle:	Feet:
SW	F(2.9,76.2)=1.9, p=0.142	F(3.2,87.5)=1.8, p=0.150	F(3.0,50.7)=1.7, p=0.185	F(3.6,61.9)=1.2, p0.313	F(3.4,58.3)=1.5, p=0.230	F(2.6,67.5)=0.4, p=0.524
Group	F(1.0,26.0)=0.3, p=0.588	F(1.0,27.0)=0.2, p=0.645	F(1.0,17.0)=1.6, p=0.218	F(1.0,17.0)=0.1, p=0.706	F(1.0,17.0)=0.1, p=0.935	F(1.0,26.0)=0.1, p=0.756
Interaction (*SW*Group*)	F(2.9,76.2)=0.2, p=0.898	F(3.2,87.5)=0.9, p=0.462	F(3.0,50.7)=0.5, p=0.655	F(3.6,61.9)=1.4, p=0.215	F(3.4,58.3)=0.6, p=0.623	F(2.6,67.5)=0.6, p=0.450

4.3.2 Instability

Sway speed measures of whole body motion were calculated from centre-of-pressure (CoP) and trunk cluster displacement over time. An example of raw data on which these measures are based is provided in figure 4.2.

Sway speed measures based on either CoP or trunk cluster data gave similar results. There was a significant main effect of *stance width* (CoP: $F(2.3,64.6)=19.2$, $p<0.001$; trunk: $F(2.7,74.4)=39.2$, $p<0.001$), such that whole-body motion increased in both groups as stance width narrowed (figure 4.3). Body motion was larger for average SCA6 group measures than the HC group as shown by a significant main effect of *group* (CoP: $F(1,28)=17.1$, $p<0.001$; trunk: $F(1,28)=19.0$, $p<0.001$). Additionally, there was a significant *stance width* x *group* interaction (CoP: $F(2.3,64.6)=7.5$, $p=0.001$; trunk: $F(2.7,74.4)=13.4$, $p<0.001$). Post-hoc t-tests revealed that there were significant group differences (all $p<0.05$) at all stance widths (table 4.5) but due to such a widespread strong effect of group this did not act to clarify the basis of the interaction. In order to better quantify the effect of stance width, power law exponents were calculated for each subject. Power law exponents were derived from the power law line fitting function displayed after each individual subject's sway speed was plotted against stance width.

Figure 4.4 illustrates similar plots to those used per subject but acts to illustrate the effect of stance width per group using group mean sway speed data. Figure 4.4 shows that exponent measures based on group mean sway speed were larger for SCA6 subjects. Analysis of power exponents using t-tests revealed significant differences between groups suggesting that narrowing stance width had a greater destabilising effect on the SCA6 group compared with healthy control subjects (table 4.6).

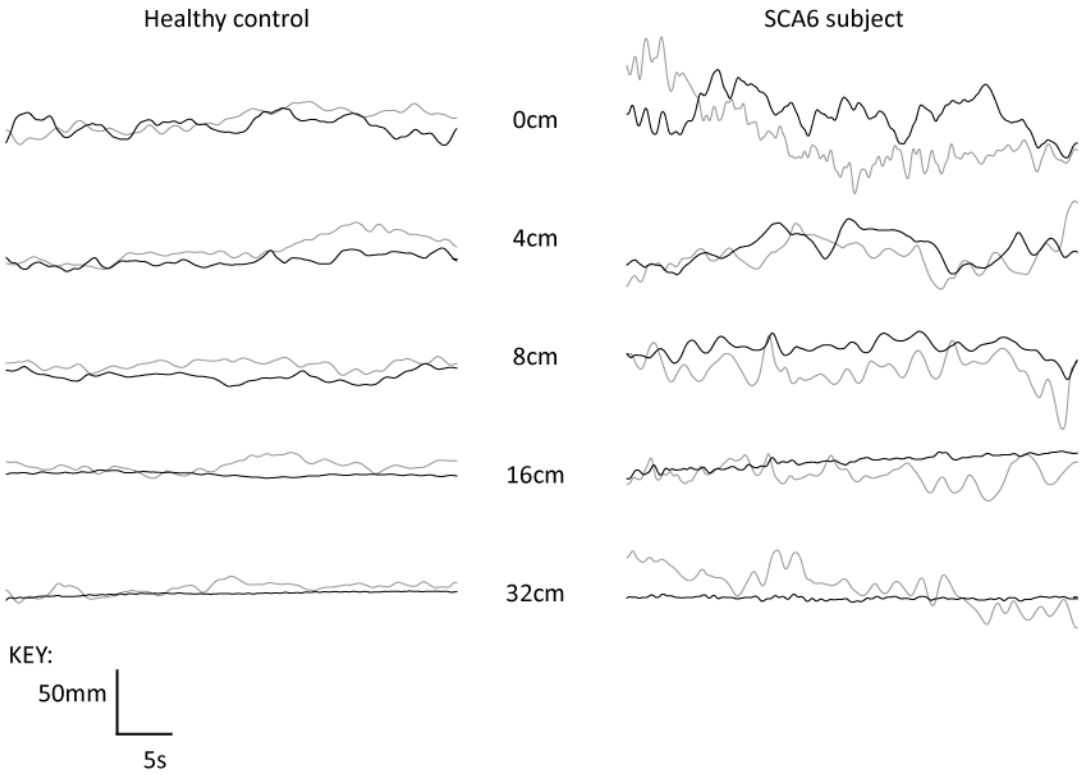


Figure 4.2: Trunk cluster raw position over time data.
Traces in the left hand column illustrate data from a typical healthy control and right hand column traces are derived from an age-, sex- and height-matched subject with SCA6. Traces are derived from 40 second durations of data collection with subjects stood in five stance widths (top to bottom row: 0, 4, 8, 16 and 32cm). Black lines illustrate cluster position over time data in the laboratory x-axis and grey lines illustrate equivalent data in the y-axis.

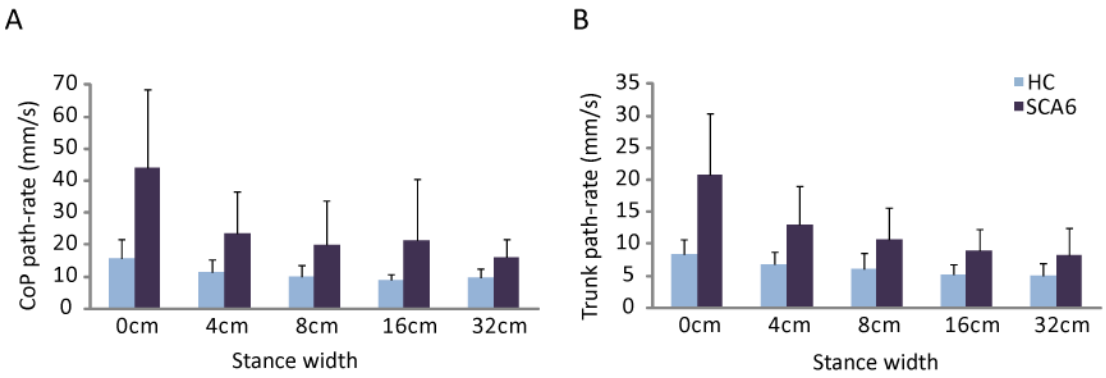


Figure 4.3: Group average total path-rate measures of whole body instability.
Bar charts illustrate group mean total path-rates based on centre-of-pressure (A) and trunk cluster (B) motion from five stance width conditions (left to right: 0, 4, 8, 16 and 32cm stance widths). Blue bars correspond to healthy control averages and purple bars to that of the SCA6 group. Error bars illustrate one standard deviation of group measures in order to provide a measure of between subjects variability.

Table 4.5: Post-hoc t-tests for CoP and trunk cluster speeds.

Measure	Stance width	HC group mean (S.D.)	SCA6 group mean (S.D.)	t-value (d.f.)	p-value
CoP	0	15.6 (6.0)	44.2 (4.0)	-4.4 (15.7) †	<0.001
	4	11.4 (4.1)	23.7 (4.2)	-3.5 (16.7) †	0.003
	8	9.9 (3.5)	20.1 (6.7)	-2.8 (28.0)	0.010
	16	9.0 (1.8)	21.4 (4.2)	-2.5 (14.3) †	0.026
	32	9.6 (2.8)	15.9 (3.9)	-3.7 (19.8) †	0.001
Trunk	0	8.4 (2.2)	20.7 (25.4)	-4.9 (15.6) †	<0.001
	4	6.8 (1.9)	13.0 (12.9)	-3.9 (16.8) †	0.001
	8	6.1 (2.3)	10.6 (14.5)	-3.1 (20.0) †	0.006
	16	5.2 (1.5)	8.9 (19.3)	-3.9 (19.6) †	0.001
	32	5.1 (1.9)	8.1 (5.8)	-2.5 (18.5) †	0.023

† Equal variances not assumed according to Levene's test (p<0.05)

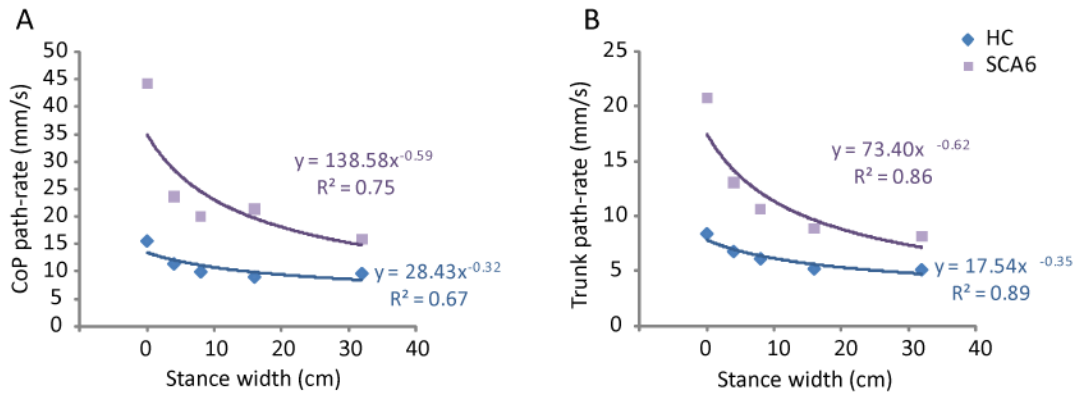


Figure 4.4: Quantifying the effect of stance width on path-rate measures using power law. Bar charts illustrate group mean total path-rates based on centre-of-pressure (A) and trunk cluster (B) motion from five stance width conditions (left to right: 0, 4, 8, 16 and 32cm stance widths). Blue markers correspond to healthy control averages and purple markers to that of the SCA6 group. Regression lines are based on group average measures and according to power law calculation.

Table 4.6: Post-hoc t-tests for CoP and trunk cluster speed power law exponents

Measure	HC group mean (S.D.)	SCA6 group mean (S.D.)	t-value (d.f.)	p-value
CoP	-0.31 (0.17)	-0.59 (0.23)	3.9 (28.0)	<0.001
Trunk	-0.36 (0.12)	-0.63 (0.22)	4.1 (28.0)	<0.001

4.3.2.1 *Directional preponderance of instability*

Mediolateral (ML) and anteroposterior (AP) whole body instability was analysed using two different types of outcome measure. Standard deviations of centre-of-pressure and trunk velocities were used as measures of how fast the body moved. Standard deviations of displacement of CoP and trunk markers were used as measures of how far the body moved away from the mean position over time.

4.3.2.1.1 *Mediolateral directional measures*

Standard deviations of ML velocities and displacement increased in both groups as stance width narrowed (figures 4.5 and 4.6).

Increased sway with reduced stance width illustrated in figures 4.5 and 4.6 is associated with a statistically significant main effect of *stance width* ([Velocities: CoP: F(1.8,49.3)=29.4, p<0.001; trunk: F(1.6,43.6)=29.4, p<0.001], [Displacement: CoP: F(1.9,52.5)=48.5, p<0.001; trunk: F(1.6,46.0)=39.3, p<0.001]). SCA6 mean measures were larger than HCs, as shown by a significant main effect of *group* ([Velocities: CoP: F(1,28)=15.6, p<0.001; trunk: F(1,28)=14.3, p<0.001], [Displacement: CoP: F(1,28)=10.2, p=0.004; trunk: F(1,28)=8.0, p=0.008]). Additional widespread *stance width* by *group* interactions were observed ([Velocities: CoP: F(1,28)=8.3 p=0.001; trunk: F(1,28)=12.6, p=0.001], [Displacement: CoP: F(1.9,52.5)=6.0 p=0.005; trunk: F(1.6,46.0)=4.8, p=0.018]). Post-hoc t-tests revealed significant group differences at the majority of stance widths. Exceptions included t-tests involving 32cm stance width centre-of-pressure data and 8cm and 32cm stance width trunk data (tables 4.7 and 4.8).

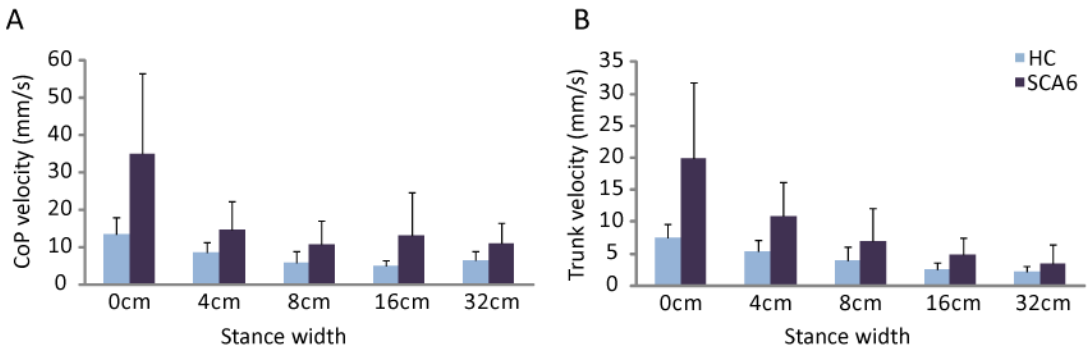


Figure 4.5: Group mean standard deviation of velocity measures in the mediolateral direction. Bar charts illustrate group mean measures based on centre-of-pressure (A) and trunk cluster (B) motion from five stance width conditions (left to right: 0, 4, 8, 16 and 32cm stance widths). Blue bars correspond to healthy control group averages and purple bars to that of the SCA6 group. Error bars illustrate standard deviations of group measures.

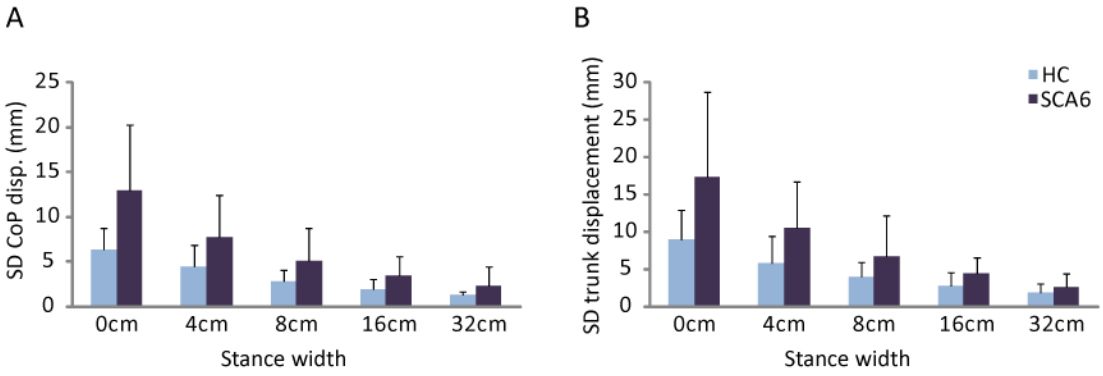


Figure 4.6: Group mean standard deviations of displacement in the mediolateral direction. Bar charts illustrate group mean measures based on centre-of-pressure (A) and trunk cluster (B) motion from five stance width conditions (left to right: 0, 4, 8, 16 and 32cm stance widths). Blue bars correspond to healthy control averages and purple bars to that of the SCA6 group. Error bars illustrate standard deviations of group measures.

Table 4.7: Post-hoc t-tests for CoP and trunk standard deviation of medio-lateral velocity data

Measure	Stance width	HC group mean (S.D.)	SCA6 group mean (S.D.)	t-value (d.f.)	p-value
CoP	0	13.4 (4.8)	35.1 (21.5)	-3.8 (15.4) †	0.002
	4	8.5 (3.0)	14.8 (7.5)	-3.0 (18.3) †	0.007
	8	6.0 (3.0)	10.8 (6.4)	-2.7 (19.9) †	0.014
	16	5.0 (1.5)	13.1 (11.5)	-2.7 (14.5) †	0.017
	32	6.4 (2.5)	10.9 (5.7)	-2.8 (19.1) †	0.010
Trunk	0	7.4 (2.1)	19.9 (11.8)	-4.0 (14.9) †	0.001
	4	5.4 (1.6)	10.9 (5.3)	-3.8 (16.7) †	0.001
	8	4.0 (2.0)	7.0 (5.2)	-2.1 (18.2) †	0.048
	16	2.6 (1.1)	4.8 (2.8)	-2.9 (18.2) †	0.010
	32	2.2 (0.9)	3.5 (3.0)	-1.6 (16.8) †	0.126

† Equal variances not assumed according to Levene's test ($p<0.05$)

Table 4.8: Post-hoc t-tests for CoP and trunk standard deviation of medio-lateral displacement data

Measure	Stance width	HC group mean (S.D.)	SCA6 group mean (S.D.)	t-value (d.f.)	p-value
CoP	0	6.4 (2.4)	12.9 (7.3)	-3.3 (28.0)	0.003
	4	4.4 (2.4)	7.7 (4.7)	-2.4 (28.0)	0.023
	8	2.9 (1.3)	5.2 (3.6)	-2.4 (17.5) †	0.030
	16	2.0 (1.2)	3.5 (2.1)	-2.5 (28.0)	0.019
	32	1.3 (0.5)	2.3 (2.1)	-1.9 (15.3) †	0.080
Trunk	0	9.0 (4.0)	17.4 (11.3)	-2.7 (17.4) †	0.014
	4	5.9 (3.6)	10.5 (6.2)	-2.5 (28.0)	0.018
	8	4.0 (1.9)	6.8 (5.5)	-1.8 (17.4) †	0.082
	16	2.7 (1.9)	4.5 (2.1)	-2.3 (28.0)	0.027
	32	1.9 (1.1)	2.7 (1.8)	-1.4 (28.0)	0.176

† Equal variances not assumed according to Levene's test ($p<0.05$)

4.3.2.1.2 Anteroposterior directional measures

Standard deviations of AP velocities and displacement behaved in a very similar manner to that of the ML measures. All measures increased in both groups as stance width narrowed (figure 4.7 and 4.8)

Widespread significant main effects of *stance width* were reported ([Velocities: CoP: $F(2.9,81.2)=11.6$, $p=0.007$; trunk: $F(3.1,85.6)=8.6$, $p<0.001$], [Displacement: CoP: $F(4.0,112.0)=3.3$, $p=0.013$; trunk: $F(3.3,92.2)=2.8$, $p=0.042$]). SCA6 group mean measures

were larger than HCs, and widespread main effects of *group* were present ([Velocities: CoP: F(1,28)=16.3, p<0.001; trunk: F(1,28)=19.2, p<0.001], [Displacement: CoP: F(1,28)=9.9, p=0.004; trunk: F(1,28)=13.0, p=0.001]). Additional *stance width* by *group* interactions were observed ([Velocities: CoP: F(2.9,81.2)=7.4 , p=0.015; trunk: F(3.1,85.6)=8.6, p<0.001], [Displacement: CoP: F(4.0,112.0)=2.8, p=0.032; trunk: F(3.3,92.2)=2.6, p=0.055]). Post-hoc t-tests revealed significant group differences at the majority of stance widths but not for that of 32cm stance width values based on centre-of-pressure and trunk standard deviations of displacement (tables 4.9 and 4.10).

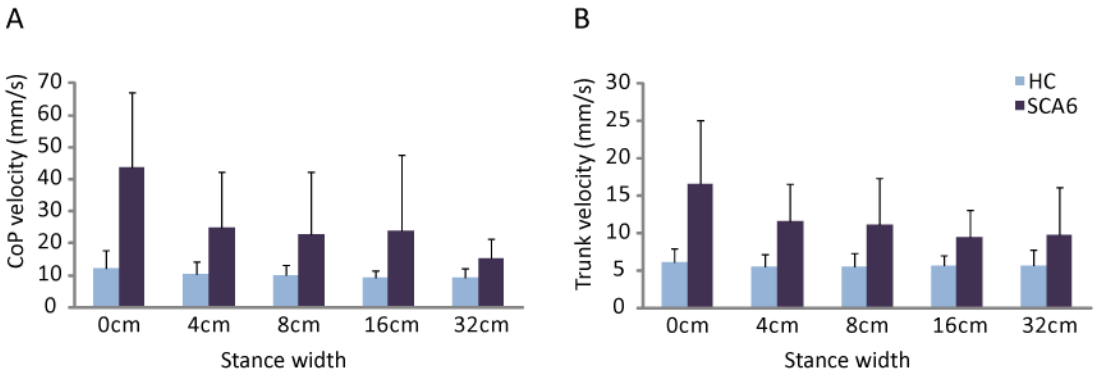


Figure 4.7: Group mean standard deviation of velocity measures in the anteroposterior direction.
Bar charts illustrate group mean measures based on centre-of-pressure (A) and trunk cluster (B) motion from five stance width conditions (left to right: 0, 4, 8, 16 and 32cm stance widths). Blue bars correspond to healthy control averages and purple bars to that of the SCA6 group. Error bars illustrate standard deviations of group measures.

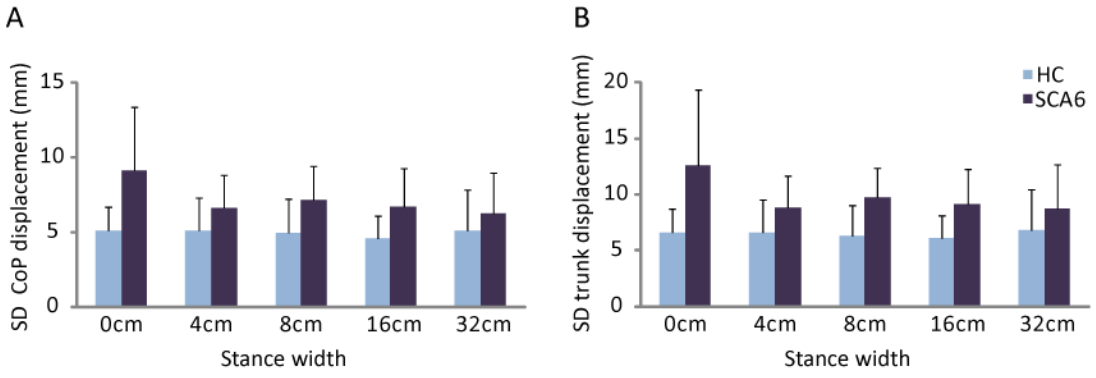


Figure 4.8: Group mean standard deviation of displacements in the anteroposterior direction.
Bar charts illustrate group mean measures based on centre-of-pressure (A) and trunk cluster (B) motion from five stance width conditions (left to right: 0, 4, 8, 16 and 32cm stance widths). Blue bars correspond to healthy control averages and purple bars to that of the SCA6 group. Error bars illustrate standard deviations of group measures.

Table 4.9: Post-hoc t-tests for CoP and trunk standard deviation of antero-posterior velocity data

Measure	Stance width	HC group mean (S.D.)	SCA6 group mean (S.D.)	t-value (d.f.)	p-value
CoP	0	12.3 (5.6)	43.8 (5.6)	-5.1 (15.6) †	<0.001
	4	10.3 (4.0)	25.0 (4.0)	-3.2 (15.5) †	0.006
	8	10.0 (3.4)	22.7 (3.4)	-2.5 (14.9) †	0.025
	16	9.5 (2.2)	23.9 (2.2)	-2.4 (14.2) †	0.032
	32	9.2 (2.8)	15.3 (2.8)	-3.6 (19.9) †	0.002
Trunk	0	6.1 (1.9)	16.6 (6.3)	-4.6 (15.3) †	<0.001
	4	5.5 (1.6)	11.6 (3.7)	-4.5 (16.9) †	<0.001
	8	5.5 (1.8)	11.1 (6.2)	-3.3 (16.4) †	0.004
	16	5.6 (1.4)	9.4 (5.0)	-3.7 (18.0) †	0.002
	32	5.7 (2.1)	9.8 (8.5)	-2.4 (17.1) †	0.029

† Equal variances not assumed according to Levene's test (p<0.05)

Table 4.10: Post-hoc t-tests for CoP and trunk standard deviation of antero-posterior displacement data

Measure	Stance width	HC group mean (S.D.)	SCA6 group mean (S.D.)	t-value (d.f.)	p-value
CoP	0	5.1 (1.6)	9.2	-3.5 (17.8) †	0.003
	4	5.1 (2.2)	6.6	-1.9 (28.0)	0.068
	8	5.0 (2.3)	7.2	-2.6 (28.0)	0.013
	16	4.6 (2.6)	6.7	-2.8 (28.0)	0.010
	32	5.1 (2.8)	6.2	1.1 (28.0)	0.287
Trunk	0	6.6 (3.6)	12.6	-3.3 (16.8) †	0.003
	4	6.7 (2.1)	8.8	2.1 (28.0)	0.046
	8	6.3 (2.7)	9.8	-3.5 (28.0)	0.001
	16	6.1 (2.8)	9.1	-3.1 (28.0)	0.005
	32	6.9 (2.1)	8.8	-1.4 (28.0)	0.174

† Equal variances not assumed according to Levene's test (p<0.05)

4.3.2.2 *Directional preponderance of instability quotients*

Quotients were calculated using AP and ML sway components to quantify directional preponderance of instability using both velocity and displacement data. (Quotient=AP-ML/AP+ML) Figures 4.9 and 4.10 illustrate these measures per stance width.

In all cases, *stance width* had a significant effect on the directional preponderance quotients ([Velocities: CoP $F(3.6,100.5)=22.6$, $p<0.001$; Trunk $F(3.1,88.0)=108.2$, $p<0.001$], [Displacement: CoP $F(3.8,106.5)=72.1$, $p<0.001$, Trunk $F(4.0,112.0)=62.4$, $p<0.001$]). No significant main effects of *group* were reported ([Velocities: CoP $F(1,28)=2.2$, $p=0.149$; Trunk $F(1,28)=0.9$, $p=0.357$], [Displacement: CoP $F(1,28)=4.1$, $p=0.052$, Trunk $F(1,28)=1.1$, $p=0.310$]). However, one *stance width* x *group* interaction was observed for centre-of-pressure standard deviations of velocity data ([Velocities: CoP $F(3.6,100.5)=3.6$, $p=0.011$; Trunk $F(3.1,88.0)=1.0$, $p=0.397$], [Displacement: CoP $F(3.8,106.5)=0.1$, $p=0.969$, Trunk $F(4.0,112.0)=0.9$, $p=0.460$]).

Post-hoc t-tests designed to explore the sole interaction reported in standard deviations of velocity data reported significant group differences at 0 and 4cm stance widths (table 4.11).

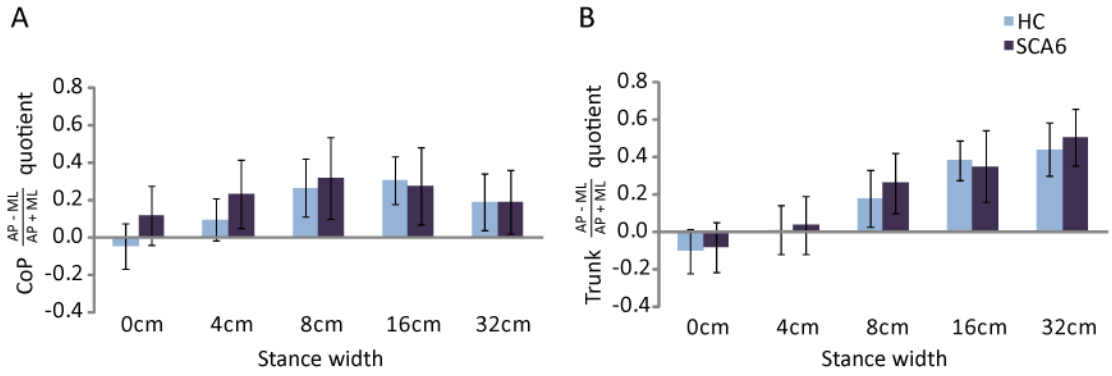


Figure 4.9: Group mean directional preponderance of sway quotients (AP-ML/AP+ML) based on standard deviations of velocity.
Bar charts illustrate group mean measures based on centre-of-pressure (A) and trunk cluster (B) directional preponderance quotients from five stance width conditions (left to right: 0, 4, 8, 16 and 32cm stance widths). Blue bars correspond to healthy control averages and purple bars to that of the SCA6 group. Error bars illustrate standard deviations of group measures.

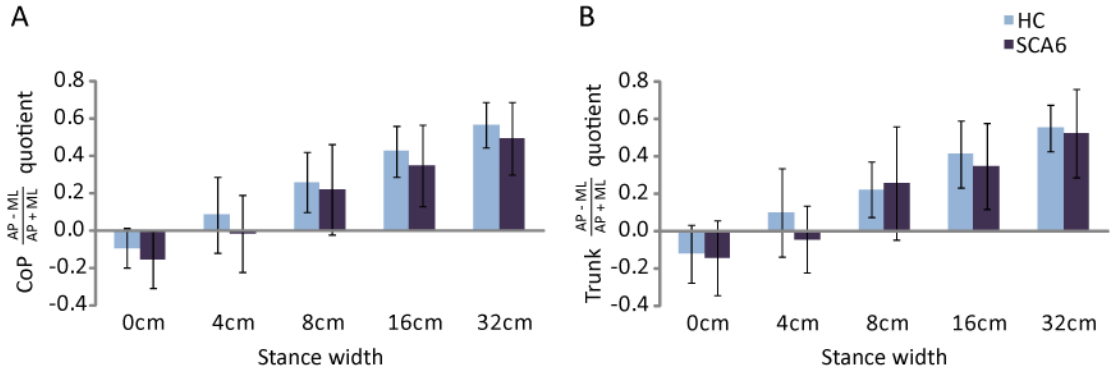


Figure 4.10: Group mean directional preponderance of sway quotients (AP-ML/AP+ML) based on standard deviations of displacement.
Bar charts illustrate group mean measures based on centre-of-pressure (A) and trunk cluster (B) directional preponderance quotients from five stance width conditions (left to right: 0, 4, 8, 16 and 32cm stance widths). Blue bars correspond to healthy control averages and purple bars to that of the SCA6 group. Error bars illustrate standard deviations of group measures.

Table 4.11: Post-hoc t-tests for CoP directional preponderance quotients of velocity.

Measure	Stance width	HC group mean (S.D.)	SCA6 group mean (S.D.)	t-value (d.f.)	p-value
CoP	0	-0.046 (0.120)	0.119 (0.157)	-3.2 (28)	0.003
	4	0.095 (0.112)	0.234 (0.180)	-2.5 (28)	0.017
	8	0.267 (0.154)	0.319 (0.217)	-0.8 (28)	0.449
	16	0.309 (0.128)	0.276 (0.208)	0.5 (28)	0.597
	32	0.189 (0.152)	0.193 (0.170)	-0.1 (28)	0.952

4.3.3 Segmental distribution of instability

Angular deviations (ADs) of joint angles were calculated in pitch and roll per stance width, per subject. Group average ADs for pitch and roll are plotted in figures 4.11 and 4.12.

In roll, effects of stance width were limited to knee and shank-on-ground measures of AD (head-on-trunk: $F(2.4, 66.0)=1.1$, $p=0.335$; trunk-on-pelvis: $F(1.6,45.1)=1.8$,$p=0.179$; hips:

F(2.2,63.5)=2.5, p=0.09; knees: F(2.0, 57.2)=3.4 , p=0.041 ; shanks-on-ground: F(1.2,34.5)=15.5 , p<0.001). An effect of *group* was solely reported for shank-on-ground ADs (head-on-trunk: F(1,28)=3.1, p=0.091 ; trunk-on-pelvis: F(1,29)=2.1, p=0.161 ; hips: F(1,29)=0.01, p=0.925; knees: F(1,29)=0.2, p=0.072 ; shanks-on-ground: F(1,28)=11.7, p=0.002). No significant interactions were reported, although shank-on-ground ADs were close to reaching significance (head-on-trunk: F(2.4, 66.0)=2.8, p=0.058 ; trunk-on-pelvis: F(1.6,45.1)=1.6, p=0.215 ; hips: F(2.2,63.5)=0.5, p=0.620; knees: F(2.0, 57.2)=2.8, p=0.672; shanks-on-ground: F(1.2,34.5)=3.2, p=0.074).

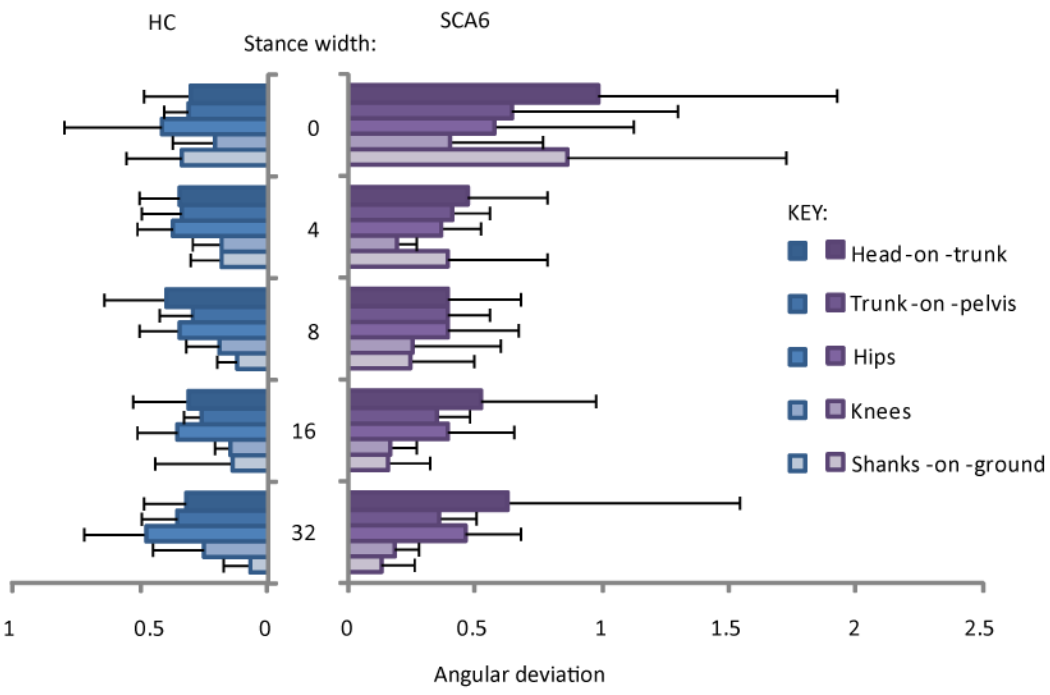


Figure 4.11: Comparing group mean joint roll instabilities.
Bar charts illustrate group mean joint roll measures of angular deviation from five stance width conditions (top to bottom: 0, 4, 8, 16 and 32cm stance widths). Blue bars correspond to healthy control averages and purple bars to that of the SCA6 group. Joints are defined by shading of colours, as set out in the key to the left of the figure. Error bars illustrate standard deviations of group measures.

In pitch, an effect of *stance width* was found at the hips and knees and shanks-on-ground (head-on-trunk: F(3.9,101.5)=1.6, p=0.183; trunk-on-pelvis: F(2.0, 58.4)=2.6, p=0.083; hips: F(1.7,49.8)=5.2, p=0.012; knees: F(2,57.2)=3.4, p=0.023; shanks-on-ground: F(2.6,72.2)=4.6, p=0.008). No group differences were found (head-on-trunk: F(1,26)=0.3, p=0.574 ; trunk-on-pelvis: F(1,29)=2.0, p=0.29 ; hips: F(1,29)=1.7, p=0.206; knees: F(1,29)=2.4, p=0.130; shanks-on-ground: F(1,28)=0.8, p=0.395). No interaction effects at any joint were found (head-on-trunk: F(3.9,101.5)=2.0, p=0.105; trunk-on-pelvis: F(2.0, 58.4)=2.3, p=0.106; hips: F(1.7,49.8)=2.3, p=0.120; knees: F(2,57.2)=1.5, p=0.243; shanks-on-ground: F(2.6,72.2)=0.1, p=0.997).

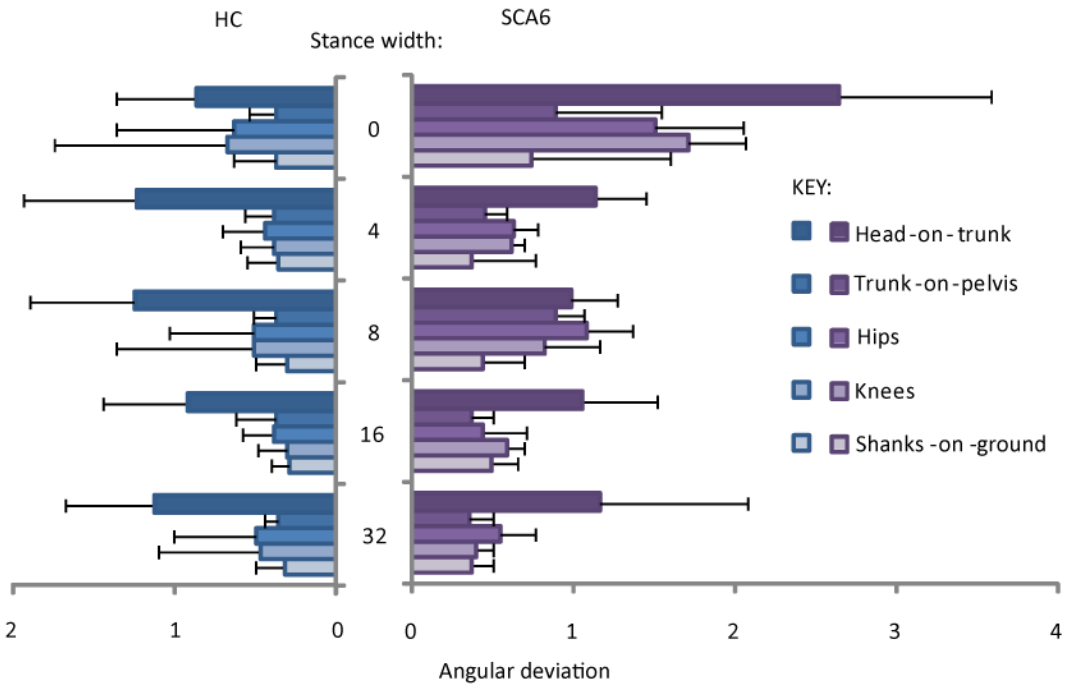


Figure 4.12: Comparing group mean joint pitch instabilities
Bar charts illustrate group mean joint pitch measures of angular deviation from five stance width conditions (top to bottom: 0, 4, 8, 16 and 32cm stance widths). Blue bars correspond to healthy control averages and purple bars to that of the SCA6 group. Joints are defined by the shading of colours, as set out by the key to the left of the figure. Error bars illustrate one standard deviation of group measures.

4.3.3.1 *Disease severity and clinical correlates*

Linear regression analysis was used to test the hypothesis that the degree of instability is related to SCA6 disease severity. Positive linear relationships were found for total SARA and instability measures. Pearson's correlation coefficients identified moderate to strong statistically significant correlations at all stance widths (table 4.12). The strongest correlation was for trunk sway speeds at a 4cm stance width (r=0.785, p=0.004).

Table 4.12: Correlation coefficients between clinical scores and sway speeds.

Measure	Stance width (cm)	SARA r (p)	Bal-SARA r (p)	FBS r (p)	Fall freq r (p)
CoP	0	0.73 (0.001)*	0.64 (0.006)*	-0.50 (0.039)	0.16 (0.740)
	4	0.68 (0.003)*	0.63 (0.007)*	-0.36 (0.150)	-0.42 (0.349)
	8	0.56 (0.020)	0.55 (0.021)	-0.44 (0.079)	-0.15 (0.749)
	16	0.51 (0.036)	0.40 (0.108)	-0.39 (0.120)	0.03 (0.942)
	32	0.68 (0.003)*	0.65 (0.005)*	-0.48 (0.051)	-0.05 (0.910)
Trunk	0	0.78 (<0.001)*	0.86 (<0.001)*	-0.58 (0.015)	-0.15 (0.746)
	4	0.78 (<0.001)*	0.88 (<0.001)*	-0.52 (0.032)	-0.23 (0.626)
	8	0.66 (0.004)*	0.71 (0.002)*	-0.52 (0.033)	0.03 (0.948)
	16	0.72 (0.001)*	0.66 (0.004)*	-0.47 (0.055)	-0.17 (0.722)
	32	0.69 (0.002)*	0.68 (0.003)*	-0.55 (0.023)	0.05 (0.920)

Key: SARA: Scale for the assessment and rating of ataxia; Bal-SARA describes just the balance sub-components of the SARA; FBS: Functional balance scale; Fall freq: Number of falls incurred over the last one month. Data indicates Pearson's coefficients and the statistical significance of the correlation in brackets. Asterisks (*) indicate significance at the adjusted level of p<0.01.

4.3.3.2 *Frequency components of postural sway*

On initial inspection of raw traces of trunk angle over time, signs of oscillatory activity between 2 and 3Hz were clearly visible, illustrated in figure 4.13. This activity appeared to wax and wane over all stance widths in an unpredictable manner, as illustrated from two collection periods of 40s duration where the two subjects clearly displaying this activity were adopting a 4cm stance width.

In an attempt to identify signs of 3Hz postural tremor or tremor that could affect posture, mean square spectrum estimates were calculated and plotted from roll and pitch measures of trunk angle over time (figure 4.14). Small peaks in power spectra were visible at 2.7 and 2.9Hz for the same subjects, whereas no indication of any 2-3Hz activity was observed in plots of other SCA6 subjects or healthy volunteers.

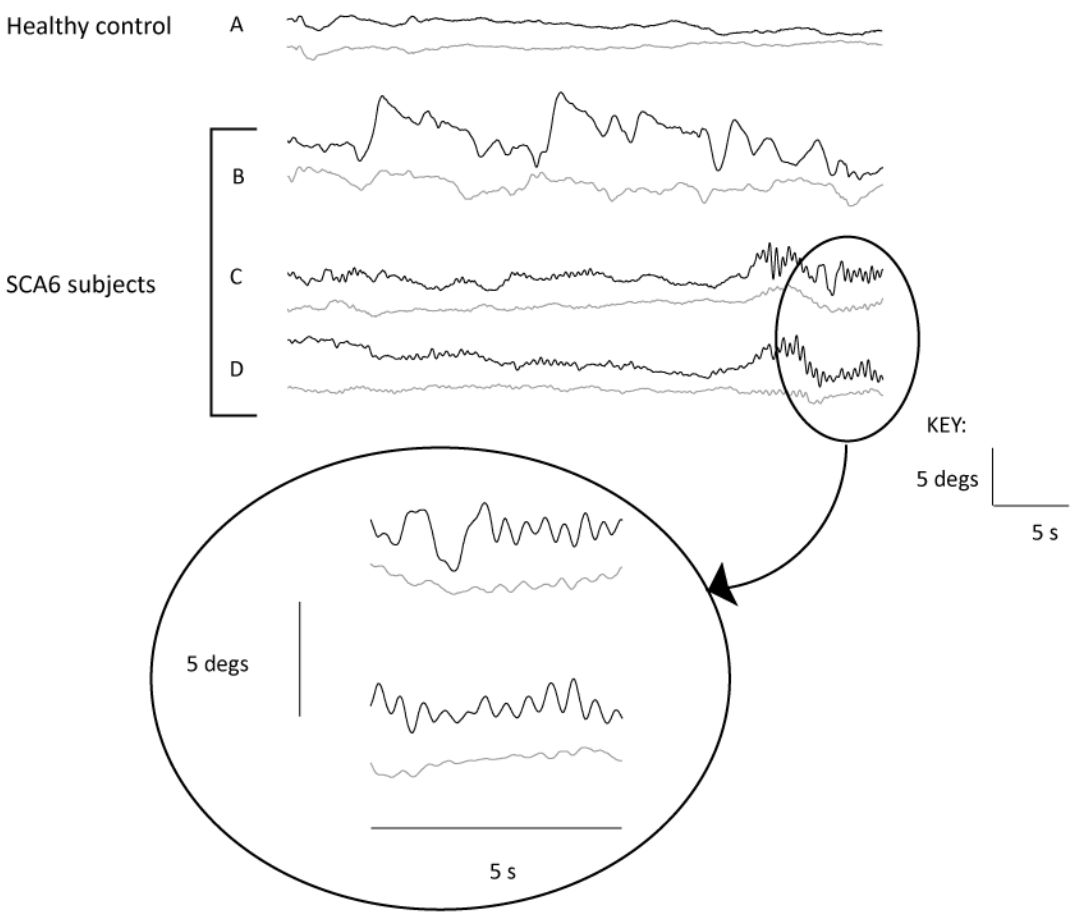


Figure 4.13: Raw trunk angle over time traces
Traces in the top row illustrate data from a typical healthy control (A). Underneath traces are derived from a typical subject with SCA6 (B) followed by two subjects displaying signs of 2-3Hz postural tremor (C and D). Traces are derived from 40 second durations of data collection with subjects stood in 4cm stance widths. Black lines illustrate trunk angle over time data in pitch and grey lines illustrate equivalent anglular data in roll.

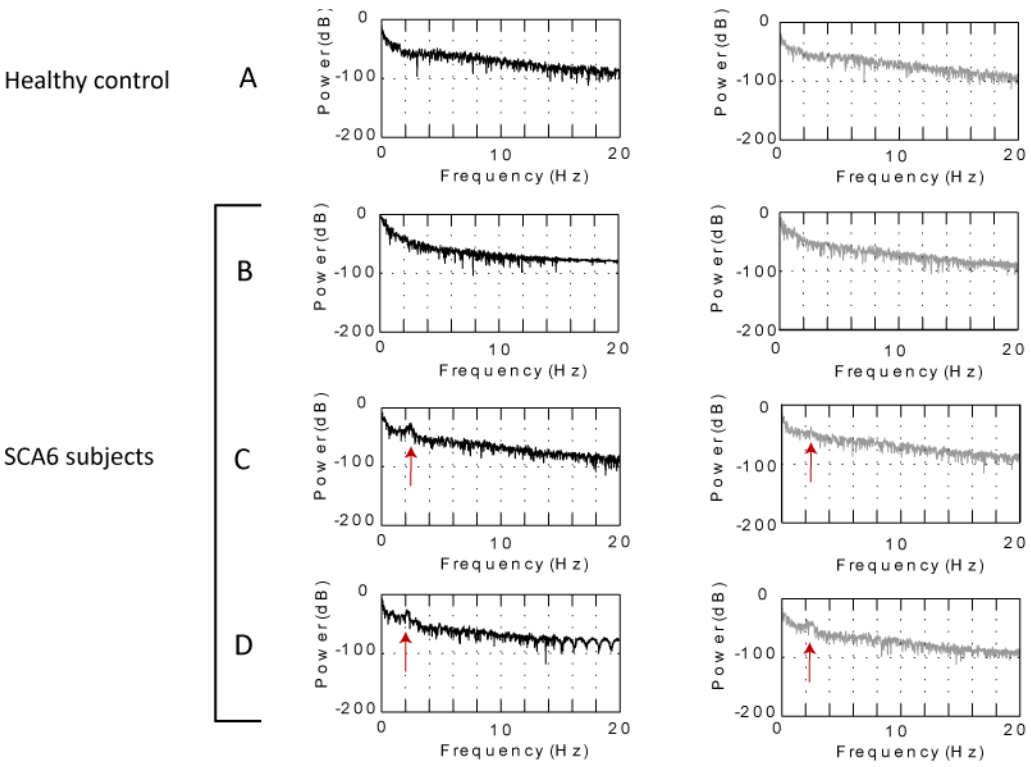


Figure 4.14: Mean-square spectrum estimates (MSSE) based on trunk angle over time data
Traces in the top row illustrate data from a typical healthy control (A). Underneath traces are from a typical subject with SCA6 (B) followed by two subjects displaying signs of 2-3Hz postural tremor (C and D), indicated by arrows. Traces are derived from 40 second durations of data collection with subjects stood in 4cm stance widths. The column to the left with black lines illustrates MSSE in pitch and grey lines to the right illustrate equivalent MMSE data in roll.

Decibel (dB) units of power were calculated and used to average the signal over five bandwidths (0-1, 1-2, 2-3, 3-4 and 4-5Hz). In using a log based formula to calculate this conventional measure of power ($10*\log_{10}(signal)$) this process also acted to improve the normality of the data in preparation for statistical analysis.

Initial analysis of average powers of signal per bandwidth showed no main effects of *stance width* (pitch: F(1.1,29.8)=3.3, p=0.078; roll: F(1.1, 29.8)=1.8, p=0.085). In order to simplify further analysis, average power measures were then averaged across *stance width* (figure 4.15).

ANOVAs showed main effects of *frequency* for both pitch and roll trunk angles measures of power (pitch: F(2.7,75.2)=760.1, p<0.001; roll: F(3.2,89.8)=522.6, p<0.001). Main effects of *group* were also present for both pitch and roll measures (pitch: F(1,28)=27.8, p<0.001; roll: F(1,28)=14.5, p=0.001). In addition to the main effects, strong *frequency x group* interactions were also reported (pitch: F(2.7,75.2)=9.6, p<0.001; roll: F(3.2,89.8)=4.8, p=0.003). Post-hoc t-tests reported group differences at all but 4-5Hz frequency bandwidths for roll power measures (outlined in table 4.13). Widespread group differences were reported for pitch power measures. On visual inspection of figure 4.17 (quantified in column 5, table 4.13), it is possible to see that the greatest increases in power occur at 2-3Hz bandwidths in both roll and pitch measures, where the greatest overall increase in power for the SCA6 group is at the 2-3Hz pitch bandwidth. This could explain the source of the interactions reported although this remains statistically unqualified.

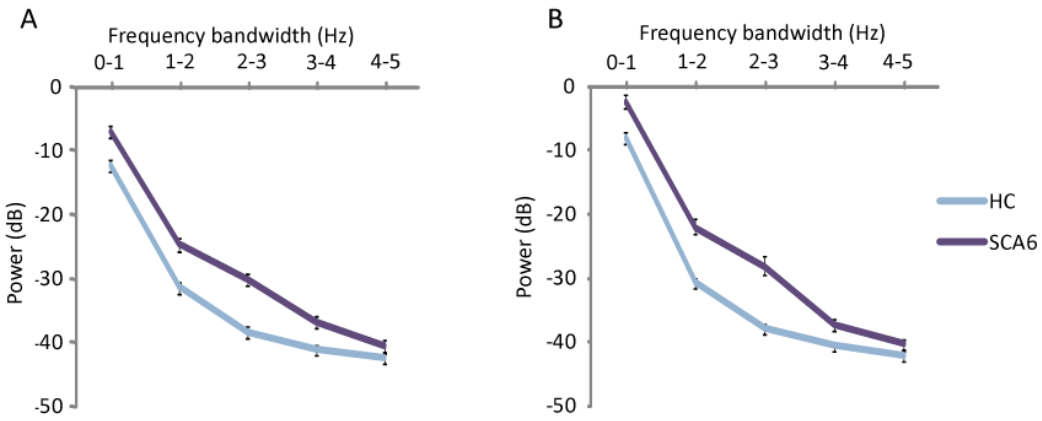


Figure 4.15: Group mean measures of power per frequency bandwith.
Power estimates of roll (A) and pitch (B) trunk angular deviations based on 40 seconds of data collection per stance width and averaged over power spectral estimates calculated for five stance widths (0, 4, 8, 16 and 32cm). Blue lines correspond to healthy control averages and purple lines to SCA6 group averages. Error bars indicate group standard deviations.

Table 4.13: Post-hoc t-tests for power measures per frequency bandwidth

Direction	Frequency bandwidth	HVS mean (SD)	SCA6 mean (SD)	(HVSmean-SCA6mean)	t (d.f.)	p-value
Roll	0-1	-1.2 (0.3)	-0.7 (0.5)	-0.53	3.3 (28)	0.003
	1-2	-3.1 (0.3)	-2.5 (0.6)	-0.67	3.7 (20.5) †	0.001
	2-3	-3.8 (0.4)	-3.0 (0.8)	-0.82	3.6 (20.3) †	0.002
	3-4	-4.1 (0.3)	-3.7 (0.5)	-0.42	2.8 (23.8) †	0.009
	4-5	-4.2 (0.3)	-4.1 (0.4)	-0.18	1.6 (28)	0.132
Pitch	0-1	-0.8 (0.3)	-0.3 (0.5)	-0.52	3.7 (28)	0.001
	1-2	-3.1 (0.2)	-2.2 (0.6)	-0.85	5.2 (18.1) †	<0.001
	2-3	-3.8 (0.3)	-2.8 (0.7)	-0.94	4.8 (17.8) †	<0.001
	3-4	-4.1 (0.2)	-3.7 (0.3)	-0.33	3.4 (28)	0.002
	4-5	-4.2 (0.2)	-4.0 (0.2)	-0.19	2.7 (28)	0.013

† Equal variances not assumed according to Levene's test ($p<0.05$)

4.4 Discussion

This investigation set out to describe freestanding, unperturbed balance behaviour in a sample of subjects with SCA6 and to explain how this behaviour is affected by stance width.

