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Gait Analysis in Cerebellar Ataxia

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To the best of my knowledge, the content of this thesis is my own work. This thesis has not been submitted for any degree or other purposes. I certify that the intellectual content of this thesis is the product of my own work and that all the assistance received in preparing this thesis and sources have been acknowledged.

iii. PUBLICATIONS

Full papers:

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3D	Three Dimensional	M/F	Male/Female
ADCA	Autosomal Dominant Cerebellar Ataxia	MD	Mean Difference
AP	Anterior/ Posterior Axis	MDS	Movement Disorder Society
asym.	asymmetry	ML	Medial/Lateral Axis
BBS	Berg Balance Scale	mm	millimetres
BMI	Body Mass Index	MoCA	Montreal Cognitive Assessment
C7	7th Cervical Vertebra	MPD	Months Post Diagnosis
CA	Cerebellar ataxia	MS	Multiple Sclerosis
CAG	cytosine-adenine-guanine	n	Number of Patients In Group
CD	Cannot Determine	NA	Not Applicable
CI	confidence Interval	NHS	National Health Service
cm	centimetres	NR	Not Reported
CoA	Coefficient of Attenuation	PD	Parkinson's Disease
COM	Centre of Mass	PIGD	Postural Instability and Gait Difficulty
CP	Cerebral palsy	PSW	Pressure Sensitive Walkway
cSD	combined Standard Deviation	R	Resultant
CV	Coefficient of Variation	REM	Random Effect Model
DLS	Double Limb Support	RMS	Root Mean Square
EMG	Electromyography	RMSR	Root mean square ratio
FC	Final Contact	RoM	Range of Motion
FRDA	Friedreich's Ataxia	s	seconds
HSP	Hereditary Spastic Ataxia	SAOA	Sporadic Adult-Onset Ataxia
IC	Initial Contact	SARA	Scale for the Assessment and Rating of Ataxia
ICARS	International Cerebellar Ataxia Rating Scale	SCA	Spinocerebellar Ataxia
ICC	IntraClass Coefficient	SD	Standard Deviation
IMU	Inertial Measurement Unit	SEE	Standard Effects Estimates
IQR	Inter Quartile Range	SEM	Standard Error of the Mean
IV	Inverse Variance	SLS	Single Limb Support
kg	kilograms	SPG7	Spastic Paraplegia 7
L/R	Left/Right	SPRS	Spastic Paraplegia Rating Scale
L5	5th Lumbar Vertebra	STP	SpatioTemporal Parameter
LEDs	Light Emitting Diode	UPDRS	Unified Parkinsons' Disease Rating Scale
LOA	Limit of Agreement	V	Vertical Axis
m	metres		

vii. ABSTRACT

Background

Cerebellar ataxias (CA) are a group of movement disorders that cause problems with balance and walking. Diagnosis and disease monitoring in CA involve subjective clinical rating scales. These methods are not sensitive to subtle longitudinal changes in mobility and there are no reliable biomarkers of disease progression in ataxia. Gait analysis techniques can objectively quantify gait and have potential to modernise clinical assessment of mobility in CA.

Methods

A systematic review and meta-analysis of available literature relating to spatiotemporal gait characteristics of CA were completed to define consistent gait abnormalities in CA. A validation study of gait analysis equipment was completed. A clinical study of instrumented gait tests in CA was undertaken with follow-up tests occurring 12-18 months and 24 months post-baseline.

Results

Meta-analysis established a consistent spatiotemporal gait pattern in CA. Our portable gait analysis system showed a good level of agreement and accuracy of gait event measurements compared with a 3D motion capture system in a healthy adult cohort (n=24).

CA (n=27) cohort displayed by reduced preferred-pace gait speed, increased step width, asymmetry, and variability, as well as impaired attenuation of upper body motion and reduced postural symmetry and regularity compared with HC (n=27). After a 12-month interval (CA n=16), no disease progression occurred. Although step width, gait asymmetry and regularity variables showed statistically significant deterioration as clinical measures did not reflect a genuine change in function.

Conclusion

A thorough characterisation of gait in CA with variables novel to an ataxic cohort has been completed. Spatiotemporal gait abnormalities and impaired dynamic stability differentiate between people with CA and HC and stratifies by disease severity. As no substantial disease progression was detected in the clinical measures or gait measures over a 12-month period, these variables require comparison to other disease groups and exploration over a longer follow-up interval to confirm their use as biomarkers for disease progression in CA.

Chapter 1. Introduction To Clinical Applications of Gait Analysis

1.1. Walking Gait

1.1.1. The Gait Cycle

Walking gait in humans is cyclic in nature and punctuated by consecutive initial contacts. An individual's body type, dictated by their sex, age and any natural asymmetries, affects their unique movement pattern (Rigas, 1984).

As depicted in Figure 1.1, one gait cycle is equivalent to a single stride and in healthy walking can be defined as between two successive heel strikes (initial contact) of the same foot (Perry and Burnfield, 1992). The healthy walking gait cycle has two well-defined phases, stance phase and swing phase, which correspond to approximately 60% and 40% of the stride, respectively. Throughout this cycle, the individual's weight redistributes continuously. In healthy walking gait, following initial contact (heel strike), one foot moves through a flat position on the floor (stance phase) during which the opposite foot lifts (final contact) and propels forward (swing phase). Then once the opposite foot contacts the floor again, the former foot begins to lift off through the foot until the point of final contact, at which point the foot enters swing phase. Here, a step is defined as period between the ipsilateral and opposite initial contacts, and stride is the period between two initial contacts of the ipsilateral initial contacts. Stance phase is the period between ipsilateral initial and final contacts where foot is in partial or full contact with the floor, and swing phase is the alternate period where the foot is not in contact with the floor. Double support phase and single support phases are where both or one foot is in contact with the floor and are sub-phases of stance. Step width can be defined as the distance between the feet, commonly measured between the middle supporting points of each foot.

1.1.2. Gait Biomechanics

The typical walking gait relies on consistent footfalls, arm swing symmetry, as well as coordinated fluctuations of trunk, neck and head movements and natural variability for appropriate gait adaptation and efficient locomotion.

One of the primary purposes of the trunk during walking is to aid the stabilisation of the head in order to maintain a relatively steady plane of sight (Grossman and Leigh, 1990). While, Demer and Viirre (1996) described the effect of walking tasks on visual-vestibular

interaction, there is also evidence that the reverse is also true i.e. vision deprivation leads to worse postural control (Tomomitsu et al., 2013).

Therefore, to attenuate oscillations of the lower body through the trunk during walking gait, the human body is equipped with passive and active mechanisms. In healthy individuals, the spine's natural S-shaped curvature distributes the mechanical stress of movement. The more inferior vertebrae (closer to the ground) carry more of the body weight and intervertebral discs add shock absorption to protect the individual bones. During walking, the head and neck largely move as a single unit undergoing frontal, vertical and lateral displacement as the body's centre of mass (COM) adjusts with the motion of the pelvis and lower limbs with each footfall (Perry and Burnfield, 1992). Counter-rotation of the head and shoulders with respect to the pelvis, during double support phases particularly, assists with gaze stabilisation. This is the point of the gait cycle where forces are the greatest in the lower body (Mulavara et al., 2002). An anterior tilt, lateral pelvic drop and transverse rotation of the pelvis occurs in walking across the gait cycle during the forward progression of the body. The amount of frontal and vertical plane COM displacement corresponds to walking speed (Thorstensson et al., 1984) with a larger displacement rate occurring with increased speed. For instance, slow-paced walking is associated with a larger mediolateral COM displacement (Orendurff et al., 2004).

Postural and dynamic instability occurs when these mechanisms break down during standing and walking, respectively. The lack of control of the body motion during these movements leads to worse balance, and an increased risk of falls. For the purpose of this thesis, instability will be defined as uncoordinated or poorly controlled upper body motion with postural stability considered during standing and dynamic stability considered during a task such as walking.

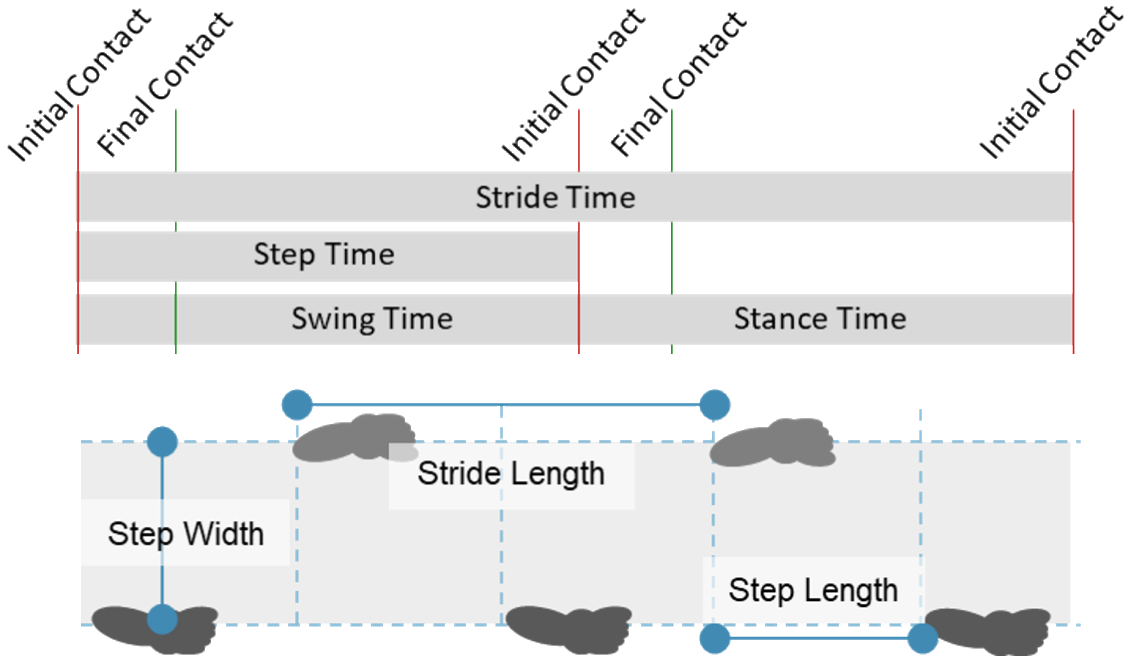

Figure 1.1: The gait cycle
The gait cycle is punctuated with initial and final contact gait events which in normal individuals walking relates to heel strike and toe-off, respectively. One gait cycle is equivalent to a single stride and equivalent to two steps with the initial contact event commonly taken as the beginning of the gait cycle. Temporal and spatial difference between gait events generates several spatiotemporal gait parameters. Swing phase is defined as the period between a final contact and initial contact when the ipsilateral foot is off the floor with stance phase occurring between initial contact and final contact events when the ipsilateral foot is on the floor. Step width is commonly defined as the distance between the middle supporting points of each foot.

1.1.3. NEUROPHYSIOLOGY OF GAIT

As a voluntary movement programme, control of walking gait involves both the nervous system and musculoskeletal systems. Walking is initiated and coordinated by a complex network of brain areas as well as reflexes which are fed into by various sensory and cognitive processes (Takakusaki, 2013)(See Figure 1.2).

Pattern generating circuits within the spinal cord produce alternating rhythmic activity in arm muscles which enables arm swing to be a partially actively controlled (Meyns et al., 2013). Due to the crossed-extensor reflex, afferent nerve fibres synapsing with interneurons on the contralateral side the spinal cord induce extension of the contralateral limb and flexion of the ipsilateral limb. These mechanisms together enable inter-limb coordination and counter-rotation of the shoulders.

The lateral and ventromedial pathways of the descending corticospinal tracts continuously monitor body position in order to control voluntary movement (i.e. a volitional process) of distal musculature, and postural reflexes respectively. The planning of goal-directed movements is performed within various areas of the cerebral cortex in coordination with subcortical regions. The motor cortex provides innervation signals to muscles in a somatotopic map, and the premotor and supplementary motor areas (PMA & SMA) are required to plan skilled voluntary movements. The posterior parietal cortex produces a visualisation of body position, while the prefrontal cortex decides appropriate actions and communicates these to the rest of the neocortex. In addition, the basal ganglia and ventral lateral nucleus provide feedback to enable the selection and initiation of movement. Throughout this process, the cerebellum coordinates proper execution of movement through corrective instructions to the primary motor cortex. Through direct and indirect control pathways, automatic and emotional processes come into effect, subject to whether the gait is stereotyped or modulated (Hamacher et al., 2015).

The breakdown of these processes due to lesions, disease and injury can lead to gait impairment. Therefore, the study of neurological gait disorders and animal models of these can clarify the brain mechanisms controlling gait further. See Section 1.2.4, for further discussion of the impact of neurological dysfunction of gait control.

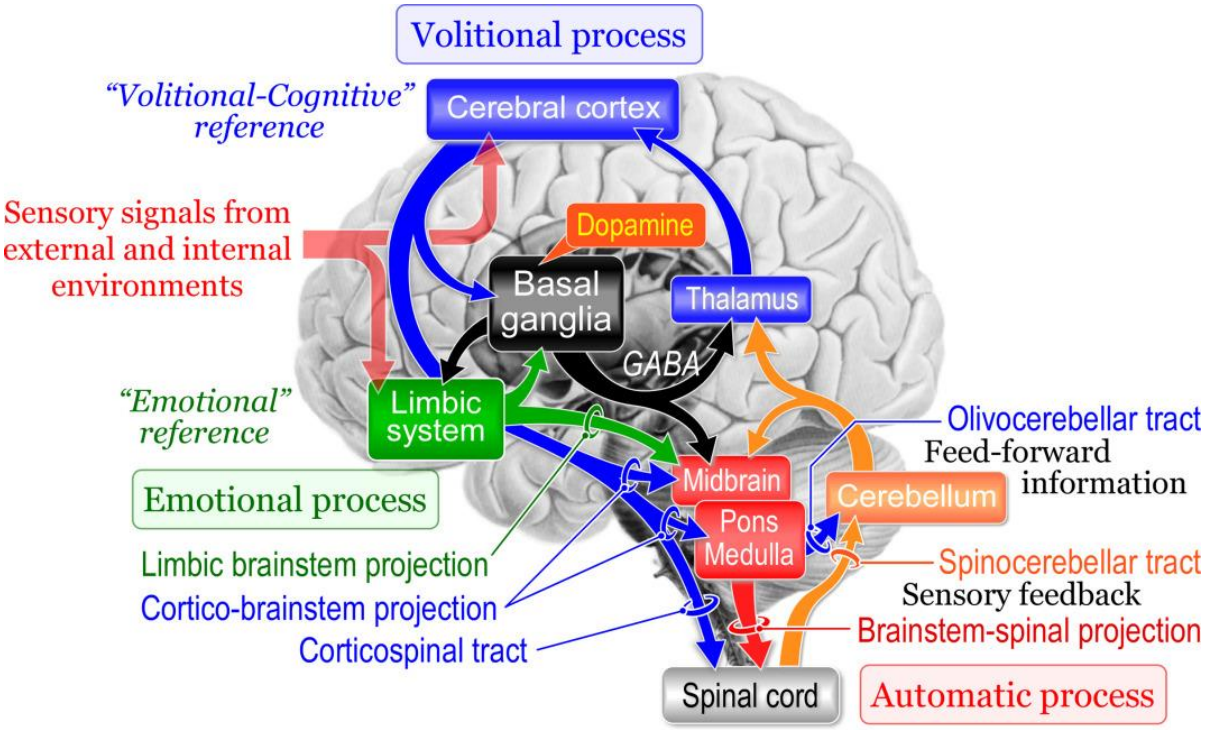

Figure 1.2: Neurophysiology of gait
Gait is controlled by involvement of volitional, automatic, and emotional signal processes. Reproduced from Neurophysiology of gait: From the spinal cord to the frontal lobe" Movement Disorders, Volume: 28, Issue: 11, Pages: 1483-1491, First published: 16 October 2013, DOI: (10.1002/mds.25669). with permission from Wiley.

1.1.4. ASSESSMENT OF GAIT

1.1.4.1. Current Standards of Gait Assessment

As abnormal gait is a common symptom of movement disorders, observation of gait is a standard feature of clinical examinations. The movement of the body within each gait cycle can be assessed in many ways, such as, in terms of the location and timings of each footfall, trunk or postural sway, as well as the movements of individual muscles and joints.

Factors such as falls risk, falls history and activity levels are clinically relevant and important to consider in determining disease severity and monitoring disease progression. An increased risk of falls is associated with gait disorders such as Parkinson's Disease (Frenklach et al., 2009), Multiple Sclerosis (Allali et al., 2016), and Cerebellar ataxia (Schniepp et al., 2014). In addition, older adults with less confidence in walking and those with movement disorders have lower levels of daily physical activity (Hausdorff et al., 2001a). These can be measured using retrospective questioning and prospective activity diaries, but such methods typically provide subjective and qualitative information. More objective measures of gait that are currently available to clinicians include rating scales such as the modified Dynamic Gait Index (Shumway-Cook et al., 2013) and gait tests such as the Timed Up and Go (Podsiadlo and Richardson, 1991) or timed walking trials. Disease-specific psychometric tests are also better able to capture the gait and balance due to their sensitivity to symptoms (e.g. Unified Parkinson's Disease Rating Scale (UPDRS) (Goetz et al., 2007)); Unified Huntington's' Disease Rating Scale (UHDRS) (Huntington Study Group, 1996); International Cerebellar Ataxia Rating Scale (ICARS) (Trouillas et al., 1997); Scale for Assessment and Rating of Ataxia (SARA) (Schmitz-Hübsch et al., 2006)). Through descriptive scoring, these semi-quantify the severity of patients' symptoms, and subjectively evaluate gait disturbances in terms of walking capabilities, speed and use of supports. Although these scales have acceptable clinical utility and are widely used (e.g. SARA, Winser et al., 2015), many items such as the retropulsion test remain sensitive to observer variability and are out-performed by objective methods like static posturography (Bloem et al., 1998).

As even the well-trained eye is unable to fully quantify gait characteristics there may be a role for instrumented gait analysis in the objective evaluation of gait disorders and to provide clinical biomarkers of disease severity and disease progression. Assessment during treadmill or over-ground walking can provide valuable information about the way in which patients walk and detect subtle changes in gait characteristics. As a feature of a validated

rating clinical scale, gait analysis could be incorporated into standard clinical practice, to increase the amount of information available to practitioners when managing patient care (Culhane et al., 2005).

1.1.4.2. Gait Analysis Techniques

The analysis of gait using instrumented techniques, enables various parameters related to the symmetry, variability, rotation and overall position of the body, limbs and joints, to be captured that otherwise would be too subtle to distinguish (Whittle, 1996). Gait analysis techniques make objective quantification of the gait pattern more accurate and readily available. A wide range of systems exist from fixed position to portable incorporating different technologies such as infrared imaging, pressure monitoring, and inertial measurement. As such the variety of systems available enable gait analysis to take place in different settings from clinic to real world. Different systems implement different approaches to capturing motion: from limb kinetics (measurement of forces associated with movement) and limb kinematics (measurement of movement), to muscle dynamics (activity and length changes). There are several methods of detection and analysis by which gait can be quantitatively examined, including methods for simultaneous measurement of upper and lower body movements (Muro-de-la-Herran et al., 2014). This is improving understanding of how the symptoms of movement disorders related to the underlying pathology as well as facilitating the development of biomarkers for disease progression.

The gold standard of laboratory gait analysis is three-dimensional video motion capture systems, which measure joint angles and limb motion. These are often used in conjunction with floor-mounted force plates to assess spatiotemporal characteristics and weight distribution, as well as modelling various aspects of movement such as joint loading patterns (Kadaba et al., 1989). The analysis relies on the trajectories of reflective markers placed at predefined anatomical locations during movement (Cappozzo et al., 2005). These systems enable computational modelling of ground reaction forces, joint reaction forces and even muscle actions that can be adapted to be highly subject-specific. However, these systems require large dedicated laboratory areas and highly skilled staff to complete assessments and process data which are often not available in a hospital setting. In addition, laboratory gait analysis restrains participant walking to a relatively small measurement volume, making it less generalisable to real-world walking gait (Lara et al., 2013).

Due to this high cost to time, space, and money, combined with high data analysis burden, more feasible methods for use in a clinical setting are pressure-sensitive floor mats and LED array gait analysis systems. For physiotherapists and researchers requiring a high throughput of participants with a quick output of results, these are the principal methods of analysing footfall to measure the spatiotemporal characteristics of gait (Webster et al., 2005).

For instance, the OptoGait photoelectric system (Microgate Inc. Bolzano, Italy) uses bars embedded with a series of LEDs to monitor footfall during over-ground or treadmill walking. Using activation thresholds to denote initial contact and final contact location and timing, spatiotemporal gait characteristics can be obtained and a patient report provided immediately for a clinical appraisal (Lee et al., 2014, Lienhard et al., 2013).

Wearable inertial sensors are another promising option to those measuring gait. These commonly contain accelerometers, gyroscopes and magnetometers and are able to record the motion of each sensor at high frequencies for short to long periods. Analysis of temporal parameters relies on the exploitation of acceleration and angular velocity signals to establish gait events (Taborri et al., 2016). There are various algorithms and approaches described in the literature which have proven highly accurate in the segmentation of gait signals in healthy cohorts and some disease cohorts such as Parkinson's Disease but may require further adaptation for implementation in assessment of pathological gait (Bruening and Ridge, 2014, Pacini Panebianco et al., 2018).

Calculation of spatial gait parameters from inertial data relies on the computation of forward displacement through the integration of acceleration signals (Bertoli et al., 2018, Kluge et al., 2017). A consensus has not yet been reached about the best method of computing these trajectories due to the importance of the location of sensor positioning. Therefore, work is underway to improve these algorithms to avoid direct measurement of spatial parameters using a second system. Computation of base of support or step width time cannot be directly measured with inertial sensors since each device is typically unable to track its spatial location relative to any others within the system and gyroscope measurements are typically associated with signal drift. Time of flight (ToF) sensors, meanwhile, measure the distance between the sensor and a surface. Therefore implementation of ToF sensors within a wearable IMU system, with placement at the ankle, could provide an estimation of step width and step count without external equipment (Bertuletti et al., 2019). Another

promising approach to solve this problem is to implement sensor-fusion algorithms to combine measurements by multiple integrated sensors. An Extended Kalman filter can be used to reduce noise in orientation measurements to provide better estimates of relative IMU displacement (Bennett et al., 2013).

Meanwhile, when worn at positions on the upper body, inertial sensors enable quantification of upper body motion and the assessment of gait quality. As imbalance is a hallmark of all movement disorders, the assessment of trunk motion during walking is just as significant as analysis of the footfall (e.g. Huntington's Disease (Medina et al., 2013), Parkinson's' Disease (Bronte-Stewart et al., 2002), and Cerebellar ataxia (Van de Warrenburg et al., 2005a)). Inertial sensors can be implemented to gather acceleration and angular velocity data in order to reliably detect gait measures (Henriksen et al., 2004). For instance, from the inertial signals at different points in the trunk, it is possible to determine the intensity and smoothness of motion and whether the forces are adequately controlled during walking. The Jerk signal (time derivative of acceleration) is the rate of change in the acceleration of movements in each anatomical plane calculated as the first-time derivative of acceleration signal (Brodie et al., 2014). This approach indicates the jerkiness of movements. Further information about the full gait pattern and the preservation of head stability can also be gained from multi-sensor systems using the attenuation coefficient (Mazzà et al., 2008, Mazzà et al., 2009). Auto-correlation coefficient analysis involves the transformation of acceleration signals to examine the regularity and symmetry of gait within periods relating to one step and one stride (first dominant period, AD1 and second dominant period, AD2 respectively) (Moe-Nilssen and Helbostad, 2004).

The wearable nature of inertial sensors and relatively low cost enables the accurate and reliable assessment of participants in a variety of settings (Hickey et al., 2017, Storm et al., 2016). Gait assessments in a clinical or laboratory setting, may not be representative of a patient's natural walking gait due to experimental conditions (Robles-García et al., 2015). Therefore at-home physical activity monitoring has the potential to evaluate a patient's gait during their daily lives. A comparison of physical activity monitors available commercially concluded that although overall accuracy was good, many of the devices examined underestimated step counts and misclassification of activity types was common (Storm et

al., 2015). Therefore, further work is required to improve algorithms and ensure that activity information is captured reliably.

While, these methods deliver vast amounts of valuable information demanding analytical expertise, progress in understanding and increasing flexibility will enable their application into clinical practice and research.

1.2. FACTORS INFLUENCING GAIT PATTERN

Everyone has a unique movement pattern, due to their specific body type, sex, and age. How features such as gait speed change over time, can reflect important long-term health information even in healthy individuals (Fritz and Lusardi, 2009). Therefore, the implication of confounding factors is important to consider in any clinical environment and various studies have worked to establish those essential to consider when evaluating gait.

1.2.1. AGEING

Normal ageing can have a noticeable effect on the way in which individuals walk. For example, there is a natural weakening of the hip musculature with age accompanied by the onset and worsening of gait instability from the ages of 40-50 (Rigas, 1984, Terrier and Reynard, 2015). A natural compensatory response to this is to establish a larger base of support, reduce step length and step frequency. Murray et al. (1969), (1970), assessed gait in healthy older men and women, and concluded that individuals with increased instability also exhibit a larger step width. A study of older adults determined that those with impaired balance responses were also prone to falls (Tucker et al., 2010). Groups of younger and older people are distinguishable by patterns of head motion smoothness (Brodie et al., 2014). It is therefore important to consider the impact of ageing when determining the meaningfulness of a change in the gait characteristics of a patient and within the context of a clinical trial or observational study, to match cohort demographics for the age when possible.

1.2.2. SEX DIFFERENCES

Due to the influence of skeletal and musculature differences between males and females, there are several sex-related changes in gait pattern (Murray et al., 1969, Murray et al., 1970). Examination of the attenuation of accelerations pelvis to head between men and women indicates altered postural control of lower body forces (Mazzà et al., 2009). In a cohort of healthy individuals around 30 years old, despite walking at the same preferred paced walking, men were found to take significantly longer strides with women

implementing a higher cadence. Differences in torso rotation were also identified as well as changes in arm swing mechanism between the sexes (Bruening et al., 2015).

These findings indicate the importance of considering sex disparities in recruitment for gait studies. In the context of clinical studies, this can add complexity where certain diseases more commonly affect one sex over the other.

1.2.3. ENVIRONMENT

It is also important to consider the environment in which gait tasks are performed when interpreting results. Since gait assessments are usually completed within gait laboratories and hospitals these are not necessarily reflective of participants' gait during daily life. The conditions of walking tasks such as the nature of activities completed, the setting and length of walking bouts can all lead to adjusted gait patterns in healthy individuals and people with movement disorders (Storm et al., 2016, Weiss et al., 2011).

In addition, patients can adjust their behaviour when being observed during assessments which may alter the gait pattern further away from their normal everyday strategies (Malchow and Fiedler, 2016, Robles-García et al., 2015, Vickers et al., 2017). It is therefore essential to ensure that the clinical or laboratory setting is kept as uniform as possible across participants to compensate for the "unnatural" setting.

The purpose of the walking assessment/study should also inform appropriate gait task selection. For instance, in order to study a participant's best possible function or gait capacity, a short distance timed task or 6-minute walk test can be implemented their speed or distance travelled. The gait strategy for these tests is arguably different from how they may walk when unobserved in their daily life.

For this reason, there has been a recent recognition in the value of multi-day physical activity assessment using specialised wearable IMUs. Physical activity monitors with a long battery life and large memory store can be worn continuously over multiple days. This offer an opportunity to assess real-world gait patterns and larger-scale activity characteristics. However, due to the unsupervised nature of such conditions, validation is required to ensure gait event detection algorithms are reliable and accurate enough to have confidence in findings. Compared with a clinic setting where the gait tasks are prescribed and more controlled, in real-world settings participants are required to adapt their walking pattern to

obstacles and events around them. This presents a challenge for people with neurological movement disorders for whom disability is common.

1.2.4. NEUROLOGICAL DISEASE

Neurological disorders are a large contributor to the number of disability-adjusted life years, to economic losses and increased social care needs worldwide (Andlin-Sobocki et al., 2005, World Health Organization, 2006). Over the next 40 years, the projected numbers of people with movement disorders are expected to increase by 1.6 times the current prevalence (Bach et al., 2011).

Since balance performance is impacted in most movement disorders, investigation of the differences between healthy and pathological gait can build an understanding of the disease pathology. The evidence surrounding the effectiveness of the existing interventions is largely based on the subjective measures as discussed in Section 1.1.4.1. Therefore, the implementation of gait analysis has the potential to revolutionise drug and intervention development methods by providing novel biomarkers for disease progression. It could also aid the identification of individuals in need of additional support (to combat an increased falls risk) and those receptive to new therapies.

However, since movement disorders are caused by a wide range of disease pathologies and are often associated with a large overlap in terms of disease features, work is needed to ensure that gait measures are disease-specific and sensitive to disease progression.

1.2.4.1. Cognitive Dysfunction

There is evidence to suggest that cognitive dysfunction interferes with gait. As previously discussed, gait and other types of movement are initiated in the brain, controlled by the basal ganglia and coordinated by the cerebellum. The areas conventionally associated with movement are also implicated in wider brain functions such as intellect, emotion and planning (Manto and Marien, 2015). Individuals with mild cognitive impairment struggle with dual-task walking tests and exhibit additional gait impairment in such conditions (Montero-Odasso et al., 2012). Since cognitive decline and dementia can be a comorbidity in several movement disorders, it is essential that these factors be monitored within a clinical study to avoid confounding gait analysis findings. This is especially true for gait tasks where participants are required to make conscious adjustments to their walking gait such as tandem walking and cued walking.

1.2.4.2. Parkinson's Disease (PD)

Parkinson's disease (PD) has received most of the research attention to date, as a target for gait analysis application due to its prevalence in the general population. As the second most common neurodegenerative disease, research into Parkinsonian gait offers an opportunity to develop clinical measures in a highly characterised movement disorder for comparison against different and more subtle gait patterns that are associated with other movement disorders. PD is caused by a degeneration of the basal ganglia and diagnosed by the presence of bradykinesia, muscular rigidity, resting tremor and postural instability (Hughes et al., 1992). PD patients (especially those with posture instability dominant subtype (PIGD)) often exhibit a distinctive pattern of gait dysfunction characterised by stooped posture, asymmetrical arm swing and shortened and quickened stride as well as freezing of gait in severe cases (Lees et al., 2009).

Research has been able to quantify these patterns of spatiotemporal characteristics, although mixed clinical subtypes, and differences in medication have been reported to impact distinguishability of gait features compared with neurotypical individuals (Bovonsunthonchai et al., 2014, Herman et al., 2014). Various studies focused on capturing the postural stability in PD using inertial sensors have also revealed that unrelated to tremor and the reduced gait velocity in this cohort, individuals with PD are unable to attenuate accelerations through the trunk (pelvis to head) sufficiently (Buckley et al., 2015), and have increased transverse jerkiness in lower trunk (Mancini et al., 2011) and the head (Brodie et al., 2015).

1.2.4.3. Cerebellar ataxia (CA)

Ataxia is both a neurological sign and the term for a group of diseases characterised by incoordination of bodily movements. Gait ataxia is clinically recognisable as a wide-based stance with truncal instability and irregular lurching steps, which causes considerable disability in patients (Stolze et al., 2002).

Cerebellar ataxia (CA) involves damage of cerebellum, but can involve the brainstem through space-occupying lesions. It is associated with balance and walking problems due to dysfunctional coordination of movements. It is distinct from sensory ataxias that result from proprioceptive abnormalities and vestibular disorders.

CA has acquired and hereditary aetiologies. The hereditary cerebellar ataxias (HCAs) affect more than 10,000 individuals in the UK (Wardle and Robertson, 2007) and are diagnosed through careful examination of family history and genetic testing. In these individuals, Autosomal Dominant, Autosomal Recessive, Mitochondrial or X-linked genetic mutations are inherited (Jayadev and Bird, 2013). Neurodegeneration leads to clinical signs characteristic of the area of the Cerebellum affected (Figure 1.3).

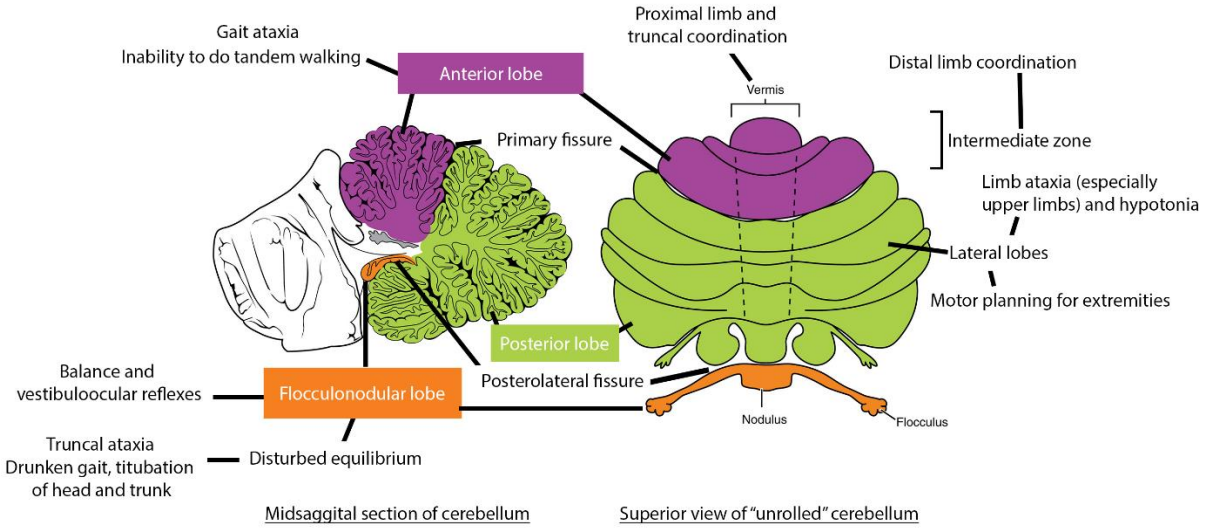

Figure 1.3: Functional anatomy of cerebellum

Anatomy of the cerebellum highlighting key zones and lobes with important functions and impact of dysfunction noted. Image adapted from Major Regions of the Cerebellum (From Wikimedia Commons, the free media repository, licensed under the Creative Commons Attribution 3.0 Unported license. Attribution: OpenStax College (Anatomy & Physiology, Connexions Web site. http://cnx.org/content/col11496/1.6/, Jun 19, 2013.) with details from Clinical Methods: The History, Physical, and Laboratory Examinations. 3rd edition Walker HK (1990)

Dysfunction of the cerebellum has consistently been correlated with balance related gait problems throughout the literature indicating the role of the cerebellum in balance control in gait. Movement dysfunctions can map to specific locations of cerebellar dysfunction such as deficits in goal-directed movements due to dysfunction of the intermediate zone of the cerebellum (Ilg et al., 2007). Studies exploring neurological lesions have elucidated details regarding the symptoms of different ataxias. For instance, degeneration of the anterior cerebellar cortex and spinocerebellum are associated with a wide staggering gait pattern and nystagmus along with vertigo where posterior lobes involved. Meanwhile, vestibulocerebellum involvement includes dysarthria, ipsilateral appendicular ataxia as symptoms (Brust, 2012).

There is considerable heterogeneity across the HCAs which leads to highly variable patterns of anticipation observed, presentation and progression experienced. Autosomal Dominant Cerebellar Ataxias (AD CA) are the most common HCAs with an estimated prevalence of between 0.001-0.005% in the general population (0.9-1.3 cases per 100,000 people) but subtype prevalence varies worldwide (Ruano et al., 2014). There are more than 40 AD CAs including Spinocerebellar Ataxias (SCA) and Episodic Ataxias (EAs).

It can be difficult to differentiate between ADCAs due to overlapping characteristics such as variable age of onset and disease course. In up to two-thirds of SCA cases, for instance, gait disturbances are the presenting symptom. However, an isolated or pure cerebellar syndrome is uncommon, since many patients also display pyramidal and extrapyramidal signs, and cognitive deficits. EAs are characterised by episodes of ataxia and dysarthria between seconds and minutes to hours following sudden shock or emotional stress.

Technological advances in molecular diagnostics have enabled the identification and classification of 40 SCAs (Sun et al., 2016), while genetic testing, magnetic resonance imaging, motor conduction studies and clinical history are highly informative to diagnosis. Unfortunately, phenotypic heterogeneity can lead to diagnostic difficulties in many individuals. This information does not impact disease management in a significant way beyond diagnosis. For instance, SCAs are progressive trinucleotide (CAG_n) repeat diseases that result in the formation of nuclear aggregates due to the translation of an abnormal polyglutamine tract in the subsequent protein. Although the age of onset shows an inverse correlation with the size of CAG repeat expansion, there is no clear correlation between CAG

repeat expansion size and disease progression. This indicates that other factors confound the prognosis and impact of the disease (Ashizawa et al., 2013).

There are no established treatments for CA and the rehabilitation and physiotherapy interventions widely employed to relieve symptoms and teach compensatory techniques are evidenced by only small studies and highly varied results. Therefore, there is a need for further investigation of gait in CA to improve understanding of pathologic gait in order to contextualise intervention effects (Marsden et al., 2016).

With the advances in molecular genetics, there is now evidence from the preclinical stage of SCAs in an effort to monitor the early disease progression (Maas et al., 2015). For instance, Rochester et al. (2014) revealed that a cohort of asymptomatic individuals with a preclinical SCA6 mutation, exhibit some gait similarities to a group diagnosed with SCA6 and these correlated with disease progression. While step time variability was significantly higher in preclinical syndrome than in controls, step velocity and step width, also correlated with total ICARS scores suggesting that gait changes are sensitive to progressing ataxia. Similarly, Velazquez-Perez et al. (2016) published the first results from a cross-sectional study of postural stability during the prodromal phase of SCA2. They described an early increase in lateral and anteroposterior sway that correlated to time until disease onset, and that was not detectable by standard clinical assessment using the SARA scale.

Further, vestibular and cerebellar gait disorders can be distinguished on basis of the pace, base of support and variability domains of walking gait patterns since patients with these diseases often maintain their walking pace to rely less on sensory feedback control (Schniepp et al., 2019, Schniepp et al., 2012). Similarly, cerebellar vermis lesion size has been shown to correlate with gait stability (Hoogkamer et al., 2015).

Early studies using instrumented analyses of gait in individuals with cerebellar syndromes described the spatiotemporal gait characteristics of CA as reduced cadence, step and length, gait velocity, and increased step and stride time and stance and swing phases (Palliyath et al., 1998, Stolze et al., 2002). Unfortunately, in these studies, participant numbers were small (just 10 and 12 per cohort respectively) and the patient cohorts were of mixed aetiology and rarely described by genetic diagnosis. There is, therefore, no clear way of retrospectively distinguishing between the different ataxia phenotypes included.

Within-person variability of gait is also increased in CA for many spatiotemporal parameters and is dependent on walking speed and related to an increased likelihood of falls (Schniepp et al., 2014, Wuehr et al., 2013). Trunk instability in individuals with CA has a huge impact on their ability to perform complex gait tasks such as sudden stopping and turning as well as complete everyday activities (Serrao et al., 2013a, Serrao et al., 2013b). The reduced velocity and spatiotemporal variability, observed in those with CA during gait are thought to be the principal mechanism of compensating for trunk instability to reduce the likelihood of falls (Schniepp et al., 2016, Schniepp et al., 2014).

Further investigation is needed to identify features that can distinguish otherwise asymptomatic population prior to genetic diagnosis but this research demonstrates that instrumented techniques have real potential to accurately measure gait deviations in early CA, promising biomarkers for disease progression.

1.2.4.4. Choreic Gait

Choreiform gait is caused by the hyperkinetic movements that occur in individuals with middle to late-stage Huntington's disease (HD) and is described as slow and wide-based, irregular, but unmistakable as a "dancing gait" associated with spontaneous knee flexion and leg raising.

Caused by functional dysregulation of the indirect pathway of the basal ganglia system, HD is diagnosed by the presence of chorea, dementia, and psychiatric disturbances (Ross et al., 2014). The differential diagnosis for HD includes a number of HD-like diseases (Schneider et al., 2007), Spinocerebellar ataxia 17 (SCA17) (Schneider et al., 2006) and early-onset Alzheimer's' Disease as well as some more easily excludable non-inherited conditions such as cerebrovascular disease (Drouin-Ouellet et al., 2015). In advanced HD, gait changes include bradykinesia, rigidity, and dystonia causing considerable overlap with previously discussed gait patterns. Studies have looked to capture gait in HD through instrumented analysis. For example, Dalton et al. (2013) implemented a single triaxial accelerometer in agreement with a computerised walkway. They were able to distinguish between premanifest and manifest HD participants and healthy control participants through variability and regularity measures such as step time variability, stride length variability, and step and stride length.

The impact of disease progression on measurable gait changes continues to be of interest as treatments are restricted to symptomatic therapies (Mestre et al., 2009). Therefore, analysis of more subtle gait characteristics such as spatiotemporal parameters, the variability of gait and features of upper body motion, has potential to distinguish the specific gait changes that differentiate HD from other gait disorders.

1.2.5. MUSCULOSKELETAL DISEASE

The musculoskeletal system is comprised of the skeleton, joints, muscles, and connective tissues and can be affected by a variety of primary or secondary disorders such as metabolic disorders, infection, injury and neurological disease.

Spasticity or muscle stiffness, for instance, is associated with increased tendon reflex activity and hypertonia, which is seen in diseases like hereditary spastic paraplegia (HSP), cerebral palsy (CP) and multiple sclerosis (MS). Due to increased muscle contraction, the common gait characteristic associated with rigidity and foot-dragging. As it can be present in individuals with certain forms of CA, it is important to make the distinction between spastic and purely ataxic gait (de Bot et al., 2012).

HSP refers to a group of genetic disorders, which in its “pure” form leads to progressive spasticity in the lower limbs and shortened strides (Salinas et al., 2008). Early gait analysis in this population identified reduced velocity, stride length, step height and knee-ankle range of motion as well as a widened base of support (Braschinsky et al., 2009, Klebe et al., 2004).

CP is a condition where hypertonia and muscle weakness (termed spastic diplegia) can be complicated by seizures and dysphagia. A considerable amount of research has been completed into the use of gait analysis in the management of CP (Baumann, 1984). There are notable similarities between CP and HSP, such as early childhood disease onset and delayed motor milestones. Therefore, gait analysis has a role here to help establish a differential diagnosis in cases where patient history is insufficient and genetic testing is not possible.

Cimolin et al. (2007) and later Piccinini et al. (2011) used gait analysis to distinguish between these conditions. These studies reported that compared to typically developing children, the pathological groups displayed lower gait velocity, higher step width and reduced step length and higher anterior pelvic tilt. The HSP cohort, however, exhibited a more normal ankle position, and a distinct motor strategy of the knee than the Spastic Diplegia group, which is more flexed during initial contact and hyperextended for longer during mid-stance.

Bonnefoy-Mazure et al. (2013) meanwhile explored upper body kinematics and determined that HSP compensated for lower limb perturbations through the use of the spine, whilst those with Spastic Diplegia used their arms more.

The gait impairment in CP, however, is not confined to lower limb rigidity and studies implementing inertial sensors have observed higher trunk accelerations and asymmetry in all three planes of motion (Saether et al., 2014). This results in balance problems and reduced gait harmony resulting in impaired gait instability for their age (Iosa et al., 2012).

Whilst further study is essential, research into HSP and CP demonstrate that gait analysis can provide a diagnostic benefit for people affected by spasticity whilst also illustrating the impact of specific musculoskeletal pathologies on walking gait.

1.3. SUMMARY

Locomotion is a complex movement, controlled by an intricate network of brain areas and affected by neurological disorders. The motivation of many research groups is either improving understanding of the various contributions to the walking gait or developing a clinical biomarker for movement disorders and neurological diseases. This research is important, as a consensus needs to be reached regarding the sensitivity and specificity of protocols and measures, prior to the incorporation of gait analysis techniques into clinical practice and development of novel treatments.

Neurological diseases and movement disorders can cause considerable disability and form a large societal and economic burden which will become greater as the population ages in coming years. Compared with healthy people, individuals with movement disorders are less stable while walking. This contributes to an inability to adapt their gait to their surroundings which can cause considerable disability and increased risk of falls. The ability to complete daily activities and independent ambulation are important to the quality of life in people with and without movement disorders. Therefore, it is vital to be able to measure these factors objectively, reliably, and accurately.

Gait analysis is now relatively common in sports therapy and physiotherapy and increasingly more research is underway into its clinical applications. By assessing gait in healthy people and individuals with movement disorders, it is possible to attain additional understanding of the neural processes of walking, the influence of upper body motion on overall gait, and the implications of neurological disease on walking. This enables the quantification of the

precise durations, dimensions and fluctuations of the gait cycle. Furthermore, if instrumented assessments of locomotion can distinguish between movement disorders and within disease subtypes, there is real clinical potential for the development of a complementary index of gait disturbance.

CA, is a heterogeneous syndrome characterised by incoordination and instability. Individuals suspected of CA are now routinely offered genetic testing but in some cases, genetic testing is unable to clarify the diagnosis. Rating scales such as the ICARS and SARA, validated for assessment of the severity of ataxia, can also have difficulty distinguishing between subtypes and monitoring disease progression. There is no disease-modifying therapies in place for CA and rehabilitation techniques are not routinely validated in terms of objective gait improvement.

Research into the various contributions to walking gait in pathological populations and the development of a clinical biomarker for movement disorders has the potential to revolutionise disease monitoring. Therefore, it is important that a consensus is reached regarding the gait characteristics of CA. Quantifying the clinically relevant change in gait characteristics and establishing reliable protocols will promote the incorporation of gait analysis techniques into everyday clinical practice and pharmaceutical trials.

1.4. AIMS AND OBJECTIVES

The long-term aim of this project is to uncover a novel gait biomarker for the progression of ataxia that is capable of tracking disease progression and is appropriate for incorporation into clinical practice.

In order to achieve this, a number of studies will be completed as part of this project:

- Completion of a Systematic Review to summarise and meta-analyse the reported gait characteristics of cerebellar ataxia (CA). Critical appraisal and quality assessment of previously reported results will instruct future work. (Chapter 2)
- In-house validation of proposed gait analysis equipment against the gold-standard of gait analysis (3D motion capture) to ensure the accurate measurement of spatiotemporal parameters and confirm the synchronisation of data capture. (Chapter 3)

- An observational gait analysis study will be completed to assess the gait characteristics of CA compared with a healthy age-matched control population. The association between upper-body motion and spatiotemporal gait parameters as well as the influence of disease severity and walking speed will be explored. (Chapter 4)
- After period of 12-months, follow up assessments of gait in the study population will be completed. A subgroup of participants will also be assessed at 24-month follow-up to explore changes over a longer time period. The ability of gait features to detect disease progression will also be investigated. (Chapter 5).

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Chapter 2. A SYSTEMATIC REVIEW OF THE GAIT CHARACTERISTICS ASSOCIATED WITH CEREBELLAR ATAXIA

The work within this chapter has been published as a paper in the Journal Gait & Posture, following peer-review. The definitive version was of this work is available under Open Access at: https://doi.org/10.1016/j.gaitpost.2017.11.024

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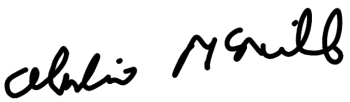
I underwent Systematic Review training at the University of York Centre for Dissemination of Research.