In doing so this study concentrated on six main themes:

1. **Whole body posture.**
2. **Quantification of whole body instability.**
3. **Directional preponderance of instability.**
4. **Distribution of instability throughout the body.**
5. **Frequency components of postural sway.**

In view of the above themes, the subsequent section will discuss the following main findings of the study: 1.) SCA6 disease processes do not appear to affect whole body posture, 2.) whole body instability measures are increased in those with SCA6, the extent of which is dependent on stance width 3.) instability appears to be of an omni-directional nature but with some conflicting evidence regarding directional preponderances related to stance width, 4.) roll motion at the ankle is significantly increased, 5.) frequency components of postural sway are generally increased and 6.) strong correlations exist between measures of disease severity and whole body instability.

The latter sections will then discuss the relevance of the results for current management of ataxia and the development of future therapies.

4.4.1 Instability and the effect of stance width

The findings of this study support prior reports of significantly increased whole-body sway in those with cerebellar ataxia [96] and contribute new knowledge regarding the nature of such instability in SCA6.

Average SCA6 group measures of instability were larger and more variable than healthy controls. Highly significant main effects of group, present in both medio-lateral and antero-posterior directional components of sway measures confirmed that SCA6 subjects are more unstable than healthy controls in both cardinal directions. In all cases group differences were accompanied with significant group by stance-width interactions, suggesting that stance width affects individuals with SCA6 differently to that of healthy subjects. In order to better explore the highly significant interactions between group and stance width, two strategies were employed. First, group differences in instability measures were analysed per stance width, revealing widespread highly significant differences. This strategy was not however sensitive enough to clarify interaction effects.

The second strategy sought to clarify interactions by evaluating how narrowing stance widths affect the proportional increase in the magnitude of instability per subject. Scatter-plots of instability measures against stance width were drawn, power law curves fitted and exponents extracted as measures of the effect of stance width per subject. These were significantly increased for SCA6 subjects meaning that as stance width narrowed, instability measures increased disproportionately relative to that of healthy controls.

The directional nature of instability was explored using a directional preponderance quotient (AP-ML/AP+ML). Positive quotients indicated an increase in antero-posterior sway relative to medio-lateral (negative quotients *vice-versa)*. Should there be equal measures of sway in each direction, this quotient would equal zero. Results showed that when subjects stood with their feet together, healthy control group mean values of instability indicated a mediolateral preponderance, but as stance widths increased so did the relative strength of the anteroposterior (AP) instability, leading to clear AP preponderances of instability from 8cm stance widths and above. This reflects the findings of Day *et al.* where the effect of stance width was previously investigated in healthy subjects [(79)]. A strong effect of stance width was observed for both groups in all measures which is comparable to these prior findings. No statistically significant group differences were reported based on these measures. This suggests that increases in the instability observed in our SCA6 group are omni-directional, which in turn suggests that SCA6 pathology is not associated with any directional preponderance.

Despite the lack of group difference in any of the measures of instability used, a significant interaction between *stance width* and *group* was reported based on centre-of-pressure

velocities. Post hoc t-tests used to further investigate this interaction revealed significant group differences at 0 and 4cm stance widths. At these stance widths, mean group quotients are positive and larger than healthy control measures, suggesting that subjects with SCA6 were more unstable in an anteroposterior direction. However, this result contrasts with data based on standard deviations of displacement where SCA6 group mean values were reduced compared with that of healthy controls, although this difference between groups was not statistically supported. This opposing trend between CoP velocity and displacement measures at 0cm and 4cm stance widths is also evident in trunk measures. The cause of this discrepancy between measures remains largely unknown. The presence of increased velocity quotients (indicating relatively increased AP velocities) with normal or reduced trend for AP displacements may suggest the presence of fast but low amplitude movements. In narrow stance widths, with the body acting as an inverted pendulum, these low amplitude movements could be due to small amplitude corrections around the ankle. This in turn may explain statistically significant increases in antero-posterior centre-of-pressure speeds but not trunk sway measures.

An alternative explanation for fast but low amplitude sway would be the presence of postural tremor. Postural tremor was indeed reported by Mauritz *et al.* [238], Diener *et al.* [96] and Van de Warrenburg [374] in those with anterior lobe cerebellar lesions, Friedriech's ataxia and other varients of SCA. Initial inspection of individual subject raw traces showed that two of seventeen of the SCA6 subjects had clear signs of postural tremor. This was of a similar nature to those with anterior lobe lesions in Mauritz *et al.*'s study in that it occurred between 2 and 3 Hertz and was predominantly in an antero-posterior direction. However, using analysis of power spectra derived from trunk angle over time data (a similar approach to that of Van de Warrenburg *et al.,* [374]) group average measures of power were found to be generally increased across bandwidths ranging from 0 to 5 Hertz. Widespread statistically significant group differences made bandwidth specific increases difficult to quantify. By subtracting average SCA6 bandwidth powers from healthy control measures it was possible to determine that 2-3Hz bandwidths held the greatest absolute increases, the largest of which was for that of pitch angular motion.

Larger pitch (AP) powers could provide support for a theory that postural tremor is responsible for an AP preponderance in SCA6 centre-of-pressure velocities but not displacement measures. However, it must be acknowledged that the difficulty in

statistically quantifying predominant frequency bandwidths ultimately questions the presence of tremor at all in SCA6. This factor, coupled with the lack of effect of stance width in postural tremor data, means that postural tremor is unlikely to fully explain the whole body instability observed in SCA6 and therefore must be considered with caution.

Overall, the initial hypothesis that all subjects with SCA6 would have 2-3 Hertz postural tremor due to the similarities in pathology with subjects with anterior lobe lesions, appears to be largely unsupported since tremor was only detected in two subjects. However, the existence of some postural tremor in the group also prevents this hypothesis from being refuted. The reason why such postural tremor would wax and wane and be limited to just two of seventeen subjects remains unclear. One theory could be that postural tremor is related to disease severity or disease duration, which in turn could be due to progression of damage of structures within the cerebellum, each associated with different functions. However, this did not appear to be the case as the subjects with tremor were neither those with the highest disease severity scores (SARA) or the longest disease durations.

An alternative theory is that some variability in terms of disease pathology exists in areas of the cerebellum, cell types or even in extra-cerebellar areas, which in turn could either be due to variability in SCA6 pathologies or even co-morbidities (such as chronic alcoholism). Despite reports by Hayashi *et al.,* describing 3 Hz postural tremor in varying types of cerebellar damage [(149)], Mauritz *et al.* [(238)] and Diener *et al.* (24) have suggested that the presence and frequency of such tremor is rather dependent on lesion location. For example, those with anterior lobe cerebellar lesions are said to exhibit 3 Hertz anteroposterior postural tremor whereas lesions specific to the vestibulocerebellum display slow <1 Hz omni-directional sway. Individuals with Friedriech's ataxia display 1.1 Hz laterally-directed sway and individuals with isolated lesions to the cerebellar hemispheres have no detectable differences in postural oscillation frequencies to that of healthy controls.

Although co-morbidities may be present, it is unlikely that this would not have been identified in the comprehensive neurological assessment undertaken with each SCA6 subject. However, despite the generally accepted homogenous nature of SCA6 presentations, recent SCA6 imaging studies have indeed suggested that subtle differences within SCA6 lesion distribution could produce variability of clinical presentation [(259,345)]. In order to explore relationships between the subtle variability of lesion location and balance

behaviour, careful analysis of each subject's magnetic resonance imaging (MRI) studies of the brain and spinal cord must be available, which was unfortunately not the case for this investigation.

Overall the results of this study suggest that instability in SCA6 is omni-directional and act to refute the general idea that anteroposterior instability is a key feature of cerebellar disease. Based on strong observed effects of stance width we can also suggest that stance width is a critical variable when attempting to quantify instability in SCA.

It is already well-documented that as stance widths narrow, whole body instability measures increase [(79)]. Consequentially most studies investigating instability control stance width between groups. However, our findings suggest that stance width has the potential to not only change the magnitude of instability but also the directional preponderance and relative rate of increase of magnitude of instability between groups. Based on these findings it seems necessary to make allowances for stance width when seeking to compare our results with those of prior studies.

Mauritz *et al.*'s early study of instability in those with cerebellar ataxia adopted a 4cm stance width with the feet splayed at an angle of approximately 30 degrees [(238)]. Although splay angle was not independently investigated in our study it is a factor that is known to affect stability [(67,241)] and for this reason was carefully controlled during data collection. Mauritz *et al.* reported prominent antero-posterior instability as a characteristic feature of cerebellar disease. Van de Warrenburg *et al.* also controlled for stance width during standing (and some functional activity tasks) by positioning feet at shoulder width [(374)]. Similar to Mauritz *et al.*'s findings, Van de Warrenburg *et al.'s* overall impression of instability in ataxic subjects was that it occurred predominantly in an antero-posterior direction.

Both of the above studies concluded that accentuated antero-posterior sway is a characteristic feature of cerebellar disease but when considering our findings with respect to the effect of stance width and what is known of splay angle it is possible that the lateral component of instability may have been underestimated. Van de Warrenburg *et al.*'s shoulder wide stance width was certainly likely to optimise lateral stability relative to AP and Mauritz *et al.,* despite using a 4cm stance width, used a relatively wide splay angle which, one could hypothesise, would also improve lateral stability.

Despite the lack of support for omni-directional instability from similar studies incorporating

physiological measures of postural stability, findings from fall analyses and postural balance perturbations provide some encouragement for this claim in this patient group [22,373,374]. A recent study of falls in cerebellar ataxia by Van de Warrenburg *et al.,* exclusively studied SCA subjects (a mixed sample of hospitalised fallers) and found that they fell frequently and in all directions as a consequence of postural instability [373]. Furthermore, with the use of platform perturbations to enable measurement of dynamic balance responses in standing subjects, Bakker *et al.,* (4) used a group of SCA subjects with relatively uncomplicated ataxia (either absent or mild extra-cerebellar clinical signs) to report that the subjects were most unstable following either backwards or lateral perturbations, once again implying that instability affected both cardinal directions.

In addition to stance width, another factor which could explain the difference in findings observed between this and prior studies is the distinct difference in pathologies which have been measured in each case. In the case of this study, only subjects with SCA6, a pure cerebellar ataxia, were recruited. Inventories of non-ataxia symptoms were used to confirm the homogeneity of the group and subjects with co-pathologies, histories of neurological illness or any musculo-skeletal problems that may impact on balance function were excluded. In the case of Diener *et al.,* and Mauritz *et al.,*'s studies, groups of subjects with different types of acquired cerebellar disease were studied [96,238]. Similarly, Van de Warrenburg *et al.,* used a relatively heterogenous group employing individuals with varied SCA types (including SCA types with spinal cord and peripheral nerve pathologies) [374]. It is therefore feasible that the findings reported in this study are unique to subjects with SCA6 and perhaps non-transferable to the wider population of cerebellar disease. Differences described by Mauritz *et al.,* according to variable cerebellar lesion locations provide some justification for this theory [238]. By studying subgroups of subjects with cerebellar disease they determined that those with anterior lobe lesions (following chronic alcoholism) had dominant anteroposterior sway. Individuals with hemisphere lesions, genetically indetermined diffuse cerebellar damage or Friedreich's ataxia, were however reported to have instability that was less dominant in this direction. They also reported that in terms of just directional components of sway some cerebellar subject data is comparable to that of the healthy control group.

We therefore postulate that individuals with SCA6 possess omni-directional instability. We also postulate that the classically observed wide stance widths adopted may be due to

narrow stance widths disproportionately increasing multi-directional instability putting individuals with SCA6 most at risk of compromising upright balance.

4.4.2 The distribution of instability

In order to understand balance in SCA6 not only the degree of instability and the directional nature but also the distribution of instability throughout the body is of interest. For this reason individual measures of joint instability were evaluated across all stance widths. This involved calculating angular deviations, which represent the average angular excursion per joint over time. Since it is feasible that posture could affect joint kinematics and therefore angular excursion, measures of average subject postures (mean angles per joint) were also calculated to provide an indication of the likelihood of this.

Initial analysis of posture revealed no significant differences between mean joint positions and although SCA6 subjects often visibly alter their posture during use of walking aids it seems reasonable to conclude that SCA6 balance impairments are unlikely to be due to fixed postural abnormalities. These findings also provide assurance that posture was unlikely to bias group differences in stability thus enabling clearer interpretations of findings derived from joint instability data and future analysis of balance.

As already discussed, it is well documented in healthy control subjects that wider stance widths are associated with improved stability in both ML and AP directions [151,186]. For healthy control subjects adopting narrow stance widths (of 8cm or less) it has been reported that most angular roll motion occurs at the ankle, whereas for wider stance width conditions, motion is distributed more evenly throughout the trunk and legs {Day, 1993 13 /id}. Angular deviation measures of instability for healthy controls in this study are comparable to these prior reports but there are two main differences in the case of SCA6 angular deviation measures. Firstly, although not statistically different, SCA6 group mean measures of angular deviation (AD) were slightly increased at all joints, across all stance widths and in both roll and pitch directions of motion compared to that of healthy controls. Secondly, statistical analysis revealed significant differences between groups for ankle angular deviations in roll.

It has been suggested that decreasing whole body sway in the ML direction with increasing stance width may be due to more efficient load shifting between legs controlled by hip abductors and adductors [394] and improved mechanical coupling between bilateral hip and

ankle joints [79]. In the case of those with SCA6, it is therefore possible that a lack of motor control at the ankle could be responsible for the observed increases in AD and general instability. An alternative theory may be that rather than a cause of instability, ankle AD is increased because it has the greatest role in controlling instability, where this is a consequence of poor control at another level. In this instance, whole body instability could be due to a combination of some or all axial joint in-coordination, each joint contributing a small role in disturbing upright stance but summating to cause gross instability.

A further alternative theory is that instability is not due to lack of motor control at all and all joint activity is increased to compensate for a sensory dysfunction, intensified when the feet are brought together due to summative biomechanical constraints. For example, with the feet together, the mechanically coupled and effectively stiffened legs-pelvis structure becomes less optimal for the production of abduction/adduction movements used to control medio-lateral sway [151]. The hips may also become less sensitive to proprioceptive stretch afferent signals which could code for changes in hip position over time; a form of feedback for overall control of balance [79]. This would reduce the overall sensitivity for the control of balance as well as efficiency of control resulting in increased instability. In contrast to the findings of this study, Oude *et al.,* previously described reductions in knee and pelvic angular measures of excursion in those with SCA and suggested a stiffening strategy as the cause of such findings [271]. The difference in results between those of Oude *et al.* and our own is not surprising given the different activities being measured in each case. In Oude *et al.*'s study, angular excursion was measured after platform perturbations (with and without knee casts), which is a very different scenario to just measuring freestanding balance.

4.4.3 Inferences for management of SCA6

SARA scores were found to correlate well with the main measures of whole body instability. These highly significant correlations may be of interest for two reasons. Firstly, they could provide clinicians with increased confidence that the already simple, validated method of assessing disease severity can provide an insight into patients' underlying level of balance impairment. Secondly, they suggest that the instability measures used may provide a more continuous and therefore potentially more sensitive method of measuring changes in disease severity over time. This may be particularly important when attempting

to assess the effectiveness of either drug or therapeutic interventions over time-periods where, due to the notoriously slow progression of the disease, no change in SARA score may be expected for up to 1-2.5 years (Schmidt-Hubsch, 2009, personal communication). However, despite potential benefits, caution must be encouraged if attempts are made to generalise these interpretations to wider populations of subjects with ataxia. Since this group of SCA6 subjects were known to present with balance impairment and possessed no additional extra-cerebellar symptoms, it is logical to hypothesise that strong correlations may be observed. It therefore also stands to reason that other ataxia types with more variable presentations of symptoms, including non-ataxia symptoms, may yield weaker correlations and hence require different interpretations of such relationships.

4.4.4 Development of future therapies

There is a clear need for therapies to be designed and trialled in order to enable research-based practice to be an option for those looking to treat SCA6 patients with balance impairments. However, in lieu of current clinical trials advising practice, clinicians must rely on clinical reasoning based on knowledge of the condition in question.

In view of our reports of increased instability in all directions, incorporating a multi-directional approach to balance exercises may be of some benefit.

Similarly, in view of the strong correlations reported between disease severity scores and instability measures at 4cm stance widths, perhaps training in this position may elicit improvements at an impairment level, which could be key to producing more general functional improvements.

Through a comprehensive examination of whole body inter-segmental instability, this study may also have highlighted the ankle as a potential therapeutic target. Increased measures of angular excursion at the level of the shank on the ground points to increased motion within the multiple foot and ankle joints. In the absence of any known passive (ligamentous) changes at the foot and ankle in SCA6, this would implicate abnormal motor activity of the invertors and evertors. Further investigation of this activity in these muscles may be of benefit in helping to identify whether this may be associated with the cause or control of instability. However, in the meantime, trials of potential treatment ideas could involve attempts to stabilise the foot/ankle complex passively using splints or dynamically through targeted muscle training.

Despite ideas for therapies based on the abnormal results of the SCA6 group in this study, it is also important to remember the normal findings. For example, it has already been discussed that increased shank-on-ground roll angular excursion is unlikely to account for the multi-direction instability observed across all stance widths, so at best targeting the ankle could help with only some of the observed balance impairment. Although group mean values for joint angular deviations were slightly increased relative to healthy subjects, a lack of statistically significant group differences also acts to refute the theory that instability is caused by general inter-segmental instability. Abnormal posture has been excluded and the role of postural tremor as a potential cause of instability remains questionable.

If the cause of balance impairment in SCA6 is to be fully understood, further research is clearly needed.

4.5 Conclusion

SCA6 subjects with isolated cerebellar degeneration and pure presentations of ataxia have accompanying omni-directional whole body instability. The extent and distribution of instability is greatly influenced by stance width. Narrow stance-widths appear to yield the biggest group differences in instability measures. There is also limited evidence of invasion of an antero-posterior preponderance to instability.

Increased ankle instability appears to feature in those with SCA6, which may be one potential target site for therapeutic intervention.

For the purpose of testing any future therapeutic interventions, instability measures (such as trunk sway speeds) from subjects stood at 4cm stance widths with minimal foot splay may provide an effective continuous outcome measure for evaluating future therapies.

The SARA appears to have some potential as a measure for evaluating SCA6 balance impairment in future clinical trials, but it would be desirable for this and other outcome measures to be properly validated for this purpose.

In addition to improved knowledge of balance impairment in SCA6 this study also highlights the need for future research to investigate the effect of variable cerebellar pathologies on instability outcome measures. In the meantime caution is advised when selecting cerebellar groups for the purpose of describing instability or trialling balance therapy interventions.

5 CHAPTER FIVE: BALANCE RESPONSES TO VESTIBULAR PERTURBATIONS

5.1 INTRODUCTION

The widespread distribution of Purkinje cell loss in SCA6 makes it feasible that lesions could affect a variety of cerebellar functional processes [129]. Prior research has suggested that the cerebellum may be involved with sensory processing such as inputting, weighting, combining and using sensory sources of information to synthesise and direct the execution of motor responses such as those used in balance control [17,397,398]. Despite reports of widespread cerebellar atrophy in SCA6, autopsies and MRI studies have revealed that atrophy of the cerebellum tends to be primarily due to Purkinje cell loss in the superior and anterior parts of the cerebellar vermis, hemispheres and the flocculus [129]. The vestibular and fastigial nuclei are additionally affected with mild to moderate gliosis [129].

Given that extracerebellar pathologies are uncommon and balance impairment is a key feature of SCA6, it seems reasonable to hypothesise that areas of Purkinje cell loss in the cerebellum may be functionally responsible for balance impairment.

Functional roles of the cerebellum have long formed the basis of scientific investigations and as discussed in chapter 1, a strong body of evidence now points to a role in vestibular processing for the vestibular and fastigial nuclei. Numerous reports have acted to support the suggestion that superior and anterior parts of the cerebellum (the spino-cerebellum) have abundant connections with the vestibular nuclei [188,227,228,229,290] and that these parts also have a role in processing vestibular afferent information alongside spinal (proprioceptive) afferent signals. The flocculonodular lobe (part of the vestibulo-cerebellum) has also been implicated in vestibular processing alongside afferent signals concerned with extra-ocular control of vision, seemingly having a key role with the vestibulo-ocular reflex (VOR) and pursuit of objects [164,329,388].

The superior and anterior vermis, vestibular and fastigial nuclei and flocculo-nodular lobe are therefore all closely associated with vestibular processing and are all structures reported as damaged in SCA6. It therefore seems feasible that vestibular processing abnormalities could be responsible for balance impairment. Suggestion that signs of central vestibular dysfunction are common in patients with SCA6 by Yu-Wai-Man *et al*. [402] further lends justification for this theory.

5.1.1 Purpose

This chapter tests this theory by investigating vestibular processing in a well-defined group of subjects with SCA6.

5.1.2 Experimental aim

To understand how vestibular processing abnormalities caused by cerebellar damage in SCA6 may be responsible for balance impairment.

5.1.3 Hypotheses

Knowledge of cerebellar connectivity, function and cerebellar damage in SCA6 discussed in chapter one has been drawn upon to set out the following hypotheses for causes of balance impairment.

1. **Vestibular processing abnormalities limit the propagation of vestibular signals within the cerebellum.** This would in turn disrupt generation of motor responses triggered by vestibular signalling of balance perturbations. Absent or smaller than normal responses to vestibular stimuli in those with SCA6, particularly in those severely affected, would provide support for this hypothesis. To test this hypothesis isolated vestibular perturbations were delivered and compared with no-stimulation but otherwise identical conditions. Whole body motion was analysed to assess the form of this motion as a response to the perturbation.
2. **Vestibular processing abnormalities affect central scaling of the afferent signal.** This would lead to generation of insufficient or under-scaled motor responses. Consistently smaller than normal responses to vestibular stimuli in those with SCA6 would provide support for this hypothesis. Correlations between disease severity and response size would further strengthen support for this hypothesis. To test this hypothesis isolated vestibular perturbations were delivered and whole body responses magnitudes measured.
3. **Integration of binaural vestibular afferent signals is disrupted**. This would involve errors at the point of combining right and left vestibular nerve afferents. If this was the case, a constant offset in the directional interpretation of the

perturbation may occur. This would lead to a constant directional bias relative to head-on-feet coordinates in motor responses. Constant directional errors in SCA6 response directions to vestibular stimulation relative to head-on-feet posture would lend support for this hypothesis. Correlations between disease severity or baseline measures of instability and the size of the directional error of the motor response would further strengthen support for this hypothesis. To test this hypothesis, isolated vestibular stimulation, designed to deliver either forward or backward vestibular perturbations, were delivered to subjects standing in head-turned postures and response directions calculated relative to starting head-on-feet positions.

4. **Integration of vestibular and proprioceptive signals is disrupted**. This would involve errors at the point of combining craniocentric vestibular signals with proprioceptive postural (head-on-feet) signals. In this case, there could be an under or overestimate of head-on-feet position or in the most extreme case, no reliable estimate of this at all. In accordance with this hypothesis, directional errors due to mis-estimation of head-on-feet positions would not be in a constant direction but rather a function of the degree and direction of head turn. Figure 5.1 uses overhead views of subject's with their heads turned either right or left to illustrate this idea. Starting head positions are visible by the inclusion of noses in diagrams and further highlighted by black full lines with arrowheads. If subjects have their head turned to the right (upper row) and receive vestibular stimulation causing a craniocentric perturbation in the direction of the right ear (using L anode, R cathode polarity GVS), they should respond by swaying in the direction of the left ear. Vice-versa, if subjects receive vestibular stimulation involving a craniocentric perturbation to the left; they respond in the direction of the right ear. These ideal response directions according to polarity are illustrated using black dotted arrows. If the angle of the head turn to the right is *overestimated* relative to the feet (right column, upper row) what results is a negative error in response angles. In contrast, if the angle of the head turn to the right is *underestimated* relative to the feet (left column, upper row) what results is a positive error in response angles. Mis-estimation of head-on-feet angles are illustrated with red head positions.

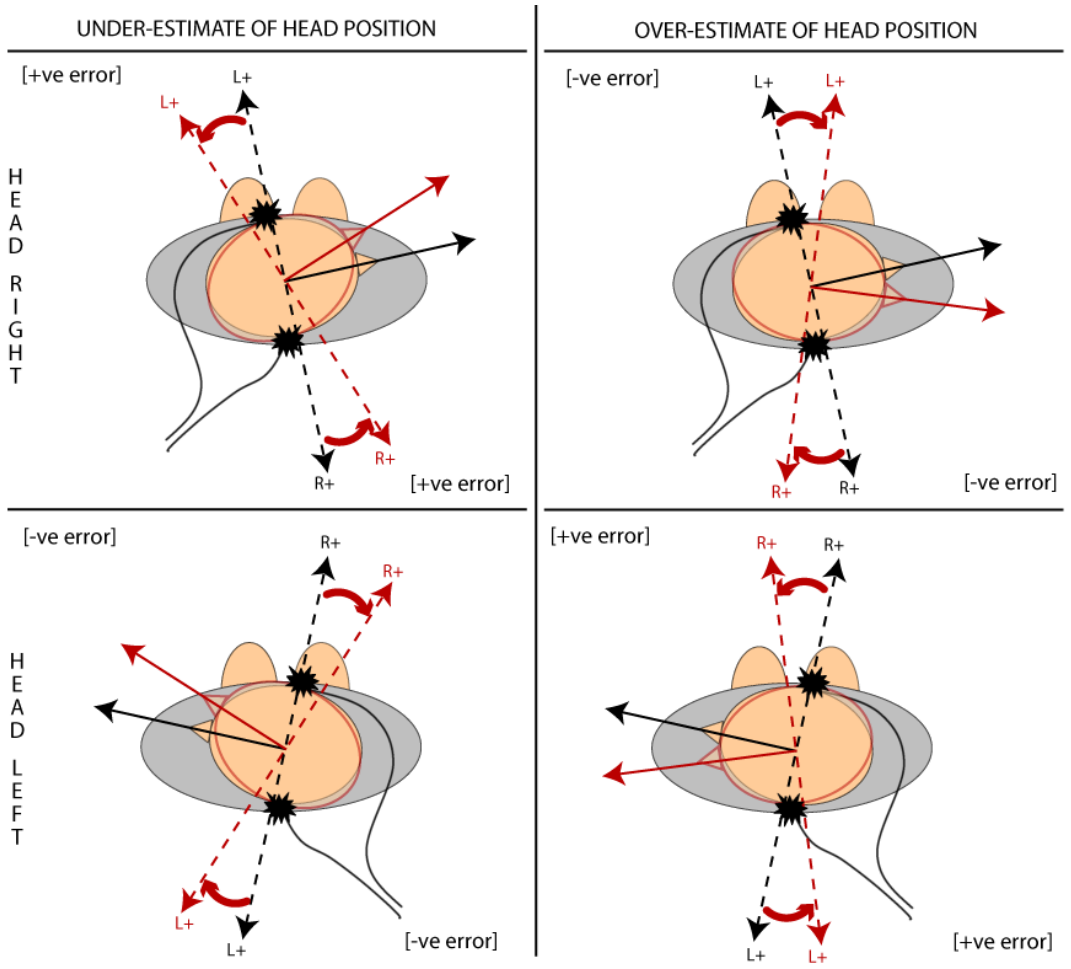


Figure 5.1: Hypotheses of head-on-feet angle mis-estimations.
Overhead views of SCA6 subject's expected response directions are provided in columns according to the hypotheses concerning mis-estimation of starting head yaw angles. Starting head positions (SHP) of subjects are highlighted by black lines projecting outwards from the naso-occipital line. Black dotted arrows show the ideal response direction relative to the SHP per polarity and head direction. Red outlines of the head and full red lines illustrate hypothesised mis-estimations of SHPs. Red dotted lines illustrate the expected response direction should the SHP be miscalculated. Thick red arrows illustrate the direction of error expected according to head turn, GVS polarity and SHP mis-estimation. Clockwise changes in response angles indicate negative errors and anticlockwise angle changes indicate positive errors.

Expected response directions according to the mis-estimation and polarity of vestibular stimulation used are illustrated by red dashed arrows. Lower rows illustrate the same principals of the hypotheses for left head turn conditions. By contrasting upper and lower figures it is possible to see that response angle errors should be equal and opposite, dependent on head turn. In order to test this hypothesis of mis-estimation of head-on-feet error, response directional errors will be calculated and compared between subjects. If subject responses have positive errors with the head right and negative errors with the head left, this would support the hypothesis of an initial under-estimate of head-on-feet

angle (left column). If they have negative errors with the head right and positive with the head left, this would support the hypothesis of an initial over-estimate of head-on-feet angle (right column). To test this hypothesis, isolated vestibular stimulation, designed to deliver either forward or backward vestibular perturbations, were delivered to subjects standing in head-turned postures.

5. **Integration of vestibular and-*visual* signals is disrupted.** This would lead to a reduced or absent effect of vision on motor response magnitudes. To test this hypothesis SCA6 responses to isolated vestibular perturbations were measured during two visual conditions: 1.) Vision intact (VI). 2.) Vision obscured (VO) with the use of liquid crystal spectacles. Quotients of response size with vision obscured to vision intact will be calculated and analysed for differences between groups of healthy volunteers and those with SCA6. If significant differences are reported and ratios are smaller for those with SCA6 then findings lend support for a vestibular-visual combining abnormality hypothesis. Further support for the hypothesis would be if reductions in ratios were to correlate with SCA6 disease severity measures or baseline measures of instability. If ratios are increased in those with SCA6, this may also lend support for this hypothesis, although this could alternatively be due to overuse of visual information as a compensatory strategy to optimise balance. Correlations between SCA6 disease severity scores and increased ratios would act to strengthen the idea that abnormal use of visual information is associated with SCA6 but would require further investigation to ascertain the nature of this association.
6. **Sensori-motor timing is not disrupted.** Based on the lack of significant peripheral and spinal nerve abnormalities reported for those with SCA6 I hypothesise that balance impairment is not caused by delayed motor responses secondary to neural signal slowing. To test this hypothesis, responses to isolated vestibular stimulation will be averaged across all available trial repeats and the latency of the earliest measure of the response will be calculated. A lack of significant differences between group latency measures reported by t-tests will in this case act to support the hypothesis.

5.1.4 Approach

Binaural galvanic vestibular stimulation (GVS) was employed to test the outlined hypotheses, described in the introduction and methods sections (chapters 1 and 2), to deliver vestibular perturbations. GVS delivers isolated vestibular nerve signals to cause controlled and repeatable experiences of balance perturbations. In response to these perturbations, standing subjects sway in the direction of the anodal ear [60,82].

In order to evaluate response magnitudes, identical doses of GVS will be delivered to a group of subjects with SCA6 and age-, sex and height-matched healthy subjects. A full description of subject characteristics per group involved in this initial testing day can be found in chapter 2.

In order to investigate directional organisation of head-referenced vestibular signals in SCA6, response directions to GVS will be delivered with subjects stood with their heads turned 90 degrees right or left (relative to feet position) under otherwise identical conditions with vision occluded. Absolute head directions will be calculated and response directions normalised to start head position (SHP) in all cases to prevent bias. Using binaural bipolar GVS, responses are expected to occur in the direction of the anodal ear [82]. By switching polarity between trials we can expect to find response directions changing according to which of the two electrodes delivered anodal current. By turning the head relative to feet position, we can further expect the response to re-orientate in laboratory space to always occur in the direction of the anodal ear [217]. Analysis of directional measures of responses will enable evaluation of vestibular and proprioceptive combining processes. Delivery of GVS whilst vision is obscured will ensure that responses will primarily be a consequence of isolated vestibular signal changes. Measurement of early force responses from 0.2s to 0.4s following stimulation onset (FSO) will allow us to assess response characteristics free from re-afferent effects. It is generally accepted that early measures of sway (from 0.2s to 1s FSO) also allow assessment of early whole body motion response characteristics free from re-afferent effects. In order to contrast these measures with later sway, likely to be modified by re-afferents, secondary analysis will include assessment of sway between 0.2s and 2s FSO.

Delivery of identical GVS perturbation conditions with *vision available* will enable comparison of response magnitudes for the purpose of evaluating vestibular and visual

combining processes. Testing all hypotheses within the same experimental protocol not only promotes efficiency but also aids randomisation of conditions to prevent subjects from predicting a trial sequence.

Disease severity and baseline sway measures collected within the same experimental session (described in chapters 3 and 4 respectively) will be compared with GVS response measures after initial analysis for differences. Strong correlations between SCA6 baseline measures of disease severity or sway speed and response measures, such as magnitudes, directional errors or effect sizes of vision, may act to support inferences that abnormalities may be due to underlying SCA6 disease pathology. Correlations with baseline sway speeds which are also present between healthy control response measures may act to challenge any inferences that SCA6 correlations are due to disease processes. Rather, this finding may suggest that any group differences are more likely an epiphenomenon of increased baseline sway.

5.2 Method

This study was conducted during testing day one, following quantification of balance behaviour in freely standing subjects (chapter 4).

Twelve conditions relevant to testing the experimental hypotheses are set out in table 5.1. Ten trial repeats per condition were collected in order to obtain an average response per condition per subject.

Table 5.1: Condition coding.

Condition no.	Condition type	Abbreviated condition code
1	Vision obscured, no stimulation, head right	VO NS HR
2	Vision obscured, no stimulation, head left	VO NS HL
3	Vision obscured, GVS (right anode, left cathode), head right	VO RA HR
4	Vision obscured, GVS (right anode, left cathode), head left	VO RA HL
5	Vision obscured, GVS (left anode, right cathode), head right	VO LA HR
6	Vision obscured, GVS (left anode, right cathode), head left	VO LA HL
7	Vision intact, no stimulation, head right	VI NS HR
8	Vision intact, no stimulation, head left	VI NS HL
9	Vision intact,, GVS (right anode, left cathode), head right	VI RA HR
10	Vision intact, GVS (right anode, left cathode), head left	VI RA HL
11	Vision intact, GVS (left anode, right cathode), head right	VI LA HR
12	Vision intact, GVS (left anode, right cathode), head left	VI LA HL

5.2.1 SUBJECTS

Subject recruitment, inclusion criteria, ethical considerations and safety equipment have been described in detail in chapter 2.

5.2.2 PROCEDURES

Subjects stood in the middle of the laboratory. Each foot was placed symmetrically over two abutting force plates where the medial border of each foot was aligned to parallel lines drawn on the floor spaced 4cm over two force plates.

Binaural bipolar galvanic vestibular stimulation (GVS) was used to create repeatable, controlled vestibular perturbations. GVS was delivered in the middle two seconds of six second long trials, the sequence of which is outlined in figure 5.2.

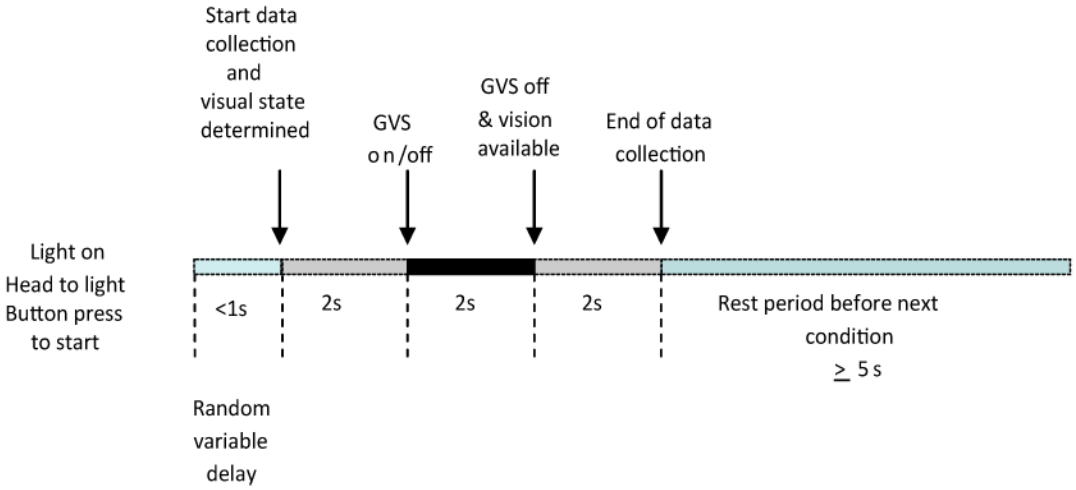


Figure 5.2: Diagramatic representation of trial sequence
Trials followed a standardised timed series of state changes according to condition. Block colour changes correspond with data collection start and stop times as well as potential plato spectacle and GVS state changes.

At the start of the procedure, subject's feet were aligned to the y-axis of the laboratory. Prior to delivery of GVS, subjects were positioned according to lighting prompts so that their head was either ±90 degrees yaw (right or left) of their feet. The availability of vision was determined using Plato spectacles within a pre-constructed control programme. The application of GVS and control of vision and posture has been explained in detail in section 2.1.5. Collectively, control of these factors enabled data collection during the different multi- sensory system variations, outlined in table 5.1. All conditions, including vision (intact/obscured), head position (right/ left) and GVS (no stimulation or stimulation; with right anode or left anode) were intermixed and randomly organised with a depth of two.

This sequence of trials was written to file and looped five times in order to achieve 10 repeats of each condition per subject.

To avoid fatigue, subjects were free to request a rest at any point and all subjects were advised to have a seated rest after every 20 trials. Subjects with SCA6 were advised to look out for feelings of tiredness and fatigue and the trial was stopped if these feelings were not recovered after a seated break. For this reason not all were able to complete the full number of trial repeats.

5.2.3 Instrumentation

5.2.3.1 Galvanic vestibular stimulation (GVS)

GVS was delivered using a custom made generator via two 2.5cm diameter self-adhesive disposable Ag/AgCl electrodes (PALS) secured to mastoid processes using Micropore (3M) tape (see figure 5.3A). Electrode gel (Signa gel, Parker Lab.) was applied to the surface electrodes to reduce impedance. Subjects' ears were taped to avoid unnecessary stimulation of cutaneous afferents (figure 5.3A).

A dose of 1mA square-wave constant current [113] was applied for 2 seconds per GVS trial. A binaural bipolar type of GVS was used where the polarity was changed according to condition to alter the direction of the response. Subjects therefore received either right anode + left cathode (GVS_r+) or left anode + right cathode (GVS_l+) stimulation conditions.

Two seated practice trials involving delivery of GVS were undertaken with each subject, once with vision intact and once with vision obscured at the start of each session involving the use of GVS (figure 5.3B). This allowed each subject to experience the sensation of the stimuli. By administering this 'practice stimuli' whilst subjects were still seated, first trial standing balance responses were still measurable whilst startle effects associated with the initial sensation of the stimuli were avoided.

Figure 5.3 outlines the session two setup. GVS electrodes are visible in figure 5.4A, which illustrates the subject setup and positioning with the laboratory.

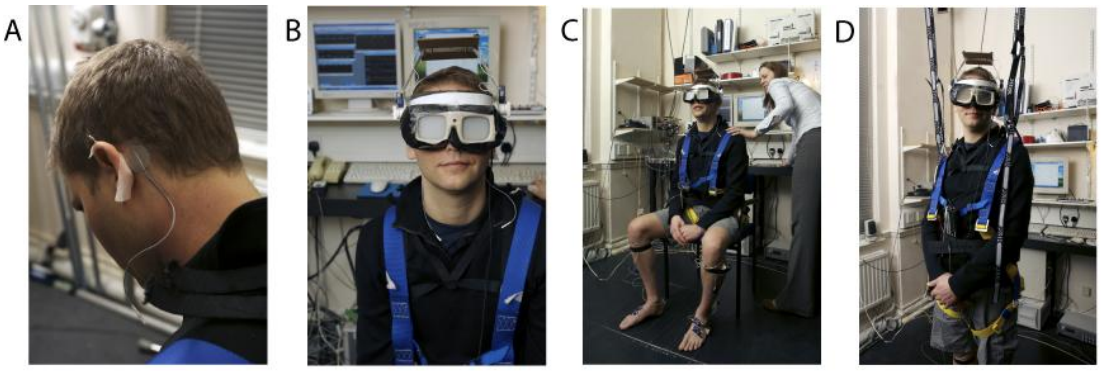


Figure 5.3: Sesssion 2 subject setup.
Ears were taped to avoid un-necessary stimulation of cutaneous afferents and electrodes applied on bilateral mastoid processes (A). Plato spectacles, coda markers and safety gear were then fitted (B). Each subject experienced two test trials whilst seated (C). In standing safety straps were attached, GVS wires were managed behind the subject and subject position was prepared for the first trial (D).

5.2.4 Control parameters

In order to standardise sensory experiences across trials and between subjects, posture, vision and visual and auditory environmental cues were controlled before and after stimuli delivery. Lighting levels were controlled in the laboratory with the use of blackout blinds and lamps.

5.2.5 Response analysis

Kinematic data collected during trials was the same type as that previously described in chapters 2 and 4, i.e. whole body motion and ground reaction forces.

*5.2.5.1 **Response form***

In order to analyse the global form of responses, force and kinematic data was averaged in laboratory x and y-axis directions across the time series for all trial repeats per visual condition. Backward responses were inverted in order to ensure that responses could be averaged across both trial repeat and condition. Maximal trial numbers were used in this way in order to optimise signal (response form) to noise (background sway) ratios. The form of these traces could then be assessed and response timings, mean magnitudes and mean directions calculated.

*5.2.5.2 **Response timings***

In order to quantify the timing of SCA6 responses, medium latency peak force responses and peak trunk excursions were calculated per subject based on average forms of response per modality, per subject. Response timings were calculated from mean force

over time data, averaged across all head turned GVS conditions with vision obscured. Data therefore incorporated 10 trial repeats per conditions 3-6, totaling 40 trials per subject. Backwards directed mean responses were then inverted (by multiplying force over time data by -1) in order to calculate one mean form of response per subject.

Calculation of timings involved finding the maximum peak in laboratory y-axis forces during the period between stimulation onset and 2.0 seconds FSO.

Latencies of force response onset and trunk sway onset and response peaks were calculated in addition to the primary force measure in order to provide further information regarding how the integration of re-afferents act to impede the force response. Force onset times refer to the medium latency force onset and were calculated by finding the time value for minimal forces between stimulation onset and 1s following stimulation onset (FSO). This also corresponds with the peak value of the short latency force response. The peak sway response was calculated from maximum peak in laboratory y-axis trunk excursion during the period between stimulation onset and the end of the trial.

Individual subject average response latency measures were statistically analysed to look for group differences using t-tests (within-subject factor: *response latency*; between subject factor: *group* (HVS, SCA6)).

5.2.5.3 Assessing response scaling

Forces were sampled from 0.2 to 0.4s following stimulation onset (FSO) and kinematic data from 0.2 to 1.0s FSO. Measures of magnitude and direction were calculated from vectors created from these samples of data. Statistical analysis of these measures employed student t-tests to assess differences between groups (within-subject factors: *response magnitude*; between subject factor: *group* (HVS, SCA6)). Prior to statistical analysis of GVS response directions, responses were normalised to start head position since this was a head referenced rather than earth referenced stimuli.

Group differences were assessed for statistical significance using T-tests (within-subject factors: *response magnitude*; between subject factor: *group* (HVS, SCA6)).

ANOVAs were additionally used to briefly assess the comparability of response magnitudes across condition (within-subject factors: *response magnitude* (forwards, backwards) and *vision* (*vision obscured, vision intact*); between subject factor: *group* (HC, SCA6).

To more precisely quantify the effect of vision, quotients created from vision intact (VI) and vision obscured (VO) data were calculated according to the formula: VO-VI/VO+VI. Positive quotient scores indicate a reduction in response magnitude with the presence of vision.

5.2.5.4 *Assessing the orientation of the response*

The same epochs following stimulation onset (fSO) can be used to calculate a response direction as previously described for calculating vector magnitudes.

The mean response direction of GVS responses is calculated relative to starting head position (rather than in laboratory coordinates) due to the craniocentric nature of the response. Starting head angles in laboratory coordinates were subtracted from angles of resultant trunk, force and centre of pressure vectors (also in laboratory coordinates). Subjects' mean starting head positions were calculated using two of four available head markers in laboratory coordinates immediately prior to stimulation onset (from -0.8 to 0 seconds). Since response directions are predicted to occur 90 degrees relative to the starting head position, the relative error to the expected direction was calculated in each case.

Circular statistic techniques (Batschelet, 1981; previously described chapter 2) are used to calculate group mean response directional error and measures of between-subject variability (using angular deviations). Group differences were assessed for statistical significance using t-tests (within-subject factors: *response direction*; between subject factor: *group* (HVS, SCA6)).

ANOVAs compared mean response errors relative to the ideal response direction between groups (ANOVAs: within-subject factors: *head direction* (head right, head left) and *polarity* (right anode & left cathode, left anode & right cathode)); between subject factor: *group* (HC, SCA6)).

5.2.5.5 *Correlations*

Baseline sway speeds were derived from trunk marker and centre-of-pressure sway speeds with subjects stood in 4cm stance widths. 4cm stance width sway speed measures were selected for use since they best correlated with disease severity scores in chapter 4. Measures of disease severity (SARA score) were available from clinical assessment of subjects, described in detail in part one of chapter 3.

Pearson's correlation coefficients calculated in SPSS quantified the strength and direction of any relationship and corresponding p-values indicating the probability of obtaining the described relationships if the null-hypotheses were true. Since baseline measures were compared with multiple response measures, derived from different measurement approaches (force change, CoP and trunk displacement over time), the chosen level of significance was adjusted from the normal convention of $p<0.05$ to the more stringent $p<0.01$. This was designed to help protect against erroneous rejection of the null hypotheses.

5.3 Results

5.3.1 General form of responses

Raw data in figure 5.4 acts to illustrate the motion of a trunk marker over the six second data collection period for head-left, vision occluded condition (i.e. motion in the x-y plane). Figure 5.4 illustrates clearly identifiable antero-posterior motion of the trunk marker in the direction of the anode during the stimulation period (thick black and red lines). Red lines represent the time epoch from which a response vector will be sampled in order to calculate magnitude and direction measures. In accordance with convention, the direction of motion of the marker is approximately 90 degrees to the starting head position of the subject, indicated in each figure by the central illustration of a subject. Prior to stimulation onset, fine lines indicate motion at baseline. This pre-stimulation sway is comparable with the 'no-stimulation' trace (also a fine grey line), which charts the motion of the marker over a full six seconds of unperturbed standing in the equivalent head position. When the thick line becomes dotted, subjects no longer received GVS and vision had become available. The dotted line illustrates an 'off-response' where subjects are observed returning to an upright position.

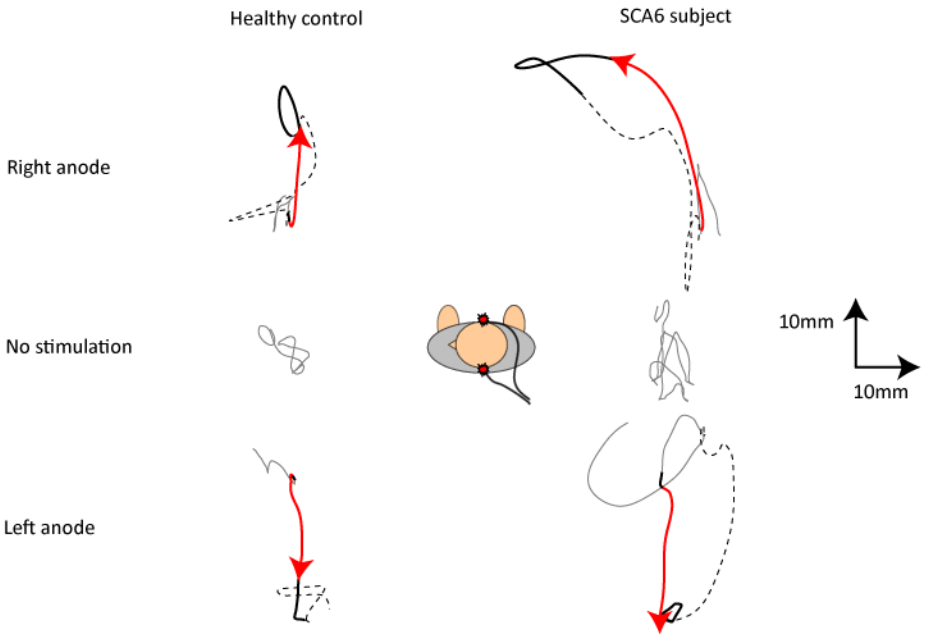


Figure 5.4: Birds eye view of individual subject single trial 2D trunk sway data (head left, vision off).
Each figure illustrates position over time data of the central point of subject's trunk cluster over each 6 second collection. The left column illustrates data from a healthy control and the right column illustrates that of the age-, sex- and height-matched SCA6 subject. Rows order stimulation condition type as labelled. Thin grey lines = no-stim periods or trials, full black lines = start and end of stimulation periods, thick red lines = measurement period within stimulation periods (used to calculate response vector), dashed line = post-stimulation recovery periods.

Figure 5.5 plots raw force and sway measures for vision obscured conditions for a typical healthy control (HC) and SCA6 subject to illustrate the emerging form of the response to GVS. These figures show that both subjects appropriately possess forms of response to GVS visible in y-axis laboratory coordinates and in the approximate direction of the anode. Background sway is also clearly visible in these figures which may even act to mask responses to GVS in early vector samples of magnitude and direction of individual trials. This potential bias of sway will particularly affect SCA6 subject measures, since it has already been established that those with SCA6 have increased levels of sway at rest (in terms of both speed and excursion of displacement).

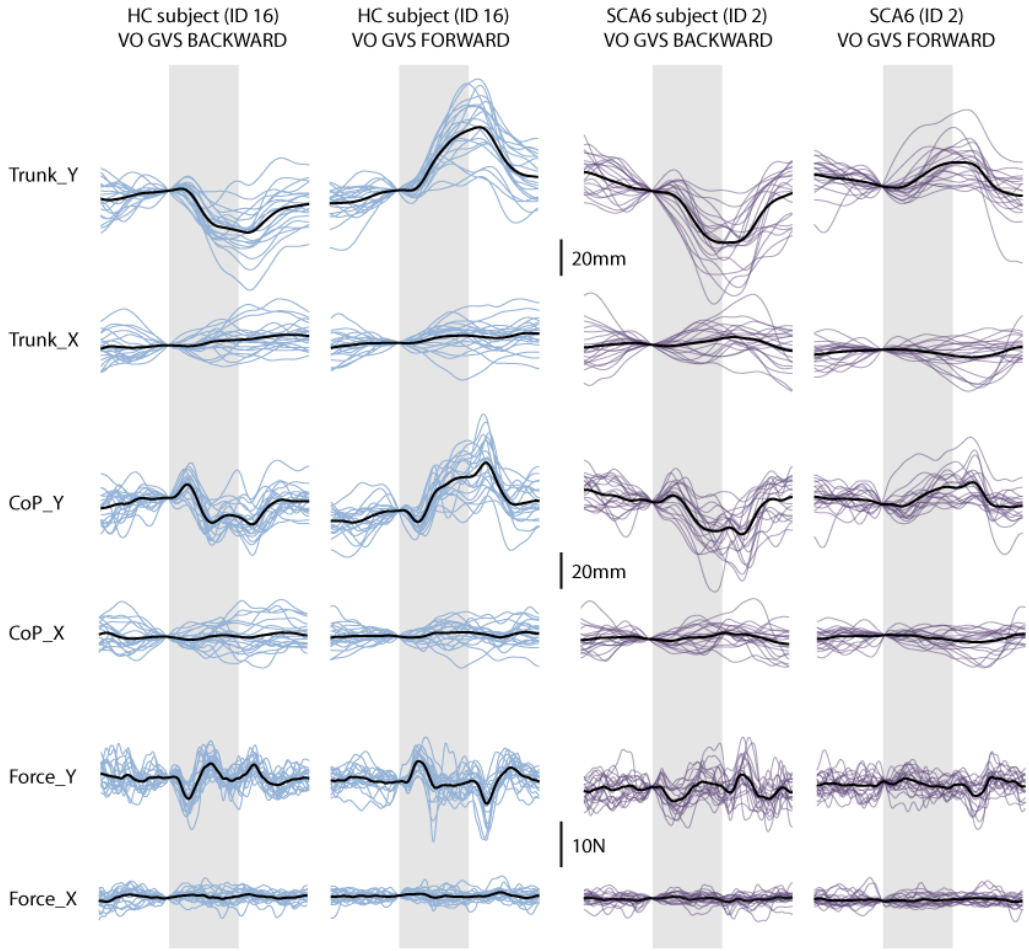


Figure 5.5: Individual subject trial-by-trial sway and force data for vision obscured GVS conditions. Left to right columns order group and condition data: 1=Healthy control backwards directed perturbations (conditions 3:VO RA HR and 6:VO LA HL), 2=Healthy control forwards directed perturbations (conditions 4:VO RA HL and 5:VO LA HR), 3=SCA6 backwards directed perturbations (conditions 3:VO RA HR and 6:VO LA HL), 4=SCA6 forwards directed perturbations (conditions 4:VO RA HL and 5:VO LA HR). Top to bottom row 1=Trunk sway laboratory (lab) Y-axis, 2=Trunk sway lab X-axis, 3=Centre-of-pressure (CoP) lab Y-axis, 4=CoP lab X-axis, 5=Force lab Y-axis, 6=Force lab X-axis. Traces illustrate 6 second durations of data collection. Shaded boxes illustrate GVS delivery. Each thin line corresponds to individual trial responses. Thick black lines illustrate the mean trace.

Figure 5.6 illustrates the overall forms of force and sway fluctuations over time for each subject. Individual lines illustrate mean force or sway fluctuations over time per subject based on ten trial repeats per condition and four GVS conditions where vision was obscured. Backwards directed responses from conditions 3:VO RA HR and 6:VO LA HL were initially inverted before averaging with conditions 4 and 5 (VO RA HL and VO LA HR) to gain the mean traces presented. Force and sway behavior under the same conditions

and trial durations but where no GVS was administered (no stimulation control conditions) is also presented in neighboring columns for comparison and to help identify responses in each dataset. In each case, individual subject responses GVS can be easily differentiated from control condition force and sway behavior.

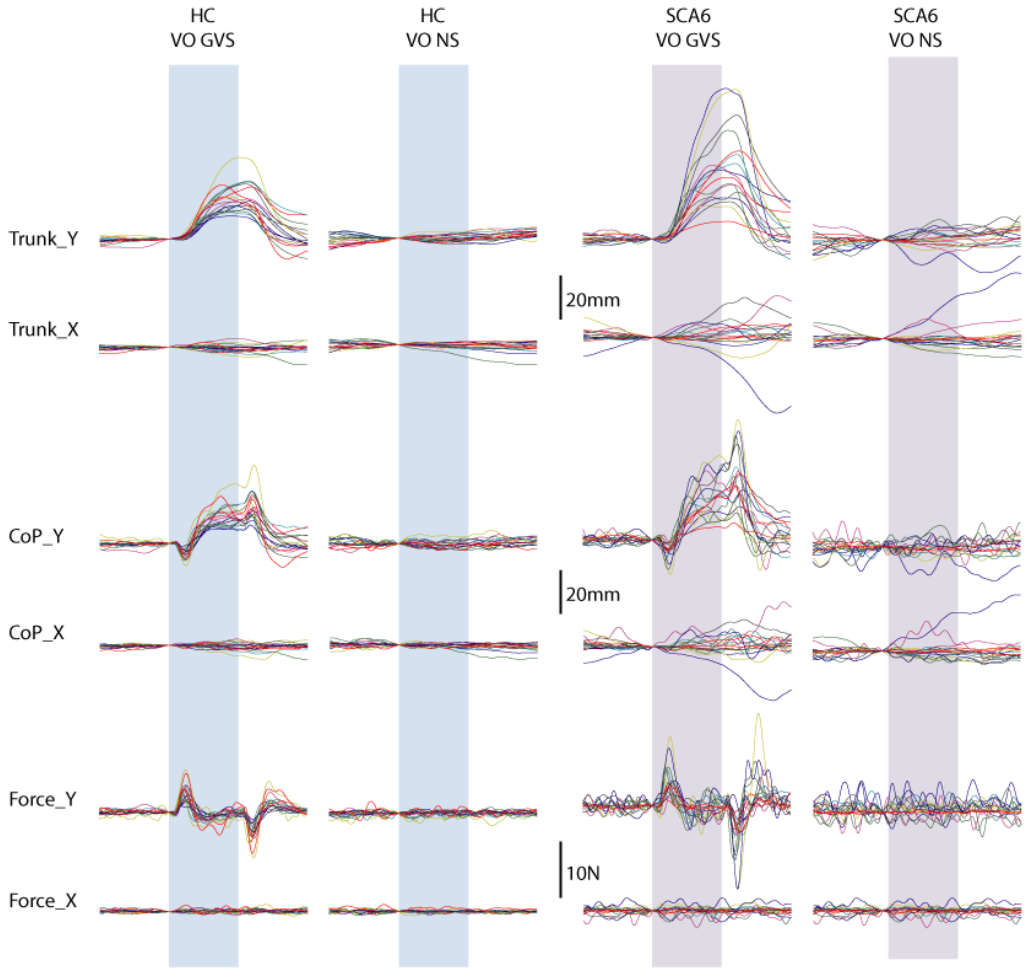


Figure 5.6: Individual subject mean responses to GVS and no stimulation condition behaviour. Left to right columns order group and condition data: 1=Healthy control GVS condition data (HC VO GVS), 2=Healthy control no stimulation condition data (HC VO NS), 3=SCA6 GVS condition data (SCA6 VO GVS), 4=SCA6 no stimulation condition data (SCA6 VO NS). Top to bottom row 1=Trunk sway laboratory (lab) Y-axis, 2=Trunk sway lab X-axis, 3=Centre-of-pressure (CoP) lab Y-axis, 4=CoP lab X-axis, 5=Force lab Y-axis, 6=Force lab X-axis. Traces illustrate 6 second durations of data collection whilst subjects stood with their head turned and had vision obscured. Each coloured line corresponds to individual subjects. Shaded boxes illustrate GVS delivery.

5.3.2 Response timings

Table 5.2 outlines the descriptive analysis of the response latency data (group means and standard deviations). Figure 5.7 illustrates the mean force responses per group with vision obscured. Group means are comparable between groups and no effect of group is reported from t-tests (table 5.2).

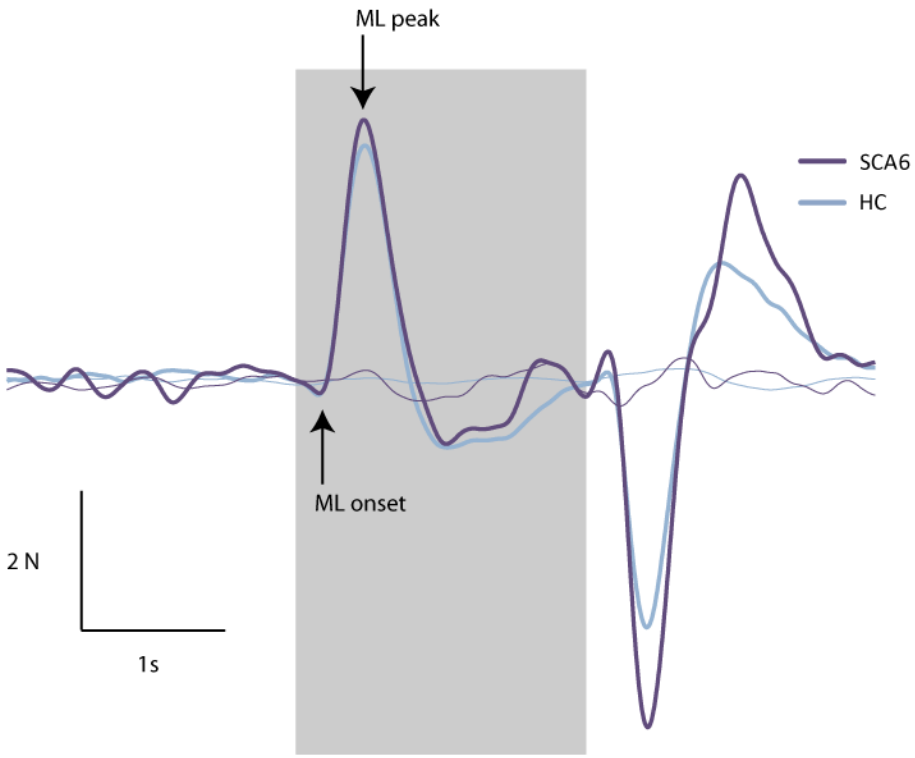


Figure 5.7: Group mean GVS response forms illustrating response latencies.
Group mean force responses plotted over time from GVS only trials with the head turned and vision obscured. GVS delivery period is indicated using a shaded background. Mean force responses in the primary response direction , y-axis, are illustrated by full lines and x-axis mean forces by fine lines. Healthy control (blue) and SCA6 (purple) forces are overlayed. Arrows indicate the measurement points of the response: the onset of the medium latency (ML) force response onset and peak.

Table 5.2: Descriptive statistics and t-tests for group mean response timing.

	HVS mean (S.D.)	SCA6 mean (S.D.)	t-value (d.f.)	p-value
Force peak (s)	0.49 (0.07)	0.51 (0.09)	-0.6 (28)	0.548
Trunk peak (s)	0.74 (0.17)	0.82 (0.13)	-1.3 (28)	0.199

5.3.3 Response magnitudes

Mean group early sway responses were of a similar magnitude between groups but later appears increased for the SCA6 group, illustrated in figure 5.8 (A-B). Significant group differences, assessed using t-tests based on early sway vector measures (0.2-1s FSO), were reported for trunk sway only (table 5.3). However, t-tests based on later vector

measures (0.2-2s FSO) reported significant group differences in both trunk and CoP sway measures (table 5.3). Mean group force responses were of a similar magnitude between groups, illustrated in figure 5.8 (C). No significant group differences in force measures were reported by t-tests.

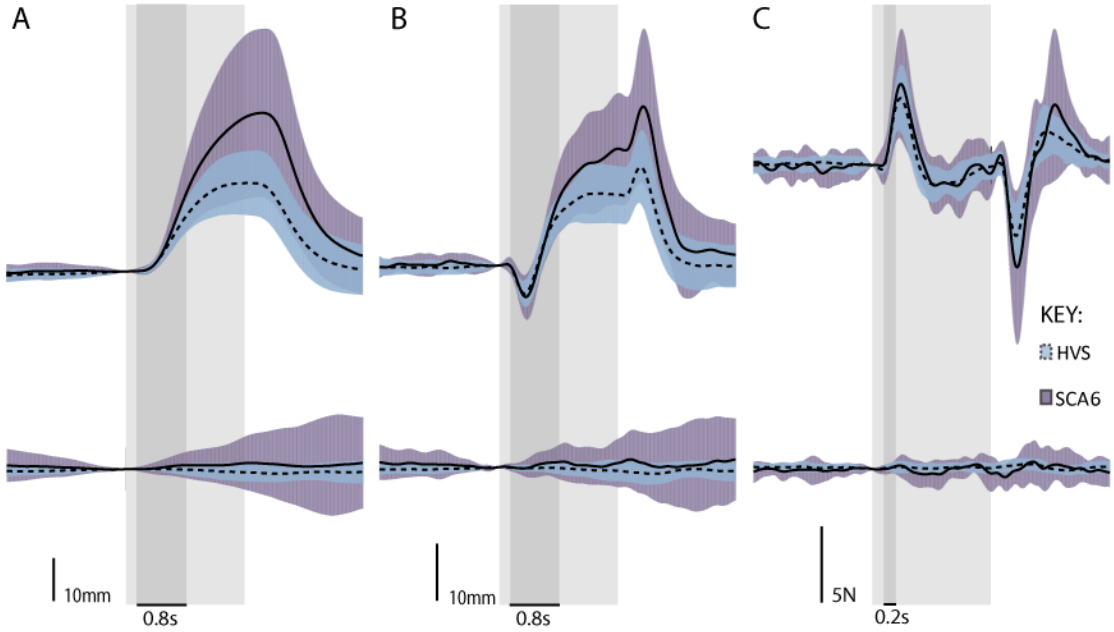


Figure 5.8: Group mean sway and force over time data for vision obscured conditions. Plotted lines correspond to group mean displacement of the trunk (A) and centre-of-pressure (B) and force changes (C) in laboratory Y- (upper plots) and X-axis directions (lower plots) over six second trial durations. Shaded areas illustrate one standard deviation of these measures around the mean to represent between-subject variability. Grey shaded boxes indicate GVS delivery. Darker shaded strips with lower labels indicate the trial duration from which data was sampled to calculate early response mean magnitudes.

Table 5.3: Descriptive statistics and t-tests for group mean response magnitudes (vision obscured).

Magnitudes	HVS mean (± 1S.D.)	SCA6 mean (± 1S.D.)	t-value (d.f.)	p-value
Trunk_1s (mm)	12.9 (3.6)	18.4 (8.0)	2.5 (19.5)†	0.024
Trunk_2s (mm)	20.5 (7.8)	38.4 (19.1)	3.4 (18.5)†	0.003
CoP_1s (mm)	9.3 (3.3)	12.2 (5.9)	1.7 (22.0)†	0.102
CoP_2s (mm)	12.5 (5.3)	22.0 (9.5)	3.4 (22.0)†	0.003
Force (N)	3.4 (1.4)	3.7 (2.8)	0.4 (20.1)†	0.674

† Equal variances not assumed according to Levene's test ($p<0.05$)

5.3.3.1 *The effect of vision on response magnituds*

Mean group responses to GVS with vision intact were similar in form to responses with vision obscured (comparing figures 5.8 and 5.9). Group differences in measures also followed the same trend as vision obscured data (comparing statistical analyses outlined in tables 5.3 and 5.4).

Mean group early sway responses were of a similar magnitude between groups but later

appear increased for the SCA6 group, illustrated in figure 5.9 (A-B). Significant group differences assessed using t-tests based on early sway vector measures (0.2-1s FSO) were reported for trunk sway only (table 5.4). However, t-tests based on later vector measures (0.2-2s FSO) reported highly significant group differences in both trunk and CoP sway measures (table 5.4). Mean group force responses were of a similar magnitude between groups, illustrated in figure 5.9 (C). No significant group differences in force measures were reported by t-tests.

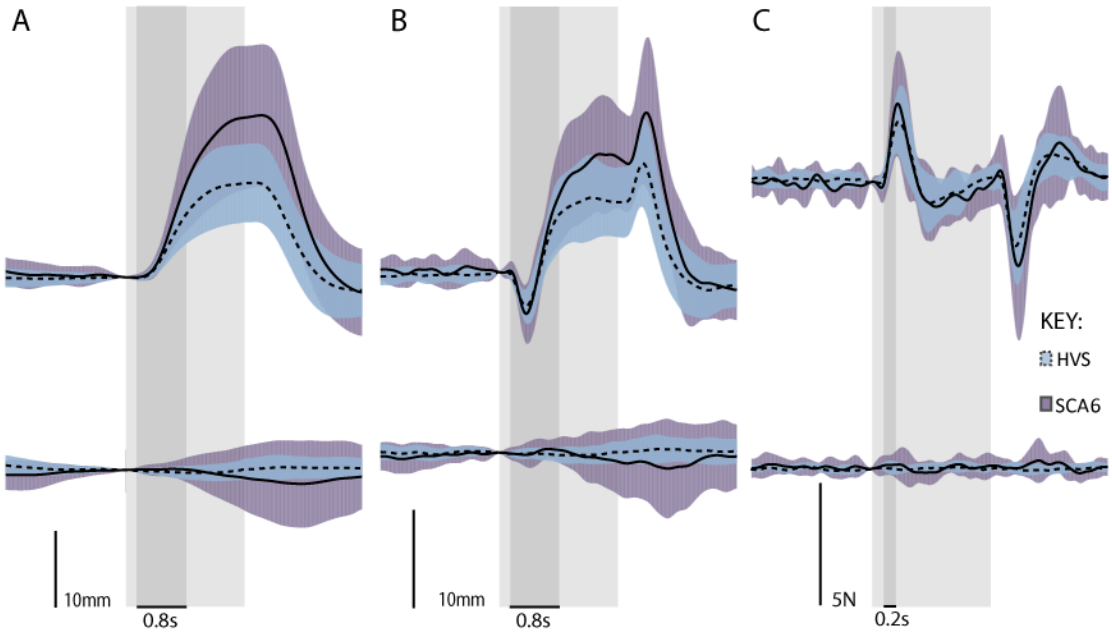


Figure 5.9: Group mean sway and force over time data for vision intact conditions.
Plotted lines correspond to group mean displacement of the trunk (A) and centre-of-pressure (B) and force changes (C) in laboratory Y- (upper plots) and X-axis directions (lower plots) over six second trial durations. Shaded areas illustrate one standard deviation of these measures around the mean to represent between-subject variability. Grey shaded boxes indicate GVS delivery. Darker shaded strips with lower labels indicate the trial duration from which data was sampled to calculate early response mean magnitudes.

Table 5.4: Descriptive statistics and t-tests for group mean response magnitudes (vision intact).

Measure	HVS mean (± 1S.D.)	SCA6 mean (± 1S.D.)	t-value (d.f.)	p-value
Trunk_1s (mm)	8.2 (3.9)	12.6 (5.5)	2.5 (28)	0.018
Trunk_2s (mm)	11.9 (5.1)	12.6 (5.5)	4.1 (28)	<0.001
CoP_1s (mm)	6.5 (4.0)	8.5 (4.5)	1.3(28)	0.214
CoP_2s (mm)	7.1 (3.4)	12.8 (4.4)	4.0 (28)	<0.001
Force (N)	2.2 (1.0)	3.3 (2.2)	1.8 (28)	0.079

ANOVAs were used to assess look for an effect of *vision*. ANOVAs reported widespread main effects of *vision* (trunk_1s: F(1,28)=50.7, p<0.001, trunk_2s: F(1,28)=43.5, p<0.001, CoP_1s: F(1,28)=25.0, p<0.001, CoP_2s: F(1,28)=3.1, p<0.001, force: F(1,28)=8.8, p=0.006). In agreement with t-test findings, main effects of *group* were found to be significant only for late CoP sway and early and late trunk sway measures (trunk_1s: F(1,28)=7.0, p=0.013, trunk_2s: F(1,28)=14.5, p=0.001, CoP_1s: F(1,28)=2.7, p=0.114, CoP_2s: F(1,28)=15.0, p=0.001, force: F(1,28)=1.2, p=0.281). No significant interactions between *group* and *vision* were reported (trunk_1s: F(1,28)=0.7, p=0.422, trunk_2s: F(1,28)=3.6, p=0.068, CoP_1s: F(1,28)=0.5, p=0.470,CoP_2s: F(1,28)=3.1, p=0.087, force: F(1,28)=2.2, p=0.148).

Group mean quotients were positive in all but SCA6 force measures, which were negative although close to zero (-0.04). Significant group differences based on t-test results were reported for force quotients (p=0.024). No other significant group differences were reported for quotient measures (table 5.5).

Table 5.5: Descriptive statistics and t-tests for group mean vision quotients

Measure	HVS mean (± 1S.D.)	SCA6 mean (± 1S.D.)	t-value (d.f.)	p-value
Trunk_1s	0.25 (0.14)	0.18 (0.16)	-1.3 (28)	0.202
Trunk_2s	0.27 (0.12)	0.22 (0.16)	-1.0 (28)	0.343
CoP_1s	0.24 (0.20)	0.18 (0.20)	-0.8 (28)	0.462
CoP_2s	0.29 (0.16)	0.23 (0.19)	-1.0 (28)	0.327
Force	0.21 (0.11)	-0.04 (0.37)	-2.5 (16.4)	0.024

† Equal variances not assumed according to Levene's test (p<0.05)

5.3.4 Response direction

Group mean yaw angles of response were similar for that of trunk and centre-of-pressure measures between the two groups illustrated in figure 5.10 and listed in table 5.6.

Main effects of head turn were reported throughout all early response measures using ANOVAs (trunk: F(1,28)=51.3, p<0.001; CoP: F(1,28)=59.8, p<0.001; force: F(1,28)=19.8, p<0.001). No main effects of *polarity* were reported (trunk: F(1,28)=3.9, p=0.057; CoP: F(1,28)=1.4, p=0.244; force: F(1,28)=0.9, p=0.357). Effects of group differed between measures; significant differences between groups were found for force measures but not trunk or CoP sway (trunk: F(1,28)=0.6, p=0.804; CoP: F(1,28)=0.02, p=0.903; force: F(1,28)=4.9, p=0.035). This could be associated with the unexpectedly large error in mean force response direction during head left, left anodal GVS conditions. This will be explored further in the following sub-section 'Force response direction abnormalities'.

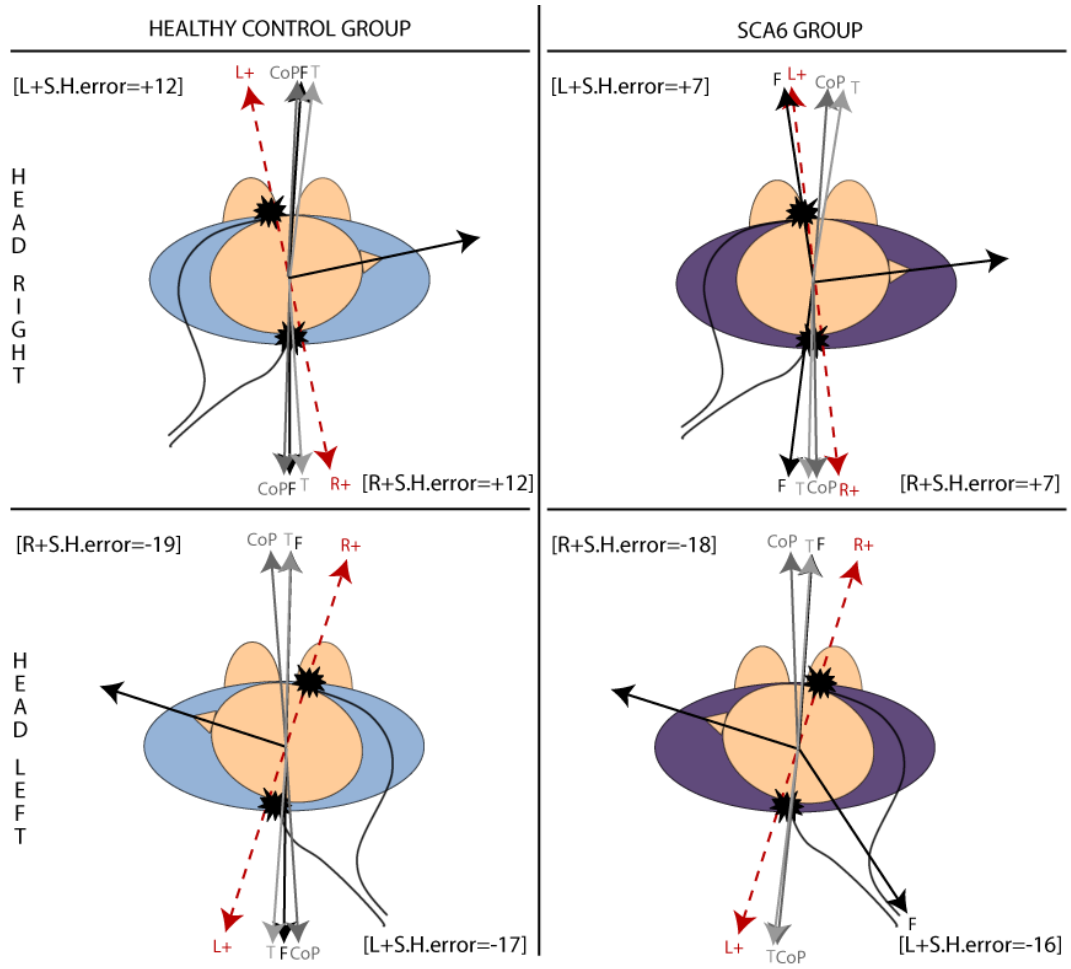


Figure 5.10: Group mean response directions per GVS condition (vision obscured).
Overhead views of group mean yaw angles of response for trunk (T), centre-of-pressure (CoP) and force (F) data. Response angles have been normalised to start head-on-feet direction (SHD) per subject. For illustration purposes group average SHD have been calculated and used to draw subject head-on-feet postures per group per head direction (further highlighted by black lines projecting outwards from the naso-occipital line). Average group SHD errors are provided in brackets according to GVS condition. Red dotted arrows show the ideal response direction relative to the SHP per condition. Greyscale arrows represent response directions per condition per data type (light=trunk, medium=CoP, dark=force). Clockwise changes in response angles indicate negative errors and anticlockwise angle changes indicate positive errors.

Table 5.6: Group mean directional errors around the ideal response direction.

	Trunk_1s (degs)		Trunk_2s (degs)		CoP_1s (degs)		CoP_2s (degs)		Force (degs)	
Condition	HVS	SCA6	HVS	SCA6	HVS	SCA6	HVS	SCA6	HVS	SCA6
3 VO RA HR	-8.2 (9.8)	-8.2 (13.9)	-2.1 (20.5)	-2.8 (17.0)	-13.8 (9.5)	-6.0 (17.2)	-8.1 (27.1)	-12.5 (21.9)	-12.1 (7.4)	1.7 (45.0)
4 VO RA HL	16.6 (11.9)	13.7 (35.1)	28.8 (17.4)	31.3 (19.1)	22.5 (10.5)	19.7 (17.0)	25.2 (15.0)	30.1 (20.3)	16.6 (11.9)	13.7 (35.1)
5 VO LA HR	-18.9 (11.3)	-16.1 (14.5)	-19.3 (14.4)	-16.0 (16.0)	-14.9 (15.0)	-11.1 (26.6)	-14.3 (15.8)	-12.5 (19.4)	-15.7 (10.6)	-14.2 (11.4)
6 VO LA HL	13.9 (11.4)	10.5 (25.4)	3.9 (29.0)	1.9 (22.5)	21.9 (11.6)	11.6 (26.4)	17.9 (35.2)	6.6 (25.9)	17.5 (7.1)	51.0 (71.5)*

Key: *= Unexpectedly large response directional error.

Significant interactions were not reported between any combination of *head direction*, *polarity* and *group* for trunk and CoP sway measures ([*head direction* and *group*; trunk: F(1,28)=0.4, p=0.546; CoP: F(1,28)=2.5, p=0.127], [*polarity* and *group*; trunk: F(1,28)=0.03, p=0.856; CoP: F(1,28)=0.8, p=0.367], [*head direction* and *polarity*; trunk: F(1,28)=0.9, p=0.361; CoP: F(1,28)=0.1, p=0.818], [*head direction*, *polarity* and *group*; trunk: F(1,28)=0.1, p=0.815; CoP: F(1,28)=0.1, p=0.765]). Two-way interactions were reported as significant between *head direction* and *polarity* but no other combination of factors for force measures ([*head direction* and *polarity*; force: F(1,28)=6.0, p=0.021], [*head direction* and *group*; F(1,28)=0.2, p=0.627], [*polarity* and *group* F(1,28)=1.5, p=0.236]). A three-way interaction was also significant between *head direction, polarity* and *group* for force measures (*head direction*, *polarity* and *group*: F(1,28)=4.2, p=0.049]).

5.3.4.1.1 Force response direction abnormalities

Figure 5.10 clearly illustrates similarities between group response errors, apart from force response errors associated with head left turns and left anodal GVS (condition 6: 'VO LA HL'). Table 5.7 also shows that within-subject variability is particularly high for this condition for SCA6 subjects (*). Despite this visible anomaly, a post-hoc t-test based on force measures for this condition did not report a significant *group* difference (t(d.f.)=-1.8(14.3), p=0.092). No other significant *group* differences in measures were reported based on t-tests of force measures for the other conditions in question in accordance with ANOVA findings (3:VO RA HR; t(d.f.)=-1.1(14.7), p=0.261; 4:VO RA HL; t(d.f.)=-0.3(28), p=0.767; 5:VO LA HR; t(d.f.)=-0.4(28), p=0.716). Despite a lack of group differences according to a t-test for condition 6 (VO LA HL), individual subject summary data for this condition does appear to identify differences between subjects, which could explain high mean and standard deviations of error for the group (table 5.7). Subject codes starred in table 5.7 indicate large response errors to the extent that mean responses are oppositely directed to what is expected. These oppositely directed force measures are not however replicated in trunk sway measures. Of particular interest are subjects 1 and 7 since these subjects were identified in chapter 4 as possessing significant amounts of 2-3Hz oscillatory sway, predominantly in pitch. Raw data plots of these subject's forces during the total trial duration are provided in rows 3 and 4 of the left column of figure 5.11. These plots show similar oscillatory activity to that observed during stance width measures of trunk sway

(chapter 4, figure 5.15). This 2-3Hz prominent oscillatory activity is not evident in healthy controls' and typical SCA6 subjects' forces (typical examples of which are provided in rows 1 and 2 of figure 5.11, respectively). Of further interest is subject 11 who also produces a large response directional error in force measures alone. Figure 5.11 illustrates raw force response data for this subject in the bottom row (5), which also appears to have some 2-3Hz oscillatory behavior. Same trial trunk sway data has been provided in the right column of figure 5.11 to show that some oscillatory behavior is detectable during parts of the trial duration for the same SCA6 subjects. This comparison illustrates that whereas the form of the response to GVS still appears detectable in trunk sway measures, the form of force response to GVS in those with oscillatory activity is difficult to detect.

Table 5.7: Individual subject mean response direction errors for condition 6 (VO LA HL)

HVS subject code	HVS force error (degs)	HVS trunk 1s sway error (degs)	SCA6 subject code	SCA6 force error (degs)	SCA6 trunk sway error (degs)
1	27.1	23.5	1*	197.9	34.5
2	29.9	20.6	2	41.0	32.1
3	18.8	16.8	3	7.6	23.2
4	11.0	15.8	4	30.7	-6.5
5	22.6	27.2	5	-1.3	19.4
6	8.4	4.0	6	21.3	0.3
7	20.8	13.5	7*	200	-56.9
8	5.4	8.8	8	10.5	0.5
9	12.8	9.8	9	4.0	-1.1
10	16.7	14.6	10	32.7	51.6
11	9.8	-19.5	11*	156.7	21.7
12	24.5	28.9	12	6.4	1.0
13	15.3	18.0	13	6.8	-0.5
14	19.5	13.2	14	48.5	32.8
15	19.8	13.0	15	1.8	5.8
16†	16.2	24.5	16††	26.2	22.7
17†	33.0	19.9	17††	37.6	21.1

Key: ††= 'Pre-symptomatic' subjects. †=Pre-symptomatic subject healthy matches *= Subjects with unexpectedly large response directional error.

Mean and standard deviation measures of late sway activity (sampled between 0.2s and 2s FSO) are provided in italics in table 5.6. Analysis of these late sway measures once again reported main effects of head direction (trunk: $F(1,28)=42.4$, $p<0.001$; CoP: $F(1,28)=56.9$, $p<0.001$). Main effects of polarity were also present, unlike earlier sway measure reports (trunk: $F(1,28)=19.7$, $p<0.001$; CoP: $F(1,28)=0.015$, $p<0.001$). No significant group differences were found (trunk: $F(1,28)=0.1$, $p=0.783$; CoP: $F(1,28)=0.3$, $p=0.614$). Only one significant interaction was reported; between *head direction* and *polarity* in trunk sway measures ($F(1,28)=5.3$, $p=0.029$). No other interactions between other combinations of factors were reported ([*head direction* and *group*; trunk: $F(1,28)=0.02$, $p=0.899$; CoP: $F(1,28)=0.1$, $p=0.822$], [*polarity* and *group*; trunk: $F(1,28)=0.001$, $p=0.979$; CoP: $F(1,28)=0.5$, $p=0.487$], [*head direction* and *polarity*; CoP:

F(1,28)=1.6, p=0.213], [*head direction*, *polarity* and *group*; trunk: F(1,28)=0.7, p=0.411; CoP: F(1,28)=1.4, p=0.252]).

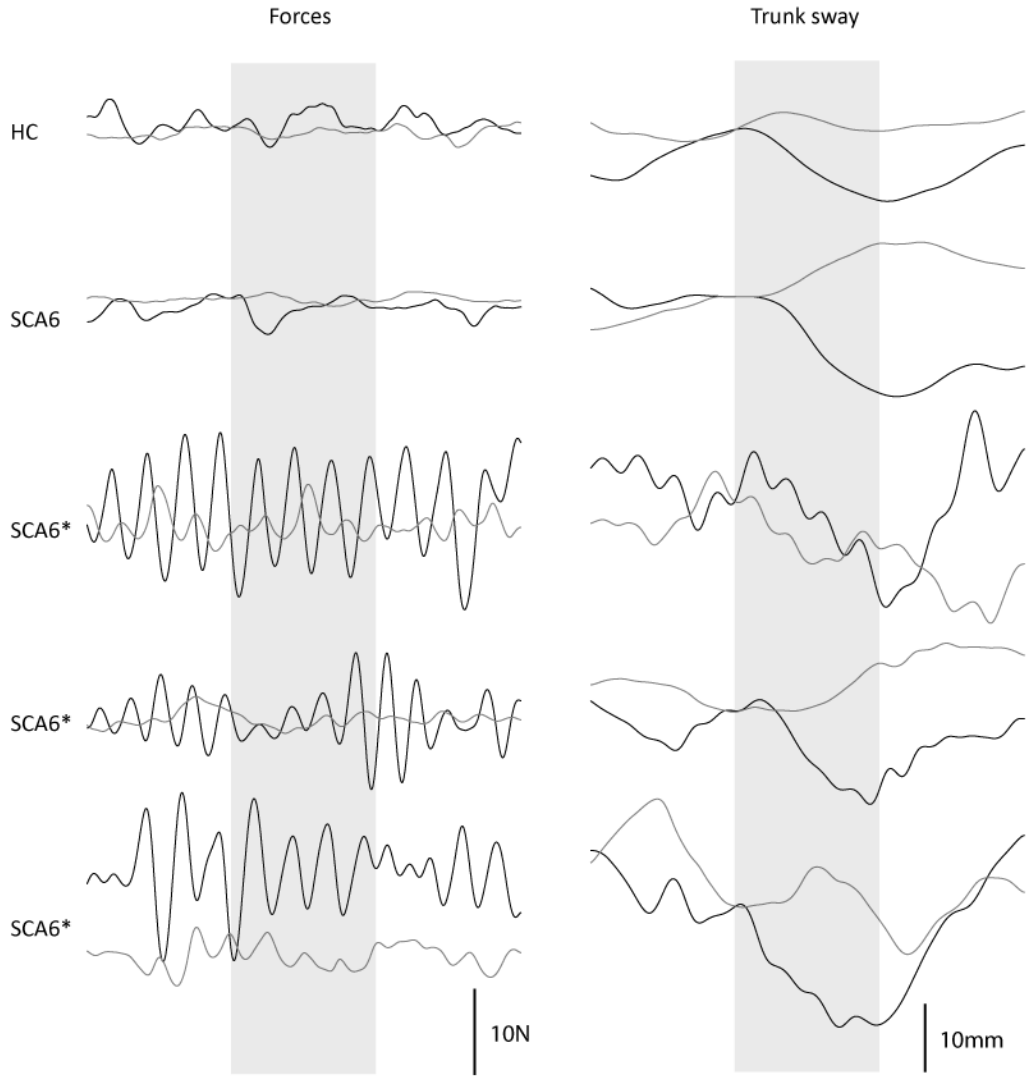


Figure 5.11: Single trial force and trunk sway data for condition 6 (VO LA HL).
Traces in the top row illustrate data from a typical healthy control (HC). Underneath traces are taken from a typical subject with SCA6 followed by three subjects displaying signs of 2-3Hz postural tremor (SCA6*, top to bottom subject no. 7, 1, 11). Traces illustrate 6 second durations of data collection whilst subjects stood with their head left and received left anodal GVS. Black lines illustrate trunk angle over time data in pitch and grey lines illustrate equivalent anglular data in roll. Grey boxes illustrate GVS delivery.

5.3.5 Correlations with disease severity and baseline sway speeds

Correlations were explored between baseline measures and all GVS response measures in order to test hypotheses set out in the introduction of this chapter. Due to the multiple ways in which responses to GVS have been measured (namely measures derived from forces and early and late latency vectors of trunk and CoP), the threshold for statistical

significance has been adjusted from p<0.05 to p<0.01.

Table 5.8 is concerned with hypotheses 1 and 2 and explores associations between baseline measures (disease severity and sway speeds) and response magnitudes. One statistically significant correlation was reported between baseline measures of trunk sway speeds and force response magnitudes for healthy control data only. Pearson's correlation coefficients for all other comparisons are weak and statistically not significant.

Table 5.9 is concerned with hypotheses 3 and 4 and explores associations between baseline measures (disease severity and sway speeds) and the size of response directional errors. Pearson's correlation coefficients for all comparisons are weak and statistically not significant.

Table 5.10 is concerned with hypothesis 5 and explores associations between baseline measures (disease severity and sway speeds) and vision quotients. Pearson's correlation coefficients for all comparisons are weak and statistically not significant.

Table 5.8: Correlations between baseline measures and mean response magnitudes.

Data type		SARA	BalSARA	Trunk sway	CoP sway
Trunk_1s	HC	-	-	0.447 (0.072)	0.298 (0.261)
	SCA6	0.230 (0.375)	0.334 (0.191)	0.347 (0.172)	0.510 (0.037)
Trunk_2s	*HC*	-	-	*0.287 (0.264)*	*-0.169 (0.518)*
	SCA6	*0.228 (0.379)*	*0.338 (0.184)*	*0.363 (0.153)*	*0.522 (0.031)*
CoP_1s	HC	-	-	0.352 (0.166)	0.537 (0.026)
	SCA6	0.222 (0.392)	0.309 (0.227)	0.348 (0.171)	0.525 (0.031)
CoP_2s	HC	-	-	0.520 (0.032)	-0.065 (0.804)
	SCA6	0.385 (0.127)	0.385 (0.127)	0.459 (0.064)	0.194 (0.456)
Force	HC	-	-	0.632 (0.006)*	0.222 (0.392)
	SCA6	-0.131 (0.617)	-0.071 (0.787)	-0.131 (0.615)	0.116 (0.658)

Key: *= Deemed as significant to p<0.01.

Table 5.9: Correlations between baseline measures and mean response directional errors.

Data type		SARA	BalSARA	Trunk sway	CoP sway
Trunk_1s	HC	-	-	-0.076 (0.771)	0.069 (0.792)
	SCA6	0.104 (0.690)	-0.026 (0.922)	0.030 (0.909)	-0.070 (0.788)
Trunk_2s	*HC*	-	-	*0.095 (0.716)*	*0.397 (0.114)*
	SCA6	*-0.065 (0.806)*	*-0.112 (0.669)*	*-0.103 (0.694)*	*-0.301 (0.694)*
CoP_1s	HC	-	-	-0.183 (0.482)	0.133 (0.611)
	SCA6	-0.088 (0.736)	-0.222 (0.392)	0.242 (0.349)	-0.133 (0.610)
CoP_2s	*HC*	-	-	*0.299 (0.244)*	*0.342 (0.179)*
	SCA6	*0.046 (0.860)*	*-0.088 (0.738)*	*-0.122 (0.641)*	*-0.247 (0.340)*
Force	HC	-	-	-0.124 (0.634)	-0.136 (0.604)
	SCA6	0.303 (0.238)	0.350 (0.168)	0.420 (0.093)	0.361 (0.311)

Table 5.10: Correlations between baseline measures and scaling effects of vision (vision quotients).

Data type		SARA	BalSARA	Trunk sway	CoP sway
Trunk_1s	HC	-	-	-0.336 (0.188)	-0.027 (0.918)
	SCA6	-0.332 (0.192)	-0.223 (0.389)	-0.114 (0.662)	-0.294 (0.253)
Trunk_2s	*HC*	-	-	*-0.002 (0.994)*	*0.190 (0.466)*
	SCA6	*-0.187 (0.472)*	*-0.137 (0.600)*	*<0.001 (0.999)*	*-0.103 (0.695)*
CoP_1s	HC	-	-	-0.291 (0.256)	-0.059 (0.821)
	SCA6	-0.165 (0.526)	-0.089 (0.735)	0.081 (0.757)	-0.140 (0.592
CoP_2s	*HC*	-	-	*0.041 (0.877)*	*0.203 (0.434)*
	SCA6	*-0.218 (0.401)*	*0.103 (0.695)*	*0.141 (0.590)*	*0.009 (0.973)*
Force	HC	-	-	0.091 (0.729)	-0.171 (0.512)
	SCA6	-0.429 (0.086)	-0.435 (0.081)	-0.528 (0.029)	-0.521 (0.032)

5.4 Discussion

This investigation aimed to study the vestibular contribution to balance control in SCA6 centring around six hypotheses:

1. **Vestibular processing abnormalities limit the propagation of vestibular signals within the cerebellum.**
2. **Vestibular processing abnormalities affect central scaling of the afferent signal.**
3. **Integration of binaural vestibular afferent signals is disrupted.**
4. **Integration of vestibular and proprioceptive signals is disrupted.**
5. **Integration of vestibular and visual signals is disrupted.**
6. **Sensori-motor timing is not disrupted.**

Through investigation of these six hypotheses I discovered that the SCA6 response to GVS is largely normal. All subjects with SCA6 had clearly identifiable responses to GVS. Normal features of the response include early force and CoP scaling, head-referenced sway response directions and timings of peak force responses. Vision also appeared to have a largely normal effect in reducing sway response magnitudes to GVS in both groups. Contrary to prior hypotheses these findings begin to provide evidence that vestibular processing is largely unaffected by SCA6 pathology. The presence and similarity in form of SCA6 and healthy control responses to GVS suggests that there is no disruption of input or propagation of vestibular signals. Analysis of response magnitudes provide the basis for this interpretation where, if any differences are notable, there is a trend for larger response magnitudes in the SCA6 group. A lack of timing abnormalities also supports the conclusion that vestibular signal propagation is largely unaffected.

However, despite the numerous similarities between groups, three main differences remain worthy of discussion. First, early trunk sway response magnitudes are increased for both vision obscured and vision intact responses to GVS. Second, SCA6 vision quotients are reduced for force measures indicating that vision is not reducing the size of initial force responses to the same extent as healthy control subjects. Third, SCA6 head-referenced force response direction measures are significantly different to healthy control directions.

These differences will be discussed in the sections below before discussing the significance of these findings for future management of SCA6.

5.4.1 Increased scaling of the sway response

As described by our primary hypothesis, an increase in trunk sway response magnitudes could be due to increased scaling governed by central processing errors. This could be due to neuronal damage in the cerebellar vermis or hemispheres, similar to reports based on animal lesioning experiments [7] or could be due to downstream errors caused by neuronal damage in output pathways such as the vestibular and fastigial nuclei [239,405].

Abnormally increased magnitudes to balance perturbations have been reported in numerous prior investigations involving subjects with cerebellar disease [155,258,366]. Using platform tilts and translations to cause perturbations with velocity and end amplitude variables, these researchers concluded that the predictive control of response scaling was impaired in a variety of types of cerebellar disease. The results of these experiments were however based on whole body position-over-time and EMG responses and due to the nature of a tilting platform, did not incorporate force/CoP measures. The nature of the platform perturbation involving all sensory systems also makes it difficult to draw true comparisons with our vestibular-only response findings, but at least on face value there appear to be similarities.

Despite significant group differences reported and mean SCA6 group increases in early trunk sway, it remains unclear why such differences were not evident in early CoP or force measures.

One explanation for solely increased trunk sway response magnitudes could be a lack of re-afferent activity impeding the response. If there was such a lack of re-afferent activity in the SCA6 group, high initial sway speeds would be maintained longer and peak medium latency displacements would be delayed relative to healthy volunteer subjects. If this were the case, SCA6 trunk and CoP response vectors, sampled over a timeframe of 0.2 to 2s following stimulation onset, would be increased and statistically significant group differences reported. Interestingly, this was the case for late trunk and CoP sway measures although peak sway timings were not different between groups.

If re-afferent dysfunction is the cause of overscaling, it seems most likely that proprioceptive re-afferents would be responsible since late SCA6 sway magnitudes were increased, regardless of whether vision was intact or obscured. If proprioceptive timing or scaling was impaired, suppression of the response based on proprioceptive re-afferent

signals may be reduced in the time sampled. This would result in larger than normal response magnitudes but normal scaling of early measures, particularly force responses, which reflects the nature of our findings. Challenges to this idea come from prior research using platform perturbations and cerebellar subjects [155,258,366]. Authors of these studies concluded that scaling abnormalities were most likely caused by predictive control of scaling and not by online changes made by re-afferents [155,258,366]. However, since these platform perturbations inherently involved proprioceptive changes from the onset of the platform perturbation, it stands to reason that late measures of sway would not vary in characteristics from earlier samples of sway and EMG changes.

Despite the support for a proprioceptive re-afferent dysfunction theory, a plausible alternate explanation for elevated early trunk and late trunk and CoP sway measures could involve changes in torque control across axial joints. Delays or problems with scaling of torque over axial joints could summate across to create differences in the way the whole body response to GVS is organised. There is some evidence to suggest that problems with scaling of torque in response to position-in-space perturbations may be a feature of cerebellar disease [31,28,81,369]. Bastian *et al*., 1996 and 2002 [31,28], Day *et al*., [81] and Topka *et al.,* [369] investigated upper limb reaching to describe increased variability, which was attributed to poor generation of interaction torques (for a review see [30]). Poor production of interaction torques was particularly problematic with multi-joint and fast reaching movements, where the greatest demand on organisation of torque is necessary. If this finding can be generalised to SCA6 subjects and across all joints in the body, then it could provide an explanation for the over-scaling observed. However, if torque over-scaling is responsible for increases in SCA6 sway magnitudes, it remains unclear as to why similar over-scaling of torque at the ankle would not produce group differences in force magnitude measures. Could the ankle joint be an exception to the rule? It is possible that feedback available from pressure receptors of the foot in addition to joint position receptors in muscles and tendons makes the ankle less susceptible to torque scaling errors than joints reliant on joint proprioceptors. Or perhaps single joint changes in torque, such as the ankle causing early force changes, are just too small to generate significant group differences in a t-test.

Another explanation for increased response magnitudes is that magnitude is an epiphenomenon of baseline instability. Initial support for this theory is presented by

exploration of correlations between baseline measures of sway speeds and response magnitudes. Trunk sway speeds and force response magnitudes stood out as being significantly correlated for the healthy control group. For healthy control subjects, as baseline trunk sway speeds increased, so too did force vector response magnitudes. However, similar correlations were not found between baseline trunk sway and force magnitudes (or any other combination of baseline sway and response magnitude measures) for the SCA6 group. This lack of similarity between groups tends to refute the idea that SCA6 increases in early and late sway measures could be an epiphenomenon of baseline instability. Furthermore, lack of a correlation between SCA6 disease severity scores and any elevated sway response measures also suggests that scaling of responses to vestibular perturbations may not be a direct consequence of disease severity increases. If this is to be believed then perhaps this provides further support for the emerging idea that vestibular processing is largely unaffected by SCA6 pathology.

In order to improve interpretation of over-scaling of sway, it seems necessary to investigate proprioceptive contributions to balance control.

5.4.2 Effect of vision on response scaling

As described in hypothesis 5, vision is normally associated with a reduction in GVS response magnitude when compared to responses under the same conditions but with vision obscured. This could be due to down-weighting of the vestibular signal [(222)], due to online re-afferent signals from the visual system [(86)] or from greater baseline stability prior to and during delivery of GVS. Regardless of the mechanism underpinning this effect we assume that if vestibular and visual signal combining processes are intact, the ratio of down-scaling of the GVS response with vision available should be the same for all subjects. If the response for SCA6 subjects is not down-scaled or the reduction in scaling is reduced then this could imply disease related disruption of this type of sensory processing. According to prior knowledge of vestibular and visual oculo-motor afferent projections to the cerebellum, sensory processing to combine vision and vestibular signals could take place in the flocculus or nodulus [(164,165,403)]. Although SCA6 cerebellar damage is known to predominantly affect more superior and anterior parts of the cerebellum, the flocculus is also a well-documented area associated with neuronal damage [(129)].

Responses measured using trunk and CoP sway and force changes immediately following

delivery of GVS provide conflicting support for the hypothesis that this effect of vision may be disrupted by SCA6 disease pathology. Trunk and CoP sway vector magnitudes of response, measured at either one or two seconds following stimulation onset produce vision quotients which are not statistically different to that of the healthy control group. These results clearly refute the initial hypothesis. However, in contrast to sway results, force vector magnitudes of response measured at 0.4 seconds following stimulation onset have a much lower group mean quotient (close to zero) and significant group differences are reported by statistical analysis. This result provides support for the hypothesis.

These conflicting findings once again raise the question of why there is a discrepancy between sway and force measures. Perhaps the simplest explanation could be that the short sampling time used to calculate force response magnitudes is most vulnerable to bias from background baseline sway. As yet, all of the factors determining response dynamics to GVS remain undetermined but it is thought to be multi-factorial. Despite control of some known variables between groups such as age, height and sex, some unknown variables will remain to bias the results in an unknown way, such as the direction and speed of sway immediately prior to onset of stimuli. If this is the cause of such discrepancy, it is feasible that it could affect the two groups measures in disproportionate ways, since SCA6 sway has been quantified as significantly faster and wider ranging than healthy control group (chapter 4). For this reason, although early force behaviour provides the most potentially interesting insight into response dynamics, it must also be interpreted with greater caution.

If we assume that the force results aren't the consequence of bias then explanation of this discrepancy between measures could either involve (i) differences in processes governing early force related scaling and inter-axial joint motion or (ii) differences in feed-forward/back visual control of balance. In the case of the former explanation, it seems unlikely that force and inter-axial joint motion should be dissociated on a processing level. However, the reported existence of microzones of the cerebellum could mean that it is plausible that scaling of motor responses across different zones of the body could be affected by disease pathology to different extents [16,17]. Currently there is little knowledge of SCA6 pathology specific to microzone systems or a microzone system within the flocculo-nodular node which would further support this idea. Perhaps more theoretical underpinning for the latter explanation exists; concerning differences in feed-forward visual

control of balance. It is feasible within this feed-forward system that delays in visual signal production (such as slow pursuit of external objects for tracking purposes) or delays in propagation of the signal could create delays in the online reweighting of vestibular signals for balance control. The consequence of this would be that early measures of response to GVS would be unchanged relative to conditions where vision is unavailable but later measures of response would be stabilised by vision, which reflects these findings. Prior research investigating eye movements in animals with flocculo-nodular lesions provide some further support for this theory since they suggest that this area is associated with slowing of pursuit related eye movements [382,403]. A recent study of eye movements in subjects with pre-symptomatic diagnosis of SCA6 also reported reduced pursuit speed [68]. Oculo-motor examinations conducted on our SCA6 patient group also suggest that delays in pursuit eye movements are present within this cohort, which could provide further support for this theory (chapter 3). However, this explanation relies on two main assumptions concerning visual control of balance. First, it assumes that the overall stabilising effect of vision prior to the application of GVS is negligible compared to the response magnitudes measured. Second, given that the original hypothesis concerned with disruption of visual and vestibular combining processes is based on prior findings of projection of oculo-motor vestibular afferents to the flocculonodular lobe, we assume that it is proprioceptive feedback rather than retinal slip signals that are affected. We therefore further assume that visual control of motion using retinal slip is not selectively used or up-weighted relative to visual control of motion using proprioceptive signals from extra-ocular musculature.

Before conclusions can be made regarding visual control of balance, further research into the visual contribution to balance in SCA6 must be undertaken.

5.4.3 Response direction abnormalities

In contrast to hypotheses 3 and 4, orientation of SCA6 sway responses were similar to those of the healthy controls, suggesting that combining processes for vestibular and proprioceptive (joint position) signals are unaffected by SCA6 disease pathology.

In contrast to sway measures, some differences between group directional orientation of forces were reported by statistical tests. On face value this could have been interpreted as evidence for disrupted combining of vestibular and proprioceptive signals, which would

have supported the prior hypothesis and conflicted with findings from sway measures. However, on further examination of SCA6 single subject mean responses and single trial data, it was discovered that strong 2-3Hz oscillatory sway existed in some trials of subjects who possessed unexpected mean response directions. The oscillatory sway waxed and waned and on some occasions carried over into trunk sway activity, primarily affecting Y-forces and Y-axis trunk sway. Two of the three subjects identified have been previously identified as having 2-3Hz postural tremor in chapter 4. The presence of this oscillatory sway in some trials appeared to have a large bias over mean trace forces per subject and appear to be the most likely cause of force directional anomalies detected in the SCA6 group.

It remains unknown as to why only a sub-set of subjects with SCA6 possess this 'postural tremor'. It also remains unknown why this tremor is not constant but rather wax and wanes. Indeed, since the oscillatory activity is not necessarily prevalent throughout trial durations, across trials or of a constant magnitude across trial repeats, it appears to have the potential to carry over into mean measures of forces and sway over time. In view of the striking effect on force measures, and the potential of carry-over into mean measure traces, this feature of SCA6 balance-related activity seems worthy of future investigation and consideration when designing future balance-related outcome measures.

Regardless of the cause of postural tremor, initial hypotheses suggesting that disruption of vestibulo-proprioceptive combining is responsible for balance impairment, seem largely refuted by these findings. A lack of correlations between response orientation errors and baseline sway speed or disease severity further supports this inference.

In contrast to these findings, recent work by Kammermeier *et al.* has concluded that vestibulo-proprioceptive combining processes are disrupted by cerebellar disease [(179)]. Kammermeier *et al.* used a constant sinusoidal type of GVS (delivered binaurally at 0.16 Hz with a 2mA peak to peak current) while subject's static head-on-trunk position was altered between 60° left and 60° right. Trunk positioning was achieved using a brace structure attached to the head and the trunk and subject's vision was controlled with the use of a dome display attached to the brace. Healthy control subjects were described as successfully able to re-orientate their response with head turn but cerebellar subjects did not achieve the same degree of re-orientation. On face value, Kammermeier et al.'s findings support the initial hypotheses of this study and challenge the results of this chapter

but it is felt that Kammermeier *et al.*'s findings should be interpreted with caution for the following reasons. The number of subjects used was not reported in the paper and results presented were based on data from a single patient with cerebellar disease and a healthy control. No group mean measures were reported and no statistical analyses of the results are presented. The nature of cerebellar disease investigated was similarly not reported. The use of sinusoidal GVS questions the assumption that the results reflect vestibulo-proprioceptive combining, since contributions from proprioceptive reafferents and factors such as expectation of how one should respond to the stimuli are likely to bias the measurements collected [138,301]. The use of passive positioning of the head-on-trunk remains unjustified but is a functionally atypical scenario and one that is open to bias if some subjects actively contribute to positioning and others remain relaxed [118,362]. The weight of the visual display in front of subject's heads is also not commented upon but could have biased results if this loading affected subjects disproportionately, as can occur in patients with disease pathologies [235]. Given the evidence presented in Kammermeier *et al*.'s paper, it is felt that this study has little to offer the understanding of vestibular-proprioceptive processing for balance control in SCA6. The main finding of this chapter, that vestibular processing for balance control in SCA6 remains largely normal, therefore remains unchallenged by this work.