My supervisors and co-authors, Dr Alisdair McNeill, Prof. Claudia Mazzà and I, contributed to the study conception and design as well as interpretation of results. I was responsible for data acquisition, and collation, meta-analysis, statistical analysis and presentation. I drafted the manuscript following guidance from training at the University of York, which was subsequently edited by Dr Alisdair McNeill and Prof Claudia Mazzà in preparation for publication. Following peer review, all authors were involved in manuscript revisions. I completed additional analyses in response to reviewer's comments which were reserved from the published article but are included here for the purposes of discussion.

Yours Sincerely,

Ellen Buckley (PhD Candidate) 

Dr Claudia Mazzà 

Dr Alisdair McNeill 

2.1. INTRODUCTION

Gait ataxia is clinically recognisable as a wide-based stance with truncal instability and irregular lurching steps, which can result in an increased risk of falls (van de Warrenburg et al., 2005b). This can be accompanied or predominated by other symptoms depending on the ataxia subtype (Stolze et al., 2002).

Presently, the principal methods of gait assessment in a clinical setting are through the use of subjective rating scales such as the Scale for the Rating and Assessment of Ataxia (SARA) (Schmitz-Hübsch et al., 2006). Although many of these are validated to detect progression of ataxia (Burk et al., 2013, Jacobi et al., 2012), there is evidence to suggest that clinical assessment scales might underestimate the severity of gait changes in cerebellar ataxia (CA) (Schniepp et al., 2016).

Instrumented gait analysis techniques quantify subtle gait characteristics that would not be detected by clinical examination. There is increasing acceptance of the use of gait analysis methods such as 3D motion capture, pressure-sensitive walkway and inertial sensor for the assessment of neurological diseases that manifest with gait changes.

Improved classification of ataxic gait disturbance and definition of biomarkers for disease progression will enable quantification of the effect of novel and existing interventions to improve disease management in CA while also clarifying the disease mechanisms in specific CA subtypes (Bates et al., 2016).

Early studies using instrumented gait analysis in individuals with cerebellar syndromes described the spatiotemporal gait characteristics of CA as reduced cadence, step and length, gait velocity, and increased step and stride time and stance and swing phases (Palliyath et al., 1998, Stolze et al., 2002). However, other studies provide conflicting results and many report inconsistencies within cohorts. There are currently no guidelines to state the clinically relevant change in gait characteristics.

With technological advances making it quicker and easier to implement gait analysis, studies exploring neurological gait disorders are becoming more prevalent. It is now possible to seek a consensus description of the gait characteristics of CA and differences compared with healthy controls. By comparing CA to healthy control cohort in preferred paced walking gait tasks, the gait pattern changes that are sensitive to this disease group and reflective of gait capacity can be quantified. This will enable an examination of the inconsistencies between

published studies and the repeatability of the spatiotemporal gait pattern. It will also allow identification of current deficits in research and guide future research by recognising further work required in the field.

2.1.1. AIMS AND OBJECTIVES

By evaluating and summarising the spatiotemporal gait characteristic measured using instrumented gait analysis techniques, this systematic review aims to answer the question: Which gait characteristics are able to differentiate between CA and controls?

This will provide an estimation of the objective gait changes in CA in a larger cohort than usually possible in single-centre clinical studies of CA and an indication of the number of participants necessary for future case-control clinical studies.

2.2. METHODS

Available literature was systematically searched, following a pre-determined protocol (PROSPERO 2016: CRD42016042149, Available from http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016042149).

Using the PICOS framework (Higgins and Green, 2013) the research question was explored in order to guide the design of search strategy and selection criteria:

- Patient population: adults (age 18yrs or older) with CA
- Intervention: no intervention required
- Comparison: healthy controls where recruited should be matched for age and sex as a minimum
- Outcome: straight-lined self-paced instrumented walking tests
- Study type: Studies of all designs were considered, except review articles, if published since 1996 and available in English. For interventional studies, only baseline gait characteristics included.

2.2.1. SEARCH STRATEGY

The search strategy and selection criteria were developed in line with the review questions and agreed on by two researchers (AM, EB). Titles and abstracts of articles within a number of electronic databases (MEDLINE via OVID, psyc-INFO via OVID, PubMed, IEEE-xplore, Cochrane trials library, web of science core collections, and Scopus) were searched systematically implementing MESH search terms and keywords where appropriate to

combine three search phrases (walking terms (Walk* or gait or Locomotion), measurement terms (Measur* OR assess* OR evaluat* OR examin* OR analysis OR analy*e OR Biomechanic OR kinematic OR instrumented) and ataxia terms (cerebellar ataxia OR gait ataxia)) (Appendix 1). Searches were completed in July 2016, repeated in November 2016, and the output restricted to those published since 1996 until the search date.

Reference lists from eligible articles as well as relevant reviews and systematic reviews were hand searched and studies identified subjected to the same selection criteria. This aimed to reduce any restrictions of the search strategy in uncovering unpublished and published evidence. Records identified were imported into EndNote (Clarivate Analytics), and processed to remove duplicate records and any older articles that remained.

2.2.2. STUDY SCREENING PROCESS

Article screening was guided by an Inclusion/ Exclusion criteria, pre-defined in line with the research question (Appendix 2). Titles and abstracts of articles identified by searches were subjected to the selection criteria by two researchers independently. References were divided between assessors in the interest of time, while 10% of articles were dual-screened to confirm appropriate decision-making and adherence to the selection criteria.

Those articles that satisfied the screening criteria moved on to full-text appraisal. This was completed in parallel by assessors and final selections made through discussion. Where articles were suspected or confirmed to report results from identical or overlapping cohorts of patients the earliest or most relevant article was selected for inclusion.

No restriction on study design was established but reviews and articles published in a non-English language were not considered. The abstracts of non-English articles were translated to check if they would be relevant. The cohort or subgroup were required to have a diagnosis of CA. Any studies related to single-sex groups were not to be considered in the interests of reflecting both sexes equally in the meta-analysis. Studies with a cardiac-related focus were also ruled out to ensure that participants did not exhibit any relevant co-morbidities. It was essential that gait is analysed through instrumented techniques, therefore any studies that reported subjectively observed gait parameters were excluded. Studies, where only activity level or single muscle activity was reported, were also excluded as the core gait characteristics were of interest for meta-analysis. In the interest of establishing a uniform gait analysis protocol, it was vital that studies reported

preferred/comfortable paced straight-line gait in a “normal” condition so those that only investigated gait within “challenged” conditions or during turn phases were not included. A control cohort was not critical for inclusion, but where included participant groups should be well matched for age and sex as a minimum and display no known morbidities. A publication date cut-off was set, with only articles published since the year 1996 considered, intending to garner results from newer, relevant studies implementing recent technological advances. Participants were not required to undergo any type of intervention as baseline gait characteristics were of most interest. References lists from eligible articles were screened to identify further references of interest.

Full-text appraisal was completed in parallel by authors and agreements come to through discussion. Where articles were suspected or confirmed to report results from identical or overlapping cohorts of patients the earliest or most relevant article was selected for inclusion. Literature searches were later repeated to uncover any relevant articles published since initial search completion.

2.2.3. Data Extraction and Synthesis

Study information and gait parameters were extracted from the selected articles and, where necessary, authors contacted to request additional results. All available study information and reported gait characteristics were collated in Microsoft Excel. Where necessary, data were extracted from published images of graphs using WebPlotDigitizer v3.9 (Rohatgi, 2015) and where necessary, authors of selected articles were contacted to clarify study details and obtain unreported results. This included requesting average and standard deviation of cohort gait characteristics where the median and interquartile range was reported and coefficient of variation where other variability measures (such as combined standard deviation) were reported. Articles, where information was not made available for assessment following repeated requests, were excluded from further analysis despite being potentially relevant studies. Where multiple subgroups were examined in a single study, data were combined to a single result following Cochrane Review guidance (Higgins and Green, 2013).

In articles where despite the cohort being of average adult age, some individual participants were younger than 18, authors were asked to provide gait data from the more limited group of adult participants.

Results were converted to common units of measurement so that all spatial parameters were expressed in terms of metres (m) and temporal parameters expressed in terms of seconds (s). Speed was expressed as metres per second (m/s), cadence as the number of steps in a minute (steps/ min) while phases of the gait cycle were expressed as a percentage of the total stride duration (%). Gait variability was reported as either Coefficient of Variation ((CV) defined as Standard Deviation (SD)/mean (%)) or combined Standard Deviation ((cSD) defined as the square root of the mean-variance of the left and right steps (cm))(Galna et al., 2013).

2.2.4. STATISTICAL ANALYSIS

For cohort demographics, descriptive statistics (average, standard deviation (SD) and range) were computed using IBM SPSS Statistics for Windows, version 23 (IBM Corp., Armonk, N.Y., USA).

Treating the complete dataset as a cohort, Pearson's' non-parametric bivariate correlation analysis was also completed to display the associations between parameters. Significant and relevant results were deemed as a correlation coefficient greater than 0.6 and lower than -0.6 and a significant p-value less than 0.05. Correlation analysis was performed for ataxia and healthy controls separately.

2.2.5. META-ANALYSIS

Meta-analysis was completed in Rstudio (version 3.3.2)(R Core Team, 2017), using the "meta" package (Schwarzer, 2007). For parameters where results were available for more than 3 studies, the weighted mean difference (MD), 95% Confidence intervals (CI) and the standardised Z-score for overall effect were computed. Heterogeneity was tested using I^2 statistic, although a single group random effect model (REM) used throughout to give a conservative approach to meta-analysis.

Forest plots were generated to display the comparison of walking gait characteristics in CA and healthy controls from preferred/ comfortable self-paced walking.

Studies without control cohorts were included in the meta-analysis but not given any weighting in the calculation of the pooled estimate. To ensure the uniformity of data processing, gait parameters that had been standardised for individual biomechanical features (e.g. leg length or height), were excluded from meta-analyses. For gait variability,

only coefficient of variation was reported commonly enough for results to be meta-analysed. The weighted mean and standard deviation of the most common parameters was also calculated implementing the weights as produced in meta-analysis to provide a summary output in Rstudio (version 3.3.2)(R Core Team, 2017) using the “weights” package (v1.0 Pasek, 2020).

2.2.5.1. Subgroup Meta-analysis

In the predefined protocol, further analysis of the effect of gait speed, rehabilitation and protocols were to be determined following data appraisal. Therefore, a subgroup meta-analysis was performed in RStudio for two identifiers: Disease group (Mixed CA, SCA, or FRDA); and gait analysis technique used (3D motion capture, pressure-sensitive walkway, inertial sensor or alternative method).

For each subgroup, a single group inverse-variance (IV) random effect model to produce the weighted mean difference, 95% Confidence intervals (CI) and the standardised Z score for overall effect was computed. Heterogeneity was tested using I^2 statistic (percentage of variation across studies that is due to heterogeneity rather than chance). This was not able to be applied for any subgroups containing only 1 study. Tests for differences between subgroups produced Chi^2 statistic and P-value. Forest plots were then generated to display weighted mean differences for each subgroup and overall effect.

2.2.6. QUALITY ASSESSMENT

Prior to data extraction, studies that were eligible for inclusion underwent a quality assessment to detect the risk of bias using an adaptation of the criteria described by Littell et al. (2008)(Appendix 3). Researchers judged for each article whether each criterion was met (Yes (Y) or No (N), could not be determined (CD), the criterion was not applicable (NA) or information was not reported (NR) and gave an overall rating of Good, Fair or Poor. Researcher’s independent findings were compared, and ratings were agreed on through discussion. This allowed appraisal of the limitations of each study following a uniform structure of enquiry but did not aim to exclude articles on the basis of their quality.

2.2.7. POWER CALCULATION AND SAMPLE SIZE ESTIMATION

Statistical power estimated following the formula, where Z value taken from random-effects model meta-analysis and N given for CA and HC cohorts.

$$d = Z/\sqrt{\frac{N_{CA} + N_{HC}}{2}}$$

Sample size (n) for each variable calculated as (Rosner et al., 2011):

$$n = \frac{\left(\left(SD_{CA}^2 + SD_{HC}^2\right)/_K\right) \times (z_{1-a/2} + z_{1-\beta})^2}{(mean\ diff.)^2}$$

Where mean difference between cohorts (CA-HC) taken from meta-analysis results for each parameter. The weighted SD was computed implementing the weights as produced by meta-analysis in Rstudio (version 3.3.2)(R Core Team, 2017) using the "weights" package (v1.0 Pasek, 2020). SD was adjusted for K, the ratio of participants per cohort (N_{CA}/N_{HC}), an alpha level 0.05 ($z_{1-a/2} = 1.96$) and statistical power 90% ($z_{1-\beta} = 1.28$). Estimates were increased by 10% and rounded up to the next whole number. Where estimation indicates that less than 30 participants are required, in order to satisfy the central limit theorem a more realistic minimum of 30 participants should be considered more appropriate to ensure an approximately normal distribution of values (Kwak & Kim, 2017).

2.3. RESULTS

2.3.1. STUDY SELECTION

In total, 3763 records were identified through searches of 6 databases and numerous reference lists. Of the 65 records that were screened as full texts, 21 articles (Caliandro et al., 2015, Chini et al., 2016, Conte et al., 2014, Ebersbach et al., 1999, Gouelle et al., 2013, Ienaga et al., 2006, Ilg et al., 2010, Ilg et al., 2007, Im et al., 2016, Martino et al., 2014, Matsushima et al., 2015, Milne et al., 2014, Mondal et al., 2015, Palliyath et al., 1998, Rochester et al., 2014, Schmitz-Hübsch et al., 2016, Schniepp et al., 2014, Seidel and Krebs, 2002, Serrao et al., 2012, Stephenson et al., 2015, Wuehr et al., 2013) were selected for data extraction. Seven other articles were considered for inclusion but deemed to incorporate cohorts that overlapped with included articles. Due to issues of data availability, 3 articles (Ilg et al., 2010, Im et al., 2016, Mondal et al., 2015) were excluded from the meta-analysis.

The included articles all reported spatiotemporal gait characteristics of CA, measured using instrumented gait analysis techniques during straight-line walking.

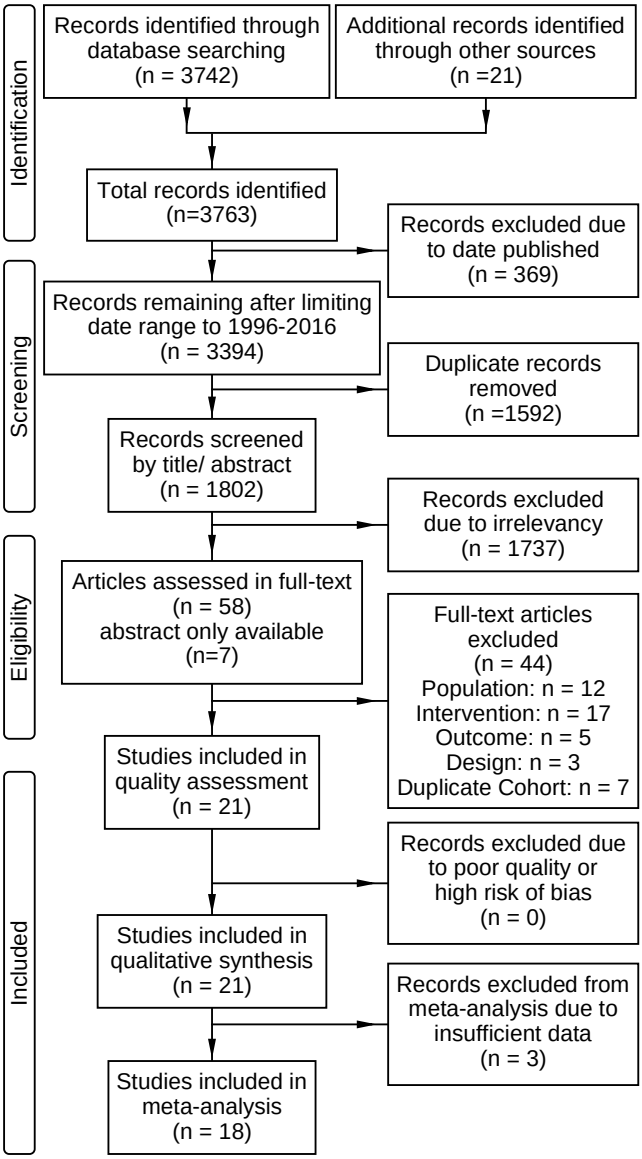


Figure 2.1: Flow Chart of Study Selection.

2.3.2. CRITICAL APPRAISAL

A summary of the 21 included articles (Caliandro et al., 2015, Chini et al., 2016, Conte et al., 2014, Ebersbach et al., 1999, Gouelle et al., 2013, Ienaga et al., 2006, Ilg et al., 2010, Ilg et al., 2007, Im et al., 2016, Martino et al., 2014, Matsushima et al., 2015, Milne et al., 2014, Mondal et al., 2015, Palliyath et al., 1998, Rochester et al., 2014, Schmitz-Hübsch et al., 2016, Schniepp et al., 2014, Seidel and Krebs, 2002, Serrao et al., 2012, Stephenson et al., 2015, Wuehr et al., 2013) is displayed in Appendix 4. On average, each study included 19.43 ± 11.33 patients, which combined, reflects gait assessments for 408 patients with established CA and 403 healthy controls, with 44.12% and 48.14% females respectively (in Table 2.1).

Although only 16 articles had control cohorts, controls were always matched to the patient cohort's age (47.3±11.23yrs) and often matched for sex. Height and mass were also matched when reported and when pooled, no significant difference was found between cohorts in any of the morphological features (BMI, mass and height, leg length) in independent t-tests ($p<0.05$). These clinical studies were completed across 10 countries (9 developed and 1 developing). In 1 paper (Gouelle et al., 2013) gait data from a limited group of adult participants were gathered from authors in order to ensure the cohort had an average age over 18 years.

Table 2.1: Summary of the Cohort Demographics

	Cases			**Controls**			
	n	**Mean Average ± SD (range)**	**k**	**n**	**Mean Average ± SD (range)**	**k**	**p Value**
Total no. (% Female)	408 (44.12%)	19.43 ± 11.33 (8-51)	21	403 (48.14%)	25.19 ± 29.03 (6-123)	16	
Age (yrs)		48.30 ± 11.23 (20.50-64.30)	21		48.34 ± 8.55 (29.60-60.90)	16	0.991
Height (cm)		170.87 ± 4.23 (165.00-176.90)	10		170.14 ± 2.74 (167.00-174.00)	6	0.697
Mass (kg)		74.90 ± 4.99 (68.00-81.00)	8		73.28 ± 3.70 (69.10-78.00)	5	0.546
Leg length (cm)		84.73 ± 6.60 (78.00-91.20)	3		85.83 ± 5.35 (80.00-90.50)	3	0.834
BMI (kg/m^2)		26.86 ± 3.33 (23.11-33.90)	8		25.03 ± 1.54 (22.60-26.60)	5	0.277
Disease duration (months)		41.25 ± 63.26 (3.70-216.00)	13				
ICARS (/100)		26.54 ± 8.52 (16.70-45.10)	9				
SARA (/30)		11.94±3.19 (8.60-16.40)	5				

See Appendix 4 for gait analysis results from each study. n = number of participants, k = number of articles featured in, results reported as average ± standard deviation (SD) (range).

Patient cohorts were very often of mixed aetiology, but most (17) stated the specific diagnoses reflected in the group. Gait characteristics of more specific ataxia types were explored in 9 studies (Gouelle et al., 2013, Ienaga et al., 2006, Ilg et al., 2010, Milne et al., 2014, Rochester et al., 2014, Schmitz-Hübsch et al., 2016, Serrao et al., 2012, Stephenson et al., 2015, Wuehr et al., 2013) encompassing Chromosome 16q-linked Autosomal Dominant Cerebellar Ataxia (16q-ADCA), Spinocerebellar Ataxias (SCA1/2/6/14), cerebellar subtype Multiple System Atrophy (MSAc), and Friedreich Ataxia (FRDA). Findings from these studies included: a correlation between plantar pressures and Double Limb Support phase (DLS) in SCA6 compared with MSAc and 16q-ADCA groups (Ienaga et al., 2006), a greater improvement with rehabilitative training in CA than afferent forms of ataxia (Ilg et al., 2010) and a longer step length measured in individuals with SCA1/2 than with FRDA (Serrao et al., 2012).

Twenty of the records included related to published articles accompanied by one conference abstract. This group of articles contains 2 intervention studies that explored the impact of rehabilitation and training on ataxic gait and 17 prospective observational studies investigating specific gait features of ataxic gait or validating new clinical tools and methods of analysis. Follow-up assessments were completed in 4 studies, of which two were training studies (Im et al., 2016) which showed significant improvements in motor performance and reduced ataxia symptoms in cerebellar ataxia. The third incorporated data as independent samples (Gouelle et al., 2013) and the remaining study (Matsushima et al., 2015), performed a follow-up assessment at 6 months on a subset of the initial cohort (n=11/51) and identified no significant difference in velocity (the only spatiotemporal parameter reported).

Disease symptoms and balance/gait deficits were rated using clinical rating scales in 17 studies. Most commonly, International Cooperative Ataxia Rating Scale (ICARS) (Trouillas et al., 1997) or Scale for the Assessment and Rating of Ataxia (SARA)(Schmitz-Hübsch et al., 2006) were implemented, with 8 other rating scales used in the included studies. The ICARS and SARA scores reported confirming that patients included here showed gait difficulties but were still capable of independent walking (Klockgether et al., 1998, Schmitz-Hübsch et al., 2006). Use of walking aids was expressly excluded in 14 studies while 11 studies excluded individuals with cognitive dysfunction.

Falls occurrence was reported in just 3 studies (Chini et al., 2016, Rochester et al., 2014, Schniepp et al., 2014) where a higher rate of falls was apparent in CA, with 43.18% (38/88) of those patients reported falling with the last 3-12 months. Between these studies, only Schniepp et al. (2014) performed an analysis exploring gait metrics associated with fall status. They reported that a history of falls is associated with an increased stride length variability and stride time variability which correlates with preferred walking speed.

To track spatiotemporal characteristics of walking, the most commonly implemented gait analysis techniques within these studies were 3D Motion Capture, employed in 9 studies, and Pressure Sensitive Walkways, used in 8 studies. Other techniques used were: triaxial inertial sensors, pressure-sensitive insoles, force plates and pressure-sensitive treadmill. LED array and surface EMG was also used in places with one study applying a pulley system attached at feet to be monitored by an optical recording device. Within the included studies, all participants completed comparable short gait tasks to assess free unassisted, straight-line, self-determined speed walking in a laboratory setting. Walkway length for different studies was between 2.2m and 20m (mean ± SD = 9.1m ± 3.4m) and was principally dictated by the equipment type used. Participants walked barefoot in each of the 9 studies where 3D motion capture was used. For all other studies, participants wore shoes or this detail was not reported.

Eight studies explored the influence of pace on gait, through trials performed at different walking speeds. Different velocity walking trials were executed in 7 studies (Ebersbach et al., 1999, Im et al., 2016, Martino et al., 2014, Milne et al., 2014, Schmitz-Hübsch et al., 2006, Schniepp et al., 2014, Stephenson et al., 2015, Wuehr et al., 2013). Participants within these studies completed walking tasks at a range of speeds between very slow and very fast. Upon full-text appraisal, fast-paced walking by patients with ataxia was consistently associated with increased cadence, step and stride length, and swing phase as well as decreased in the stance and DLS phases, compared with preferred- and slow-paced walking. Meanwhile, the variability of stride time and stride length, shows a U-shaped curve with the minimal CV magnitude observed in preferred paced walking and highest CV magnitude detected in slow-paced walking (Schniepp et al., 2014, Wuehr et al., 2013).

Although 42 gait parameters were identified, only 14 were reported frequently enough to be explored further through meta-analysis. A summary of gait metrics reported by each article can be seen in Appendix 4 and Figure 2.2 displays the frequency of these gait metrics.

2.3.3. Quality Assessment

Upon quality assessment, 10 articles were rated "good" with low risk of bias, 10 rated "fair" with some risk of bias (Appendix 5). None were deemed to be of "poor" quality and at too high risk of bias for inclusion, but insufficient data were available from one study (Mondal et al., 2015) to reach a full rating. Score breakdown can be seen in Figure 2.3.

2.3.4. Statistical/ Descriptive Analysis

The included articles reported several distinct spatiotemporal gait characteristics measured during walking at a self-selected pace. A summary of each study's average and standard deviation of gait characteristics outcome with units displayed in Appendix 6.

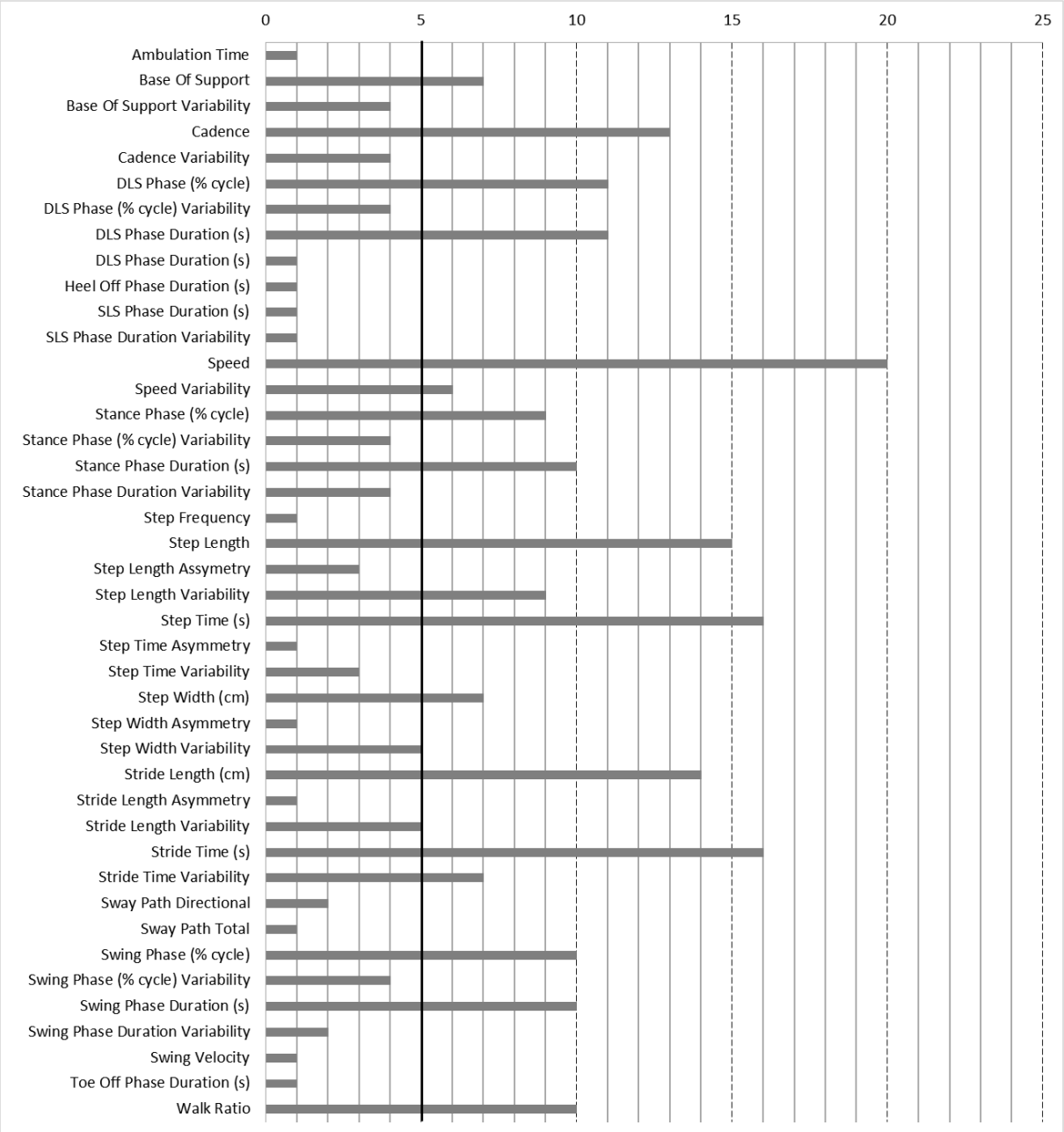


Figure 2.2: Frequency of gait metrics reporting

Frequency of reporting of gait parameters by the articles included in the study with units indicated. Those reported by more than 5 studies were considered for meta-analysis.

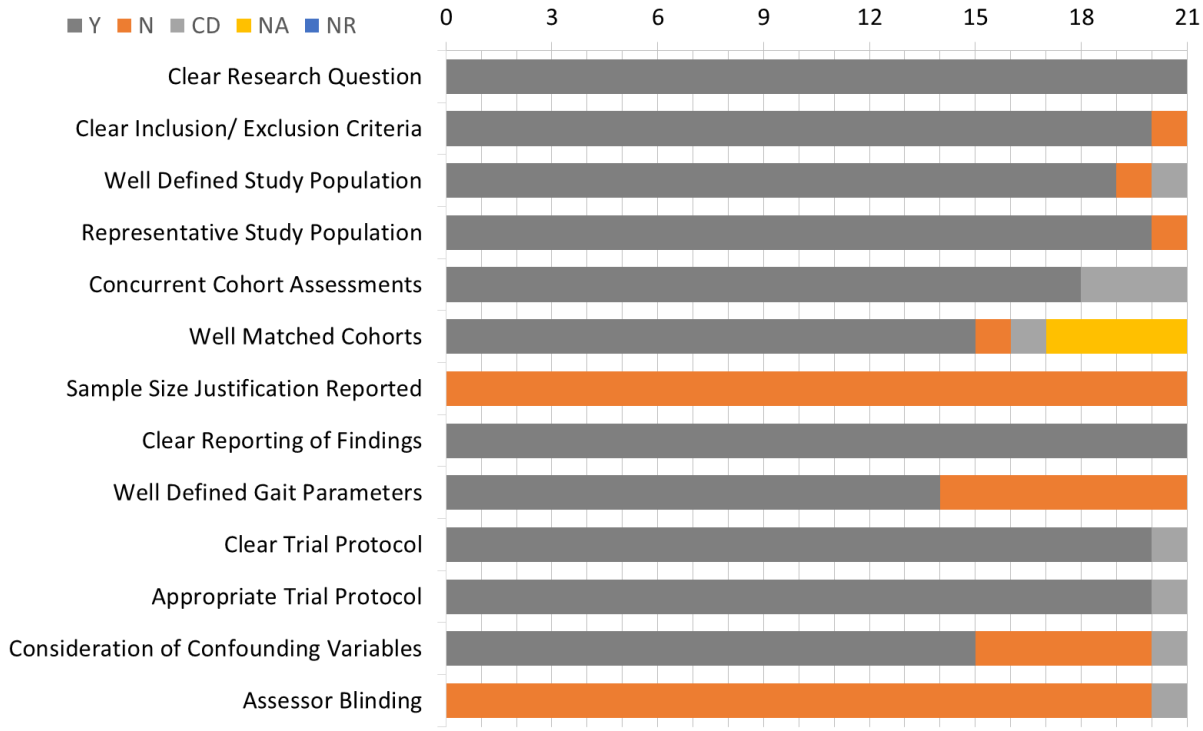


Figure 2.3: Quality assessment score breakdown
Break down of ratings for 21 included articles in quality assessment. Abbreviations: “Y” Yes; “N” No; “CD” Cannot determine; “NA” not applicable; “NR” Not reported.

2.3.5. META-ANALYSIS

The included articles reported several distinct spatiotemporal gait characteristics measured during straight-line walking at a self-selected pace.

Meta-analysis was completed for 14 spatiotemporal gait parameters extracted from 18 primary studies. Other parameters lacked enough evidence to assess between cohort differences. Exclusion of results standardised to leg length or height led to some data being excluded from the meta-analysis. A summary of the overall cohort weighted mean values for each gait metric can be seen in Table 2.2.

In the patient dataset (Appendix 7), correlation analysis showed significant positive relationships between disease severity and ICARS score (r=0.725, p=0.027), and between mass and BMI (r=0.857, p=0.014). The only significant correlations between gait parameters were speed with step length (r=0.893, p=0.007) and speed with stride length (r=0.829, p=0.042). However, in the control cohort (Appendix 7) the only significant correlation was between step length and speed (r=0.964, p=0.000).

2.3.5.1. Pace

Walking speed was studied by 14 studies (Caliandro et al., 2015, Ebersbach et al., 1999, Gouelle et al., 2013, Ilg et al., 2007, Matsushima et al., 2015, Milne et al., 2014, Palliyath et al., 1998, Rochester et al., 2014, Schmitz-Hübsch et al., 2016, Schniepp et al., 2014, Seidel and Krebs, 2002, Serrao et al., 2012, Stephenson et al., 2015, Wuehr et al., 2013) and in ataxia (n=281) preferred walking speed was significantly reduced compared with healthy controls (n=345) (REM, MD=-0.36m/s, 95% CI (-0.43, -0.29), p<0.01, I^2=0%) (Figure 2.4a). Similarly, in the 10 studies that reported cadence (number of steps per min) (Ebersbach et al., 1999, Gouelle et al., 2013, Ienaga et al., 2006, Matsushima et al., 2015, Milne et al., 2014, Palliyath et al., 1998, Rochester et al., 2014, Schmitz-Hübsch et al., 2016, Schniepp et al., 2014, Stephenson et al., 2015) the ataxia cohort (n=208) demonstrated significantly reduced cadence than healthy controls (n=267) (REM, MD=-13.28 steps/min, 95% CI (-19.99, -6.58), p<0.01, I^2=99%) (Figure 2.4b).

Table 2.2: Summary overall weight mean gait metrics

	Cases			Controls			
	n	**Mean Average ± SD**	**k**	**n**	**Mean Average ± SD**	**k**	**P value**
Pace							
Speed (m/s)	281	0.91± 0.16	14	345	1.27 ± 0.15	12	**<0.01**
Cadence (steps/min)	208	98.68 ± 10.85	10	267	111.97 ± 6.71	8	**<0.01**
Spatial							
Step Length (m)	139	0.54 ± 0.09	7	251	0.68 ± 0.06	7	**<0.01**
Stride Length (m)	94	1.17 ± 0.01	5	142	1.37 ± 0.04	3	**0.01**
Base Width (m)	192	0.17 ± 0.04	10	241	0.11 ± 0.03	8	**<0.01**
Temporal							
Step Time (s)	42	0.63 ± 0.01	3	158	0.51 ± 0.02	3	**0.01**
Stride Time (s)	120	1.21 ± 0.06	7	177	1.03 ± 0.04	6	**<0.01**
Gait Cycle							
Swing Phase (% cycle)	54	33.92 ± 3.44	4	146	39.25 ± 0.14	3	**<0.01**
Stance Phase (% cycle)	57	65.99 ± 2.78	4	161	60.55 ± 0.22	4	**<0.01**
Double Limb Support Phase (% cycle)	126	22.50 ± 6.77	7	170	16.76 ± 7.26	5	**<0.01**
Variability							
Step Length Variability (%CV)	78	8.96 ± 1.94	5	184	3.07 ± 0.71	5	**<0.01**
Stride Length Variability (%CV)	80	6.82 ± 1.70	4	142	1.95 ± 0.24	3	**<0.01**
Stride Time Variability (%CV)	116	5.54 ± 1.05	6	187	2.24 ± 0.36	5	**<0.01**
Speed Variability (%CV)	40	7.68 ± 4.31	3	148	3.46 ± 0.49	3	0.20

Weighted scores obtained from the random-effect model meta-analysis. Abbreviations: “n” number of patients, “k” number of studies, “SD” standard deviation

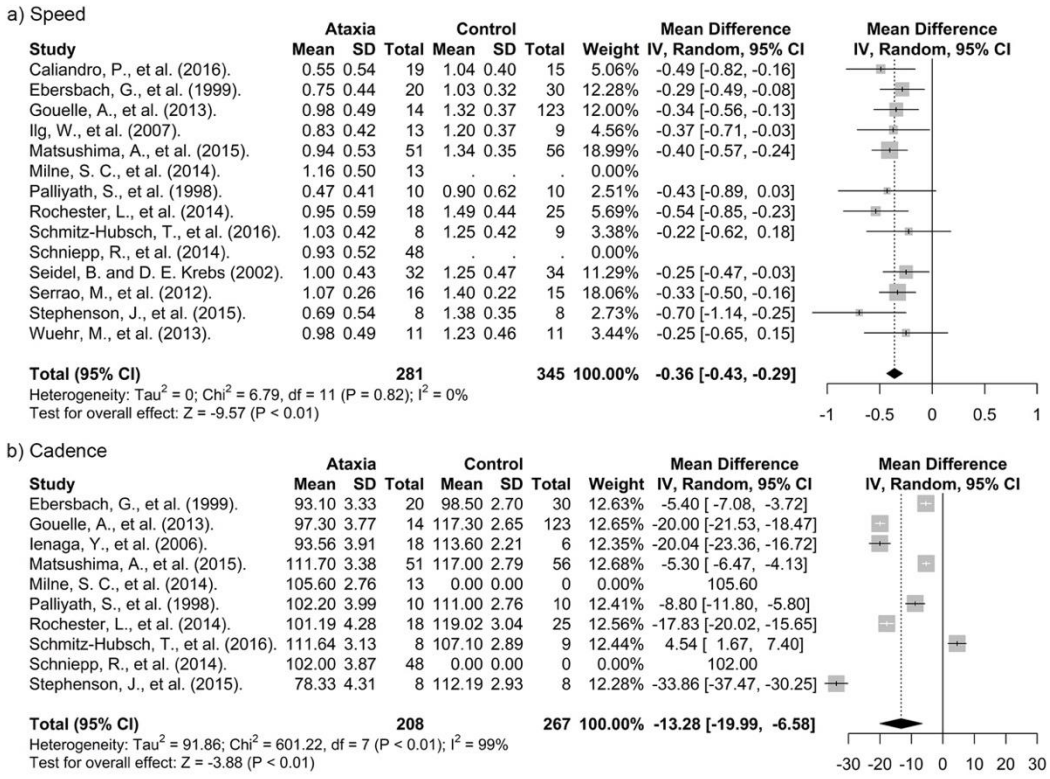


Figure 2.4: Pace parameter meta-analysis results
Mean difference in a) speed (m/s) and b) cadence (steps per min) during self-selected pace walking.

2.3.5.2. Spatial

Step length, was studied by 7 studies (Caliandro et al., 2015, Gouelle et al., 2013, Ilg et al., 2007, Matsushima et al., 2015, Rochester et al., 2014, Serrao et al., 2012, Stephenson et al., 2015) and was significantly reduced in ataxia cohort (n=139) compared to healthy controls (n=251) (-0.14m (-0.20, -0.08), $p<0.01$, $I^2=0\%$) Figure 2.5a). Stride length was also significantly reduced in ataxia (n=94) compared to healthy controls (n=142) (REM, MD=-0.20m, 95% CI (-0.36, -0.04), $p=0.01$, $I^2=0\%$) as reported by 5 studies (Gouelle et al., 2013, Milne et al., 2014, Schniepp et al., 2014, Stephenson et al., 2015, Wuehr et al., 2013) (Figure 2.5b). Walking base width was studied by 10 studies (Caliandro et al., 2015, Gouelle et al., 2013, Ienaga et al., 2006, Ilg et al., 2007, Milne et al., 2014, Rochester et al., 2014, Schmitz-Hübsch et al., 2016, Schniepp et al., 2014, Seidel and Krebs, 2002, Serrao et al., 2012, Wuehr et al., 2013) and people with ataxia (n=192) demonstrated significantly increased walking base width compared with healthy controls (n=241) (REM, MD=-0.06m, 95% CI (0.02, 0.10), $p<0.01$, $I^2=0\%$) (Figure 2.5c).

2.3.5.3. Temporal

As reported by 3 studies (Gouelle et al., 2013, Palliyath et al., 1998, Rochester et al., 2014), step time is significantly increased in ataxia (n=42), compared with healthy controls (n=158) (REM, MD=0.11s, 95% CI (0.03, 0.20), $p=0.01$, $I^2=0\%$) (Figure 2.6a). Stride time was examined by 7 studies (Gouelle et al., 2013, Ilg et al., 2007, Palliyath et al., 1998, Schmitz-Hübsch et al., 2016, Schniepp et al., 2014, Serrao et al., 2012, Wuehr et al., 2013) and overall, the ataxia cohort (n=120) demonstrated significantly increased stride time than healthy controls (n=177) (REM, MD=0.18s, 95% CI (0.08, 0.27), $p<0.01$, $I^2=0\%$) (Figure 2.6b).

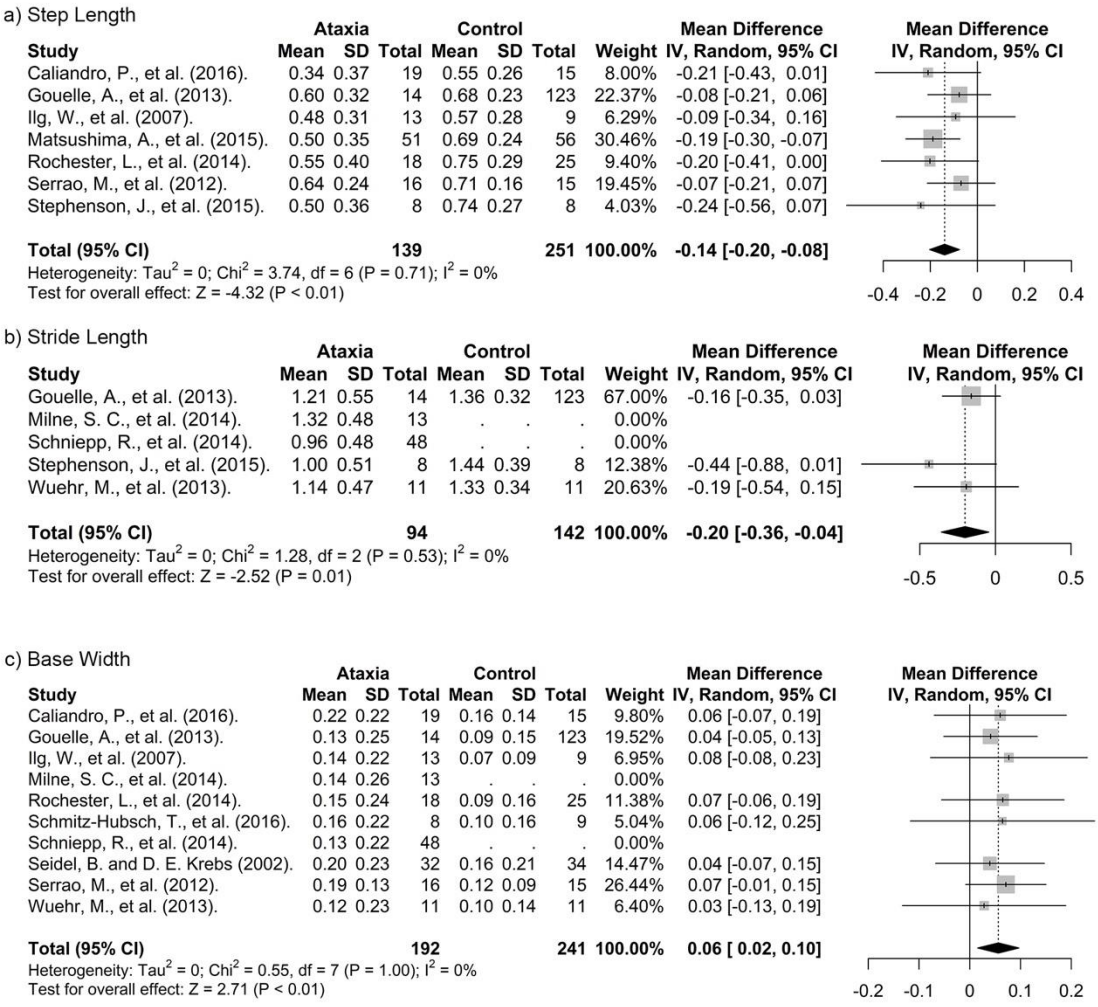


Figure 2.5: Spatial parameter meta-analysis results
Mean difference in a) step length (cm), b) stride length (cm) and c) base width (cm) during self-selected pace walking.

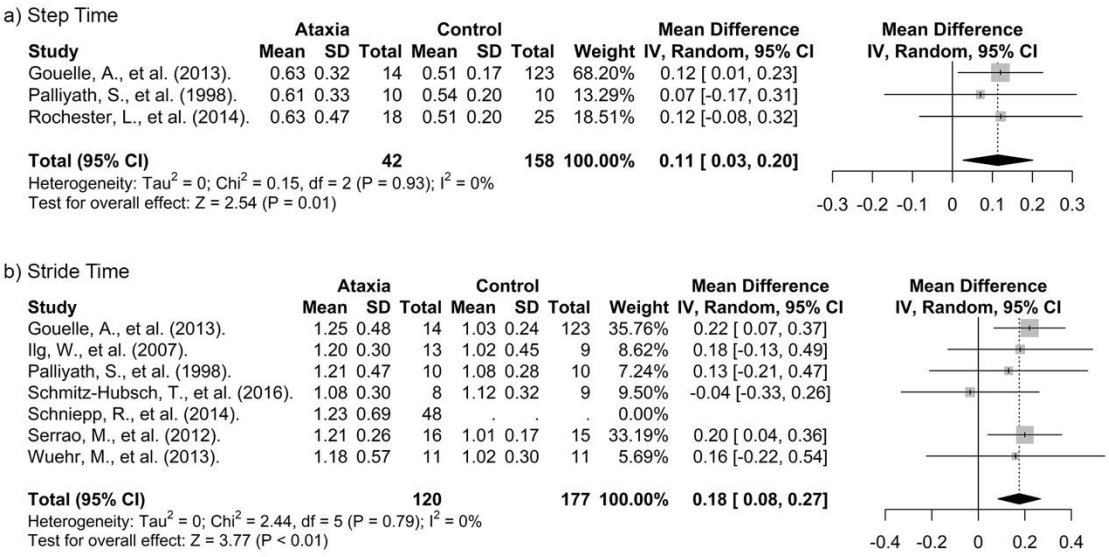


Figure 2.6: Temporal parameter meta-analysis results
Mean difference in a) step time (s) and b) stride time (s) during self-selected pace walking.

2.3.5.4. Gait Cycle

The swing phase of the gait cycle was explored by 4 studies (Caliandro et al., 2015, Gouelle et al., 2013, Milne et al., 2014, Stephenson et al., 2015). People with ataxia (n=54) exhibited a significantly reduced swing phase proportion than healthy controls (n=146) (REM, MD=-5.33%, 95% CI (-9.18, -1.43), $p<0.01$, $I^2=97\%$) (Figure 2.7a). Stance phase accounted for a significantly increased portion of the gait cycle in the ataxia cohort (n=57) than in healthy controls (n=161) (REM, MD=5.44%, 95% CI (2.12, 8.76), $p<0.01$, $I^2=97\%$) as reported by 4 studies (Caliandro et al., 2015, Gouelle et al., 2013, Serrao et al., 2012, Stephenson et al., 2015) (Figure 2.7b). Double limb support phase was studied by 7 studies (Caliandro et al., 2015, Gouelle et al., 2013, Milne et al., 2014, Schmitz-Hübsch et al., 2016, Schniepp et al., 2014, Serrao et al., 2012, Stephenson et al., 2015) and the ataxia cohort (n=126) demonstrated significantly increased double limb support phase proportion than controls (n=170) (REM, MD=5.74%, 95% CI (3.81, 7.68), $p<0.01$, $I^2=93\%$) (Figure 2.7c).

2.3.5.5. Variability

As shown in Figure 2.8a, the variability of step length was investigated by 5 studies (Ebersbach et al., 1999, Gouelle et al., 2013, Ienaga et al., 2006, Palliyath et al., 1998, Serrao et al., 2012). The ataxia cohort (n=78) demonstrated significantly increased step length variability compared to controls (n=184) (REM, MD=5.88 %CV, 95% CI (3.42, 8.34), $p<0.01$, $I^2=97\%$). Variability of stride length was also significantly increased in people with ataxia (n=80) compared to healthy controls (n=142) (REM, MD=4.87 %CV, 95% CI (2.29, 7.45), $p<0.01$, $I^2=95\%$) (Gouelle et al., 2013, Palliyath et al., 1998, Schmitz-Hübsch et al., 2016, Schniepp et al., 2014) (Figure 2.8b). Variability of stride time was considered by 6 studies (Ebersbach et al., 1999, Gouelle et al., 2013, Palliyath et al., 1998, Schmitz-Hübsch et al., 2016, Schniepp et al., 2014, Serrao et al., 2012), confirming a significant increase in ataxia (n=116) compared with healthy controls (n=187) (REM, MD=3.17 %CV, 95% CI (1.97. 4.37), $p<0.01$, $I^2=91\%$) (Figure 2.8c).

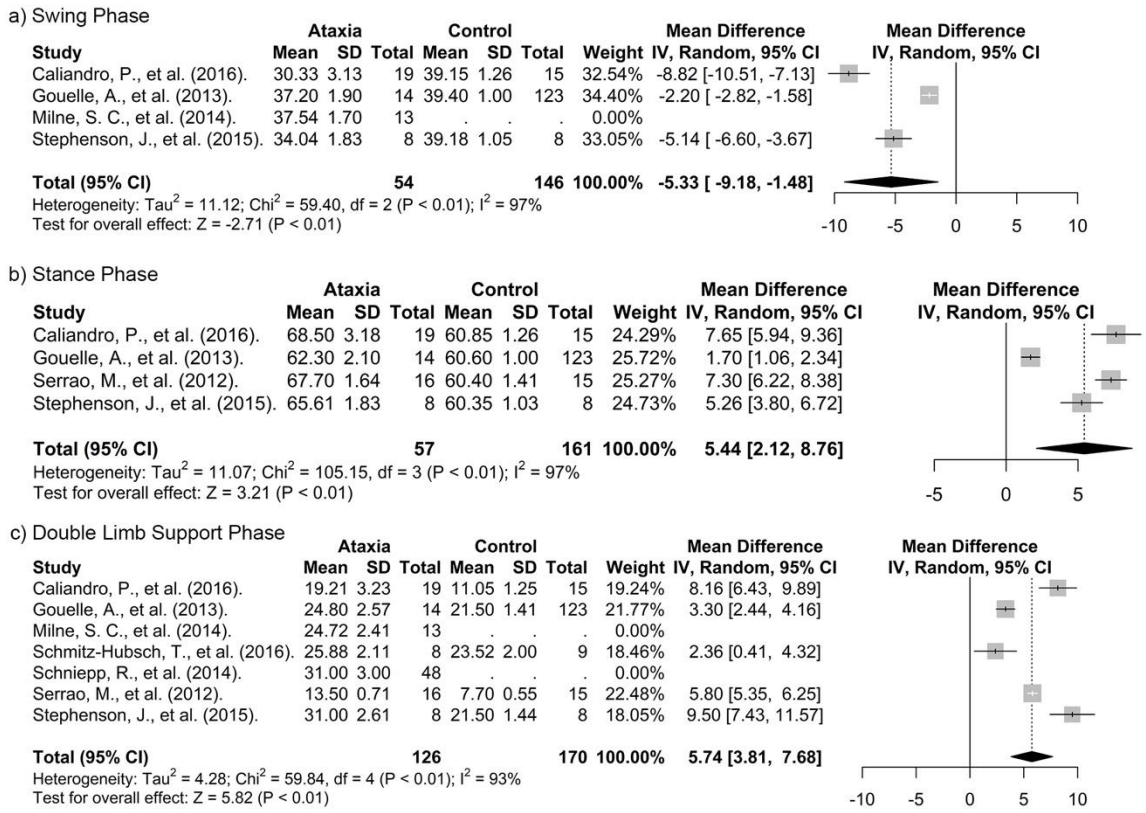


Figure 2.7: Gait cycle parameter meta-analysis results
Mean difference in a) swing phase (%), b) stance phase (%) and c) Double Limb Support (DLS) phase (%) during self-selected paced walking.

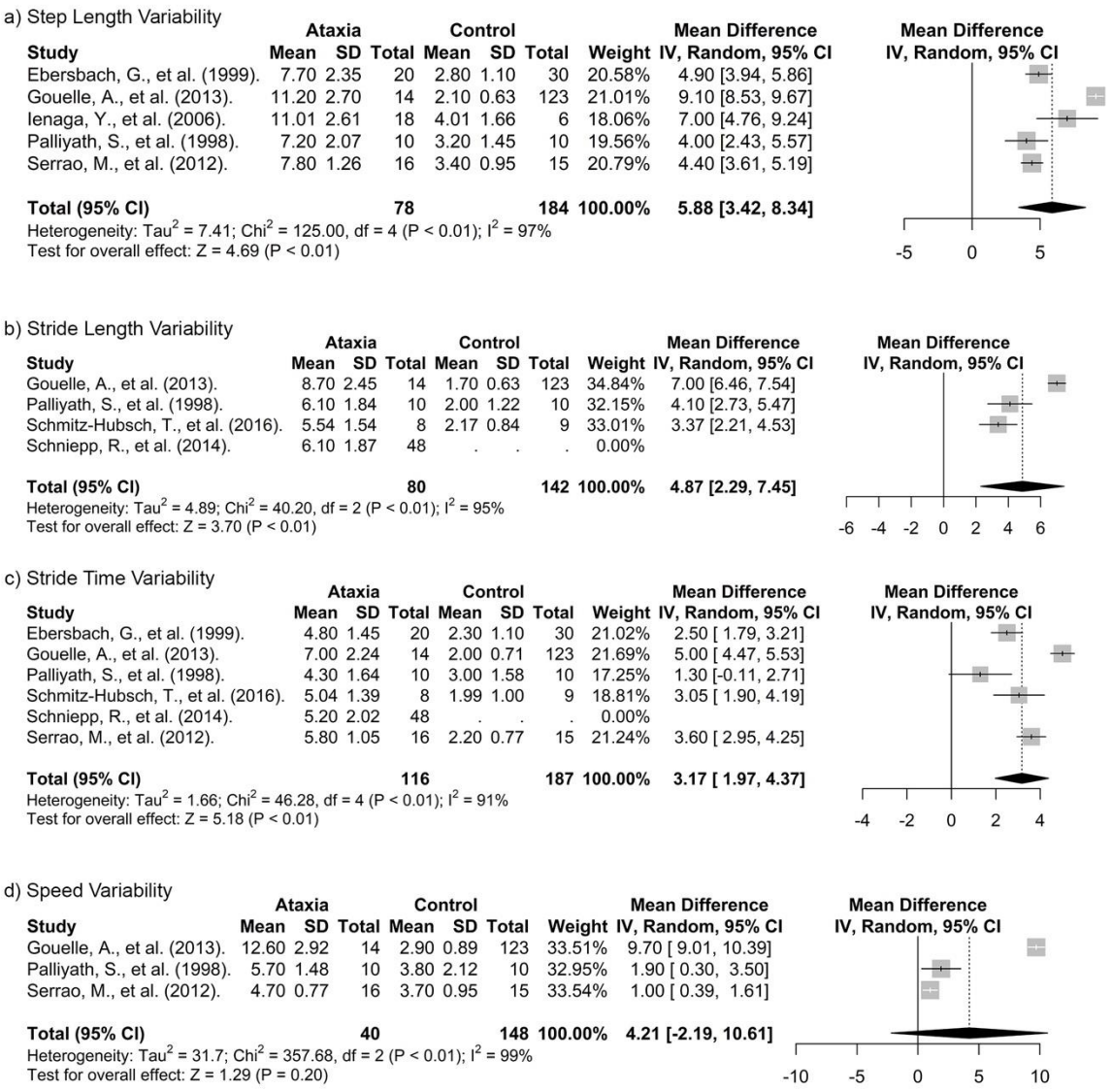


Figure 2.8: Variability parameter meta-analysis results
Mean difference in a) step length variability (% CV), b) stride length variability (% CV), c) stride time variability (% CV) and d) speed variability (% CV) during self-selected paced walking.

2.3.5.6. Subgroup Analysis

Subgroup meta-analysis was completed to explore the effect of disease type and equipment implemented. Due to the number of confounding variables within the dataset these results are considered with caution.

Equipment influence

All but one of the gait metrics (stride length) were analysed for differences incurred by the type of equipment implemented, 3D motion capture, pressure-sensitive walkway, inertial sensor or other (Appendix 8). Of those investigated, 4 metrics (swing %, stance %, step length variability and speed variability) showed significant ($p<0.05$) subgroup differences (Table 2.3). However, for three of these subgroup analyses (swing %, stance %, and speed variability), the studies had consistent cohort diagnosis and equipment used making it problematic to extract the influence of either on the combined result.

Mean difference in swing % meanwhile was significantly lower compared with healthy controls was observed in Mixed CA via 3D motion capture than FRDA via pressure-sensitive walkway (REM, MD =-8.82, 95% CI (-10.36, -7.28) vs MD =-3.62, 95% CI (-6.50, -0.74) respectively, $p<0.01$). Also, the reverse is true with stance % significantly higher than healthy controls in Mixed CA measured via 3D motion capture than in FRDA measured via pressure-sensitive walkway (REM, MD =7.41, 95% CI (6.52, 8.30) vs MD =3.45, 95% CI (-0.04, 6.93) respectively, $p=0.03$). Speed variability was significantly lower compared with healthy controls in Mixed CA measured via 3D motion capture than in FRDA patients measured with a pressure-sensitive walkway (REM, MD =-8.82, 95% CI (-10.36, -7.28) vs MD =-3.62, 95% CI (-6.50, -0.74) respectively, $p<0.01$).

For the remaining significantly different result (step length variability), it appears that the pressure-sensitive walkway detected a larger step length variability than that measured by 3D Motion capture (REM, MD =9.10, 95% CI (7.68, 10.52) vs MD =5.01, 95% CI (3.48, 6.54) respectively, $p<0.01$). However, since two of the subgroups contained only 1 study, heterogeneity analysis was not completed, and the validity of this result cannot be confirmed.

Table 2.3: Equipment subgroup meta-analysis summary

	Comparison	Comparator Groups	Chi^2	Df	P value	No. Papers per comparator group	No. Papers in meta-analysis
Pace							
Speed	Equipment	3D-MC vs other vs PSW vs Inertial sensor	1.07	3	0.79	5 vs 1 vs 7 vs 1	12
Cadence	Equipment	Other vs PSW vs 3D-MC vs Inertial sensor	5.48	3	0.14	1 vs 6 vs 2 vs 1	8
Spatial							
Step Length	Equipment	3D-MC vs PSW vs Inertial sensor	1.01	2	0.6	3 vs 3 vs 1	7
Base Width	Equipment	3D-MC vs PSW	0.08	1	0.78	4 vs 6	8
Temporal							
Step Time	Equipment	PSW vs 3D-MC	0.13	1	0.72	2 vs 1	3
Stride Time	Equipment	PSW vs 3D-MC	0.36	1	0.55	4 vs 3	6
Gait Cycle							
Swing % Cycle	Diagnosis & equipment	Mixed CA & 3DMC vs FRDA & PSW	9.75	1	**<0.01**	1 vs 3	3
Stance % Cycle	Diagnosis & equipment	Mixed CA & 3DMC vs FRDA & PSW	4.66	1	**0.03**	2 vs 2	4
DLS % Cycle	Equipment	PSW vs 3D-MC	0.61	1	0.43	5 vs 2	5
Variability							
Step Length Variability	Equipment	Other vs PSW vs 3D-MC	23.68	2	**<0.01**	1 vs 1 vs 3	5
Stride Length Variability	Equipment	PSW vs 3D-MC	0.31	1	0.58	3 vs 1	3
Stride Time Variability	Equipment	Other vs PSW vs 3D-MC	2.12	2	0.35	1 vs 2 vs 2	5
Speed Variability	Diagnosis & equipment	FRDA & PSW vs mixed CA & 3DMC	102.68	1	**<0.01**	1 vs 2	3

Where Diagnosis and Equipment are combined in analysis, the grouped articles were consistent in ataxia diagnosis and technique used meaning that alternative grouping was unnecessary. The reduced number of articles given weight in the meta-analysis reflects the exclusion of results where a control cohort was not present. Abbreviations: CA = cerebellar ataxia, FRDA = Friedreich's Ataxia, SCA = Spinocerebellar Ataxia, 3D-MC = 3-Dimensional Motion Capture, PSW = Pressure Sensitive Walkway.

Diagnosis influence

Of the 8 studies assessing specific ataxias key subgroups, pure cerebellar and those including afferent ataxias were the main diagnoses available for comparison. In a subgroup analysis by disease diagnosis, significant differences are seen in swing %, stance %, DLS%, Step length variability, stride length variability, stride time variability and speed variability (Appendix 8).

The influence of disease diagnosis on gait could be assessed separately from the equipment used for four metrics (Table 2.4):

- DLS% - compared with healthy controls, the weighted mean difference is significantly different in FRDA and Mixed CA vs SCA (REM, MD =6.35, 95% CI (0.27, 12.42) vs MD =6.85, 95% CI (4.55, 9.15) vs 2.36 95% CI (0.40, 4.32) respectively, $p<0.01$).
- Step length variability – when compared with healthy controls FRDA significantly higher MD than Mixed CA (REM, MD =9.10, 95% CI (7.68, 10.52) vs MD =4.92, 95% CI (3.93, 5.92) respectively, $p<0.01$)
- Stride length variability – when compared with healthy controls, FRDA exhibit a significantly larger MD than Mixed CA and SCA (REM, MD =7.00, 95% CI (5.71, 8.29) vs MD =4.10, 95% CI (2.73, 5.47) vs MD =3.37, 95% CI (2.17, 4.57) respectively, $p<0.01$)
- Stride time variability – when compared with healthy controls FRDA significantly higher MD than Mixed CA and SCA (REM, MD =5.00, 95% CI (3.82, 6.18) vs MD =2.60, 95% CI (1.45, 3.76) vs MD =3.05, 95% CI (1.88, 4.21) respectively, $p<0.01$)

However, within each of these, a small number of studies within subgroups were present which leads to doubt on the validity of this analysis.

Table 2.4: Disease subgroup meta-analysis summary

	Comparison	Comparator Groups	Chi^2	Df	P value	No. Papers per comparator group	No. Papers in meta-analysis
Pace							
Speed	Diagnosis	Mixed CA vs FRDA vs SCA	0.51	2	0.77	8 vs 3 vs 3	12
Cadence	Diagnosis	Mixed CA vs FRDA vs SCA	5.32	2	0.07	5 vs 3 vs 2	8
Spatial							
Step Length	Diagnosis	Mixed CA vs FRDA vs SCA6	0.41	2	0.81	4 vs 2 vs 1	7
Stride Length	Diagnosis	FRDA vs mixed CA	0.06	1	0.8	3 vs 2	3
Base Width	Diagnosis	Mixed CA vs FRDA vs SCA	0.1	2	0.95	5 vs 2 vs 3	8
Temporal							
Step Time	Diagnosis	FRDA vs mixed CA	0.04	1	0.85	1 vs 2	3
Stride Time	Diagnosis	FRDA vs mixed CA vs SCA	1.43	2	0.49	1 vs 4 vs 2	6
Gait Cycle							
Swing % Cycle	Diagnosis & equipment	Mixed CA & 3DMC vs FRDA & PSW	9.75	1	**<0.01**	1 vs 3	3
Stance % Cycle	Diagnosis & equipment	Mixed CA & 3DMC vs FRDA & PSW	4.66	1	**0.03**	2 vs 2	4
DLS % Cycle	Diagnosis	Mixed CA vs FRDA vs SCA	8.92	2	**0.01**	3 vs 3 vs 1	5
Variability							
Step Length Variability	Diagnosis	Mixed CA vs FRDA	22.33	1	**<0.01**	4 vs 1	5
Stride Length Variability	Diagnosis	FRDA vs mixed CA vs SCA	17.62	2	**<0.01**	1 vs 2 vs 1	3
Stride Time Variability	Diagnosis	Mixed CA vs FRDA vs SCA	9.13	2	**0.01**	4 vs 1 vs 1	5
Speed Variability	Diagnosis & equipment	FRDA & PSW vs mixed CA & 3DMC	102.68	1	**<0.01**	1 vs 2	3

Where Diagnosis and Equipment are combined in analysis, the grouped articles were consistent in ataxia diagnosis and technique used meaning that alternative grouping was unnecessary. The reduced number of articles given weight in the meta-analysis reflects the exclusion of results where a control cohort was not present. Abbreviations: CA = cerebellar ataxia, FRDA = Friedreich's Ataxia, SCA = Spinocerebellar Ataxia, 3D-MC = 3-Dimensional Motion Capture, PWS = Pressure Sensitive Walkway.

2.3.6. POWER CALCULATION AND SAMPLE SIZE ESTIMATE

On the basis of these results, the sample size calculation has been completed (Table 2.5). This indicates that for the majority of spatiotemporal gait parameters investigated here, 13 or less participants per group is required to achieve statistical power in a two-sided test. This estimate excludes DLS time and speed variability which require 43 and 42 participants respectively. However, central limit theorem indicates that studies should include at least 30 participants therefore, the design of studies investigating these gait variables in CA compared with HC to avoid underestimating the required number of participants, a larger cohort size should be considered (Kwak & Kim, 2017).

Table 2.5: Sample size calculation for future studies

	Mean Diff.	Z	Effect Size	Sample size required
Pace				
Speed	-0.36 m/s	-9.6	**-0.5**	6*
Cadence	-13.3 steps/min	-3.9	**-0.3**	14*
Spatial				
Step Length	-14 **c**m	-4.3	**-0.3**	14*
Stride Length	-20 cm	-2.5	**-0.2**	5*
Base Width	6 cm	2.7	**0.2**	10*
Temporal				
Step Time	110 ms	2.5	**0.3**	2*
Stride Time	180 ms	3.8	**0.3**	3*
Gait Cycle				
Swing % Cycle	-5.3 %	-2.7	**-0.3**	14*
Stance % Cycle	5.4 %	3.2	**0.3**	9*
DLS % Cycle	5.7 %	5.8	**0.5**	47
Variability				
Step Length Variability	5.9 %	4.7	**0.4**	4*
Stride Length Variability	4.9 %	3.7	**0.4**	3*
Stride Time Variability	3.2 %	5.2	**0.4**	3*
Speed Variability	4.2 %	1.3	0.1	46

Results of sample size calculation. Mean diff. (CA-HC) and Z value taken from random-effects model meta-analysis. Where sample size required indicated as less than 30 (*), a larger cohort than reported should be considered more appropriate.

2.4. DISCUSSION

This systematic review objectively evaluated the existing evidence base for the spatiotemporal gait characteristics of adult CA. The 21 included studies reflect quantitative gait assessments for 408 CA patients and 403 healthy controls. This forms a larger cohort than typically available in an individual descriptive study. Each individual study confirmed that cohort demographics (age, sex, height, leg length and Body Mass Index (BMI)) were equivalent and no significant differences between cases and control characteristics are present in the meta-analysis.

2.4.1. HEADLINE RESULTS

Following our searches and subsequent scrutiny of the literature from the last 20 years, twenty-six studies were identified that considered spatiotemporal gait characteristics in individuals with CA, as measured by instrumented analysis techniques during preferred paced steady-state walking.

There is strong evidence that during preferred paced walking, CA patients display the following gait differences against healthy controls:

- reduced walking speed and cadence
- reduced step length, stride length, and swing phase
- increased base width, stride time, step time, stance phase and double limb support phase
- increased variability of step length, stride length, and stride time.

These adjustments were significantly different ($p<0.01$) and consistently associated with a z-score greater than the 95% critical z-score (1.96). The gait parameters that were greatest affected in CA (in terms of z-score) were speed, double limb support phase duration (%cycle) and stride time variability followed by step length variability and step length. Although this suggests that these may be most useful in clinical practice, further research is necessary to consider a number of contributing factors.

2.4.2. HETEROGENEITY OF RESULTS

Significant amounts of between-study heterogeneity were observed in some meta-analyses of gait metrics while for other gait metrics analysed, large confidence intervals were found within individual studies. Unfortunately, due to limitations of the dataset, it is not possible to

formally explore the influence of distinct confounding influences such as ataxia diagnosis type separately from equipment used, the interactions between upper body and spatiotemporal gait parameters, or the effect of changing velocity or disease progression on gait characteristics.

One important consideration is the influence of technical restrictions of equipment on study design, walking protocol and parameter definitions. This impacts the length of the walkway, whether participants complete the walking task barefoot and the ability of participants to reach steady-state walking pace which together can affect walking characteristics (Franklin et al., 2015, Sustakoski et al., 2015). Also, it should be noted that, despite studies validating equipment and techniques, differences in analytical approach may affect the results attained.

The reduced walking speed reported by all studies in CA had large overlapping confidence intervals. The decreased cadence in patients exhibited smaller confidence intervals, heterogeneity between studies was significant. The studies reporting an increased step time and stride time in CA showed large overlapping confidence intervals in meta-analysis with low overall heterogeneity. Also, step length and stride length were both reduced in CA but large overlapping confidence intervals in meta-analysis leads to low heterogeneity. The increased step width in CA was associated with large overlapping confidence intervals with low heterogeneity in meta-analysis. Furthermore, the changes to gait cycle proportions (reduced Swing%, and increased stance%, and DLS% phase) were associated with significant heterogeneity despite small confidence intervals within each study. And, the increased variability of step length, stride length, stride time and speed were all accompanied by a large amount of heterogeneity overall.

The heterogeneity revealed in these analyses implies that results may have limited compatibility despite the systematic review design intending to reduce this. For instance, the parameters taken forward to meta-analysis were those most commonly reported in these articles. This was intended to provide the best opportunity for evaluation in the largest number of participants. Only studies with adult ataxia were included to reduce the impact of age on the gait. Moreover, the pooled estimate for ataxic and healthy populations was calculated only where results were reported in more than 3 studies and only data collected during preferred speed straight-line self-paced walking and at baseline assessment were

considered for meta-analysis. This was intended to restrict protocol design and avoid the effect of an intervention or changes to speed.

Subgroup analysis, therefore, offers a chance to explore these changes further and whether ataxia diagnosis and equipment used were able to account for this heterogeneity. These gait metrics with large between-study heterogeneity, had apparent subgroup differences especially related to the specific disease diagnosis although equipment type may also influence findings.

For instance, the equipment used had significant implications in four gait metrics with pressure-sensitive walkways perceiving a higher mean difference swing %, lower stance % mean difference and greater mean difference variability of speed and step length than 3D motion capture. Also, despite walkway length being equipment dependent, in correlation analysis, walkway length did not correlate with any of the gait metrics. There was insufficient data available to perform further formal analysis on aspects such as the number of steps/ passes so there may remain differences in gait analysis and protocols contributing to heterogeneity.

In reality, these comparisons are more likely to be confounded by disease diagnosis and cohort differences as there were a small number of studies within each meta-analysis. From a clinical standpoint, differences between ataxia subtypes are an important factor and the values for healthy controls were similar across the systems. In subgroup analysis to examine the influence of disease diagnosis on the gait measures directly, as well as the above associations, 4 gait metrics showed a significant subgroup difference. The weighted mean difference was significantly lower for SCA than FRDA and mixed CA in DLS%, significantly higher for step length variability, stride length variability and stride time variability in FRDA than mixed CA and SCA. Since values for healthy controls were consistent across the meta-analyses for each metric and most studies were related with large confidence intervals, there may be a diagnosis-specific gait pattern. Better classification of mixed CA cohorts may have enabled a reduced heterogeneity of these results.

Of the 8 studies assessing specific ataxias key subgroups, pure cerebellar and those including afferent ataxias were the main diagnoses available for comparison. FRDA for instance, has a younger age at onset than other forms of ataxia included in studies with a mixed CA cohort (Harding, 1981). However, in correlation analysis, neither age nor disease duration

significantly correlated to any of the changes in gait metrics in the CA cohort. Therefore, it is unclear whether results related to disease diagnosis or cohort specific patient demographics.

In both the Ataxia and Control cohorts, there were significant correlations between walking speed and step length, and in the Ataxia cohort walking speed also correlated with stride length. This demonstrates the importance of walking speed on the spatial features of gait. Unfortunately, there was not enough consistent data available in the literature to produce a formal analysis of gait changes in different speed walking using data. However for those that did report different speed walking gait patterns, a these findings is outlined in section 2.4.3.

2.4.3. IMPLICATIONS FOR PRACTICE

Our findings indicate a clear pattern of walking gait pattern modifications in ataxia and how it compares against healthy controls. The changes observed may reflect a compensation for incoordination and trunk instability (Bunn et al., 2013), intending to reduce the falls risk common to these patients. Reduced velocity of self-selected walking and increased sagittal gait variability (Schniepp et al., 2014), as well as widened gait (Chini et al., 2016), correlate with the increased risk of falls detected by clinical measures. It is thought that increased gait variability directly reflects imbalance during walking in CA and is related to the presence of cerebellar damage (Serrao et al., 2017b, Serrao et al., 2012). Also an increased step width, and decreased step length occur, to compensate for reduced balance performance by enlarging base of support, reducing forward progression (McAndrew Young and Dingwell, 2012, Serrao et al., 2012). This provides better control of the changing centre of gravity during walking. However, since the reduced preferred walking speed will inherently lead to gait alterations due to the interplay of gait pattern characteristics, these changes may not be specific to CA pathophysiology.

Although upper body metrics were reported in a minority of studies, there is evidence to indicate that exaggerations in trunk flexion-extension and an increased trunk rotation are present in CA to increase stability (Conte et al., 2014). In this way, gait velocity and spatiotemporal parameters are preserved and maintain an energy-efficient gait. In CA, patients display increased trunk instability in all 3 directions but the anterior-posterior direction particularly (Chini et al., 2016, Matsushima et al., 2015, van de Warrenburg et al., 2005b). While the overall instability correlates negatively with ICARS score, and positively

with disease stage, this anterior-posterior instability may contribute to fall direction (Fonteyn et al., 2010).

Of course, by design, these results are limited to assessment of self-selected paced walking in ataxia compared with a healthy control cohort and does not account for different paced walking, use of walking aids, cued walking tasks, longitudinal changes or differences with non-ataxic disease cohorts. Therefore, they reflect functional gait capacity in cerebellar ataxia and may not be applicable to real-world walking gait performance which may present a greater challenge to people with ataxia.

A number of articles report that in cerebellar ataxia, walking at preferred speed minimises the gait abnormalities and recommend analysis of gait at a wide range of speeds (Wuehr et al., 2013). However, since subjective rating scales incorporating preferred self-selected paced walking remain the main method of clinical gait assessment, our findings clarify ataxic gait characteristics as they would appear in a typical assessment. As the preferred self-selected speed gait pattern captured in clinical/ lab setting reflects what patients choose to do this has relevance to comfortable real-life walking. However, since real-world walking requires adaptation to speed and gait pattern, quantifying the gait pattern of different walking speeds in clinical/lab settings uses the more challenging gait task to establish an individual's functional capacity. In ataxia patients, with increasing speed walking, gait is characterised by increased cadence, step and stride length, and swing% phase as well as decreases in the stance% and DLS% phases (Milne et al., 2014). A nonlinear correlation is reported in stride time variability and stride length variability, with the highest CV in slow-paced walking, and preferred paced walking associated with the minimal CV magnitude (Schniepp et al., 2014, Wuehr et al., 2013). Many of these speed-dependent gait changes are also observed in healthy adults (Hebenstreit et al., 2015, Thomas et al., 2017), and are more pronounced with age (Menz et al., 2004). However, in controls, gait variability is less closely associated with speed changes to allow flexibility and adaptability of walking strategy (Beauchet et al., 2017). In Multiple Sclerosis (Comber et al., 2017), fast-paced walking is reported to be more sensitive to gait changes, therefore, this complexity makes it unclear whether fast or slow walking is more clinically sensitive in CA. It appears that different compensation strategies are at play in fast and slow-paced walking. For instance, while more strongly significant differences have been reported in swing, stance and DLS phase between

patients and controls in fast walking, than in preferred paced walking (Stephenson et al., 2015), the increased variability of slow-paced walking is correlated with falls risk (Schniepp et al., 2014). Further, spatiotemporal parameters of gait measured in slow-paced conditions correlate with a fewer number of clinical markers than in fast and preferred paced walking (Milne et al., 2014).

There is also evidence to suggest that gait has the potential to distinguish between neurological gait disorders, differentiate forms of CA and be sensitive to disease progression although these questions were not formally analysed in this study. For instance, Parkinson's Disease (PD) and Huntington's disease (HD), two diseases of the basal ganglia, are also characterised by decreased stride/step length with a reduced walking velocity (Scafetta et al., 2009) but have a number of differences from CA and each other. In PD, cadence remains normal, and a linear relationship between stride length and velocity is maintained, comparable to healthy controls (Ebersbach et al., 1999, Ilg et al., 2007, Stolze et al., 2002). Gait variability is increased compared with healthy controls but remains lower than in CA (Moon et al., 2016) although changes to step width are unclear, (either decreased or unaffected). However, in manifest HD, increased step width and even more increased gait variability are apparent while stride time is not significantly different from PD (Dalton et al., 2013, Hausdorff et al., 1997, Moon et al., 2016, Stolze et al., 2002). Furthermore, although a significant increase in width of walking base was found in the meta-analysis reported here, it has previously been suggested that stride width may not be a disease-specific gait characteristic but a compensation for the instability that occurs in many gait disorders (Seidel and Krebs, 2002). While it is likely that through objective gait analysis, movement disorders of the basal ganglia can be distinguished from those of cerebellar origin, it is not possible to appraise specific changes across different pathologies from the present dataset (Scafetta et al., 2009).

Clarification of the objective differences between forms of ataxia has the potential to improve understanding of the underlying disease. While a number of studies explored the differences between specific forms of CA there is insufficient evidence to categorically define the interaction between disease type and gait changes. However, there appears to be different gait features present between ataxia subtypes which may relate to the underlying disease differences, such as patterns of cerebellar degeneration, the presence of pyramidal

signs and disease duration. This may contribute by affecting components of gait, or the patient's ability to apply compensations. Further work is required to clarify these interactions and their influence on falls status and link to clinical markers (Fonteyn et al., 2010, Milne et al., 2014).

The studies included here that explored longitudinal gait changes were not sufficiently able to provide a conclusive description of gait disturbances with disease progression. However, follow-up articles to two studies included here have recently been published (Serrao et al., 2017a, Zesiewicz et al., 2017). In Friedreich Ataxia (FRDA) and mixed CAs, at 2 year and 4-year follow-up assessments respectively, with time a reduced gait speed, an increase in gait variability, cadence and stride length, and step length as well as reduced swing and increased DLS phases were apparent. In comparison with baseline characteristics, these changes reflect an increase in gait instability with disease progression. These studies also observed that gait variability was able to predict loss of independent gait, and disease severity (measured by Friedreich's Ataxia Rating Scale (FARS) or SARA) was significantly different at follow-up from baseline. FARS scores changes correlated well with objective gait characteristics, while SARA scores did not. Due to the complex nature of these findings, further assessment of the objective gait characteristics within a longitudinal study is required to clarify the impact of disease progression on different CA subtypes.

These corroborate with the earliest descriptions of ataxic gait and reflect overall walking disability (Stolze et al., 2002). Step and stride length were also shorter in ataxic individuals than healthy controls. Serrao et al. (2012) for example, studied the gait pattern of individuals with SCA 1 or 2 and Friedreich's Ataxia (FRDA) as well as healthy controls. All spatiotemporal characteristics evaluated were significantly different in ataxia patients versus healthy individuals. In addition, a significantly shortened step length was observed in those with FRDA than SCA1/2.

Increased duration of DLS phase, stance time, step time, stride time and swing phases were observed in patients when compared with controls. Mari et al. (2014) explored the muscle activations underlying spatiotemporal parameters (STPs) in SCA1/2 or sporadic adult-onset ataxia of unknown aetiology (SAOA). They hypothesised that joint rigidity in ataxia patients provides compensation for balance deficits, which is reflected in the cycle phase distributions. Increased co-contraction of the antagonist muscles at both the knee and ankle

joints control the forward motion in the same leg and reduce the influence of the motion of the opposite leg.

A wider base of support is commonly present in individuals with CA than in healthy controls (Palliyath et al., 1998). This was reflected in the pooled estimates for the base of support and step width from the studies included. Unfortunately, due to technical limitations, studies are often unable to measure step width despite its importance in this population. Dynamic instability is thought to be reflected in this widened gait and to correlate with a history of falls (Chini et al., 2016).

Meanwhile, patients also exhibited increased variability in step length, step width, stride length and stride time. Conte et al. (2014) for example, measured trunk oscillations and their relationship with spatiotemporal parameters using an optoelectronic infrared camera system. Movements in the frontal and sagittal planes were found to correlate with the variability of swing phase. This indicates that exaggerations in trunk flexion-extension may be associated with controlling foot placements and preserving the spatiotemporal parameters of gait to increase stability.

Furthermore, the 2 studies exploring the effect of rehabilitation and physical training as an intervention showed significant improvements in motor performance and reduced ataxia symptoms. Therefore, this shows promise for objective quantification of training and therapy effects in CA.

The sample size estimate calculated from the results of this meta-analysis indicate that between n=2 and n=47 individuals (n = 13 ± 15 mean ± SD) is a necessary recruitment target to establish differences in gait characteristics between CA and HC in case controls studies reporting these variables. Although for many variables this is lower than the participant numbers recruited to the studies, for DLS phase and speed variability the estimate are greater than recruited. Since there were statistically significant differences between cohorts, and heterogeneity within cohorts, this estimate may be inflated as the clinically relevant difference may be larger than these results indicate. These estimates should be considered in the planning of future studies and effect size should always be established when reporting findings from studies of this nature.

2.4.4. STRENGTHS AND LIMITATIONS

In assessment of the methodological quality, all included studies were of a sufficiently high quality to be considered suitable, although some limitations were apparent, and a few concerns remain. Findings should be interpreted in the context of its strengths and weaknesses.

Many studies considered confounding variables, and all completed concurrent cohort assessments in an appropriate trial protocol. For instance, walkway lengths were relatively consistent between studies and mostly considered long enough to analyse a sufficient number of steps collected from steady-state gait. Gait metrics were mostly well-defined and findings, research questions and inclusion/ exclusion criteria were clearly reported. Study populations were usually well-defined, and cohorts were representative and evenly matched for age, BMI and sex to restrict their influence on gait parameters. Patients with non-clinically "pure" ataxia were commonly excluded to avoid the involvement of other neurological systems.

There are several limitations of the included studies that should be taken into account. Primarily, heterogeneity analysis revealed disparity between studies in meta-analyses for cadence, swing (%cycle), stance (%cycle), double limb support phase (%cycle), step length variability, stride length variability, stride time variability and speed variability, but large within-study variability in the remaining variables (speed, base width, stride length, step length, step time, stride time).

The comparative rarity of CA in the general population can lead to recruitment difficulties in observational clinical studies and in fact many of these studies recruited less than fifteen participants per cohort (19.43 (±11.33) patients and 25.19 (±29.03) healthy controls in each study). It is essential that studies report an effect size justification and attempt to reach statistical power where possible in order to reliably determine precise differences between cohorts.

Meanwhile, some intervention studies did not assess healthy individuals as control participants, as might be expected. In addition, a number of the studies reported results for specific parameters of interest and did not consider all possible parameters of gait despite possible associations.

Many of the patient cohorts were either not fully characterised in terms of diagnosis or several ataxia subtypes were grouped despite potential differences in the ataxia syndrome (Burk et al., 2003). Disease severity was inconsistently characterised with a variety of rating scales employed. Most of the patients studied completed the walking task unaided, reflecting the relatively low disease severity in the cohort. This is a common problem in gait analysis studies as more severely affected patients are unable to take part without additional support.

In addition, some articles did not report the full results of gait parameters analysed, opting to present a combined measure, or secondary analysis, for example, the results of correlation analyses or the variability of gait parameters. However, several authors made additional data available for this systematic review. Gait metrics were mostly well-defined and findings, research questions and inclusion/ exclusion criteria were clearly reported.

Due to the heterogeneous nature of clinical studies, these were not deemed to be fatal flaws but informed restrictions on data included in the meta-analysis. To overcome protocol differences and the influence of changing gait strategies with speed, only spatiotemporal gait characteristics measured using instrumented gait analysis techniques during preferred-paced straight-line walking in a laboratory setting at baseline assessment were considered and standardised data excluded from the meta-analysis.

Meanwhile, it should be considered that in walking gait, many characteristics are inherently interdependent. Therefore, while considered separately here, step/ stride periods, and swing/ stance/DLS phases inevitably contribute to each other (Hebenstreit et al., 2015, Lord et al., 2013). Also, although results were excluded from meta-analysis where for contributing factors such as gait velocity and biomechanical features were controlled through standardisation, it is important to bear in mind that these do influence gait characteristics in the individual.

2.5. CONCLUSION

This systematic review provides a consensus description of clarifies the spatiotemporal gait characteristics associated with ataxic gait disturbance in a large cohort of people with CA compared with a healthy control cohort. Since CA is a rare disease, individual observational studies typically have difficulty recruiting a large cohort so this provides a more thorough estimate of the features that distinguish CA from HC.

Taken together it appears that in CA, an gait variability increases and to compensate for this, walkers increase the width of the base of support, take smaller steps and increase the duration of foot contact to floor. Reducing swing phase portion of the gait cycle, they progress forward at a slower pace. The significant differences in spatiotemporal parameters uncovered by our meta-analysis reflect the considerable gait disability seen in these patients compared with healthy controls. People with CA exhibit a reduced balance performance, and increased risk of falls therefore these gait changes may reflect protective compensation mechanisms to improve trunk stability. These measures may also have potential as markers of disease progression due to their sensitivity to disease severity in CA.

Advances in technology, have enabled gait analysis techniques to be more widely employed and genetic testing is also more readily available (Nemeth et al., 2013, Wren et al., 2011). To accompany this, an increase in the quality of research and reporting in the future is needed to aid clinical decision making. Key criticisms such as studies lacking control cohorts, small participant numbers and specific genetic diagnoses should be addressed in future research. High-quality research and reporting are needed to explore specific genetic diagnoses and identify biomarkers for disease progression in order to develop well-evidenced clinical guidelines and interventions for CA.

It is not possible from this data to formally analyse the gait associated with different forms of CA, risk of falls or disease progression or to identify which changes to the gait pattern occur as a result of specific gait stabilization mechanisms. However, a consensus description based on an objective evaluation of the existing evidence base for the gait characteristics of adult CA has been provided as well as a discussion of the inconsistencies between published studies which can guide further research.

2.6. REFERENCES

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Chapter 3. VALIDATION OF THE MICROGATE OPTOGAIT PHOTOELECTRIC SYSTEM & ADPM OPAL TRIAXIAL INERTIAL SENSORS IN PREPARATION FOR CLINIC-BASED GAIT ANALYSIS

3.1. INTRODUCTION

Clinical assessment of gait relies on subjective measures such as disease-specific clinical rating scales, or costly laboratory-based motion capture systems (Baker et al., 2016). However, affordable portable systems have recently been developed. These enable a cost-effective method of assessing the gait pattern during overground walking. This gives an opportunity for gait analysis to objectively quantify gait in a clinical setting.

3.1.1. OPTOGAIT INSTRUMENTED PHOTOELECTRIC WALKWAY

The OptoGait instrumented photoelectric walkway (Microgate S.r.l., Italy) is one such system. The OptoGait consists of a series of bars with embedded Light Emitting Diodes (LEDs) which transmit between the bars. As a participant walks through the assessment area, the spatial location and timing of each footfall is detected by monitoring the activation of an LED series. Different LED filters are applied to dictate the number of LED required to be activated to indicate a gait event. Through its software's internal algorithms, a variety of spatiotemporal parameters such as the length, durations and proportions of participants' gait cycle are computed in real-time. The validity of the system to derive spatiotemporal gait parameters has been explored in previous studies.

Lienhard et al. (2013), evaluated walking characteristics in 15 patients (9 men, 6 women) who had undergone unilateral total knee arthroplasty 2–14 months previously but were able to walk without walking aids, and 15 healthy age-matched controls, comparing the OptoGait to the GAITrite mat (CIR System Inc., Clifton, NJ, USA). This study, reported high discriminant validity for the OptoGait, detecting the same cohort level differences as the criterion instrument. Concurrent validity was also high with Intraclass Coefficients (0.933-0.999, $p<0.001$), and low %limits of agreement (%LoA) and standard error of the estimate (SEE). However, a heteroscedastic pattern was reported for stance time, swing time, cadence and walking speed, and the OptoGait consistently measured longer stride time, stance time, shorter swing time and reduced cadence, walking speed and step length.

More recently, Gomez Bernal et al. (2016) tested intrasession and intersession reliability of the OptoGait in a larger cohort of 126 healthy participants. Across all gait parameters

captured by the OptoGait, only acceleration, progressive step time (total time spent in each step) and progressive distance (total distance walked/run by a patient) showed less than good to excellent intra-session agreement (ICC<0.6). Intrasession variability was greater than 10% for acceleration, progressive step time, distance, heel contact phase, foot flat phase and take-off phase. Intersession reliability was good with no significant differences observed for the spatiotemporal gait parameters between sessions 2 weeks apart. Excellent session reliability (ICC >0.7) was observed for all gait parameters except acceleration which displayed low session agreement (ICC<0.2) and high variability (140.24%CV). All other variables demonstrated good intersession variability (<10%CV) except the progressive distance, heel contact phase and foot flat phase (11.75%, 38.63% and 13.31% respectively). For both sessions, low intra-session SEM values were also reported in this study for all variables except progressive distance (session 1: 0.0072-2.7288%; session 2: 0.0071-3.4961%). This pattern was also apparent for intersession standard error of the mean (SEM) values (0.0044-1.8281% excluding progressive distance).

These results indicate that a systematic difference is often present between instruments. Therefore, further validation is required prior to clinical implementation to explore the limitations of the OptoGait system and the source of the apparent inaccuracies. These articles went on to suggest that some systematic difference was potentially due to the height of the LEDs from the ground. Authors reasoned that the low threshold for gait event detection led to anticipation of heel-strike and delay in detection of toe-off. This results in the underestimation of swing time and overestimation of stance time compared with the criterion instrument.

To compensate for the height of the LEDs in an effort to reduce this effect, the manufacturers recommend the OptoGait system be configured so that a triggering threshold of 3 or more LEDs be required to detect a footfall. Therefore, only when 4 consecutive LEDs are interrupted/uninterrupted is a initial contact/final contact gait event perceived, respectively. Recently, a study has investigated the validity of using this LED threshold to filter data (Healy et al., 2019). The authors concluded that in a cohort of 18 healthy participants that a threshold of 3 LEDs (vs 0, 1 or 2 LEDs) was an acceptable adjustment to ensure accurate detection of gait events compared with the Vicon Motion Capture system and force plates. For the majority of variables, all four settings exhibited high concurrent

validity with the motion capture system (ICCs ranging 0.690-0.999, p<0.001). Significant differences between systems were observed for stance phase, swing phase, and gait speed in the 0 LED and 1 LED setting, with the OptoGait differing by a maximum of 0.04s greater and lower for stance and swing phase, respectively. Gait speed was a maximum of 0.007m/s slower compared to motion capture. For the 2 LED and 3 LED settings, ICCs ranged 0.831-0.999 and 0.717-1.000 respectively (within good to excellent ranges) while %LOA were within ±2% for most gait parameters. Even with the adjustment, %LOA for stance and swing phase were slightly greater at ±5%.

These previous studies have also criticised the one-dimensional measurement possible with the default configuration. However, the system can be configured in a two-dimensional configuration with a "boosted" transmission bar available to enable an extended walkway capable of measuring step width and tracking mediolateral step trajectory. To date, only a single study has reported results using this feature of the OptoGait system but did so without thorough validation (Gorecka et al., 2018).

When configured in the two-dimensional formation, the OptoGait uses the bar perpendicular to the walkway to determine the centre point of each footfall. The shortest mediolateral distance between these points is defined as the step width. There are difficulties associated with validating the measurement of step width since different protocols employ different definitions of the measure is not established. To the best of our knowledge, this measure has not been validated thoroughly in previous studies.

3.1.2. TRIAXIAL INERTIAL MEASUREMENT UNITS (IMUS)

Triaxial inertial measurement units (IMUs) provide an alternative method of objectively measuring an individual's gait pattern. These wireless, wearable sensors, provide a high frequency, synchronised measurement of motion using accelerometers, gyroscopes and magnetometers. Dependent on IMU placement, spatiotemporal gait parameters can be assessed (Esser et al., 2011), as well as postural changes by monitoring upper body motion. This offers an opportunity to monitor gait within more flexible gait tasks including clinic-based and real-world walking rather than being restricted to a lab-based environment.

Various algorithms have been developed to detect gait events from inertial data captured by sensors placed at the ankles or feet without floor-based equipment. A recent article explored 17 gait segmentation algorithms from the literature for the analysis of 35 healthy

participants straight-line self-selected speed walking using triaxial IMU, motion capture and force platforms (Pacini Panebianco et al., 2018). The authors concluded that shank- and foot-based algorithms performed better for gait event detection than trunk-based algorithms. A systematic bias was reported (higher for trunk than foot) which resulted in a delay of initial contact (IC) events and anticipation of toe-off (TO) events and a further underestimation of stance time. Compared with acceleration-based algorithms, angular velocity-based algorithms were deemed to perform less accurately at detecting toe-off and computing stance time but were more repeatable for IC and TO gait event detection and stance time. However, most algorithms performed comparably for quantification of step time although the differences in stance time and gait event detection (particularly final contact) indicate the importance of IMU positioning and computational approach.

3.1.3. AIMS AND OBJECTIVES

Taken together, the OptoGait photoelectric bars and ADPM Opal sensors triaxial inertial sensors potentially provides a portable gait system that is capable of measuring both the spatiotemporal and upper body motion characteristics during over-ground walking within a clinic environment.

Prior to use of the OptoGait/ADPM Opal sensors in a clinical setting, a group of healthy control participants from the University of Sheffield were recruited to take part in a validation study. The Vicon 3D motion capture system will be used as the reference device/gold standard.

This experiment will enable the optimisation of our data analysis and confirm the accuracy of the three system's and algorithm's footfall detection in a controlled laboratory setting. The impact of the algorithm on gait parameter calculations were examined.

The influence of gait speed on the accuracy of the gait analysis systems were investigated to aid interpretation of findings in future pathological cohorts.

3.2. METHODS

3.2.1. STUDY INFORMATION

This study is incorporated by the generic research project "Innovative techniques for human movement analysis" for the purposes of validating tools and analysis using healthy controls. The study was conducted, according to the Declaration of Helsinki, and received ethical

approval by the University Ethics Committee (reference number 015433, approved 11/07/2017). All testing took place at the Gait Analysis Laboratory, Department of Mechanical Engineering, Sheffield. Participants were given at least 24 hours to read through the information sheet and ask questions before informed consent was obtained from all participants.

3.2.2. PARTICIPANTS

In accordance with the approved protocol at the time of ethics application, healthy able-bodied adults with no known morbidities were recruited from with the staff and students of the University of Sheffield by word of mouth or by email.