5.4.4 Inferences for management of SCA6

In view of the likelihood that increased response magnitudes to vestibular perturbations are not due to vestibular processing abnormalities, vestibular rehabilitation exercises are unlikely to be effective in treating balance dysfunction in SCA6. This confirms what has long been experienced in practice by physiotherapists attempting to use vestibular rehabilitation to treat balance dysfunction in patients with a range of types of ataxia [59].

Training balance via perturbations involving vestibular sensory signals should provide an effective means of delivery but since responses to vestibular perturbations are largely normal, there is no clear indication to selectively train balance by vestibular perturbations or vestibular exercises.

Repetitive practice of functional balance activities could be effective in attempting to reduce over-scaling and should not at this stage be discounted. The success of this practice will however likely be dependent on the nature of the processes causing the over-

scaling. Some investigation of training coordination and balance within the context of functional activity has already taken place with good effects reported [161]. Equally, coordination training involving upper limb pointing activity with the goal to reaching a target has shown improvements in both speed and accuracy following training [369]. Training via repetitive platform perturbations has produced some positive improvements in older adults with balance impairments and for this reason may have some justification for trialling with SCA6 subjects [224].

The use of vision appears to be beneficial in reducing sway response magnitudes even though it does not seem to affect early force production in the same way. For this reason individuals with SCA6 may benefit from ensuring their home is well-lit and the use of nightlights may help towards fall prevention. Since the stabilising effect of vision on sway is largely normal, training of balance activity with the eyes closed does not seem to be indicated.

If future research acts to support the idea that proprioceptive re-afferent signals are in some way impaired then increasing the sensory drive of these signals may optimise balance control. The use of insoles and vibratory insoles by Perry *et al*. [283], has revealed some promising improvements in balance when used by aging subjects or those with diabetic neuropathy. The use of hard flooring in the home to optimise activation of foot sole pressure receptors should be weighed against the risk of injury from falling.

5.5 Conclusion

Vestibular processing for balance control is largely unimpaired by SCA6 disease pathology. Despite strong hypothesis that scaling and directional orientation abnormalities could be responsible for balance impairment in SCA6, the evidence presented here suggests that this is not the case.

Although not conclusive, early investigation of the effect of vision on balance behaviour does appear to differ significantly between SCA6 and healthy controls. Late sway behaviour in all postural and visual conditions also appears to be significantly increased in magnitude for SCA6 subjects.

Future research into proprioceptive and visual contributions to balance control is necessary in order to establish if sensory processing could be responsible for balance impairment in SCA6.

6 CHAPTER 6: A COMPARISON OF BALANCE RESPONSES TO ISOLATED PROPRIOCEPTIVE, VISUAL AND VESTIBULAR PERTURBATIONS

6.1 INTRODUCTION

Sensory end organs are not typically associated with SCA6 disease pathology [41,66,75,196,316,325]. It is therefore unlikely that balance dysfunction in SCA6 is caused by problems with detection of sensory balance cues at a peripheral level. Widespread Purkinje loss in the cerebellum, particularly in the antero-superior parts of the vermis, the flocculus and the vestibular and fastigial nuclei [129] could however disrupt processing of any of these sensory systems for the purpose of balance control.

As discussed in chapter 5, sensory processing within the cerebellum could be responsible for integration of multi-sensory information, determination of perturbation directions, magnitudes and inter-segmental organisation of the whole body response. Chapter 5 began to investigate these processes by employing isolated vestibular perturbations. However, despite strong theoretical justifications for primarily targeting the vestibular channel, the absence of a deficit in the vestibular contribution or any major differences between groups in measures of early responses to GVS suggests that impaired vestibular processing is not the primary cause of balance dysfunction in SCA6. Working from the original hypothesis that impaired sensory processing is responsible for SCA6 balance impairment, the investigation must now address the role of vision and proprioception in balance control.

Chapter five started to investigate the role of vision in balance control by assessing how vision affected responses to GVS. Significant differences in indexes indicating the effect of vision were reported between groups for force measures. This finding suggests that early in the response to GVS, vision is used less than normal to reduce responses to GVS. This could be due to disease related changes in areas known to have neurons sensitive to visual and vestibular afferent sensory signals, such as the flocculus and fastigial nuclei [164,165,403]. However, despite being a useful measure of responses to isolated sensory stimuli (i.e. early enough to remain free from re-afferent effects), forces were also found to be the measure potentially most susceptible to bias of baseline postural sway. Moving visual scenery (MVS) to evoke isolated visual balance perturbations in standing subjects

was therefore used to more rigorously examine the role of vision in balance control in SCA6.

Chapter five also began to investigate the proprioceptive contribution to balance control by assessing how postural information from joint proprioceptors could contribute towards the directional organisation of balance responses to GVS. It was concluded that responses were appropriately directionally organised and therefore proprioceptive channels responsible for coding whole body posture were appropriately combining with craniocentric vestibular signals. However, despite normal orientations of responses, some uncertainty regarding proprioceptive functioning remains given that later sway response sizes, representative of responses modulated by re-afferent signals, were found to be larger for the SCA6 group than healthy controls. This finding posed the question of whether re-afferent signals from proprioceptors were unable to contribute towards downscaling later response magnitudes and ultimately signal an arrest of the response. This could be caused by SCA6 disease pathology preventing combining of proprioceptive reafferents with vestibular afferents that are specifically concerned with signalling the scaling of body motion (rather than the direction). Recent animal lesioning studies suggest that the anterior vermis, vestibular and fastigial nuclei may have roles in this function [52,227,309,312]. This experimental study was designed to attempt to clarify if late sway responses to GVS in those with SCA6 could be due to disordered sensory processing of proprioceptive information. Muscle vibrators were used to evoke isolated proprioceptive balance perturbations in standing subjects from which SCA6 responses could be assessed and compared with those of healthy controls.

6.2 Experimental aim

To understand how proprioceptive and visual processing abnormalities caused by cerebellar damage in SCA6 may be responsible for balance impairment.

6.3 Hypotheses

Knowledge of cerebellar connectivity, function and cerebellar damage in SCA6 set out in chapter 1 has been drawn upon to set out the following hypotheses for causes of balance impairment.

7. **Impaired processing of proprioceptive afferent signals limit central scaling**

of the afferent signal. This would lead to generation of insufficient or under-scaled motor responses to isolated proprioceptive stimulation. Consistently smaller than normal responses to vestibular stimuli in those with SCA6 would provide support for this hypothesis. Correlations between disease severity and response size would further strengthen support for this hypothesis. To test this hypothesis isolated proprioceptive perturbations were delivered and whole body response magnitudes measured.

8. **Impaired processing of visual self-motion information disrupts central scaling of the afferent signal.** This would lead to generation of insufficient or under-scaled motor responses to isolated visual stimulation. Consistently smaller than normal responses to visual stimuli in those with SCA6 would provide support for this hypothesis. Correlations between disease severity and response size would further strengthen support for this hypothesis. To test this hypothesis isolated moving visual scenery (MVS) perturbations were delivered and whole body response magnitudes measured.
9. **The absence of extra-cerebellar disease pathologies will not lead to timing abnormalities.** Since extra-cerebellar pathologies are not characteristic of SCA6 [75,196,325], clinical characterisation of the sample reveals only mild extra-cerebellar symptoms in a minority of subjects (chapter 3), and responses to GVS were normally timed, I hypothesise that cortical, spinal or peripheral nerve disease pathology will not cause significant timing errors for responses to either proprioceptive or visual perturbations.

6.4 Approach

This study takes a similar approach to the prior investigation of GVS (chapter 5) in that it employs single sensory channel perturbations in standing subjects in order to measure whole body responses. A moving visual scene (MVS) was used to generate visual balance perturbations, which moved either clockwise or counter-clockwise at a controlled velocity, faster than the average speed of trunk sway in healthy subjects. Proprioceptive perturbations employed custom-made muscle vibrators (VIBS) stuck over muscle bellies and connective tissue of bilateral ankle musculature (ankle dorsi- and plantar-flexors; tibialis anteriors, lower muscle bellies of medial and lateral gastrocnemius, upper muscle

bellies of soleus and overlying connective tissue of the tendo-achilles). Vestibular perturbations were once again delivered using galvanic vestibular stimulation (GVS) to provide a direct comparison of response behaviour between perturbation types.

Throughout the investigation, subjects stood with their head 90 degrees in yaw right of their feet. This ensured that response directions to all stimuli would be either orientated forward or backward over the feet. The main reason for administering GVS with subject's heads turned is that when subjects are stood face forwards, the size of response to GVS is known to diminish and become harder to measure with stance widths wider than the feet together position [80]. Subjects with cerebellar disease experience balance difficulties with feet together stance (quantified in chapter 4) and for this reason the perturbation experiments needed to be undertaken with the feet wider apart. Subjects therefore stood with their feet apart but with their head turned. This position is less destabilising than feet together stance whilst still evoking clearly measurable forward-backward sway responses [118,159,217]. Apart from generating measurable responses under safe standing positions, this posture also enabled easy positioning of muscle vibrators and moving visual scenery to similarly evoke forward-backward sway, as previously described by Adamcova and Hlavacka [3].

Responses to stimuli were compared with other sensory system modalities on same subject samples from data collected on the same experimental session. MVS and vibrator parameters of use were taken from previous reports of their use in the literature and further decided on using pilot work on healthy controls. GVS parameters were identical to that previously described in chapter 5.

Leg muscle vibrators attached over the ankle plantar- and dorsi-flexors (triceps surae and tibialis anterior muscles, respectively) will stimulate stretch receptors in the underlying muscle and tendon to mock-up the experience of a stretch due to either a forwards or backwards toppling of the body. Moving visual scenery (MVS) creates a visual sense of having toppled either forwards or backwards. This MVS pivoted about subject's ankle joints to most accurately replicate the experience of postural sway.

The same approach to recording and measuring responses to these perturbations was used as described in chapter five. Response measurements were derived from whole body motion analysis and these were compared with baseline instability and disease severity measures using correlation analysis. Response timing, magnitudes, and directional

orientation will be evaluated per modality. Identical doses of muscle vibration (frequency and amplitude of vibration), visual scene motion (speed and amplitude of motion) and (GVS configuration and current) were delivered to a group of subjects with SCA6 and age-, sex and height-matched healthy subjects (described in chapter 2). This enabled comparison of responses between healthy and SCA6 subjects. Although pilot work has shown that it is possible to achieve similar response magnitudes and directions through careful selection of stimuli parameters, ultimately doses cannot be standardised across modality and it seems unlikely that the responses will be directly comparable between modalities for this reason. The comparability of responses will briefly be assessed in order to evaluate how differences in response biomechanics may affect overall response characteristics.

Due to positive reports of habituation affecting balance responses for vibration and MVS stimuli (plus some conflicting reports of habituation affecting responses to GVS) the first five blocks of response were assessed for habituation. It is not likely that responses incur a learning effect since the modality type and direction of perturbation were randomly delivered in blocks of eight trials.

It is expected that visual acuity had little effect on response measures given that all subjects were instructed to wear corrective lenses during experimentation. Perception of vibration thresholds, however, may be expected to correlate with either the onset of responses to vibratory stimuli or the magnitude of the response. Equally vibration thresholds could correlate with baseline sway speeds if impaired vibration thresholds are in some way representative of overall proprioceptive dysfunction. Where significant group differences were reported by initial analysis, correlations were explored between these response measures and baseline measures of disease severity and instability (sway speeds). Where strong correlations are found, this acts to strengthen hypotheses that response abnormalities are a consequence of disease pathology.

6.5 Method

This study was conducted during the final testing day. Clinical assessment (outlined in chapter 3) took place at the outset of the session. A measure of balance behaviour in freely standing subjects was taken in order to compare same session perturbation response measures. Baseline balance measures were taken following the same procedure

as described for chapter 4 but involved only one collection with the feet at 4cm stance width.

Three different types of sensory perturbation, introduced in chapter 1, were manipulated in order to create forward and backward whole body sway in the sagittal plane. This ensured that roughly the same effectors contributed to the motor response, or at least were available to contribute to the response. To achieve forward and backward sway using muscle vibration, two sets of independently controlled vibrators were stuck over ankle dorsi- and plantar-flexors bilaterally and selectively activated to cause forward or backward responses.

To achieve forward and backward sway using GVS or MVS stimuli, subjects were stood with their head turned 90 degrees to the right to face the moving visual scene. As described in chapter 5, right anodal GVS applied to subjects standing in this head-turned position will cause them to sway backwards, whereas left anodal GVS will cause subjects to sway forwards. Backwards sway can similarly be achieved by rotating the MVS clockwise about the ankle joint (anti-clockwise motion will induce forwards sway). This posture was used throughout all trials.

Randomisation of forward and backward conditions of all stimuli coupled with two additional no stimulation trials per block, prevented subjects from being able to predict how they may need to respond. It also enabled evaluation of the effect that stimuli will have on two independently directed motor responses. Inclusion of two no stimulation trials not only acted to decrease the likelihood of subjects guessing trial conditions but also decreased the intensity of the workload and created a control condition against which stimuli responses can be compared.

Table 6.1 describes the stimuli used per condition type. Aside from no stimulation conditions, odd numbered conditions in table 6.1 are predicted to produce backward directed responses and even numbers produce forward directed responses. Stimuli and no-stimuli trials were intermixed and randomly delivered to a depth of one with 10 repeats of each (i.e. 8 conditions totalling 80 trials).

Table 6.1: Condition coding.

Condition no.	Condition type	Abbreviated condition code
1	No stimulation	NS
2	No stimulation	NS
3	GVS (right anode, left cathode)	GVS_r+
4	GVS (left anode, right cathode)	GVS_l+
5	Vibration (bilateral plantar-flexors: Triceps surae)	VIB_Pf
6	Vibration (bilateral dorsi-flexors: Tibialis anterior)	VIB_Df
7	Moving visual scene (clockwise)	MVS_cw
8	Moving visual scene (anti-clockwise)	MVS_acw

6.5.1 PROCEDURES

Subjects were fitted with infra-red lights (part of the Coda whole body motion analysis system), safety harness, GVS electrodes and leg vibrators. The nature of this equipment and the application procedures involved are described in chapter 2.

Subjects stood in the middle of the laboratory and over the origin of a single force plate. The medial border of each foot was aligned to parallel lines drawn on the force plate spaced 8cm apart. Subjects stood initially facing away from a moving visual scene (MVS). The MVS was positioned parallel to force plate lines, to the right of subjects (figure 6.1). The pivot point of the MVS was positioned in line with each subject's ankle joint. Subjects were then asked to turn their head 90 degrees to the right to look at the display after which the display was moved to a distance of 40cm perpendicular to subjects' eyes. A visual restrictor was then fitted around subject's eyes to prevent them from seeing any peripheral information which was not part of the MVS display during testing (also visible in figure 6.1). Prior to the onset of each trial, subject's heads were positioned 90 degrees yaw right of their feet so that they were squarely looking at the MVS. Once the researcher was satisfied with subject positioning, the trial started with a button press.

Each stimulus was delivered in the middle two seconds of 6 second long trials after a randomised delay, the sequence of which is outlined in figure 6.2. Once each trial ends, the subject is notified by a beep and instructed by the researcher to look away from the display. The subject is directed to look at a picture on a wall, positioned in front and slightly to the left. The purpose of this was to refresh subject's vision with a rather more visually interesting environment and to promote physical turning to the left to avoid neck and upper back stiffness. This activity also provided time for the MVS to move to re-align the display with the vertical in preparation for the subsequent trial. A light illuminated when this MVS

mechanism was reset and the researcher used this as a cue to ask the subject to turn back to face the MVS. To avoid fatigue, subjects were free to request a rest at any point and all subjects were advised to have a seated rest after every 16 trials (20% milestones of the total trial duration). Subjects with SCA6 were advised to look out for feelings of tiredness and fatigue and the trial was stopped if these feelings were not recovered after a seated break.

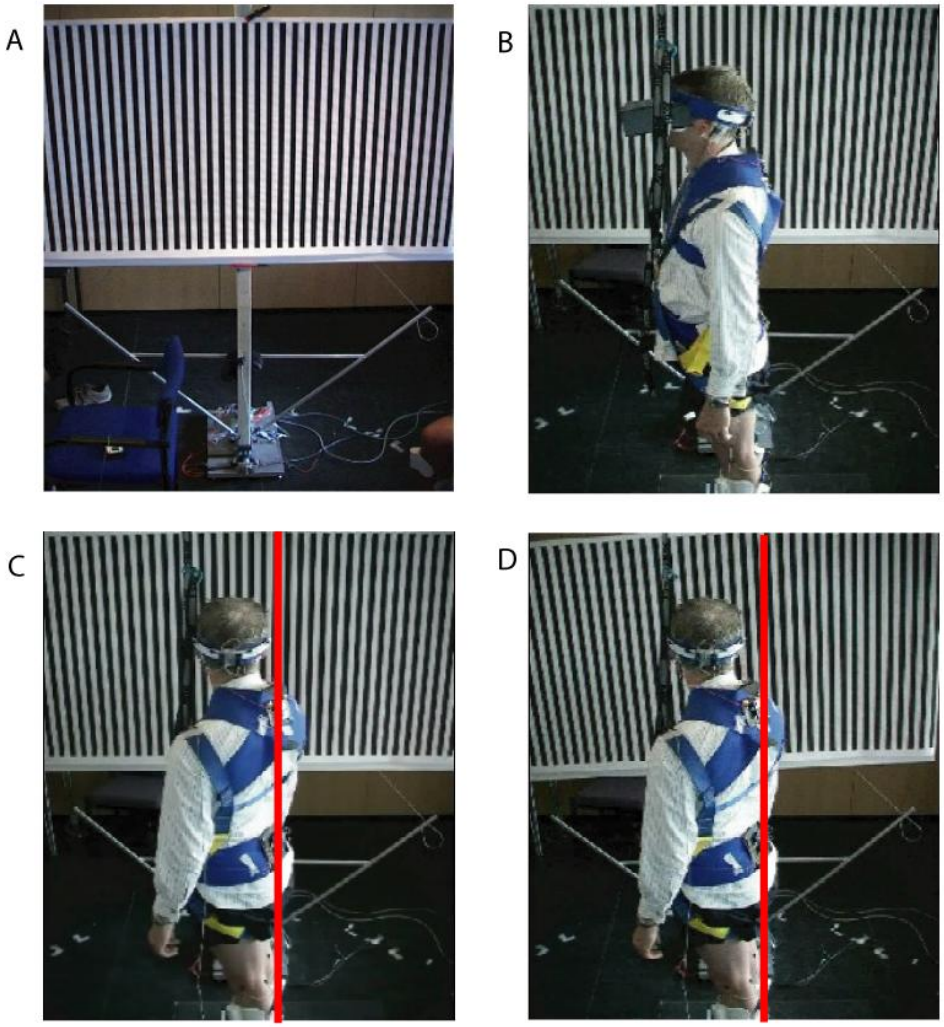


Figure 6.1: The experimental setup and procedural steps.
MVS apparatus pivoted about a low level axis designed to be consistent with the experience of rotating visual environments associated with postural sway (A). Subjects stood perpendicular to the MVS, donning all motion analysis LEDs, GVS electrodes, vibrators and a visual restrictor (B). Subjects stood with their ankles aligned to the pivot pointof the MVS (B). Subjects were instructed to look away from the MVS until ready to commence each trial (B). Subjects were instructed to look directedly at the moving visual scene prior to the button press starting each trial (C). Subjects randomly experienced each sensory condition and visibly swayed in response to perturbation trials (D). Red lines have been superimposed over images in order to help identify sway.

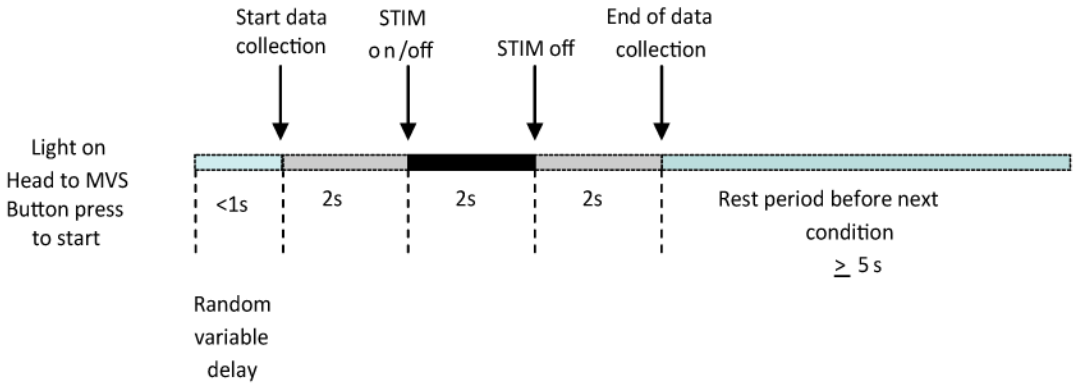


Figure 6.2: Diagramatic representation of trial sequence
Trials followed a standardised timed series of state changes according to condition. Block colour changes correspond with data collection start and stop times as well as potential stimuli delivery start and stop times. Stimuli varied according to condition (either GVS, VIB or MVS).

6.5.2 INSTRUMENTATION

6.5.2.1 Vibrators (VIBS)

Two 2.5 gram eccentric brass mass, 8cm long axis, 12v brushed DC motor vibrators embedded in a 10cm (2cm diameter) sealed cylindrical plastic tube and silicone leg-conforming mould were stuck over dorsi and plantarflexor muscles using double sided tape. This novel method of application helped to standardise the force of vibration on the underlying soft tissue, which in turn would help to standardise amplitude of vibration (at a fixed 100Hz frequency), both variables known to affect receptor activation firing [72,370].

To apply the vibrators, tibialis anterior muscles were first palpated whilst subjects maintained ankle dorsi-flexion in sitting. The vibrators were positioned distal to the tibial plateau and with the longitudinal axis of the vibrator in a central position along the length of the palpable muscle belly. A second set of two vibrators powered in tandem were attached over triceps surae muscles. Positioning involved palpation of the lower borders of the medial and lateral gastrocnemius and a line drawn between the two whilst subjects sat and plantar-flexed their ankles. Vibrators were positioned lengthways to span symmetrically across this line, with wings spanning horizontally around the semi-circumference of the calf. This theoretically resulted in stimulating lower muscle spindles in fibres of gastrocnemius, as well as underlying muscle spindles of soleus and Golgi tendon organs of tendo-achilles.

Vibrators were powered to vibrate at a frequency of 100Hz, in accordance with prior

published reports of use of vibrators for the purpose of evoking balance perturbations [116]. Pilot work confirmed that 100Hz vibration caused measurable whole body sway and was well tolerated by subjects throughout multiple trial repeats. Vibration was delivered for two seconds per trial whilst subjects stood with their head 90 degrees yaw right of their feet.

Two seated practice trials involving delivery of tibialis anterior vibration (VIB_Df) and triceps surae vibration (VIB_Pf) were undertaken with each subject with vision intact at the start of the session. This allowed each subject to experience the sensation of the stimuli. By administering this 'practice stimuli' whilst subjects were still seated, first trial standing balance responses were still measurable whilst startle effects associated with the initial sensation of the stimuli were avoided.

*6.5.2.2 **Moving visual scenery (MVS)***

A moving visual scene (MVS) was positioned to the right of subjects with the ground-level pivot point in-line with subjects' ankle joints (figure 6.1). Movement about this low pivot point was designed to ensure that the induced illusion of motion of the display is physiologically significant, i.e. that it resembles the experience of feedback from whole body sway [192].

Motion of the screen was achieved using a 24v brushed direct current motor and a reduction gearbox to increase the torque (mains powered). The display was connected by a two metre arm, made of rigid fibreglass/aluminium honeycomb, to the axis of the motor. Additional aluminium arms with a crossbeam and steal ties further improved the rigidity of the arm. Motion of the structure, which resembles an inverted pendulum, was optimised with the inclusion of viscous damping at the base of the structure (visible in figure 6.1A).

Speed of motion (8 degs/s), displacement amplitude (16 degs) and displacement time (2s) variables were then controlled by LabView software, which also monitored the functioning of the MVS online in order to ensure accurate delivery of visual perturbations.

A large (A0 size)), lightweight (5mm width polystyrene foamboard) screen was constructed in order to ensure that the screen information provided would be the only visual input during trials (even if the head was to move position during the trial duration). This was achieved in conjunction with the use of a visual restrictor (visible in figure 6.1B).

Highly contrasting (100%:0% greyscale) thick 2cm stripes were selected for use as part of the visual display. During piloting, these were found to cause repeatable, measurable

perturbations in healthy subjects and did not induce any visual illusions or perceived motion of the scene when static. Vertical lines also ensured that subjects would receive standardised visual flow information regardless of subject height variations.

High contrast was used in order to ensure that all subjects could detect all available information indicating motion within the display, even if contrast sensitivity was reduced in older subjects [209].

Eight degree per second rotational motion speed settings and 2 second motion duration variables were programmed in LabView, software LabView software also controlled return movement of the MVS into an upright position after completion of a MVS condition trial. Each trial terminated with an audible beep after data collection was complete, which acted as a cue to the subject to look away from the MVS. Whilst looking away from the MVS and wearing a visual restrictor, subjects did not see the return of the MVS. This beep occurred after every trial (for all perturbation modalities) and therefore did not act as a feedback cue for MVS condition trials. Once the MVS had returned to an upright position, feedback from LabView triggered a 'go' light and subjects were asked to once again turn to look at the static display in preparation for the next trial. A central control computer was used to select a condition per trial and randomise conditions across trial repeats.

6.5.2.3 Galvanic vestibular stimulation (GVS)

GVS was delivered using a custom made generator via two 6cm^2 carbon-rubber electrodes secured to skin overlying mastoid processes using 3M tape (previously illustrated in chapter 5, figure 5.3A). Electrode gel (Signa gel, Parker Lab.) was applied to the surface electrodes to reduce impedance. Subjects' ears were taped with Micropore (3M) tape to avoid unnecessary stimulation of cutaneous afferents.

Binaural bipolar (1mA square-wave constant current) was applied for 2 seconds per GVS trial. Subjects received either right anode + left cathode (GVS_r+) or left anode + right cathode (GVS_l+) stimulation conditions.

A single seated practice trial involving delivery of GVS was undertaken with each subject at the start of each session. This allowed each subject to experience the sensation of the stimuli. By administering this 'practice stimuli' whilst subjects were still seated, first trial standing balance responses were still measurable whilst startle effects associated with the initial sensation of the stimuli were avoided.

6.5.3 Control parameters

In order to standardise sensory experiences across trials and between subjects, posture, vision and visual and auditory environmental cues were controlled before and after stimuli delivery.

Subjects donned earplugs throughout this experimental session (session 3) due to the high-pitch mechanical noise generated by the MVS upon movement and noise generated by vibrators. From the onset of vibration and moving visual scene motion it could be argued that subjects could consciously detect the stimuli (audibly as well as from cutaneous and proprioceptive receptors for vibration and visual receptors for MVS) and in turn cognitively drive or resist the response [105]. Use of 32dB earplugs and background white noise to mask equipment noise and analysis of early measures response (0.2-0.4s following stimulation onset) should however remain free from such potential bias.

Lighting levels were controlled in the laboratory with the use of blackout curtains and lamps. Shadows cast from the subject onto the laboratory surroundings could provide a form of visual feedback and for this reason spot lighting was directed to eliminate in-view shadows. A visual restrictor, displayed in figure 6.1B, was fitted around each subject's eyes to limit visual field and in doing so, standardise the volume of visual information available per subject. It also acted to avoid subjects detecting shadows cast by their own body on the screen and to limit roaming of visual fixation point during trials.

6.5.4 Response analysis

Kinematic data collected during trials was the same as that previously described in chapters 4 and 5, i.e. whole body motion and ground reaction forces.

Moving visual scenery perturbation onset times were adjusted by +0.35s to accommodate the delay in motion onset incurred by the apparatus after triggering in Coda.

*6.5.4.1 **Response form***

In order to analyse the global form of responses, force and kinematic data was averaged across the time series for all trial repeats per modality. Backward responses were inverted in order to ensure that responses could be averaged across both trial repeat and condition per modality. Maximal trial numbers were used were used in this way in order to optimise signal (response form) to noise (background sway) ratios. The form of these traces could then be assessed and response timings, mean magnitudes and mean directions

calculated.

6.5.4.2 Response timings

In order to quantify the timing of SCA6 responses, medium latency peak force responses and peak trunk excursions were calculated per subject based on average forms of response per modality, per subject.

These calculations involved finding the maximum peak in forces during the period between stimulation onset and 2.0 seconds FSO. The peak sway response was calculated from maximum peak in trunk excursion during the period between stimulation onset and the end of the trial.

Individual subject average response latency measures were statistically analysed to look for group differences using t-tests (within-subject factor: *response latency*; between subject factor: *group* (HVS, SCA6)).

6.5.4.3 Assessing response scaling

Forces were sampled from 0.2 to 0.4s following stimulation onset (FSO) and kinematic data from 0.2 to 1.0s FSO. Measures of magnitude and direction were calculated from vectors created from these samples of data. Statistical analysis of these measures employed student t-tests to assess differences between *groups*. Prior to statistical analysis of GVS response directions, responses were normalised to start head position since this was a head referenced rather than earth referenced stimuli.

Group differences were assessed for statistical significance using T-tests (within-subject factors: *response magnitude*; between subject factor: *group* (HVS, SCA6)).

ANOVAs were additionally used to briefly assess the comparability of response magnitudes across modality type: Within-subject factors: *response magnitude* (forwards, backwards) and *modality* (*vibration (VIB), moving visual scenery (MVS), galvanic vestibular stimulation (GVS)*); between subject factor: *group* (HC, SCA6).

6.5.4.4 Determining effects of response direction on scaling

In order to investigate the effect of the type of motor response (i.e. a forward or backwards response) on response scaling, mean vector magnitude measures were calculated per subject per response direction. Mean magnitude measures were calculated according to the sampling method described above. Mean magnitude measures were statistically analysed using ANOVAs to assess group and response direction factors (ANOVAs: within-

subject factors: *response direction* (forwards, backwards; between subject factor: *group* (HVS, SCA6)).

ANOVAs were additionally used to briefly assess the comparability of response magnitude across *modality* type: Within-subject factors: *modality* (*vibration (VIB), moving visual scenery (MVS), galvanic vestibular stimulation (GVS)*); between subject factor: *group* (HC, SCA6).

6.5.4.5 Assessing the orientation of the response

The same epochs following stimulation onset (FSO) can be used to calculate a response direction as previously described for calculating vector magnitudes.

Calculation of mean response direction relative to starting head position (rather than in laboratory coordinates) was undertaken for GVS responses due to the craniocentric nature of the response. Starting head angles in laboratory coordinates were subtracted from angles of resultant trunk, force and centre of pressure vectors (also in laboratory coordinates). Subjects' mean starting head positions were calculated using two of four available head markers in laboratory coordinates immediately prior to stimulation onset (from -0.8 to 0 seconds). Since response directions are predicted to occur 90 degrees relative to the feet for VIB and MVS modalities and 90 degrees relative to the starting head position using GVS, the relative error to the expected direction was calculated in each case.

Circular statistic techniques (Batschelet, 1981; previously described in Chapter 2, textbox3, equation 1) were used to calculate group mean response directional error and measures of between-subject variability (using angular deviations).

Group differences were assessed for statistical significance using T-tests (within-subject factors: *response direction*; between subject factor: *group* (HVS, SCA6)).

ANOVAs to assess the effect of perturbation direction on response directional error (ANOVAs: within-subject factors: *perturbation direction* (forwards, backwards; between subject factor: *group* (HVS, SCA6)). ANOVAs were additionally used to briefly assess the comparability of response directional error across modality type: Within-subject factors: *modality* (*vibration (VIB), moving visual scenery (MVS), galvanic vestibular stimulation (GVS)*); between subject factor: *group* (HC, SCA6).

6.5.4.6 *Screening for habituation effects*

In order to assess for habituation effects, which may be expected to occur for moving visual scene and vibration conditions but are unlikely to occur with galvanic vestibular stimulation [24,63,358], responses across five initial repeats of same modality stimuli were calculated. Single trial response vector magnitudes were calculated using the same method as that employed to calculate response vector magnitudes for mean time series data. These vector magnitudes were then averaged (means calculated) across forward and backward conditions per modality per block of trials per subject. This mean measure includes one forward and one backward directed response. This ensured that effects of trial repeat could be assessed whilst avoiding variable presentation orders which result from randomising the delivery of conditions (ten conditions, depth of one).

Ideally up to ten same-condition repeats were available for comparison between subjects, but some trial repeats had to be deleted due to major artefacts or where subjects made unwanted voluntary movements. The first five same-condition repeats were therefore selected for use and statistically analysed using ANOVAs (within-subject factors: *trial repeat* (1,2,3,4,5); between subject factor: *group* (HVS, SCA6)).

6.5.4.7 *Correlations*

Where significant group differences were detected, correlations were explored between mean measures of subjects' responses to perturbations and their respective measures of baseline postural sway (trunk and CoP speeds) and disease severity scores (SARA and Bal-SARA).

Baseline measures of instability were derived from same session measures of trunk marker and centre-of-pressure speeds of motion in the x-y plane with subjects stood in 4cm stance widths. 4cm stance width sway speed measures were selected for use since they were found to best correlate with disease severity scores in chapter 4. Measures of disease severity (SARA score) were available from clinical assessment of subjects, described in detail in part one of chapter 3.

Pearson's correlation coefficients calculated in SPSS quantified the strength and direction of any relationships and corresponding p-values indicated the probability of obtaining the described relationships if the null-hypotheses were true. Since multiple response measures (including response magnitude and direction) derived from different measurement approaches (force change, CoP and trunk displacement over time) were compared with

baseline measures, the chosen level of significance was adjusted from the normal convention of $p<0.05$ to the more stringent $p<0.01$. This was designed to help protect against erroneous rejection of the null hypotheses.

6.6 Results

6.6.1 General form of responses

Raw data in figure 6.3 illustrate motion of a trunk marker in the x-y plane over six seconds of data collection for vibrator (figure 6.3a) and moving visual scene perturbations (figure 6.3b). Comparable with figure 5.4 in chapter 5, these figures illustrate motion of the trunk marker during the stimulation period (thick black and red lines). Red lines represent the time epoch from which a response vector will be sampled in order to calculate magnitude and direction measures. In accordance with expectation, the direction of motion of the marker is either forward or backward of the subject, indicated in figure.6.3 with the help of the central illustration of a subject. Prior to stimulation onset, fine lines indicate motion at baseline. This pre-stimulation sway is comparable with the 'no-stimulation' trace (also a fine grey line), which charts the motion of the marker over a full six seconds of unperturbed standing in the equivalent standing posture. When the thick line becomes dotted, subjects no longer received vibration. The dotted line illustrates an 'off-response' where subjects are observed returning to an upright position.

Figures 6.4-6.6 illustrate overall form of force and sway fluctuations over time for each subject following vibrator (figure 6.4), moving visual scene (figure 6.5) and GVS (figure 6.6) perturbations. Individual lines illustrate mean force or sway fluctuations over time per subject based on ten trial repeats per condition. Backwards directed responses were initially inverted before averaging with forwards directed responses in order to gain mean traces per modality. Each individual coloured line therefore represents the mean of twenty modality specific trials per subject. Force and sway behavior under the same conditions and trial durations but where no stimulation was administered (no stimulation control conditions: 'ns') is also presented in neighbouring columns for comparison and to help identify responses in each dataset. In each case, individual subject responses are easily differentiated from control condition force and sway behavior.

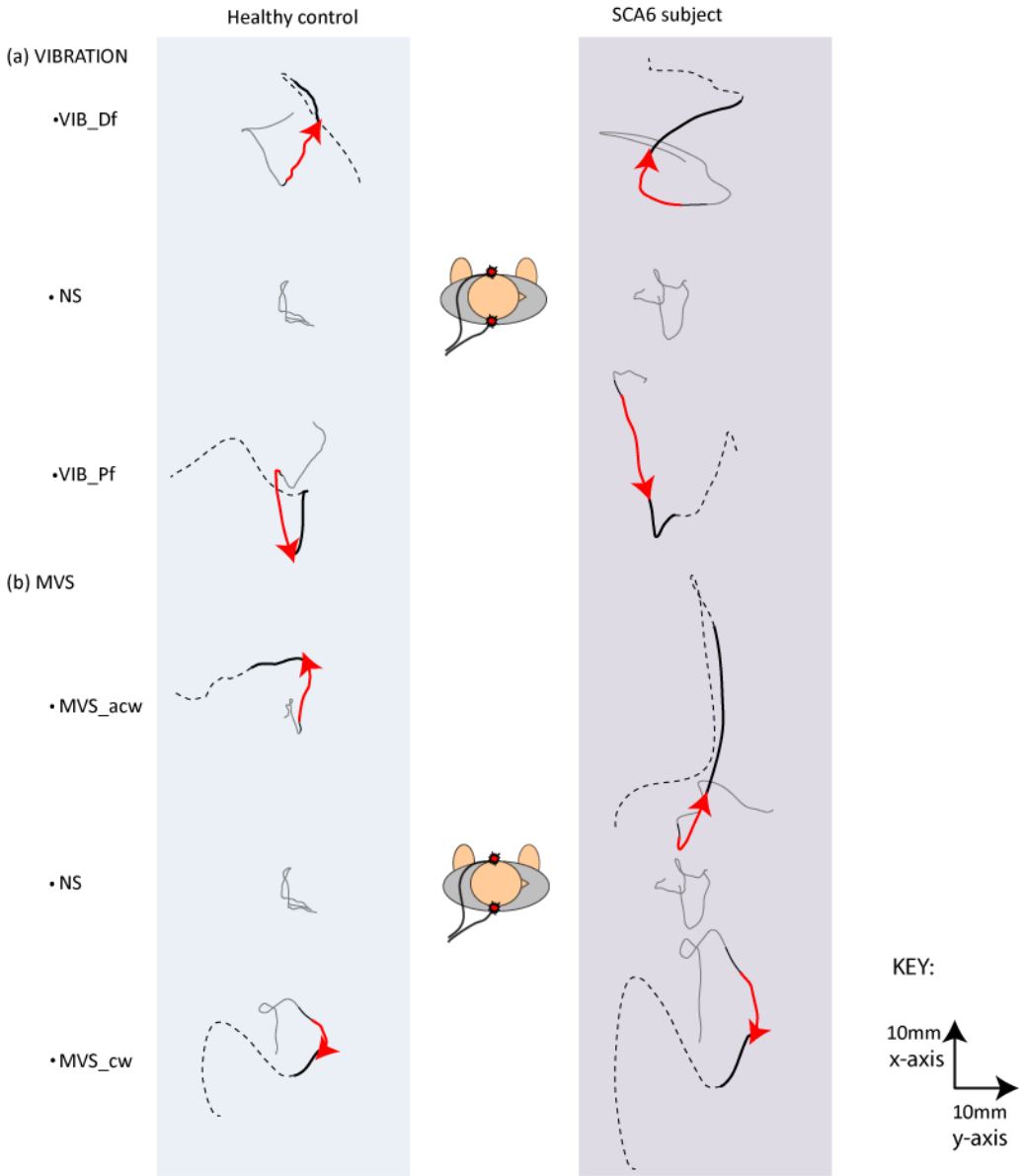


Figure 6.3: Birds eye view of individual subject single trial 2D trunk sway data.
Position changes over time of subject's trunk cluster over 6 seconds. The left column illustrates data from a healthy control and the right column illustrates that of the age-, sex- and height-matched SCA6 subject. The upper half of the figure illustrates responses to vibrator stimuli and the lower half to MVS . Rows order stimulation condition. Thin grey lines = no-stim periods or trials, full black lines = start and end of stimulation periods, thick red lines = measurement period within stimulation periods (used to calculate response vector), dashed line = post-stimulation recovery periods.

These figures show that subjects possess forms of response to stimuli visible in x-axis laboratory coordinates. In line with positioning of subjects in the laboratory, this corresponds with antero-posterior motion. Background sway activity is also clearly visible in mean traces despite prior averaging across twenty trial repeats.

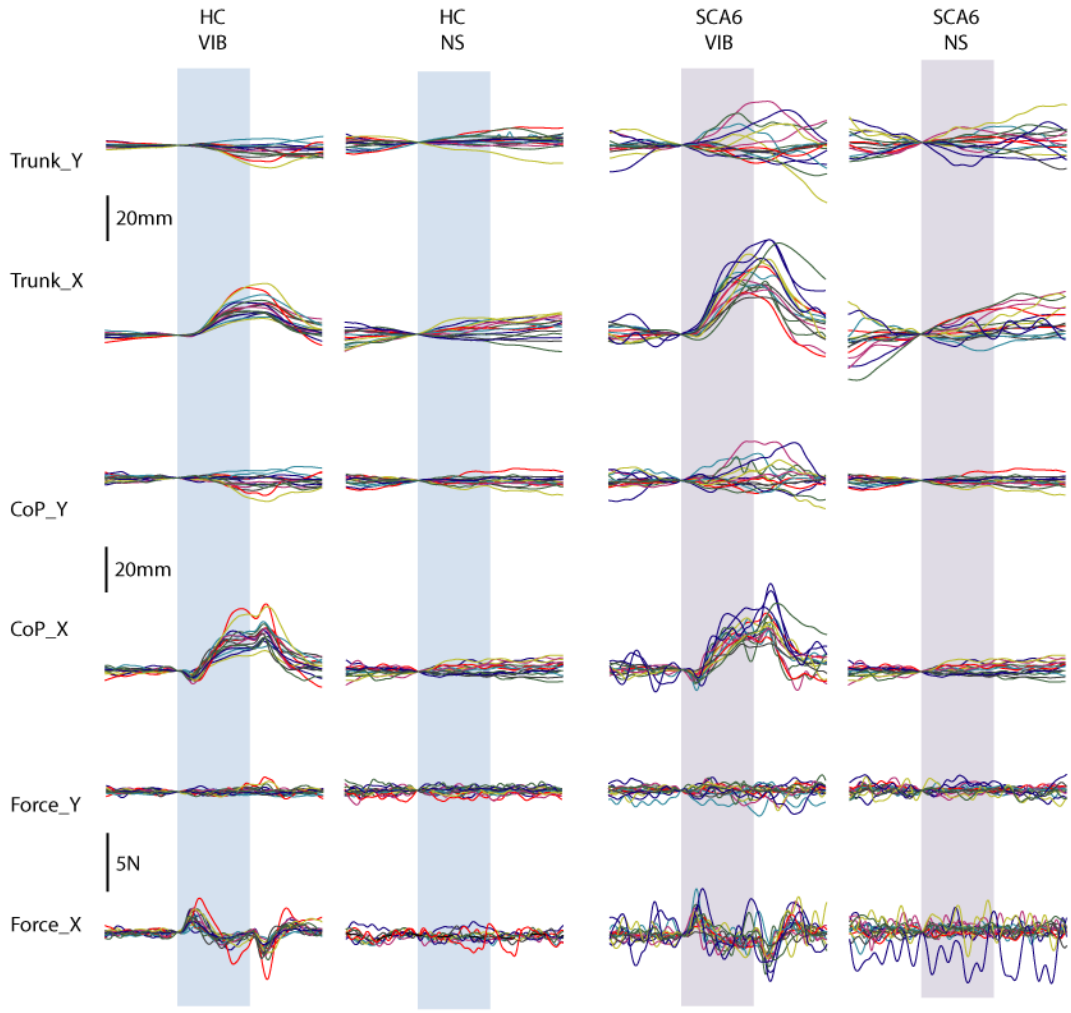


Figure 6.4: Mean sway and force fluctuations for VIB and no stimulation conditions.
Traces illustrate 6 second durations of data collection whilst subjects stood with their head turned. Each coloured line corresponds to indivdual subjects. Shaded boxes illustrate vibrator delivery. Left to right columns order group and condition data: 1=Healthy control vibrator perturbation data, 2=Healthy control no stimulation condition data, 3=SCA6 vibrator perturbation data, 4=SCA6 no stimulation condition data. Top to bottom rows order measures taken (X=Laboratory x-axis, Y=Laboratory y-axis).

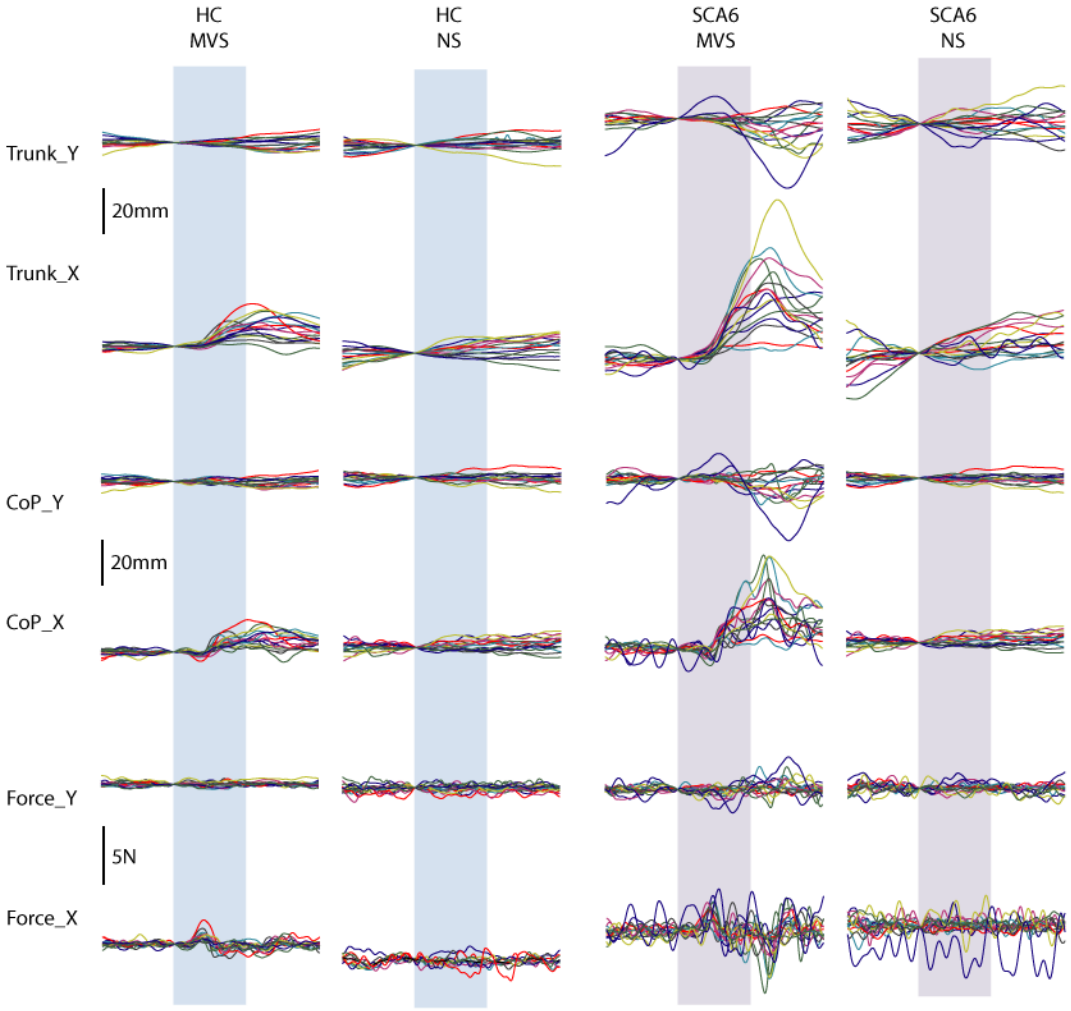


Figure 6.5: Mean sway and force fluctuations for MVS and no stimulation conditions.
Traces illustrate 6 second durations of data collection whilst subjects stood with their head turned. Each coloured line corresponds to indivdual subjects. Shaded boxes illustrate MVS delivery. Left to right columns order group and condition data: 1=Healthy control vibrator perturbation data, 2=Healthy control no stimulation condition data, 3=SCA6 MVS perturbation data, 4=SCA6 no stimulation condition data. Top to bottom rows order measures taken (X=Laboratory x-axis, Y=Laboratory y-axis).

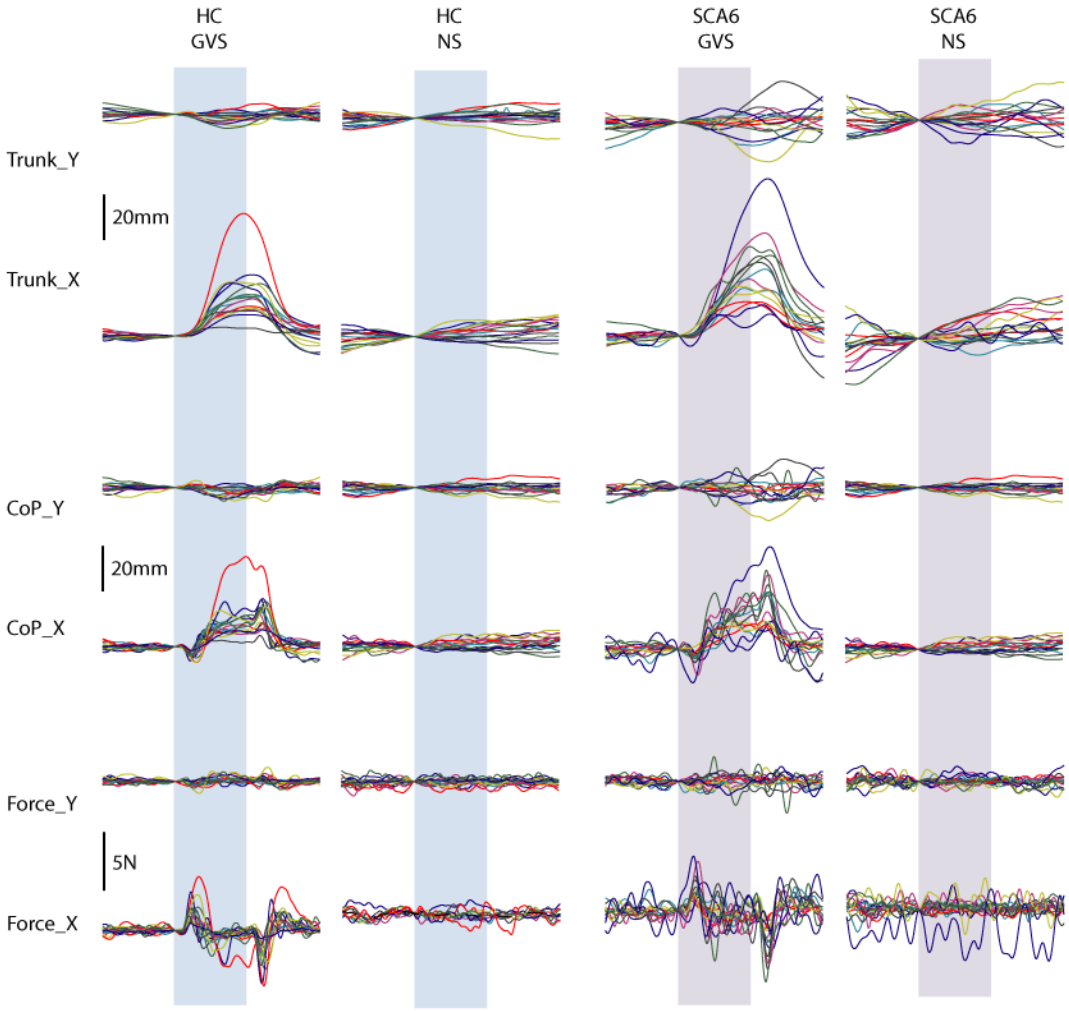


Figure 6.6: Mean sway and force fluctuations for GVS and no stimulation conditions.
Traces illustrate 6 second durations of data collection whilst subjects stood with their head turned. Each coloured line corresponds to indivdual subjects. Shaded boxes illustrate GVS delivery. Left to right columns order group and condition data: 1=Healthy control vibrator perturbation data, 2=Healthy control no stimulation condition data, 3=SCA6 GVS perturbation data, 4=SCA6 no stimulation condition data. Top to bottom rows order measures taken (X=Laboratory x-axis, Y=Laboratory y-axis).

6.6.2 Response timings

Response timings were calculated from mean force over time data, averaged across all same sensory condition trial repeats. Backwards directed mean responses were inverted in order to calculate one global form of response per modality per subject (illustrated in figures 6.4-6.6). Mean response over time data therefore incorporated ten trial repeats per condition and two conditions per modality per subject (total trial repeats per modality, per subject=20).

Figure 6.7 illustrates group mean force responses over time for each modality type. The highest point of the curve after onset of stimuli (0.2-2.0s FSO) seen in these figures is said to illustrate the peak timing of the force response. T-tests report significant differences between group force response timings for MVS only, where mean SCA6 timings are 120ms delayed relative to HC group mean (MVS_Fpeak: p=0.049, table 6.2).

The peak sway response, represented by the highest point of the trunk x-axis displacement from stimulation onset onwards (0.2s-4s FSO), was also calculated assessed for group differences. At this point, re-afferent signals from all sensory systems act to arrest the response and begin to return the subject to an upright position. A significant group difference was reported for peak trunk sway response timings following GVS stimuli only, where mean SCA6 timings are 220ms delayed relative to HC group mean (GVS_Tpeak: p=0.036, table 6.2).

Table 6.2: Descriptive statistics and t-tests for group mean response timings to stimuli.

Measure	HVS mean (± 1S.D.)	SCA6 mean (± 1S.D.)	t-value (d.f.)	p-value
VIB_Fpeak (s)	0.45 (0.10)	0.43 (0.10)	-0.4 (30)	0.714
MVS_Fpeak (s)	0.83 (0.13)	0.95 (0.21)	2.1 (30)	0.049
GVS_Fpeak (s)	0.50 (0.08)	0.50 (0.08)	-0.1 (28)	0.888
VIB_Tpeak (s)	2.25 (0.24)	2.10 (0.39)	-1.3 (30)	0.202
MVS_Tpeak (s)	2.39 (0.41)	2.50 (0.38)	-0.8 (30)	0.432
GVS_Tpeak (s)	1.97 (0.27)	2.19 (0.27)	2.2 (28)	0.036

Equal variances are all assumed according to Levene's test ($p<0.05$)

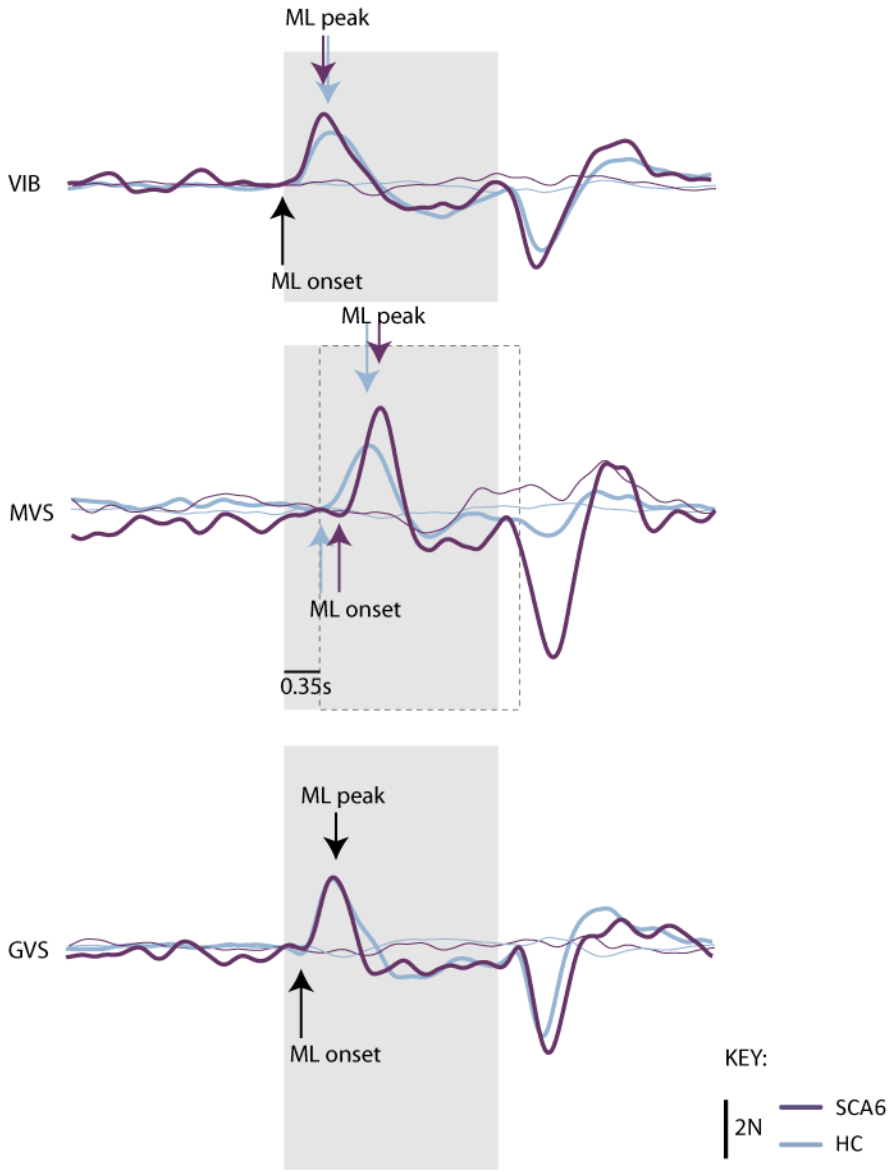


Figure 6.7: Group mean forces in x- and y-laboratory coordinates illustrating response latencies. Laboratory x- and y-axis force responses averaged across trial repeat, condition and group subjects are presented per modality. Mean antero-posterior forces (x-axis) are illustrated by full lines and medio-lateral forces (y-axis) by fine lines. Arrows indicate the measurement points of the response: the onset of the medium latency (ML) force response onset and peak. Stimulation periods are indicated by the shaded background. Mean onset of MVS motion incurred a 0.35s mechanical delay. Grey dashed border outlines the modified sampling period in order to ensure equivalent measurement of forces between modalites.

6.6.3 Response magnitude scaling

Mean group trunk sway, CoP excursion and force responses to vibration, MVS and GVS are presented in figures 6.8-6.10 respectively. Colour-coded shading around mean group traces indicate one standard deviation either side of the mean which represents between-subject variability of sway over time.

6.6.3.1 ***Vibration***

The form of trunk sway, CoP excursion and force group mean response to vibration appear similar, although slightly increased for the SCA6 group (figure 6.8). Significant group differences, assessed using t-tests based on early sway vector magnitude responses to vibration (0.2-1s FSO), were reported for trunk and CoP sway data (table 6.3). Later measures of trunk sway (0.2-2s FSO) were also significantly different between groups but CoP sway magnitude measures did not reach the $p<0.05$ level of significance (table 6.3). No significant group differences in force measures were reported by t-tests (table 6.3).

6.6.3.2 ***Moving visual scenery***

SCA6 mean group trunk sway and CoP excursion following *moving visual scenery* (MVS) are visibly increased throughout the duration of the perturbation compared with healthy control equivalents, illustrated in figure 6.9. SCA6 mean group force responses are also increased compared with healthy control equivalents and the same trend is observed for the 'off-response', i.e. the response observed after the MVS motion stopped (figure 6.9C). Widespread significant group differences were reported by t-tests for all trunk sway, CoP excursion and force response magnitude data (table 6.4).

6.6.3.3 ***Galvanic vestibular stimulation***

The form of trunk sway, CoP excursion and force group mean response to *GVS* appear similar, although slightly increased for the SCA6 group (figure 6.10). T-tests reported no significant differences between groups for early trunk sway, CoP excursion and force measures (table 6.5). Significant group differences were reported for later trunk sway vector magnitude measures (0.2-1s FSO), but not for CoP sway data (table 6.5).

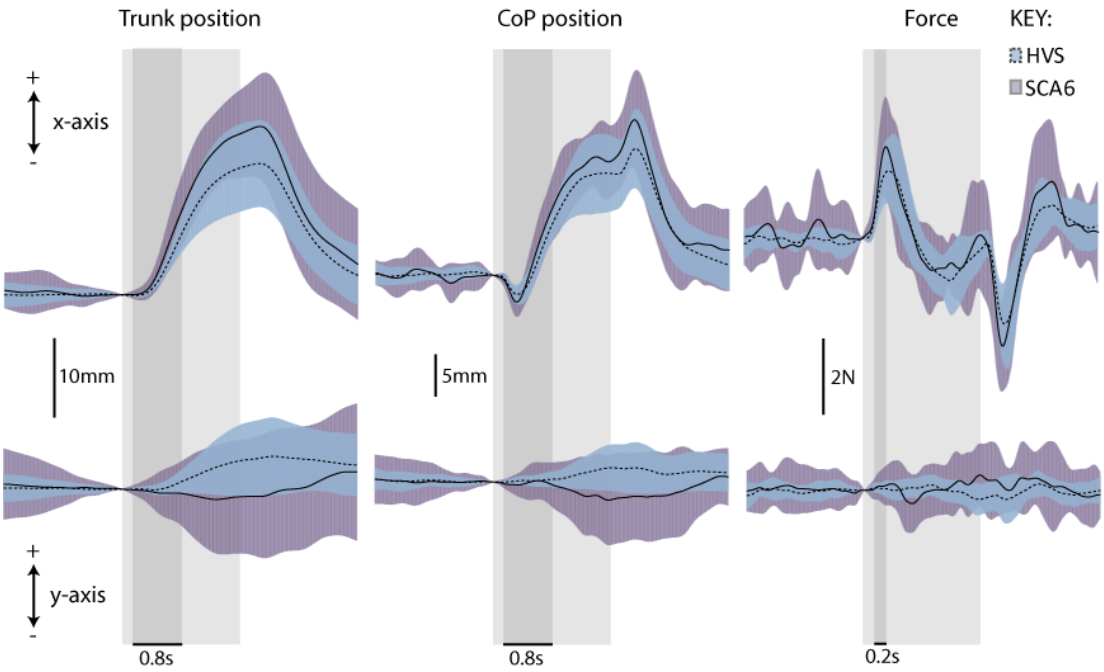


Figure 6.8: Group mean position and force over time data VIB conditions.
Plotted lines correspond to group mean displacement of the trunk, centre-of-pressure and changes in force over six seconds of trial durations in laboratory x and y-axis directions. Shaded areas illustrate one standard deviation of these measures in both directions around the mean to represent between-subject variability. Grey shaded boxes indicate stimuli delivery and darker grey boxes indicate the trial duration from which data is sampled to calculate mean response measures. Centrally located vertical labelled lines indicate the scale for each data type.

Table 6.3: Descriptive statistics and t-tests for group mean response magnitudes to vibration.

Measure	HVS mean (± 1S.D.)	SCA6 mean (± 1S.D.)	t-value (d.f.)	p-value
VIB_Trunk_1s (mm)	8.1 (2.5)	11.2 (4.4)	2.5 (23.9)[†]	0.020
VIB_Trunk_2s (mm)	17.3 (6.2)	21.9 (5.7)	2.2 (30)	0.038
VIB_CoP_1s (mm)	6.5 (2.2)	8.8 (3.7)	2.2 (24.3)[†]	0.042
VIB_CoP_2s (mm)	12.5 (4.6)	14.9 (4.0)	1.5 (30)	0.139
VIB_Force_0.4s (N)	1.3 (0.7)	1.8 (1.1)	1.4 (30)	0.169

[†] Equal variances not assumed according to Levene's test ($p<0.05$)

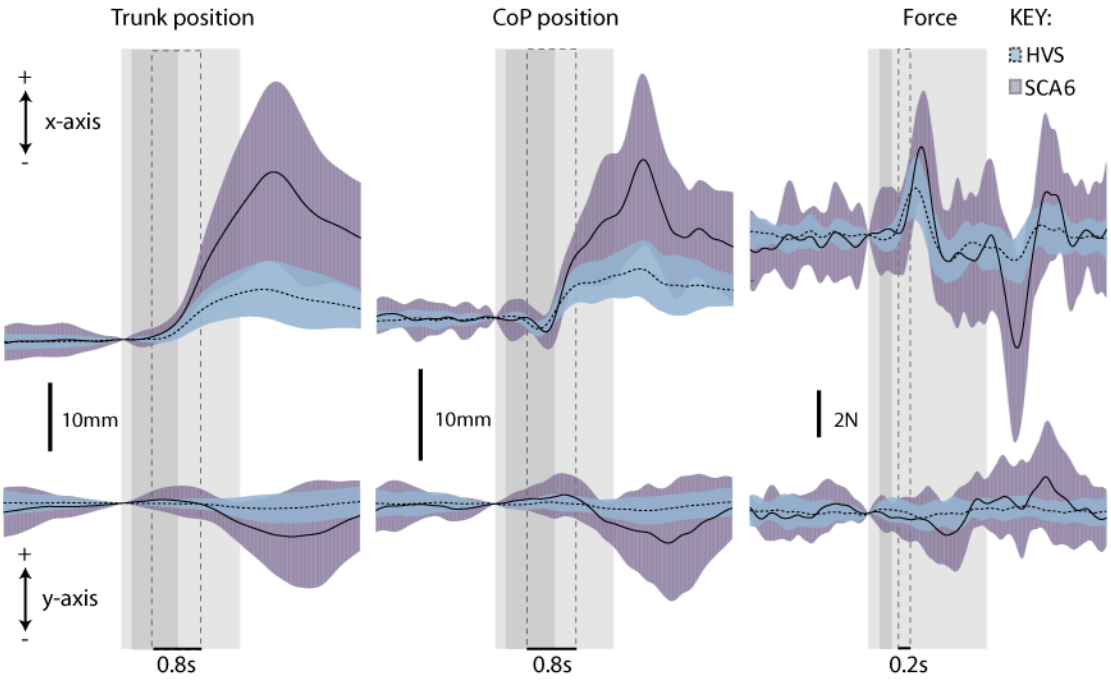


Figure 6.9: Group mean position and force over time data MVS conditions.
Plotted lines correspond to group mean displacement of the trunk, centre-of-pressure and changes in force over six seconds of trial durations in laboratory x and y-axis directions. Shaded areas illustrate one standard deviation of these measures in both directions around the mean to represent between-subject variability. Grey shaded boxes indicate stimuli delivery and darker grey boxes indicate the trial duration from which data is sampled to calculate mean response measures. Centrally located vertical labelled lines indicate the scale for each data type. Samples of data have been shifted forward by 35ms compared with other modalities in order to account for the discovery of a 35ms mechanical delay before onset of movement in MVS apparatus.

Table 6.4: Descriptive statistics and t-tests for group mean response magnitudes to MVS stimuli.

Measure	HVS mean (± 1S.D.)	SCA6 mean (± 1S.D.)	t-value (d.f.)	p-value
MVS_Trunk_1s (mm)	4.6 (2.3)	9.9 (4.4)	4.3 (22.4)[†]	<0.001
MVS_Trunk_2s (mm)	7.6 (3.8)	24.0 (12.4)	5.1 (17.8)[†]	<0.001
MVS_CoP_1s (mm)	4.3 (2.2)	7.1 (3.4)	2.8 (30)	0.010
MVS_CoP_2s (mm)	6.2 (3.0)	16.8 (8.9)	4.5 (18.3)[†]	<0.001
MVS_Force_0.4s (N)	0.7 (0.4)	1.5 (0.8)	3.6 (22.0)[†]	0.002

[†] Equal variances not assumed according to Levene's test (p<0.05)

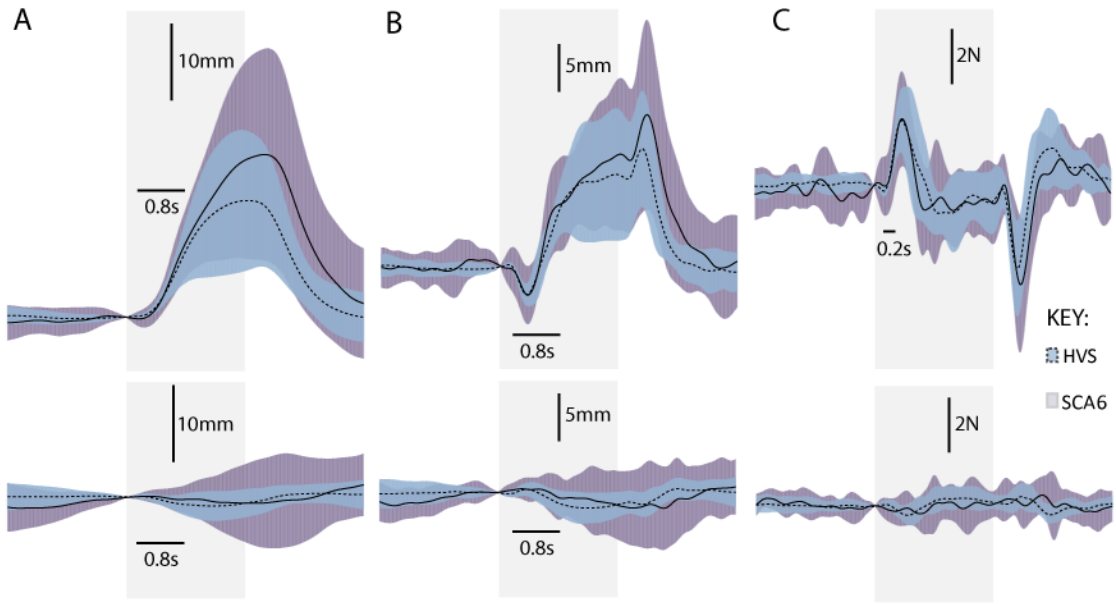


Figure 6.10: Group mean position and force over time data involving GVS perturbations. Plotted lines correspond to group mean displacement of the trunk (A) and centre-of-pressure (B) and force changes (C) over six seconds slices of trial durations. Upper row plots illustrate changes in position and force data in the laboratory x-axis. Lower plots illustrate changes in the laboratory y-axis. Shaded areas illustrate one standard deviation of these measures around the mean to represent between-subject variability. Grey shaded boxes indicate GVS delivery. Vertical labelled lines indicate the scale for Y-axis displacement or force. Horizontal labelled bars indicate the trial duration from which data was sampled to calculate mean magnitudes.

Table 6.5: Descriptive statistics and t-tests for group mean response magnitudes to vestibular stimuli.

Measure	HVS mean (± 1S.D.)	SCA6 mean (± 1S.D.)	t-value (d.f.)	p-value
GVS_Trunk_1s (mm)	8.6 (4.0)	10.6 (3.5)	1.5 (29)	0.142
GVS_Trunk_2s (mm)	15.2 (9.1)	22.9 (11.1)	2.1 (29)	0.043
GVS_CoP_1s (mm)	6.1 (2.7)	7.4 (4.6)	1.0 (29)	0.332
GVS_CoP_2s (mm)	9.7 (6.8)	13.6 (5.7)	1.8 (29)	0.091
GVS_Force_0.4s (N)	2.2 (1.0)	2.2 (1.1)	0.1 (29)	0.964

† Equal variances not assumed according to Levene's test ($p<0.05$)

6.6.4 DIRECTIONAL ORIENTATION OF RESPONSE

Group mean response directions to sensory stimuli are similar between groups and modalities (table 6.6, figure 6.11).

Table 6.6: Group mean angular error around the ideal response direction.

	Condition: Ideal angle:	VIB_Df -90	VIB_Pf +90	MVS_acw -90	MVS_cw +90	GVS_l+ -90	GVS_r+ +90
Trunk_1s (degs)	HC	-7.9 (12.6)	11.1 (12.7)	-17.8 (49.4)	16.4 (43.4)	-22.1 (13.9)	-3.2 (20.6)
	SCA6	-20.2 (24.1)	17.2 (30.2)	-6.2 (33.0)	-1.1 (15.4)	-11.3 (24.6)	5.1 (22.2)
Trunk_2s (degs)	HC	-6.0 (15.8)	16.9 (13.8)	-6.3 (57.1)	10.1 (32.3)	-21.3 (16.0)	9.9 (26.0)
	SCA6	6.6 (57.7)	-0.7 (14.9)	-14.5 (42.8)	-6.5 (25.7)	-25.4 (40.8)	2.5 (23.4)
CoP_1s (degs)	HC	4.5 (13.6)	14.8 (28.5)	2.6 (20.4)	3.5 (38.5)	-15.7 (14.2)	-13.6 (26.0)
	SCA6	-8.9 (27.1)	9.4 (15.6)	0.7 (45.0)	-2.4 (52.8)	-8.7 (40.1)	-7.1 (22.6)
CoP_2s (degs)	HC	-0.1 (17.1)	-5.6 (24.6)	-22.8 (44.3)	4.4 (30.5)	-21.3 (15.6)	8.8 (33.2)
	SCA6	8.1 (57.3)	14.4 (44.2)	-10.5 (38.7)	-14.5 (23.0)	-26.1 (50.2)	-5.3 (25.5)
Force (degs	HC	-11.9 (47.9)	14.4 (44.2)	-17.8 (46.6)	-13.3 (63.9)	-12.9 (9.9)	-10.0 (5.9)
	SCA6	-3.0(61.7)	26.6 (56.9)	-7.2 (53.3)	4.7 (49.1)	-5.7 (15.2)	32.8 (73.4)

6.6.4.1 Vibration

Main effects of *direction* were reported solely for early trunk sway (Trunk_1s) responses to *vibration* (table 6.7). No main effects of *group* were reported for any measure of response direction. A *direction x group* interaction was reported for early CoP sway (CoP_1s) responses to vibration (p=0.025, table 6.7). However, post-hoc t-tests report no statistically significant group differences for early CoP sway for either forward (VIB_Df: -1.8(22), p=0.093) or backward (VIB_Pf: 1.9(22.6), p=0.067) directed responses to *vibration*.

6.6.4.2 Moving visual scenery

Main effects of *direction* were solely reported for early trunk sway responses to *MVS* (Trunk_1s, table 6.8). No main effects of *group* were reported for any measure (table 6.8). No *direction x group* interactions were reported for any measure.

6.6.4.3 Galvanic vestibular stimulation

Main effects of *direction* were reported for early and late trunk sway measures (Trunk_1s, Trunk_2s), late CoP excursion (CoP_2s) and force measures of responses to *GVS* (table 6.9). No main effects of *direction* were reported for early CoP excursion. ANOVAs reported a main effect of *group* solely for force response directions to GVS (p=0.013, table 6.9). This is consistent with prior reports in chapter 5.

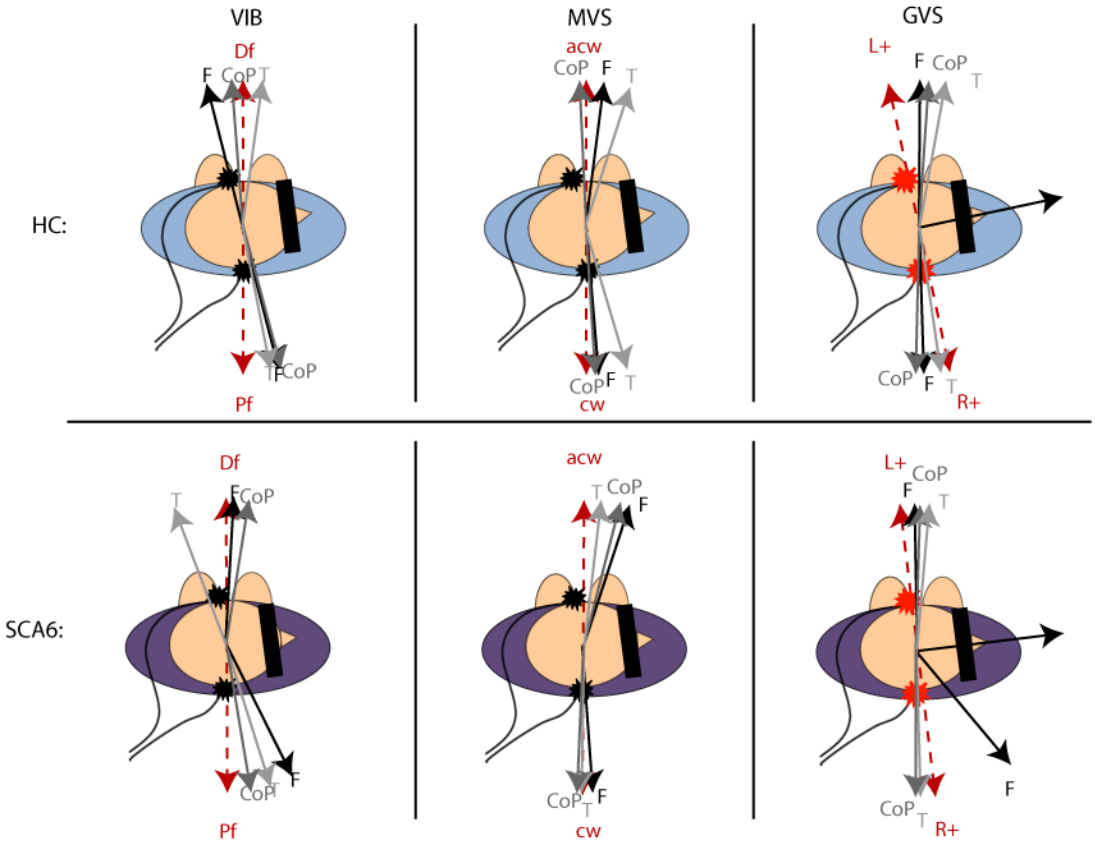


Figure 6.11: Group mean response directions per GVS condition (vision obscured).
Overhead views of group mean yaw angles of response for trunk (T), centre-of-pressure (CoP) and force (F) data. Response angles have been normalised to start head-on-feet direction (SHD) for GVS responses. Red dotted arrows show the ideal response direction per condition. Greyscale arrows represent response directions per condition per data type (light=trunk, medium=CoP, dark=force). Clockwise changes in response angles indicate negative errors and anticlockwise angle changes indicate positive errors.

Table 6.7: Statistical analysis of mean direction of responses to *vibrator stimuli (VIB)*.

ANOVA factors:	Direction	Group	Interaction (*Dir*Group*)
Trunk_1s (degs)	F(1,30)=23.5, p<0.001	F(1,30)=0.4, p=0.528	F(1,30)=2.5, p=0.123
Trunk_2s (degs)	F(1,30)=1.8, p=0.191	F(1,30)=0.1, p=0.833	F(1,30)=1.6, p=0.221
CoP_1s (degs)	F(1,30)=2.3, p=0.141	F(1,30)=0.1, p=0.827	F(1,30)=5.6, p=0.025
CoP_2s (degs)	F(1,30)=0.1, p=0.806	F(1,30)=0.2, p=0.668	F(1,30)=1.8, p=0.192
Force (degs)	F(1,30)=4.6, p=0.040	F(1,30)=0.6, p=0.443	F(1,30)=0.02, p=0.900

Table 6.8: Statistical analysis of mean direction of responses to *moving visual stimuli* (*MVS*).

ANOVA factors:	Direction	Group	Interaction (*Dir*Group*)
Trunk_1s (degs)	F(1,30)=5.6, p=0.024	F(1,30)=0.1, p=0.778	F(1,30)=3.1, p=0.088
Trunk_2s (degs)	F(1,30)=1.1, p=0.305	F(1,30)=2.0, p=0.165	F(1,30)=0.1, p=0.720
CoP_1s (degs)	F(1,30)=0.01, p=0.923	F(1,30)=0.2, p=0.650	F(1,30)=0.03, p=0.868
CoP_2s (degs)	F(1,30)=1.5, p=0.234	F(1,30)=0.2, p=0.685	F(1,30)=2.7, p=0.111
Force (degs)	F(1,30)=0.3, p=0.588	F(1,30)=1.5, p=0.237	F(1,30)=0.1, p=0.804

Table 6.9: Statistical analysis of mean direction of responses to *vestibular stimuli* (*GVS*).

ANOVA factors:	Direction	Group	Interaction (*Dir*Group*)
Trunk_1s (degs)	F(1,28)=9.3, p=0.005	F(1,28)=3.7, p=0.065	F(1,28)=0.1, p=0.775
Trunk_2s (degs)	F(1,28)=23.2, p<0.001	F(1,28)=0.6, p=0.431	F(1,28)=0.1, p=0.710
CoP_1s (degs)	F(1,28)=0.2, p=0.628	F(1,28)=0.8, p=0.368	F(1,28)=0.1, p=0.813
CoP_2s (degs)	F(1,28)=12.3, p=0.002	F(1,28)=1.2, p=0.294	F(1,28)=0.6, p=0.437
Force (degs)	F(1,28)=4.3, p=0.048	F(1,28)=7.0, p=0.013	F(1,28)=2.9, p=0.100

6.6.4.4 Determining effects of the motor response direction on scaling

Group mean magnitudes of response were generally larger for backward responses to *vibration* (VIB_Pf) than forward directed responses (VIB_Df) with the exception of force response magnitude measures (table 6.9, columns 1-2). Group mean magnitudes of response similar for backward (MVS_cw) and forward directed (MVS_acw) responses to *moving visual scenery* for response magnitude measures (table 6.8, columns 3-4). Group mean magnitudes of response similar for backward (GVS_r+) and forward directions (GVS_l+) of responses to *vestibular stimulation* (table 6.9, columns 5-6).

Table 6.10: Group mean response magnitudes according to direction.

Condition: Ideal angle:		VIB_Df -90	VIB_Pf +90	MVS_acw -90	MVS_cw +90	GVS_l+ -90	GVS_r+ +90
Trunk_1s (mm)	HC	7.0 (2.7)	9.7 (3.8)	4.6 (2.5)	5.2 (2.3)	9.0 (4.2)	8.7 (4.7)
	SCA6	11.5 (1.0)	13.6 (6.7)	11.0 (5.7)	9.7 (7.3)	9.9 (6.1)	12.6 (4.6)
Trunk_2s (mm)	HC	13.8 (6.8)	22.2 (9.7)	8.0 (4.0)	9.5 (4.8)	17.6 (9.8)	14.9 (10.5)
	SCA6	17.6 (8.6)	30.9 (12.7)	28.1 (13.3)	24.5 (17.6)	20.5 (12.6)	27.6 (13.9)
CoP_1s (mm)	HC	5.8 (2.3)	7.5 (2.9)	7.7 (3.9)	4.9 (2.4)	6.1 (3.0)	6.2 (3.5)
	SCA6	8.1 (6.9)	10.8 (5.6)	4.1 (2.5)	7.8 (5.1)	7.0 (3.0)	8.7 (5.1)
CoP_2s (mm)	HC	10.4 (4.8)	15.4 (7.2)	6.1 (2.8)	9.5 (4.8)	12.0 (7.9)	9.0 (7.5)
	SCA6	11.3 (5.0)	21.7 (8.5)	18.7 (9.1)	17.4 (10.9)	11.8 (6.2)	17.0 (7.3)
Force (N)	HC	1.9 (1.0)	1.0 (0.7)	0.6 (0.4)	0.8 (0.5)	2.3 (1.2)	2.1 (0.9)
	SCA6	3.1 (2.2)	1.5 (1.5)	1.8 (1.2)	1.4 (0.8)	3.0 (2.2)	1.9 (0.9)

6.6.4.5 Vibration

ANOVAs reported main effects of *direction* for force measures and late measures of sway (Trunk_2s and CoP_2s) following *vibration* (table 6.10). Widespread main effects of *group* were reported (table 6.10). No significant *direction x group* interactions were reported for response magnitudes to *vibration* (table 6.10). Group average measures show that late sway measures were associated with larger response magnitudes for backward directed responses (VIB_Pf conditions) but for force measures, the opposite trend is seen.

Notably, this method of analysis reports significant differences in measures, which previously failed to reach the level of significance when using t-tests to compare response magnitudes, taken from average responses to all vibration trials (collapsed across *VIB_Pf* and *VIB_Df* conditions).

6.6.4.6 Moving visual scenery

ANOVAs reported no main effects of *direction* for any measure following MVS stimuli (table 6.11). Widespread main effects of *group* were reported by ANOVAs (table 6.11). This is in agreement with prior reports of significant *group* effects based on response magnitudes collapsed across both directional conditions of *MVS stimulation* using t-tests ('response magnitude scaling' section). A single *direction x group* interaction was reported for force measures (table 6.11). Post-hoc t-tests report a highly significant difference between groups following backward MVS (MVS_cw: t(df)= 3.2(16.3), p=0.005) but no significant difference between group forces following forward directed MVS (MVS_acw: t(df)= 1.3(30), p=0.197). Mean SCA6 group measures were larger for both forward and backward MVS

conditions (table 6.9). Collectively these findings suggest that the interaction is due to significantly increased SCA6 force responses to backwards MVS but similar sized force responses between groups for forward directed MVS perturbations.

6.6.4.7 *Galvanic vestibular stimulation*

ANOVAs reported a main effect of *direction* for GVS force data (p=0.023), but no other response measures (table 6.12). Main effects of *group* were only reported for longer timed measures of trunk sway (Trunk_2s). Significant *direction x group* interactions were reported for longer timed measures of trunk sway, CoP excursion and forces (Trunk_2s: p=0.015; CoP_2s: 0.003; Force: 0.023). Post-hoc t-tests reported no significant differences between groups for forward (GVS_l+) directed perturbations (trunk_2s t(df): 0.7(28), p=0.515; CoP_2s t(df): -0.2(28), p=0.860), whereas backward directed mean response magnitudes were significantly different (trunk_2s t(df): 2.9(28), p=0.007; CoP_2s t(df): 3.1(28), p=0.005).

Table 6.11: Statistical analysis of mean magnitudes of response to *VIB* according to direction.

ANOVA factors:	Direction	Group	Interaction (*Dir*Group*)
Trunk_1s	F(1, 30)=1.9, p=0.179	F(1, 30)=7.8, p=0.009	F(1, 30)=0.04, p=0.838
Trunk_2s	*F(1, 30)=18.6, p<0.001*	*F(1, 30)=7.1, p=0.012*	*F(1, 30)=0.9, p=0.340*
CoP_1s	F(1, 30)=2.8, p=0.103	F(1, 30)=6.7, p=0.015	F(1, 30)=0.2, p=0.695
CoP_2s	*F(1, 30)=20.6, p<0.001*	*F(1, 30)=5.0, p=0.033*	*F(1, 30)=2.6, p=0.116*
Force	F(1, 30)=11.3, p=0.002	F(1, 30)=6.1, p=0.020	F(1, 30)=0.8, p=0.393

Table 6.12: Statistical analysis of mean magnitudes of response to *MVS* according to direction.

ANOVA factors:	Direction	Group	Interaction (*Dir*Group*)
Trunk_1s	F(1,30)=0.1, p=0.803	F(1,30)=18.6, p<0.001	F(1,30)=0.6, p=0.429
Trunk_2s	F(1,30)=0.2, p=0.657	F(1,30)=27.4, p<0.001	F(1,30)=1.3, p=0.266
CoP_1s	F(1,30)=3.5, p=0.560	F(1,30)=10.3, p=0.003	F(1,30)=0.2, p=0.653
CoP_2s	F(1,30)=0.02, p=0.899	F(1,30)=22.4, p<0.001	F(1,30)=1.4, p=0.240
Force	F(1,30)=0.3, p=0.571	F(1,30)=14.0, p=0.001	F(1,30)=5.3, p=0.028

Table 6.13: Statistical analysis of mean magnitudes of response to *GVS* according to direction.

ANOVA factors:	Direction	Group	Interaction (*Dir*Group*)
Trunk_1s	F(1, 28)=0.9, p=0.347	F(1, 28)=2.5, p=0.126	F(1, 28)=1.9, p=0.184
Trunk_2s	F(1, 28)=0.9, p=0.359	F(1, 28)=4.3, p=0.048	F(1, 28)=6.9, p=0.015
CoP_1s	F(1, 28)=1.2, p=0.277	F(1, 28)=1.3, p=0.270	F(1, 28)=1.3, p=0.267
CoP_2s	F(1, 28)=0.4, p=0.552	F(1, 28)=2.9, p=0.099	F(1, 28)=10.7, p=0.003
Force	F(1, 28)=5.8, p=0.023	F(1, 28)=0.2, p=0.675	F(1, 28)=2.6, p=0.118

6.6.5 Screening for habituation effects

In order to assess effects of habituation, responses to individual modality perturbations were analysed over *trial repeat* using ANOVAs (within-subject factor: *trial repeat* [trial 1, 2, 3, 4, 5], between-subject factor: *group* [HC, SCA6]). Tables 12-14 provide a summary of this statistical analysis.

Significant main effects of *trial repeat* were reported by ANOVAs for longer timed measures of trunk sway (Trunk_2s) for responses to both *vibration* and *GVS* (VIB: p=0.028, GVS: p=0.034; tables 12 and 14). No other statistically significant effects of *trial repeat* were reported for other measures of response to vibration, GVS or MVS (tables 12-14). Despite statistically significant effects of *trial repeat* reported, bar charts plotting group mean late trunk response response magnitudes by trial repeat do not illustrate decreasing magnitudes across successive trials (figure 6.12). This presentation of data is not consistent with habituation effects.

Main effects of *group* were reported for all response magnitude measures for both *vibration* and *MVS* stimuli (table 6.12-13, mid column). Main effects of *group* were only reported for late latency trunk sway magnitudes of response to *GVS* (table 6.14, mid column). No significant *group* x *trial repeat* interactions were reported (table 6.12-6.14).

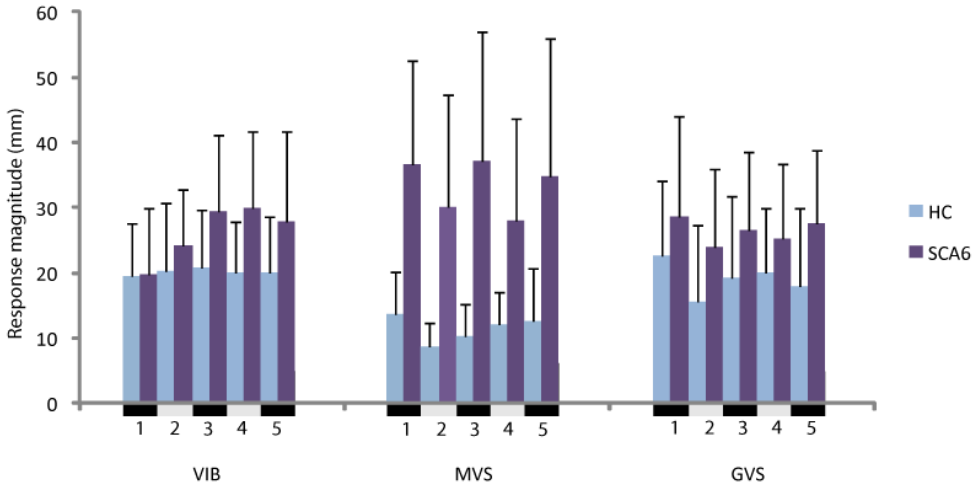


Figure 6.12: Assessing habituation effects using mean response magnitudes across trial repeats. Group mean magnitudes from the first five trials (1, 2, 3, 4, 5) are presented for each modality assessed (VIB=Vibration, MVS=Moving visual scene, GVS=Galvanic vestibular stimulation). Mean magnitudes are taken from trunk sway response vectors. Error bars illustrate one standard deviation around the mean, representing between-subject variability of measures.

6.14: Statistical analysis of mean magnitudes of response to *VIB* according to trial repeat.

ANOVA factors:	Trial repeat	Group	Interaction (*TR*Group*)
Trunk_1s	F(3.3, 98.3)=0.9, p=0.435	F(1,30)=11.5, p=0.002*	F(3.3, 98.3)=0.4, p=0.749
Trunk_2s	*F(3.8, 112.7)=2.9, p=0.028**	*F(1,30)=5.1, p=0.032**	*F(3.8, 112.7)=2.2, p=0.079*
CoP_1s	F(3.0, 91.3)=1.6, p=0.191	F(1,30)=10.3, p=0.003*	F(3.0, 91.3)=0.7, p=0.553
CoP_2s	*F(2.9, 87.3)=0.4, p=0.734*	*F(1,30)=5.9, p=0.021**	*F(2.9, 87.3)=0.3, p=0.851*
Force	F(1.6, 47.5)=2.4, p=0.110	F(1,30)=9.6, p=0.004*	F(1.6, 47.5)=1.6, p=0.211

Table 6.15: Statistical analysis of mean magnitudes of response to *MVS* according to trial repeat.

ANOVA factors:	Trial repeat	Group	Interaction (*TR*Group*)
Trunk_1s	F(3.3,97.5)=0.8, p=0.499	F(1,30)=25.1, p<0.001*	F(3.3,97.5)=1.5, p=0.216
Trunk_2s	*F(3.7,112.3)=2.0, p=0.099*	*F(1,30)=38.0, p<0.001**	*F(3.7,112.3)=1.3, p=0.271*
CoP_1s	F(3.9,117.1)=0.3, p=0.872	F(1,30)=14.7, p<0.001*	F(3.9,117.1)=0.9, p=0.471
CoP_2s	*F(3.7,109.8)=2.1, p=0.089*	*F(1,30)=29.6, p<0.001**	*F(3.7,109.8)=1.1, p=0.342*
Force	F(2.2,65.3)=0.5, p=0.631	F(1,30)=17.8, p<0.001*	F(2.2,65.3)=1.0, p=0.370

Table 6.16: Statistical analysis of mean magnitudes of response to *GVS* according to trial repeat.

ANOVA factors:	Trial repeat	Group	Interaction (*TR*Group*)
Trunk_1s	F(3.6, 102.0)=2.0, p=0.107	F(1,28)=4.7, p=0.038*	F(3.6, 102.0)=0.9, p=0.471
Trunk_2s	*F(3.8, 114.6)=2.7, p=0.034**	*F(1,28)=4.1, p=0.052*	*F(3.8, 114.6)=0.5, p=0.725*
CoP_1s	F(3.7, 112.1)=1.9, p=0.174	F(1,28)=3.8, p=0.062	F(3.7, 112.1)=1.8, p=0.141
CoP_2s	*F(3.9, 116.4)=0.5, p=0.757*	*F(1,28)=3.3, p=0.081*	*F(3.9, 116.4)=1.3, p=0.262*
Force	F(3.5, 106.2)=1.0, p=0.418	F(1, 28)=2.3, p=0.140	F(3.5, 106.2)=0.4, p=0.822

6.6.6 Comparability of responses between modalities

The magnitude of sway and force response measures is variable across modalities. ANOVAs (within-subject factor: modality [VIB, MVS, GVS], between-subject factor: group [HC, SCA6]) report main effects of *modality* on response magnitudes for early trunk, CoP and force measures (Trunk_1s, CoP_1s, Force) but not for later timed measures of trunk and CoP excursion (table 6.15). Main effects of *group* are reported for early and later timed measures of trunk and CoP excursion but not force (table 6.15). *Modality x group* interactions are reported solely for later timed measures of trunk and CoP excursion (table 6.5).

Repeated ANOVAs (within-subject factor: *modality* [VIB, MVS, GVS], between-subject factor: none) were employed to explore this effect of *modality* on group response magnitudes for these measures (Trunk_2s, CoP_2s). ANOVAs report significant effects of *modality* for healthy control but not SCA6 measures (Trunk_2s: [HC: F(2.0,27.5)=14.5, p<0.001], [SCA6: F(2.0,27.6)=0.04, p=0.956]; CoP_2s: [HC: F(2.0,27.2)=9.9, p=0.001],

[SCA6: F(1.7,24.1)=0.5, p=0.604]).This suggests that the interactions are likely to be due to significant differences in response magnitudes between *modalities* for the healthy control group but non-significant differences between SCA6 scores .

The directional error of sway and force response measures also seems to vary across modalities (table 6.16). ANOVAs (within-subject factor: modality [VIB, MVS, GVS], between-subject factor: group [HC, SCA6]) report main effects of *modality* on response directional error for early and late trunk and CoP measures but not force (table 6.16). No main effects of *group* are reported for any measure (table 6.16). No *modality x group* interactions are reported for any measure (table 6.16).

Where main effects of modality were reported in the absence of group differences, response directions were collapsed across groups and mean (plus standard deviation) directions per modality calculated ([Trunk_2s: VIB=3.2 (13.6), MVS=-1.5 (31.1), GVS=-8.8 (13.2)], [CoP_2s: VIB=-0.8 (16.7), MVS=-11.4 (16.0), GVS=-11.0 (17.4)]). Tests of within-subject contrasts for longer timed measures of sway (0.2-2s FSO trunk and CoP measures) compared response directions between all modalities. Significant differences between *vibration* and *MVS* modalities were reported (Trunk_2s: F(1,28)=11.5, p=0.002, CoP_2s: (1,28)=5.5, p=0.026). Significant differences between *vibration* and *GVS* were also reported (Trunk_2s: F(1,28)=9.1, p=0.005, CoP_2s: (1,28)=5.7, p=0.024). No significant differences were however reported between *MVS* and *GVS* (Trunk_2s: F(1,28)=1.5, p=0.228, CoP_2s: (1,28)=0.04, p=0.853). It therefore seems likely that vibration evoked the most different response direction, despite having a mean value which least deviated from the ideal (expected) angle.

Table 6.17: Statistical analysis of the effect of perturbation type on response magnitudes.

ANOVA factors:	Modality	Group	Interaction (*Mod*Group*)
Trunk_1s	F(2.0,55.1)=6.9, p=0.002	F(1,28)=10.5, p=0.003	F(2.0, 55.1)=1.9, p=0.167
Trunk_2s	F(2.0,55.5)=2.3, p=0.112	F(1,28)=19.6, p<0.001	F(2.0, 55.5)=3.4, p=0.042
CoP_1s	F(1.8,49.0)=3.7, p=0.037	F(1,28)=4.6, p=0.041	F(1.8, 49.0)=0.5, p=0.570
CoP_2s	F(2.0,55.2)=2.6, p=0.088	F(1,28)=13.5, p=0.001	F(2.0,55.2)=3.7, p=0.032
Force	F(1.8,50.9)=15.9, p<0.001	F(1,28)=3.1, p=0.091	F(1.8,50.9)=2.0, p=0.155

Table 6.18: Statistical analysis of the effect of perturbation type on response directional error.

ANOVA factors:	Modality	Group	Interaction (*Mod*Group*)
Trunk_1s	F(2, 56.0)=5.4, p=0.007	F(1, 28)=0.03, p=0.865	F(2,56.0)=0.6, p=0.545
Trunk_2s	F(1.9, 54.3)=8.3, p=0.001	F(1, 28)=0.6, p=0.432	F(1.9, 54.3)=1.8, p=0.184
CoP_1s	F(1.7, 47.9)=4.0, p=0.031	F(1, 28)=0.1, p=0.707	F(1.7, 47.9)=1.1, p=0.345
CoP_2s	F(2.0, 56.0)=4.9, p=0.011	F(1, 28)=2.0, p=0.170	F(2.0, 56.0)=1.1, p=0.357
Force	F(2.0, 56.0)=0.6, p=0.581	F(1, 28)=1.5, p=0.225	F(2.0, 56.0)=1.0, p=0.359

6.6.7 CORRELATIONS

Correlations were explored between baseline measures and all perturbation response measures where significant group differences have been detected in order to test hypotheses set out in the introduction of this chapter. Due to the multiple ways in which responses to perturbations have been measured (namely measures derived from forces and early and late latency vectors of trunk and CoP), the threshold for statistical significance has been adjusted from p=0.05 to p=0.01.

Baseline measures include disease severity scores (SARA and Bal-SARA sub-score) and 4cm stance width sway speeds (derived from trunk marker and CoP speeds validated for use in chapter 4). Biosthesiometer measures of vibration thresholds have also been included as baseline measures, given that vibration thresholds could affect response magnitudes. Response measures include response *timings* and *magnitudes* for each perturbation modality; *vibration*, *MVS* and *GVS*.

The same correlations have been explored between healthy control measures of baseline sway and response measures. The rationale for this is that some features of responses to single-sensory perturbations may normally correlate with baseline balance behavior (sway speed) but disease related SCA6 changes may disrupt this normal correlation.

6.6.7.1 Response timings

Healthy control peak force responses to GVS significantly correlated with baseline measures of trunk sway speed (r=661, p=0.007) but not with baseline measures of CoP speed (r=0.395, p=0.145). This correlation was not significant for any other comparison of healthy controls timings (table 6.17). No correlations between baseline SCA6 data and response timings were reported (table 6.17).

Table 6.19: Correlation coefficients for *baseline measures* and response *timings*.

		SARA	BalSARA	Trunk sway	CoP sway
VIB_F	HC	-	-	0.030 (0.912)	-0.029 (0.915)
	SCA6	0.011 (0.968)	0.087 (0.748)	0.095 (0.727)	0.184 (0.496)
MVS_F	*HC*	-	-	-0.234 (0.383)	-0.335 (0.205)
	SCA6	0.161 (0.552)	0.313 (0.238)	0.260 (0.332)	0.253 (0.344)
GVS_F	HC	-	-	0.661 (0.007)	0.395 (0.145)
	SCA6	-0.083 (0.768)	-0.034 (0.906)	-0.074 (0.794)	-0.009 (0.975)
VIB_T	HC	-	-	-0.174 (0.520)	-0.407 (0.118)
	SCA6	-0.219 (0.415)	0.047 (0.863)	0.249 (0.352)	0.291 (0.274)
MVS_T	HC	-	-	-0.190 (0.480)	-0.412 (0.113)
	SCA6	0.164 (0.545)	0.288 (0.280)	0.146 (0.590)	0.173 (0.522)
GVS_T	HC	-	-	-0.333 (0.225)	-0.308 (0.264)
	SCA6	-0.244 (0.380)	0.066 (0.814)	0.216 (0.440)	0.263 (0.344)

6.6.7.2 *Response magnitudes*

Vibration

Significant correlations are reported between healthy control measures of baseline sway speeds (trunk and CoP measures) and late timed measures (0.2-2s FSO) of (a) trunk sway magnitude (Baseline trunk: r=0.546, p=0.029; Baseline CoP: r=0.541, p=0.031) and (b) CoP magnitude ([Baseline trunk: r=0.572, p=0.020, Baseline CoP: r=0.539, p=0.031]). These correlations were not significant in similar comparisons of SCA6 measures (table 6.18).

Moving visual scenery

A clear trend between SCA6 disease severity scores (total SARA score) and magnitude measures of (a) force (r=0.503, p=0.047), (b) early timed measures of trunk sway (Trunk_1s: r=0.536, p=0.018), (c) early CoP (CoP_1s: r=0.497 p=0.050) and (d) late trunk sway (Trunk_2s: r=0.536, p=0.032) responses appears to exist for MVS (table 6.19). This indicates that as disease severity increases, so too did the size of the sway response to moving visual scenery. This finding cannot be deemed significant given the heightened p-value threshold adopted in an attempt to correct for multiple comparisons. However, given that the trend is seen in the majority of measures, it seems worthy of comment. Early trunk sway magnitudes are plotted against SARA score in figure 6.13, alongside response magnitudes to vibration and GVS.

No other significant correlations were reported for SCA6 or healthy control between baseline measures and response magnitude data (table 6.19).

Galvanic vestibular stimulation

Significant correlations are reported between healthy control baseline trunk sway speeds and GVS magnitude measures of (a) early timed measures of trunk sway (Trunk_1s:

r=0.696, p=0.003), (b) early CoP (CoP_1s: r=0.664, p=0.005) and (d) late trunk sway (Trunk_2s: r=0.512, p=0.043) responses (table 6.X3). Significant correlations are also reported between healthy control baseline CoP speeds and GVS magnitude measures of (a) early timed measures of (a) force (r=0.542, p=0.030), (b) trunk sway (Trunk_1s: r=0.636, p=0.008) and (c) early CoP (CoP_1s: r=0.564, p=0.023) responses (table 6.X3). No other significant correlations were reported for healthy control or SCA6 between baseline measures and response magnitude data (table 6.20).

Table 6.20: Correlation coefficients for *baseline measures* and response *magnitudes* to VIB.

		SARA	BalSARA	Trunk sway	CoP sway
Trunk_1s	HC	-	-	0.289 (0.277)	0.417 (0.108)
	SCA6	0.378 (0.149)	0.331 (0.210)	0.258 (0.335)	0.307 (0.248)
Trunk_2s	HC	-	-	0.546 (0.029)	0.541 (0.031)
	SCA6	0.180 (0.505)	0.180 (0.504)	0.321 (0.225)	0.328 (0.216)
CoP_1s	HC	-	-	0.047 (0.862)	0.216 (0.421)
	SCA6	0.261 (0.329)	0.264 (0.323)	0.223 (0.406)	0.284 (0.286)
CoP_2s	HC	-	-	0.572 (0.020)	0.539 (0.031)
	SCA6	0.015 (0.957)	-0.101 (0.709)	0.143 (0.596)	0.100 (0.713)
Force	HC	-	-	0.152 (0.575)	0.283 (0.289)
	SCA6	0.353 (0.180)	0.378 (0.149)	0.495 (0.051)	0.518 (0.040)

Table 6.21: Correlation coefficients for *baseline measures* and response *magnitudes* to MVS.

Data type		SARA	BalSARA	Trunk sway	CoP sway
Trunk_1s	HC	-	-	0.241 (0.369)	0.091 (0.739)
	SCA6	0.536 (0.018)	0.401 (0.124)	0.267 (0.317)	0.206 (0.445)
Trunk_2s	HC	-	-	0.372 (0.157)	0.098 (0.717)
	SCA6	0.536 (0.032)	0.348 (0.186)	0.174 (0.520)	0.083 (0.760)
CoP_1s	HC	-	-	0.127 (0.638)	0.041 (0.881)
	SCA6	0.497 (0.050)	0.416 (0.109)	0.465 (0.069)	0.435 (0.092)
CoP_2s	HC	-	-	0.370 (0.158)	0.129 (0.635)
	SCA6	0.433 (0.094)	0.263 (0.326)	0.132 (0.627)	0.031 (0.910)
Force	HC	-	-	0.442 (0.086)	0.364 (0.166)
	SCA6	0.396 (0.129)	0.503 (0.047)	0.437 (0.091)	0.410 (0.115)

Table 6.22: Correlation coefficients for *baseline measures* and response *magnitudes* to GVS.