3.2.3. PROTOCOL

Participants were advised to dress comfortably and wear flat-soled everyday shoes during testing. This reduced any impact of participants' attire on walking gait and enables the equipment to detect footfalls without difficulty while ensuring results would be relevant to our proposed procedure for the clinical gait analysis study (Chapter 4). Height, mass and leg length were also measured for purposes of data standardisation. Following the completion of the proforma, reflective markers adhered to participant's lower limbs and three ADPM Opal inertial sensors were also attached at the ankles and lower back was attached to the participant as described in Section 3.2.4.

Then, each participant was asked to complete 10 short preferred paced gait tasks along a walkway of approximately 8m in length within the volume of the Vicon Motion Capture system and the assessment area of the OptoGait 5m system with the 1m "Boosted" transmission bar add-on. Data collection sessions lasted 45mins-1hour per participant excluding configuration of the systems which was completed before their arrival.

3.2.4. EQUIPMENT

The Vicon 3D motion capture system was the primary tool implemented to validate the OptoGait/ ADPM Opal sensors system. All equipment was set up following the manufacturer's guidance as detailed in Figure 3.1. The software was run concurrently upon the same desktop computer to assist synchronisation.

The Vicon 3D Motion Capture Camera system (Vicon Motion Systems Ltd), incorporates 10 MX T-series infrared cameras (MXT160, firmware 502) sampling at 100Hz with focal length

approx. 17.4mm, and 2 video cameras. Dynamic calibration to 1500 valid wand frames was completed resulting in average image error between 0.15-0.21mm and world error between 0.10-0.24mm and static calibration to set the global coordinate system for the capture volume. Motion capture was limited to the lower limbs as a full-motion analysis was not required to appraise footfall. Nine 14mm reflective markers were placed on the lower limbs through manual palpation of specific bone prominences and secured using double-sided adhesive tape (Table 3.1, Figure 3.2). These positions comprised the calcaneus, and 2nd metatarsal head on each foot as well as the lower right shank to allow orientation of the skeleton at a later date. Markers were also placed in two sets of additional locations at lateral malleolus and 5th metatarsal head or inferior to the lateral malleolus and anterior to the lateral malleolus as reference markers. The latter set was initially used then updated to the former to provide a more stable reference frame. The experiment was run through Vicon Nexus 2.7 (Vicon Motion Systems Ltd) using a customised protocol incorporating marker templates, skeleton calibration and synchronisation capabilities via the Vicon MX Giganet unit. Force plates were not incorporated in the protocol in order to capture multiple steps within a trial and allow participants to walk without “aiming” for the platform.

The OptoGait (Microgate S.r.l., Italy), consists of a series of bars (100cm x 8cm) with 96 Light Emitting Diodes (LEDs) embedded at intervals of 1.041cm and height 3mm from floor which transmit between the bars at 1000Hz. The 5m system with the 1m “Boosted” transmission bar add-on was configured in a two-dimensional layout to provide an assessment area of 4m x 1m (Figure 3.3). An activation threshold of 3 LEDs was set according to the manufacturer’s recommendations to compensate for the height of the LEDs from the floor. Due to this filtering threshold, when more than 2 LEDs are covered, an initial contact gait event is indicated and following a stance period, a final contact gait event occurs when the foot is raised from the floor until only 2 LEDs are covered. Recordings were captured by the OptoGait software at 1000Hz and synchronised to the Vicon, using a custom synchronization configuration file (.gpo in Appendix 10) synchronisation output cable via MX giganet. The OptoGait (version 1.12.1, 2018) was configured to require an external start trigger signal to begin recording and time out after 20 seconds of recording.

Three ADPM Opal triaxial inertial sensors (APDM Inc.) were attached on the Left and Right Ankles at the lower shank and at the lower back in line with the 5th Lumbar vertebrae using

Velcro and elastic straps. Through the Motion Studio software (APDM Inc.) movement was sampled at 128Hz and recordings were synchronised with the Vicon via a custom sync output cable (6pin digital I/O connector to RCA phono) at the MX giganet, implementing the "duration.gpo" synchronization configuration file (available from Vicon). Motion Studio was configured to require an external start and stop trigger signal to begin and end recordings.

Following data extraction, signals were processed through custom-written algorithms (performed in MATLAB) to filter, resample data to 100Hz, detect the gait events and segment data on a stride-to-stride basis. For further details see Section 3.2.5.

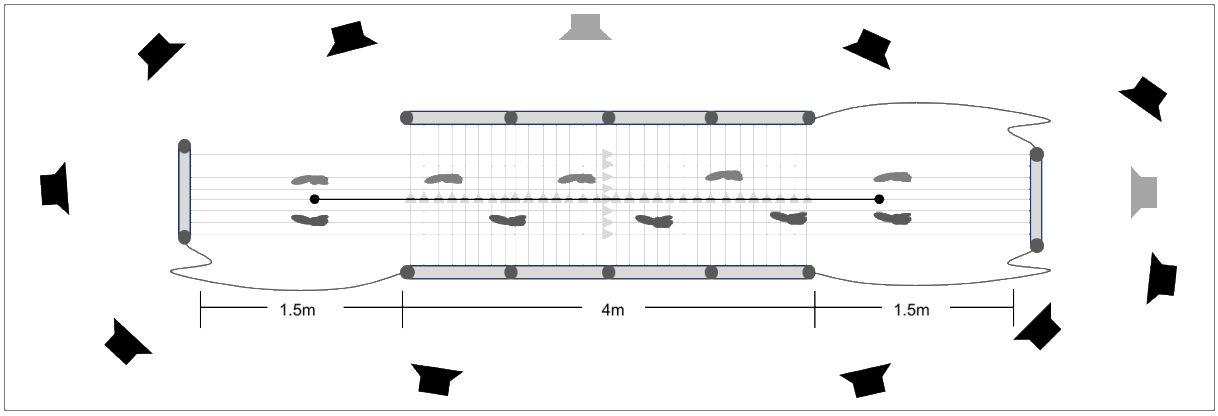

Figure 3.1: Depiction of motion capture laboratory.
Depiction of motion capture system comprising 10 3D infrared cameras (black camera icons), 2 digital cameras (grey camera icons) as well as the OptoGait photoelectric system in a 2D orientation. This provides 7m capture space and walkway.

Table 3.1: Marker information

Marker label	Position description		
RHeel/LHeel	(Right and Left) On the calcaneus at the same height above the plantar surface of the foot as the toe marker		
RToe/LToe	(Right and Left) Over the second metatarsal head, on the mid-foot side of the equinus break between fore-foot and mid-foot		
LShank	Left Midshank (For Orientation)		
Additional reference markers			
Set 1 (P7-18,P20-24)		Set 2 (P1-6,P19)	
Ank1	inferior to the lateral malleolus	**LMET05**	5th Metatarsal
Ank2	anterior to the lateral malleolus	**LLMAL**	On the lateral malleolus along an imaginary line that passes through the transmalleolar axis

Marker position descriptions with the two alternative reference marker sets and the participants they were implemented for.

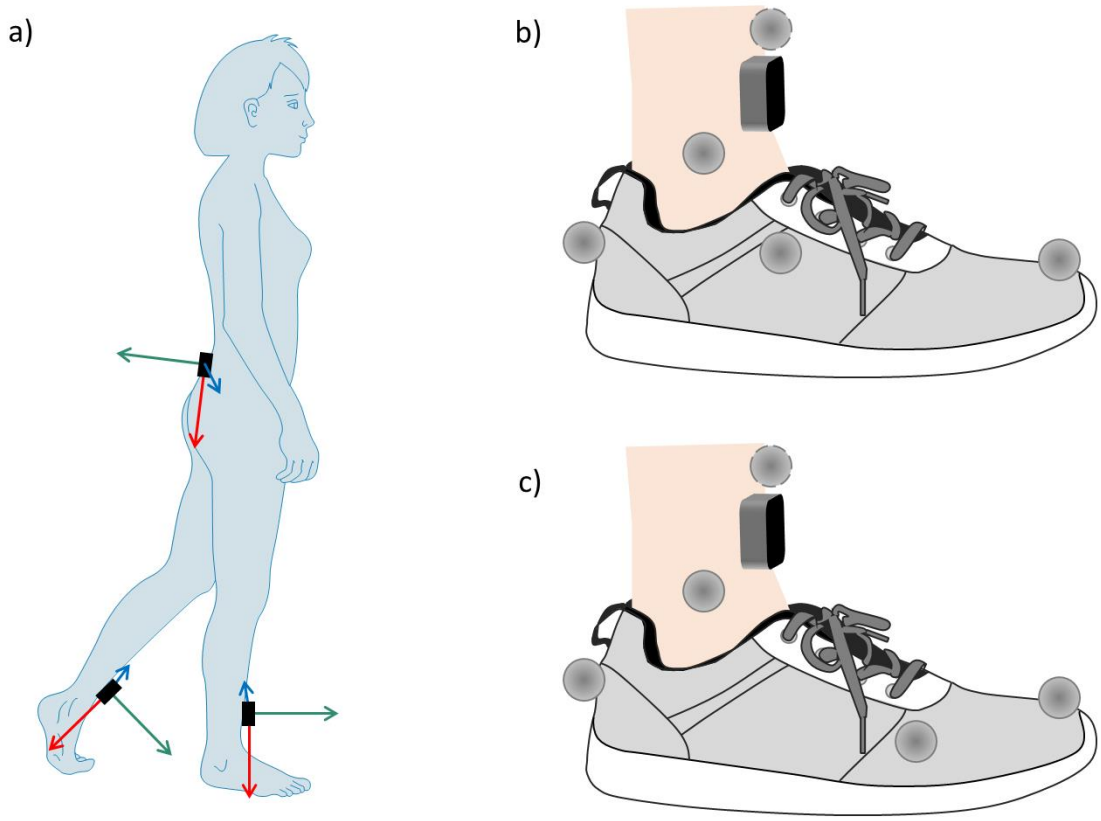

Figure 3.2: Sensor & marker location
a) Inertial sensors were positioned at ankles on the anterior aspect of the distal tibia and at the lower back in line approximately with 5th Lumbar vertebrae. b & c) reflective markers were positioned on shoes in locations as defined in Table 3.1 at calcaneus, and 2nd metatarsal head with two sets of additional reference markers used to identify foot segments and body orientation.

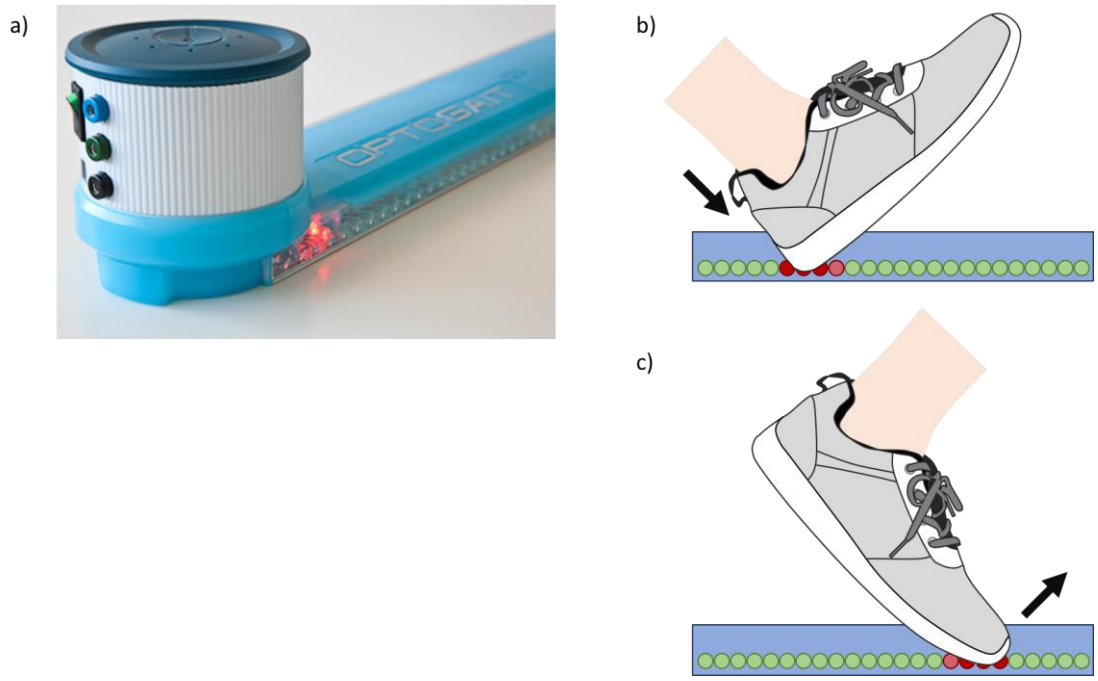

Figure 3.3: OptoGait LED settings
a) The OptoGait bars are embedded with LEDs at 1cm intervals approximately 3mm above the ground. b) Heel strike gait events are classified by interruption of 3 LEDs or more c) Toe-off gait events classified as the removal of interruption of 3LEDs.

3.2.5. DATA PROCESSING AND ANALYSIS

Initial and final gait events and a number of spatiotemporal gait parameters were extracted following the methods described below. For the 3 systems within the experiment, initial and final contact gait events, and temporal gait parameters (stride time, step time, stance time and swing time) were extracted, expressed in seconds. Spatial parameters (step length, stride length and step width) were extracted from the Vicon and OptoGait, expressed in cm In order to ensure uniform comparisons between systems, data were resampled to a resolutions common to all systems: frequency 100Hz, spatial resolution 1cm or 1mm. Resampling used a linear interpolation to down-sample data sequences. Values for all gait events and temporal gait parameters were synchronised to 100Hz, meanwhile, step and stride length values were sampled to 1cm resolution and step width values sampled to 1mm resolution.

3.2.5.1. Vicon Motion Capture System

Trajectory data from Vicon Motion Capture was analysed using MATLAB (Mathworks Inc., Natick, MA, USA) through custom computational programmes created in collaboration with Dr Lorenza Angelini.

A 2nd order lowpass digital bidirectional Butterworth filter with a cut-off frequency of 20Hz was applied to motion capture trajectories. The smoothed trajectory data from right and left heel and toe markers was automatically searched to identify peaks related to final contact and initial contact gait events where velocity deviates/ approaches 0 m/s respectively.

From the timing of gait events, stride time, step time, stance time and swing time were then computed. From the spatial location of these gait events step length and stride length were computed. Step width was computed as the distance between the mid-point of each foot (on toe-heel axis) at midstance (midpoint between initial contact and final contact where velocity is 0 m/s). All gait parameters were exported to be compared to results from other systems.

3.2.5.2. ADPM Opal Triaxial Inertial Sensors

Motion inertial data from the ADPM Opal triaxial inertial sensors were analysed using MATLAB (Mathworks Inc., Natick, MA, USA) through custom computational programmes created in collaboration with Dr Fabio Storm, Dr Christopher Buckley and Dr Lorenza Angelini.

Gait data were segmented at turn events to indicate straight-line segments of walking using x-axis gyroscope signals from upper body sensors. Direction change was indicated by changes in smoothed orientation signals (locally weighted quadratic polynomial regression function).

Gait events were determined following the method used by Salarian et al. (2004). This algorithm is widely used and well established. This was selected as reports indicated to have a high repeatability for IC and FC gait event detection and high accuracy for IC despite a less accurate detection compared with acceleration-based algorithm (Pacini Panebianco et al., 2018). Using gyroscope data from the left and right ankle sensors, a subject-specific threshold and range were used to indicate the signal peaks corresponding to left and right mid-swing phases during the central steady walking segment of each pass. The timing of each heel strike (initial contact) and toe-off (final contact) gait events were then identified from the shank sensor angular velocity. Since each midswing period of the gait cycle is associated with a large positive peak in the shank angular velocity with the highest value occurring at the timing of the midswing. Initial control was detected as the nearest local minimum after the midswing point. A low-pass FIR filter was applied to angular velocity signals with a cutoff frequency of 30Hz and pass-band attenuation of less than 0.5 dB to smooth the spurious peaks in the signal (Salarian et al., 2004). These settings were reported in the literature and have been validated in a cohort of people with Parkinson's disease .The signal was searched preceding the midswing point, to identify the local minimum corresponding to the final contact events (Figure 3.4)(Aminian et al., 2002).

From the timing of these gait events, stride time, step time, stance time and swing time were then computed and all were exported to be compared to results from other systems

3.2.5.3. Microgait OptoGait photoelectric walkway

The Optogait system's software automatically detects the temporal and spatial location using intersecting LED transmissions. Appropriate identification of footfalls was verified visually, and trial results exported and imported into Matlab for further processing.

All trial data were scrutinised using semi-automated computational scripts to identify footfalls where both initial contact and final contact were considered to begin within the system. Such invalid data were removed to ensure accurate detection of initial and final contact events for calculation of gait parameters. For the purposes of validation, initial

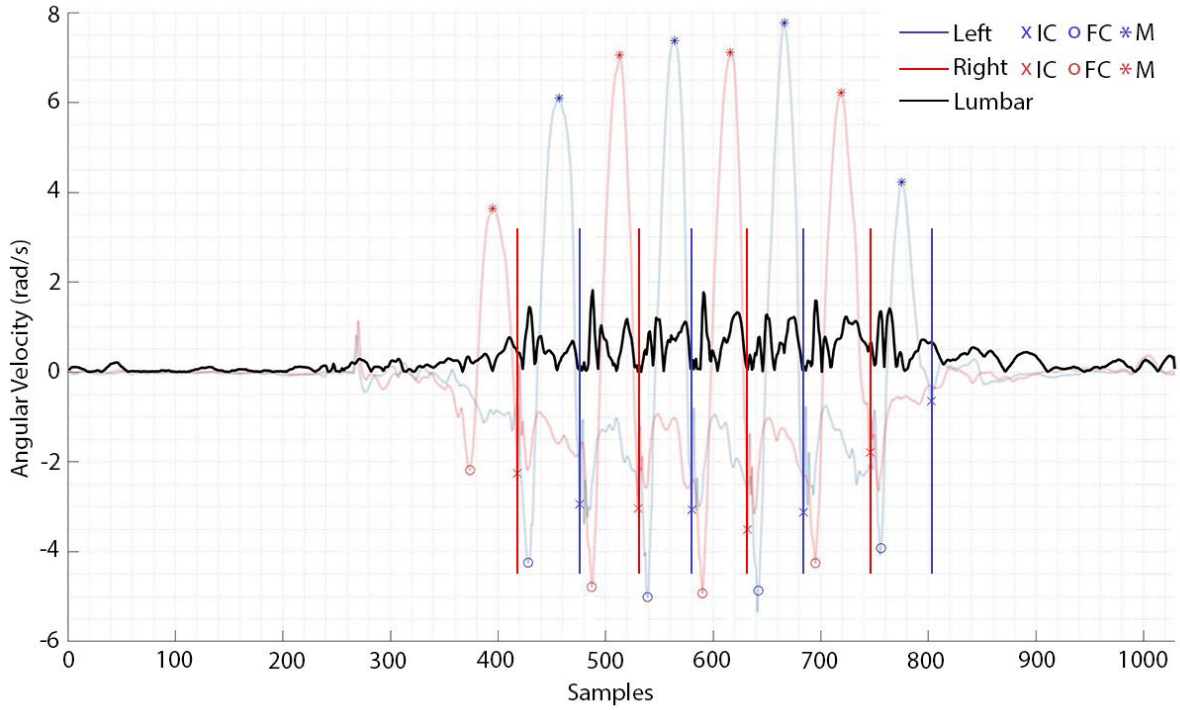

Figure 3.4: ADPM Opal sensors gait event plot
Example angular velocity signals from right ankle (red), left ankle (blue) and lumbar (black) IMUs, with all gait events and included gait data (first to last IC) marked. *: midswing (“M”), x: initial contact (“IC”), O: final contact (“FC”).

contact (heel strike) split time from the external trigger time, step time, stride time, swing time and stance time were extracted as well as step length, stride length and step width. Final contact time was computed as initial contact plus stance time for each step.

3.2.6. SYSTEM COMPARISON

Custom written MATLAB scripts were implemented to combine data from the three systems. For each trial, the first step common to the three systems was identified manually (Table 3.2). Data were aligned to ensure correct computation of between-system differences.

3.2.7. STATISTICAL ANALYSIS

The analysis was limited to the gait events occurring within the OptoGait assessment area and Vicon motion capture volume in order to cross-validate step detection.

Data were not normalised in order to retain the unadjusted results. Differences and absolute differences and averages of gait event timing and temporal gait parameters detected by the 3 systems were computed on a step by step basis between Vicon-OptoGait, Vicon-Opal and OptoGait-Opal systems. As spatial gait events were only computed by the Vicon and OptoGait differences (Equation 3.1) and absolute differences (Equation 3.2) between the 2 systems (Vicon-OptoGait) were computed on a step by step basis.

Equation 3.1: System Difference = system 2 - system 1

Equation 3.2: System Absolute Difference = [system 1 - system 2]

For each valid trial, mean difference and average values were calculated to avoid pseudo-replication of data. Gait speed was computed for each stride, from the Vicon system and a mean value computed for each trial.

Equation 3.3: Speed (m/s) = stride length (m) / stride time (s)

Shapiro-Wilks Normality test was used to examine the distribution of values. The following statistical tests were used to check the validity of the gait event detection by the two systems:

- Intraclass correlation coefficient analysis with a two-way random, single measures model for absolute agreement and R^2 (coefficient of determination) through linear regression analysis to indicate consistency of measurements.

- Calculation of standard error of estimate (SEE) and paired T-Test were used to assess relative agreement.
- Pearson's Correlation to examine the influence of speed on system accuracy on a trial by trial basis

P-values of less than 0.05 were considered significant. Correlation coefficients greater than 0.6 were considered to indicate good to an excellent inter-rater agreement in line with Cicchetti (1994).

Correlation and Bland Altman plots were generated to display the relationships between values measured by the 3 systems and the differences between these (Bland and Altman, 1986). For both the differences and absolute differences 95% Limits of Agreement (LoA, Equation 3.3) were calculated to indicate the level of systematic bias and precision of the measurements and the %LoA (Equation 3.4) for difference between measurement systems was used as an indication of the maximum expected bias for future studies.

Equation 3.4: $LoA = \text{mean diff} \pm SD_{diff} \times 1.96$

Equation 3.5: $\%LoA = LoA_{diff} / \text{mean} \times 100$

Table 3.2: Step matching strategy

Step Reference	L/R	Vicon	OptoGait	Opal
1	L	1		1
2	**R**	**2**	**1**	**2**
3	**L**	**3**	**2**	**3**
4	**R**	**4**	**3**	**4**
5	**L**	**5**	**4**	**5**
6	**R**	**6**	**5**	**6**
7	**L**	**7**	**6**	**7**
8	R	8		8

Example approach to matching data on a step by step basis. Only gait events that were concurrently measured by all three systems were included (bold). On a trial by trial basis, gait events were matched to exclude those that were not within the OptoGait capture volume.

3.3. RESULTS

3.3.1. PARTICIPANT CHARACTERISTICS

During four assessment sessions, 24 healthy controls (16 females) were recruited. The group had an average age of 27±8 years [range 21-54 yrs], an average BMI of 22.8±2.5 kg/m^2 [19.4-27.3 kg/m^2], reflecting an average height 172.5±9.2 cm [158 - 197.5cm], and mass 67.9±9.2 kg [52-82 kg]. Participants had an average leg length (to ankle) of 89.7±7.3cm [77-100cm]. Most participants reported no exclusionary medical history although one participant reported a history of Ulcerative Colitis and one reported a previous Right-Anterior Cruciate Ligament reconstruction which was not active at the time of assessment.

3.3.2. VALIDITY OF DATA

Each participant was asked to complete at least 10 trials with additional repeats requested where issues were evident during data collection. In some circumstances, data (n=10) were later found to be unusable, however valid data were captured for 230 trials from 24 participants. For the 10 trials excluded, 5 trials were data recorded from 1 participant, add 2 trials were recorded from a 2nd participant with the other 3 trials excluded from 3 individual participants. Reasons for exclusion were: data file was corruption (n=1), incorrect gait event detection by the one of the system/ algorithms (Vicon n=2 , OptoGait n=5), or problems with synchronisation of the systems occurred for at least one of the systems (Opal n=1, OptoGait n=2). For one trial, the OptoGait mislabelled the steps as left/right so step width was not calculated and this was removed from this analysis.

3.3.3. GAIT EVENTS

From data 230 valid walking trials, a total of 972 initial contact and 1012 final contact gait events were detected from the three gait analysis systems. This equates to an average of 4.2 initial contacts and 4.4 final contact events per participant. Table 3.3 and Table 3.4 display the median and interquartile range (IQR) of Initial Contact (Heel Strike) and Final Contact (Toe-Off) gait events timing detected by the three gait analysis systems as well as the system differences and absolute differences with significant differences indicated. The correlations of Heel Strike and Toe-off gait events detected between the three systems are also displayed. Figure 3.5 and Figure 3.6 display the correlations of three system measurements, and Bland-Altman plots for differences and absolute differences between systems for both gait events.

Table 3.3: Gait Event Results - Initial Contact

COMPARISON	Vicon-OptoGait	Vicon-Opals	OptoGait-Opals
ICC(2, 1) (95% CI)	1.000 (0.996, 1.000)**	1.000 (1.000, 1.000)**	1.000 (0.999, 1.000)**
R^2	1.000	1.000	1.000
Absolute System Difference (Mean [+95% LoA])	0.02s [0.05s]	0.02s [0.05s]	0.03s [0.07s]
System Difference (Mean [±95% LoA])	0.02s [-0.01s, 0.05s]	0.01s [-0.05s, 0.06s]	-0.02s [-0.07s, 0.04s]
SEE	0.017s	0.027s	0.028s
p	<0.001	<0.001	<0.001

Abbreviations: ICC: intraclass coefficient, CI: confidence interval, LoA: Limits of Agreement, IQR: interquartile range, n: number of participants, Opals: ADPM Opal sensors, ** p<0.01 *p<0.05

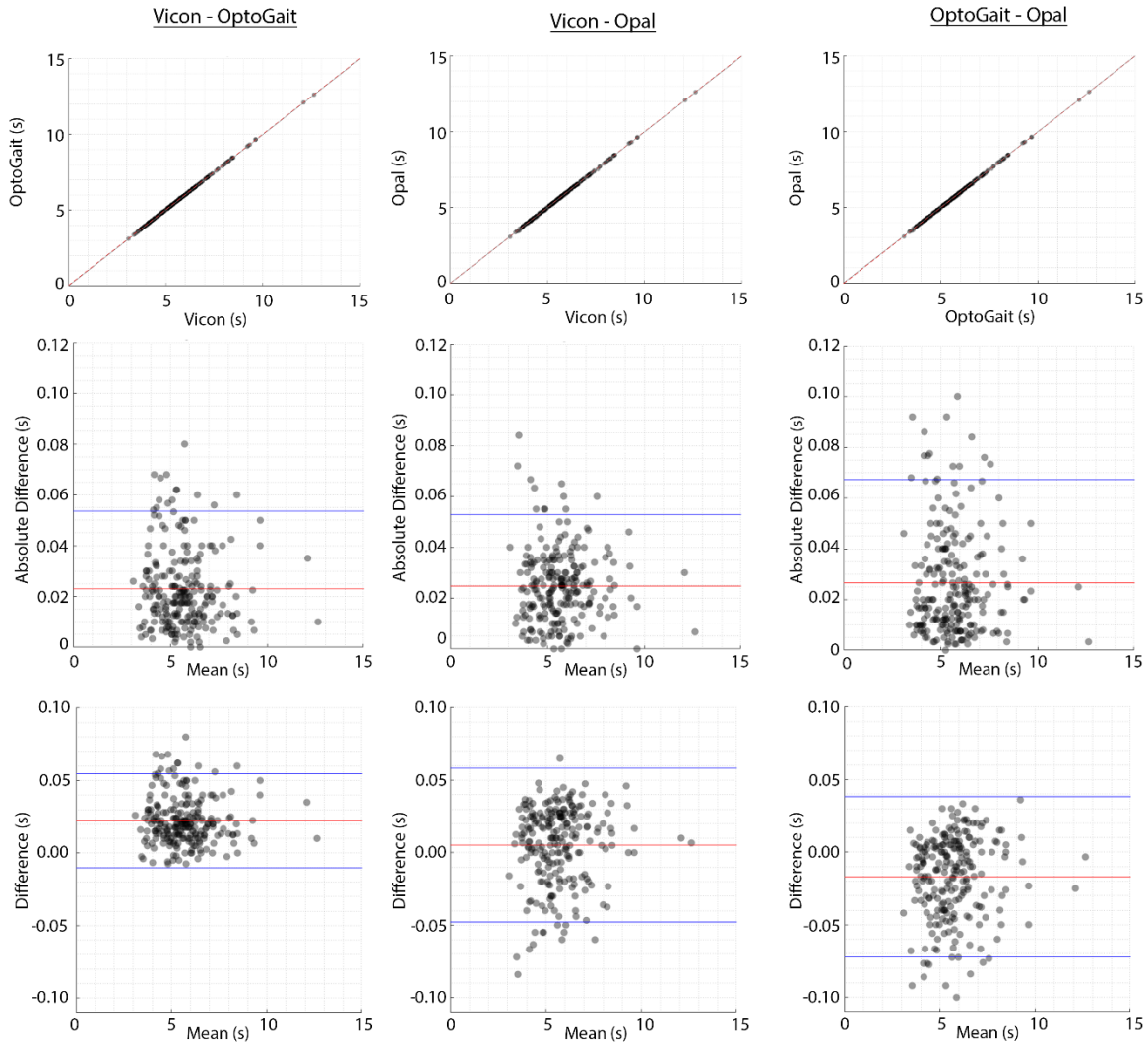

Figure 3.5: Gait Events graphs – Initial contact
Correlation of initial contact gait event (s) measurements by different systems Vicon:OptoGait, OptoGait:Opal, Vicon:Opal. Correlation plots display reference line (black) and correlation line between systems (red). Bland Altman plots display the mean of system measurements against the difference/ absolute difference between systems measurements with mean difference (red) and 95% Limits of Agreements indicated (blue). Abbreviation: s, seconds

Table 3.4: Gait Event Results - Final Contact

COMPARISON	Vicon-OptoGait	Vicon-Opals	OptoGait-Opals
ICC(2, 1) (95% CI)	0.999 (0.924, 1.000)**	1.000 (0.998, 1.000)**	1.000 (0.999, 1.000)**
R^2	1.000	1.000	1.000
Absolute System Difference (Mean [+95% LoA])	0.04s [0.07s]	0.03 [0.07]	0.03s [0.06s]
System Difference (Mean [±95% LoA])	-0.04s [-0.07s, -0.01s]	-0.02 [-0.07, 0.03]	0.02s [-0.03s, 0.06s]
SEE	0.017s	0.024s	0.024s
p	<0.001	<0.001	<0.001

Abbreviations: ICC: intraclass coefficient, CI: confidence interval, SEE: Standard Error Estimate, LoA: Limits of Agreement, IQR: interquartile range, n: number of participants, Opals: ADPM Opal sensors, ** p<0.01 *p<0.05

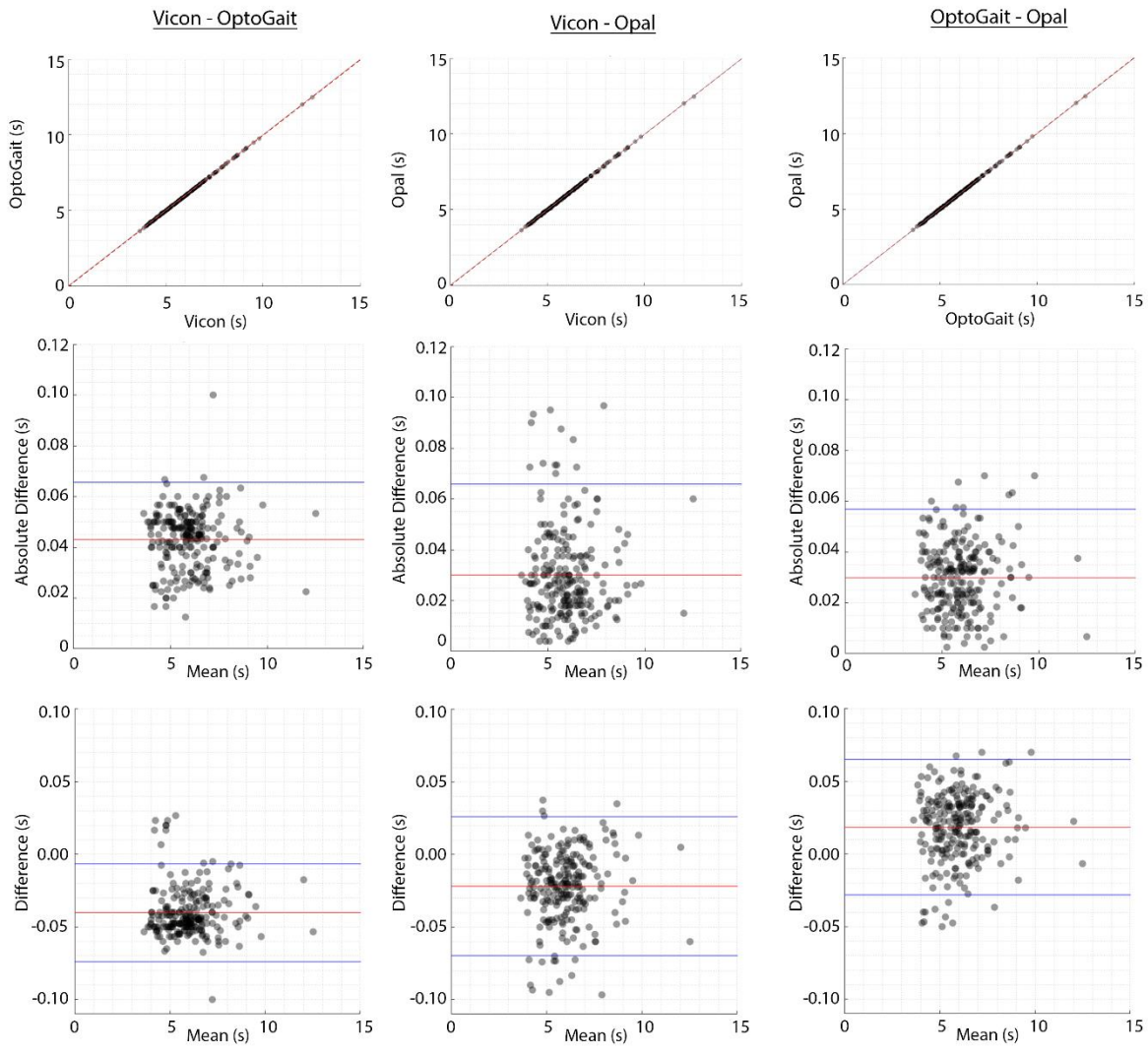

Figure 3.6: Gait Events graphs – Final Contact
Correlation of final contact gait event (s) measurements by different systems Vicon:OptoGait, OptoGait:Opal, Vicon:Opal. Correlation plots display reference line (black) and correlation line between systems (red). Bland Altman plots display the mean of system measurements against the difference/ absolute difference between systems measurements with mean difference (red) and 95% Limits of Agreements indicated (blue). Abbreviation: s, seconds

3.3.4. GAIT PARAMETERS

From successive gait events in 230 valid walking trials, temporal gait parameters were computed by all 3 systems. A total of 742 step times, 511 stride times, 860 stance times and 662 swing times were calculated and contributed to results for the cohort. Spatial gait parameters computed by the Vicon and OptoGait provided 776 step lengths, 546 stride lengths and 676 step widths. Table 3.5 to Table 3.9 display the cohort's mean±SD for gait parameters from the gait analysis systems with significant differences indicated. The correlations of gait parameters captured by the three systems are also displayed.

Figure 3.7 to Figure 3.11 display the correlation of three system measurements, and Bland-Altman plots for differences and absolute differences between systems.

Table 3.5: Gait Parameter Results - Step time

	Vicon	**OptoGait**	**Opals**
Mean±SD	0.55s±0.05s	0.55s±0.05s	0.55s±0.05s
COMPARISON	**Vicon-OptoGait**	**Vicon-Opals**	**OptoGait-Opals**
ICC(2, 1) (95% CI)	0.989 (0.986, 0.992)**	0.981 (0.975, 0.985)**	0.987 (0.983, 0.990)**
R^2	0.979	0.963	0.974
Absolute System Difference (Mean [+95% LoA])	0.01s [0.03s]	0.01s [0.04s]	0.01s [0.03s]
System Difference (Mean [±95% LoA])	-0.001s [-0.01s, 0.01s]	-0.001s [-0.02s, 0.02s]	-0.001s [-0.02s, 0.01s]
SEE	0.007s	0.009s	0.007s
p	0.112	0.021	0.174

Abbreviations: ICC: intraclass coefficient, CI: confidence interval, SEE: Standard Error Estimate, LoA: Limits of Agreement, IQR: interquartile range, n: number of participants, Opals: ADPM Opal sensors, ** p<0.01 *p<0.05

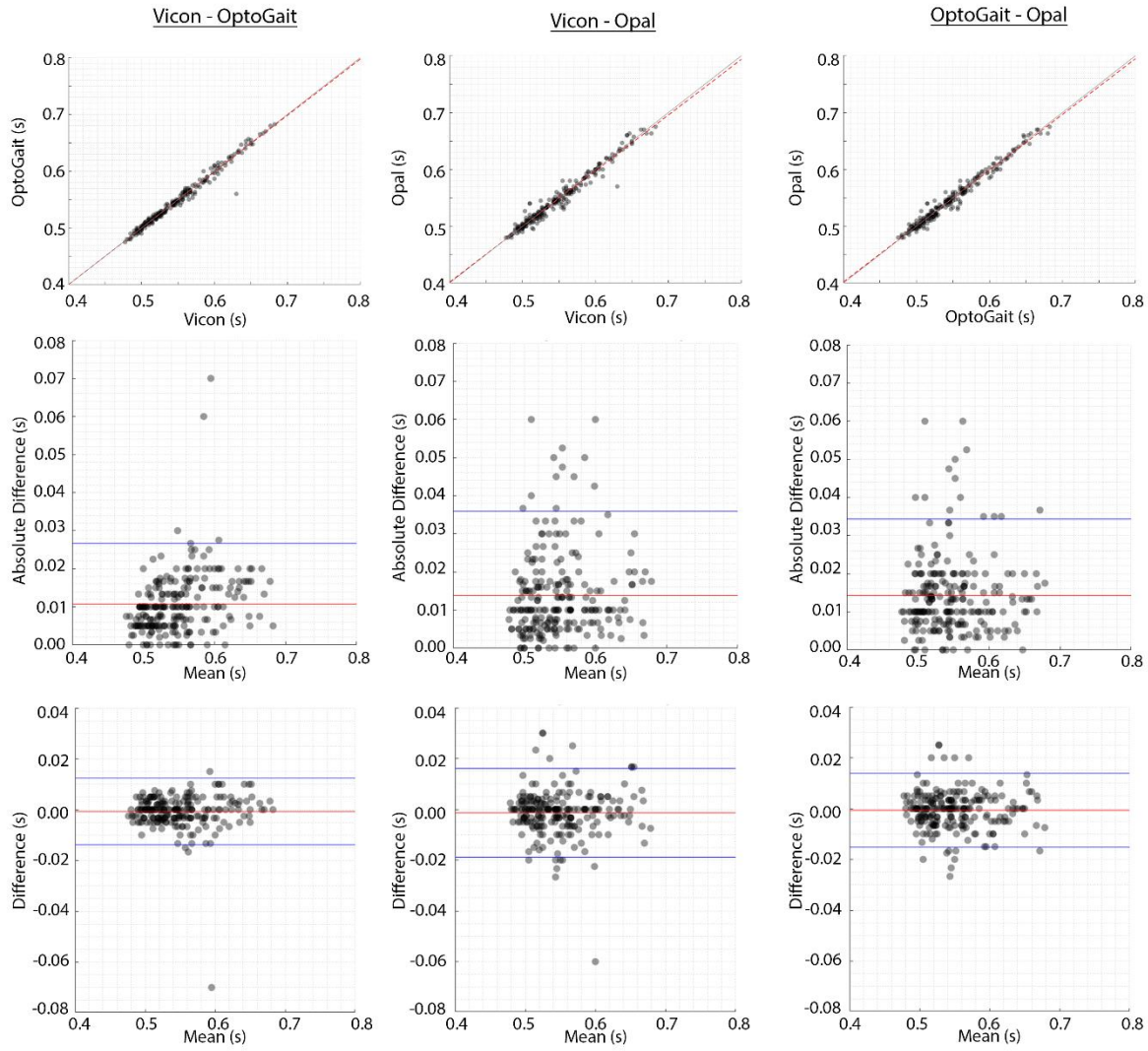

Figure 3.7: Gait parameter graphs - Step time
Comparison of step time (s) measurements by different systems Vicon:OptoGait, OptoGait:Opal, Vicon:Opal. Correlation plots display reference line (black) and correlation line between systems (red). Bland Altman plots display the mean of system measurements against the difference/ absolute difference between systems measurements with mean difference (red) and 95% Limits of Agreements indicated (blue). Abbreviation: s, seconds

Table 3.6: Gait parameter results - Stride time

	Vicon	**OptoGait**	**Opals**
Mean±SD	1.09s±1.14s	1.09s±1.14s	1.09s±1.14s
COMPARISON	**Vicon-OptoGait**	**Vicon-Opals**	**OptoGait-Opals**
ICC(2, 1) (95% CI)	0.998 (0.997, 0.998)**	0.995 (0.993, 0.996)**	0.995 (0.994, 0.996)**
R^2	0.996	0.989	0.990
Absolute System Difference (Mean [+95% LoA])	0.01s [0.02]	0.01s [0.03]	0.01s [0.03]
System Difference (Mean [±95% LoA])	0.00s [-0.02, 0.02]	0.00s [-0.03, 0.03]	0.00s [-0.03, 0.03]
SEE	0.009s	0.014s	0.013s
p	0.179	0.413	0.972

Abbreviations: ICC: intraclass coefficient, CI: confidence interval, SEE: Standard Error Estimate, LoA: Limits of Agreement, IQR: interquartile range, n: number of participants, Opals: ADPM Opal sensors, ** p<0.01 *p<0.05

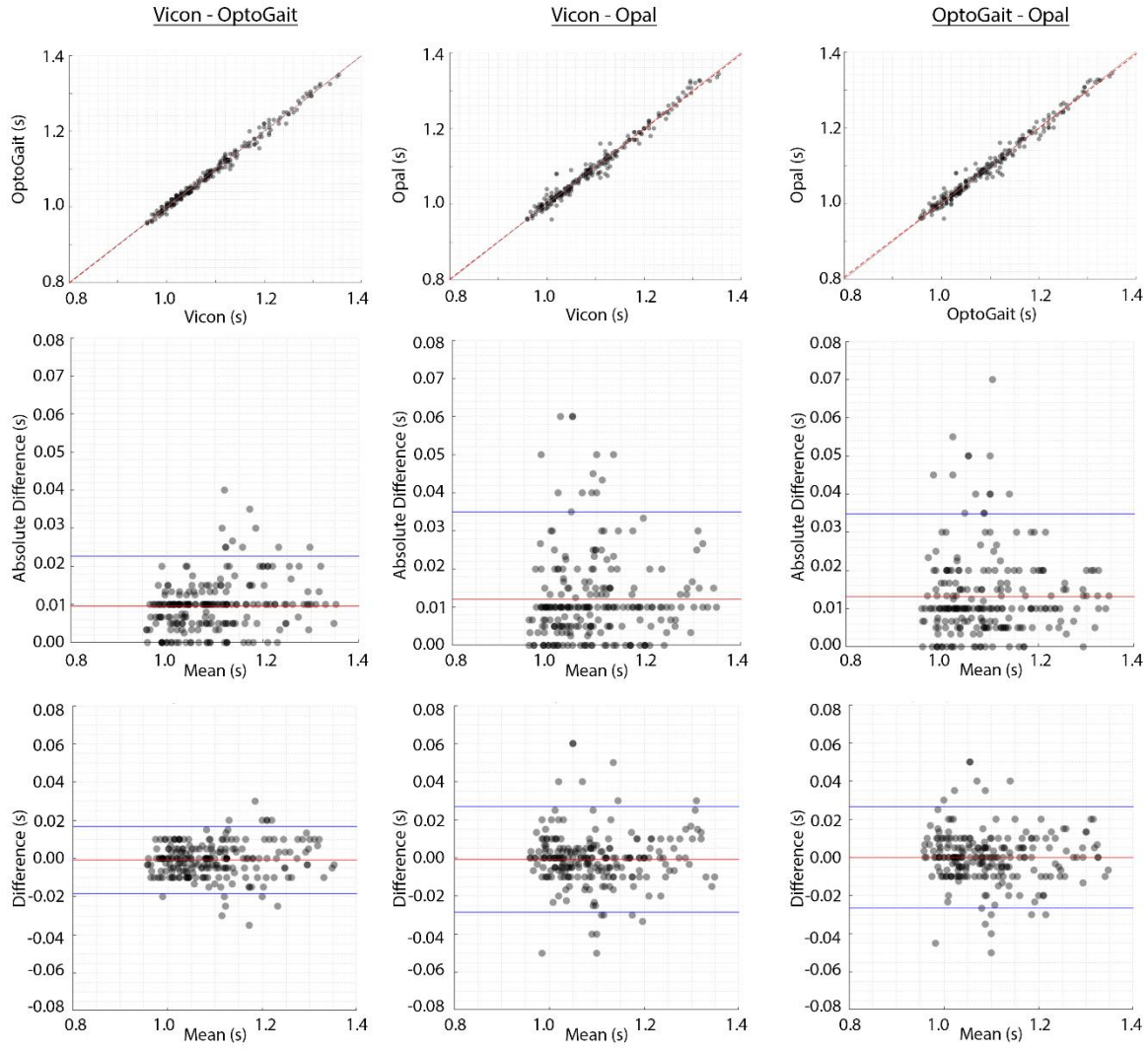

Figure 3.8: Gait parameter graphs - Stride Time
Comparison of Stride Time (s) measurements by different systems Vicon:OptoGait, OptoGait:Opal, Vicon:Opal. Correlation plots display reference line (black) and correlation line between systems (red). Bland Altman plots display the mean of system measurements against the difference/ absolute difference between systems measurements with mean difference (red) and 95% Limits of Agreements indicated (blue). Abbreviation: s, seconds

Table 3.7: Gait parameter graphs - Stance time

	Vicon	**OptoGait**	**Opals**
Mean±SD)	0.68±0.07	0.62±0.06	0.66±0.07
COMPARISON	**Vicon-OptoGait**	**Vicon-Opals**	**OptoGait-Opals**
ICC(2, 1) (95% CI)	0.651 (-0.076, 0.883)**	0.857 (0.466, 0.939)**	0.800 (0.164, 0.924)**
R^2	0.851	0.907	0.886
Absolute System Difference (Mean [+95% LoA])	0.06 [0.11]	0.03 [0.06]	0.04 [0.08]
System Difference (Mean [±95% LoA])	-0.06 [-0.12, 0.00]	-0.02 [-0.07, 0.02]	0.04 [-0.01, 0.08]
SEE	0.024	0.020	0.023
p	<0.001	<0.001	<0.001

Abbreviations: ICC: intraclass coefficient, CI: confidence interval, SEE: Standard Error Estimate, LoA: Limits of Agreement, IQR: interquartile range, n: number of participants, Opals: ADPM Opal sensors, ** p<0.01 *p<0.05