Data type		SARA	BalSARA	Trunk sway	CoP sway
Trunk_1s	HC	-	-	0.696 (0.003)	0.636 (0.008)
	SCA6	0.021 (0.940)	-0.048 (0.865)	0.000 (0.999)	-0.101 (0.719)
Trunk_2s	HC	-	-	0.512 (0.043)	0.434 (0.093)
	SCA6	-0.314 (0.254)	-0.368 (0.176)	-0.410 (0.129)	-0.468 (0.079)
CoP_1s	HC	-	-	0.664 (0.005)	0.564 (0.023)
	SCA6	0.146 (0.603)	0.208 (0.457)	0.312 (0.258)	0.269 (0.332)
CoP_2s	HC	-	-	0.433 (0.094)	0.349 (0.186)
	SCA6	-0.434 (0.106)	-0.509 (0.053)	-0.430 (0.110)	-0.512 (0.051)
Force	HC	-	-	0.331 (0.211)	0.542 (0.030)
	SCA6	0.166 (0.555)	0.046 (0.871)	0.171 (0.542)	-0.001 (0.996)

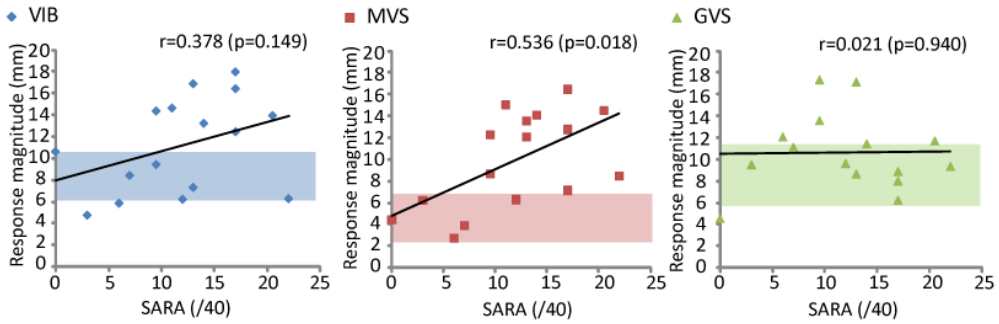


Figure 6.13: Mean response magnitudes to vibrator, MVS and GVS perturbations relative to disease severity. SCA6 group subjects' mean response magnitudes to vibrator (VIB), moving visual scenery (MVS) and galvanic vestibular stimulation (GVS) perturbations relative to disease severity (SARA) scores. Horizontal coloured bands illustrate ranges of one standard deviation either side of mean healthy control group response magnitudes. Lines of best fit illustrate the directional trend in the relationship between SCA6 measures. Pearson's correlation coefficients (r) and p-values indicate the strength and significance of correlations.

6.6.7.3 *Vibration thresholds*

Threshold measures of vibration perception did not correlate significantly with measures of force response to vibratory stimuli for either group (table 6.21). Furthermore, threshold measures of vibration did not correlate significantly with measures of peak trunk response (i.e. the time at which the response had begun to terminate) to any stimuli for either group (table 6.21).

Significant correlations are reported between healthy control vibration perception thresholds and vibration response magnitudes of (a) early timed measures of trunk sway (Trunk_1s: r=0., p=0.), (b) late trunk sway (Trunk_2s: r=0., p=0.) and (c) late CoP responses (CoP_2s: r=0., p=0.). No other significant correlations were reported for healthy control or SCA6 vibration thresholds and response data (magnitude or directional error) to vibration perturbations (table 6.22).

Table 6.23: Correlation coefficients for *vibration thresholds* and response *timings*.

		VIB_Force	VIB_Trunk	MVS_Trunk	GVS_Trunk
Group	HC	0.283 (0.288)	-0.062 (0.819)	0.126 (0.643)	-0.420 (0.119)
	SCA6	0.012 (0.963)	-0.038 (0.888)	-0.104 (0.700)	-0.178 (0.526)

Table 6.24: Correlation coefficients for *vibration thresholds* and response *magnitudes*.

Group	Trunk_1s	Trunk_2s	CoP_1s	CoP_2s	Force
HC	0.561 (0.024)	0.817 (<0.001)	0.186 (0.490)	0.778 (<0.001)	0.388 (0.138)
SCA6	-0.126 (0.642)	-0.020 (0.940)	-0.180 (0.506)	0.165 (0.540)	-0.070 (0.797)

6.7 Discussion

This study aimed to find out if disrupted proprioceptive or visual processing could contribute to SCA6 balance impairment, centring around three hypotheses:

1. **Impaired processing of proprioceptive afferent signals disrupt central scaling of the afferent signal.**
2. **Impaired processing of visual self-motion information disrupts central scaling of the afferent signal.**
3. **The absence of extra-cerebellar disease pathology will not cause timing errors in motor responses to proprioceptive or moving visual scenery perturbations.**

Vestibular perturbations were once again included in order to compare responses to all sensory perturbations between two samples of SCA6 and healthy control subjects.

The main finding for this study is that balance responses to proprioceptive, visual and vestibular perturbations remain intact. All subjects had clearly identifiable responses to proprioceptive, visual and vestibular stimuli, which are in some cases increased in magnitude but certainly not reduced compared with healthy control responses.

In contrast to recent suggestions that proprioceptive processing for balance control is disrupted by SCA pathology [179], the evidence presented here suggests that proprioceptive processing is largely normal. Normal features of the response to vibration include the timing of the force response, force magnitudes of response and late CoP displacements. Early measures of CoP displacement, trunk sway and later trunk sway measures were, however, increased in magnitude. Despite significant increases in these response magnitudes, no correlations with baseline measures of sway speeds or disease severity were reported.

Responses to visual perturbations were intact and sway responses were normally directionally orientated. Responses were however increased in magnitude across all measures and a trend exists for these measures to correlate with disease severity scores. The strongest correlation occurred between early trunk sway magnitudes and SARA scores. Force responses were also significantly delayed and directionally disorientated; possibly a sampling error associated with the delay in timing. The mean SCA6 peak force response was 80ms later than healthy control equivalents. Group differences in response

magnitudes and timings present the clearest group differences of this study and, although they cannot explain balance impairment in SCA6 subjects standing with their eyes closed, they could significantly contribute to balance impairment. Further discussion of these findings will ensue in the following sub-sections.

Responses to vestibular perturbations were largely normal in terms of timing, response magnitudes and directional orientation. GVS responses in chapter 5 were interpreted as largely normal and these findings further support that interpretation. However, differences between groups were present for late trunk sway response magnitude measures, where the mean SCA6 response was increased in magnitude relative to that of the healthy controls. Despite significant group differences, no correlations between these increased magnitudes and baseline sway or disease severity measures were found.

Neither group appeared to habituate to the stimuli or be differentially affected by the directional nature of the perturbations. It is therefore unlikely that habituation effects or directional mechanics of the response biased these findings. However, given that modality type did appear to affect response magnitudes and directions, we cannot assume that the mechanics and coordination of the response is comparable between stimuli types. For this reason, interpretation of the results will focus on group differences. The coordination of responses to each modality type may be pertinent to understanding balance impairment in SCA6 but remains beyond the scope of this particular study and has not been further analysed for this reason.

As per the findings in chapter 5, discrepancies in findings between different measures are again of note. Variations in force measures relative to CoP and trunk sway was discussed in chapter 6 and causative hypotheses remain valid for the results of this chapter. Since all measures were recorded simultaneously, without time lags incurred, the data collection process remains free from bias but ultimately the equipment used to measure ground reaction force activity versus trunk sway does incur slight differences in filter design and in terms of inherent resolution of signals (chapter 3). However, these differences are likely to cause a negligible effect on the overall form of each signal. Bias due to the fundamental nature of each measure could however explain the descrepancies between findings. Motion of the trunk, for example, does not behave in an identical manner to that of centre-of-pressure changes over time [176]. Centre-of-presssure measures are more representative of ankle torque fluctuations, which tend to be of a ballistic nature

encompassing a range of frequencies. Trunk sway is rather the consequence of ankle torque activity damped by the axial joints in the chain between the ankle and upper trunk and further biased by the resultant motion occurring at these multiple joints.

6.7.1 Increased sway response magnitudes

The most increased SCA6 sway responses relative to that of healthy controls were observed following moving visual scenery. All measures of force, centre-of-pressure and trunk displacement were significantly increased across all measurement epochs. Furthermore, there was a clear trend for response magnitude measures from early CoP and all trunk sway measures to correlate with SARA scores. This suggests that an association exists between disease severity and use of vision for balance.

The observed increase in response magnitudes to MVS could be explained by direct or indirect disrupted sensory processing or perhaps as the consequence of altered eye movement impairments.

6.7.1.1 ***Could disrupted sensory processing alter response magnitudes?***

It is possible that the damaged cerebellum has a direct role in scaling the gain of a response to the visual afferent signal, which is impaired in those with SCA6 as a consequence of disease related neuronal damage. If the damaged area was directly concerned with visual processing, it would seem more likely that the signal would be reduced or absent. This would naturally result in responses that were also reduced rather than increased in magnitude. However, if the output from the damaged area was responsible for inhibiting an already formed 'visual self-motion signal' in some way, then the net result would be an increase in response magnitude relative to healthy controls. The plausibility of this idea in turn depends on the nature of the inhibiting factor. Numerous imaging and animal lesioning studies have shown that vestibular afferents and visual signals converge in the flocculus, fastigial and vestibular nuclei [17,164,165,404]. Perhaps incongruent vestibular information, normally able to down-weight visual signals, could be responsible for the lack of inhibition and the resulting larger than necessary response. Alternatively, perhaps impaired down-weighting of the response may be due to impaired convergence of proprioceptive on visual signals, or even convergence of a combined signal (from already integrated vestibular and proprioceptive signals).

A slightly different explanation for increased response magnitudes to MVS could point to

the use of visual cues as a compensatory mechanism for a deficit elsewhere. This idea stems from the study of how sensory system signals compensate for the loss of what seems to be the principal contributor to balance control; the proprioceptive system [71,83]. In normal circumstances, the proprioceptive, vestibular and visual systems all contribute information (or votes) for control of balance, where the proprioceptive system generally appears to contribute the most, followed by the vestibular and visual systems [84]. When the contributions of one system become limited, the remaining systems may have a larger share of the total vote [84]. As sensory systems achieve more of the vote, overall whole body stability is improved but responses to isolated sensory systems that are intact become relatively larger. In support of this idea, increased magnitudes of responses to GVS sitting balance perturbations are seen to occur when proprioceptive system is impaired [83]. These are further increased when the subject closes their eyes, making vision redundant and providing only re-afferent vestibular information concerning whole body motion during the response. The plausibility of this idea to explain the over-responses to MVS here depends on either the vestibular or proprioceptive systems being in some way impaired in SCA6. Given that the there is no end organ dysfunction in SCA6, this means that these systems would need to be impaired at a processing level. On face value, processing of both vestibular and proprioceptive information appears to be normal, given that all subjects have identifiable forms of response for both stimuli and response magnitudes were neither smaller than healthy controls nor directionally unorganised. If anything, responses to these sensory systems behave in the same way as those to moving visual stimuli in that they all tend to evoke larger than normal responses. For example, early trunk sway and CoP excursion responses were on average larger in the SCA6 group following muscle vibration and late trunk sway responses were on average larger following GVS (GVS responses were larger still relative to healthy controls when vision was additionally obscured in chapter 5). In this way, although response magnitudes to MVS appear the most dramatic of the three types, all could be interpreted as behaving in a compensatory manner for a still unknown deficit. If we continue to work on the assumption that the observed over-responses to stimuli are compensatory, this presents two new hypotheses for causes of SCA6 balance impairment:

1. Sensory mechanisms of balance are intact but responses to sensory stimuli, themselves dependent on coordination of joint torques throughout the body, are

disrupted by a widespread distribution of incoordinated movement.

2. Despite normal processing of proprioceptive afferent signals from musculature and connective tissue, disrupted cutaneous control of balance from foot sole receptors are responsible for balance impairment.

These remaining un-investigated areas will be revisited when discussing future research ideas in the final chapter of this thesis.

6.7.1.2 Could oculomotor impairments alter response magnitudes?

Increased response magnitudes to MVS could be due to abnormal eye movements such as slowed pursuit or saccade speeds, established to be a clinical feature of the sample in chapter 3. The implication is that if pursuit or saccades are too slow, maintenance of foveation of the moving image would be unsuccessful. This would result in a failed attempt to gain an estimate of self-motion speed for accurate scaling of response gains. In this scenario it is possible that this could trigger a hypermetric, almost default, response in an attempt to arrest the perceived balance perturbation. Indeed, abnormal features associated with SCA6 such as slowed pursuit, slowed saccades and end-range horizontal nystagmus could lead to a hypermetric initial response, as is sometimes reported of SCA6 saccades when pursuing an object [(359)]. Dysmetria of foot placement during locomotion has also recently been associated with dysmetric eye movements guiding motion [(76,232)]. These ideas may be consistent with the findings of Jahn *et al*., which showed that a head referenced visual cue can be more stabilising to those with acquired forms of oculomotor disorders than an earth referenced cue. The inference being that visual cues coupled with impaired eye movements can in some way de-stabilise individuals [(173)]. However, similar experiments conducted with subjects who have congenital versions of nystagmus do not seem to destabilise with earth-fixed visual cues or respond differently to movement of visual scenery [(136)]. Despite erratic eye movements, these subjects do not report any blurring of the image relative to this movement. Researchers have hypothesised that balance is unaffected by errant eye movements in these subjects with congenital oculomotor disorders because the efference copy of eye movements is used to anticipate and cancel the effect of the retinal flow information [(92,139)]. In the case of our subjects, oculo-motor abnormalities are acquired rather than congenital but blurring or movement of the visual image with eye movements is not a common symptom. The visual-ocular reflex

has also been reported as normal in terms of magnitude and direction [58,359]. These points imply that vision should be effectively used to stabilise balance, as was the case overall for responses to GVS in chapter 5. However, oculomotor impairments remain prominent features of SCA6 [129], nystagmus is thought to be one of the earliest symptoms of the disease, if not the first symptom [68] and pursuit is significantly slowed [359]. Anecdotally subjects with SCA6 often report periods of their life where their vision was blurred and made them feel nauseous but this often does not persist beyond the diagnosis of their condition. Double vision or visual disturbances as well as episodic symptoms (such as paroxysmal vertigo, dizziness and migraine; often evoked with head movements) reportedly occur at some point in time in approximately half of the SCA6 population [1,337]. Perhaps oculo-motor abnormalities were at one point perceptual but become compensated for over time, almost unnoticed alongside the slow onset and progression of the condition. Furthermore, if slowed pursuit were to result in a default, hypermetric response, perhaps there is a threshold speed for the effect to become notable. The positive linear relationship reported between disease severity and most measures of response magnitudes to moving visual stimuli would further suggest that slowing of pursuit would need to relate to the hypermetria of the response.

6.7.2 Timing delays

Initial force responses to MVS show that there is a notable delay of 120ms in onset timings. This delay could be a consequence of slowed efferent signals as part of the motor response, but this is unlikely given the lack of spinal and peripheral nerve damage in SCA6 and the lack of notable delays in responses to the other stimuli. More plausible explanations once again implicate disruption at a processing level disruption of oculo-motor control of balance.

Reports of cerebellar disease affecting timing of motor activity have been extensively reported but tend to focus on reaction times to upper limb activity rather than balance behaviour [26,35,42,81,143,170,245,260]. Although not specifically or exclusively testing subjects with SCA6, reaction times concerned with movement of the upper limb when pointing at a visual target are reported to incur timing delays between 100ms [81] and 200ms [42,260] in subjects with cerebellar disease. With visual feedback deceleration of the pointing movement was impaired in those with cerebellar disease. Fast directional changes were

observed towards the latter part of the movement which did serve to reduce, but not completely resolve, endpoint pointing-to-target errors compared with non-vision conditions [35,81]. Miall *et al*. propose that the reason for these endpoint errors and general loss of smoothness when moving to a visual target with visual feedback of the movement is that the visual feedback pathways incur a delay of between 100 and 200ms [245]. Investigations of healthy controls with delayed visual feedback of finger movement reveal strikingly similar abnormalities in upper limb movement to that of the cerebellar patients [245]. This theory and prior research provides support for the idea that SCA6 subjects incur delays when responding to MVS which could contribute towards overall balance impairment.

The question remains of how SCA6 cerebellar damage could cause timing delays in visual information. As suggested by Day *et al*. and Miall *et al*., this could be directly due to central delays in sensory processing [81,245]. Alternatively, if proprioceptive afferents from extra-ocular muscles significantly contribute to visual control of balance, delayed responses could be secondary to delays in eye movement initiation or slowed pursuit.

6.7.2.1 ***Could processing impairments cause timing delays?***

According to the ideas set out in the introduction, it is possible that damage to the cerebellum or the deep cerebellar nuclei caused by SCA6 disease pathology could disrupt the contribution of vision for balance control. The idea that two pathways are involved in visual processing is well established [73,130,250,376]. The primary pathway involves processing of visual information in the cortex before decending signals are passed to the cerebellum, brainstem and spinal efferents [250]. In view of cortical processing, if this signal is used to drive a balance response, the motor response is likely to be of a long latency due to the many cortical synapses. The second or ‘accessory’ pathway projects via the superior colliculus and the thalamus to the cerebellar nuclei and posterior cerebellum before making afferent connections to the visual areas of the cerebral cortex [376,377]. It could be thought of as the sub-cortical visual system. There is some evidence to suggest that the accessory pathway could have a prominent role in combining retinal flow with vestibular and proprioceptive signals to generate head referenced coordinates for retinal flow: Information which is of primary concern in balance control [376]. If this pathway is at some point damaged by SCA6 disease pathology, then processing of retinal flow information concerned with the discrimination of self-motion for balance control could be disrupted.

The vestibular or fastigial nuclei and the flocculus are all possible known areas of SCA6 damage which could affect this function [17,122,164,165,404]. The flocculus seems a particularly likely target, since it is known to be reduced in size by SCA6 pathology and is known to be an area associated with gain control of fast ocular movements governed by head motion (the vestibulo-ocular reflex) [164,165,187,302,381,403]. Perhaps this accessory pathway is impaired in SCA6 but the cortical loop of the primary pathway remains; still useful in organising a motor response but incurring a 'delay' due to cortical processing time.

6.7.2.2 Could oculomotor impairments cause timing delays?

Some reports of normal reactive saccades to visual stimuli suggest latencies of 200ms [260]. This can further be reduced to just 80ms if the movement of the visual stimuli can be predicted [260]. Like-wise when visual stimuli are being tracked (using visual pursuit), latencies of just 80ms can be achieved, perhaps another example of predictive motion of visual cues can optimise oculo-motor activity [260]. Nagal *et al*. 2008 reports that subjects with cerebellar disease have delayed oculo-motor responses to visual stimuli but are able to decrease latencies with predictive knowledge of visual stimuli motion [260]. They are however unable to decrease latencies as effectively with increasing visual motion speeds or amplitudes [260]. This could be due to the inability of eye movements to match speeds of the visual stimuli secondary to cerebellar disease pathology limiting pursuit speeds.

In Nagel *et al*.'s 2008 investigations, eye movement latencies and speed are outcomes of responses to visual stimuli but in this study, eye movements generated by MVS could be the signal responsible for driving the whole body response. A review by Guerraz and Bronstein presents evidence together from their own work and that of others to make a strong argument for such extra-ocular control of posture and equilibrium [139]. Thus if afferent balance perturbing signals are delayed, so too will be the response.

6.7.3 Inferences for current management of SCA6

Regardless of the cause of delayed and over-scaled responses to visual self-motion cues, these findings could, as Miall *et al*. predict, be a disabling feature of cerebellar disease [245]. One approach to treating this 'over-use' of visual motion cues for balance is to use optokinetic stimuli and balance exercises. Pavlou *et al*. describe such an approach when treating patients diagnosed with visual vertigo, who appear over-sensitive to various forms of optokinetic stimuli [279]. The findings of Pavlou *et al*.'s study demonstrate improvements

in balance but it may be worth noting that the primary improvements were seen in dizziness and visual vertigo symptoms, which are also the principal presenting problems in their patient group. However, this approach has some potential as treatment for balance impairments in SCA6 if the degree of impairment is in any way related to use of visual stimuli. The lack of correlation between postural instability in standing (sway speeds) and response magnitudes to MVS may suggest that such desensitisation training would have little effect on unperturbed postural sway but it remains feasible that benefit from such training would be gained in environments where moving visual cues are prevalent.

Despite over-responses to MVS, visual flow created from relatively slow self-motion from natural postural sway does seem to successfully evoke oculo-motor compensatory movements [260,359] and have a stabilising effect on balance [356,374]. If therapy was to focus on training avoidance of visual motion cues such like that achieved in patients with visual vertigo [281,279], the stabilising effect of low velocity visual cues must be carefully preserved in those with SCA6.

Furthermore, training with the use of optokinetic stimuli may help to avoid responding inappropriately to incongruous visual cues, perhaps even preventing erroneous responses to stimuli that represent object-motion. However, this training approach is unlikely to correct the timing delay observed in the response to MVS.

Indeed, if over-responses to MVS are a form of compensatory strategy for a deficit elsewhere, delayed response timings are going to impair the effectiveness of such a strategy. Before the exact nature of such a deficit is ascertained, perhaps attempting to selectively sensitise systems which we know to be largely intact would be a better option, i.e. the vestibular and (musculo-fascial) proprioceptive systems. Here the aim of such an approach would be to increase the role of proprioceptive and vestibular sensory control to take over the compensatory role of the visual system. On face value, training with the eyes closed would be one way of achieving this, but the availability of vision once the eyes reopen could instantly ‘re-weight’ the sensory contributions to balance and negate the training effects.

Perhaps a better approach would be to design a novel therapy which aims to selectively train sensitivity of balance responses to vestibular and proprioceptive stimuli whilst simultaneously training avoidance of fast incongruous moving visual stimuli.

6.7.4 Future work

An understanding of how ocular movements behave in response to moving visual scenery would also help to clarify how oculo-motor impairments may affect the use of retinal flow and reafferents from eye musculature. Use of an eye-tracker during perturbations may serve to allow optimal comparisons between eye movement and balance behaviour in an attempt to find out if the two are governed by similar processes or are in some way dissociable.

Given the evidence for impaired motor learning in cerebellar disease, it is conceivable that subjects with SCA6 may not habituate to vibration or MVS to the same rate as healthy controls. Indeed when first analysing response magnitudes to MVS one plausible explanation could have been that healthy controls habituated across trial repeat but SCA6 subjects did not, rather than the magnitude of their responses being increased. However, habituation was not evident in either group for any perturbation modality and no comment can be made on the basis of these results regarding habituation or learning effects. Future studies investigating learning effects to moving visual scenery which involve only one type of stimuli with known perturbation speeds and directions may better suit this purpose. Investigation of SCA6 subject's ability to identify object versus self-motion visual cues would also be of use for future therapy planning. For this purpose, protocols where subjects are able to detect non-self-motion cues in background scenery or parallax cues could be employed.

6.8 Conclusion

Balance responses to isolated proprioceptive, visual and vestibular sensory stimuli are intact. Proprioceptive and vestibular processing for balance control in particular, appear largely unimpaired by SCA6 disease pathology.

Responses to moving visual scenery were significantly increased in magnitude and on average incurred a delay of 80ms. Increased magnitudes correlated with disease severity but timing delays did not. The mechanisms responsible for increased response magnitudes and the delays incurred following visual stimuli remain undetermined but could be due to central processing errors or secondary to eye movement abnormalities.

7 CHAPTER 7: GENERAL DISCUSSION

7.1 THE PROBLEM REVISITED

This thesis set out to explore balance impairment in subjects with SCA6. Balance impairment is a common feature of cerebellar disease and often the presenting problem in those with SCA6. Improved knowledge of balance impairment and the impact of this on function and falling are needed in order to facilitate improved management of the condition. An improved understanding of mechanisms responsible for balance impairment is needed to advise on the development of future therapies targeting balance impairment.

7.2 AIM AND INITIAL THEORIES REVISITED

Based on reports of cerebellar function and neural projections between structures, the role of the cerebellum in sensory processing for balance control was targeted as a potential cause of balance impairment when damaged. The overall aim of the thesis was to identify abnormal characteristics of balance in subjects with SCA6 which could point to disrupted sensory control. For this purpose, initial theories of how sensory processing for balance control may be disrupted in SCA6 were presented in chapter 1. Initial theories centred on vestibular control of balance:

- **Responses to vestibular signalled balance perturbations are insufficient in magnitude due to Purkinje cell death in the anterior cerebellar vermis.**
- **Responses to vestibular afferent information signalling balance perturbations are temporally delayed due to Purkinje cell death in the anterior cerebellar vermis.**
- **Responses to vestibular afferent information signalling balance perturbations are inappropriately spatially orientated due to Purkinje cell death in the anterior cerebellar vermis.**
- **Responses to vestibular perturbations are prolonged due to impaired combining of vestibular with proprioceptive signals in the vestibular and fastigial nuclei.**
- **Responses to vestibular perturbations are inappropriately scaled by vision.**
- **Motor response activity will not be temporally delayed in those with SCA6 due to the lack of spinal or peripheral nerve disease pathology.**

The study of balance impairment began by investigating SCA6 disease and normal standing balance characteristics before investigating whole body responses following isolated single sensory perturbations.

7.3 Summary and interpretation of findings

7.3.1 Main findings

Despite SCA6 disease pathology affecting parts of the cerebellum associated with sensory processing, this study presents evidence to suggest that sensory mechanisms of balance control are largely intact.

The main findings concerning sensory processing in SCA6 are:

- **Vestibular perturbation** responses were intact with some significant increases in early sway response magnitudes.
    - Responses to vestibular perturbations were appropriately directionally orientated across head turn postures.
    - A normal effect of vision on magnitudes of response to vestibular perturbations was evident in sway measures. However, SCA6 force response magnitudes were not affected by vision, unlike heathy controls where response magnitudes were reduced.
    - Correlations between response magnitude measures were weak and statistically non-significant.
- **Proprioceptive perturbation** responses are intact, with some significant differences in early and late sway behaviour.
    - Correlations between response magnitude measures were weak and statistically non-significant.
- **Visual perturbation** response onsets are present but significantly delayed and significantly increased in magnitude.
    - Trends exist for sway response magnitudes to correlate with baseline disease severity scores.
- **General** increases in trunk sway magnitude measures are observed throughout responses to all perturbation types just prior to cessation of the stimuli.

Collectively these findings suggest relatively normal functioning of vestibular and muscle proprioceptor signals for balance control. Of all reported differences between groups,

timing delays and increases in response magnitudes following moving visual scenery yielded the most significant differences. Although this finding would not explain balance impairment in SCA6 subjects when stood with their eye's closed, disrupted visual control of balance could contribute to balance impairment when subject's eyes are open.

Given that responses to sensory perturbations were intact and largely normal in form, it seems likely that sensory processing is not principally responsible for SCA6 balance impairment. Instead, perhaps mechanisms involved with the organisation of motor responses may be responsible. Coordination of the motor response and control of interacting joint torques are certainly aspects of motor control with the potential to affect balance if disrupted. Widespread significant increases in late trunk sway response magnitudes reported following all sensory stimuli in chapters 5 and 6 may be consistent with the idea that hypermetric responses are due to whole body in-coordination. Alternatively, these increased late responses, particularly increased following responses to GVS with vision obscured, could be the consequence of impaired re-afferent control of the response. Normal response orientations following GVS delievery with head turns and normal forms of responses to proprioceptive perturbations suggest that this sensory system is largely intact but cutaneous contributions have not been investigated. Impaired cutaneous control of balance could therefore provide an alternate explanation for late hypermetria of responses. These ideas will be revisited when discussing future research ideas at the end of this chapter.

7.3.2 Secondary findings

In order to generally gain a better understanding of balance dysfunction in SCA6 and to make comparisons with later measures of response behaviour to sensory perturbations, disease and balance characteristics were investigated. These studies established the following secondary findings:

- **Disease severity and sway speed measures of unperturbed standing balance appear to be linearly correlated.**
- **Measures of disease severity from total SARA scores appear to be sensitive to longitudinal progression of SCA6 disease but have limitations, given that it may take six months or more for scores to change by just 1 point.**
- **Balance sub-scores taken from the SARA better correlate with sway speed**

measures of unperturbed standing balance than do total SARA scores.

- **Whole body sway speeds are increased across a range of postures.**
- **Whole body sway speeds increase disproportionately with narrowing stance widths.**
- **Instability appears to be of an omni-directional nature but there is some evidence to suggest that an antero-posterior preponderance exists when feet are positioned less than 8cm apart.**
- **Joint instability is significantly increased at the ankle, particularly in roll.**
- **Frequency components of postural sway are generally increased with signs of particularly increased antero-posterior sway between 2 and 3Hz in a few subjects.**
- **Prevalence of 2-3Hz background postural tremor in some collections of responses to balance perturbations seems to bias mean measures of response direction.**

These findings provide a better understanding of balance impairment for future therapy design and design of outcome measures which may have potential to measure balance. The clinical application of these findings will be revisited in the latter half of this chapter.

7.3.3 How do these findings contribute towards knowledge of cerebellar functioning for balance control?

Initial theories concerning how SCA6 balance impairment may be caused by disrupted cerebellar processing were introduced in chapter one. The initial emphasis of the overall investigation of balance was on vestibular control of balance due to the strength of a couple of animal lesioning studies suggesting that parts of the cerebellum overlapping SCA6 disease pathology may have a role with vestibular processing [7,227,228,229]. These studies implicated the anterior cerebellar vermis as an area concerned with response magnitude scaling and orientation, based on vestibular and proprioceptive signalling. These studies underpinned initial theories of how balance impairment could be caused by SCA6 disease pathology. The anterior cerebellar vermis is known to be an area particularly affected by Purkinje cell destruction in those with SCA6 [129]. Theories relating cerebellar structure to function were then further supported by studies investigating neural projections and activity in animal brains [18,194,292,377,379]. These animal studies once again implicated

the anterior vermis as one of the areas to which vestibular afferents project via the vestibular and fastigial nuclei. The vestibular nuclei and fastigial nuclei also reportedly receive significant numbers of proprioceptive afferents [4,313,393]. These sites were also suggested as areas where proprioceptive and vestibular afferents interact. Based on these reported interactions, derived from animal neural recording studies, we could infer that these areas could also have a role in balance control. As is the case for the anterior cerebellar vermis, the vestibular and fastigial nuclei are both areas known to be damaged by SCA6 disease processes [129,345]. The ability to generalise cerebellar functions proposed by prior animal studies to subjects with SCA6, five main assumptions were made: 1.) Cerebellar topography of cats is functionally similar to humans. 2.) Neural projections of vestibular and proprioceptive afferent signals in cats are similar to humans. 3.) Lesioning techniques used in cat experiments successfully damaged only the anterior cerebellar vermis 4.) The selective loss of Purkinje cells in SCA6 is equivalent to general lesioning of the area, 5.) The chronicity of condition in most subjects with SCA6 would not affect sensory processing secondary to neuroplasticity changes.

However, contrary to expectation, SCA6 responses to vestibular perturbations were largely normal. Rather than being reduced in magnitude (which would be consistent with vestibular processing deficit) responses were if anything slightly increased. Responses were normally timed and normally directionally orientated. Where increased responses existed, they did not significantly correlate with disease severity. Based on these findings, we could infer that the anterior cerebellar vermis does not use vestibular and proprioceptive afferent signals to organise motor responses for balance control. The problem in making such a statement is that this function could be compensated for by the remaining cerebellar cells (Purkinje or non-Purkinje) or in the remaining intact parts of the cerebellum (or wider brain).

Regardless of the reason for the largely normal responses to vestibular perturbations, it seems unlikely that vestibular processing impairments are responsible for SCA6 balance impairment and therefore session three went on to explore cerebellar associations with visual and proprioceptive processing (chapter 6).

Literature concerning how motor responses to isolated proprioceptive perturbations were affected by cerebellar lesioning in animals or humans was not available. However, abundant projections from proprioceptive receptors (particularly from the lower limb

muscles) to the anterior lobe of the cerebellum via spino-cerebellar tracts provided sufficient justification to hypothesise that impaired cerebellar processing could impair balance [195,313]. Animal studies suggesting convergence of proprioceptive signals with vestibular or visual signals in the anterior vermis [8,54,227,230,228,229], posterior and inferior parts of the cerebellum [292,401] and fastigial nuclei [52,122,134] provide further support for the idea that the cerebellum may have a role in processing of proprioceptive signals. However, largely normal responses to proprioceptive perturbations seem to refute initial hypotheses of proprioceptive dysfunctioning causing impaired balance. If one were to assume that SCA6 disease processes affect all parts of the cerebellum, it may be possible to interpret this finding as evidence against a role of the cerebellum in proprioceptive control of balance. However, although widespread effects of SCA6 disease have been reported in the cerebellum, antero-superior structures tend to be affected more than postero-inferior structures. Given that the exact site of cerebellar processing of proprioceptive signals remains largely unknown, it therefore seems unwise to interpret the finding in this way.

Literature concerned with how vision is affected by cerebellar lesions was found to be principally directed at understanding changes in vestibulo-ocular reflexes (VOR) [10,27,122,334,403] or visual pusuit[187,311,354,403], rather than focussing on balance control. However VOR studies and control of eye movements have some bearing on understanding visual control of balance, especially since SCA6 subjects are known to have slowed pursuit and nystagmus [359]. In particular stabilisation of the eye in the socket is necessary if retinal or extra-ocular signals are to provide reliable forms of self-motion information. Flocculus lesioning in animals seemed to have a significant effect on VOR scaling and pursuit speeds [164,165,403]. Given that human autopsy and imaging studies have suggested that SCA6 disease moderately affects the flocculus [129], hypotheses were generated suggesting that visual control of balance could be impaired, Although animal lesioning studies targeted the flocculus, neural recordings of the vestibular and fastigial nuclei also highlight convergence of visual and proprioceptive signals in these areas [17,404]. Convergence of proprioceptive and visual signals seem essential for balance control given that exteroceptive retinal information can only advise on self-motion if contextualised with eye-in-socket, eye-in-head, head-on-body and general body schema information. The potential for damaged a flocculus, vestibular and fastigial nuclei to result in impaired visual control of balance was therefore hypothesised for those with SCA6.

Widespread significant increases in magnitude, which correlated with disease severity scores provided some support for this hypothesis, although it remains unknown why responses were increased rather than decreased in magnitude. Potential theories explaining these increases were presented in detail in the discussion of chapter 6, centring around ideas of (i) selective use of the primary and accessory visual pathways, (ii) oculo-motor impairments (iii) lack of inhibition from interconnecting structures or even (iv) compensatory up-scaling of visual signals for a deficit elsewhere.

Timing delays in force response initiation also pointed to disrupted visual control of balance. Timing abnormalities seem more difficult to explain based on cerebellar damage alone but it remains conceivable that the cerebellum may have some role in timing of motor responses [26]. Possible alternate explanations for this finding follow the same themes as those set out for magnitude increases and have been discussed in detail in chapter 6. Overall, although this finding is of considerable interest for management of SCA6 balance impairment, it remains difficult to make any conclusions concerning role of the cerebellum in processing vision for balance control without further study.

7.4 Limitations of methods

Parametric techniques were selected for use throughout all investigations concerned with the analysis of kinematic and force data. Although this approach was justified in terms of the continuous nature of the measures, the relatively small sample size involved with these studies act to question this approach. Overall the parametric approach has provided a simple method of identifying main effects of key variables and group. The approach also reflects that of other studies in the field using kinematic techniques to examine balance in cerebellar disease which have involved groups of between ten and fifteen subjects [160,161,367]. There is no doubt that this study would have benefitted from a larger sample of subjects but recruitment has remained hindered by the low incidence of SCA6 within the United Kingdom as well as the relative stringent inclusion criteria adopted. At the outset of the study, it was not possible to conduct sample size calculations given that data was not available concerning measures of standing balance, measures of response to perturbations or natural variability of these measures within the SCA6 population.

In order to optimise sample size, recruitment was ongoing throughout the study and all persons with SCA6 who met inclusion criteria and gave consent were offered participation.

It may have been possible to increase the available population further if inclusion criteria had been relaxed. Other types of SCA or subjects with relatively pure cerebellar ataxia presentations but lacking genetic confirmation of disease could have been included. However, since this study focuses on describing balance impairment in pure cerebellar disease, it seemed wise to optimise the homogeneity of the patient group by excluding such candidates.

Subjects less able to mobilise independently or stand with their eyes closed could have been given the opportunity to participate. However, given the use of balance perturbations in the laboratory environment, this would have put people at a much higher risk of falling and certainly would have increased the occurrence of fatigue within response trials. As it stands, at no point did any subject fall within any of the trials. There were occasions when subjects required light touch or took a step to stabilise but these were relative rare and in no way as upsetting as the experience of having fallen.

Fatigue remained a problem and acted to limit the total number of trial repeats obtained per condition for a few SCA6 subjects during session two. This informed the design of session three, which in turn optimised compliance during this session but limited the volume of new information that could be achieved. For example, follow-up assessment of balance using the FBS, knowledge of how responses to vibratory stimuli behaved with and without vision and use of different intensities of stimuli had to be discarded in order to avoid fatigue. Total trial repeats were also compromised to some extent. Ten repeats per condition are generally accepted as sufficient to increase signal to noise ratio but when investigating subjects with higher speeds and excursions of background sway, this increases the noise and reduces the chance of establishing an unbiased signal. In hindsight, additional conditions and trial repeats would have been preferable but the total time taken would once again have increased the chance of fatigue.

In addition to near-fall trials, some data was lost as a consequence of marker dropout or the presence of severe artefacts caused by electrical noise in marker signals. Again, inclusion of additional trial repeats to create some redundancy would have undoubtedly have been preferable but this was not always possible for the same fatigue and compliance-related reasons already discussed.

7.5 Further study

7.5.1 Vestibular control of balance

Although vestibular responses appear largely normal based on the results of this study, investigation of vestibular processing for balance control in SCA6 has been in no way exhausted. Future investigation of response magnitudes relative to a series of GVS intensities may provide a better understanding of scaling processes. Likewise, varied intensities of muscle vibration and MVS motion would surely provide more information of scaling processes for proprioceptive and visual signals. Relative single sensory gains (input dose: output response magnitude) would also be interesting to compare across modalities and between groups.

Use of bilateral monoaural GVS to change response direction relative to varied unilateral GVS currents may provide additional knowledge of the how vestibular signals are able to combine to orientate a response.

Delivery of GVS whilst measuring eye movements may also contribute further towards knowledge of SCA6 oculomotor impairments. Given that oculomotor abnormalities are well-established features of SCA6, eye movement onset times and motion velocities, part of the vestibulo-ocular reflex, are likely to be of interest especially if extra-ocular (efferent or re-afferent) signals are important contributors to balance control.

7.5.2 Proprioceptive control of balance

Despite incorporating proprioceptive, visual and vestibular isolated perturbations to measure responses to balance, deficits in sensory contributions to balance control were not found any one sensory channel. Although the approach was successful in targeting single sensory channels with balance perturbing stimuli, the approach failed to take the role of cutaneous receptors in the foot sole into account. It is possible that afferents from these cutaneous type of receptors, known to have a significant role in proprioception and balance, have a different mechanism of processing to that of other proprioceptors (namely muscle spindle and Golgi tendon organ afferents) within the cerebellum. Cutaneous receptors may have less to offer with regards to total body schema but may offer feedback concerning ankle position (via skin stretch direction and distribution) and whole body position over the support surface (via coding of the distribution of pressure changes) [163,177]. Ideally future investigations of balance control in SCA6 will begin by investigating

the role of this sensory contributor to balance control. Cutaneous receptors responsible for measuring pressure by skin deformation and stretch in the soles of the foot, like muscle spindles, are sensitive to vibratory stimuli. Vibration of foot soles has been described as an effective means of delivering balance perturbations, but the delivery of stimuli in this way may impair the use of our primary measure of response latency; peak ground reaction forces. An alternative method of measuring latency would need to be established.

The role of cutaneous afferents in the foot could similarly be investigated using the same general procedure and measurement methods outlined in this study for delivering single sensory perturbations. Since cutaneous receptors, such as RA1, SA2 and Pacian receptors are known to be sensitive to vibration, these could be targeted in the same way as muscle proprioceptors with vibrator application and controlled stimulation [163,177,184]. Investigations have already provided evidence that cutaneous afferents in human foot soles contribute significantly to balance by using such an approach [183,307,365]. Furthermore, these studies show that vibration of specific regions of plantar-sole vibration can induce directionally predictable balance responses in healthy subjects [183,307,365]. Measurement of force responses, currently the key measure of response timings, may of course be compromised with vibration noise due to the positioning of vibrators under the feet in standing subjects. In view of this, perhaps EMG of calf muscles could be used as a substitute early response measure.

Alongside investigation of responses to cutaneous perturbations, it would also be interesting to assess perceptual thresholds to pressure and vibration on different areas of the foot. Correlations between response timings or magnitudes and perceptual thresholds may strengthen support for the hypothesis that cutaneous proprioception deficits contribute to balance impairment in SCA6. Perception of foot sole vibration may however remain unaffected given that we predict that the deficit may be in processing of this signal for balance control.

A different approach to investigating cutaneous contributions to balance control in SCA6 could employ foot cooling. If there was a deficiency in processing signals from cutaneous receptors of the feet, I would predict that the normal increase in body sway seen in healthy subjects after foot cooling will be proportionally less in those with SCA6. Using such an approach, healthy subjects have been seen to become more unstable when standing, proprioceptive reflex behaviour is seen to change and responses to vestibular balance

perturbing stimuli increase in magnitude [109,270,320].

7.5.3 VISUAL CONTROL OF BALANCE

As described in chapter 6, there is a strong need for future investigation of the visual contribution to balance control.

A relatively simple addition to measuring responses to MVS would be to fit subjects with an eye-tracking device. Perhaps this would be instrumental in determining whether eye movement delays or speed of motion could be directly associated with, or even responsible for balance response delays and increased magnitudes.

Aside from determining the role of eye movements in control of balance, the following questions, prompted by the findings of this study seem worthy of future investigation:

- Are SCA6 responses to visual stimuli the consequence of sub-cortical visual processing impairments?
- Are SCA6 responses to visual stimuli the consequence of cortical processing impairments?
- Is it just self-motion information where delays are observed or do delays feature more globally in motion detection of visual stimuli?
    - Do subjects with SCA6 have problems differentiating object-motion from self-motion?
        - If subjects have difficulty detecting self-motion, what is the default; do they erroneously 'respond' to all retinal flow signals or respond less often than necessary to real self-motion signals?
        - If subjects erroneously respond more or less often to object-motion than healthy controls, do the number of errors or altered response magnitudes correlate with disease severity or slowing of ocular pursuit movements?
        - How quickly can self-motion be detected perceptually?
    - Are subjects with SCA6 able to suppress a response to retinal flow stimuli which is caused by self-generated motion, i.e. retinal flow patterns from internally generated head on body or eye in socket motion?
        - If subjects do erroneously respond more to self-generated visual signals, do the number of errors or response magnitude of these

errors correlate with disease severity or slowing of ocular pursuit movements?

Determining whether cortical or sub-cortical visual pathways could in some way be dissociated and isolating impaired functioning of either one of these systems presents a challenge to which there is not an obvious answer.

Dissociation of impairments in self versus object-motion may be a little easier to investigate. Based on the findings of this study, where responses to MVS are larger than healthy control matches, it seems reasonable to hypothesise that visual signals are more likely to be erroneously interpreted as self-motion signals than avoided. Perhaps this could be investigated by analysing postural responses to conditions resembling self-motion versus conditions providing obvious object-motion cues. Alternatively or additionally, eye movement responses could be assessed in each case and the accuracy of perceptual accounts of whether motion was judged to be self or object-motion could be used to correlate measures of response times and magnitudes.

Cortical influences on visual contributions to balance control could also be investigated by studying habituation of responses to MVS. In the present study, these effects were not observed, the likely consequence of randomised delivery of multiple and varied condition types. However, protocols involving repetitive same-stimuli conditions coupled with expectation of delivery have reported relatively fast habituation to MVS in healthy subjects. Using these paradigms, awareness of object motion even in lieu of earth-referenced cues in the visual environment should cause subjects to reduce response magnitudes with trial repeats. Should SCA6 subjects not normally habituate, this could support the idea that cortical contributions to visual control of balance are impaired.

7.5.4 COORDINATION OF THE MOTOR RESPONSE

The motor response to sensory perturbations has not been assessed in any detail to date. Using the data already collected, the relative segmental composition of responses could be analysed and sequential motion of body parts analysed for differences between groups. Incoordination of movement is a well-described feature of cerebellar disease [160,254,255] and one with the potential to affect balance. Positive SARA scores rating coordination in chapter 3 demonstrated that incoordination of movement certainly affected our SCA6 group members. Chapter 4 went on to describe a general trend for SCA6 joint excursion

over time measures to be increased compared with healthy controls, with significant differences reported at the ankle. Chapters 5 and 6 then went on to report significant increases in SCA6 trunk sway response magnitudes following all perturbation types. In all cases, in-coordination of movement could at least in part explain these findings.

Motor control in those with ataxia has long been an area of interest of interest to researchers in the field. Investigations to date have focussed on incoordination and timing of movement during reaching activities and gait [35,103,160,255,317]. However, recent work by Ilg *et al*. [161] has highlighted an association between incoordination and balance control. Although not specifically investigating this association Ilg *et al*. discovered that subjects undertaking a regime of coordination exercises significantly improved measures of disease severity and balance [161].

It has been outside the scope of this thesis to analyse and discuss incoordination of movement but clearly this presents a major area worthy of future investigation in those with SCA6.

7.6 Clinical application

7.6.1 Development of targeted therapies

7.6.1.1 ***Training***

Training of balance under destabilising moving visual scenery conditions may be effective in limiting use of visual cues known to be associated with timing and magnitude errors. As discussed in chapter 6, this approach has been effective in reducing motion sickness symptoms and improving measures of balance in patients with vestibular disorders and visual vertigo [281,280,279]. The rationale behind this approach is that by training balance in front of incongruent visual cues, balance control becomes less sensitive to or less dependent on visual contributions [281,279]. For this therapy to be effective, the precise nature of visual processing abnormalities would need to be similar to that of subjects with visual vertigo and other sensory systems would need to remain functioning appropriately in order for balance to remain under some form of sensory control. A slight concern with this approach is that we have established that vision can stabilise standing balance in those with SCA6 (chapter 5) and aside from abnormal processing of responses to visual perturbations, use of vision to stabilise in unperturbed situations is clearly worth preserving. If a ‘desensitisation to visual stimuli’ approach was to be adopted, care with the

design of the therapy is needed so as not to cause detrimental effects to balance.

Instead of desensitising the sensory system which is thought to be functioning abnormally, perhaps a better approach would be to attempt to increase the relative contributions or sensitivities of sensory systems thought to be functioning normally.

Given that vestibular and muscle proprioceptive system function appears to be largely unaffected in subjects with SCA6, training could incorporate repetitive balance perturbations to target these systems.

Functional balance exercises, particularly everyday activities such as turning on the spot and stepping, which scored low in our assessment of functional balance (FBS) could be undertaken. This would serve to initially focus training on management of internal forces which are self-generated but have the potential to affect balance. Training in a visually sparse environment may help to target vestibular and proprioceptive systems without excluding vision as a potential contributor. Platform perturbation training for management of external forces could also be undertaken. It is likely that this would present a more difficult a task for subjects and therefore could act as a progression in training activity once improvements are seen in unperturbed balance activities (i.e. with self-generated force management). An alternative to platform perturbations would be to use muscle vibrators, GVS or both stimuli to deliver balance perturbations under sparse visual conditions. A progression from delivery of expected to unexpected balance perturbations could also be incorporated using this approach.

A slightly different approach could involve selectively targeting vestibular and proprioceptive systems thought to be functioning normally with GVS and muscle vibration with the aim of increasing the sensitivity of these channels to end receptor activation. Use of muscle vibration in ankle dorsi- and plantarflexors or hip abductors and peroneii muscles could be trialled for this purpose. Simultaneous use of GVS and lower limb muscle vibration to mock up directionally congruent signals of balance perturbation may also serve to optimise preferential use of these signals over cutaneous or visual inputs.

In addition to the use of these modalities to train sway responses, stepping responses could be also be trained using larger magnitude perturbations. This would act as a higher level progression in therapy since larger perturbation magnitudes are inherently more challenging and involve a higher risk of causing falls. Disorganised stepping responses has been linked to falls in elderly subjects secondary to neuromuscular age-related changes

[248]. Training stepping responses to arrest potential falls reportedly helps prevent falls in those with age related balance impairments [224]. Falls are common in SCA6 and, as demonstrated by the results of our fall assessment (chapter 3), are most often due to loss of balance [114,373]. There is some evidence to suggest that stepping responses in cerebellar subjects are less organised, which in turn could lead to increased falls [297]. Training of stepping responses to arrest falls and general fall prevention advice would therefore likely to be of benefit in preventing injury and improving confidence with balance for SCA6 persons.

*7.6.1.2 **Adaptation***

If there is a deficiency in sensory processing of cutaneous receptor foot sole signals, modalities such as edged or vibrating in-soles insoles could be trialled in order to see if an increased afferent signal from receptors could increase the chance of some of this signal being used at a processing level. The use of such modalties has been shown to be effective in persons with diabetic peripheral neuropathy or peripheral nerve changes associated with aging [283,293]. Despite positive outcomes reported in these groups, this approach may be flawed when attempted with SCA6 persons, given that we hypotheses that cerebellar processing is impaired and not a peripheral function.

A less controversial adaptive therapy option could involve the use of lateral ankle splints. The rationale here is that support of the ankle would improve stability of the ankle complex. If normal ankle torque control is dependent on cutaneous receptor activity in the foot sole and this is impaired in those with SCA6, the consequence could be increased instability at the ankle. Interestingly, of all the joints analysed when subjects did not receive balance perturbations (chapter 4) the most increased joint instability was found to occur at the ankle, particularly for roll motion. This is consistent with prior reports of instability in the frontal plane [22,155,238]. A lateral splint would therefore stabilise the ankle complex in lieu of active control. Splinting about the back of the foot seems less indicated, since postural involvement of soleus and gastrocnemius and a lesser extent, tibialis anterior, means that muscle spindles and Golgi tendon organs in these structures could be used to compensate for loss of cutaneous control of balance by increasing the role of these proprioceptors in the detection of postural sway in the anteroposterior direction.

Aside from splinting, the design of mobility aids for this patient group could be modified too.

Traditionally walking sticks have been designed to exert load down as well as providing a form of sensory feedback between the upper limb and support surfaces. Patients without weakness of lower limb injury, such as SCA6 do not require a load bearing function but the proprioceptive contribution could remain of value. In view of this, walking sticks could be designed to possess greater overall stability, including a larger distal contact area with the ground and better proximal contact area with the hand. Traditional walking stick ferrel bases are circular in design with a radius of no more than 2cm and the vertical position of the stick is often in front of the grip. Perhaps a square based ferrel would be a better option for ataxic subjects. A square design, with slight rocker edges at the front and back to facilitate use during walking, would help to direct placement of the stick and to generate directionally meaningful proprioceptive feedback. An increase in ferrel area of $10cm^2$ does not seem unreasonable given that the natural carrying angle of the arm would act to keep this out of the way of lower limbs during use, even if wide stance widths are adopted. Positioning the stick more directly under the shaft of the forearm may also help generate directionally meaningful proprioceptive feedback.

7.6.2 LONGITUDINAL MONITORING

At the outset of this project, the scale for the assessment and rating of ataxia (SARA) was already been validated as a measure capable of assessing disease severity [(324)]. In the last year, additional data concerning change in score per year has acted to validate this measure for the purpose of monitoring disease progression (SARA score mean yearly change: 1.38 points, standard deviation: 2.8) [(322)]. This validation study was based on a group of subjects with SCA1, 2,3 and 6. Significant change in scores per year presented here (SARA score yearly change: 1.9, standard deviation: 1.1, $p<0.001$) further act to provide support for the SARA as a longitudinal measure.

The attempts to longitudinally measure balance over the duration of this study were less successful. The functional balance scale (FBS) appears to have the potential as a useful measure of balance given the high correlations reported between this score and SARA scores ($r=-0.796$, $p<0.001$). However, due to time costs and fatigue inducing effects of using this scale reported by subjects during session one, undertaking of this measure was unfortunately not repeated during the final session. The sensitivity to change over one year was therefore not assessed.

Sway speed laboratory derived measures of balance also produced high overall correlations with SARA scores but sway speeds were not seen to change between days (trunk sway speeds: p=0.917, CoP speeds: p=0.534). Potential confounding variables concerning this finding were discussed in chapter 3. Despite this finding, it is felt that overall correlations coupled with the potential for this scoring method to provide a more sensitive measure for change warrant further investigation of this method as a longitudinal measure.

The Bal-SARA score (balance related composite sub-scores of the SARA) may be a quicker alternative to the FBS. Based on the clinical assessment findings, there remains a strong correlation between Bal-SARA and FBS scores (r= -0.731, p=0.001) and with total SARA scores (r=0.888, p<0.001). However, unfortunately session one scores were not significantly different to scores at plus one year (0.093), which means that it is unlikely that clinicians would be able to track deterioration in balance on a yearly basis.

Fall frequencies did not correlate with any measure but it is interesting that subjects with a Bal-SARA score of just one already experience falls. Perhaps with a little further investigation a positive Bal-SARA score could act as an indicator for a physiotherapy referral, where fall prevention techniques could be discussed to prevent initial injury and reduce fear of falling impacting on function and quality of life.

Functional independence measures (FIM) only weakly correlated with SARA measures of disease severity and did not significantly change in one year. To some degree no change or minimal change in scores over a year is promising finding since it suggests that subjects are able to optimise function despite progressive disease severity which could merely relate to the slowness of progression or could be an indication of good management of the condition. Despite correlations with SARA, the FIM was initially designed to assess function in those with spinal cord injury. Most subjects gained high scores using the FIM because functional limitations often did not require assistance from others (the degree of assistance with activity being the principal factor determining FIM scoring). Perhaps a better approach to assessing function in ataxia would involve designing a score where subjects have access to a category which indicates preservation of independent function but with difficulties incurred.

7.6.3 Outcome measures

In order to assess treatment effects during trials of future therapies, outcome measures with the potential to be sensitive to change over the trial duration need to be available and knowledge of how these may change with natural progression over this time is also necessary.

It has not been within the scope of this study to assess the efficacy of potential treatment outcome measures. However, a body of support is developing for the SARA [114,322,325,324]. Correlations presented in this study between the SARA and measures of balance provide some additional support for the role of the SARA as a balance outcome measure until better options are available.

Sway speeds have potential as balance outcome measures, given that they are quantitative and potentially sensitive to small changes in balance. Possibly for these attributes, they have already begun to be used to evaluate the effects of novel pharmaceutical treatments for SCA6 [158]. However, before these sway speeds can be used with confidence as therapy outcome measures, a better understanding of confound variables must be established. Equally, data concerning rate-of-change in score relative to natural disease progression must be also be established under same condition trials.

7.7 Overall conclusion

Individuals with SCA6 are more unstable in both cardinal directions when standing. Measures of instability correlate with disease severity, especially when adopting narrow stance widths. Individuals become progressively more unstable as stance width narrows and ankle instability seems to be a feature in those with SCA6.

Despite significant increases in instability, responses to isolated single sensory balance perturbations were largely normal. A trend exisited for responses to vestibular, proprioceptive and moving visual stimuli to be generally increased in magnitude, with some significant differences reported between groups.

Timing delays and increases in response magnitudes following isolated moving visual stimuli featured as the main abnormal findings. These findings require further investigation before conclusions can be made concerning the underlying mechanisms responsible. Although of interest, impaired processing of vision for balance control cannot explain balance impairment observed when vision is unavailable,

This thesis presents evidence that sensory processing for balance control in SCA6 is largely normal. The study provides a significant early contribution towards understanding sensory mechanisms of balance control in pure cerebellar disease.

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9 APPENDICES

APPENDIX 1: STUDY OF DISEASE PATHOLOGIES WITH GVS

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APPENDIX 2: SUBJECT CODING

Table 1: Key linking subject number for thesis purpose with anonymous subject code held on consent sheets.

Group	No.	Subj. code	Group	No.	Subj. code
SCA6	1	167	HC	1	170
SCA6	2	195	HC	2	124
SCA6	3	65	HC	3	103
SCA6	4	188	HC	4	152
SCA6	5	98	HC	5	86
SCA6	6	80	HC	6	187
SCA6	7	151	HC	7	36
SCA6	8	138	HC	8	8
SCA6	9	128	HC	9	116
SCA6	10	2	HC	10	59
SCA6	11	67	HC	11	173
SCA6	12	161	HC	12	31
SCA6	13	20	HC	13	132
SCA6	14	69	HC	14	16
SCA6	15	198	HC	15	53
SCA6	16	136	HC	16	73
SCA6	17	52	HC	17	68
SCA6	18	176	HC	18	76
SCA6	19	14	HC	19	119
SCA6	20	155	HC	20	149
SCA6	21	84	HC	21	47
			HC	22	96
			HC	23	114
			HC	24	21
			HC	25	101
			HC	26	42
			HC	27	158
			HC	28	159

APPENDIX 3: MATLAB ANALYSIS FILES

Used with TC BALAN routines and Matlab v.7.8.0 (R2009a)

```
%CHAPTER 3 AND 4 STANCE WIDTH BASIC CALCULATIONS
clc
clear all
[dirnum, trnum] = getcondir('0cm', 'ALL');
[dirnum,trnum] = con2sub(dirnum,trnum);

%KINEMATICS
getxyzdir(dirnum,trnum)
clear z
getdatdir(dirnum,trnum,'TIMC');

%TRUNK CLUSTER DATA
% [x,y] = filtMN(10,TIMC*200,x,y); %filtfilt
butter at 20Hz

TRBACK_X = dekin (x,5);
TRBACK_Y = dekin (y,5);
TLBACK_X = dekin (x,6);
TLBACK_Y = dekin (y,6);
BRBACK_X = dekin (x,7);
BRBACK_Y = dekin (y,7);
BLBACK_X = dekin (x,8);
BLBACK_Y = dekin (y,8);
RFOOT_X = dekin (x,19);
LFOOT_X = dekin (x,21);

[TRBACK_X,TRBACK_Y,TLBACK_X,TLBACK_Y,BRBACK_X,BRBA
CK_Y,BLBACK_X,BLBACK_Y] =
filtMN(10,TIMC*200,TRBACK_X,TRBACK_Y,TLBACK_X,TLBA
CK_Y,BRBACK_X,BRBACK_Y,BLBACK_X,BLBACK_Y);
%filtfilt butter at 20Hz

CBACK_X = NaNvaravg(TRBACK_X, TLBACK_X, BRBACK_X,
BLBACK_X);
CBACK_Y = NaNvaravg(TRBACK_Y, TLBACK_Y, BRBACK_Y,
BLBACK_Y);

% figure(1)
% Mstack(TIMC,CBACK_X, CBACK_Y)

%TRUNK CLUSTER STD DISPLACEMENT
CBACK_Xsd = (NaNstdTC(CBACK_X));
CBACK_Ysd = (NaNstdTC(CBACK_Y));

%TRUNK CLUSTER VELOCITIES
TIMCvel=TIMC(2:(size(TIMC))-1,:); %time register
for centdiff
CBACK_Xvel=(CBACK_X(3:(size(TIMC)),:,:)-
CBACK_X(1:(size(TIMC))-2,:,:))./(TIMC(3,1)-
TIMC(1,1)); %Central difference method
CBACK_Yvel=(CBACK_Y(3:(size(TIMC)),:,:)-
CBACK_Y(1:(size(TIMC))-2,:,:))./(TIMC(3,1)-
TIMC(1,1)); %Central difference method
CBACK_spd =
sqrt(((CBACK_Xvel).^2)+((CBACK_Yvel).^2));
CBACK_spd_avg = (NaNmeanTC(CBACK_spd));
CBACK_Xvel_sd = (NaNstdTC(CBACK_Xvel));
CBACK_Yvel_sd = (NaNstdTC(CBACK_Yvel));
CBACK_spd_sd = (NaNstdTC(CBACK_spd));

%TRUNK CLUSTER PATHRATES
PRCBACK =
(NaNsumTC(sqrt(((CBACK_X(2:(size(TIMC)),:,:)-
CBACK_X(1:(size(TIMC)-
1),:,:)).^2)+((CBACK_Y(2:(size(TIMC)),:,:)-
CBACK_Y(1:(size(TIMC)-
1),:,:)).^2)))./(length(TIMC)/200)); %Pathrate of
each trial, 1st (length(TIMC)/200)s ie without vis
period
PRCBACK_X =
((NaNsumTC(sqrt(((CBACK_X(2:(size(TIMC)),:,:)-
CBACK_X(1:(size(TIMC)-
1),:,:)).^2))))./(length(TIMC)/200)); %Pathrate of
ML components of each trial, 1st
(length(TIMC)/200)s ie without vis period
PRCBACK_Y =
((NaNsumTC(sqrt(((CBACK_Y(2:(size(TIMC)),:,:)-
CBACK_Y(1:(size(TIMC)-
1),:,:)).^2))))./(length(TIMC)/200)); %Pathrate of
AP components each trial, 1st (length(TIMC)/200)s
ie without vis period

%FORCES
getdatdir(dirnum,trnum,'TIMC,FP1X,FP1Y,FP1Z,FP2X,F
P2Y,FP2Z,CP1X,CP1Y,CP2X,CP2Y');
[FP1X,FP1Y,FP1Z] =
filtMN(20,TIMC*200,FP1X,FP1Y,FP1Z); %filtfilt
butter at 20Hz
[FP2X,FP2Y,FP2Z] =
filtMN(20,TIMC*200,FP2X,FP2Y,FP2Z); %filtfilt
butter at 20Hz

%Assess the raw forces
%trplot(TIMC,FP1X, FP1Y)%plot all forces over time
% figure (2)
% trplot(TIMC, FP1Z, FP2Z)
FX = FP1X+FP2X; FY = FP1Y+FP2Y; %compute total
force
%CENTRE OF PRESSURE DATA

[CP1X,CP1Y] = filtMN(20,TIMC*200,CP1X,CP1Y);
%filtfilt butter at 20Hz
[CP2X,CP2Y] = filtMN(20,TIMC*200,CP2X,CP2Y);
%filtfilt butter at 20Hz
LW = FP1Z./(FP1Z+FP2Z);
RW = FP2Z./(FP1Z+FP2Z);
CPX = (CP1X.*LW) + (CP2X.*RW);
CPY = (CP1Y.*LW) + (CP2Y.*RW);

%Calculating COP path-rates
PRCoP = (sum(sqrt(((CPX(2:(size(TIMC)),:,:)-
CPX(1:(size(TIMC)-
1),:,:)).^2)+((CPY(2:(size(TIMC)),:,:)-
CPY(1:(size(TIMC)-
1),:,:)).^2)))./(length(TIMC)/200))'; %Pathrate of
each trial, 1st (length(TIMC)/200)s ie without vis
period
PRCoPX = ((sum(sqrt(((CPX(2:(size(TIMC)),:,:)-
CPX(1:(size(TIMC)-
1),:,:)).^2))))./(length(TIMC)/200))'; %Pathrate
of ML components of each trial, 1st
(length(TIMC)/200)s ie without vis period
PRCoPY = ((sum(sqrt(((CPY(2:(size(TIMC)),:,:)-
CPY(1:(size(TIMC)-
1),:,:)).^2))))./(length(TIMC)/200))'; %Pathrate
of AP components each trial, 1st
(length(TIMC)/200)s ie without vis period

%CP STD DISPLACEMENT
CPXsd = (std(CPX(1:(size(TIMC)),:,:)))';
CPYsd = (std(CPY(1:(size(TIMC)),:,:)))';

%CP VELOCITIES
TIMCvel=TIMC(2:(size(TIMC))-1,:); %time register
for centdiff
CPXvel=(CPX(3:(size(TIMC)),:,:)-
CPX(1:(size(TIMC))-2,:,:))./(TIMC(3,1)-TIMC(1,1));
%Central difference method
CPYvel=(CPY(3:(size(TIMC)),:,:)-
CPY(1:(size(TIMC))-2,:,:))./(TIMC(3,1)-TIMC(1,1));
%Central difference method
CPspd = sqrt(((CPXvel).^2)+((CPYvel).^2));

CPspd_avg = (mean(CPspd))';
CPXvel_sd = (std(CPXvel))';
CPYvel_sd = (std(CPYvel))';
CPspd_sd = (std(CPspd))';

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%CHAPTER 4 FREQUENCY ANALYSIS NOT USING TC BALAN
ROUTINES
clear all
clc
sq ='''''; %define single quote for use in strings

[FileName,PathName] =
uigetfile('*.mat','MultiSelect','on','select
multiple files');

for n=1:length(FileName)%start the patient
matfiles here and loop through
    %work through files
    nfile= [PathName FileName{n}]; %curly braces
required to index files
    text = ['load ' sq nfile sq ' A3Dspace_Thorax
FILE_NAME' ];
    %SPARE ANGLES: A3Dseg_HeadonThorax
A3Dseg_ThoraxonPelvis A3Dseg_RhipJoint
    %A3Dseg_LhipJoint A3Dseg_RkneeJoint
A3Dseg_LkneeJoint
    %A3Dseg_RankleJoint A3Dspace_Rshank
A3Dspace_Lshank
    %A3Dseg_LankleJoint A3Dspace_Rfoot
A3Dspace_Lfoot
    eval(text);
    for i=1:5
      if isnan(A3Dspace_Thorax{i})==0
      x=A3Dspace_Thorax{i};
    Fs = 200;                          % Sampling
frequency
    t  = 0:1/Fs:40;                    % Time vector
    x = (A3Dspace_Thorax{i}(:,2)-
mean(A3Dspace_Thorax{i}(:,2)));% Raw signal zeroed
to start
    hp = spectrum.periodogram('hamming');  %
Create periodogram

    % Create options object and set properties
    hpopts = psdopts(hp,x);
    set(hpopts,'Fs',Fs,'SpectrumType','onesided');

    figure (1)
    subplot(5,1,i)
    plot(t(1:length(x)),x);
    figure (2)
    subplot(5,1,i)
    msspectrum(hp,x,hpopts);
    hpsd = psd(hp,x,hpopts);
```

```
    power_freqdomainR01(n,i) = avgpower(hpsd, [0
1]);
    power_freqdomainR12(n,i) = avgpower(hpsd, [1
2]);
    power_freqdomainR23(n,i) = avgpower(hpsd, [2
3]);
    power_freqdomainR34(n,i) = avgpower(hpsd, [3
4]);
    power_freqdomainR45(n,i) = avgpower(hpsd, [4
5]);

    %10*log10(power_freqdomain)%This converts the
above average power
    %measure into dB
    Fs = 200;                       % Sampling
frequency
    t  = 0:1/Fs:40;                 % Time vector
    x = (A3Dspace_Thorax{i}(:,1)-
mean(A3Dspace_Thorax{i}(:,1)));% Raw signal zeroed
to start
    hp = spectrum.periodogram('hamming');  %
Create periodogram

    % Create options object and set properties
    hpopts = psdopts(hp,x);
    set(hpopts,'Fs',Fs,'SpectrumType','onesided');

    figure (4)
    subplot(5,1,i)
    plot(t(1:length(x)),x);
    figure (5)
    subplot(5,1,i)
    msspectrum(hp,x,hpopts);
    v = axis; axis([0 5 v(3) v(4)]);   % Zoom in
Y.
    hpsd = psd(hp,x,hpopts);% This is the
periodogram mean sqaure spectral
    v = axis; axis([0 5 v(3) v(4)]);   % Zoom in
Y.
    power_freqdomainP01(n,i) = avgpower(hpsd, [0
1]);
    power_freqdomainP12(n,i) = avgpower(hpsd, [1
2]);
    power_freqdomainP23(n,i) = avgpower(hpsd, [2
3]);
    power_freqdomainP34(n,i) = avgpower(hpsd, [3
4]);
    power_freqdomainP45(n,i) = avgpower(hpsd, [4
5]);
     end
  end
end
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%CHAPTER 5 GVS ANALYSIS
clc
clear all
[dirnum, trnum] = getcondir('nvHRns, nvHLns',
'ALL');%BACKWARDS
[dirnum,trnum] = con2sub(dirnum,trnum);
%KINEMATICS
l=size(trnum,2);
Number1=zeros(17,1:l);
for n=1:17;
    count=0;
    for m=1:l
        if trnum(n,m)> 0.5;
            count=count+1;

        end
    Number1(n,1)=count;
    end
end
clear dirnum
clear trnum

[dirnum, trnum] = getcondir('vHLl+, vHRr+, vHRl+,
vHLr+', 'ALL');%BACKWARDS
[dirnum,trnum] = con2sub(dirnum,trnum);

l=size(trnum,2);
Number=zeros(17,1:l);
for n=1:17;
    count=0;
    for m=1:l;
        if trnum(n,m)> 0.5;
            count=count+1;

        end
    Number(n,1)=count;
    end
end
Number2=Number-Number1;
p=1:l; %How many total trial repeats are expected?

getxyzdir(dirnum,trnum);
clear z

FRHEAD_X = dekin (x,1);
FRHEAD_Y = dekin (y,1);
BRHEAD_X = dekin (x,2);
BRHEAD_Y = dekin (y,2);
TRBACK_X = dekin (x,5);
TRBACK_Y = dekin (y,5);
TLBACK_X = dekin (x,6);
TLBACK_Y = dekin (y,6);
BRBACK_X = dekin (x,7);
BRBACK_Y = dekin (y,7);
BLBACK_X = dekin (x,8);
BLBACK_Y = dekin (y,8);

clear x
clear y

getdatdir(dirnum,trnum,'TIMC')

[TRBACK_X,TRBACK_Y,TLBACK_X,TLBACK_Y,BRBACK_X,BRBA
CK_Y,BLBACK_X,BLBACK_Y] =
filtMN(20,TIMC*200,TRBACK_X,TRBACK_Y,TLBACK_X,TLBA
CK_Y,BRBACK_X,BRBACK_Y,BLBACK_X,BLBACK_Y);
%filtfilt butter at 20Hz


for n=1:17
    for nn=(Number1(n,1)+1):Number;
        [TRBACK_X(:,n,nn)]=(TRBACK_X(:,n,nn).*-1);
        [TRBACK_Y(:,n,nn)]=(TRBACK_Y(:,n,nn).*-1);
        [TLBACK_X(:,n,nn)]=(TLBACK_X(:,n,nn).*-1);
        [TLBACK_Y(:,n,nn)]=(TLBACK_Y(:,n,nn).*-1);
        [BRBACK_X(:,n,nn)]=(BRBACK_X(:,n,nn).*-1);
        [BRBACK_Y(:,n,nn)]=(BRBACK_Y(:,n,nn).*-1);
        [BLBACK_X(:,n,nn)]=(BLBACK_X(:,n,nn).*-1);
        [BLBACK_Y(:,n,nn)]=(BLBACK_Y(:,n,nn).*-1);
    end
end

    PERT = repmat(2,17,1); % this puts the
threshold for stim onset into time units
    saveevent(PERT);



[TIMal, TRBACK_Xal] = align_t(PERT,TIMC,
TRBACK_X);
[TIMal, TLBACK_Xal] = align_t(PERT,TIMC,
TLBACK_X);
[TIMal, BRBACK_Xal] = align_t(PERT,TIMC,
BRBACK_X);
[TIMal, BLBACK_Xal] = align_t(PERT,TIMC,
BLBACK_X);
[TIMal, TRBACK_Yal] = align_t(PERT,TIMC,
TRBACK_Y);
[TIMal, TLBACK_Yal] = align_t(PERT,TIMC,
TLBACK_Y);
[TIMal, BRBACK_Yal] = align_t(PERT,TIMC,
BRBACK_Y);
[TIMal, BLBACK_Yal] = align_t(PERT,TIMC,
BLBACK_Y);
[TIMal, FRHEAD_Xal] = align_t(PERT,TIMC,
FRHEAD_X);
[TIMal, BRHEAD_Xal] = align_t(PERT,TIMC,
BRHEAD_X);
[TIMal, FRHEAD_Yal] = align_t(PERT,TIMC,
FRHEAD_Y);
[TIMal, BRHEAD_Yal] = align_t(PERT,TIMC,
BRHEAD_Y);

%Average start head angle calculations
AVbBRHEAD_Xal=zeros(length(TIMal),17);
AVbBRHEAD_Yal=zeros(length(TIMal),17);
AVbFRHEAD_Xal=zeros(length(TIMal),17);
AVbFRHEAD_Yal=zeros(length(TIMal),17);

for n=1:17;
        counter=Number(n,1);
            [AVbBRHEAD_Xal(1:length(TIMal),n)] =
(sum(BRHEAD_Xal(:,n,(1:counter)),3))./counter;
%trunk
            [AVbBRHEAD_Yal(1:length(TIMal),n)] =
(sum(BRHEAD_Yal(:,n,(1:counter)),3))./counter;
%trunk
            [AVbFRHEAD_Xal(1:length(TIMal),n)] =
(sum(FRHEAD_Xal(:,n,(1:counter)),3))./counter;
%trunk
            [AVbFRHEAD_Yal(1:length(TIMal),n)] =
(sum(FRHEAD_Yal(:,n,(1:counter)),3))./counter;
%trunk

            [subAVbBRHEAD_Xal] =
(sum(AVbBRHEAD_Xal,2))./17; %trunk
            [subAVbBRHEAD_Yal] =
(sum(AVbBRHEAD_Yal,2))./17; %trunk
            [subAVbFRHEAD_Xal] =
(sum(AVbFRHEAD_Xal,2))./17; %trunk
            [subAVbFRHEAD_Yal] =
(sum(AVbFRHEAD_Yal,2))./17; %trunk
    end

for n=1:17;
    x1(n,1)=(NaNvaravg(0.9,0.0,TIMal,
AVbFRHEAD_Xal(:,n)))-
(NaNvaravg(0.9,0.0,TIMal,AVbBRHEAD_Xal(:,n)));
    y1(n,1)=(NaNvaravg(0.9,0.0,TIMal,
AVbFRHEAD_Yal(:,n)))-
(NaNvaravg(0.9,0.0,TIMal,AVbBRHEAD_Yal(:,n)));
    START_HEADb(n,1) =
(atan2(y1(n),x1(n)).*180./pi);%
end
subAVSTART_HEADb =
(atan2(((NaNvaravg(0.9,0.0,TIMal,
```

```
subAVbBRHEAD_Yal))-
(NaNvaravg(0.9,0.0,TIMal,subAVbFRHEAD_Yal))),...

((NaNvaravg(0.9,0.0,TIMal, subAVbBRHEAD_Xal))-
(NaNvaravg(0.9,0.0,TIMal,subAVbFRHEAD_Xal)))).*180
./pi);

%Average trunk sway response calculations
CBACK_Xal = NaNvaravg(TRBACK_Xal, TLBACK_Xal,
BRBACK_Xal, BLBACK_Xal);
CBACK_Yal = NaNvaravg(TRBACK_Yal, TLBACK_Yal,
BRBACK_Yal, BLBACK_Yal);

[CBACK_Xal] = subavg(0.0,0.0,TIMal,CBACK_Xal);
%trunk
[CBACK_Yal] = subavg(0.0,0.0,TIMal,CBACK_Yal);
%trunk

AVbBACK_Xal=zeros(1:length(TIMal),17);
AVbBACK_Yal=zeros(1:length(TIMal),17);

    for n=1:17;
      counter=Number(n,1);
    [AVbBACK_Xal(1:length(TIMal),n)] =
(sum(CBACK_Xal(:,n,(1:counter)),3))./counter;
%trunk
    [AVbBACK_Yal(1:length(TIMal),n)] =
(sum(CBACK_Yal(:,n,(1:counter)),3))./counter;
%trunk
    [subAVbBACK_Xal] = (sum(AVbBACK_Xal,2))./17;
%trunk
    [subAVbBACK_Yal] = (sum(AVbBACK_Yal,2))./17;
%trunk
    end
GrandAvTXmean = [mean(AVbBACK_Xal')]';
GrandAvTYmean = [mean(AVbBACK_Yal')]';
GrandAvTXsd = [std(AVbBACK_Xal')]';
GrandAvTYsd = [std(AVbBACK_Yal')]';

T_RESPMAG_Xhab = (getval_t(2.0,TIMal, CBACK_Xal))-
(getval_t(0.2,TIMal, CBACK_Xal)); %trunk
T_RESPMAG_Yhab = (getval_t(2.0,TIMal, CBACK_Yal))-
(getval_t(0.2,TIMal, CBACK_Yal)); %trunk
T_RESPMAGhab =
sqrt(((T_RESPMAG_Xhab.^2)+(T_RESPMAG_Yhab.^2)));%a
verage vector mag per subject

THab=zeros(17,100);
for m=1:17
    for n=1:10
        THab(m,trnum(m,n))= T_RESPMAGhab(m,n);
    end
end


T_RESPMAG_X = (getval_t(2.0,TIMal, AVbBACK_Xal))-
(getval_t(0.2,TIMal, AVbBACK_Xal)); %trunk
T_RESPMAG_Y = (getval_t(2.0,TIMal, AVbBACK_Yal))-
(getval_t(0.2,TIMal, AVbBACK_Yal)); %trunk
T_RESPMAGb =
sqrt(((T_RESPMAG_X.^2)+(T_RESPMAG_Y.^2)));%average
vector mag per subject
T_RESPDIRb =
(atan2((T_RESPMAG_Y),(T_RESPMAG_X)).*180./pi);%ave
rage resp direction per subject
T_NORMRESPDIRb = T_RESPDIRb + START_HEADb;

subT_RESPMAG_X = (getval_t(2.0,TIMal,
subAVbBACK_Xal))-(getval_t(0.2,TIMal,
subAVbBACK_Xal)); %trunk %trunk
subT_RESPMAG_Y = (getval_t(2.0,TIMal,
subAVbBACK_Yal))-(getval_t(0.2,TIMal,
subAVbBACK_Yal)); %trunk
subAVbT_RESPMAG =
sqrt(((subT_RESPMAG_X.^2)+(subT_RESPMAG_Y.^2)));%a
verage vector mag of collapsed av group response
subAVbT_RESPDIR =
(atan2((subT_RESPMAG_Y),(subT_RESPMAG_X)).*180./pi
);%average vector resp direction of collapsed av
group response
subAVbT_NORMRESPDIR = subAVbT_RESPDIR +
subAVSTART_HEADb;

%FORCES
tic
getdatdir(dirnum,trnum,'FP1X,FP1Y,FP1Z,FP2X,FP2Y,F
P2Z,CP1X,CP1Y,CP2X,CP2Y');
toc

[FP1X,FP1Y,FP1Z] =
filtMN(20,TIMC*200,FP1X,FP1Y,FP1Z); %filtfilt
butter at 20Hz
[FP2X,FP2Y,FP2Z] =
filtMN(20,TIMC*200,FP2X,FP2Y,FP2Z); %filtfilt
butter at 20Hz

FX = FP1X+FP2X; FY = FP1Y+FP2Y; %compute total
force

for n=1:17
    for nn=(Number1(n,1)+1):Number
        [FX(:,n,nn)]=(FX(:,n,nn).*-1);
        [FY(:,n,nn)]=(FY(:,n,nn).*-1);
    end
end
```

```
[TIMal, FXal] = align_t(PERT,TIMC, FX);
[TIMal, FYal] = align_t(PERT,TIMC, FY);

[FXal] = subavg(0.0,0.0,TIMal,FXal);
[FYal] = subavg(0.0,0.0,TIMal,FYal);

AVbFXal=zeros((length(TIMal)),17);
AVbFYal=zeros((length(TIMal)),17);

    for n=1:17
        counter=Number(n,1);
    [AVbFXal(1:length(TIMal),n)] =
(sum(FXal(:,n,(1:counter)),3))./counter; %trunk
    [AVbFYal(1:length(TIMal),n)] =
(sum(FYal(:,n,(1:counter)),3))./counter; %trunk
    [subAVbFXal] = (sum(AVbFXal,2))./17; %trunk
    [subAVbFYal] = (sum(AVbFYal,2))./17; %trunk
    end
GrandAvFXmean = [mean(AVbFXal')]';
GrandAvFYmean = [mean(AVbFYal')]';
GrandAvFXsd = [std(AVbFXal')]';
GrandAvFYsd = [std(AVbFYal')]';

F_RESPMAG_Xhab = (getval_t(0.4,TIMal, FXal))-
(getval_t(0.2,TIMal, FXal)); %trunk
F_RESPMAG_Yhab = (getval_t(0.4,TIMal, FYal))-
(getval_t(0.2,TIMal, FYal)); %trunk
F_RESPMAGhab =
sqrt(((F_RESPMAG_Xhab.^2)+(F_RESPMAG_Yhab.^2)));%a
verage vector mag per subject

FHab=zeros(17,100);
for m=1:17
    for n=1:10
        FHab(m,trnum(m,n))= F_RESPMAGhab(m,n);
    end
end


F_RESPMAG_X = (getval_t(0.4,TIMal, AVbFXal))-
(getval_t(0.2,TIMal, AVbFXal)); %trunk
F_RESPMAG_Y = (getval_t(0.4,TIMal, AVbFYal))-
(getval_t(0.2,TIMal, AVbFYal)); %trunk
F_RESPMAGb =
sqrt(((F_RESPMAG_X.^2)+(F_RESPMAG_Y.^2)));%average
vector mag per subject
F_RESPDIRb =
(atan2((F_RESPMAG_Y),(F_RESPMAG_X)).*180./pi);%ave
rage resp direction per subject
F_NORMRESPDIRb = F_RESPDIRb + START_HEADb;%average
normalised resp direction per subject

subF_RESPMAG_X = (getval_t(0.4,TIMal,
subAVbFXal))-(getval_t(0.2,TIMal, subAVbFXal));
%trunk
subF_RESPMAG_Y = (getval_t(0.4,TIMal,
subAVbFYal))-(getval_t(0.2,TIMal, subAVbFYal));
%trunk
subAVbF_RESPMAG =
sqrt(((subF_RESPMAG_X.^2)+(subF_RESPMAG_Y.^2)));%a
verage vector mag of collapsed av group response
subAVbF_RESPDIR =
(atan2((subF_RESPMAG_Y),(subF_RESPMAG_X)).*180./pi
);%average vector resp direction of collapsed av
group response
subAVbF_NORMRESPDIR = subAVbF_RESPDIR +
subAVSTART_HEADb;

%CENTRE OF PRESSURE DATA

[CP1X,CP1Y] = filtMN(20,TIMC*200,CP1X,CP1Y);
%filtfilt butter at 20Hz
[CP2X,CP2Y] = filtMN(20,TIMC*200,CP2X,CP2Y);
%filtfilt butter at 20Hz

%Working out weightings and sorting into
compatible matrix design

            LW = FP1Z./(FP1Z+FP2Z);
            RW = FP2Z./(FP1Z+FP2Z);
            [AVCPX] = (CP1X.*LW) +
(CP2X.*RW);%Mean X trace per subject
            [AVCPY] = (CP1Y.*LW) +
(CP2Y.*RW);%Mean Y trace per subject

for n=1:17
    for nn=(Number1(n,1)+1):Number
        [AVCPX(:,n,nn)]=(AVCPX(:,n,nn).*-1);
        [AVCPY(:,n,nn)]=(AVCPY(:,n,nn).*-1);
    end
end

[TIMal, CPXal] = align_t(PERT,TIMC, AVCPX);
[TIMal, CPYal] = align_t(PERT,TIMC, AVCPY);

[CPXal] = subavg(0.0,0.0,TIMal,CPXal);
[CPYal] = subavg(0.0,0.0,TIMal,CPYal);

AVbCPXal=zeros((length(TIMal)),17);
AVbCPYal=zeros((length(TIMal)),17);

    for n=1:17;
        counter=Number(n,1);
            [AVbCPXal(1:length(TIMal),n)] =
```

```
          (sum(CPXal(:,n,(1:counter)),3))./counter
;%
            [AVbCPYal(1:length(TIMal),n)] =

          (sum(CPYal(:,n,(1:counter)),3))./counter
;%
            [subAVbCPXal] =
(sum(AVbCPXal,2))./counter; %Mean group traces
            [subAVbCPYal] =
(sum(AVbCPYal,2))./counter; %
    end

GrandAvCPXmean = [mean(AVbCPXal')]';
GrandAvCPYmean = [mean(AVbCPYal')]';
GrandAvCPXsd = [std(AVbCPXal')]';
GrandAvCPYsd = [std(AVbCPYal')]';

CP_RESPMAG_Xhab = (getval_t(2.0,TIMal, CPXal))-
(getval_t(0.2,TIMal, CPXal)); %trunk
CP_RESPMAG_Yhab = (getval_t(2.0,TIMal, CPYal))-
(getval_t(0.2,TIMal, CPYal)); %trunk
CP_RESPMAGhab =
sqrt(((CP_RESPMAG_Xhab.^2)+(CP_RESPMAG_Yhab.^2)));
%average vector mag per subject

CPHab=zeros(17,100);
for m=1:17
    for n=1:10
        CPHab(m,trnum(m,n))= F_RESPMAGhab(m,n);
    end
end

CP_RESPMAG_X = (getval_t(2.0,TIMal, AVbCPXal))-
(getval_t(0.2,TIMal, AVbCPXal)); %
CP_RESPMAG_Y = (getval_t(2.0,TIMal, AVbCPYal))-
(getval_t(0.2,TIMal, AVbCPYal)); %
CP_RESPMAGb =
sqrt(((CP_RESPMAG_X.^2)+(CP_RESPMAG_Y.^2)));%avera
ge vector mag per subject
CP_RESPDIRb =
(atan2((CP_RESPMAG_Y),(CP_RESPMAG_X)).*180./pi);%a
verage resp direction per subject
CP_NORMRESPDIRb = CP_RESPDIRb + START_HEADb;

subCP_RESPMAG_X = (getval_t(2.0,TIMal,
subAVbCPXal))-(getval_t(0.2,TIMal, subAVbCPXal));
%trunk
subCP_RESPMAG_Y = (getval_t(2.0,TIMal,
subAVbCPYal))-(getval_t(0.2,TIMal, subAVbCPYal));
%trunk
subAVbCP_RESPMAGb =
sqrt(((subCP_RESPMAG_X.^2)+(subCP_RESPMAG_Y.^2)));
%average vector mag of collapsed av group response
subAVbCP_RESPDIRb =
(atan2((subCP_RESPMAG_Y),(subCP_RESPMAG_X)).*180./
pi);%average vector resp direction of collapsed av
group response
subAVbCP_NORMRESPDIRb = subAVbCP_RESPDIRb -
subAVSTART_HEADb;

%RESPONSE LATENCY CALCULATIONS
Fb_PEAKSL = max_int_t(0.1,0.4,TIMal, AVbFYal);

for n=1:17
    for m=1:p
        if Fb_PEAKSL(n,m)==2.105;
        Fb_PEAKSL(n,m)=NaN;
        end
    end
end

Fb_PEAKML = min_int_t(0.3,4.0,TIMal, AVbFYal);

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%CHAPTER 6 SENSORY PERTURBATION ANALYSIS SCRIPT
%ANALYSES ONE SENSORY MODALITY AT A TIME
%VIBRATION: 'HRvibTA' (FORWARDS), 'HRvibTS'
(BACKWARDS)
%MVS: 'HRmvs-' (FORWARDS), 'HRmvs+' (BACKWARDS)
%GVS: 'HRgvsl+' (FORWARDS), 'HRgvsr+' (BACKWARDS)
clc
clear all
[dirnum, trnum] = getcondir('HRvibTA', 'ALL');%
ENTER BACKWARDS COND NAMES
[dirnum,trnum] = con2sub(dirnum,trnum);
%KINEMATICS

l=size(trnum,2);

Number1=zeros(16,1:l);
for n=1:16
    count=0;
    for m=1:l
        if trnum(n,m)> 0.5;
            count=count+1;

        end
    Number1(n,1)=count;
    end
end
clear dirnum
clear trnum

[dirnum, trnum] = getcondir('HRvibTA,HRvibTS',
'ALL');%BACKWARDS, FORWARDS
[dirnum,trnum] = con2sub(dirnum,trnum);

l=size(trnum,2);

Number=zeros(16,1:l);
for n=1:16
    count=0;
    for m=1:l
        if trnum(n,m)> 0.5;
            count=count+1;

        end
    Number(n,1)=count;
    end
end
Number2=Number-Number1;

p=1:l; %How many total trial repeats are expected?

getxyzdir(dirnum,trnum);
clear z
getdatdir(dirnum,trnum,'TIMC, ADC25');

FRHEAD_X = dekin (x,1);
FRHEAD_Y = dekin (y,1);
BRHEAD_X = dekin (x,2);
BRHEAD_Y = dekin (y,2);
TRBACK_X = dekin (x,5);
TRBACK_Y = dekin (y,5);
TLBACK_X = dekin (x,6);
TLBACK_Y = dekin (y,6);
BRBACK_X = dekin (x,7);
BRBACK_Y = dekin (y,7);
BLBACK_X = dekin (x,8);
BLBACK_Y = dekin (y,8);

clear x
clear y
[TRBACK_X,TRBACK_Y,TLBACK_X,TLBACK_Y,BRBACK_X,BRBA
CK_Y,BLBACK_X,BLBACK_Y] =
filtMN(20,TIMC*200,TRBACK_X,TRBACK_Y,TLBACK_X,TLBA
CK_Y,BRBACK_X,BRBACK_Y,BLBACK_X,BLBACK_Y);
%filtfilt butter at 20Hz

vibOUT=subavg(0,2,TIMC,ADC25); %moving visual
scene output

for n=1:16
    for nn=(Number1(n,1)+1):Number
        [TRBACK_X(:,n,nn)]=(TRBACK_X(:,n,nn).*-1);
        [TRBACK_Y(:,n,nn)]=(TRBACK_Y(:,n,nn).*-1);
        [TLBACK_X(:,n,nn)]=(TLBACK_X(:,n,nn).*-1);
        [TLBACK_Y(:,n,nn)]=(TLBACK_Y(:,n,nn).*-1);
        [BRBACK_X(:,n,nn)]=(BRBACK_X(:,n,nn).*-1);
        [BRBACK_Y(:,n,nn)]=(BRBACK_Y(:,n,nn).*-1);
        [BLBACK_X(:,n,nn)]=(BLBACK_X(:,n,nn).*-1);
        [BLBACK_Y(:,n,nn)]=(BLBACK_Y(:,n,nn).*-1);
    end
end

position = cross_val_t(6,1.5,3.5,TIMC,vibOUT);
%this finds the threshold where the ADC starts to
rise above the baseline the answer refers to the
position of the value in the array

for n=1:16
     for m=1:l
        if position(n,m)==0;
           position(n,m) = 3.0;

        end

    end
end
    PERT = position; % this puts the threshold for
stim onset into time units
    saveevent(PERT);

[TIMal, TRBACK_Xal] = align_t(PERT,TIMC,
TRBACK_X);
[TIMal, TLBACK_Xal] = align_t(PERT,TIMC,
TLBACK_X);
[TIMal, BRBACK_Xal] = align_t(PERT,TIMC,
BRBACK_X);
[TIMal, BLBACK_Xal] = align_t(PERT,TIMC,
BLBACK_X);
[TIMal, TRBACK_Yal] = align_t(PERT,TIMC,
TRBACK_Y);
[TIMal, TLBACK_Yal] = align_t(PERT,TIMC,
TLBACK_Y);
[TIMal, BRBACK_Yal] = align_t(PERT,TIMC,
BRBACK_Y);
[TIMal, BLBACK_Yal] = align_t(PERT,TIMC,
BLBACK_Y);
[TIMal, FRHEAD_Xal] = align_t(PERT,TIMC,
FRHEAD_X);
[TIMal, BRHEAD_Xal] = align_t(PERT,TIMC,
BRHEAD_X);
[TIMal, FRHEAD_Yal] = align_t(PERT,TIMC,
FRHEAD_Y);
[TIMal, BRHEAD_Yal] = align_t(PERT,TIMC,
BRHEAD_Y);

%Average start head angle calculations
```

```
AVbBRHEAD_Xal=zeros(length(TIMal),16);
AVbBRHEAD_Yal=zeros(length(TIMal),16);
AVbFRHEAD_Xal=zeros(length(TIMal),16);
AVbFRHEAD_Yal=zeros(length(TIMal),16);

for n=1:16;
        counter=Number(n,1);
            [AVbBRHEAD_Xal(1:length(TIMal),n)] =

          (sum(BRHEAD_Xal(:,n,(1:counter)),3))./co
unter; %trunk
            [AVbBRHEAD_Yal(1:length(TIMal),n)] =

          (sum(BRHEAD_Yal(:,n,(1:counter)),3))./co
unter; %trunk
            [AVbFRHEAD_Xal(1:length(TIMal),n)] =

          (sum(FRHEAD_Xal(:,n,(1:counter)),3))./co
unter; %trunk
            [AVbFRHEAD_Yal(1:length(TIMal),n)] =

          (sum(FRHEAD_Yal(:,n,(1:counter)),3))./co
unter; %trunk
    end

for n=1:16;
    x1(n,1)=(NaNvaravg(0.9,0.0,TIMal,
AVbFRHEAD_Xal(:,n)))-
(NaNvaravg(0.9,0.0,TIMal,AVbBRHEAD_Xal(:,n)));
    y1(n,1)=(NaNvaravg(0.9,0.0,TIMal,
AVbFRHEAD_Yal(:,n)))-
(NaNvaravg(0.9,0.0,TIMal,AVbBRHEAD_Yal(:,n)));
    START_HEADb(n,1) =
(atan2(y1(n),x1(n)).*180./pi)-90;%Need to subtract
90 here because the markers are at 90 degs to the
nose direction
end



%Average trunk sway response calculations
CBACK_Xal = NaNvaravg(TRBACK_Xal, TLBACK_Xal,
BRBACK_Xal, BLBACK_Xal);
CBACK_Yal = NaNvaravg(TRBACK_Yal, TLBACK_Yal,
BRBACK_Yal, BLBACK_Yal);

[CBACK_Xal] = subavg(0.0,0.0,TIMal,CBACK_Xal);
%trunk
[CBACK_Yal] = subavg(0.0,0.0,TIMal,CBACK_Yal);
%trunk

AVbBACK_Xal=zeros(1:length(TIMal),16);
AVbBACK_Yal=zeros(1:length(TIMal),16);

    for n=1:16;
      counter=Number(n,1);
    [AVbBACK_Xal(1:length(TIMal),n)] =
          (sum(CBACK_Xal(:,n,(1:counter)),3))./cou
nter; %trunk
    [AVbBACK_Yal(1:length(TIMal),n)] =
          (sum(CBACK_Yal(:,n,(1:counter)),3))./cou
nter; %trunk
    end

GrandAvTXmean = [mean(AVbBACK_Xal')]';
GrandAvTYmean = [mean(AVbBACK_Yal')]';
GrandAvTXsd = [std(AVbBACK_Xal')]';
GrandAvTYsd = [std(AVbBACK_Yal')]';

T_RESPMAG_Xhab = (getval_t(2.0,TIMal, CBACK_Xal))-
(getval_t(0.2,TIMal, CBACK_Xal)); %trunk
T_RESPMAG_Yhab = (getval_t(2.0,TIMal, CBACK_Yal))-
(getval_t(0.2,TIMal, CBACK_Yal)); %trunk
T_RESPMAGhab =
sqrt(((T_RESPMAG_Xhab.^2)+(T_RESPMAG_Yhab.^2)));%a
verage vector mag per subject

THab=zeros(16,100);
for m=1:16
    for n=1:10
        THab(m,trnum(m,n))= T_RESPMAGhab(m,n);
    end
end

T_RESPMAG_X = (getval_t(2.0,TIMal, AVbBACK_Xal))-
(getval_t(0.2,TIMal, AVbBACK_Xal)); %trunk
T_RESPMAG_Y = (getval_t(2.0,TIMal, AVbBACK_Yal))-
(getval_t(0.2,TIMal, AVbBACK_Yal)); %trunk
T_RESPMAGb =
sqrt(((T_RESPMAG_X.^2)+(T_RESPMAG_Y.^2)));%average
vector mag per subject
T_RESPDIRb =
(atan2((T_RESPMAG_Y),(T_RESPMAG_X)).*180./pi);%ave
rage resp direction per subject
T_NORMRESPDIRb = T_RESPDIRb + START_HEADb;

%FORCES
getdatdir(dirnum,trnum,'TIMC,FP1X,FP1Y,FP1Z,CP1X,C
P1Y');

[FP1X,FP1Y,FP1Z] =
filtMN(20,TIMC*200,FP1X,FP1Y,FP1Z); %filtfilt
butter at 20Hz

FX = FP1X; FY = FP1Y; FZ = FP1Z; %compute total
force

for n=1:16
    for nn=(Number1(n,1)+1):Number
        [FX(:,n,nn)]=(FX(:,n,nn).*-1);
        [FY(:,n,nn)]=(FY(:,n,nn).*-1);
    end
end


[TIMal, FXal] = align_t(PERT,TIMC, FX);
[TIMal, FYal] = align_t(PERT,TIMC, FY);

[FXal] = subavg(0.0,0.0,TIMal,FXal);
[FYal] = subavg(0.0,0.0,TIMal,FYal);

AVbFXal=zeros((length(TIMal)),16);
AVbFYal=zeros((length(TIMal)),16);

    for n=1:16
        counter=Number(n,1);
    [AVbFXal(1:length(TIMal),n)] =
(sum(FXal(:,n,(1:counter)),3))./counter; %trunk
    [AVbFYal(1:length(TIMal),n)] =
(sum(FYal(:,n,(1:counter)),3))./counter; %trunk
    [subAVbFXal] = (sum(AVbFXal,2))./16; %trunk
    [subAVbFYal] = (sum(AVbFYal,2))./16; %trunk
    end
GrandAvFXmean = [mean(AVbFXal')]';
GrandAvFYmean = [mean(AVbFYal')]';
GrandAvFXsd = [std(AVbFXal')]';
GrandAvFYsd = [std(AVbFYal')]';

F_RESPMAG_Xhab = (getval_t(0.4,TIMal, FXal))-
(getval_t(0.2,TIMal, FXal)); %trunk
F_RESPMAG_Yhab = (getval_t(0.4,TIMal, FYal))-
(getval_t(0.2,TIMal, FYal)); %trunk
F_RESPMAGhab =
sqrt(((F_RESPMAG_Xhab.^2)+(F_RESPMAG_Yhab.^2)));%a
verage vector mag per subject

FHab=zeros(16,100);
for m=1:16
    for n=1:10
        FHab(m,trnum(m,n))= F_RESPMAGhab(m,n);
    end
end

F_RESPMAG_X = (getval_t(0.4,TIMal, AVbFXal))-
(getval_t(0.2,TIMal, AVbFXal)); %trunk
F_RESPMAG_Y = (getval_t(0.4,TIMal, AVbFYal))-
(getval_t(0.2,TIMal, AVbFYal)); %trunk
F_RESPMAGb =
sqrt(((F_RESPMAG_X.^2)+(F_RESPMAG_Y.^2)));%average
vector mag per subject
F_RESPDIRb =
(atan2((F_RESPMAG_Y),(F_RESPMAG_X)).*180./pi);%ave
rage resp direction per subject
F_NORMRESPDIRb = F_RESPDIRb + START_HEADb;%average
normalised resp direction per subject

%CENTRE OF PRESSURE DATA

[CP1X,CP1Y] = filtMN(20,TIMC*200,CP1X,CP1Y);
%filtfilt butter at 20Hz

for n=1:16
    for nn=(Number1(n,1)+1):Number
        [CP1X(:,n,nn)]=(CP1X(:,n,nn).*-1);
        [CP1Y(:,n,nn)]=(CP1Y(:,n,nn).*-1);
    end
end

[TIMal, CPXal] = align_t(PERT,TIMC, CP1X);
[TIMal, CPYal] = align_t(PERT,TIMC, CP1Y);

[CPXal] = subavg(0.0,0.0,TIMal,CPXal);
[CPYal] = subavg(0.0,0.0,TIMal,CPYal);

AVbCPXal=zeros((length(TIMal)),16);
AVbCPYal=zeros((length(TIMal)),16);

    for n=1:16;
        counter=Number(n,1);
            [AVbCPXal(1:length(TIMal),n)] =
(sum(CPXal(:,n,(1:counter)),3))./counter;%
            [AVbCPYal(1:length(TIMal),n)] =
(sum(CPYal(:,n,(1:counter)),3))./counter;%
            [subAVbCPXal] =
(sum(AVbCPXal,2))./counter; %Mean group traces
            [subAVbCPYal] =
(sum(AVbCPYal,2))./counter; %
    end
GrandAvCPXmean = [mean(AVbCPXal')]';
GrandAvCPYmean = [mean(AVbCPYal')]';
GrandAvCPXsd = [std(AVbCPXal')]';
GrandAvCPYsd = [std(AVbCPYal')]';

CP_RESPMAG_Xhab = (getval_t(2.0,TIMal, CPXal))-
(getval_t(0.2,TIMal, CPXal)); %trunk
CP_RESPMAG_Yhab = (getval_t(2.0,TIMal, CPYal))-
(getval_t(0.2,TIMal, CPYal)); %trunk
CP_RESPMAGhab =
sqrt(((CP_RESPMAG_Xhab.^2)+(CP_RESPMAG_Yhab.^2)));
%average vector mag per subject

CPHab=zeros(16,100);
```

```
for m=1:16
    for n=1:10
        CPHab(m,trnum(m,n))= F_RESPMAGhab(m,n);
    end
end

CP_RESPMAG_X = (getval_t(2.0,TIMal, AVbCPXal))-
(getval_t(0.2,TIMal, AVbCPXal)); %
CP_RESPMAG_Y = (getval_t(2.0,TIMal, AVbCPYal))-
(getval_t(0.2,TIMal, AVbCPYal)); %
CP_RESPMAGb =
sqrt(((CP_RESPMAG_X.^2)+(CP_RESPMAG_Y.^2)));%avera
ge vector mag per subject
CP_RESPDIRb =
(atan2((CP_RESPMAG_Y),(CP_RESPMAG_X)).*180./pi);%a
verage resp direction per subject
CP_NORMRESPDIRb = CP_RESPDIRb + START_HEADb;

subCP_RESPMAG_X = (getval_t(2.0,TIMal,
subAVbCPXal))-(getval_t(0.2,TIMal, subAVbCPXal));
%trunk
subCP_RESPMAG_Y = (getval_t(2.0,TIMal,
subAVbCPYal))-(getval_t(0.2,TIMal, subAVbCPYal));
%trunk
subAVbCP_RESPMAGb =
sqrt(((subCP_RESPMAG_X.^2)+(subCP_RESPMAG_Y.^2)));
%average vector mag of collapsed av group response
subAVbCP_RESPDIRb =
(atan2((subCP_RESPMAG_Y),(subCP_RESPMAG_X)).*180./
pi);%average vector resp direction of collapsed av
group response
subAVbCP_NORMRESPDIRb = subAVbCP_RESPDIRb -
subAVSTART_HEADb;

%RESPONSE LATENCY CALCULATIONS
Fb_PEAKSL = max_int_t(0.1,0.4,TIMal, AVbFXal);

for n=1:12
    for m=1:p
        if Fb_PEAKSL(n,m)==0.105;
        Fb_PEAKSL(n,m)=NaN;
        end
    end
end

Fb_PEAKML = min_int_t(0.2,1.5,TIMal, AVbFXal);
Tb_ONSETML = max_int_t(0.3,2.0,TIMal,
AVbBACK_Xal);
Tb_PEAKML = min_int_t(0.5,3.0,TIMal, AVbBACK_Xal);
```