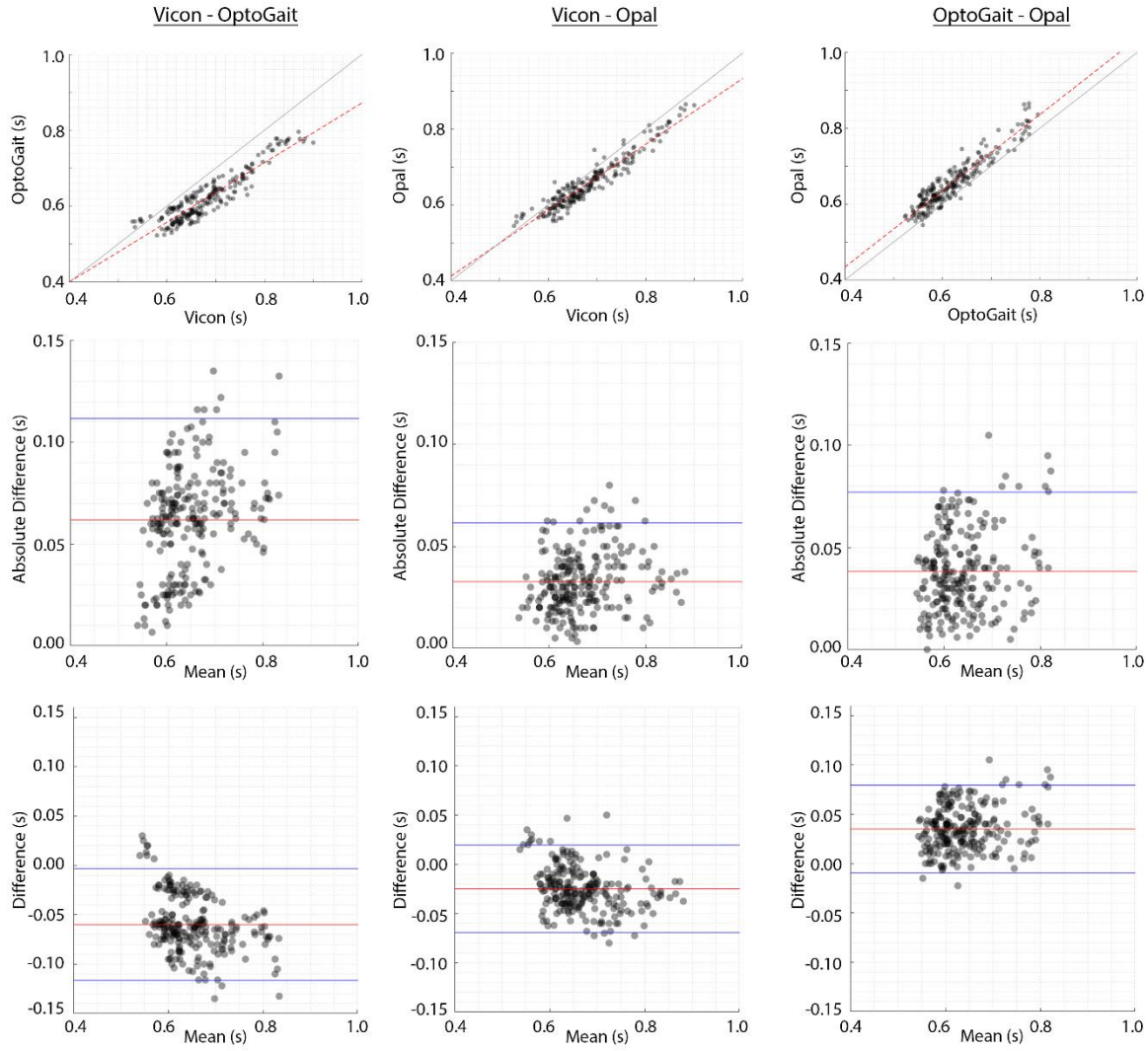

Figure 3.9: Gait parameter graphs - Stance Time
Comparison of Stance Time (s) measurements by different systems Vicon:OptoGait, OptoGait:Opal, Vicon:Opal. Correlation plots display reference line (black) and correlation line between systems (red). Bland Altman plots display the mean of system measurements against the difference/ absolute difference between systems measurements with mean difference (red) and 95% Limits of Agreements indicated (blue). Abbreviation: s, seconds

Table 3.8: Gait parameter graphs - Swing time

	Vicon	**OptoGait**	**Opals**
Mean±SD	0.42±0.03	0.48±0.04	0.44±0.03
COMPARISON	**Vicon-OptoGait**	**Vicon-Opals**	**OptoGait-Opals**
ICC(2, 1) (95% CI)	0.266 (-0.074, 0.605)**	0.466 (-0.071, 0.737)**	0.582 (0.100, 0.784)**
R^2	0.482	0.632	0.609
Absolute System Difference (Mean [+95% LoA])	0.06 [0.11]	0.03 [0.06]	0.04 [0.08]
System Difference (Mean [±95% LoA])	0.06 [0.01, 0.11]	0.02 [-0.02, 0.06]	-0.04 [-0.08, 0.01]
SEE	0.027	0.021	0.021
p	<0.001	<0.001	<0.001

Abbreviations: ICC: intraclass coefficient, CI: confidence interval, SEE: Standard Error Estimate, LoA: Limits of Agreement, IQR: interquartile range, n: number of participants, Opals: ADPM Opal sensors, ** p<0.01 *p<0.05

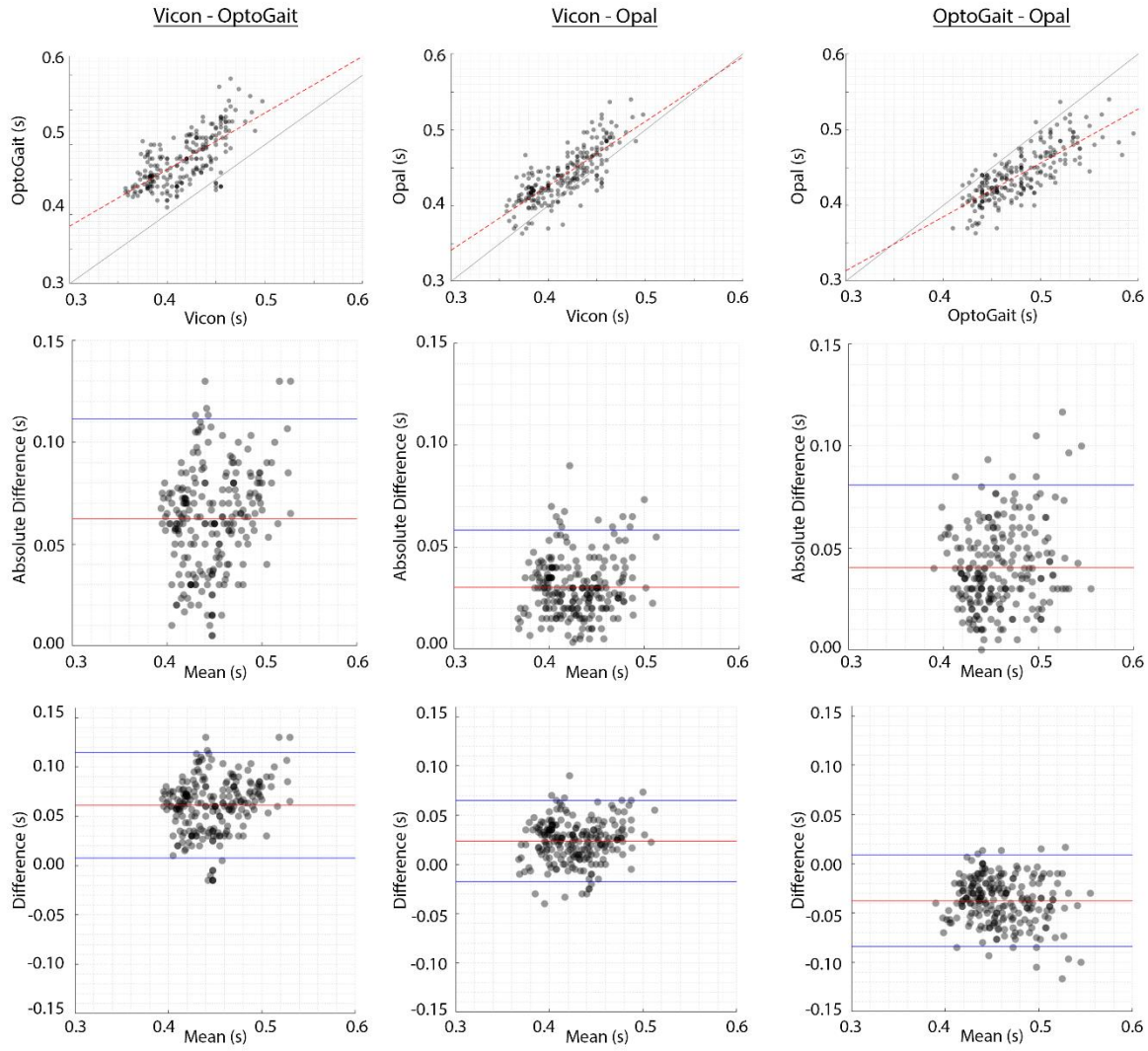

Figure 3.10: Gait parameter graphs - Swing Time
Comparison of Swing Time (s) measurements by different systems Vicon:OptoGait, OptoGait:Opal, Vicon:Opal. Correlation plots display reference line (black) and correlation line between systems (red). Bland Altman plots display the mean of system measurements against the difference/ absolute difference between systems measurements with mean difference (red) and 95% Limits of Agreements indicated (blue). Abbreviation: s, seconds

Table 3.9: Gait parameter graphs – Step Length, stride length, step width

Step Length	
Vicon Mean (SD)	73 (7)
OptoGait Mean (SD)	73 (7)
COMPARISON	
ICC(2, 1) (95% CI)	0.986 (0.984, 0.988)**
R^2	0.995
Absolute System Difference (Mean [+95% LoA])	1 [2]
System Difference (Mean [±95% LoA])	0 [-1, 1]
SEE	0.483
p	0.519
Stride Length	
Vicon Mean (SD)	146 (16)
OptoGait Mean (SD)	146 (16)
COMPARISON	
ICC(2, 1) (95% CI)	0.996 (0.995, 0.997)**
R^2	0.998
Absolute System Difference (Mean [+95% LoA])	1 [2]
System Difference (Mean [±95% LoA])	0 [-1, 2]
SEE	0.718
p	0.233
Step Width	
Vicon Mean (SD)	9.3 (2.4)
OptoGait Mean (SD)	12.5 (3.1)
COMPARISON	
ICC(2, 1) (95% CI)	0.668 (-0.072, 0.882)**
R^2	0.621
Absolute System Difference (Mean [+95% LoA])	3.3 [6.9]
System Difference (Mean [±95% LoA])	3.2 [-0.5, 7.0]
SEE	1.924
p	<0.001

Abbreviations: ICC: intraclass coefficient, CI: confidence interval, SEE: Standard Error Estimate, LoA: Limits of Agreement, IQR: interquartile range, n: number of participants, ** p<0.01 *p<0.05

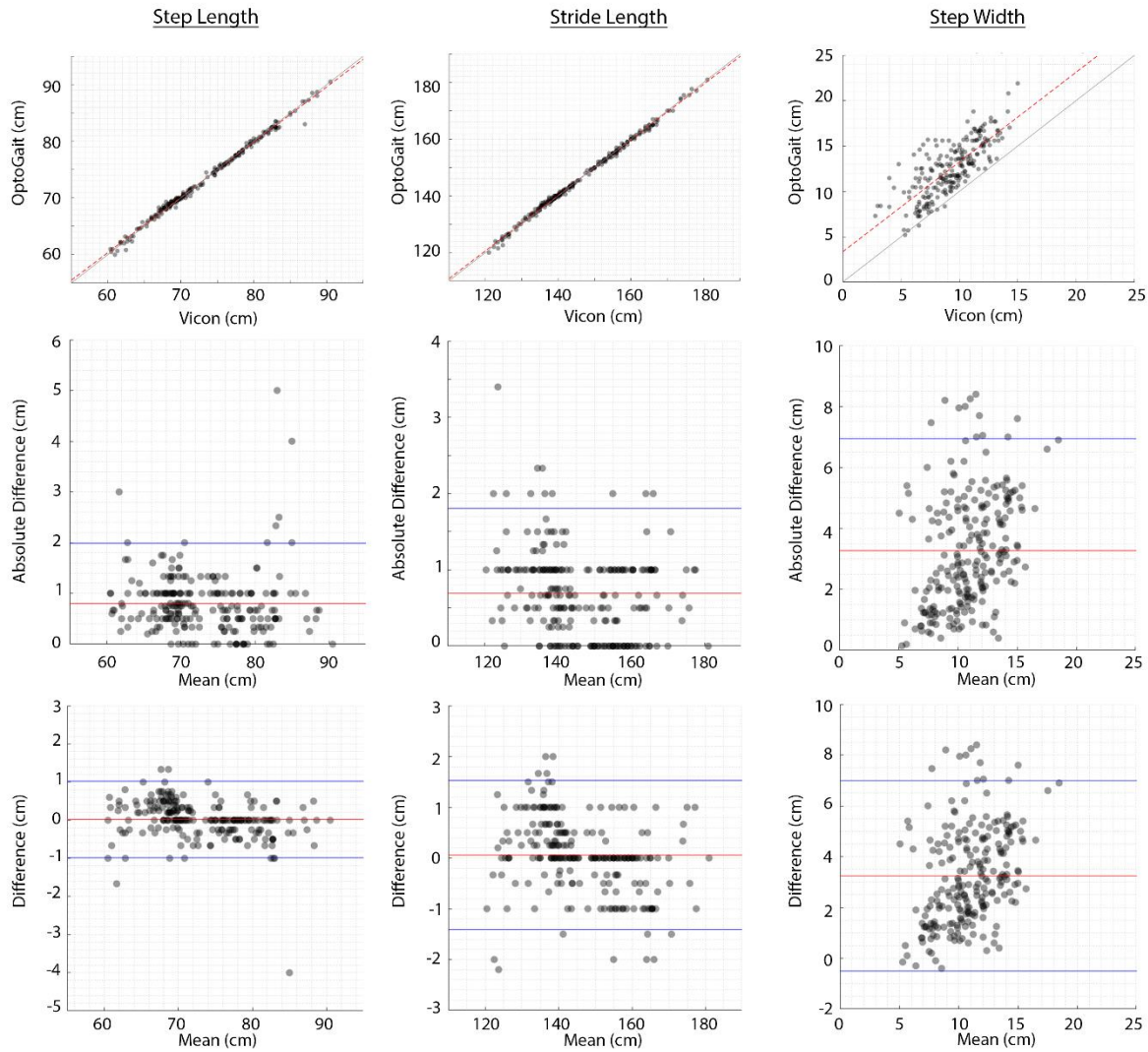

Figure 3.11: Gait parameter graphs - Step Length, stride length, step width
Comparison of measurements of Step Length, Stride Length and Step Width by Vicon and OptoGait. Correlation plots display reference line (black) and correlation line between systems (red). Bland Altman plots display the mean of system measurements against the difference/ absolute difference between systems measurements with mean difference (red) and 95% Limits of Agreements indicated (blue). Abbreviation: cm, centimetre

3.3.5. CORRELATION WITH SPEED

On a trial by trial basis where valid data were available, the correlation of differences in gait event and gait parameters with gait speed from the Vicon (Table 3.10) was examined. Average gait speed was 1.34±0.2m/s (range: 0.98-1.79m/s).

Of the 230 valid trials, 1 trial was excluded from correlation analysis for step width due to procedural issues with the OptoGait bar. Meanwhile, for one other trial, too few gait events were captured concurrently by the 3 systems to denote a stride so was excluded for stride time and stride length correlations.

None of the comparisons resulted in a strong significant correlation between gait speed and measurement differences ($|r|<0.5$) indicating gait speed did not impact the agreement of the gait event and gait parameter measurements.

Table 3.10: Correlation between gait speed and system differences

		n	Vicon:OptoGait		Vicon:Opal		OptoGait:Opal	
			r	p	r	p	r	p
Absolute difference	Initial Contact	229	-0.324	<0.001	0.016	0.812	-0.042	0.523
	Final Contact	229	0.127	0.055	0.228	<0.001	0.032	0.634
	Step Time	229	-0.249	<0.001	-0.024	0.721	0.019	0.770
	Stride Time	229	-0.273	<0.001	0.051	0.440	0.069	0.299
	Stance Time	229	-0.417	<0.001	-0.231	<0.001	-0.145	0.028
	Swing Time	229	-0.452	<0.001	-0.211	0.001	-0.212	0.001
	Step Length	229	-0.153	0.021				
	Stride Length	229	-0.293	0.000				
	Step Width	228	-0.041	0.535				
Difference	Initial Contact	229	-0.345	<0.001	-0.221	<0.001	-0.009	0.891
	Final Contact	229	0.027	0.680	-0.152	0.021	-0.177	0.007
	Step Time	229	0.007	0.912	0.061	0.358	0.062	0.353
	Stride Time	229	0.039	0.559	0.087	0.190	0.065	0.326
	Stance Time	229	0.441	<0.001	0.373	<0.001	-0.191	0.004
	Swing Time	229	-0.463	<0.001	-0.347	<0.001	0.226	<0.001
	Step Length	229	-0.289	<0.001				
	Stride Length	229	-0.307	<0.001				
	Step Width	228	-0.037	0.578				

Results of Pearson's correlation analysis between gait speed and system absolute differences/ differences on a trial by trial basis. Abbreviations: n number of trials, r correlation coefficient, p p-value indicating correlation significance

3.4. DISCUSSION

The present study explored the accuracy and precision of the OptoGait photoelectric system and ADPM Opal triaxial inertial sensors compared with the Vicon motion capture system as the gold standard criterion instrument in a cohort of 24 healthy adult participants (16 females). Valid data were captured and analysed for all participants and, a large number of trials and steps were captured from each participant available for statistical analysis. Exclusion of unusable trial data was necessary for 10 trials where data file was corrupted, incorrect gait event detection by the one of the systems, or problems with synchronisation of the systems occurred for at least one of the systems. Since issues commonly occurred in the same participants, there may have been a recurring issue with the configuration that was corrected for other trials.

3.4.1. GAIT EVENTS

The mean difference between Vicon and OptoGait system measurements for initial contact and final contact gait events were 0.02s (±0.03s 95%LoA, $p<0.001$) and -0.04s (±0.03s 95%LoA, $p<0.001$) respectively indicating that the OptoGait produced a small but statistically significant delay in detection of initial contact and anticipation of the final contact event. Gait event values displayed strong significant correlations between systems (IC: 1.000 (0.996, 1.000), p=0.001; FC: 0.999 (0.924, 1.000), $p<0.001$, (ICC(2,1)(95%CI)).

When compared with the Vicon, gait events values from ADPM Opal IMUs were significantly different: 0.01s (±0.05s 95%LoA, p=0.004) and -0.02s (±0.05s 95%LoA, $p<0.001$) for initial contact and final contact respectively. Similar to Vicon:OptoGait results, strong significant correlations were present between the Vicon and ADPM Opal sensors gait event values (IC: 1.000 (1.000, 1.000), $p<0.001$; FC: 1.000 (0.998, 1.000), $p<0.001$ (ICC(2,1) 95%CI))).

In comparison of gait event values measured by the OptoGait and ADPM Opal sensors, a significant difference of -0.02s (±0.06s 95%LoA, $p<0.001$) and 0.02s (±0.05s 95%LoA, $p<0.001$) were observed for initial contact and final contact respectively. This indicates that the ADPM Opal sensors initial contact detection is anticipated and final contact delayed compared with the OptoGait and that the ADPM Opal sensors provides an intermediate gait event value to the Vicon and OptoGait. However strong ICCs were exhibited between systems (IC: 1.000 (0.999, 1.000); FC: 1.000 (0.999, 1.000) (ICC(2,1) 95%CI, $p<0.01$)).

Taken together it seems that although a small statistically significant systematic bias is present, the concurrent validity appears to be excellent as indicated by strong significant ICC values. Since the data from the three systems was resampled to 100Hz, the 95%LoA reported can be considered excellent.

The selection of LED filter greatly impacts the detection of gait event by the OptoGait and is related to the gait task performed. For instance while, to study walking by healthy adults with the OptoGait, the use of 2in/2out and 3in/3out filter settings are valid (Healy et al., 2019). Therefore, the use of a 3in/3out filter in the present study results in a pattern of initial contact delay and final contact anticipation following results reported in the literature for both OptoGait and ADPM Opal sensors validation compared with motion capture.

Final contact gait event detection also appears inherently associated with a higher system difference than initial contact gait event detection. Previous studies have identified similar issues with final contact gait event detection from the IMUs. Since the algorithms implemented here rely on the identification of gait events from angular velocity signals measured by gyroscopes at the lower shank, this strategy is fundamentally different from gait event detection when using marker trajectories in motion capture techniques. Therefore, differences are common when comparing shank worn IMU data to motion capture analysis. Since the position of inertial sensors on the front rather than the lateral side of the shank, some impact on the accuracy of the gait event detection algorithms is present. Panebianco et al. (2018) also reported significant differences between foot-based algorithms and shank- or trunk-based algorithms for initial contact however, foot- and shank-based algorithms displayed comparable accuracy and repeatability. Meanwhile, significant differences were identified between all sensor positions for final contact detection with foot-based algorithms performing with higher accuracy and repeatability than shank-based algorithms. The authors also described a delay in initial contact detection and anticipation of final contact detection as corroborated here.

3.4.2. GAIT PARAMETERS

3.4.2.1. Temporal Gait Parameters

The calculation of step time was not significantly different between the Vicon:Optogait and OptoGait:Opals gait analysis systems (-0.01s-0.01s, ±2.4%, 95%LoA, p=0.112; -0.02s-0.02s,±2.6%, 95%LoA, p=0.174). Although results indicate a statistically significant difference

in step time measured by Vicon:Opals (-0.02s-0.01s, ±3.2%, 95%LoA, p=0.021), this difference was within acceptable ranges. Strong significant correlations are present across the three instrument comparisons (ICC(2,1)>0.90, p<0.001; R^2>0.9). For stride time, no statistically significant system differences were present within the comparisons between the 3 instruments (-0.02s-0.02s, ±1.6%, 95%LoA, p=0.179; -0.03s-0.03s, ±2.5%, 95%LoA, p=0.413; -0.03s-0.03s, ±2.4%, 95%LoA, p=0.972) and strong significant correlations can be observed (ICC(2,1)>0.90, p<0.001; R^2>0.9). Therefore, step time and stride time display an acceptable accuracy and reliability between instruments, with a difference less than ±3.2% (Table 3.11).

The meta-analysis of gait measures in healthy control and CA cohorts in Chapter 2 indicates that a mean difference of 110ms and 180ms is present for step time and stride time between the cohorts. Therefore, this level of agreement will be sensitive enough to detect a difference in similar groups in future studies.

Significant differences in measurement of stance time, and swing phase by the OptoGait were detected which follows previously reported findings and the behaviour of gait event detection measurements (Lee et al., 2014, Lienhard et al., 2013). Measurements of stance time from the three systems show a lower consistency but fair level of agreement (ICC(2,1)>0.60, p<0.001; R^2>0.8) and larger differences between systems (Vicon:OptoGait -0.12-0.00, ±8.7%, 95%LoA, p<0.001; Vicon:Opal -0.07-0.02, ±6.6%, 95%LoA, p<0.001; OptoGait:Opal -0.01-0.08, ±7.0%, 95%LoA, p<0.001), indicating a systematic bias in the measurement. As stance time is inherently linked with any differences in the initial and final contact gait events detection, it follows that OptoGait to Opals displaying the a positive error in stance time values while Vicon:OptoGait and Vicon:Opal comparison indicate a negative average differences. In addition, as gait events obtained from ADPM Opal sensors are intermediate to those obtained from the Vicon and OptoGait, the stance time values are also intermediate to the other two systems. For swing time measurement by the systems, correlations are less precise indicating less reliable measurement (ICC(2,1): 0.266-0.629, p<0.001; R^2: 0.48-0.63) and 95%LoA are within similar ranges (Vicon:OptoGait 0.01s-0.11s, ±12.0%; Vicon:Opal -0.02s-0.06s ±9.6%; OptoGait:Opal -0.08s-0.01s, ±10.1%). Therefore, stance and swing time display larger differences, a systematic bias and weaker consistency of measurements between systems. Again, the ADPM Opal sensors values for swing time are intermediate measurements by the other two systems (Figure 3.12). Therefore, stance time

and swing time display poorer precision accuracy and reliability between instruments, with a expected difference approximately ±9.0% (Table 3.11).

These results are comparable to results from previous literature. Similar to findings by Panebianco et al. (2018), for the APDM Opal IMU compared with the Vicon Motion Capture system, the initial contact delay and final contact anticipation, results in very little difference in step time and stride time. However, since the computation of stance and swing time accumulates the small differences in initial and final contact gait event. Similarly, for the OptoGait comparison to the Vicon 3D motion capture system, while step and stride time intervals consistent and show good level of accuracy, stance and swing time are associated with lower precision and agreement (Healy et al., 2019).

Taken together, as the gait event detection by the OptoGait is intermediate to Vicon and ADPM Opal sensors, an under-/ overestimation of stance and swing time measurements respectively are apparent by both the ADPM Opal IMU system and OptoGait photoelectric system compared with Vicon measurements (Figure 3.12). Since the between-system differences 95%LoA for the OptoGait and Opals are between 2.4-10.1% for these temporal measures while some systematic bias is present the accuracy is within acceptable levels.

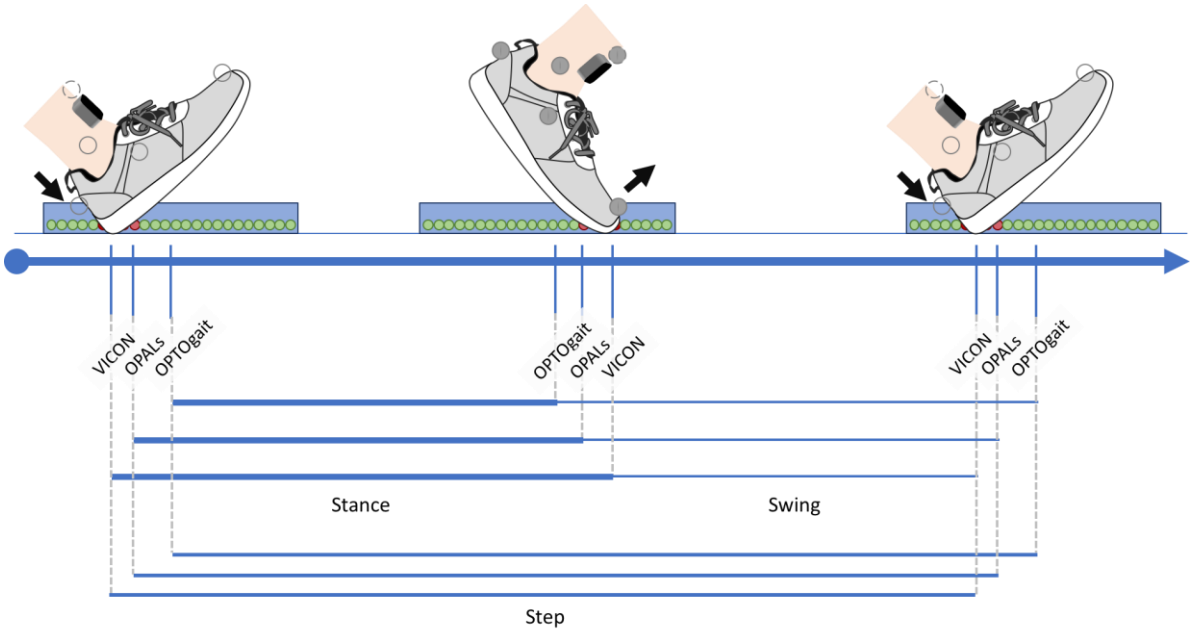

Figure 3.12: Depiction of system differences
Depiction of the difference between gait event detection by the three systems and the impact on temporal gait parameter calculation. Since initial contact detection by the OptoGait are slightly delayed and final contact detection is slightly anticipated, compared with the Vicon and ADPM Opal sensors systems, stance/swing proportions are impacted. Measurements of step and stride duration are unaffected.

Table 3.11: Summary of 95% limit of agreement (%) for possible system differences

Gait Parameter	Threshold (Vicon-OptoGait, Vicon-Opal, OptoGait-Opal)
Step Time	2.4%; 3.2%; 2.6%
Stride Time	1.6%; 2.5%; 2.4%
Stance Time	8.7%; 6.6%, 7.0%
Swing Time	12.0%; 9.6%; 10.1%
Step Length	1.4%
Stride Length	1.0%
Step Width	34.6%

Summary of 95% limit of agreement (expressed as +LoA%) as indication of possible differences between gait parameters measurements.

3.4.2.2. Spatial Gait Parameters

For the spatial gait parameters, only comparisons between OptoGait and Vicon were completed, in order to focus on the systems capable of direct spatial measurements. The measurement of step length and stride length were both associated with small non-significant differences between systems (0cm (-1cm, 1cm), ±1.4% p=0.519; 0cm (-1cm, 2cm) ±1.0% 95%LoA, p=0.233) and excellent correlations (ICC(2,1)>0.90, p<0.001, R^2>0.9). Since the spatial resolution of the OptoGait system is 1.041cm this level of agreement can be considered excellent (Cicchetti 1994). A previous study also indicated that step length and stride length measurements by the OptoGait using the same LED in/out filter settings correlate strongly with measurement by a 3D motion capture system (ICC(2,1), step length: 0.987 (0.962-0.995, 95%CI); stride length: 0.998 (0.995-0.999 95%CI)) with %LOA of ±2% (Healy et al., 2019). Therefore, the measurements here are within previously reported values and are sensitive enough to measure the mean difference of 14cm and 20cm necessary to differentiate between HC and CA.

Measurement of step width was associated with a poor agreement between systems (ICC(2,1)=0.459, p<0.001) and a significant differences between systems (3.2cm (-0.5cm-7.0cm), ±34.6% 95%LoA, p<0.001), although the overestimation is a relatively consistent compared with the Vicon (R^2>0.6). This larger system difference is likely due to the fundamentally different definitions of step width between the two systems. For the Vicon, step width was defined as the mediolateral distance between midfoot positions (toe to heel) at midswing (initial contact to final contact), the OptoGait by default, defined step width, as the distance between midfoot positions as identified by LED activations. Although the OptoGait detects LED activations across a 2D area, it is unable to detect the angle of foot position which is especially important when considering step width measurement. The study protocol was designed prioritise the maximum length of the walkway for capture of a natural walking gait. Therefore, although force plates (a gold-standard measurement system for spatial measures of gait event) would provide a more precise measurement of the real footfall location, these were not implemented in the present study. To overcome this, a lateral reflective marker common to all participant's may have allowed for a more realistic position estimate of the midfoot point. With this in mind, the study approach may not be appropriate to adequately assess the OptoGait method of step width measurement. Further research is required to explore this impact further and this threshold should be considered

when interpreting future results of clinical studies. Meta-analysis of gait characteristics measured in CA and HC indicate that the cohorts are differentiated by a difference in step width of 6 cm. As this is within the limits of agreement for the OptoGait system, measurements of step width should be interpreted with caution.

3.4.2.3. Correlation with speed

Correlation analysis indicates that some significant but weak correlations exist between the system differences for gait events and gait parameters and participant gait speed from OptoGait and Vicon. However, no strong significant correlations were present between system differences and participant gait speed on a trial by trial basis, therefore, the between system agreement for the OptoGait and Vicon is not correlated with the participant's gait speed.

Since correlations between gait speed and system accuracy were weak in this study, it is likely that slower gait speed does not confound gait assessment by the OptoGait or ADPM Opal sensors. Gait speed is inherently interdependent with cadence and stride length as well as stance/swing phase (Kirtley et al., 1985). People with gait impairments typically walk slower than healthy individuals, and gait speed can indicate functional ability (Perry et al., 1995) and falls risk (Maki, 1997). Therefore, it is important to explore the impact of gait speed on system accuracy when contemplating an appropriate system to use and to ensure that differences are not exacerbated in slow paced walking. The influence of speed on measurement accuracy is important when considering the use of the OptoGait and Opal systems within a non-laboratory setting where the 3D motion capture system is unavailable within experiments involving pathological cohorts. Therefore, the measurement agreement assessments of gait in patients with movement disorders will be minimally affected by pathological speed change.

However, all participants within the current study were healthy participants and trial gait speeds within the present dataset ranged from 0.98m/s-1.79m/s. Many patients with gait impairments walk considerably slower than the healthy participants within this study (Pearson et al., 2004). As these were not within the range of functional dependence or requiring intervention (Fritz and Lusardi, 2009), more research is required in a disease cohort to explore this further.

3.5. STRENGTHS AND LIMITATIONS

This study incorporated a healthy control cohort in order to reduce possible impact of comorbidities on the measurements. Therefore, further validation of the systems in cohorts of people with movement disorders is necessary to establish the validity of the systems for measurement of pathological gait pattern. In the literature in people with neurological disorders (Moon et al., 2016), and cerebellar ataxia specifically (Schniepp et al., 2014) variability and asymmetry of the gait measures is commonly effected. However, the validity of these measures was not assessed in this study in the interest of focussing on the average value for the measure. Healy et al (2019) indicated that with the LED filter settings used in this study (3in, 3out), there was no difference in the %LOA for left and right measurements. Therefore, as asymmetry is measured based on average of left and right measurements (Godfrey et al., 2015) it can be inferred that the validity of asymmetry would not be impacted differently from the overall gait measure.

The measures that displayed the poorest accuracy and precision to the gold standard measurement was step width. As discussed, a systematic bias and large limit of agreement present, likely reflect the different estimation methods employed so future studies should be wary of this measurement until further validation is completed. Researchers should consider whether incorporation of an offset is necessary to correct the systematic bias detected here.

Some data was excluded from analysis due to issues with the detection of the gait events by the OptoGait which is possibly related to differences in footwear and gait speed. Issues with synchronisation of the systems may pose an issue if data is to be segmented by gait events detected by another system. The requirement to exclude data from analysis may pose an issue in future implementation of the Optogait system. Since repeating trials is not always possible in people with pathological gait, who may be prone to fatigue, it is important to capture data as reliably as possible. To ensure repeatability of trials, issues should be monitored and minimised wherever possible through proper configuration. However, testing was quick to complete, lasting between 45mins to 1 hour for each participant, which indicating a low burden to participants.

3.6. CONCLUSION

In summary, the OptoGait and ADPM Opal sensors show good to excellent agreement with the Vicon Motion Capture system and excellent accuracy for initial contact and final contact gait events, as well as step time, stride time, step length and stride length. A slight delay in recognition of initial contact gait event and anticipation of final contact gait event by the OptoGait instrumented walkway, and to a lesser extent the ADPM Opal IMU system, was detected. These disagreements compound to impact the reliability of stance and swing time measurements. Step Width was consistently measured larger by the OptoGait than the Vicon likely due to the differing parameters definitions therefore this should be considered in future studies incorporating this system.

Taken together, thresholds for acceptable measurements can be inferred from %LoA in preparation for interpretation of clinical gait assessments (Table 3.11). These will be considered as a reference in the following chapters of this thesis. Measures where values vary greater than %LoA>5% will be interpreted with caution.

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Chapter 4. Analysis Of Gait In Hereditary Cerebellar Ataxia

4.1. Introduction

Cerebellar ataxia (CA) is a neurodegenerative disease where dysfunction of the cerebellum leads to problems with balance performance. It causes considerable disability and is associated with an increased risk of falls (Fonteyn et al., 2010). Speed of disease progression is indicative of survival (Diallo et al., 2019).

At present, no disease-modifying therapies are available, however, gait analysis has the potential to provide an objective tool to determine disease severity and monitor disease progression as part of clinical practice and clinical trials. Prior to this implementation, full characterisation of gait impairment and the quality of postural control in ataxia is essential (Buckley et al., 2019).

The spatiotemporal gait characteristics of CA have been explored previously (Chapter 2, Buckley et al., 2018). CA manifests as a reproducible gait pattern: reduced preferred cadence and walking pace, increased gait variability, as well as increased width of the base of support, shorter steps and lower swing phase proportion and higher stance phase proportion compared with healthy controls.

The postural support is an important consideration when quantifying gait impairment in CA since patients are at an increased risk of falls and long-term disability. Previous studies of balance in patients with CA have focused on posturography (standing balance) (Bunn et al., 2013, Diener et al., 1984, Ilg et al., 2018). From these studies, it is apparent that CA is characterised by larger postural responses than observed in healthy controls (Horak and Diener, 1994, Mummel et al., 1998), which progresses in line with the natural history of the disease (Nanetti et al., 2017, Zesiewicz et al., 2017) and is impacted disproportionately by dual-task conditions (Jacobi et al., 2015). These studies have also shown that measures of postural control have the potential to contribute to the differential diagnosis of hereditary ataxia subtypes (Schwabova et al., 2012). Posturography studies indicate that during stance, ataxia is associated with increased forward trunk flexion and reduced knee flexion (Küng et al., 2009). Other studies have reported ineffective anticipatory postural adjustments in ataxic individuals from the assessment of upper limb motion (Bruttini et al., 2015) and gait initiation (Timmann and Horak, 2001).

Meanwhile, motion capture studies have observed large trunk displacements, and exaggerated ankle instability in ataxic cohorts as well as impaired head and trunk range of motion and displacement (Conte et al., 2014). More recently insufficient coordination between the upper and lower body segments was identified in terms of angular position and angular velocity (Caliandro et al., 2017).

Inertial sensors offer a more flexible approach to movement analysis in comparison to motion capture. A number of variables have been developed to capture various aspects of posture quality during gait. These have mostly been used in the monitoring of Parkinson's Disease and ageing (Siragy and Nantel, 2018) and are not commonly used to examine Ataxic cohorts. Therefore, there is still an opportunity to expand the characterisation of ataxic gait.

Ataxic gait has previously been expressed as a reduced smoothness both in terms of Jerk signal (Baldinotti et al., 2010, Fazio et al., 2013), and harmonic ratio (Ilg et al., 2019) as well as magnitude of accelerations which correlates with disease severity (Shirai et al., 2015). Meanwhile, step regularity (autocorrelation coefficient) and degree of body sway (ratio of direction root mean square to root mean square vector magnitude) are also impacted (Matsushima et al., 2015). In addition, impaired angular displacement and velocity of trunk motion have been identified in CA during walking (Van de Warrenburg et al., 2005a). Many of these variables, the jerk signal especially, are inherently confounded by the movement speed (Hogan and Sternad, 2009). The jerk ratio was proposed as a dimensionless parameter that is able to assess stability during walking while avoiding speed as a confounding factor (Brodie et al., 2014).

Although, many gait studies have only implemented a single waist-worn sensor, postural coordination includes upper trunk and forehead. Therefore, to measure gait quality entirely, the Coefficient of Attenuation can be implemented to assess attenuation of acceleration between levels of the trunk. In people with CA, the reduced intersegmental coordination results in a highly variable walking pattern which requires postural adjustment on a step to step basis (Ilg et al., 2018). This means they are unable to compensate for the inherent instability of walking and falls are common especially during slow-paced walking (Schniepp et al., 2016). Since a reduction in walking speed is a common compensation for individuals experiencing reduced balance performance, it is important to fully understand the pathophysiological mechanisms behind this.

Therefore, the examination of the impact of changing gait speed, disease severity, as well as the upper body motion, is warranted. Also, simultaneously studying postural control and spatiotemporal parameters will allow the full characterisation of the ataxic gait pattern. This will establish the limits of the sensitivity of gait measurement as a biomarker for disease severity, gait disability and risk of falls in CA. Identification of biomarkers specific to disease severity and sensitive to disease progression is necessary to develop well-evidenced clinical guidelines and interventions for CA.

4.1.1. AIMS AND OBJECTIVES

This study aimed to objectively quantify the CA gait pattern and differentiate CA from healthy individuals. Spatiotemporal gait parameters and upper-body motion characteristics will be measured concurrently. This will enable:

- Characterisation of CA gait in preferred-paced walking, while examining the influence of gait speed.
- Comparison against clinical measures of disease severity (Scale for Assessment and Rating of Ataxia (SARA) and balance performance (Berg Balance Scale, BBS).

4.2. METHODS

4.2.1. STUDY INFORMATION

This observational case-control study is incorporated by STH19282 and SCH2048 “Gait Analysis in Cerebellar Ataxia and Hereditary Spastic Paraparesis”, which is sponsored by the Sheffield Children’s Hospital. This project aims to detect subtle gait characteristics of ataxia. This study was conducted, according to the Declaration of Helsinki, and received ethical approval by the North West - Liverpool East Research Ethics Committee (REC: 16/NW/0343). Local approvals were obtained from the Sheffield Children’s Hospital as study sponsor and the Sheffield Teaching Hospitals Trust as the site of data collection. All testing took place at the Clinical Research Facility at the Northern General Hospital, Sheffield. All participants signed an informed consent form. Data collection took place between October 2016 and August 2018.

4.2.2. PARTICIPANTS

Participants with a diagnosis of CA were recruited, as well as healthy individuals as control participants. Individuals were identified through the Sheffield Clinical Genetics Service in the

context of the following criteria. This was intended to confirm CA diagnosis and participants' ability to consent as well as the ability to complete the walking tasks unaided although some participants used walking aids in daily life.

Inclusion:

- Confirmed diagnosis of cerebellar ataxia
- Capable of giving consent

Exclusion:

- Under 18 years old
- Unable to walk for 10m unaided
- Other comorbidities that affect walking e.g. knee replacement

Participant Information Sheets were distributed to those identified, detailing the study and inviting them to take part (Appendix 11). Volunteers were also sought through Ataxia UK and its local patient support group via posters (Appendix 12).

A cohort of healthy controls was recruited amongst participant's family members and university staff. Following recruitment and data collection in a large cohort of healthy controls, a number of healthy participants were selected based on the patient cohort's average age.

4.2.3. PROTOCOL & CLINICAL ASSESSMENT

Prior to each assessment visit, written informed consent was established (Appendix 13). Then guided by a structured medical interview, participants underwent examination including medical history and neurological examination (Appendix 14) with findings captured via a standard clinical report form.

Participants were advised to dress comfortably and wear their own flat-soled everyday shoes during testing. This reduced any impact of participant's attire on walking gait and enables the equipment to detect footfalls without difficulty whilst preserving their comfortable walking pattern and in the interests of safety.

Height and mass measurements were taken to establish Body Mass Index (BMI) as well as the measurement of exterior leg length (greater trochanter of the hip to the floor) for the purposes of data standardisation.

A clinical assessment of the participants cognition, balance and ataxia symptoms/severity were assessed using the Montreal Cognitive Assessment (MoCA, Nasreddine et al., 2005), the Berg Balance Scale (BBS, Berg et al., 1995) and the Scale for Assessment of Ataxia (SARA, Schmitz-Hübsch et al., 2006), respectively. The MoCA provides a measure of cognitive function, with a score of less than 24 out of 30 considered abnormal. Meanwhile, the BBS and SARA are validated methods of assessing falls risk and ataxia severity. The BBS provides a score out of 56, with less than 41 referring to medium to high risk of falls and change of 8 points indicating a genuine change in function. Meanwhile, the SARA rates symptoms out of 40 with a change of 8 overtime referring to a clinically relevant change. A score of 8 or lower has previously been defined as a cut off for independent gait status (Kim et al., 2011). The $SARA_{gait\&posture}$ ($SARA_{G\&P}$) subscore was calculated as the sum of gait, stance and sitting subscores (Lawerman et al., 2017)

Later, participants performed a short gait task, walking back and forth at least six times along a walkway of approximately 10m in length (total distance walked ≈60m). This allowed a suitable number of steps to be recorded without causing fatigue. For trials where a low number of steps are captured, for instance, due to a participant's increased stride length and cadence, additional passes were completed.

Each participant's gait was assessed using the OptoGait photoelectric 5m gait analysis system with Boosted transmission bar (Microgate Corporation, Bolzano, Italy) while wearing five ADPM Opal triaxial inertial sensors (APDMInc, Portland, OR, USA) (see section 4.2.4 for further information on equipment used).

Participants were asked to complete walking trial at a self-selected speed with instructions to "look straight ahead until turning on the spot at the end of the walkway and returning". The use of different speeds enabled assessment of the influence of perceived gait speed on gait parameters. A short period of quiet standing was recorded at the start and end of each trial in order to discriminate starting and ending gait events during data analysis.

In the interests of safety, participants were permitted to look at the floor to recognise the end of the system and requested not to step out of the system. Participants were instructed to allow sufficient space to turn comfortably at the end of each pass and advised that the test can be paused at any time should they need to rest for a short time and stopped if necessary. Participants were allowed a break between trials although in many cases this was

unnecessary. Examiners were on hand at all times at either end of the walkway so did not guard the participants as they walked the trial. Data collection sessions lasted 1-1.5hours per participant excluding configuration of the systems which was completed before their arrival.

4.2.4. EQUIPMENT

Gait analysis was performed on participants using two gait analysis systems: the OptoGait LED array system (Microgate Corporation, Bolzano, Italy) and the ADPM Opal system of triaxial inertial sensors (APDMInc, Portland, OR, USA) as previously validated (see Chapter 3).

All data gathered for the purposes of the study was backed up to an encrypted external hard drive and stored in a locked cupboard within the Sheffield Institute for Translational Neuroscience, the University of Sheffield alongside completed study report forms. Signed consent forms were stored within the site file and lists of recruited participants maintained regularly.

The OptoGait 5m system was configured in a two-dimensional formation (as depicted in Figure 4.1a) to provide a 10m x 2m capacity of the system with approximately 4m of two-dimensional assessment space. To compensate for the height of LEDs from the ground, the system was configured to register a heel-strike event when at least 3 LEDs are activated during the participant's footfall following manufacturers recommendations. The threshold of 3 LEDs was also used to register a final contact event. OptoGait's built-in software captures and records data to measure several spatiotemporal gait parameters, including step width, with a spatial resolution of 1.041cm and sampling frequency of 1000Hz.

Meanwhile, each participant's motion during walking was also assessed with an inertial measurement unit (IMU) system (ADPM Opal sensors via Motion Studio software, APDM Inc., Portland, OR, USA). These contain an accelerometer, a gyrometer and a magnetometer, sampling movement at 128Hz in three directions (x-axis pointing downward, y-axis pointing laterally and z-axis pointing forward) (Figure 4.1b). Sensors were attached to the patient via velcro straps and adhesive tape at five positions: the forehead, top of the back in line with the 7th Cervical vertebra (C7) to represent the level of the shoulders, bottom of the back in line with the 5th lumbar vertebra (L5) to represent the level of the pelvis and on the ventral side of the left and right ankles (Figure 4.1c). These positions were selected to represent the 3 segments of the trunk. Correct orientation of the devices was confirmed prior to the start of trials.

In order to synchronise data capture between the two systems, a custom-made cable was acquired to connect the IMU and photoelectric systems and external “trigger” signal configured to initiate and terminate recordings. Further details of this can be found in Appendix 15.

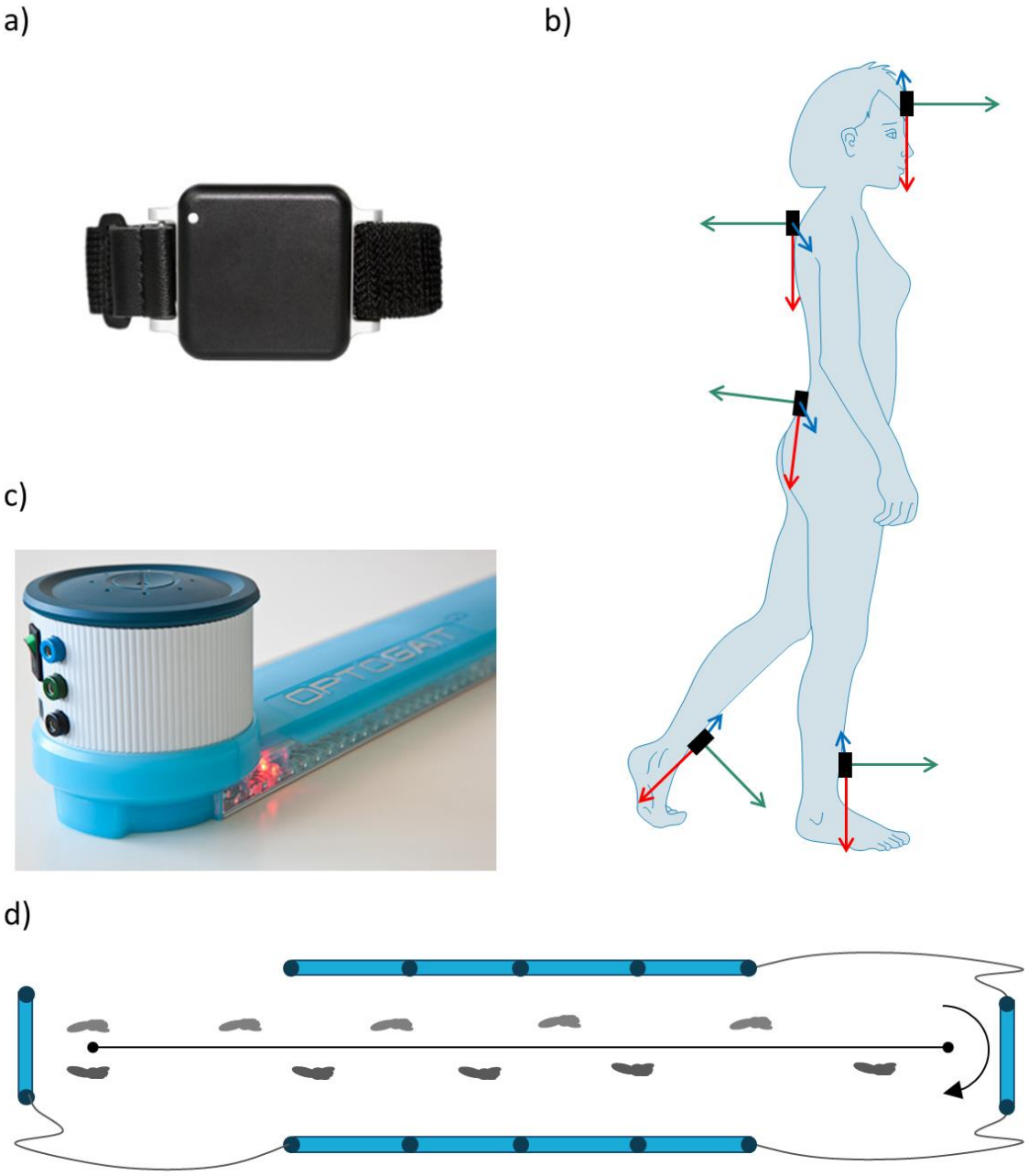

Figure 4.1: Gait analysis equipment outline
a) ADPM Opal triaxial inertial sensor with Velcro strap attachment b) position of IMU sensor attachments at both lower shanks, forehead, upper trunk (7th cervical vertebrae), lower back (5th lumbar vertebrae) c) the OptoGait system contains LEDs at regular intervals which transmit across the walkway d) the walkway was assembled in a two-dimensional configuration with bars either side and at either end.

4.2.5. DATA ANALYSIS

4.2.5.1. Spatiotemporal Gait Parameters

The OptoGait photoelectric systems software automatically detects the temporal and spatial location using intersecting LED transmissions. Appropriate identification of footfalls was verified visually and trial results exported to Microsoft Excel. Only footfalls where both initial contact and final contact were considered to begin within the system were included to ensure accurate detection of initial and final contact events for calculation of gait parameters.

Gait parameters of interest here include measurement of speed (m/s), cadence (steps/ min), step time (s), stride time (s), step length (cm), stride length (cm), step width (cm), walking base (cm), stance phase (% cycle), swing phase (% cycle), single support phase (% cycle), double limb support phase (% cycle). The OptoGait system is also able to compute the duration and proportion of finer cycle phases such as pre-swing, loading response, contact, flat, propulsive, and flight. For further explanation of gait parameters, see Figure 1.1.

In order to verify accuracy of the gait event detection with results of our validation study (Chapter 3), initial contact (heel strike) time (s) from the external trigger time as well as step time (s), stride time (s) and stance time (s) were extracted and final contact time (s) computed as initial contact plus stance time.

For each walking trial captured, descriptive statistics (average and standard deviation (SD) of Left, Right and All steps) were computed for each gait parameter using MATLAB (Mathworks Inc., Natick, MA, USA) through custom computational programmes in preparation for cohort level-analysis. The within-person variability of these parameters was considered through the calculation of the coefficient of variation (CV, expressed as a percentage) (Equation 4.1) where SD and mean are calculated for each gait measure for left and right combined.

$$\text{Equation 4.1: Coefficient of Variation } (\%) = {}^{\text{SD}}/_{\text{mean}} \times 100$$

Coefficient of variation is a commonly used measure of overall within-person gait variability and previously reported in ataxic cohorts (Ebersbach et al., 1999, Gouelle et al., 2013, Ienaga et al., 2006, Palliyath et al., 1998, Schmitz-Hübsch et al., 2016, Schniepp et al., 2014, Serrao et al., 2012)).Meanwhile, computing left-right asymmetry (Equation 4.2) from absolute

$$\text{Equation 4.2: } Asymmetry = \left[mean_{\ Left} - mean_{Right}\right]$$

difference of mean gait measures recorded for left and right feet enables an appreciation of step to step differences (Godfrey et al., 2015).

4.2.5.2. Upper body Motion Gait Parameters

Motion inertial data were analysed using MATLAB (Mathworks Inc., Natick, MA, USA) in the same way as Chapter 3. Trial data were segmented into single straight-line sections of passes by assessing the location of turn phases using the peak in the mediolateral angular velocity from the lumbar sensor (Figure 4.2). Direction change was also indicated by changes in smoothed orientation signals (locally weighted quadratic polynomial regression function). Gait events were identified using the method defined by Salarian et al., (2004) (as Chapter 3, see Figure 3.4). From the timing of these gait events, a temporal parameters were computed (stride time, step time, stance time) for comparison again the OptoGait system.

A number of variables were calculated on a stride-stride basis from upper body sensors. The acceleration signals from the pelvis, shoulder and forehead were transformed to a horizontal-vertical orthogonal coordinate system as described by Moe-Nilssen et al (1998). This assumes that the device is positioned securely so that the measured anteroposterior (AP) acceleration vector is in the sagittal plane relative to a walking participant throughout the gait cycle but corrects for the forward inclination of the trunk during walking to ensure the accuracy of later analysis. Computational analysis of transformed signals was then completed to included: Root Mean Square (RMS) of accelerations (at each of the three levels) (Helbostad and Moe-Nilssen, 2003), Coefficient of Attenuation (between the three levels) (Mazza et al., 2008), followed by Harmonic Ratio (Latt et al., 2008), RMS Jerk and Jerk Ratio (also at the three levels, (Brodie et al., 2014, Fazio et al., 2013)). Auto-correlation coefficient analysis for step and stride durations were computed for each pass within the walking trial (Moe-Nilssen and Helbostad, 2004). Meanwhile, root mean square ratio (RMSR) normalises directional acceleration by vector magnitude to control for walking speed (Sekine et al., 2013). Details of the analysis of motion at the head, trunk and pelvis levels can be found in Table 4.1. Descriptive analysis of upper-body gait parameters was then completed per participant in MATLAB prior to export in preparation for cohort statistical analysis.

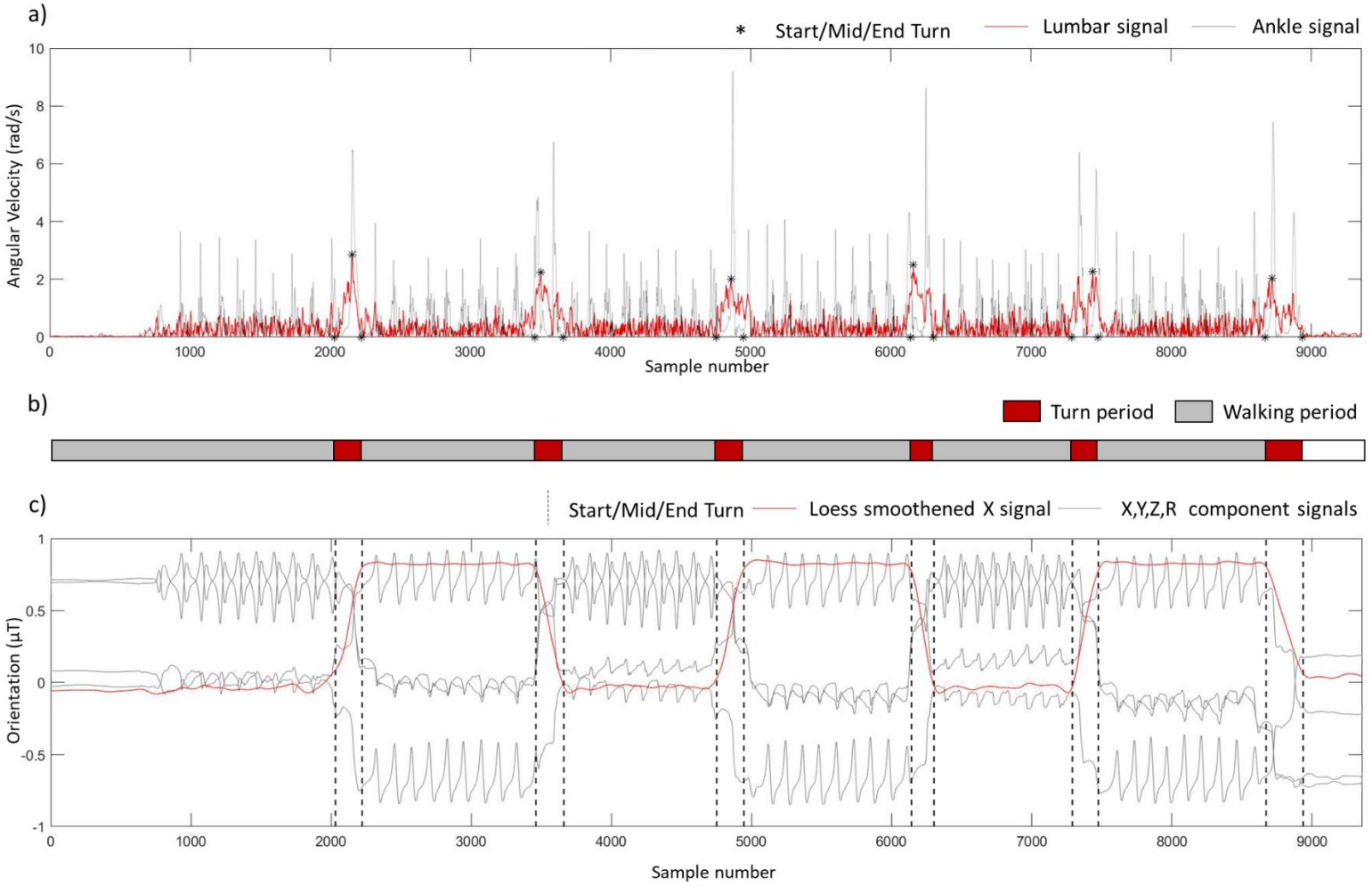

Figure 4.2: Depiction of segmentation strategy for inertial gait signals.
a) Absolute value of angular velocity signal from lumbar and ankle sensors to identify turn events b) segments of walking trial related to walking and turning c) identification of turns based on the change in smoothed orientation signal.

Table 4.1: Upper Body motion parameters analysis calculations

Measure (with reference)	Description	Computation performed
RMS Accelerations (Helbostad et al 2003)	Measure of the magnitude of accelerations	Root of mean square of Accelerations for each stride in AP, ML, V at the head, shoulder, Pelvis
RMS Jerk (Fazio et al 2013)	RMS of the first time derivate of each component of the acceleration signal	Root of mean square of differentiation of acceleration signals in AP, ML, V at the head, shoulder, pelvis.
Harmonic ratio (Latt et al 2008)	Measure of step to step asymmetry of acceleration components within a stride	Discrete Fourier transform for each of the acceleration components measured at head, shoulder, pelvis. The fundamental frequency was set equal to the stride frequency. For the AP and V components: $HR = \frac{\Sigma \text{amp . of even harmonics}}{\Sigma \text{amp . of odd harmonics}}$ For the ML component: $HR = \frac{\Sigma \text{amp . Of odd harmonics}}{\Sigma \text{amp . Of even harmonics}}$
Coefficient of Attenuation (Mazza et al 2008)	Measure of degree of attenuation of accelerations in AP, ML, V achieved by the upper body between pelvis & head, pelvis & shoulder, and shoulder & head.	$C_{PH} = \left(1 - \frac{RMS_H}{RMS_P}\right) \times 100$ $C_{PS} = \left(1 - \frac{RMS_S}{RMS_P}\right) \times 100$ $C_{SH} = \left(1 - \frac{RMS_H}{RMS_S}\right) \times 100$
Jerk Ratio (Brodie et al 2014)	Normally distributed and dimensionless measure of stability	Log ratio of RMS Jerk AP/V, ML/V at head, shoulder, pelvis
Root mean square ratio (Sekine et al 2013)	Normalised for vector magnitude to control for walking speed	Ratio of root mean square acceleration in each direction (RMSx) to the root mean square vector magnitude (RMST) in AP, ML, V at head, shoulder, pelvis
Autocorrelation coefficients (Moe-Nilssen and Helbostad 2004)		
Step regularity index (AD1 coefficient)	Measure of the regularity across consecutive steps	Peak value at the first dominant period in AP, ML, V at head, shoulder, pelvis
Stride regularity index (AD2 coefficient)	Measure of the regularity across consecutive strides	Peak value at the second dominant period in AP, ML, V at head, shoulder, pelvis
Auto-Symmetry	Ratio of step/stride regularity	Symmetry = $AD1/AD2$ In AP, ML, V at head, shoulder, pelvis

4.2.6. STATISTICAL ANALYSIS

Power analysis was completed based on the results from our systematic review of spatiotemporal gait characteristics (Chapter 2, (Cohen, 1988, Wolf and Wolf, 1986)). This calculation indicates that for many spatiotemporal gait measures an between 2-47 patients are required to achieve statistical power for the majority of spatiotemporal parameters between CA and HC (Chapter 4). The variable requiring the largest number of participants per group were speed variability and DLS phase percentage requiring 46 and 47 individuals respectively (Table 2.5). As this has been calculated based on results of a meta-analysis, this estimate may over-inflate the difference between cohorts and should only be used as a guide. Since upper body variables of motion have not been consistently measured in CA previously, it is not possible to calculate the appropriate sample size.

Participant results for each system were assembled into a single data table and imported into SPSS Statistics (version 23, IBM) for cohort level statistical analysis. Descriptive analysis (average and standard deviation) was completed for demographic characteristics.

In order to check the validity of the gait event detection by the two systems, a number of statistical tests were used including Paired samples t-test, intraclass correlation coefficient for random effects consistency (ICC(2,1)), standard effects estimates (SEE).

Descriptive analysis was also completed for spatiotemporal gait characteristics and upper body motion gait measures to compare ataxic and healthy control cohorts during the preferred speed trial. Normality of the datasets was tested using Shapiro Wilks tests, then between-group differences assessed through independent t-tests (parametric) and Wilcoxon signed-rank tests (non-parametric) following Levene's tests for equality of variance. A significant result was indicated by p-value <0.05. No adjustment for multiple comparison was made but effect sizes calculated to examine the statistical power for the test.

Z score (Equation 4.3) and effect size calculated (Equation 4.4) where thresholds of 0.1, 0.3, and 0.5 were recommended by Field (2018) for small, medium, and large effect sizes, respectively.

Equation 4.3: $$Z = \frac{mean_{CA} - mean_{HC}}{\sqrt{SD_{CA} + SD_{HC}/_2}}$$

Equation 4.4: $$d = Z/\sqrt{\frac{N_{CA} + N_{HC}}{2}}$$

Pearson's Correlation/ Spearman's Rho Correlation analyses were completed for all variables to observe those that correlate with the SARA and BBS scores and gait speed.

To examine the influence of disease severity, participants were separated into subgroups related to the SARA scores (≤8 vs >8). For normally distributed data, one-way ANOVA tests and Welch's tests of equality of means followed by post hoc Tukey/ Games Howell tests for multiple comparisons. Where non-normally distributed data were indicated by Shapiro-Wilks tests, Kruskal-Wallis tests were completed followed by Mann Whitney U tests for each subgroup comparison. Univariate regression analyses, adjusted for age, sex and gait speed, as covariates, were used to determine subgroup differences in gait variables.

To aid selection of parameters that may be sensitive to longitudinal change in preparation for Chapter 5 (longitudinal assessment), those measures that were significantly different between CA vs HC, able to discriminate HC to mild ataxia and mild ataxia to moderate ataxia in both hypotheses tests and adjusted regression analyses were considered. This approach intended to reduce to the number of measures selected, avoiding those that are considerably interrelated with speed and interchangeable with other variables (i.e. swing/ single support phase). Z scores for the selected variables for the CA cohort were displayed in radar plots to indicate the between group differences in hypotheses tests and adjusted regression analyses where HC cohort specified as Z=0.

Partial correlation analysis was completed to examine the association between spatiotemporal and upper body variables independent of gait speed.

4.3. RESULTS

4.3.1. PARTICIPANT CHARACTERISTICS

27 CA patients were recruited to the present study. The participants in the ataxic cohort reported high blood pressure, depression, vertigo, and benign prostatic hyperplasia but we were not made aware of any disqualifying medical history or medications (Table 4.2). From a group of healthy participants, 27 individuals were selected to provide an age-matched control cohort (Table 4.3). Table 4.4 contains the summarised demographics of the patient and control cohorts. No significant differences were discovered between the cohorts in age, height, mass or leg length. The patient cohort performed significantly worse on the SARA and BBS reflecting their reduced functional status and disease severity. A significant difference was also observed in the MoCA but all scores from the ataxic cohort were

considered to be within the normal range. Disease severity subgroups (≤/>8 SARA) were comparable on all demographic characteristics but there was a significant difference in SARA scores ($p<0.01$), $SARA_{G\&P}$ ($p<0.001$) and BBS Scores ($p<0.01$) (Table 4.5). The moderate ataxia group differed significantly from Healthy control and Mild Ataxia cohorts in the MoCA.

Table 4.2: Ataxic cohort participant summary

Participant Number	Sex (Male/Female)	Age (years)	Height (cm)	Mass (kg)	Leg length (cm)	Right/Left Handed	Alcohol (Units Per Week)	Cerebellar ataxia Diagnosis	Diagnosis Duration (years)	Falls history (Yes/No)	SARA total (/40)	SARA gait&posture (/18)	MoCA (/30)	BBS (/56)	UMN signs present?
P01	F	52	161	54	78	R	0	SCA6	6	N	14.5	6	29	53	N
P02	M	58	150	70	82	R	14	SPG7	10	N	15	4	24	43	Y
P03	M	54	174	70	77	R	5	SPG7	21	N	14	4	26	43	Y
P04	M	51	162	82	78	L	0	•		N	10	3	27	41	Y
P05	M	58	182	82	74	R	0	SPG7		Y	13	5	27	36	Y
P06	M	53	187	81	90	R	6	SPG7	3	N	6	1	25	56	N
P07	F	55	160	56	74	R	5	SCA6	21	Y	2	1	30	56	N
P08	M	52	180	90	83	R	2	AD FHx	42	Y	13	5	26	31	Y
P09	M	49	181	91	82	R	0	SPG7	10	Y	15	7	27	39	Y
P10	M	52	175	91	73	R	23	SPG7	16	N	8.5	4	30	39	Y
P11	F	61	171	60	80	R	3	SCA6	4	Y	2.5	1	29	56	N
P12	F	45	170	73	79	R	10	SCA6	6	N	4.5	2	26	54	
P13	M	65	186	105	87	L	30	SCA6	10	N	10	5	25	42	N
P14	F	57	161	41	84	R	0	SCA6	6	N	18	5	27	29	N
P15	M	63	188	97	74	R	10	SPG7	2	N	11	6	26	36	Y
P16	F	66	171	62	92	R	5	SPG7	0	N	4.5	2	24	44	N
P17	M	65	181	63	75	L	5	•	10	N	10.5	4	28	51	N
P18	M	37	175	73	73	R	0	•		N	11	3	25	41	N
P19	F	26	161	56	67	R	5	CACNA1A missense		Y	8	3	30	47	N
P20	M	53	175	73	83	R	0	SPG7	7	Y	8.5	5	26	39	Y
P21	F	19	161	62	67	R	5	SCA6	0.5	N	11.5	4	28	47	N
P22	F	63	131	68	79	L	5	SCA6	1.5	N	11.5	4	26	52	N
P34	M	50	181	86	102	L	0	•	4	N	13.5	4	28	40	N
P35	M	62	178	82	96	R	5	•	20	N	11.5	3	27	40	N
P36	M	67	170	113	80	L	28	SCA6		N	2	1	29	55	N
P37	F	56	168	86	75	R		SCA6	6	Y	9	5	29	35	
P38	M	71	167	81	83	R	5	SCA6	6	N	8.5	3	28	52	N

Abbreviations: M-Male, F-Female, •- no genetic diagnosis available at time of testing. SCA6 – spinocerebellar ataxia 6, SPG7 – spastic paraplegia 7, AD FHX – autosomal dominant family history, Y-Yes, N-No, UMN-upper motor neuron signs, SARA- Scale for Assessment and Rating of Ataxia, BBS – Berg Balance Scale, MoCA-Montreal Cognition Assessment.

Table 4.3: Control participant characteristics

Participant	Sex (M/F)	Age (years)	Height (cm)	Mass (kg)	Leg length(cm)	Right/Left Handed	Alcohol (Units Per Week)	MoCA (/30)	BBS (/56)
C02	F	49	162	80	74	R	8	30	56
C03	F	59	167	74	78	R	14	28	56
C04	F	62	175	65	79	R	30	30	56
C05	F	55	161	79	75	R	0	28	56
C06	F	52	158	53	72	R	5	29	56
C07	M	59	173	82	74	R	10	27	56
C08	M	47	188	86	73	R	40	30	56
C09	M	72	161	92	83	R	2	27	56
C10	F	62	173	54	80	R	14	27	56
C11	F	54	173	95	78	R	0	29	56
C12	M	65	170	70	73	R	0	28	56
C13	M	45	179	80	77	R	0	28	56
C14	M	49	185	73	77	R	14	28	56
C16	F	35	161	66	70	R	14	29	56
C17	F	46	170	72	94	R	6	28	56
C18	M	66	172	146	79	R	3	28	56
C21	F	59	176	86	79	R	5	29	56
C23	F	44	173	79	96	R	5	30	55
C24	M	45	193	85	105	R	14	29	55
C25	F	50	161	113	71	R	0	29	56
C26	M	65	161	81	85	R	5	27	56
C27	F	64	157	60	73	R	0	28	56
C28	M	57	175	60	85	R	0	30	56
C29	M	58	161	71	75	R	0	28	56
C30	F	52	163	75	75	R	0	27	56
C31	F	53	161	80		L	5	28	56
C32	F	44	168	74	85	R	5	30	56

Abbreviations: M-Male, F-Female, Y-Yes, N-No, BBS – Berg Balance Scale, MoCA-Montreal Cognition Assessment.

Table 4.4: Cohort demographics

	Cerebellar ataxia (n=27, 10F)	**Healthy Control (n=27, 16F)**	**p**
Age (years)	55 [51, 63]	54 [47, 62]	0.63
Height (cm)	171 [161, 181]	170 [161, 175]	0.38
Mass (kg)	73 [62, 86]	79 [70, 85]	0.82
Leg Length (cm)	80 [75, 83]	78 [74, 83]	0.40
Diagnosis subtype	11 SCA6, 9 SPG7, AD FHx, CACNA1A	----	----
Duration of diagnosis	9.6±9.6yrs	----	----
Falls history	19 Non-Fallers, 8 Fallers	----	----
Alcohol intake	6.6±8.4	7.4±9.6	----
$SARA_{Total}$ (/40)	10.5 [8.0, 13.0]	----	----
$SARA_{Gait\&Posture}$ (/18)	4 [3, 5]	----	----
BBS (/56)	43 [39, 52]	56 [56, 56]	**<0.001**
MoCA (/30)	27.0 [26, 29]	28 [28, 29]	**<0.01**
UMN signs	9	----	----

Data reported as median [Interquartile Range]. Abbreviations: n-number participants, F-number of female participants, SARA-Scale for Assessment and Rating of Ataxia, BBS-Berg Balance Scale, MoCA-Montreal Cognitive Assessment, UMN-Upper motor neuron, SCA-Spinocerebellar ataxia, SPG- Spastic paraplegia, AD FHx-Autosomal dominant family history, CACNA1A-Calcium Voltage-Gated Channel Subunit Alpha1 A missense mutation

Table 4.5: Disease subgroup cohort demographics

	Healthy Control (n=27, 16F)	**Mild Ataxia (n=7, 5F)**	**Moderate Ataxia (n=20, 5F)**	**p (Post hoc)**
Age (yrs)	54 [47, 62]	55 [45, 66]	55.0 [51, 63]	0.88
Height (cm)	170 [161, 175]	170 [161, 171]	175 [161, 181]	0.48
Mass (kg)	7 [70, 85]	62 [56, 81]	82 [69, 89]	0.34
Leg Length (cm)	78 [74, 83]	80 [74, 90]	79 [75, 83]	0.65
Diagnosis subtype	----	4 SCA6, 2 SPG7, CACNA1A	7 SCA6, 8 SPG7, AD FHx	
Duration of diagnosis	----	6.8±8.2yrs	10.5±10.0yrs	0.47
Falls history	----	3 Fallers	5 Fallers	0.39
Alcohol intake	7.4±9.6	8.9±8.7	5.7±8.3	0.41
SARA (/40)	----	4.5 [2.0, 6.0]	11.5 [10.0, 13.9]	**<0.001**
$SARA_{Gait\&Posture}$ (/18)	----	1 [1, 2]	4 [4, 5]	**<0.001**
BBS (/56)	56 [56, 56]	55 [47, 56]	41 [37, 46]	**<0.001**[a,b,c]
MoCA (/30)	28 [28, 29]	29 [25, 30]	27 [26, 28]	**<0.01**[a,b]

Data reported as median [Interquartile Range]. Between group differences indicated by significance level from statistics tests conducted as discussed where posthoc test results indicates by a: healthy control vs mild ataxia b: healthy control vs moderate ataxia c: mild ataxia vs moderate ataxia. Abbreviations: n-number participants, F-number of female participants, SARA-Scale for Assessment and Rating of Ataxia, BBS – Berg Balance Scale, MoCA-Montreal Cognitive Assessment, UMN- Upper motor neuron, SCA-Spinocerebellar ataxia, SPG- Spastic paraplegia, AD FHx-Autosomal family history, CACNA1A -Calcium Voltage-Gated Channel Subunit Alpha1 A missense mutation

4.3.2. GAIT ASSESSMENT

4.3.2.1. Validity of Data Collection

During manual verification of each participant's trial data for the OptoGait system, issues were present within some the participant trials. These issues were related to the detection of footfall location with invalid flight time and overlooked steps. For passes within walking trials where unresolvable issues were identified, the steps before/after the problem step were removed from analysis dependent on the location of the step within the pass in order to retain as much data as possible.

For both healthy controls and CA participants, a mean 34.4±4.8 steps were captured by the OptoGait, while the ADPM Opal sensors algorithms detected 30.3±9.5 steps. A total of 866 steps (404 and 462 steps in ataxia and controls respectively) were captured by both systems synchronously. There were also 666 stride times and 1066 stance time durations captured.

Table 4.6 and Table 4.7 shows the results of the intercorrelation coefficient and paired T-Test results. Values for initial contact and final contact gait events as well as step time, stride time and stance times estimated by the two systems showed good to excellent agreement. Although, there was a significant mean difference in stance time between systems, these differences were comparable to values identified previously (Chapter 3).

Figure 4.3 and Figure 4.4 displays Bland-Altman plots for the correlation of differences and absolute differences between systems by trial, labelled by cohort membership within each trial completed. No clear clustering of data points is apparent for the cohorts, indicating that accuracy is equal for ataxic and healthy individuals.

Table 4.6: Study Gait Event comparison

	Initial Contact (n=36)	**Final Contact (n=36)**
ICC(2, 1) (95% CI)	1.000 (0.998,1.000)**	1.000 (0.996,1.000)**
R^2	1.000	1.000
Absolute System Difference (Mean [95% LoA])	0.06s [0.01s, 0.11s]	0.08s [0.07s, 0.09s]
System Difference (Mean [95% LoA])	-0.06s [-0.11s, -0.01s]	-0.08 [-0.09s, -0.07s]
SEE	0.03	0.02
p	<0.001	<0.001

Between system comparison reported for trials capture for 15 Ataxia participants and 21 healthy controls. Abbreviations: n-number of gait events contributing to statistical tests. ** p<0.01

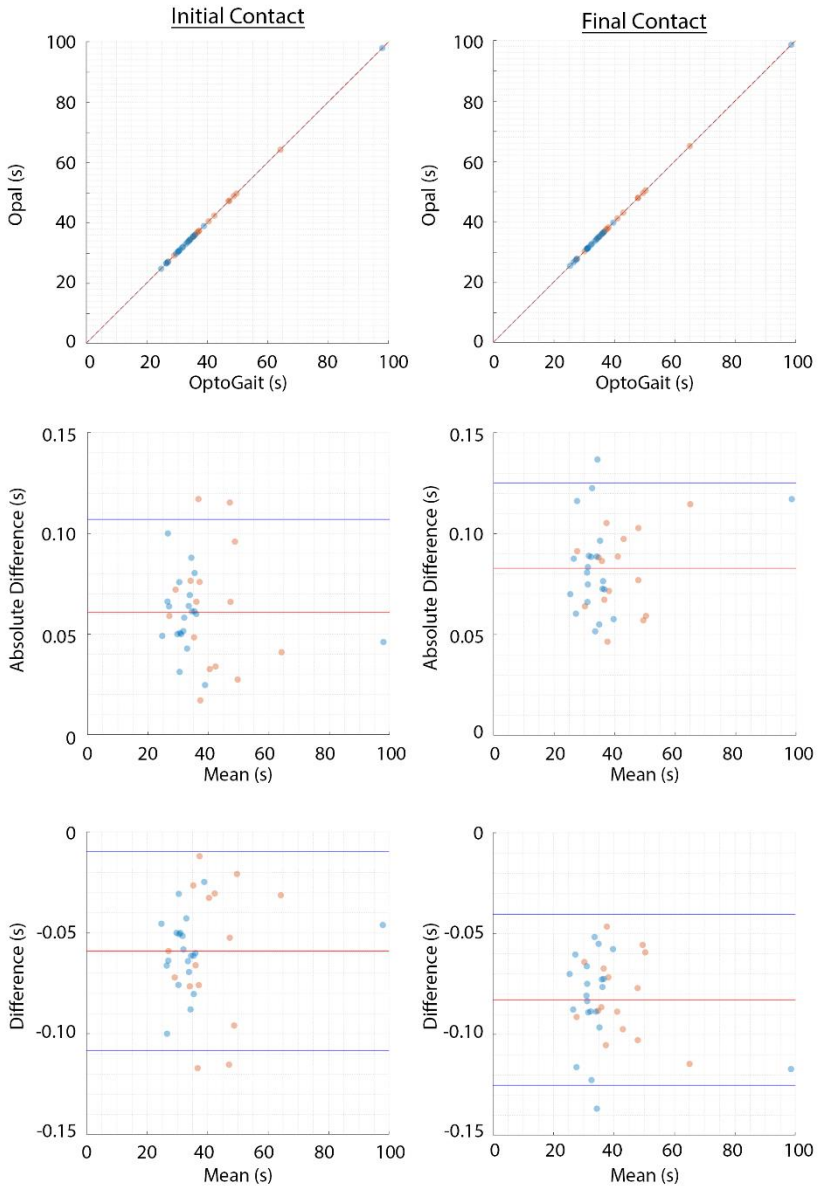

Figure 4.3: Study Gait Event comparison
Results plotted for Initial contact and final contact gait events measured in healthy controls (blue) and cerebellar ataxia (red) as above. Correlation plots for OptoGait: Opal values include reference line x=y (--) and correlation line (..). Bland altman plots for differences and absolute differences between systems plotted against mean value with mean difference (---)and 95%CI (-.-) indicated.

Table 4.7: Study Temporal Gait Parameter Comparison

	Step Time	**Stride Time**	**Stance Time**
OptoGait Mean (SD)	0.55s (0.05)	1.10 (0.10)	0.63 (0.08)
Opal Mean (SD)	0.55s (0.05)	1.10 (0.02)	0.66 (0.08)
ICC(2, 1) (95% CI)	0.997 (0.993, 0.998)**	0.998 (0.997, 0.999)**	0.856 (0.592, 0.939)**
R^2	0.993	0.997	0.804
Absolute System Difference (Mean [95% LoA])	0.02s [0.00s, 0.05s]	0.02s [0.00s, 0.04s]	0.04s [0.01s, 0.08s]
System Difference (Mean [95% LoA])	0.00s [-0.01s, 0.01s]	0.00s [-0.01s, 0.01s]	-0.02s [-0.09, 0.05]
SEE	0.004s	0.01s	0.03s
p	0.321	0.197	<0.001

Between system comparison reported for trials capture for 15 Ataxia participants and 21 healthy controls. Abbreviations: n-number of gait events contributing to statistical tests. ** p<0.01

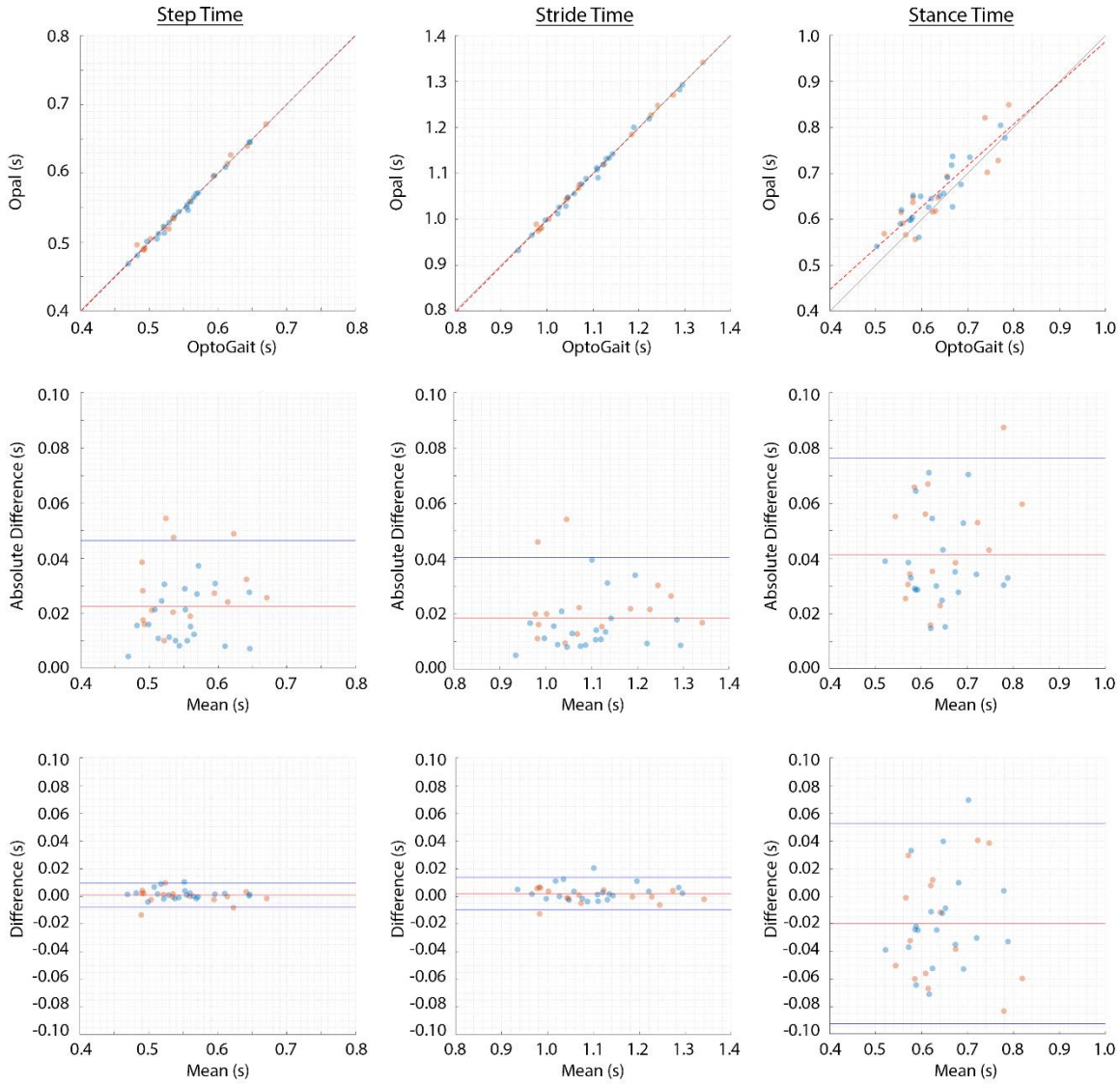

Figure 4.4: Study Gait Parameter Comparison
Results plotted for step time, stride time and stance time gait parameters measured in healthy controls (blue) and cerebellar ataxia (red) as above. Correlation plots for OptoGait: Opal values include reference line x=y (--) and correlation line (..). Bland altman plots for differences and absolute differences between systems plotted against mean value with mean difference (---) and 95%CI (-.-) indicated.

4.3.2.2. Spatiotemporal Gait Parameters

Table 4.8 shows spatiotemporal gait characteristics measured during preferred paced walking. Self-paced walking gait velocity was on average lower in the patient cohort than the control cohort (1.13±0.25m/s vs 1.34±0.20m/s, $p<0.01$). While step length and stride length were both significantly shorter in the patient cohort than controls (62.1±9.8cm vs 71.7±8.0cm, $p<0.001$; 124.5±19.7cm vs 143.5±16.0 cm, $p<0.001$ respectively), step width was significantly larger in the ataxic cohort on average (16.9±5.0cm vs 11.7±2.9cm, $p<0.001$). For the temporal parameters, no significant differences were observed. Significant step to step asymmetry was observed in the ataxic cohort compared with the control cohort for cadence (1.2 [0.5, 2.0] steps per min vs 0.5 [0.2s, 0.7] steps per min, $p<0.01$), stride time (0.01s [0.01, 0.02] vs 0.01s [0.002, 0.01], $p<0.01$), swing time (0.01±0.01s vs 0.00±0.00, $p<0.01$), swing phase (0.8 [0.3, 1.4]% vs 0.4 [0.2, 0.6]%, $p<0.01$) and single limb support (SLS) (0.9 [0.5, 1.4]s vs 0.5 [0.1, 0.9]s, $p<0.01$). Gait analysis reveals a significantly greater variability (coefficient of variation, %CV) in the majority of spatiotemporal gait parameters, in the ataxic group than in controls with the exclusion of step width variability.

Across all the spatiotemporal gait characteristics and upper body motion measures, strong significant correlations with the disease severity (SARA score) were observed in very few variables. Those spatiotemporal variables indicating the strongest association with the SARA score were stride length variability, step length variability, swing time/ phase variability and SLS time variability.

Correlation analysis based on speed in the ataxic cohort indicates that many spatiotemporal variables are associated with patient speed. For instance, cadence, stride length, step length as well as swing phase and SLS phase exhibit a good to an excellent positive correlation with gait speed. Meanwhile, the following parameters showed a good to an excellent negative correlation with speed: stride time, step time, stance time, DLS, stance phase, along with the variability of cadence, stride time, stance time, swing time, SLS, swing time phase, and SLS phase. Correlation analysis based on BBS scores in the ataxic cohort indicates that many variables are associated with an impaired balance performance related to increased risk of falls: speed, cadence, stride time, step time, stance time, DLS, stance phase, swing phase, SLS phase, DLS phase, as well as many measures of variability (cadence (%CV), swing time (%CV), SLS (%CV), swing phase (%CV), SLS phase (%CV)) (Table 4.8).

Table 4.8: Spatiotemporal Gait Parameters with mean, symmetry and variability measures.

				Correlation (r)			
	CerebellarAtaxia (n=27)	**HealthyControl (n=27)**	**p**	**SARA**	**BBS**	**Speed**	**d**
Spatiotemporal Measures							
Speed (m/s)	1.13 (0.25)	1.34 (0.20)	**<0.01**	-0.451*	**0.568****	---	-0.06
Cadence (steps/min)	108.7 [98.4, 117.4]	111.6 [107.0, 119.1]	0.312	-0.446*	**0.532****	**0.705****	-0.18
Stride Time (s)	1.10 [1.03, 1.22]	1.08 [1.01, 1.12]	0.280	0.446*	**-0.532****	**-0.709****	0.02
Step Time (s)	0.55 [0.51, 0.61]	0.54 [0.50, 0.56]	0.312	0.435*	**-0.557****	**-0.719****	0.02
Stride Length (cm)	124.5 (19.7)	143.5 (16.0)	**<0.001**	-0.301	0.432*	**0.909****	**-0.61**
Step Length (cm)	62.1 (9.8)	71.7 (8.0)	**<0.001**	-0.299	0.425*	**0.906****	**-0.44**
Step Width (cm)	16.9 (5.0)	11.7 (2.9)	**<0.001**	0.364	**-0.545****	-0.438**	**0.36**
Stance Time (s)	0.63 [0.58, 0.74]	0.60 [0.57, 0.66]	0.177	0.488**	**-0.667****	**-0.808****	0.02
Swing Time (s)	0.47 (0.05)	0.46 (0.03)	0.828	0.152	0.013	-0.022	0.00
SLS (s)	0.47 (0.05)	0.46 (0.03)	0.828	0.152	0.013	-0.022	0.00
DLS (s)	0.18 [0.13, 0.21]	0.14 [0.12, 0.19]	0.169	0.452*	**-0.735****	**-0.800****	0.02
Stance perc. (%cycle)	57.7 [56.6, 59.1]	56.5 [55.9, 58.6]	0.180	0.323	**-0.617****	**-0.711****	0.11
Swing perc. (%cycle)	42.3 [40.9, 43.4]	43.5 [41.4, 44.1]	0.204	-0.321	**0.613****	**0.710****	-0.10
SLS perc. (%cycle)	41.7 [40.8, 43.8]	43.3 [41.7, 44.1]	0.172	-0.356	**0.690****	**0.731****	-0.09
DLS perc. (%cycle)	16.3 [12.6, 18.4]	13.5 [11.5, 17.0]	0.192	0.336	**-0.643****	**-0.730****	0.14
Asymmetry Measures							
Speed (m/s)	0.01 [0.01, 0.02]	0.01 [0.003, 0.02]	0.299	-0.052	-0.117	0.152	0.01
Cadence (steps/min)	1.2 [0.5, 2.00]	0.5 [0.2, 0.72]	**<0.01**	-0.064	0.119	-0.030	0.13
Stride Time (s)	0.01 [0.01, 0.02]	0.01 [0.002, 0.01]	**<0.01**	0.034	-0.084	-0.216	0.01
Step Time (s)	0.01 [0.001, 0.02]	0.01 [0.001, 0.01]	0.088	0.001	-0.112	-0.091	0.01
Stride Length (cm)	1.1 [0.4, 1.60]	0.5 [0.3, 1.33]	0.268	0.418*	-0.270	0.060	0.06
Step Length (cm)	0.9 [0.7, 2.30]	0.9 [0.4, 1.49]	0.346	0.212	-0.266	-0.055	0.07
Step Width (cm)	1.4 [0.6, 2.41]	0.8 [0.3, 1.72]	0.071	-0.298	0.201	0.049	0.05
Stance Time (s)	0.005 [0.002, 0.01]	0.004 [0.002, 0.01]	0.250	0.056	-0.202	0.132	0.01
Swing Time (s)	0.01 [0.01, 0.02]	0.00 [0.00, 0.01]	**<0.001**	0.439*	-0.405*	-0.437**	0.01
SLS (s)	0.01 [0.004, 0.02]	0.00 [0.001, 0.01]	**<0.01**	0.485*	-0.426*	-0.342*	0.01
DLS (s)	0.004 [0.001, 0.01]	0.005 [0.002, 0.01]	0.653	0.229	-0.284	0.050	0.00
Stance perc. (%cycle)	0.5 [0.2, 1.3]	0.5 [0.3, 0.7]	0.413	0.068	-0.290	0.112	0.08
Swing perc. (%cycle)	0.8 [0.3, 1.4]	0.4 [0.2, 0.6]	**<0.01**	0.357	-0.050	-0.122	0.12
SLS perc. (%cycle)	0.9 [0.5, 1.4]	0.5 [0.1, 0.9]	**<0.01**	0.442*	-0.446*	-0.215	0.10
DLS perc. (%cycle)	0.5 [0.2, 1.0]	0.4 [0.1, 0.8]	0.421	-0.047	-0.125	0.029	0.04

Variability Measures							
Speed (%CV)	5.4 [4.2, 7.7]	3.0 [2.5, 4.5]	**<0.001**	0.472*	-0.538**	-0.462**	0.26
Cadence (%CV)	3.5 [2.9, 5.9]	1.6 [1.3, 2.3]	**<0.001**	0.385*	-0.445*	**-0.615****	**0.31**
Stride Time (%CV)	3.5 [2.9, 5.8]	1.6 [1.3, 2.3]	**<0.001**	0.392*	-0.461*	**-0.619****	**0.31**
Step Time (%CV)	5.7 [4.3, 7.7]	2.8 [2.4, 3.7]	**<0.001**	0.483*	-0.455*	-0.491**	**0.34**
Stride Length (%CV)	3.7 [2.5, 6.0]	2.2 [1.9, 3.0]	**<0.001**	**0.545****	**-0.640****	-0.415**	0.21
Step Length (%CV)	5.6 [4.2, 8.4]	3.1 [2.7, 3.8]	**<0.001**	**0.583****	**-0.745****	-0.488**	**0.33**
Step Width (%CV)	27.8 [20.2, 38.3]	29.5 [22.9, 41.9]	0.551	0.037	0.171	0.250	-0.06
Stance Time (%CV)	5.1 [4.0, 6.8]	3.1 [2.5, 3.5]	**<0.001**	0.472*	-0.454*	**-0.532****	0.29
Swing Time (%CV)	5.9 [4.1, 8.1]	2.5 [2.3, 3.2]	**<0.001**	**0.629****	**-0.745****	**-0.620****	**0.31**
SLS (%CV)	5.9 [4.1, 8.1]	2.5 [2.3, 3.2]	**<0.001**	**0.629****	**-0.745****	**-0.620****	**0.31**
DLS (%CV)	14.5 [10.5, 22.4]	10.9 [8.3, 15.2]	**<0.05**	0.102	0.128	0.145	0.29
Stance perc. (%CV)	3.2 [2.4, 4.9]	1.9 [1.5, 2.1]	**<0.001**	0.325	-0.315	-0.467**	0.25
Swing perc. (%CV)	4.4 [3.2, 6.6]	2.5 [1.9, 2.9]	**<0.001**	**0.511****	**-0.578****	**-0.634****	0.26
SLS perc. (%CV)	4.4 [3.7, 6.8]	2.9 [2.2, 3.5]	**<0.001**	**0.559****	**-0.616****	-0.497**	0.26
DLS perc. (%CV)	11.6 [8.6, 21.1]	9.4 [6.2, 12.3]	**<0.05**	0.057	0.134	0.139	**0.56**

Results for mean, symmetry, and variability measures of spatiotemporal gait parameters. Accompanied with results of parametric test used reported as mean(SD), and non-parametric test used reported as median [IQR]. Pearson's/Spearmans correlation test used between parameters and SARA, BBS, and gait speed: |r|>0.6 * p<0.05, **p<0.01. |d|>0.3 indicates medium or larger effect size. Missing data: SLS asym and DLS asym (n=26). Abbreviations: n-number participants, r-correlation coefficient, s-seconds, cm-centimetres, %CV-coefficient of variation, SLS-single limb support, DLS-double limb support, perc.-percentage cycle

4.3.2.3. Upper body Motion Gait Parameters

Table 4.9 shows upper body motion gait characteristics measured during preferred paced walking. At the trunk and forehead, magnitude (Root mean square (RMS) acceleration) of the mediolateral (ML) axis of acceleration signals is significantly increased in CA vs healthy controls while those in the Vertical (V) axis are significantly reduced at the level of the trunk. Signal jerk is significantly increased in CA in the ML axis at the trunk and forehead and in the AP axis at the forehead. Values for stability, as measured by Jerk Ratio (which normalises to vertical (V) signal), was significantly higher in ML at all three sensor positions and in AP at the forehead in the CA cohort.