APPENDIX 4: V3D PIPELINES

```
Import_Codamotion_Files
! /FILE_NAME=
! /CONVERTED_FILE_NAME=
;

Explicit
/EVENT_NAME=Start
! /FRAME=
/TIME=1
;

Explicit
/EVENT_NAME=Stop
! /FRAME=
/TIME=40
;

Explicit
/EVENT_NAME=Avoid
! /FRAME=
/TIME=0
;

Explicit
/EVENT_NAME=Resume
! /FRAME=
/TIME=0
;

Interpolate
/SIGNAL_TYPES=TARGET
! /SIGNAL_NAMES=
! /SIGNAL_FOLDER=ORIGINAL
! /RESULT_SUFFIX=
! /RESULT_FOLDER=PROCESSED
/MAXIMUM_GAP=40
! /NUM_FIT=3
! /POLYNOMIAL_ORDER=3
;

Lowpass_Filter
/SIGNAL_TYPES=TARGET
! /SIGNAL_NAMES=
/SIGNAL_FOLDER=PROCESSED
! /RESULT_SUFFIX=
! /RESULT_FOLDER=PROCESSED
! /FILTER_CLASS=BUTTERWORTH
/FREQUENCY_CUTOFF=6
! /NUM_REFLECTED=6
! /TOTAL_BUFFER_SIZE=6
! /NUM_BIDIRECTIONAL_PASSES=1
;

! Recalc used here so that landmark signals will
be recrated using processed targets before they
are used in subsequent functions
Recalc
;

First_Derivative
/SIGNAL_TYPES=TARGET
! /SIGNAL_NAMES=
/SIGNAL_FOLDER=PROCESSED
! /RESULT_SUFFIX=
/RESULT_FOLDER=VELOCITY
;

First_Derivative
/SIGNAL_TYPES=LANDMARK
! /SIGNAL_NAMES=
/SIGNAL_FOLDER=ORIGINAL
! /RESULT_SUFFIX=
/RESULT_FOLDER=VELOCITY
;

Second_Derivative
/SIGNAL_TYPES=TARGET
! /SIGNAL_NAMES=
/SIGNAL_FOLDER=PROCESSED
! /RESULT_SUFFIX=
/RESULT_FOLDER=ACCELERATION
;

Second_Derivative
/SIGNAL_TYPES=LANDMARK
! /SIGNAL_NAMES=
/SIGNAL_FOLDER=ORIGINAL
! /RESULT_SUFFIX=
/RESULT_FOLDER=ACCELERATION
;

Compute_Planar_Angle
/SIGNAL_TYPES=LANDMARK+LANDMARK+LANDMARK+LANDMARK
/SIGNAL_NAMES=_REYE+_REAR+LAB_ORIGIN+LAB_Y
/SIGNAL_FOLDER=ORIGINAL+ORIGINAL+ORIGINAL+ORIGINAL
/RESULT_NAME=A2d_Reid'sR_YZ
! /RESULT_FOLDER=PROCESSED
/COMPUTE_3PT_ANGLE=FALSE
! /REFERENCE_SEGMENT=LAB
/PROJECTION_PLANE=YZ
/USE_RIGHT_HAND_RULE=FALSE
/USE_0_TO_360_DEGREES=FALSE
;

Compute_Planar_Angle
/SIGNAL_TYPES=LANDMARK+LANDMARK+LANDMARK+LANDMARK
/SIGNAL_NAMES=_LEYE+_LEAR+LAB_ORIGIN+LAB_Y
/SIGNAL_FOLDER=ORIGINAL+ORIGINAL+ORIGINAL+ORIGINAL
/RESULT_NAME=A2d_Reid'sL_YZ
! /RESULT_FOLDER=PROCESSED
/COMPUTE_3PT_ANGLE=FALSE
! /REFERENCE_SEGMENT=LAB
/PROJECTION_PLANE=YZ
/USE_RIGHT_HAND_RULE=FALSE
/USE_0_TO_360_DEGREES=FALSE
;

Compute_Planar_Angle
/SIGNAL_TYPES=LANDMARK+LANDMARK+LANDMARK+LANDMARK
/SIGNAL_NAMES=_RGH+_L4+LAB_ORIGIN+LAB_Z
/SIGNAL_FOLDER=ORIGINAL+ORIGINAL+ORIGINAL+ORIGINAL
/RESULT_NAME=A2d_ThoraxR_YZ
! /RESULT_FOLDER=PROCESSED
/COMPUTE_3PT_ANGLE=FALSE
! /REFERENCE_SEGMENT=LAB
/PROJECTION_PLANE=YZ
/USE_RIGHT_HAND_RULE=FALSE
/USE_0_TO_360_DEGREES=FALSE
;

Compute_Planar_Angle
/SIGNAL_TYPES=LANDMARK+LANDMARK+LANDMARK+LANDMARK
/SIGNAL_NAMES=_LGH+_L4+LAB_ORIGIN+LAB_Z
/SIGNAL_FOLDER=ORIGINAL+ORIGINAL+ORIGINAL+ORIGINAL
/RESULT_NAME=A2d_ThoraxL_YZ
! /RESULT_FOLDER=PROCESSED
/COMPUTE_3PT_ANGLE=FALSE
! /REFERENCE_SEGMENT=LAB
/PROJECTION_PLANE=YZ
/USE_RIGHT_HAND_RULE=FALSE
/USE_0_TO_360_DEGREES=FALSE
;

Compute_Planar_Angle
/SIGNAL_TYPES=LANDMARK+LANDMARK+LANDMARK+LANDMARK
/SIGNAL_NAMES=_RIC+_RGT+LAB_ORIGIN+LAB_Z
/SIGNAL_FOLDER=ORIGINAL+ORIGINAL+ORIGINAL+ORIGINAL
/RESULT_NAME=A2d_PelvisR_YZ
! /RESULT_FOLDER=PROCESSED
/COMPUTE_3PT_ANGLE=FALSE
! /REFERENCE_SEGMENT=LAB
/PROJECTION_PLANE=YZ
/USE_RIGHT_HAND_RULE=FALSE
/USE_0_TO_360_DEGREES=FALSE
;

Compute_Planar_Angle
/SIGNAL_TYPES=LANDMARK+LANDMARK+LANDMARK+LANDMARK
/SIGNAL_NAMES=_LIC+_LGT+LAB_ORIGIN+LAB_Z
/SIGNAL_FOLDER=ORIGINAL+ORIGINAL+ORIGINAL+ORIGINAL
/RESULT_NAME=A2d_PelvisL_YZ
! /RESULT_FOLDER=PROCESSED
/COMPUTE_3PT_ANGLE=FALSE
! /REFERENCE_SEGMENT=LAB
/PROJECTION_PLANE=YZ
/USE_RIGHT_HAND_RULE=FALSE
/USE_0_TO_360_DEGREES=FALSE
;

Compute_Planar_Angle
/SIGNAL_TYPES=LANDMARK+LANDMARK+LANDMARK+LANDMARK
/SIGNAL_NAMES=_RGT+_RLK+LAB_ORIGIN+LAB_Z
/SIGNAL_FOLDER=ORIGINAL+ORIGINAL+ORIGINAL+ORIGINAL
/RESULT_NAME=A2d_ThighR_YZ
! /RESULT_FOLDER=PROCESSED
/COMPUTE_3PT_ANGLE=FALSE
! /REFERENCE_SEGMENT=LAB
/PROJECTION_PLANE=YZ
/USE_RIGHT_HAND_RULE=FALSE
/USE_0_TO_360_DEGREES=FALSE
;

Compute_Planar_Angle
/SIGNAL_TYPES=LANDMARK+LANDMARK+LANDMARK+LANDMARK
/SIGNAL_NAMES=_LGT+_LLK+LAB_ORIGIN+LAB_Z
/SIGNAL_FOLDER=ORIGINAL+ORIGINAL+ORIGINAL+ORIGINAL
/RESULT_NAME=A2d_ThighL_YZ
! /RESULT_FOLDER=PROCESSED
/COMPUTE_3PT_ANGLE=FALSE
! /REFERENCE_SEGMENT=LAB
/PROJECTION_PLANE=YZ
/USE_RIGHT_HAND_RULE=FALSE
/USE_0_TO_360_DEGREES=FALSE
;
```

```
Compute_Planar_Angle
/SIGNAL_TYPES=LANDMARK+TARGET+LANDMARK+LANDMARK
/SIGNAL_NAMES=_RLK+RLFIB+LAB_ORIGIN+LAB_Z
/SIGNAL_FOLDER=ORIGINAL+PROCESSED+ORIGINAL+ORIGINA
L
/RESULT_NAME=A2d_ShankR_YZ
! /RESULT_FOLDER=PROCESSED
/COMPUTE_3PT_ANGLE=FALSE
! /REFERENCE_SEGMENT=LAB
/PROJECTION_PLANE=YZ
/USE_RIGHT_HAND_RULE=FALSE
/USE_0_TO_360_DEGREES=FALSE
;

Compute_Planar_Angle
/SIGNAL_TYPES=LANDMARK+TARGET+LANDMARK+LANDMARK
/SIGNAL_NAMES=_LLK+LLFIB+LAB_ORIGIN+LAB_Z
/SIGNAL_FOLDER=ORIGINAL+PROCESSED+ORIGINAL+ORIGINA
L
/RESULT_NAME=A2d_ShankL_YZ
! /RESULT_FOLDER=PROCESSED
/COMPUTE_3PT_ANGLE=FALSE
! /REFERENCE_SEGMENT=LAB
/PROJECTION_PLANE=YZ
/USE_RIGHT_HAND_RULE=FALSE
/USE_0_TO_360_DEGREES=FALSE
;

Compute_Planar_Angle
/SIGNAL_TYPES=LANDMARK+LANDMARK+LANDMARK+LANDMARK
/SIGNAL_NAMES=_RHALLUX+_RCALC+LAB_ORIGIN+LAB_Y
/SIGNAL_FOLDER=ORIGINAL+ORIGINAL+ORIGINAL+ORIGINAL
/RESULT_NAME=A2d_FootR_YZ
! /RESULT_FOLDER=PROCESSED
/COMPUTE_3PT_ANGLE=FALSE
! /REFERENCE_SEGMENT=LAB
/PROJECTION_PLANE=YZ
/USE_RIGHT_HAND_RULE=FALSE
/USE_0_TO_360_DEGREES=FALSE
;

Compute_Planar_Angle
/SIGNAL_TYPES=LANDMARK+LANDMARK+LANDMARK+LANDMARK
/SIGNAL_NAMES=_LHALLUX+_LCALC+LAB_ORIGIN+LAB_Y
/SIGNAL_FOLDER=ORIGINAL+ORIGINAL+ORIGINAL+ORIGINAL
/RESULT_NAME=A2d_FootL_YZ
! /RESULT_FOLDER=PROCESSED
/COMPUTE_3PT_ANGLE=FALSE
! /REFERENCE_SEGMENT=LAB
/PROJECTION_PLANE=YZ
/USE_RIGHT_HAND_RULE=FALSE
/USE_0_TO_360_DEGREES=FALSE
;

Compute_Planar_Angle
/SIGNAL_TYPES=LANDMARK+LANDMARK+LANDMARK+LANDMARK
/SIGNAL_NAMES=_LEAR+_REAR+LAB_X+LAB_ORIGIN
/SIGNAL_FOLDER=ORIGINAL+ORIGINAL+ORIGINAL+ORIGINAL
/RESULT_NAME=A2d_Head_XZ
! /RESULT_FOLDER=PROCESSED
/COMPUTE_3PT_ANGLE=FALSE
! /REFERENCE_SEGMENT=LAB
/PROJECTION_PLANE=XZ
/USE_RIGHT_HAND_RULE=FALSE
/USE_0_TO_360_DEGREES=FALSE
;

Compute_Planar_Angle
/SIGNAL_TYPES=LANDMARK+LANDMARK+LANDMARK+LANDMARK
/SIGNAL_NAMES=_LGH+_RGH+LAB_X+LAB_ORIGIN
/SIGNAL_FOLDER=ORIGINAL+ORIGINAL+ORIGINAL+ORIGINAL
/RESULT_NAME=A2d_Thorax_XZ
! /RESULT_FOLDER=PROCESSED
/COMPUTE_3PT_ANGLE=FALSE
! /REFERENCE_SEGMENT=LAB
/PROJECTION_PLANE=XZ
/USE_RIGHT_HAND_RULE=FALSE
/USE_0_TO_360_DEGREES=FALSE
;

Compute_Planar_Angle
/SIGNAL_TYPES=LANDMARK+LANDMARK+LANDMARK+LANDMARK
/SIGNAL_NAMES=_LIC+_RIC+LAB_X+LAB_ORIGIN
/SIGNAL_FOLDER=ORIGINAL+ORIGINAL+ORIGINAL+ORIGINAL
/RESULT_NAME=A2d_Pelvis_XZ
! /RESULT_FOLDER=PROCESSED
/COMPUTE_3PT_ANGLE=FALSE
! /REFERENCE_SEGMENT=LAB
/PROJECTION_PLANE=XZ
/USE_RIGHT_HAND_RULE=FALSE
/USE_0_TO_360_DEGREES=FALSE
;

Compute_Planar_Angle
/SIGNAL_TYPES=LANDMARK+LANDMARK+LANDMARK+LANDMARK
/SIGNAL_NAMES=_LLK+_RLK+LAB_X+LAB_ORIGIN
/SIGNAL_FOLDER=ORIGINAL+ORIGINAL+ORIGINAL+ORIGINAL
/RESULT_NAME=A2d_Shanks_XZ
! /RESULT_FOLDER=PROCESSED
/COMPUTE_3PT_ANGLE=FALSE
! /REFERENCE_SEGMENT=LAB
/PROJECTION_PLANE=XZ
/USE_RIGHT_HAND_RULE=FALSE
/USE_0_TO_360_DEGREES=FALSE
;
```

```
Compute_Planar_Angle
/SIGNAL_TYPES=LANDMARK+LANDMARK+LANDMARK+LANDMARK
/SIGNAL_NAMES=_LCALC+_RCALC+LAB_X+LAB_ORIGIN
/SIGNAL_FOLDER=ORIGINAL+ORIGINAL+ORIGINAL+ORIGINAL
/RESULT_NAME=A2d_Feet_XZ
! /RESULT_FOLDER=PROCESSED
/COMPUTE_3PT_ANGLE=FALSE
! /REFERENCE_SEGMENT=LAB
/PROJECTION_PLANE=XZ
/USE_RIGHT_HAND_RULE=FALSE
/USE_0_TO_360_DEGREES=FALSE
;

Compute_Planar_Angle
/SIGNAL_TYPES=LANDMARK+LANDMARK+LANDMARK+LANDMARK
/SIGNAL_NAMES=_RGT+_RLK+LAB_ORIGIN+LAB_Z
/SIGNAL_FOLDER=ORIGINAL+ORIGINAL+ORIGINAL+ORIGINAL
/RESULT_NAME=A2d_ThighR_XZ
! /RESULT_FOLDER=PROCESSED
/COMPUTE_3PT_ANGLE=FALSE
! /REFERENCE_SEGMENT=LAB
/PROJECTION_PLANE=XZ
/USE_RIGHT_HAND_RULE=FALSE
/USE_0_TO_360_DEGREES=FALSE
;

Compute_Planar_Angle
/SIGNAL_TYPES=LANDMARK+LANDMARK+LANDMARK+LANDMARK
/SIGNAL_NAMES=_LGT+_LLK+LAB_ORIGIN+LAB_Z
/SIGNAL_FOLDER=ORIGINAL+ORIGINAL+ORIGINAL+ORIGINAL
/RESULT_NAME=A2d_ThighL_XZ
! /RESULT_FOLDER=PROCESSED
/COMPUTE_3PT_ANGLE=FALSE
! /REFERENCE_SEGMENT=LAB
/PROJECTION_PLANE=XZ
/USE_RIGHT_HAND_RULE=FALSE
/USE_0_TO_360_DEGREES=FALSE
;

Compute_Planar_Angle
/SIGNAL_TYPES=LANDMARK+LANDMARK+LANDMARK+LANDMARK
/SIGNAL_NAMES=_RMK+_RLK+LAB_X+LAB_ORIGIN
/SIGNAL_FOLDER=ORIGINAL+ORIGINAL+ORIGINAL+ORIGINAL
/RESULT_NAME=A2d_ShankR_XZ
! /RESULT_FOLDER=PROCESSED
/COMPUTE_3PT_ANGLE=FALSE
! /REFERENCE_SEGMENT=LAB
/PROJECTION_PLANE=XZ
/USE_RIGHT_HAND_RULE=FALSE
/USE_0_TO_360_DEGREES=FALSE
;

Compute_Planar_Angle
/SIGNAL_TYPES=LANDMARK+LANDMARK+LANDMARK+LANDMARK
/SIGNAL_NAMES=_LLK+_LMK+LAB_X+LAB_ORIGIN
/SIGNAL_FOLDER=ORIGINAL+ORIGINAL+ORIGINAL+ORIGINAL
/RESULT_NAME=A2d_ShankL_XZ
! /RESULT_FOLDER=PROCESSED
/COMPUTE_3PT_ANGLE=FALSE
! /REFERENCE_SEGMENT=LAB
/PROJECTION_PLANE=XZ
/USE_RIGHT_HAND_RULE=FALSE
/USE_0_TO_360_DEGREES=FALSE
;

Compute_Planar_Angle
/SIGNAL_TYPES=LANDMARK+TARGET+LANDMARK+LANDMARK
/SIGNAL_NAMES=_RMT1+RHEAD5TH+LAB_X+LAB_ORIGIN
/SIGNAL_FOLDER=ORIGINAL+PROCESSED+ORIGINAL+ORIGINA
L
/RESULT_NAME=A2d_FootR_XZ
! /RESULT_FOLDER=PROCESSED
/COMPUTE_3PT_ANGLE=FALSE
! /REFERENCE_SEGMENT=LAB
/PROJECTION_PLANE=XZ
/USE_RIGHT_HAND_RULE=FALSE
/USE_0_TO_360_DEGREES=FALSE
;

Compute_Planar_Angle
/SIGNAL_TYPES=TARGET+LANDMARK+LANDMARK+LANDMARK
/SIGNAL_NAMES=LHEAD5TH+_LMT1+LAB_X+LAB_ORIGIN
/SIGNAL_FOLDER=PROCESSED+ORIGINAL+ORIGINAL+ORIGINA
L
/RESULT_NAME=A2d_FootL_XZ
! /RESULT_FOLDER=PROCESSED
/COMPUTE_3PT_ANGLE=FALSE
! /REFERENCE_SEGMENT=LAB
/PROJECTION_PLANE=XZ
/USE_RIGHT_HAND_RULE=FALSE
/USE_0_TO_360_DEGREES=FALSE
;

Compute_Planar_Angle
/SIGNAL_TYPES=LANDMARK+LANDMARK+LANDMARK+LANDMARK
/SIGNAL_NAMES=_REYE+_REAR+_C7+_L4
/SIGNAL_FOLDER=ORIGINAL+ORIGINAL+ORIGINAL+ORIGINAL
/RESULT_NAME=A2d_Head On Thorax Angle_YZ
! /RESULT_FOLDER=PROCESSED
/COMPUTE_3PT_ANGLE=FALSE
```

```
! /REFERENCE_SEGMENT=LAB
/PROJECTION_PLANE=YZ
/USE_RIGHT_HAND_RULE=FALSE
/USE_0_TO_360_DEGREES=TRUE
;

Compute_Planar_Angle
/SIGNAL_TYPES=LANDMARK+LANDMARK+LANDMARK+LANDMARK
/SIGNAL_NAMES=_C7+_L4+_RIC+_RGT
/SIGNAL_FOLDER=ORIGINAL+ORIGINAL+ORIGINAL+ORIGINAL
/RESULT_NAME=A2d_Thorax on Pelvis Angle_YZ
! /RESULT_FOLDER=PROCESSED
/COMPUTE_3PT_ANGLE=FALSE
! /REFERENCE_SEGMENT=LAB
/PROJECTION_PLANE=YZ
/USE_RIGHT_HAND_RULE=FALSE
/USE_0_TO_360_DEGREES=TRUE
;

Compute_Planar_Angle
/SIGNAL_TYPES=LANDMARK+LANDMARK+LANDMARK+LANDMARK
/SIGNAL_NAMES=_RIC+_RGT+_RGT+_RLK
/SIGNAL_FOLDER=ORIGINAL+ORIGINAL+ORIGINAL+ORIGINAL
/RESULT_NAME=A2d_Right Hip Angle_YZ
! /RESULT_FOLDER=PROCESSED
/COMPUTE_3PT_ANGLE=FALSE
! /REFERENCE_SEGMENT=LAB
/PROJECTION_PLANE=YZ
/USE_RIGHT_HAND_RULE=FALSE
/USE_0_TO_360_DEGREES=TRUE
;

Compute_Planar_Angle
/SIGNAL_TYPES=LANDMARK+LANDMARK+LANDMARK+LANDMARK
/SIGNAL_NAMES=_LIC+_LGT+_LGT+_LLK
/SIGNAL_FOLDER=ORIGINAL+ORIGINAL+ORIGINAL+ORIGINAL
/RESULT_NAME=A2d_Left Hip Angle_YZ
! /RESULT_FOLDER=PROCESSED
/COMPUTE_3PT_ANGLE=FALSE
! /REFERENCE_SEGMENT=LAB
/PROJECTION_PLANE=YZ
/USE_RIGHT_HAND_RULE=FALSE
/USE_0_TO_360_DEGREES=TRUE
;

Compute_Planar_Angle
/SIGNAL_TYPES=LANDMARK+LANDMARK+LANDMARK+TARGET
/SIGNAL_NAMES=_RGT+_RLK+_RLK+RLFIB
/SIGNAL_FOLDER=ORIGINAL+ORIGINAL+ORIGINAL+PROCESSE
D
/RESULT_NAME=A2d_Right Knee Angle_YZ
! /RESULT_FOLDER=PROCESSED
/COMPUTE_3PT_ANGLE=FALSE
! /REFERENCE_SEGMENT=LAB
/PROJECTION_PLANE=YZ
/USE_RIGHT_HAND_RULE=FALSE
/USE_0_TO_360_DEGREES=TRUE
;

Compute_Planar_Angle
/SIGNAL_TYPES=LANDMARK+LANDMARK+LANDMARK+TARGET
/SIGNAL_NAMES=_LGT+_LLK+_LLK+LLFIB
/SIGNAL_FOLDER=ORIGINAL+ORIGINAL+ORIGINAL+PROCESSE
D
/RESULT_NAME=A2d_Left Knee Angle_YZ
! /RESULT_FOLDER=PROCESSED
/COMPUTE_3PT_ANGLE=FALSE
! /REFERENCE_SEGMENT=LAB
/PROJECTION_PLANE=YZ
/USE_RIGHT_HAND_RULE=FALSE
/USE_0_TO_360_DEGREES=TRUE
;

Compute_Planar_Angle
/SIGNAL_TYPES=LANDMARK+TARGET+LANDMARK+LANDMARK
/SIGNAL_NAMES=_RLK+RLFIB+_RCALC+_RHALLUX
/SIGNAL_FOLDER=ORIGINAL+PROCESSED+ORIGINAL+ORIGINA
L
/RESULT_NAME=A2d_Right Ankle Angle_YZ
! /RESULT_FOLDER=PROCESSED
/COMPUTE_3PT_ANGLE=FALSE
! /REFERENCE_SEGMENT=LAB
/PROJECTION_PLANE=YZ
/USE_RIGHT_HAND_RULE=FALSE
/USE_0_TO_360_DEGREES=TRUE
;

Compute_Planar_Angle
/SIGNAL_TYPES=LANDMARK+TARGET+LANDMARK+LANDMARK
/SIGNAL_NAMES=_LLK+LLFIB+_LCALC+_LHALLUX
/SIGNAL_FOLDER=ORIGINAL+PROCESSED+ORIGINAL+ORIGINA
L
/RESULT_NAME=A2d_Left Ankle Angle_YZ
! /RESULT_FOLDER=PROCESSED
/COMPUTE_3PT_ANGLE=FALSE
! /REFERENCE_SEGMENT=LAB
/PROJECTION_PLANE=YZ
/USE_RIGHT_HAND_RULE=FALSE
/USE_0_TO_360_DEGREES=TRUE
;

Compute_Planar_Angle
/SIGNAL_TYPES=LANDMARK+LANDMARK+LANDMARK+LANDMARK
/SIGNAL_NAMES=_LEYE+_REYE+_RGH+_LGH
/SIGNAL_FOLDER=ORIGINAL+ORIGINAL+ORIGINAL+ORIGINAL
/RESULT_NAME=A2d_Head on Thorax Angle_XZ
! /RESULT_FOLDER=PROCESSED
/COMPUTE_3PT_ANGLE=FALSE
! /REFERENCE_SEGMENT=LAB
/PROJECTION_PLANE=XZ
/USE_RIGHT_HAND_RULE=FALSE
/USE_0_TO_360_DEGREES=FALSE
;

Compute_Planar_Angle
/SIGNAL_TYPES=LANDMARK+LANDMARK+LANDMARK+LANDMARK
/SIGNAL_NAMES=_LGH+_RGH+_RIC+_LIC
/SIGNAL_FOLDER=ORIGINAL+ORIGINAL+ORIGINAL+ORIGINAL
/RESULT_NAME=A2d_Thorax on Pelvis Angle_XZ
! /RESULT_FOLDER=PROCESSED
/COMPUTE_3PT_ANGLE=FALSE
! /REFERENCE_SEGMENT=LAB
/PROJECTION_PLANE=XZ
/USE_RIGHT_HAND_RULE=FALSE
/USE_0_TO_360_DEGREES=FALSE
;

Compute_Planar_Angle
/SIGNAL_TYPES=LANDMARK+LANDMARK+LANDMARK+LANDMARK
/SIGNAL_NAMES=_RIC+_RGT+_RLK+_RGT
/SIGNAL_FOLDER=ORIGINAL+ORIGINAL+ORIGINAL+ORIGINAL
/RESULT_NAME=A2d_Right Hip Angle_XZ
! /RESULT_FOLDER=PROCESSED
/COMPUTE_3PT_ANGLE=FALSE
! /REFERENCE_SEGMENT=LAB
/PROJECTION_PLANE=XZ
/USE_RIGHT_HAND_RULE=FALSE
/USE_0_TO_360_DEGREES=FALSE
;

Compute_Planar_Angle
/SIGNAL_TYPES=LANDMARK+LANDMARK+LANDMARK+LANDMARK
/SIGNAL_NAMES=_LIC+_LGT+_LLK+_LGT
/SIGNAL_FOLDER=ORIGINAL+ORIGINAL+ORIGINAL+ORIGINAL
/RESULT_NAME=A2d_Left Hip Angle_XZ
! /RESULT_FOLDER=PROCESSED
/COMPUTE_3PT_ANGLE=FALSE
! /REFERENCE_SEGMENT=LAB
/PROJECTION_PLANE=XZ
/USE_RIGHT_HAND_RULE=FALSE
/USE_0_TO_360_DEGREES=FALSE
;

Compute_Planar_Angle
/SIGNAL_TYPES=LANDMARK+LANDMARK+TARGET+LANDMARK
/SIGNAL_NAMES=_RGT+_RLK+RLFIB+_RLK
/SIGNAL_FOLDER=ORIGINAL+ORIGINAL+PROCESSED+ORIGINA
L
/RESULT_NAME=A2d_Right Knee Angle_XZ
! /RESULT_FOLDER=PROCESSED
/COMPUTE_3PT_ANGLE=FALSE
! /REFERENCE_SEGMENT=LAB
/PROJECTION_PLANE=XZ
/USE_RIGHT_HAND_RULE=FALSE
/USE_0_TO_360_DEGREES=FALSE
;

Compute_Planar_Angle
/SIGNAL_TYPES=LANDMARK+LANDMARK+TARGET+LANDMARK
/SIGNAL_NAMES=_LGT+_LLK+LLFIB+_LLK
/SIGNAL_FOLDER=ORIGINAL+ORIGINAL+PROCESSED+ORIGINA
L
/RESULT_NAME=A2d_Left Knee Angle_XZ
! /RESULT_FOLDER=PROCESSED
/COMPUTE_3PT_ANGLE=FALSE
! /REFERENCE_SEGMENT=LAB
/PROJECTION_PLANE=XZ
/USE_RIGHT_HAND_RULE=FALSE
/USE_0_TO_360_DEGREES=FALSE
;

Compute_Planar_Angle
/SIGNAL_TYPES=LANDMARK+LANDMARK+TARGET+LANDMARK
/SIGNAL_NAMES=_RMK+RLK+RHEAD5TH+_RMT1
/SIGNAL_FOLDER=ORIGINAL+ORIGINAL+PROCESSED+ORIGINA
L
/RESULT_NAME=A2d_Right Ankle Angle_XZ
! /RESULT_FOLDER=PROCESSED
/COMPUTE_3PT_ANGLE=FALSE
! /REFERENCE_SEGMENT=LAB
/PROJECTION_PLANE=XZ
/USE_RIGHT_HAND_RULE=FALSE
/USE_0_TO_360_DEGREES=FALSE
;

Compute_Planar_Angle
/SIGNAL_TYPES=LANDMARK+LANDMARK+LANDMARK+TARGET
/SIGNAL_NAMES=_LLK+_LMK+_LMT1+LHEAD5TH
/SIGNAL_FOLDER=ORIGINAL+ORIGINAL+ORIGINAL+PROCESSE
D
/RESULT_NAME=A2d_Left Ankle Angle_XZ
! /RESULT_FOLDER=PROCESSED
/COMPUTE_3PT_ANGLE=FALSE
! /REFERENCE_SEGMENT=LAB
/PROJECTION_PLANE=XZ
/USE_RIGHT_HAND_RULE=FALSE
/USE_0_TO_360_DEGREES=FALSE
;

Compute_Model_Based_Data
/RESULT_NAME=Head Angle
/FUNCTION=JOINT_ANGLE
```

```
/SEGMENT=RHE
/REFERENCE_SEGMENT=LAB
/RESOLUTION_COORDINATE_SYSTEM=
! /USE_CARDAN_SEQUENCE=FALSE
! /NORMALIZATION=FALSE
/NORMALIZATION_METHOD=TRUE
! /NORMALIZATION_METRIC=
/NEGATEX=FALSE
/NEGATEY=FALSE
/NEGATEZ=FALSE
! /AXIS1=X
! /AXIS2=Y
! /AXIS3=Z
;

Compute_Model_Based_Data
/RESULT_NAME=Thorax Angle
/FUNCTION=JOINT_ANGLE
/SEGMENT=RTA
/REFERENCE_SEGMENT=LAB
/RESOLUTION_COORDINATE_SYSTEM=
! /USE_CARDAN_SEQUENCE=FALSE
! /NORMALIZATION=FALSE
/NORMALIZATION_METHOD=TRUE
! /NORMALIZATION_METRIC=
/NEGATEX=FALSE
/NEGATEY=FALSE
/NEGATEZ=FALSE
! /AXIS1=X
! /AXIS2=Y
! /AXIS3=Z
;

Compute_Model_Based_Data
/RESULT_NAME=Pelvis Angle
/FUNCTION=JOINT_ANGLE
/SEGMENT=RPV
/REFERENCE_SEGMENT=LAB
/RESOLUTION_COORDINATE_SYSTEM=
! /USE_CARDAN_SEQUENCE=FALSE
! /NORMALIZATION=FALSE
/NORMALIZATION_METHOD=TRUE
! /NORMALIZATION_METRIC=
/NEGATEX=FALSE
/NEGATEY=FALSE
/NEGATEZ=FALSE
! /AXIS1=X
! /AXIS2=Y
! /AXIS3=Z
;

Compute_Model_Based_Data
/RESULT_NAME=Right Thigh Angle
/FUNCTION=JOINT_ANGLE
/SEGMENT=RTH
/REFERENCE_SEGMENT=LAB
/RESOLUTION_COORDINATE_SYSTEM=
! /NORMALIZATION=FALSE
/NORMALIZATION_METHOD=TRUE
! /NORMALIZATION_METRIC=
/NEGATEX=FALSE
/NEGATEY=FALSE
/NEGATEZ=FALSE
! /AXIS1=X
! /AXIS2=Y
! /AXIS3=Z
;

Compute_Model_Based_Data
/RESULT_NAME=Left Thigh Angle
/FUNCTION=JOINT_ANGLE
/SEGMENT=LTH
/REFERENCE_SEGMENT=LAB
/RESOLUTION_COORDINATE_SYSTEM=
! /NORMALIZATION=FALSE
/NORMALIZATION_METHOD=TRUE
! /NORMALIZATION_METRIC=
/NEGATEX=FALSE
/NEGATEY=FALSE
/NEGATEZ=FALSE
! /AXIS1=X
! /AXIS2=Y
! /AXIS3=Z
;

Compute_Model_Based_Data
/RESULT_NAME=Right Shank Angle
/FUNCTION=JOINT_ANGLE
/SEGMENT=RSK
/REFERENCE_SEGMENT=LAB
/RESOLUTION_COORDINATE_SYSTEM=
! /NORMALIZATION=FALSE
/NORMALIZATION_METHOD=TRUE
! /NORMALIZATION_METRIC=
/NEGATEX=FALSE
/NEGATEY=FALSE
/NEGATEZ=FALSE
! /AXIS1=X
! /AXIS2=Y
! /AXIS3=Z
;

Compute_Model_Based_Data
/RESULT_NAME=Left Shank Angle
/FUNCTION=JOINT_ANGLE
/SEGMENT=LSK
/REFERENCE_SEGMENT=LAB
/RESOLUTION_COORDINATE_SYSTEM=
! /NORMALIZATION=FALSE
/NORMALIZATION_METHOD=TRUE
! /NORMALIZATION_METRIC=
/NEGATEX=FALSE
/NEGATEY=FALSE
/NEGATEZ=FALSE
! /AXIS1=X
! /AXIS2=Y
! /AXIS3=Z
;

Compute_Model_Based_Data
/RESULT_NAME=Right Foot Angle
/FUNCTION=JOINT_ANGLE
/SEGMENT=RFT
/REFERENCE_SEGMENT=LAB
/RESOLUTION_COORDINATE_SYSTEM=
! /NORMALIZATION=FALSE
/NORMALIZATION_METHOD=TRUE
! /NORMALIZATION_METRIC=
/NEGATEX=FALSE
/NEGATEY=FALSE
/NEGATEZ=FALSE
! /AXIS1=X
! /AXIS2=Y
! /AXIS3=Z
;

Compute_Model_Based_Data
/RESULT_NAME=Left Foot Angle
/FUNCTION=JOINT_ANGLE
/SEGMENT=LFT
/REFERENCE_SEGMENT=LAB
/RESOLUTION_COORDINATE_SYSTEM=
! /USE_CARDAN_SEQUENCE=FALSE
! /NORMALIZATION=FALSE
/NORMALIZATION_METHOD=TRUE
! /NORMALIZATION_METRIC=
/NEGATEX=FALSE
/NEGATEY=FALSE
/NEGATEZ=FALSE
! /AXIS1=X
! /AXIS2=Y
! /AXIS3=Z
;

Compute_Model_Based_Data
/RESULT_NAME=Head on Thorax Angle
/FUNCTION=JOINT_ANGLE
/SEGMENT=RHE
/REFERENCE_SEGMENT=RTA
/RESOLUTION_COORDINATE_SYSTEM=
! /USE_CARDAN_SEQUENCE=FALSE
! /NORMALIZATION=FALSE
/NORMALIZATION_METHOD=TRUE
! /NORMALIZATION_METRIC=
/NEGATEX=FALSE
/NEGATEY=FALSE
/NEGATEZ=FALSE
! /AXIS1=X
! /AXIS2=Y
! /AXIS3=Z
;

Compute_Model_Based_Data
/RESULT_NAME=Thorax on Pelvis Angle
/FUNCTION=JOINT_ANGLE
/SEGMENT=RTA
/REFERENCE_SEGMENT=RPV
/RESOLUTION_COORDINATE_SYSTEM=
! /USE_CARDAN_SEQUENCE=FALSE
! /NORMALIZATION=FALSE
/NORMALIZATION_METHOD=TRUE
! /NORMALIZATION_METRIC=
/NEGATEX=FALSE
/NEGATEY=FALSE
/NEGATEZ=FALSE
! /AXIS1=X
! /AXIS2=Y
! /AXIS3=Z
;

Compute_Model_Based_Data
/RESULT_NAME=Right Hip Angle
/FUNCTION=JOINT_ANGLE
/SEGMENT=RPV
/REFERENCE_SEGMENT=RTH
/RESOLUTION_COORDINATE_SYSTEM=
! /USE_CARDAN_SEQUENCE=FALSE
! /NORMALIZATION=FALSE
/NORMALIZATION_METHOD=TRUE
! /NORMALIZATION_METRIC=
/NEGATEX=FALSE
/NEGATEY=FALSE
/NEGATEZ=FALSE
! /AXIS1=X
! /AXIS2=Y
! /AXIS3=Z
;
```

```
Compute_Model_Based_Data
/RESULT_NAME=Left Hip Angle
/FUNCTION=JOINT_ANGLE
/SEGMENT=RPV
/REFERENCE_SEGMENT=LTH
/RESOLUTION_COORDINATE_SYSTEM=
! /USE_CARDAN_SEQUENCE=FALSE
! /NORMALIZATION=FALSE
/NORMALIZATION_METHOD=TRUE
! /NORMALIZATION_METRIC=
/NEGATEX=FALSE
/NEGATEY=FALSE
/NEGATEZ=FALSE
! /AXIS1=X
! /AXIS2=Y
! /AXIS3=Z
;

Compute_Model_Based_Data
/RESULT_NAME=Right Knee Angle
/FUNCTION=JOINT_ANGLE
/SEGMENT=RTH
/REFERENCE_SEGMENT=RSK
/RESOLUTION_COORDINATE_SYSTEM=
! /USE_CARDAN_SEQUENCE=FALSE
! /NORMALIZATION=FALSE
/NORMALIZATION_METHOD=TRUE
! /NORMALIZATION_METRIC=
/NEGATEX=FALSE
/NEGATEY=FALSE
/NEGATEZ=FALSE
! /AXIS1=X
! /AXIS2=Y
! /AXIS3=Z
;

Compute_Model_Based_Data
/RESULT_NAME=Left Knee Angle
/FUNCTION=JOINT_ANGLE
/SEGMENT=LTH
/REFERENCE_SEGMENT=LSK
/RESOLUTION_COORDINATE_SYSTEM=
! /USE_CARDAN_SEQUENCE=FALSE
! /NORMALIZATION=FALSE
/NORMALIZATION_METHOD=TRUE
! /NORMALIZATION_METRIC=
/NEGATEX=FALSE
/NEGATEY=FALSE
/NEGATEZ=FALSE
! /AXIS1=X
! /AXIS2=Y
! /AXIS3=Z
;

Compute_Model_Based_Data
/RESULT_NAME=Right Ankle Angle
/FUNCTION=JOINT_ANGLE
/SEGMENT=RSK
/REFERENCE_SEGMENT=RFT
/RESOLUTION_COORDINATE_SYSTEM=
! /USE_CARDAN_SEQUENCE=FALSE
! /NORMALIZATION=FALSE
/NORMALIZATION_METHOD=TRUE
! /NORMALIZATION_METRIC=
/NEGATEX=FALSE
/NEGATEY=FALSE
/NEGATEZ=FALSE
! /AXIS1=X
! /AXIS2=Y
! /AXIS3=Z
;

Compute_Model_Based_Data
/RESULT_NAME=Left Ankle Angle
/FUNCTION=JOINT_ANGLE
/SEGMENT=LSK
/REFERENCE_SEGMENT=LFT
/RESOLUTION_COORDINATE_SYSTEM=
! /USE_CARDAN_SEQUENCE=FALSE
! /NORMALIZATION=FALSE
/NORMALIZATION_METHOD=TRUE
! /NORMALIZATION_METRIC=
/NEGATEX=FALSE
/NEGATEY=FALSE
/NEGATEZ=FALSE
! /AXIS1=X
! /AXIS2=Y
! /AXIS3=Z
;

Metric_StdDev
/RESULT_METRIC_NAME=SD
/APPLY_AS_SUFFIX_TO_SIGNAL_NAME=TRUE
! /RESULT_METRIC_FOLDER=PROCESSED
/SIGNAL_TYPES=TARGET+LANDMARK+LINK_MODEL_BASED
! /SIGNAL_NAMES=
! /SIGNAL_FOLDER=PROCESSED+ORIGINAL+ORIGINAL
! /SIGNAL_COMPONENTS=ALL_COMPONENTS
/EVENT_SEQUENCE=Start+Stop
/EXCLUDE_EVENTS=Avoid+Resume
/GENERATE_MEAN_AND_STDDEV=FALSE
/APPEND_TO_EXISTING_VALUES=FALSE
;


Export_Data_To_Matfile

Metric_Root_Mean_Squared
/RESULT_METRIC_NAME=RMS
/APPLY_AS_SUFFIX_TO_SIGNAL_NAME=TRUE
! /RESULT_METRIC_FOLDER=PROCESSED
/SIGNAL_TYPES=TARGET+LANDMARK+LINK_MODEL_BASED
! /SIGNAL_NAMES=
! /SIGNAL_FOLDER=PROCESSED+ORIGINAL+ORIGINAL
! /SIGNAL_COMPONENTS=ALL_COMPONENTS
/EVENT_SEQUENCE=Start+Stop
/EXCLUDE_EVENTS=Avoid+Resume
/GENERATE_MEAN_AND_STDDEV=FALSE
/APPEND_TO_EXISTING_VALUES=FALSE
;


Metric_Minimum
/RESULT_METRIC_NAME=MIN
/APPLY_AS_SUFFIX_TO_SIGNAL_NAME=TRUE
! /RESULT_METRIC_FOLDER=PROCESSED
/SIGNAL_TYPES=TARGET+LANDMARK+LINK_MODEL_BASED
! /SIGNAL_NAMES=
! /SIGNAL_FOLDER=PROCESSED+ORIGINAL+ORIGINAL
! /SIGNAL_COMPONENTS=ALL_COMPONENTS
/EVENT_SEQUENCE=Start+Stop
/EXCLUDE_EVENTS=Avoid+Resume
/GENERATE_MEAN_AND_STDDEV=FALSE
/APPEND_TO_EXISTING_VALUES=FALSE
/CREATE_GLOBAL_MINIMUM=FALSE
;

Metric_Mean
/RESULT_METRIC_NAME=MEAN
/APPLY_AS_SUFFIX_TO_SIGNAL_NAME=TRUE
! /RESULT_METRIC_FOLDER=PROCESSED
/SIGNAL_TYPES=TARGET+LANDMARK+LINK_MODEL_BASED
! /SIGNAL_NAMES=
! /SIGNAL_FOLDER=PROCESSED+ORIGINAL+ORIGINAL
! /SIGNAL_COMPONENTS=ALL_COMPONENTS
/EVENT_SEQUENCE=Start+Stop
/EXCLUDE_EVENTS=Avoid+Resume
/GENERATE_MEAN_AND_STDDEV=FALSE
/APPEND_TO_EXISTING_VALUES=FALSE
;

Metric_StdDev
/RESULT_METRIC_NAME=SD
/APPLY_AS_SUFFIX_TO_SIGNAL_NAME=TRUE
! /RESULT_METRIC_FOLDER=PROCESSED
/SIGNAL_TYPES=DERIVED
! /SIGNAL_NAMES=
/SIGNAL_FOLDER=PROCESSED
! /SIGNAL_COMPONENTS=ALL_COMPONENTS
/EVENT_SEQUENCE= Start+Stop
/EXCLUDE_EVENTS= Avoid+Resume
/GENERATE_MEAN_AND_STDDEV=FALSE
/APPEND_TO_EXISTING_VALUES=FALSE
;

Metric_Maximum
/RESULT_METRIC_NAME=MAX
/APPLY_AS_SUFFIX_TO_SIGNAL_NAME=TRUE
! /RESULT_METRIC_FOLDER=PROCESSED
/SIGNAL_TYPES=DERIVED
! /SIGNAL_NAMES=
/SIGNAL_FOLDER=PROCESSED
! /SIGNAL_COMPONENTS=ALL_COMPONENTS
/EVENT_SEQUENCE=Start+Stop
/EXCLUDE_EVENTS=Avoid+Resume
/GENERATE_MEAN_AND_STDDEV=FALSE
/APPEND_TO_EXISTING_VALUES=FALSE
! /CREATE_GLOBAL_MAXIMUM=FALSE
;


Metric_Minimum
/RESULT_METRIC_NAME=MIN
/APPLY_AS_SUFFIX_TO_SIGNAL_NAME=TRUE
! /RESULT_METRIC_FOLDER=PROCESSED
/SIGNAL_TYPES=DERIVED
! /SIGNAL_NAMES=
/SIGNAL_FOLDER=PROCESSED
! /SIGNAL_COMPONENTS=ALL_COMPONENTS
/EVENT_SEQUENCE=Start+Stop
/EXCLUDE_EVENTS=Avoid+Resume
/GENERATE_MEAN_AND_STDDEV=FALSE
/APPEND_TO_EXISTING_VALUES=FALSE
! /CREATE_GLOBAL_MINIMUM=FALSE
;

Metric_Root_Mean_Squared
/RESULT_METRIC_NAME=RMS
/APPLY_AS_SUFFIX_TO_SIGNAL_NAME=TRUE
! /RESULT_METRIC_FOLDER=PROCESSED
/SIGNAL_TYPES=DERIVED
! /SIGNAL_NAMES=
/SIGNAL_FOLDER=PROCESSED
! /SIGNAL_COMPONENTS=ALL_COMPONENTS
/EVENT_SEQUENCE=Start+Stop
/EXCLUDE_EVENTS=Avoid+Resume
/GENERATE_MEAN_AND_STDDEV=FALSE
/APPEND_TO_EXISTING_VALUES=FALSE
;
```

```
/FILE_NAME=LMBSubjXXvis3Ddate.mat
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+TARGET+TARGET+TARGET+TARGET+TARGET+TARGET+TARGET+TARGET+LINK_MODEL_BASED+LINK_MODEL_BASED+LINK_M
ODEL_BASED+LINK_MODEL_BASED+LINK_MODEL_BASED+LINK_MODEL_BASED+LINK_MODEL_BASED+LINK_MODEL_BASED+LINK_MODEL_BASE
D+DERIVED+DERIVED+DERIVED+DERIVED+DERIVED+DERIVED+DERIVED+DERIVED+DERIVED+DERIVED+DERIVED+DERIVED+DERIV
ED+DERIVED+DERIVED+DERIVED+DERIVED+DERIVED+DERIVED+LINK_MODEL_BASED+LINK_MODEL_BASED+LINK_MODEL_BASED+L
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DMARK+LANDMARK+LANDMARK+LANDMARK+LANDMARK+LANDMARK+LANDMARK+LANDMARK+LANDMARK+LANDMARK+LANDMARK+LANDMA
RK+LANDMARK+LANDMARK+LANDMARK+LANDMARK+LANDMARK+LANDMARK+LANDMARK+LANDMARK+LANDMARK+METRIC+METRIC+METRIC+METRIC
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B+RUFIB+LUFFIB+LUFIB+RLFIB+RCALC+LLFIB+LCALC+RBASE5TH+RHEAD5TH+LBASE5TH+LHEAD5TH+Head Angle+Thorax Angle+Pelvis
Angle+Right Thigh Angle+Left Thigh Angle+Right Shank Angle+Left Shank Angle+Right Foot Angle+Left Foot
Angle+A2d_Reid'sR_YZ+A2d_Reid'sL_YZ+A2d_ThoraxR_YZ+A2d_ThoraxL_YZ+A2d_PelvisR_YZ+A2d_PelvisL_YZ+A2d_ThighR_YZ+A
2d_ThighL_YZ+A2d_ShankR_YZ+A2d_ShankL_YZ+A2d_Head_XZ+A2d_Thorax_XZ+A2d_Pelvis_XZ+A2d_ThighR_XZ+A2d_ThighL_XZ+A2
d_ShankR_XZ+A2d_ShankL_XZ+A2d_Shanks_XZ+A2d_FootR_XZ+A2d_FootL_XZ+A2d_Feet_XZ+Head on Thorax Angle+Thorax on
Pelvis Angle+Right Hip Angle+Left Hip Angle+Right Knee Angle+Left Knee Angle+Right Ankle Angle+Left Ankle
Angle+A2d_Head On Thorax Angle_YZ+A2d_Head on Thorax Angle_XZ+A2d_Thorax on Pelvis Angle_YZ+A2d_Thorax on
Pelvis Angle_XZ+A2d_Right Hip Angle_YZ+A2d_Right Hip Angle_XZ+A2d_Left Hip Angle_YZ+A2d_Left Hip
Angle_XZ+A2d_Right Knee Angle_YZ+A2d_Right Knee Angle_XZ+A2d_Left Knee Angle_YZ+A2d_Left Knee
Angle_XZ+A2d_Right Ankle Angle_YZ+A2d_Right Ankle Angle_XZ+A2d_Left Ankle Angle_YZ+A2d_Left Ankle
Angle_XZ+A2d_FootR_YZ+A2d_FootL_YZ+FRHEADMEAN+FLHEADMEAN+BRBACKMEAN+BLHEADMEAN+TRBACKMEAN+TLBACKMEAN+BRBACKMEAN
+BLBACKMEAN+TRPELVISMEAN+TLPELVISMEAN+BRPELVISMEAN+BLPELVISMEAN+RUFFIBMEAN+RUFIBMEAN+LUFFIBMEAN+LUFIBMEAN+RLFIB
MEAN+RCALCMEAN+LLFIBMEAN+LCALCMEAN+RBASE5THMEAN+RHEAD5THMEAN+LBASE5THMEAN+LHEAD5THMEAN+_C7+_L4+_LASI+_LCALC+_LE
AR+_LEYE+_LGH+_LGT+_LHALLUX+_LIC+_LLK+_LMK+_LMT1+_MEYES+_NUCH+_RASI+_RCALC+_REAR+_REYE+_RGH+_RHALLUX+_RIC+_RLK+
_RMK+_RMT1+_T10+_T5+_C7MEAN+_L4MEAN+_LASIMEAN+_LCALCMEAN+_LEARMEAN+_LEYEMEAN+_LGHMEAN+_LGTMEAN+_LHALLUXMEAN+_LI
CMEAN+_LLKMEAN+_LMKMEAN+_LMT1MEAN+_MEYESMEAN+_NUCHMEAN+_RASIMEAN+_RCALCMEAN+_REARMEAN+_REYEMEAN+_RGHMEAN+_RHALL
UXMEAN+_RICMEAN+_RLKMEAN+_RMKMEAN+_RMT1MEAN+_T10MEAN+_T5MEAN+Head AngleSD+Thorax AngleSD+Pelvis AngleSD+Right
Thigh AngleSD+Left Thigh AngleSD+Right Shank AngleSD+Left Shank AngleSD+Right Foot AngleSD+Left Foot
AngleSD+A2d_Reid'sR_YZSD+A2d_Reid'sL_YZSD+A2d_ThoraxR_YZSD+A2d_ThoraxL_YZSD+A2d_PelvisR_YZSD+A2d_PelvisL_YZSD+A
2d_ThighR_YZSD+A2d_ThighL_YZSD+A2d_ShankR_YZSD+A2d_ShankL_YZSD+A2d_Head_XZSD+A2d_Thorax_XZSD+A2d_Pelvis_XZSD+A2
d_ThighR_XZSD+A2d_ThighL_XZSD+A2d_ShankR_XZSD+A2d_ShankL_XZSD+A2d_Shanks_XZSD+A2d_FootR_XZSD+A2d_FootL_XZSD+A2d
_Feet_XZSD+Head on Thorax AngleSD+Thorax on Pelvis AngleSD+Right Hip AngleSD+Left Hip AngleSD+Right Knee
AngleSD+Left Knee AngleSD+Right Ankle AngleSD+Left Ankle AngleSD+A2d_Head On Thorax Angle_YZSD+A2d_Head on
Thorax Angle_XZSD+A2d_Thorax on Pelvis Angle_YZSD+A2d_Thorax on Pelvis Angle_XZSD+A2d_Right Hip
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Angle_YZSD+A2d_Right Knee Angle_XZSD+A2d_Left Knee Angle_YZSD+A2d_Left Knee Angle_XZSD+A2d_Right Ankle
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D
/OUTPUT_NAMES=M_FRhead+M_FLhead+M_BRhead+M_BLhead+M_TRback+M_TLback+M_BRback+M_BLback+M_TRpelvis+M_TLpelvis+M_B
Rpelvis+M_BLpelvis+M_RUFfib+M_RUBfib+M_LUFfib+M_LUBfib+M_RLfib+M_Rcalc+M_LLfib+M_Lcalc+M_RB5th+M_RH5th+M_LB5th+
M_LH5th+A3Dspace_Head+A3Dspace_Thorax+A3Dspace_Pelvis+A3Dspace_RThigh+A3Dspace_LThigh+A3Dspace_Rshank+A3Dspace_
Lshank+A3Dspace_Rfoot+A3Dspace_Lfoot+A2Dspace_Head_RreidsYZ+A2Dspace_Head_LreidsYZ+A2Dspace_RthoraxYZ+A2Dspace_
LthoraxYZ+A2Dspace_RpelvisYZ+A2Dspace_LpelvisYZ+A2Dspace_RthighYZ+A2Dspace_LthighYZ+A2Dspace_RshankYZ+A2Dspace_
LshankYZ+A2Dspace_HeadXZ+A2Dspace_ThoraxXZ+A2Dspace_PelvisXZ+A2Dspace_RthighXZ+A2Dspace_LthighXZ+A2Dspace_Rshan
kXZ+A2Dspace_LshankXZ+A2Dspace_ShanksXZ+A2Dspace_RfootXZ+A2Dspace_LfootXZ+A2Dspace_FeetXZ+A3Dseg_HeadonThorax+A
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2Dseg_RhipJointYZ+A2Dseg_RhipJointXZ+A2Dseg_LhipJointYZ+A2Dseg_LhipJointXZ+A2Dseg_RkneeJointYZ+A2Dseg_RkneeJoin
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eg_LankleJointXZ+A2Dspace_RfootYZ+A2Dspace_LfootYZ+MdispMEAN_FRhead+MdispMEAN_FLhead+MdispMEAN_BRhead+MdispMEAN
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is+MdispMEAN_BRpelvis+MdispMEAN_BLpelvis+MdispMEAN_RUFfib+MdispMEAN_RUBfib+MdispMEAN_LUFfib+MdispMEAN_LUBfib+Md
ispMEAN_RLfib+MdispMEAN_Rcalc+MdispMEAN_LLfib+MdispMEAN_Lcalc+MdispMEAN_RB5th+MdispMEAN_RH5th+MdispMEAN_LB5th+M
dispMEAN_LH5th+M_C7+M_L4+M_LASI+M_LCALC+M_LEAR+M_LEYE+M_LGH+M_LGT+M_LHALLUX+M_LIC+M_LLK+M_LMK+M_LMT1+M_MEYES+M_
NUCH+M_RASI+M_RCALC+M_REAR+M_REYE+M_RGH+M_RHALLUX+M_RIC+M_RLK+M_RMK+M_RMT1+M_T10+M_T5+MdispMEAN_C7+MdispMEAN_L4
+MdispMEAN_LASI+MdispMEAN_LCALC+MdispMEAN_LEAR+MdispMEAN_LEYE+MdispMEAN_LGH+MdispMEAN_LGT+MdispMEAN_LHALLUX+Mdi
spMEAN_LIC+MdispMEAN_LLK+MdispMEAN_LMK+MdispMEAN_LMT1+MdispMEAN_MEYES+MdispMEAN_NUCH+MdispMEAN_RASI+MdispMEAN_R
CALC+MdispMEAN_REAR+MdispMEAN_REYE+MdispMEAN_RGH+MdispMEAN_RHALLUX+MdispMEAN_RIC+MdispMEAN_RLK+MdispMEAN_RMK+Md
ispMEAN_RMT1+MdispMEAN_T10+MdispMEAN_T5+A3DspaceSD_Head+A3DspaceSD_Thorax+A3DspaceSD_Pelvis+A3DspaceSD_Rthigh+A
3DspaceSD_Lthigh+A3DspaceSD_Rshank+A3DspaceSD_Lshank+A3DspaceSD_Rfoot+A3DspaceSD_Lfoot+A2DspaceSD_Head_RreidsYZ
+A2DspaceSD_Head_LreidsYZ+A2DspaceSD_RthoraxYZ+A2DspaceSD_LthoraxYZ+A2DspaceSD_RpelvisYZ+A2DspaceSD_LpelvisYZ+A
2DspaceSD_RthighYZ+A2DspaceSD_LthighYZ+A2DspaceSD_RshankYZ+A2DspaceSD_LshankYZ+A2DspaceSD_HeadXZ+A2DspaceSD_Tho
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SD_LankleJoint+A2DsegSD_HeadonThoraxYZ+A2DsegSD_HeadonThoraxXZ+A2DsegSD_ThoraxonPelvisYZ+A2DsegSD_ThoraxonPelvi
sXZ+A2DsegSD_RhipJointYZ+A2DsegSD_RhipJointXZ+A2DsegSD_LhipJointYZ+A2DsegSD_LhipJointXZ+A2DsegSD_RkneeJointYZ+A
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A2DsegSD_LankleJointYZ+A2DsegSD_LankleJointXZ+A2DspaceSD_RfootYZ+A2DspaceSD_LfootYZ
! /PARAMETER_NAMES=
! /PARAMETER_GROUPS=
! /OUTPUT_PARAMETER_NAMES=
/USE_NAN_FOR_DATANOTFOUND=TRUE
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