The CA cohort also displayed a Root Mean Square Ratio (RMSR) that was significantly increased in the ML axis and reduced in vertical axis at all 3 sensor positions compared with the age-matched healthy cohort. AP RMSR was also significantly increased at the head.

Attenuation (Coefficient of Attenuation, CoA) of AP components of acceleration signal between the pelvis and head, and trunk and head were significantly impaired in CA cohort compared with healthy controls. Meanwhile, attenuation of the vertical acceleration component was significantly higher in moving from the pelvis to shoulder and lower in moving from shoulder to head in the ataxic cohort than in the healthy cohort.

Step and stride regularity (AD1, AD2) were significantly different across all three signal components and the resultant signal between cohorts at all three sensor positions. Meanwhile, step to step asymmetry of acceleration components within a stride (indicated by Harmonic Ratio), shows a significantly lower result for AP, ML and vertical components for the CA cohort at the lumbar and trunk sensors and the ML and vertical components at the forehead. For upper body motion metrics, harmonic ratio (lumbar and trunk in AP, lumbar, trunk and forehead in vertical), and autocorrelation coefficients ($AD1_{ML}$ lumbar, $AD2_{V}$ lumbar, trunk and forehead, $AD2_{AP}$ lumbar, $AD2_{ML}$ lumbar, $AD2_{V}$ forehead) correlate most strongly with SARA score.

Meanwhile, of the postural control variables tested, lumbar AP component and forehead vertical component Harmonic Ratio, trunk step regularity in vertical component and stride regularity at lumbar in AP and ML, trunk in AP and vertical and forehead in vertical, as well as trunk ML RMSR all showed a good to excellent strength, significant correlation with BBS score (Table 4.9).

Table 4.9: Upper body Motion Gait Parameters

		Cerebellar Ataxia (n=27)	Healthy Control (n=23-27)	p	Correlation (r) SARA	BBS	d
Lumbar							
Magnitude (ms^{-2})	AP	1.61 (0.35)	1.77 (0.38)	0.126	-0.281	0.371	-0.04
	ML	1.59 (0.38)	1.41 (0.37)	0.093	0.126	0.146	0.04
	V	2.13 (0.64)	2.33 (0.59)	0.249	-0.479*	0.409*	-0.04
	R	3.55 (0.81)	3.58 (0.76)	0.865	-0.310	0.408*	-0.01
Jerk (ms^{-3})	AP	44.58 (13.23)	45.27 (13.19)	0.853	-0.273	0.430*	-0.03
	ML	54.53 (15.73)	46.20 (14.26)	0.051	0.190	0.210	**0.30**
	V	56.66 (20.64)	55.72 (17.22)	0.860	-0.3800	0.376	0.03
	R	39.61 (12.01)	36.11 (8.73)	0.238	-0.312	0.466*	0.15
Harmonic Ratio	AP	2.42 (0.66)	3.36 (0.81)	**<0.001**	**-0.657****	**0.570****	-0.15
	ML	2.05 (0.49)	2.45 (0.54)	**<0.01**	**-0.552****	0.390*	-0.08
	V	2.53 (0.64)	3.65 (0.60)	**<0.001**	**-0.679****	**0.517****	-0.20
RMSR	AP	0.47 [0.44, 0.49]	0.52 [0.43, 0.56]	0.060	-0.169	0.214	-0.02
	ML	0.47 [0.38, 0.50]	0.37 [0.35, 0.44]	**<0.01**	0.459*	-0.343	0.03
	V	0.60 (0.08)	0.65 (0.07)	**<0.05**	-0.498**	0.212	-0.03
Jerk Ratio (dB)	AP /V	-0.99 (0.98)	-0.89 (0.92)	0.709	0.237	-0.009	-0.01
	ML /V	-0.07 (1.32)	-0.84 (1.15)	**<0.05**	**0.605****	-0.301	0.10
Step Regularity	AP	0.73 [0.62, 0.80]	0.86 [0.82, 0.90]	**<0.001**	**-0.594****	0.367	-0.07
	ML	-0.45 [-0.61, -0.30]	-0.66 [-0.79, -0.50]	**<0.001**	**0.706****	-0.491**	0.06
	V	0.73 [0.57, 0.82]	0.90 [0.86, 0.91]	**<0.001**	**-0.677****	**0.517****	-0.08
	R	0.62 [0.47, 0.72]	0.78 [0.67, 0.83]	**<0.001**	**-0.616****	**0.640****	-0.06
Stride Regularity	AP	0.71 (0.13)	0.87 (0.04)	**<0.001**	**-0.624****	**0.575****	-0.08
	ML	0.52 [0.38, 0.58]	0.78 [0.64, 0.83]	**<0.001**	**-0.627****	**0.658****	-0.07
	V	0.68 [0.55, 0.80]	0.89 [0.87, 0.91]	**<0.001**	**-0.598****	**0.608****	-0.08
	R	0.66 (0.14)	0.81 (0.05)	**<0.001**	**-0.619****	**0.707****	-0.07
AutoSymmetry	AP	1.00 [0.94, 1.04]	0.98 [0.93, 1.05]	0.733	0.144	-0.292	-0.01
	ML	-0.96 (0.19)	-0.93 (0.15)	0.508	0.110	0.183	-0.01
	V	1.01 [0.97, 1.06]	0.99 [0.97, 1.03]	0.540	-0.127	-0.122	0.00
	R	0.97 [0.81, 1.01]	0.95 [0.82, 0.98]	0.540	-0.032	-0.065	0.01
Trunk							
Magnitude (ms^{-2})	AP	1.11 [0.91, 1.27]	0.99 [0.93, 1.35]	0.934	-0.037	0.132	-0.01
	ML	1.26 (0.26)	0.97 (0.18)	**<0.001**	0.369	**-0.528****	0.09
	V	1.90 (0.53)	2.20 (0.48)	**<0.05**	-0.450*	0.433*	-0.06
	R	2.75 (0.57)	2.83 (0.63)	0.636	-0.325	0.280	-0.01
Jerk (ms^{-3})	AP	32.34 [21.99, 41.34]	25.94 [20.18, 33.79]	0.197	-0.184	0.198	0.09
	ML	22.77 (7.15)	17.98 (5.96)	**<0.05**	-0.028	0.033	0.26
	V	40.79 (11.31)	38.47 (10.37)	0.446	-0.165	0.272	0.10
	R	31.68 (9.42)	28.66 (9.57)	0.258	-0.133	0.216	0.14

Harmonic Ratio	AP	1.82 (0.35)	2.49 (0.50)	**<0.001**	**-0.502****	0.478*	-0.14
	ML	2.84 (0.63)	3.40 (0.78)	**<0.01**	-0.292	0.110	-0.09
	V	2.69 [2.48, 3.31]	4.22 [3.80, 5.15]	**<0.001**	**-0.660****	0.608**	-0.21
RMSR	AP	0.40 [0.37, 0.43]	0.39 [0.34, 0.42]	0.492	0.127	-0.052	0.00
	ML	0.48 (0.12)	0.35 (0.07)	**<0.001**	0.475*	**-0.613****	0.05
	V	0.68 [0.62, 0.76]	0.80 [0.75, 0.83]	**<0.001**	-0.358	**0.527****	-0.05
Jerk Ratio (dB)	AP /V	-1.28 [-2.17, -0.48]	-1.64 [-2.24, -1.07]	0.415	-0.125	0.009	0.02
	ML /V	-2.59 (1.08)	-3.40 (0.85)	**<0.01**	0.129	-0.277	0.11
Step Regularity	AP	0.51 (0.16)	0.75 (0.10)	**<0.001**	-0.435*	**0.510****	-0.10
	ML	-0.62 (0.15)	-0.71 (0.12)	**<0.05**	0.361	-0.032	0.04
	V	0.74 (0.16)	0.93 (0.02)	**<0.001**	**-0.628****	**0.561****	-0.09
	R	0.57 (0.17)	0.81 (0.06)	**<0.001**	**-0.683****	**0.667****	-0.10
Stride Regularity	AP	0.59 (0.17)	0.81 (0.09)	**<0.001**	-0.429*	**0.634****	-0.09
	ML	0.61 [0.54, 0.72]	0.72 [0.67, 0.77]	**<0.05**	-0.274	0.092	-0.04
	V	0.74 (0.16)	0.91 (0.03)	**<0.001**	**-0.565****	**0.605****	-0.08
	R	0.60 (0.16)	0.83 (0.04)	**<0.001**	**-0.581****	**0.664****	-0.10
AutoSymmetry	AP	0.91 [0.80, 1.05]	0.95 [0.90, 0.97]	0.430	0.033	-0.246	0.00
	ML	-1.05 [-1.08, -1.00]	-1.04 [-1.11, -0.95]	0.899	-0.036	0.139	-0.01
	V	1.02 (0.10)	1.02 (0.03)	0.848	-0.061	-0.219	0.00
	R	0.98 (0.19)	0.97 (0.07)	0.763	-0.222	0.115	0.00
Forehead							
Magnitude (ms^{-2})	AP	1.00 [0.75, 1.18]	0.75 [0.61, 1.10]	0.087	0.338	-0.162	0.03
	ML	1.20 [0.98, 1.51]	0.91 [0.75, 1.22]	**<0.05**	0.403*	-0.325	0.05
	V	1.94 (0.54)	2.11 (0.49)	0.242	-0.354	0.371	-0.03
	R	2.66 (0.54)	2.59 (0.54)	0.661	-0.036	0.150	0.01
Jerk (ms^{-3})	AP	20.65 (8.16)	14.01 (5.74)	**<0.01**	0.331	-0.129	**0.35**
	ML	22.02 [13.82, 32.78]	14.13 [10.85, 17.82]	**<0.01**	0.250	-0.104	**0.37**
	V	44.22 (12.99)	39.39 (10.35)	0.146	-0.073	0.319	0.20
	R	31.05 (8.77)	29.09 (8.19)	0.410	-0.267	0.387*	0.09
Harmonic Ratio	AP	1.46 (0.31)	1.59 (0.49)	0.263	0.024	-0.020	-0.03
	ML	2.72 (0.55)	3.17 (0.78)	**<0.05**	-0.134	0.242	-0.08
	V	2.34 [1.99, 2.92]	3.92 [3.24, 4.30]	**<0.001**	**-0.681****	**0.622****	-0.22
RMSR	AP	0.38 (0.08)	0.33 (0.08)	**<0.05**	**0.623****	**-0.512****	0.02
	ML	0.47 (0.13)	0.39 (0.12)	**<0.05**	**0.538****	**-0.543****	0.03
	V	0.71 [0.65, 0.84]	0.83 [0.76, 0.88]	**<0.01**	-0.437*	0.448*	-0.04
Jerk Ratio (dB)	AP /V	-3.47 (1.52)	-4.74 (1.67)	**<0.01**	**0.573****	**-0.525****	0.14
	ML /V	-3.14 (1.62)	-4.35 (1.44)	**<0.01**	0.437*	-0.442*	0.14
Step Regularity	AP	0.41 [0.32, 0.52]	0.58 [0.47, 0.72]	**<0.001**	-0.092	0.182	-0.06
	ML	-0.63 (0.13)	-0.70 (0.11)	**<0.05**	0.182	-0.240	0.03
	V	0.69 [0.57, 0.84]	0.92 [0.88, 0.93]	**<0.001**	**-0.677****	**0.558****	-0.09

	R	0.51 (0.19)	0.71 (0.10)	**<0.001**	**-0.694****	**0.747****	-0.07
Stride Regularity	AP	0.51 (0.12)	0.69 (0.12)	**<0.001**	-0.274	0.421*	-0.07
	ML	0.63 (0.12)	0.70 (0.09)	**<0.05**	-0.213	0.305	-0.03
	V	0.71 [0.59, 0.84]	0.91 [0.89, 0.92]	**<0.001**	**-0.675****	**0.621****	-0.08
	R	0.54 (0.17)	0.72 (0.10)	**<0.001**	**-0.667****	**0.777****	-0.07
AutoSymmetry	AP	0.84 [0.68, 1.06]	0.88 [0.79, 0.96]	0.808	-0.001	-0.122	0.00
	ML	-1.00 [-1.06, -0.96]	-1.01 [-1.08, -0.94]	0.704	-0.034	0.059	0.01
	V	1.01 [0.95, 1.05]	1.01 [0.99, 1.03]	0.853	-0.126	-0.247	0.00
	R	0.99 [0.81, 1.06]	0.99 [0.92, 1.06]	0.823	-0.153	-0.030	0.00
Coefficient of Attenuation (%)							
Pelvis:Head	AP	34.28 (22.63)	48.14 (22.50)	**<0.05**	**-0.519****	0.474*	**-0.40**
	ML	16.77 [-2.16, 42.08]	21.77 [1.55, 46.21]	0.473	-0.341	0.474*	-0.08
	V	7.31 (14.11)	7.88 (10.12)	0.864	-0.389*	0.165	-0.02
	R	22.72 (14.08)	25.52 (11.79)	0.431	-0.412*	0.429*	-0.11
Pelvis:Shoulder	AP	31.94 [12.92, 40.55]	40.38 [13.59, 51.01]	0.250	-0.125	0.228	-0.02
	ML	15.12 [1.47, 34.58]	29.74 [15.35, 36.78]	0.061	-0.18	**0.548****	**-0.30**
	V	9.58 (8.91)	4.05 (8.43)	**<0.05**	-0.258	0.018	0.26
	R	21.22 [13.17, 28.73]	21.48 [12.61, 28.14]	0.710	-0.07	0.410*	0.03
Shoulder:Head	AP	4.20 [-6.87, 21.70]	22.27 [0.73, 37.60]	**<0.05**	-0.422*	0.408*	**-0.47**
	ML	2.85 [-8.52, 20.88]	2.21 [-23.89, 14.42]	0.364	-0.384*	0.135	0.17
	V	0.67 [-10.83, 5.89]	3.00 [-0.09, 8.12]	**<0.05**	-0.173	0.125	**-0.30**
	R	4.42 [-4.46, 9.98]	7.13 [2.59, 9.88]	0.236	-0.451*	0.266	-0.17

Results for upper body motion variables at lumbar, trunk and forehead positions and coefficient of attenuation (between levels). Accompanied with results of parametric test used reported as mean±SD, and non-parametric test used reported as median (IQR). Pearson's/Spearmans correlation test used between parameters and SARA, and BBS: |r|>0.6 * p<0.05, **p<0.01. |d|>0.3 indicates medium or larger effect size. Missing data: lumbar, trunk and forehead magnitude, jerk, harmonic ratio, RMSR and jerk ratio (HC n=25); step regularity, stride regularity, autosymmetry (HC n=23)

4.3.3. GAIT INFLUENCES

Further analysis was completed to examine the impact of disease severity on the gait pattern through participant stratification based on SARA score. The resulting Mild Ataxia (SARA ≤8, n=7) and Moderate Ataxia (SARA>8, n=20) were compared against the healthy control group. Between-group differences are displayed in Table 4.10 and Table 4.11. Many of the significant differences observed between CA and HC cohorts appear to be a result of a more severe gait phenotype in the moderate ataxia patient subgroup. However, for select variables such as asymmetry of cadence, step length and stride length as well as magnitude of ML forehead accelerations, the mild ataxia cohort appears to deviate from the typical course of gait impairment.

Univariate analysis of spatiotemporal gait characteristics, adjusted for age, gender and gait speed as covariates, indicates group differences independent of these confounding factors. Many spatiotemporal variables retain significant differences between the healthy and ataxic cohorts. For instance, following adjustment for these factors, there remained a significant difference between cohorts in step/ stride length (CA vs HC: MD=-3.2cm, $p<0.05$, MD= -6.2cm, $p<0.05$) and step width (CA vs HC: 2.95cm, $p<0.01$) as well as Cadence asymmetry (MD 0.92steps/min, $p<0.001$) and Stride Time asymmetry (MD=0.007s, $p<0.01$) (Table 4.12). Meanwhile, gait variability measures that retained a significant difference between cohorts, showed an adjusted mean increase of 1.10% to 10.47% in ataxia patients compared with healthy controls. Difference between disease severity subgroup analysis is also retained in a univariate analysis adjusted for age, sex and gait speed in with step width, cadence asymmetry, stride time asymmetry and a number of gait variability measures (Table 4.13). While with increased disease severity, step width, and gait variability measures increase, cadence asymmetry is significantly increased in mild and moderate ataxia groups with respect to healthy controls.

In upper body motion parameters , adjusted significant differences were observed between ataxic and healthy control cohorts, in step to step asymmetry (harmonic ratio) at lumbar and trunk sensor positions in AP, ML, vertical components and at forehead in ML, vertical (range MD, AP: -0.67 to -0.61, ML: -0.85 to -0.35; V: -1.26 to -0.84)(Table 4.14). Adjusted values for magnitude and jerk of ML accelerations at the trunk (MD=0.22ms^{-2}, $p<0.01$, MD = 7.98ms^{-2}, $p<0.001$ respectively) and jerkiness of accelerations at the head, AP and ML axis also show

significant differences between cohorts (MD = 6.04ms^{-3}, p<0.01; MD=8.80ms^{-3}, p=0.01 respectively). In addition, significant differences were observed in Jerk Ratio ML/V at the trunk level (MD: 0.77, p=0.02) and CoA_{PS} in vertical axis (MD: 7.33, p=0.01). Significant differences were also retained between cohorts at lumbar and trunk sensor positions in AP, ML, vertical axes and at forehead in AP, vertical axes, in step regularity (range MD, AP: -0.18 to -0.10, ML: 0.10 to 0.12; V: -0.12 to -0.10), and stride regularity (range MD, AP: -0.16 to -0.09, ML: -0.09 to -0.09; V: -0.10 to -0.09)(Table 4.14). After adjusting for age, sex and speed, the univariate analysis also confirm many differences between analysis of disease severity subgroups are independent of these factors (Table 4.15). The harmonic ratio shows a significant reduction in more severely affected patients at the lumbar position in AP, ML, vertical axes, at trunk AP, ML, vertical axes and forehead vertical axis. Step regularity shows significant differences between disease severity subgroups: decreased at the lumbar position in AP, and vertical axes, trunk position in AP, vertical, R axes and forehead position in vertical, R axis and increased at the lumbar position in ML axis with increased disease severity. Meanwhile, stride regularity shows significant differences between disease severity subgroups: decreased at the lumbar position in AP, vertical, R axes, trunk position in AP, vertical, R, axes and forehead position in AP, vertical axis and increased at the lumbar position in ML axis with increased disease severity. Jerk at the forehead position also retains significant increases in AP, ML axis in the more severely affected patients.

Between-group differences for selected variables represented by Z scores are displayed in Figure 4.5. These variables were significantly different between HC and CA as well as differentiating HC to mild ataxia or mild ataxia to moderate ataxia and were robust against confounding by gait speed, age, and sex.

Partial correlation analysis of the selected variables indicated that independent of gait speed, step width and stride length variability both negatively correlate with trunk AP component stride regularity (Table 4.16). Step length variability and stride length variability correlate negatively with forehead resultant step regularity. Step length variability also correlates with lumbar resultant stride regularity and trunk harmonic ratio in AP axis.

Table 4.10: Disease severity subgroups - Spatiotemporal gait parameters

	Healthy Control (n=27)	**Mild Ataxia (n=7)**	**Moderate Ataxia (n=20)**	**p (Posthoc)**
Spatiotemporal Measures				
Speed (m/s)	1.33 [1.23, 1.44]	1.30 [1.19, 1.51]	1.07 [0.91, 1.27]	**<0.001**[b,c]
Cadence (steps/min)	111.6 [107.0, 119.1]	112.3 [108.2, 121.8]	108.3 [97.3, 115.2]	0.164
Stride Time (s)	1.08 [1.01, 1.12]	1.07 [0.99, 1.11]	1.11 [1.04, 1.24]	0.159
Step Time (s)	0.54 [0.50, 0.56]	0.53 [0.49, 0.55]	0.56 [0.53, 0.62]	0.117
Stride Length (cm)	143.5 (16.0)	137.1 (14.6)	120.0 (19.6)	**<0.001**[b]
Step Length (cm)	71.7 (8.0)	68.4 (7.3)	59.9 (9.8)	**<0.001**[b]
Step Width (cm)	11.7 (2.9)	12.6 (2.6)	18.4 (4.8)	**<0.001**[b,c]
Stance Time (s)	0.60 [0.57, 0.66]	0.58 [0.55, 0.64]	0.66 [0.61, 0.75]	**<0.05**[b,c]
Swing Time (s)	0.46 (0.03)	0.47 (0.04)	0.47 (0.06)	0.972
SLS (s)	0.46 (0.03)	0.47 (0.04)	0.47 (0.06)	0.972
DLS (s)	0.14 [0.12, 0.19]	0.13 [0.06, 0.16]	0.18 [0.15, 0.23]	**<0.05**[b,c]
Stance perc. (%cycle)	56.5 [55.9, 58.6]	56.6 [53.4, 57.1]	58.4 [57.1, 59.2]	**<0.05**[b,c]
Swing perc. (%cycle)	43.5 [41.4, 44.1]	43.4 [42.9, 47.8]	41.6 [40.8, 42.9]	**<0.05**[b,c]
SLS perc. (%cycle)	43.3 [41.7, 44.1]	43.8 [42.8, 46.7]	41.6 [40.6, 42.8]	**<0.05**[b,c]
DLS perc. (%cycle)	13.5 [11.5, 17.0]	12.6 [6.8, 14.2]	16.7 [13.8, 18.6]	**<0.05**[b,c]
Asymmetry Measures				
Speed (m/s)	0.01 [0.003, 0.02]	0.01 [0.01, 0.01]	0.01 [0.01, 0.02]	0.495
Cadence (steps/min)	0.5 (0.4)	1.6 (1.4)	1.3 (0.9)	**<0.01**[b]
Stride Time (s)	0.01 [0.002, 0.01]	0.01 [0.004, 0.02]	0.01 [0.01, 0.02]	**<0.01**[b]
Step Time (s)	0.01 [0.001, 0.01]	0.01 [0.001, 0.01]	0.01 [0.002, 0.03]	0.183
Stride Length (cm)	0.5 [0.3, 1.33]	0.2 [0.1, 1.39]	1.1 [0.6, 1.73]	**<0.05**[c]
Step Length (cm)	0.9 [0.4, 1.49]	0.8 [0.3, 3.00]	1.1 [0.7, 2.27]	0.423
Step Width (cm)	0.8 [0.3, 1.72]	2.1 [0.9, 2.79]	1.2 [0.5, 2.08]	0.062[a]
Stance Time (s)	0.004 [0.002, 0.01]	0.005 [0.001, 0.01]	0.01 [0.002, 0.01]	0.422
Swing Time (s)	0.004 [0.002, 0.01]	0.002 [0.001, 0.01]	0.01 [0.01, 0.02]	**<0.001**[b,c]
SLS (s)	0.004 [0.001, 0.01]	0.01 [0.002, 0.01]	0.01 [0.005, 0.02]	**<0.01**[b,c]
DLS (s)	0.005 [0.002, 0.01]	0.002 [0.001, 0.01]	0.004 [0.001, 0.01]	0.331
Stance perc. (%cycle)	0.5 [0.3, 0.7]	0.2 [0.1, 1.5]	0.5 [0.3, 1.3]	0.486
Swing perc. (%cycle)	0.4 [0.2, 0.6]	0.3 [0.2, 0.9]	0.9 [0.5, 2.0]	**<0.01**[b]
SLS perc. (%cycle)	0.5 [0.1, 0.9]	0.6 [0.4, 1.0]	1.1 [0.6, 1.7]	**<0.05**[b]
DLS perc. (%cycle)	0.4 [0.1, 0.8]	0.5 [0.2, 0.7]	0.5 [0.1, 1.1]	0.721
Variability Measures				
Speed Var. (%CV)	3.0 [2.5, 4.5]	4.2 [2.8, 4.8]	5.5 [4.8, 8.1]	**<0.001**[b,c]
Cadence Var. (%CV)	1.6 [1.3, 2.3]	3.3 [2.2, 3.5]	4.3 [3.2, 6.0]	**<0.001**[a,b]
Stride Time Var. (%CV)	1.6 [1.3, 2.3]	3.3 [2.2, 3.4]	4.3 [3.2, 5.8]	**<0.001**[a,b]
Step Time Var. (%CV)	2.8 [2.4, 3.7]	4.3 [3.3, 5.2]	6.3 [5.1, 8.2]	**<0.001**[a,b,c]
Stride Length Var. (%CV)	2.2 [1.9, 3.0]	2.3 [1.9, 2.6]	4.4 [3.3, 6.7]	**<0.001**[b,c]
Step Length Var. (%CV)	3.2 (0.9)	3.6 (1.0)	7.7 (3.1)	**<0.001**[b,c]
Step Width Var. (%CV)	31.2 (9.9)	33.9 (8.5)	28.1 (12.9)	0.433
Stance Time Var. (%CV)	3.1 [2.5, 3.5]	3.7 [3.3, 4.7]	5.6 [4.4, 7.8]	**<0.001**[a,b,c]
Swing Time Var. (%CV)	2.5 [2.3, 3.2]	3.5 [3.3, 4.1]	6.6 [4.8, 8.7]	**<0.001**[a,b,c]
SLS Var. (%CV)	2.5 [2.3, 3.2]	3.5 [3.3, 4.1]	6.6 [4.8, 8.7]	**<0.001**[a,b,c]
DLS Var. (%CV)	10.9 [8.3, 15.2]	13.1 [10.1, 40.8]	14.5 [10.8, 21.0]	0.108
Stance perc. Var. (%CV)	1.9 [1.5, 2.1]	2.2 [1.9, 8.1]	3.2 [2.9, 4.8]	**<0.001**[a,b]
Swing perc. Var. (%CV)	2.5 [1.9, 2.9]	2.7 [2.3, 3.7]	5.0 [3.9, 6.6]	**<0.001**[b,c]
SLS perc. Var. (%CV)	2.9 [2.2, 3.5]	2.6 [2.4, 4.3]	5.2 [4.2, 7.9]	**<0.001**[b,c]
DLS perc. Var. (%CV)	9.4 [6.2, 12.3]	12.4 [8.4, 29.2]	11.3 [8.7, 20.2]	0.066[b]

CA group separated in mild (SARA ≤8) and moderate ataxia (SARA>8) normally distributed data reported as mean (SD), non-normally distributed data reported as median [IQR]. Results of one-way ANOVA tests and Kruskal Wallis tests with significant post hoc test results indicated a: healthy control vs mild ataxia b: healthy control vs moderate ataxia c: mild ataxia vs moderate ataxia. Missing data: SLS asym. and DLS asym. (n=26)

Table 4.11: Disease severity subgroups - Upper body motion Gait Parameters

		Healthy Control (n=23-27)	Mild Ataxia (n=7)	Moderate Ataxia (n=20)	p (Posthoc)
Lumbar					
Magnitude (ms^{-2})	AP	1.77 (0.38)	1.79 (0.30)	1.55 (0.35)	0.107
	ML	1.41 (0.37)	1.47 (0.27)	1.63 (0.40)	0.153
	V	2.33 (0.59)	2.47 (0.81)	2.01 (0.54)	0.121
	R	3.58 (0.76)	3.83 (0.90)	3.45 (0.78)	0.547
Jerk (ms^{-3})	AP	45.27 (13.19)	49.71 (13.87)	42.79 (12.87)	0.484
	ML	46.20 (14.26)	47.23 (10.40)	57.09 (16.68)	0.050[b]
	V	55.72 (17.22)	65.25 (23.59)	53.65 (19.25)	0.378
	R	36.11 (8.73)	43.08 (16.31)	38.40 (10.36)	0.303
Harmonic Ratio	AP	3.36 (0.81)	3.24 (0.54)	2.14 (0.43)	**<0.001[b,c]**
	ML	2.45 (0.54)	2.50 (0.35)	1.89 (0.44)	**<0.001[b,c]**
	V	3.65 (0.60)	3.17 (0.30)	2.31 (0.58)	**<0.001[a,b,c]**
RMSR	AP	0.52 [0.43, 0.56]	0.49 [0.48, 0.51]	0.46 [0.43, 0.47]	0.065[b,c]
	ML	0.39 (0.06)	0.39 (0.06)	0.48 (0.08)	**<0.001[b,c]**
	V	0.65 (0.07)	0.64 (0.08)	0.58 (0.07)	**<0.05[b]**
Jerk Ratio (dB)	AP/V	-0.89 (0.92)	-1.13 (0.93)	-0.94 (1.02)	0.842
	ML/V	-0.84 (1.15)	-1.29 (0.98)	0.35 (1.16)	**<0.001**
Step Regularity	AP	0.85 (0.06)	0.81 (0.10)	0.65 (0.13)	**<0.001[b,c]**
	ML	-0.65 (0.16)	-0.67 (0.14)	-0.39 (0.13)	**<0.001[b,c]**
	V	0.88 (0.05)	0.83 (0.10)	0.63 (0.16)	**<0.001[b,c]**
	R	0.74 (0.12)	0.73 (0.09)	0.55 (0.15)	**<0.001[b,c]**
Stride Regularity	AP	0.88 [0.84, 0.90]	0.87 [0.79, 0.89]	0.70 [0.58, 0.76]	**<0.001[b,c]**
	ML	0.72 (0.15)	0.69 (0.16)	0.46 (0.14)	**<0.001[b,c]**
	V	0.88 (0.05)	0.84 (0.10)	0.64 (0.14)	**<0.001[b,c]**
	R	0.81 (0.05)	0.79 (0.08)	0.61 (0.12)	**<0.001[b,c]**
Symmetry.	AP	1.01 (0.20)	0.98 (0.03)	0.99 (0.14)	0.868
	ML	-0.93 (0.15)	-0.99 (0.08)	-0.95 (0.22)	0.661
	V	1.02 (0.15)	1.01 (0.04)	1.02 (0.13)	0.962
	R	0.95 [0.82, 0.98]	0.95 [0.91, 1.00]	0.98 [0.80, 1.02]	0.820
Trunk					
Magnitude (ms^{-2})	AP	1.15 (0.43)	1.13 (0.44)	1.09 (0.22)	0.846
	ML	0.97 (0.18)	1.07 (0.28)	1.33 (0.22)	**<0.001[b]**
	V	2.20 (0.48)	2.22 (0.65)	1.79 (0.45)	**<0.05[b]**
	R	2.76 [2.48, 3.28]	2.63 [2.27, 4.11]	2.73 [2.41, 3.07]	0.784
Jerk (ms^{-3})	AP	29.98 (18.40)	35.14 (23.71)	31.62 (10.51)	0.766
	ML	17.98 (5.96)	22.57 (8.13)	22.84 (7.01)	**<0.05[b]**
	V	38.47 (10.37)	41.72 (10.76)	40.47 (11.75)	0.725
	R	28.66 (9.57)	32.62 (10.64)	31.35 (9.24)	0.508
Harmonic Ratio	AP	2.49 (0.50)	2.20 (0.35)	1.68 (0.25)	**<0.001[b,c]**
	ML	3.53 [2.73, 3.89]	3.14 [2.68, 3.58]	2.49 [2.25, 3.25]	**<0.05[b]**
	V	4.47 (0.92)	4.07 (1.52)	2.57 (0.51)	**<0.001[b]**
RMSR	AP	0.40 (0.07)	0.38 (0.06)	0.41 (0.05)	0.585
	ML	0.35 (0.07)	0.38 (0.11)	0.51 (0.11)	**<0.001[b,c]**
	V	0.80 [0.75, 0.83]	0.77 [0.68, 0.83]	0.66 [0.60, 0.73]	**<0.001[b,c]**
Jerk Ratio (dB)	AP/V	-1.40 (1.15)	-1.39 (1.70)	-1.16 (0.84)	0.761
	ML/V	-3.40 (0.85)	-2.80 (0.82)	-2.52 (1.17)	**<0.05[b]**
Step Regularity	AP	0.75 (0.10)	0.65 (0.14)	0.46 (0.13)	**<0.001[b,c]**
	ML	-0.71 (0.12)	-0.67 (0.09)	-0.60 (0.16)	**<0.05[b]**
	V	0.93 [0.91, 0.95]	0.94 [0.85, 0.96]	0.70 [0.61, 0.81]	**<0.001[b,c]**
	R	0.81 (0.06)	0.74 (0.11)	0.52 (0.16)	**<0.001**
Stride Regularity	AP	0.84 [0.75, 0.87]	0.80 [0.52, 0.85]	0.54 [0.44, 0.65]	**<0.001[b,c]**
	ML	0.71 (0.11)	0.65 (0.08)	0.60 (0.16)	**<0.05[b]**
	V	0.91 (0.03)	0.88 (0.08)	0.69 (0.15)	**<0.001[b,c]**
	R	0.83 (0.04)	0.72 (0.11)	0.56 (0.15)	**<0.001[b,c]**

Symmetry.	AP	0.95 [0.90, 0.97]	0.92 [0.83, 0.98]	0.89 [0.76, 1.07]	0.733
	ML	-1.03 (0.14)	-1.08 (0.18)	-1.04 (0.10)	0.683
	V	1.02 (0.03)	1.02 (0.02)	1.02 (0.12)	0.981
	R	0.97 (0.07)	1.04 (0.06)	0.96 (0.22)	0.443
Forehead					
Magnitude (ms^{-2})	AP	0.86 (0.33)	0.79 (0.29)	1.07 (0.28)	**<0.05**
	ML	1.00 (0.37)	0.88 (0.34)	1.37 (0.32)	**<0.001**[b,c]
	V	2.11 (0.49)	2.19 (0.63)	1.85 (0.49)	0.168
	R	2.59 (0.54)	2.63 (0.61)	2.67 (0.53)	0.897
Jerk (ms^{-3})	AP	14.01 (5.74)	14.56 (7.21)	22.78 (7.50)	**<0.001**[b]
	ML	15.11 (6.36)	16.01 (7.52)	25.17 (9.76)	**<0.001**[b]
	V	39.39 (10.35)	43.81 (11.94)	44.36 (13.63)	0.350
	R	29.09 (8.19)	33.88 (10.65)	30.06 (8.09)	0.426
Harmonic Ratio	AP	1.59 (0.49)	1.39 (0.35)	1.49 (0.30)	0.452
	ML	3.17 (0.78)	2.71 (0.66)	2.72 (0.53)	0.066
	V	3.92 [3.24, 4.30]	3.41 [2.92, 4.09]	2.10 [1.94, 2.49]	**<0.001**
RMSR	AP	0.33 (0.08)	0.30 (0.09)	0.40 (0.06)	**<0.01**
	ML	0.39 (0.12)	0.33 (0.10)	0.52 (0.10)	**<0.001**
	V	0.81 (0.09)	0.83 (0.11)	0.69 (0.11)	**<0.001**
Jerk Ratio (dB)	AP/V	-4.74 (1.67)	-5.10 (1.42)	-2.90 (1.10)	**<0.001**
	ML/V	-4.35 (1.44)	-4.61 (1.37)	-2.63 (1.38)	**<0.001**
Step Regularity	AP	0.58 (0.18)	0.48 (0.19)	0.39 (0.15)	**<0.01**
	ML	-0.70 (0.11)	-0.62 (0.13)	-0.64 (0.13)	0.124
	V	0.90 (0.05)	0.87 (0.10)	0.64 (0.16)	**<0.001**
	R	0.71 (0.10)	0.71 (0.13)	0.45 (0.15)	**<0.001**
Stride Regularity	AP	0.69 (0.12)	0.55 (0.16)	0.50 (0.11)	**<0.001**
	ML	0.70 (0.09)	0.61 (0.13)	0.63 (0.12)	0.076
	V	0.90 (0.05)	0.87 (0.09)	0.64 (0.15)	**<0.001**
	R	0.72 (0.10)	0.72 (0.13)	0.48 (0.14)	**<0.001**
Symmetry	AP	0.84 (0.19)	0.93 (0.22)	0.83 (0.28)	0.605
	ML	-1.01 [-1.08, -0.94]	-1.02 [-1.08, -0.96]	-1.00 [-1.03, -0.95]	0.834
	V	1.01 [0.99, 1.03]	1.02 [0.96, 1.02]	1.00 [0.92, 1.06]	0.979
	R	0.99 [0.92, 1.06]	0.99 [0.95, 1.01]	0.99 [0.81, 1.12]	0.957
Coefficient of Attenuation (%)					
Pelvis:Head	AP	48.14 (22.50)	53.49 (20.20)	27.56 (19.72)	**<0.01**
	ML	20.00 (40.67)	40.07 (17.90)	7.99 (33.42)	0.129
	V	7.88 (10.12)	10.32 (5.19)	6.25 (16.11)	0.745
	R	25.52 (11.79)	30.64 (6.91)	19.94 (15.01)	0.123
Pelvis:Shoulder	AP	40.38 [13.59, 51.01]	46.50 [18.35, 54.32]	31.78 [11.93, 39.33]	0.197
	ML	25.38 (23.38)	25.52 (17.70)	10.80 (27.32)	0.114
	V	4.05 (8.43)	9.22 (5.73)	9.70 (9.91)	0.077
	R	21.48 [12.61, 28.14]	24.35 [13.17, 32.87]	20.46 [13.20, 28.62]	0.747
Shoulder:Head	AP	22.27 [0.73, 37.60]	27.66 [-4.55, 36.62]	1.64 [-13.65, 13.79]	**<0.01**
	ML	2.21 [-23.89, 14.42]	22.80 [3.83, 37.62]	-4.37 [-12.21, 11.00]	0.070
	V	3.89 (6.61)	0.93 (6.30)	-4.08 (13.27)	**<0.05**
	R	6.88 (10.27)	9.18 (7.90)	0.41 (12.30)	0.076

CA group separated in mild (SARA ≤8) and moderate ataxia (SARA>8) normally distributed data reported as mean (SD), non-normally distributed data reported as median[IQR]. Results of one-way ANOVA tests and Kruskal Wallis tests with significant post hoc test results indicated a: healthy control vs mild ataxia b: healthy control vs moderate ataxia c: mild ataxia vs moderate ataxia. Missing data: lumbar, trunk and forehead magnitude, jerk, harmonic ratio, RMSR and jerk ratio (HC n=25); step regularity, stride regularity, autosymmetry (HC n=23)

Table 4.12: Univariate analysis adjusted for age, sex, gait speed – Spatiotemporal Parameters

	Cerebellar ataxia (n=27)	**Healthy Control (n=27)**	**p**
Spatiotemporal Measures			
Speed (m/s)	----	----	----
Cadence (steps/min)	112.7 (1.4)	106.8 (1.4)	**<0.01**
Stride Time (s)	1.08 (0.02)	1.14 (0.02)	**<0.05**
Step Time (s)	0.54 (0.01)	0.57 (0.01)	**<0.05**
Stride Length (cm)	130.9 (1.6)	137.1 (1.6)	**<0.05**
Step Length (cm)	65.3 (0.8)	68.5 (0.8)	**<0.05**
Step Width (cm)	15.7 (0.7)	12.8 (0.7)	**<0.01**
Stance Time (s)	0.62 (0.02)	0.68 (0.02)	**<0.05**
Swing Time (s)	0.47 (0.01)	0.47 (0.01)	0.97
SLS (s)	0.47 (0.01)	0.47 (0.01)	0.97
DLS (s)	0.15 (0.03)	0.21 (0.03)	0.11
Stance perc. (%cycle)	56.8 (0.6)	58.51 (0.64)	0.08
Swing perc. (%cycle)	43.4 (0.6)	41.44 (0.64)	**<0.05**
SLS perc. (%cycle)	43.4 (0.7)	41.36 (0.67)	**<0.05**
DLS perc. (%cycle)	13.3 (1.3)	17.16 (1.30)	0.06
Asymmetry			
Speed (m/s)	0.023 (0.005)	0.010 (0.005)	0.10
Cadence (steps/min)	1.41 (0.16)	0.48 (0.16)	**<0.001**
Stride Time (s)	0.013 (0.002)	0.006 (0.002)	**<0.01**
Step Time (s)	0.015 (0.003)	0.006 (0.003)	**<0.05**
Stride Length (cm)	2.08 (0.58)	0.80 (0.58)	0.15
Step Length (cm)	1.53 (0.23)	1.08 (0.23)	0.20
Step Width (cm)	1.79 (0.28)	1.03 (0.28)	0.07
Stance Time (s)	0.009 (0.002)	0.006 (0.002)	0.47
Swing Time (s)	0.013 (0.003)	0.008 (0.003)	0.19
SLS (s)	0.011 (0.002)	0.007 (0.002)	0.13
DLS (s)	0.005 (0.002)	0.007 (0.00)	0.29
Stance perc. (%cycle)	1.09 (0.23)	0.51 (0.23)	0.10
Swing perc. (%cycle)	1.19 (0.23)	0.55 (0.23)	0.07
SLS perc. (%cycle)	1.09 (0.19)	0.78 (0.19)	0.28
DLS perc. (%cycle)	0.66 (0.13)	0.57 (0.13)	0.63
Variability Measures			
Speed (%CV)	5.5 (0.4)	3.79 (0.4)	**<0.01**
Cadence (%CV)	4.0 (0.3)	2.09 (0.3)	**<0.001**
Stride Time (%CV)	3.9 (0.3)	2.12 (0.3)	**<0.001**
Step Time (%CV)	6.5 (0.6)	3.24 (0.6)	**<0.001**
Stride Length (%CV)	4.1 (0.4)	2.75 (0.4)	**<0.05**
Step Length (%CV)	6.0 (0.4)	3.88 (0.4)	**<0.01**
Step Width (%CV)	31.5 (2.2)	29.28 (2.2)	0.51
Stance Time (%CV)	5.6 (0.4)	3.49 (0.4)	**<0.001**
Swing Time (%CV)	5.6 (0.9)	4.48 (0.9)	0.44
SLS (%CV)	5.6 (0.9)	4.48 (0.9)	0.44
DLS (%CV)	21.0 (2.2)	10.52 (2.2)	**<0.01**
Stance perc. (%CV)	4.7 (0.6)	1.76 (0.6)	**<0.01**
Swing perc. (%CV)	4.7 (1.0)	4.02 (1.0)	0.65
SLS perc. (%CV)	5.4 (1.4)	4.88 (1.4)	0.79
DLS perc. (%CV)	60.0 (24.2)	0.69 (24.2)	0.11

Data are adjusted mean ± SEM. Abbreviation: SLS – single limb support, DLS – double limb support, %CV – coefficient of variation. Univariate analysis for group differences. Missing data: SLS asym. and DLS asym. (n=26)

Table 4.13: Univariate disease severity subgroup analysis adjusted for age, sex, gait speed – Spatiotemporal Parameters

	Healthy Control (n=27)	**Mild Ataxia (n=7)**	**Moderate Ataxia (n=20)**	**p (Post hoc)**
Spatiotemporal Measures				
Speed (m/s)	----	----	----	**----**
Cadence (steps/min)	106.4 (1.4)	109.5 (2.6)	114.4 (1.8)	**<0.01**[b]
Stride Time (s)	1.15 (0.02)	1.12 (0.04)	1.05 (0.02)	**<0.05**[b]
Step Time (s)	0.58 (0.01)	0.56 (0.02)	0.53 (0.01)	**<0.05**[b]
Stride Length (cm)	137.4 (1.6)	134.0 (2.9)	129.3 (2.0)	**<0.05**[b]
Step Length (cm)	68.7 (0.8)	66.9 (1.5)	64.4 (1.0)	**<0.05**[b]
Step Width (cm)	12.5 (0.7)	13.7 (1.3)	16.8 (0.9)	**<0.01**[b]
Stance Time (s)	0.68 (0.02)	0.65 (0.04)	0.60 (0.03)	0.06
Swing Time (s)	0.47 (0.01)	0.47 (0.02)	0.46 (0.01)	0.93
SLS (s)	0.47 (0.01)	0.47 (0.02)	0.46 (0.01)	0.93
DLS (s)	0.22 (0.03)	0.18 (0.05)	0.14 (0.03)	0.23
Stance perc. (%cycle)	58.6 (0.7)	57.4 (1.2)	56.4 (0.8)	0.17
Swing perc. (%cycle)	41.4 (0.7)	43.0 (1.2)	43.6 (0.8)	0.13
SLS perc. (%cycle)	41.3 (0.7)	42.8 (1.3)	43.8 (0.9)	0.11
DLS perc. (%cycle)	17.3 (1.3)	14.3 (2.5)	12.8 (1.7)	0.15
Asymmetry Measures				
Speed (m/s)	0.008 (0.005)	0.007 (0.010)	0.032 (0.007)	**<0.05**[b]
Cadence (steps/min)	0.50 (0.16)	1.53 (0.30)	1.35 (0.21)	**<0.05**[a,b]
Stride Time (s)	0.006 (0.002)	0.014 (0.003)	0.013 (0.002)	0.08[a]
Step Time (s)	0.005 (0.003)	0.006 (0.005)	0.020 (0.003)	**<0.01**[b]
Stride Length (cm)	0.54 (0.57)	-0.02 (1.05)	3.17 (0.72)	**<0.05**[b]
Step Length (cm)	1.07 (0.23)	1.42 (0.43)	1.58 (0.30)	0.68
Step Width (cm)	1.04 (0.29)	1.88 (0.53)	1.75 (0.36)	0.50
Stance Time (s)	0.006 (0.002)	0.007 (0.004)	0.010 (0.003)	1.00
Swing Time (s)	0.007 (0.003)	0.007 (0.005)	0.017 (0.003)	0.18
SLS (s)	0.006 (0.002)	0.006 (0.004)	0.014 (0.003)	0.09
DLS (s)	0.007 (0.002)	0.005 (0.003)	0.005 (0.002)	1.00
Stance perc. (%cycle)	0.54 (0.24)	1.37 (0.43)	0.94 (0.29)	1.00
Swing perc. (%cycle)	0.47 (0.23)	0.53 (0.42)	1.53 (0.29)	**<0.05**[b]
SLS perc. (%cycle)	0.75 (0.20)	0.87 (0.36)	1.21 (0.26)	0.60
DLS perc. (%cycle)	0.57 (0.13)	0.68 (0.24)	0.65 (0.17)	1.00
Variability Measures				
Speed Var. (%CV)	3.7 (0.4)	4.5 (0.7)	6.0 (0.5)	**<0.01**[b]
Cadence Var. (%CV)	2.1 (0.3)	4.0 (0.5)	4.0 (0.4)	**<0.01**[a,b]
Stride Time Var. (%CV)	2.1 (0.3)	3.8 (0.5)	4.0 (0.3)	**<0.001**[a,b]
Step Time Var. (%CV)	3.1 (0.6)	5.4 (1.0)	7.1 (0.7)	**<0.001**[b]
Stride Length Var. (%CV)	2.6 (0.4)	2.5 (0.7)	5.0 (0.5)	**<0.01**[b,c]
Step Length Var. (%CV)	3.6 (0.4)	4.0 (0.8)	7.0 (0.5)	**<0.001**[b,c]
Step Width Var. (%CV)	29.3 (2.3)	31.7 (4.2)	31.4 (2.9)	1.00
Stance Time Var. (%CV)	3.4 (0.4)	4.9 (0.7)	5.9 (0.5)	**<0.01**[b]
Swing Time Var. (%CV)	4.4 (1.0)	5.3 (1.8)	5.7 (1.2)	1.00
SLS Var. (%CV)	4.4 (1.0)	5.3 (1.8)	5.7 (1.2)	1.00
DLS Var. (%CV)	10.3 (2.2)	19.2 (4.2)	21.9 (2.9)	**<0.05**[b]
Stance perc. Var. (%CV)	1.9 (0.6)	5.6 (1.1)	4.2 (0.8)	0.11[a]
Swing perc. Var. (%CV)	4.1 (1.0)	5.0 (1.8)	4.5 (1.2)	1.00
SLS perc. Var. (%CV)	4.8 (1.5)	5.0 (2.7)	5.7 (1.9)	1.00
DLS perc. Var. (%CV)	-7.6 (24.1)	-7.5 (44.6)	94.7 (30.7)	0.06

Data are adjusted mean ± SEM. Abbreviation: SLS – single limb support, DLS – double limb support. Univariate analysis for differences between disease severity subgroup analysis with post hoc tests a: healthy control vs mild ataxia b: healthy control vs moderate ataxia c: mild ataxia vs moderate ataxia. Missing data: SLS asym. and DLS asym. (n=26)

Table 4.14: Univariate analysis adjusting for age, sex, gait speed – Upper body Motion Gait Parameters

		Cerebellar ataxia (n=27)	Healthy Control (n=27)	p
Lumbar				
Magnitude (ms^{-2})	AP	1.73 (0.06)	1.65 (0.06)	0.42
	ML	1.65 (0.00)	1.34 (0.07)	**<0.01**
	V	2.35 (0.07)	2.09 (0.00)	**<0.05**
	R	3.81 (0.11)	3.29 (0.11)	**<0.01**
Jerk (ms^{-3})	AP	48.45 (2.22)	41.09 (2.32)	**<0.05**
	ML	56.90 (2.85)	43.64 (2.98)	**<0.01**
	V	62.55 (2.94)	49.36 (3.07)	**<0.01**
	R	42.83 (1.71)	32.63 (1.78)	**<0.001**
Harmonic Ratio	AP	2.55 (0.15)	3.22 (0.15)	**<0.01**
	ML	2.07 (0.10)	2.42 (0.11)	**<0.05**
	V	2.66 (0.12)	3.50 (0.13)	**<0.001**
RMSR	AP	0.46 (0.01)	0.51 (0.01)	**<0.05**
	ML	0.44 (0.01)	0.41 (0.01)	0.18
	V	0.61 (0.01)	0.63 (0.01)	0.36
Jerk Ratio (dB)	AP/V	-1.07 (0.19)	-0.80 (0.21)	0.40
	ML/V	-0.37 (0.22)	-0.51 (0.24)	0.69
Step Regularity	AP	0.72 (0.02)	0.82 (0.02)	**<0.01**
	ML	-0.51 (0.03)	-0.60 (0.03)	**<0.05**
	V	0.73 (0.02)	0.83 (0.02)	**<0.01**
	R	0.64 (0.03)	0.70 (0.03)	0.12
Stride Regularity	AP	0.75 (0.02)	0.83 (0.01)	**<0.01**
	ML	0.57 (0.03)	0.66 (0.03)	**<0.05**
	V	0.73 (0.02)	0.83 (0.02)	**<0.01**
	R	0.69 (0.02)	0.70 (0.02)	**<0.01**
Symmetry.	AP	0.90 (0.03)	1.02 (0.04)	0.40
	ML	-0.93 (0.03)	-0.95 (0.04)	0.71
	V	1.01 (0.03)	1.03 (0.03)	0.52
	R	0.95 (0.04)	0.91 (0.04)	0.54
Trunk				
Magnitude (ms^{-2})	AP	1.15 (0.07)	1.09 (0.72)	0.55
	ML	1.23 (0.04)	1.01 (0.05)	**<0.01**
	V	2.08 (0.06)	2.01 (0.06)	0.39
	R	2.91 (0.09)	2.66 (0.10)	0.07
Jerk (ms^{-3})	AP	35.69 (3.27)	26.57 (3.41)	0.08
	ML	24.31 (1.23)	16.33 (1.29)	**<0.001**
	V	43.59 (1.90)	35.46 (1.99)	**<0.01**
	R	34.05 (1.73)	26.10 (1.81)	**<0.01**
Harmonic Ratio	AP	1.85 (0.09)	2.45 (0.09)	**<0.001**
	ML	2.70 (0.14)	3.56 (0.14)	**<0.001**
	V	3.08 (0.21)	4.34 (0.22)	**<0.001**
RMSR	AP	0.40 (0.01)	0.40 (0.01)	0.69
	ML	0.44 (0.01)	0.40 (0.01)	0.09
	V	0.71 (0.01)	0.75 (0.02)	0.07
Jerk Ratio (dB)	AP/V	-1.16 (0.23)	-1.47 (0.25)	0.40
	ML/V	-2.61 (0.21)	-3.38 (0.21)	**<0.05**
Step Regularity	AP	0.54 (0.02)	0.72 (0.03)	**<0.001**
	ML	-0.61 (0.03)	-0.73 (0.03)	**<0.05**
	V	0.78 (0.02)	0.89 (0.02)	**<0.01**
	R	0.61 (0.02)	0.76 (0.03)	**<0.001**
Stride Regularity	AP	0.62 (0.03)	0.78 (0.03)	**<0.001**
	ML	0.61 (0.03)	0.70 (0.03)	**<0.05**
	V	0.78 (0.02)	0.87 (0.02)	**<0.01**
	R	0.64 (0.02)	0.79 (0.02)	**<0.001**

Symmetry.	AP	0.95 (0.07)	0.96 (0.07)	0.92
	ML	-1.03 (0.03)	-1.06 (0.03)	0.49
	V	1.01 (0.01)	1.04 (0.02)	0.29
	R	0.98 (0.03)	0.97 (0.03)	0.87
Forehead				
Magnitude (ms^{-2})	AP	0.97 (0.05)	0.89 (0.05)	0.24
	ML	1.19 (0.06)	1.06 (0.07)	0.20
	V	2.10 (0.07)	1.93 (0.07)	0.09
	R	2.76 (0.07)	2.48 (0.07)	**<0.05**
Jerk (ms^{-3})	AP	20.36 (1.18)	14.32 (1.23)	**<0.01**
	ML	23.33 (1.53)	14.53 (1.60)	**<0.001**
	V	47.69 (1.86)	35.63 (1.94)	**<0.001**
	R	33.64 (1.32)	26.29 (1.38)	**<0.001**
Harmonic Ratio	AP	1.44 (0.08)	1.61 (0.09)	0.20
	ML	2.62 (0.14)	3.28 (0.14)	**<0.01**
	V	2.71 (0.16)	3.80 (0.17)	**<0.001**
RMSR	AP	0.35 (0.01)	0.36 (0.01)	0.93
	ML	0.43 (0.02)	0.44 (0.02)	0.82
	V	0.76 (0.02)	0.77 (0.02)	0.69
Jerk Ratio (dB)	AP/V	-3.98 (0.23)	-4.18 (0.24)	0.57
	ML/V	-3.44 (0.28)	-4.02 (0.30)	0.19
Step Regularity	AP	0.43 (0.03)	0.57 (0.03)	**<0.01**
	ML	-0.62 (0.03)	-0.72 (0.03)	**<0.05**
	V	0.74 (0.02)	0.86 (0.02)	**<0.001**
	R	0.57 (0.03)	0.65 (0.03)	**<0.05**
Stride Regularity	AP	0.53 (0.02)	0.68 (0.02)	**<0.001**
	ML	0.63 (0.02)	0.70 (0.02)	0.06
	V	0.74 (0.02)	0.85 (0.02)	**<0.01**
	R	0.60 (0.02)	0.65 (0.02)	0.10
Symmetry.	AP	0.87 (0.05)	0.82 (0.05)	0.52
	ML	-1.00 (0.02)	-1.05 (0.02)	0.13
	V	1.00 (0.02)	1.02 (0.02)	0.60
	R	0.98 (0.04)	1.02 (0.05)	0.59
Coefficient of Attenuation (%)				
Pelvis:Head	AP	40.12 (3.22)	42.30 (3.22)	0.66
	ML	25.37 (6.45)	10.94 (6.45)	0.14
	V	8.81 (2.52)	6.38 (2.52)	0.53
	R	26.17 (2.09)	22.07 (2.09)	0.20
Pelvis:Shoulder	AP	30.96 (4.95)	29.61 (4.95)	0.86
	ML	22.22 (4.30)	17.77 (4.30)	0.50
	V	10.48 (1.81)	3.15 (1.81)	**<0.01**
	R	22.77 (2.24)	17.30 (2.24)	0.12
Shoulder:Head	AP	11.47 (4.53)	15.43 (4.53)	0.56
	ML	3.31 (5.00)	-7.52 (5.00)	0.16
	V	-2.07 (2.03)	3.18 (2.03)	0.09
	R	4.34 (1.99)	5.23 (1.99)	0.77

Univariate analysis for group differences in upper body motion gait parameters at lumbar, trunk and forehead levels and coefficient of analysis between levels. Data are adjusted mean ± SEM. Abbreviation: AP – anteriorposterior, ML – mediolateral, V – vertical, R – resultant, RMSR – root mean square ratio, Missing data: lumbar, trunk and forehead magnitude, jerk, harmonic ratio, RMSR and jerk ratio (HC n=25); step regularity, stride regularity, autosymmetry (HC n=23)

Table 4.15: Univariate disease severity analysis adjusting for age, sex, gait speed – Upper body Motion Gait Parameters

		Healthy Control (n=23-27)	Mild Ataxia (n=7)	Moderate Ataxia (n=20)	p (Post hoc)
Lumbar					
Magnitude (ms^{-2})	AP	1.64 (0.06)	1.64 (0.11)	1.77 (0.08)	0.50
	ML	1.30 (0.07)	1.35 (0.13)	1.81 (0.09)	**<0.001**[b,c]
	V	2.08 (0.08)	2.25 (0.14)	2.40 (0.10)	0.07
	R	3.25 (0.11)	3.51 (0.19)	3.97 (0.13)	**<0.01**[b]
Jerk (ms^{-3})	AP	40.63 (2.37)	45.03 (4.21)	50.22 (2.90)	0.07
	ML	41.77 (2.76)	43.13 (4.91)	64.05 (3.37)	**<0.001**[b,c]
	V	48.80 (3.14)	58.39 (5.57)	64.71 (3.83)	**<0.05**[b]
	R	32.16 (1.81)	39.36 (3.21)	44.63 (2.21)	**<0.001**[b]
Harmonic Ratio	AP	3.31 (0.15)	3.18 (0.26)	2.23 (0.18)	**<0.001**[b,c]
	ML	2.48 (0.10)	2.49 (0.18)	1.86 (0.12)	**<0.01**[b,c]
	V	3.56 (0.12)	3.08 (0.22)	2.45 (0.15)	**<0.001**[b]
RMSR	AP	0.51 (0.01)	0.48 (0.03)	0.45 (0.02)	**<0.05**[b]
	ML	0.40 (0.01)	0.40 (0.03)	0.46 (0.02)	0.1
	V	0.63 (0.01)	0.63 (0.02)	0.60 (0.02)	0.51
Jerk Ratio (dB)	AP/V	-0.80 (0.21)	-1.05 (0.38)	-1.07 (0.26)	0.7
	ML/V	-0.60 (0.24)	-1.01 (0.42)	-0.04 (0.29)	0.2
Step Regularity	AP	0.83 (0.02)	0.79 (0.04)	0.69 (0.03)	**<0.01**[b]
	ML	-0.62 (0.03)	-0.63 (0.05)	-0.44 (0.04)	**<0.01**[b,c]
	V	0.84 (0.02)	0.80 (0.04)	0.69 (0.03)	**<0.01**[b]
	R	0.71 (0.03)	0.70 (0.05)	0.60 (0.03)	0.1
Stride Regularity	AP	0.11 (0.02)	0.80 (0.03)	0.72 (0.02)	**<0.001**[b]
	ML	0.67 (0.03)	0.63 (0.05)	0.53 (0.03)	**<0.05**[b]
	V	0.10 (0.02)	0.80 (0.03)	0.70 (0.02)	**<0.001**[b]
	R	0.78 (0.02)	0.76 (0.03)	0.66 (0.02)	**<0.01**[b]
Symmetry.	AP	1.03 (0.04)	0.99 (0.06)	0.97 (0.04)	0.67
	ML	-0.97 (0.04)	-1.02 (0.06)	-0.89 (0.04)	0.25
	V	1.04 (0.03)	1.02 (0.05)	1.00 (0.04)	0.79
	R	0.91 (0.05)	0.92 (0.08)	0.97 (0.05)	0.73
Trunk					
Magnitude (ms^{-2})	AP	1.08 (0.07)	1.06 (0.13)	1.20 (0.09)	0.60
	ML	0.99 (0.05)	1.09 (0.08)	1.31 (0.06)	**<0.01**[b]
	V	2.00 (0.06)	2.05 (0.11)	2.09 (0.07)	0.66
	R	2.64 (0.10)	2.76 (0.17)	2.99 (0.12)	0.12
Jerk (ms^{-3})	AP	25.95 (3.49)	31.11 (6.20)	38.07 (4.27)	0.15
	ML	15.80 (1.27)	20.43 (2.26)	26.32 (1.55)	**<0.001**[b]
	V	34.71 (1.98)	38.07 (3.51)	46.45 (2.42)	**<0.01**[b]
	R	25.48 (1.81)	29.48 (3.22)	36.42 (2.21)	**<0.01**[b]
Harmonic Ratio	AP	2.51 (0.09)	2.23 (0.15)	1.65 (0.10)	**<0.001**[b,c]
	ML	3.64 (0.14)	3.32 (0.24)	2.38 (0.17)	**<0.001**[b,c]
	V	4.48 (0.20)	4.10 (0.36)	2.55 (0.24)	**<0.001**[b,c]
RMSR	AP	0.40 (0.01)	0.38 (0.03)	0.40 (0.02)	0.69
	ML	0.40 (0.01)	0.42 (0.03)	0.44 (0.02)	0.2
	V	0.76 (0.02)	0.73 (0.03)	0.70 (0.02)	0.12
Jerk Ratio (dB)	AP/V	-1.51 (0.25)	-1.49 (0.45)	-0.99 (0.31)	0.48
	ML/V	-3.41 (0.22)	-2.81 (0.39)	-2.51 (0.27)	0.05
Step Regularity	AP	0.73 (0.02)	0.62 (0.04)	0.50 (0.03)	**<0.001**[b]
	ML	-0.74 (0.03)	-0.70 (0.05)	-0.56 (0.04)	**<0.01**[b]
	V	0.90 (0.02)	0.87 (0.04)	0.73 (0.02)	**<0.001**[b,c]
	R	0.78 (0.03)	0.71 (0.04)	0.56 (0.03)	**<0.001**[b,c]
Stride Regularity	AP	0.79 (0.03)	0.70 (0.05)	0.57 (0.03)	**<0.001**[b]
	ML	0.71 (0.03)	0.66 (0.05)	0.59 (0.03)	0.06
	V	0.88 (0.02)	0.84 (0.03)	0.75 (0.02)	**<0.01**[b]

	R	0.80 (0.02)	0.69 (0.04)	0.62 (0.03)	**<0.001**[a,b]
Symmetry.	AP	0.95 (0.07)	0.91 (0.13)	0.96 (0.09)	0.95
	ML	-1.07 (0.03)	-1.11 (0.05)	-0.98 (0.03)	0.09
	V	1.04 (0.02)	1.04 (0.03)	0.99 (0.02)	0.22
	R	0.98 (0.03)	1.05 (0.06)	0.94 (0.04)	0.37
Forehead					
Magnitude (ms^{-2})	AP	0.87 (0.05)	0.83 (0.08)	1.05 (0.06)	0.08
	ML	1.03 (0.06)	0.94 (0.11)	1.32 (0.08)	**<0.05**[b,c]
	V	1.92 (0.07)	2.03 (0.13)	2.14 (0.09)	0.19
	R	2.45 (0.07)	2.54 (0.12)	2.88 (0.09)	**<0.01**[b]
Jerk (ms^{-3})	AP	13.56 (1.15)	14.76 (2.04)	23.26 (1.40)	**<0.001**[b,c]
	ML	13.40 (1.44)	14.99 (2.55)	27.66 (1.75)	**<0.001**[b,c]
	V	34.51 (1.84)	39.43 (3.26)	51.99 (2.24)	**<0.001**[b,c]
	R	25.95 (1.41)	31.12 (2.50)	34.95 (1.72)	**<0.01**[b]
Harmonic Ratio	AP	1.61 (0.09)	1.42 (0.16)	1.45 (0.11)	0.44
	ML	3.32 (0.14)	2.89 (0.26)	2.48 (0.18)	**<0.01**[b]
	V	3.90 (0.16)	3.41 (0.29)	2.35 (0.20)	**<0.001**[b,c]
RMSR	AP	0.35 (0.01)	0.33 (0.03)	0.37 (0.02)	0.58
	ML	0.43 (0.02)	0.38 (0.04)	0.46 (0.02)	0.27
	V	0.78 (0.02)	0.79 (0.03)	0.75 (0.02)	0.59
Jerk Ratio (dB)	AP/V	-4.25 (0.24)	-4.48 (0.42)	-3.72 (0.29)	0.33
	ML/V	-4.14 (0.30)	-4.30 (0.52)	-3.00 (0.36)	0.07
Step Regularity	AP	0.57 (0.03)	0.46 (0.06)	0.42 (0.04)	**<0.05**[b]
	ML	-0.72 (0.03)	-0.64 (0.05)	-0.61 (0.03)	0.06
	V	0.87 (0.02)	0.83 (0.04)	0.69 (0.03)	**<0.001**[b,c]
	R	0.66 (0.03)	0.67 (0.05)	0.51 (0.03)	**<0.01**[b,c]
Stride Regularity	AP	0.68 (0.03)	0.54 (0.04)	0.52 (0.03)	**<0.001**[a,b]
	ML	0.70 (0.03)	0.61 (0.04)	0.64 (0.03)	0.16
	V	0.86 (0.02)	0.83 (0.04)	0.70 (0.02)	**<0.001**[b,c]
	R	0.67 (0.02)	0.67 (0.04)	0.56 (0.03)	**<0.05**[b]
Symmetry.	AP	0.83 (0.05)	0.91 (0.09)	0.85 (0.06)	0.73
	ML	-1.06 (0.03)	-1.05 (0.04)	-0.97 (0.03)	0.11
	V	1.02 (0.02)	1.01 (0.04)	1.00 (0.03)	0.82
	R	1.02 (0.05)	1.01 (0.08)	0.97 (0.06)	0.8
Coefficient of Attenuation					
Pelvis:Head	AP	42.88 (3.29)	44.87 (6.07)	37.68 (4.17)	0.59
	ML	11.25 (6.63)	27.91 (12.25)	24.06 (8.43)	0.34
	V	6.38 (2.60)	8.85 (4.80)	8.79 (3.30)	0.82
	R	22.01 (2.15)	25.73 (3.98)	26.40 (2.74)	0.44
Pelvis:Shoulder	AP	30.08 (5.08)	34.74 (9.39)	29.01 (6.46)	0.88
	ML	17.12 (4.40)	16.92 (8.12)	24.96 (5.59)	0.59
	V	2.84 (1.85)	7.92 (3.41)	11.80 (2.35)	**<0.05**[b]
	R	5.48 (2.04)	6.45 (3.76)	3.25 (2.58)	0.77
Shoulder:Head	AP	15.76 (4.65)	14.19 (8.60)	10.06 (5.91)	0.79
	ML	-6.22 (5.05)	13.95 (9.33)	-2.17 (6.42)	0.15
	V	3.50 (2.07)	0.56 (3.83)	-3.42 (2.63)	0.18
	R	5.48 (2.03)	6.45 (3.76)	3.25 (2.58)	0.77

Data are adjusted mean ± SEM. Abbreviation: AP – anteriorposterior, ML – mediolateral, V – vertical, R – resultant, RMSR – root mean square ratio. Univariate analysis for differences between disease subgroups with post hoc tests for upper body motion gait parameters at lumbar, trunk and forehead levels and coefficient of analysis between levels a: healthy control vs mild ataxia b: healthy control vs moderate ataxia c: mild ataxia vs moderate ataxia. Missing data: lumbar, trunk and forehead magnitude, jerk, harmonic ratio, RMSR and jerk ratio (HC n=25); step regularity, stride regularity, autosymmetry (HC n=23).

Figure 4.5: Key results presented as Z Scores
Z scores computed for between-group differences and group differences adjusted for sex, age and gait speed for spatiotemporal gait characteristics and upper body Motion Gait Parameters.
Abbreviations: HR Harmonic Ratio, AD1 Step regularity, AD2 Stride Regularity, AP anteroposterior, ML mediolateral, V vertical, R resultant.

Table 4.16: Between parameter correlations upper body motion vs spatiotemporal gait parameters

				Asymmetry		Variability						
			Step Width	Cadence	Stride Time	Speed	Cadence	Stride Time	Step Time	Stride Length	Step Length	Stance Time
Lumbar	Harmonic Ratio	AP	**-0.396***	0.218	0.146	-0.329	0.034	-0.012	-0.010	**-0.433***	**-0.447***	-0.042
		ML	0.052	0.049	0.051	-0.321	-0.041	-0.055	-0.081	-0.361	**-0.431***	-0.125
		V	**-0.420***	0.006	-0.093	-0.260	-0.152	-0.207	-0.199	-0.320	**-0.447***	-0.245
	Step Regularity	AP	**-0.405***	0.202	0.071	-0.308	-0.083	-0.141	-0.050	-0.324	-0.266	-0.132
		ML	0.047	-0.209	-0.142	0.151	-0.067	-0.009	-0.038	0.277	0.285	-0.038
		V	-0.212	0.080	0.015	-0.224	-0.170	-0.241	-0.260	-0.215	-0.380	-0.178
	Stride Regularity	AP	**-0.492***	0.066	-0.104	-0.366	-0.095	-0.171	-0.124	**-0.474***	**-0.460***	-0.281
		ML	-0.149	0.060	-0.029	-0.210	0.010	-0.054	-0.031	**-0.397***	-0.356	-0.075
		V	-0.291	-0.018	-0.093	-0.219	-0.168	-0.259	-0.325	-0.309	**-0.433***	-0.240
		R	**-0.397***	-0.029	-0.142	-0.368	-0.078	-0.120	-0.102	**-0.492***	**-0.635****	-0.205
Trunk	Harmonic Ratio	AP	-0.367	-0.065	-0.092	**-0.435***	-0.247	-0.242	-0.227	**-0.463***	**-0.560****	-0.322
		ML	0.119	-0.035	-0.003	-0.126	0.188	0.171	0.009	-0.190	-0.199	0.069
		V	-0.156	-0.137	-0.104	-0.382	-0.266	-0.299	-0.338	**-0.416***	**-0.411***	-0.314
	Step Regularity	AP	-0.385	-0.061	-0.159	-0.220	-0.105	-0.132	-0.026	-0.318	-0.376	-0.117
		ML	-0.187	0.028	-0.040	-0.148	-0.155	-0.251	-0.292	-0.269	**-0.429***	-0.176
		V	-0.124	-0.187	-0.277	-0.280	-0.110	-0.168	-0.160	**-0.430***	**-0.476***	-0.303
	Stride Regularity	AP	**-0.568****	-0.111	-0.281	-0.312	-0.122	-0.170	-0.081	**-0.513****	**-0.449***	-0.250
		ML	-0.347	-0.029	-0.155	-0.144	-0.155	-0.263	-0.277	-0.320	**-0.417***	-0.240
		V	-0.199	-0.226	-0.349	-0.264	-0.163	-0.222	-0.151	**-0.426***	**-0.390***	-0.315
Forehead	Smoothness	AP	**0.404***	-0.230	-0.096	0.104	-0.067	0.034	0.034	0.257	0.261	-0.014
		ML	0.263	-0.385	-0.298	0.168	-0.130	-0.073	-0.064	0.240	0.162	-0.082
	Harmonic Ratio	V	**-0.395***	0.198	0.155	-0.351	-0.051	-0.088	-0.186	**-0.427***	**-0.469***	-0.179
	Step Regularity	V	-0.214	0.303	0.211	-0.142	-0.018	-0.077	-0.112	-0.148	-0.271	-0.083
		R	-0.376	0.100	0.013	**-0.444***	-0.021	-0.074	-0.193	**-0.529****	**-0.552****	-0.305
	Stride Regularity	AP	-0.162	-0.236	-0.303	-0.205	-0.250	-0.237	-0.117	-0.240	-0.106	-0.328
		V	-0.350	0.138	0.006	-0.206	-0.038	-0.115	-0.147	-0.281	**-0.432***	-0.176

Correlation matrix for spatiotemporal gait characteristics compared with upper body motion variables. * p<0.05, ** p<0.01, Orange highlight = r>0.5 or r<-0.5. Abbreviations: AP-anteroposterior, ML-mediolateral, V-vertical, R-resultant

4.4. DISCUSSION

This observational study examines the gait characteristics exhibited by individuals with CA as well as healthy controls. Spatiotemporal and upper-body motion characteristics of gait (as validated in Chapter 3) were measured synchronously. We also examined their association with established measures of disease severity (Scale for Assessment and Rating of Ataxia, SARA) and falls risk (Berg Balance Scale, BBS).

4.4.1. PARTICIPANT CHARACTERISTICS

The cohorts were matched for age, and no significant differences were observed in body structure characteristics (height, mass, leg length). Upon clinical assessment, UMN signs such as spasticity were common among the ataxic participants, but no participants showed signs of cognitive impairment. Patient SARA scores reflect a relatively mild phenotype in this cohort with all patients capable of independent gait but some reliant on walking aids in daily life. $SARA_{gait\&posture}$ score indicates that the participants within the CA cohort all exhibited some gait and posture related signs and the moderate ataxia subgroup had worse gait and posture subscores than the mild ataxia severity subgroup. Meanwhile, BBS scores indicate that the patient cohort has a low risk of falls, with the moderate disease severity subgroup at a greater risk of falls than the mild disease severity subgroup.

4.4.2. GAIT ASSESSMENT

Gait analysis included assessment of spatiotemporal gait parameters from a photoelectric system and evaluation of upper body motion parameters using IMUs during the straight-line, steady-state phase of walking trials.

4.4.2.1. Validity of Data Collection

Validation of system synchronisation was completed to explore the influence of older age and disease severity on system accuracy. The detection of initial contact and final contacts associated with heel strike and toe-off gait events was associated with a high discriminant and concurrent validity. There was a high correlation in all measures (ICC(2, 1) (95% CI)) and small absolute System Difference and System Difference). Here we verified that gait events are detected by the OptoGait and ADPM Opal sensors at an accuracy of <0.1s (Table 4.6, Figure 4.3). This is in the order of previous results (Chapter 3) where the OptoGait and ADPM Opal sensors were compared to the Vicon 3D Motion Capture system.

High agreement was also observed between systems in step time, stride time or stance time. The OptoGait system was configured in reference to manufacturers recommendations (3 LED in/out). A recent publication has indicated that LED thresholds do not need to be as stringent as these recommendations (Healy et al., 2019), however, gait events detected here were within acceptable ranges and showed good precision between systems. Upon examination of the relationship between system differences and measured values for gait events and gait parameters for healthy and ataxic participants (Figure 4.3, Figure 4.4), data points did not appear to cluster by cohort. This indicates that the accuracy of gait event detection and gait parameter calculation was not confounded by diagnosis of ataxia.

4.4.2.2. Spatiotemporal Gait Parameters

Overall, the preferred paced walking of the patient cohort appears to be a lower velocity than the preferred paced walking of the control cohort. Similar to previous findings, (Chapter 2), the ataxic cohort exhibit a shorter step and stride length compared with controls. Step width was larger in ataxic participants on average, reflecting the hallmark characteristic of ataxia (Stolze et al., 2002). In humans, an individual's step width is selected in order to minimise the metabolic cost of walking (Donelan et al., 2001). In people with PD, step width is increased in challenging walking tasks incorporating different surfaces (Caetano et al., 2009).Therefore, in Ataxia, the increase in step width reflects the participant's preference to expand their base of support due to gait instability. Temporal parameters were not significantly affected between cohorts in our study in unadjusted statistical analysis. Gait variability, relates to the accuracy of foot placement during walking. Here, in the ataxic group, average variability (%CV) is higher in the majority of gait parameters compared with the controls, which corroborates findings across the published literature (Ebersbach et al., 1999, Gouelle et al., 2013, Ienaga et al., 2006, Palliyath et al., 1998, Schmitz-Hübsch et al., 2016, Schniepp et al., 2014, Serrao et al., 2012). An increased asymmetry was also observed in cadence, stride time, swing time and SLS time as well as swing phase perc. and SLS phase perc. in the CA cohort. This may reflect asymmetrical weakness and spasticity, which commonly affects people with CA.

4.4.2.3. Upper body Motion Gait Parameters

Meanwhile, as postural motion data and spatiotemporal gait parameters have been acquired in synchronisation it is possible to explore specific biomechanical interactions in CA. Here in an ataxic cohort, we have observed significantly lower vertical RMS acceleration signal at the trunk and increased ML RMS acceleration signal at the trunk and forehead. These changes reflect a reduced intensity of trunk rotation and increased intensity of flexion/extension motion during walking gait. Fazio et al. (2013) described a lower RMS resultant acceleration at the lower back in 24 ataxia patients compared with 24 healthy controls. Shirai et al. (2015) meanwhile, observed significantly increased ML and reduced vertical and AP RMS acceleration at the lower back and upper back in 25 patients with spinocerebellar degeneration compared with 25 healthy controls. Hickey et al. (2016) also identified that increased ML accelerations in the upper body during gait correlated with disease severity in individuals with mild to moderate ataxia.

Changes in harmonic ratio indicate that people with ataxia exhibited greater step to step asymmetry and reduced rhythmicity of AP, ML and vertical acceleration components at the lumbar and trunk sensors and the ML and vertical components at the forehead. This implies that ataxic individuals display lower stability of the upper body segment during walking compared with healthy controls. This corroborates recent findings during lab-based, supervised free and real-life walking in ataxia using a single waist-worn sensor (Ilg et al., 2019).

Autocorrelation analysis indicates that step and stride regularity were significantly impaired in ataxia across all three signal components and the resultant signal at all three sensor positions compared with controls. Here, our ataxia cohort compared with healthy individuals also displayed a significantly increased body sway (RMSR) in ML axis and reduced in vertical component at all 3 sensor positions and increased body sway in AP axis at the head. Matsushima et al. (2015) reported that in gait tests with a waist-worn triaxial accelerometer, people with CA exhibit lower step regularity in AP and vertical axis as well as increased body sway (RMSR in ML axis).

Attenuation of upper body oscillations during walking gait is vital to ensure an efficient locomotion (Mazza et al., 2008). Our results indicate that people with ataxia display less effective attenuation of AP accelerations pelvis to trunk and trunk to head causing

increased lateral bending of the trunk during walking gait. Further, while ML accelerations are consistently increased throughout the upper body in ataxia relating to uncontrolled trunk flexion, vertical direction accelerations appear to display an impaired coupling of the trunk segments resulting in increased rotation of the upper trunk but not the pelvis or forehead. This builds on the work from Conte et al. (2014) who recognised, in motion capture studies, that people with ataxia, during walking is characterised by increased forward flexing, lateral bending and rotation.

In our cohort of people with CA, jerk signal was significantly increased in the ML axis at the trunk and forehead and in the AP axis at the forehead. Although vertical jerk is inherently associated with gait speed, the slower ataxic cohort did not exhibit significant differences at any level of the lower back. Further, using Jerk Ratio as a speed-independent measure of stability, the CA cohort was significantly higher in ML/V ratio at all three sensor positions and in AP/V ratio at the forehead. Again this reflects impaired control of postural gait changes in this cohort. Fazio et al. (2013) described lower RMS jerk values in ataxia patients at the thoracic level therefore, these differing results may indicate there may be differences between study participants and gait tests.

4.4.3. GAIT INFLUENCES

In the present study, a number of gait metrics show good correlations with the SARA as a measure of disease severity. Meanwhile, in subgroup analysis, in terms of the spatiotemporal gait parameters, the mild ataxia group, appears to form an intermediate phenotype, characterised by a reduction in stride length, step length, and increase in step width compared with healthy controls. For speed and many asymmetry measures, the mild ataxia group remains in line with control cohort results while differentiating from the moderate ataxia group. A number of temporal gait variability measures display a significant difference between disease severity subgroups and healthy controls. This indicates that increased gait variability may be an early gait change in CA that is further worsened with disease severity. These variables retained significant differences when adjusted for age, sex and gait speed in univariate analysis.

For the upper body motion measures extracted from the acceleration signals, the Mild Ataxia cohort also appears to form a phenotype intermediate to the Healthy and Moderate Ataxia cohorts particularly in the HR_V measured at Lumbar position. Therefore, changes to

rhythmicity of gait may represent an early indicator of ataxia. However, the Moderate Ataxia group differentiates from the Mild Ataxia and Healthy cohorts in many other variables, independent of gait speed. In particular, HR_{AP} at lumbar and trunk, HR_{ML} lumbar and trunk, HR_V at lumbar, trunk and forehead; AD1 and AD2 lumbar in AP, ML, vertical and R, trunk in AP, vertical and R, and forehead in vertical and resultant components. Therefore, increased severity of ataxia is associated with an exacerbation of rhythmicity and regularity. Since these variables are able to distinguish between mild and moderate ataxia independent of changes in gait speed, they may show promise as robust biomarkers of disease progression in future work.

4.4.4. CLINICAL CONTEXT OF FINDINGS

Here we hypothesised that disease-related differences (disease severity and genetic diagnoses) in upper-body motion during gait would complement spatiotemporal gait parameters.

Analysis of trunk stability in walking gait has proven to be an interesting area of research in PD and Multiple Sclerosis but is not yet established in CA research and clinical practice. Spatiotemporal gait changes in individuals with CA are a form of compensation for trunk instability (Bunn et al., 2013), therefore assessing the two aspects of gait in synchronisation is highly advantageous to the research community.

Our results also indicate the advantage of performing instrumented gait analysis over un-instrumented alternatives such as the timed-up and go or six-minute walk test. These alternative walking tasks can obtain information regarding gait speed and exercise capacity which can indicate a disability. However, they do not have the temporal resolution to characterise gait changes on a stride by stride basis. This limits their use as an objective biomarker for disease severity.

To the best of our knowledge, very little investigation of head motion during walking gait in CA has previously been reported. In this cohort, jerkiness, rhythmicity and regularity of the head motion, correlate well with clinical measures, differentiate healthy controls from people with ataxia and mild severity ataxia from moderately severe ataxia. The differential findings from the trunk and head measurements indicates a potential uncoupling of the neck and shoulders in people with CA.Therefore, there may be additional value in including

these measures in the gait assessment protocol and this should be considered when designing future studies.

Since we have not formally assessed neurological impairments through neuroimaging techniques such as MRI or CT, it is not possible to draw direct correlation between gait impairments and physical abnormalities in the brain. However, previous studies have identified atrophy and lesions in the brains of individuals with ataxia and compared gait characteristics in different neurological conditions. For instance, since the lateral cerebellum receives visual input to plan stepping during walking, lesions in this region lead to foot placement issues (Cerminara et al., 2005, Walker HK, 1990). While we have observed this phenomenon in our spatiotemporal gait parameters such as gait variability, the upper body motion parameters add detail about the impact of stepping on postural control during gait. Here, in people with cerebellar ataxia, gait instability was objectively measured as uncontrolled forward flexing, and lateral bending as well as increased gait variability. This may be a result of a un/conscious compensation for loss of coordination during walking or part of the clinical manifestation of ataxia. Differentiating between compensatory responses and pathological gait changes is essential to the development of gait as a biomarker for disease severity and balance performance. While for some variables, the mild ataxia cohort values are in line with the healthy control group for other results, the mild ataxia group show an intermediate phenotype with respect to the control and moderate ataxia group. Variables that distinguish early ataxia from healthy controls, as well as those distinguishing mild from moderate ataxia, have potential as biomarkers of disease progression. Our findings were further explored by univariate analysis including age, sex and gait speed as covariates. Many variables retained significant differences between cohorts and disease severity subgroups demonstrating that these findings are independent of age, sex and gait speed. This is particularly important as many gait variables exhibit considerable interdependency especially with gait speed (Hebenstreit et al., 2015).

In ataxia, reduced intersegmental coordination, instability of walking and increased frequency of falls are common especially during slow-paced walking (Schniepp et al., 2016). The Berg Balance scale (BBS) was developed as a marker of falls risk and balance performance. Here, many variables correlate with a reduced BBS score: speed, cadence, step width and gait variability measures are especially correlated with the BBS score as well

as asymmetry, and regularity of upper body motion. To enable efficient walking gait, a level of variability is necessary to be able to adapt to a changing environment. This gait variability is consistent amongst young and older adults (Herssens et al., 2018) but increased variability can be a measure of gait instability and related to an increased risk of falls (Hausdorff et al., 2001b). Meanwhile, a systematic review of falls in PD indicates that non-fallers display a lower ML and V motion at head and pelvis (Creaby and Cole, 2018). Meanwhile, the literature also indicates that AP gait stability also correlates with a history of falls (Chini et al., 2016). Previous studies have shown that harmonic ratios of the head are associated with fall risk (Menz et al., 2003) in healthy individuals. Although many of the cohort differences correlate with BBS scores, we were not able to corroborate this in the present ataxia cohort since a detailed falls assessment was not undertaken.

In the present study, people with ataxia walked significantly slower than healthy controls and many spatiotemporal and variability gait parameters correlated with gait speed similar to previous studies (Wuehr et al., 2013). Our findings from linear regression analyses incorporating gait speed as a confounding variable, indicate that the ataxic gait pattern is not just a result of the change in gait speed. Therefore, our findings suggest the additional value of implementing an instrumented gait test rather than clinical rating scales and un-instrumented alternatives where only gait speed and exercise capacity are measured objectively.

Meanwhile, partial correlation analysis indicates that independent of gait speed, step width, step length variability and stride length variability show negative correlations with postural control variables. These results suggest that asymmetry of truncal lateral bending, the stride regularity of truncal lateral bending and lumbar motion, and step regularity of overall forehead motion are associated with increased spatiotemporal gait impairment.

Looking forward to longitudinal assessment many gait characteristics and quality parameters are able to characterise disease severity in the patient cohort and distinguish mild ataxia from healthy controls. For instance, speed, step width, variability, attenuation, postural symmetry, and regularity measures show differences between disease severity subgroups and many correlate with BBS score. Therefore, these parameter(s) have the potential to detect subtle gait changes as a result of disease progression over time.

4.4.5. LIMITATIONS

Some data within trials were excluded due to technical difficulties with data capture and/ or analysis software and as such the results reported here reflect fewer steps within trials than were originally captured. Despite completing visual checks at the time of assessment and taking precautions to ensure data validity, some issues with the technique persisted, particularly for the OptoGait. For instance, occasional steps were identified as having an invalid flight time and other steps were overlooked by the built-in algorithm. As much data was retained as possible by removing sections or passes of walking trials where issues were identified so that outcomes were provided for every participant.

It should also be noted that despite clear instructions to wear flat-soled outdoor shoes, differences in participant's footwear will inherently influence gait (Franklin et al., 2015). In addition, since our ataxic participants needed to be comfortable completing walking tests unaided, our findings are only generalisable to a relatively mild phenotype. Meanwhile, small differences in the walkway length (<1m) may have occurred with repeated assessment sessions and changing venues although an effort was made to keep the system as similar as possible.

A previous sample size estimate based on the previous literature suggested that the cohort of 27 people with ataxia and 27 healthy control participants recruited in this study would be sufficient for the spatiotemporal characteristics. As a consensus gait pattern has not been established for the upper body motion characteristics a sample size calculation for these was not possible. However, effect size estimation based on the results of this study, indicate that a larger cohort is still needed to confirm these findings and we may not have reached significance. Therefore, these findings should be considered preliminary and warranting further study in a larger cohort.

It is also possible that individual characteristics such as disease features, and sex disparity have influenced the ability to observe between-cohort differences. The inclusion/exclusion criteria restricted recruitment to individuals that were capable of walking unaided for the purpose of the testing. Although some participants did report use of walking aids in their daily life, the recruited cohort of people with ataxia inherently exhibit a mild phenotype. This will limit the generalisability of these results to the wider ataxia population. Differences in gait due to sex have been previously explored in healthy individuals (Mazzà

et al., 2008). While, there is no conclusive indication of sex influencing ataxia onset and symptoms, it is important to recognise that in the present study, recruitment was not controlled on the basis of sex resulting in 37.0% and 59.3% females in CA and HC cohorts respectively. Therefore, some differences between cohorts may exist due to the disparate male: female ratio and should be considered in future work. However, univariate analysis with age, sex and gait speed as covariate factors was completed in an attempt to control for these confounding variables and our key findings are reported independent of these factors.

In addition, due to the limited number of participants recruited, subgroup analyses to investigate the influence of disease diagnosis was not completed at this time. The most prevalent genetic diagnoses recruited were spinocerebellar ataxia 6 (SCA6) which is considered a "pure" cerebellar ataxia, and spastic paraplegia 7 (SPG7) which is primarily characterised by weakness and spasticity but is associated with ataxia. Due to the clinical differences between the syndromes, it is possible that there are underlying differences in the pathology which could impact the gait pattern. This limitation will be investigated further in the future.

As established in Chapter 3, the OptoGait and ADPM Opal sensors systems have a limit to their precision and accuracy. Although the agreement between the two systems was less than in the validation study, values for gait event detection and gait parameter calculation correlate well and are within reasonable ranges. Our measurement of step width in particular should also be interpreted with care since validation study indicated that a systematic bias (±3.76cm, 95%LoA) is present in the estimation. Previous findings have indicated that slow walking can interfere with the accuracy of gait event detection using inertial sensors (Feng et al., 2017). Although this was not explicitly explored here, despite the slow walking speed exhibit by people with CA and healthy control participants, our validity findings are comparable to others (Pacini Panebianco et al., 2018). In addition, Bland-Altman plots did not indicate that ataxia cohort membership leads to inaccurate gait event detection and gait parameter calculation compared with healthy controls. Gait speed has a large influence on many gait parameters. Although our additional analysis allows us to explore group differences while using gait speed as a covariate, further work may explore the influence of speed changes on the gait pattern further.

In addition, a large number of gait variables were explored in this study. This was intended to avoid restricting the hypotheses to variables that have already been reported and allow a holistic view of the gait pattern to be assembled. However, as already discussed many aspects of the gait pattern are fundamentally interrelated and associated with gait speed in particular. Therefore, it is important to subsume variables where possible and to be informed by the clinical features of a movement disorder. This will be considered going forward in the selection of gait variables for longitudinal assessment in a subset of participant and for future clinical use. For instance, while gait speed has been selected for further consideration, cadence and step/ stride time have not due to their interdependency. In addition, while overall trunk motion can be reflected in the resultant values for gait measures, the clinical value of individual components will also be considered in future work. Partial correlation analysis also indicated that step variability, stride variability and step width show interdependence with postural asymmetry, stride regularity and step regularity. Therefore, further work is required to explore if these spatiotemporal gait parameters are interchangeable with postural control variables and which variables are most relevant to patient stratification in ataxia. Further work is also required to explore these variables with respect to a detailed falls assessment.

4.5. CONCLUSION

Here ataxic gait is characterised by excessive sagittal, lateral and vertical oscillations as well as insufficient coordination between the upper and lower body segments. Speed, step width, gait variability as well as step to step asymmetry, step regularity and stride regularity all show promise as biomarkers of gait ataxia. In individuals with CA, spatiotemporal gait changes such as increased step width and gait asymmetry appear to be a form of compensation for lateral instability. This indicates the advantage of assessing the two aspects of gait in synchronisation.

Since some spatiotemporal gait variables may be interchangeable for postural control variables, further work in a larger cohort is required to validate the ability of these variables to classify ataxic gait through multivariate regression analysis. Patients with a pre-symptomatic/mild ataxia phenotype can be differentiated from more severely affected patients and healthy controls using gait as a biomarker. Further work is required to examine

longitudinal gait changes in ataxia over time and to expand examination of differences between disease diagnoses and falls history.

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Chapter 5. Gait Analysis For The Longitudinal Assessment Of Hereditary cerebellar ataxia

5.1. Introduction

Presently, in the clinical care of people with cerebellar ataxia (CA), clinicians rely on clinical assessment tools to measure an individual's disease severity and disease progression. In CA, slowly progressing neurodegeneration causes damage to the cerebellum and worsening incoordination and balance performance. The rate of progression can vary between individuals and specific ataxia diagnoses (Schmitz-Hübsch et al., 2016). This limited ability of current rating scales to monitor symptom changes over short-term periods indicates their unsuitability to measure the effect of interventions and treatment.

Very few longitudinal studies have explored objectively measured gait changes over time in adult ataxia and have so far provided inconsistent results (Milne et al., 2018). For instance, in a cohort of 18 individuals with degenerative and static cerebellar damages, although stance time percentage and step width correlated with International Cerebellar Ataxia Rating Scale (ICARS) scores, no significant changes were observed over a 12 month period (Morton et al., 2010). In a 4-year follow-up study meanwhile, gait decline was quantified as reduced step length and hip, knee, and ankle joint RoM and increased trunk rotation range of motion (RoM) as well as stride length and step length variability (Serrao et al., 2017a). A study of postural stability during gait and standing indicated that autocorrelation and Root Mean Square Ratio may also have potential in the longitudinal assessment of cerebellar disease (Matsushima et al., 2015). Previous studies in Friedrich's Ataxia, indicated that gait velocity and double limb support percentage as well as swing/stance percentage gait cycle and knee range of movement are particularly promising in measuring disease progression (Vasco et al., 2016, Zesiewicz et al., 2017). Since gait velocity has been proposed as a 6th vital sign (Fritz and Lusardi, 2009), it follows that gait impairment over time may manifest as reduced gait speed.

Reliable normative values for spatiotemporal parameters and upper body motion are needed and establishing the degree of change in gait parameters that reflect genuine disease progression is vital to distinguish the pattern of gait disturbances for different movement disorders (Hollman et al., 2011). Therefore, gait analysis techniques potentially provide a measure that can be monitored over time better than current clinical methods.

We have previously established gait pattern in CA during the systematic review (Chapter 2) and baseline assessment (Chapter 4) and the gait analysis system accuracy through the study of gait event detection in healthy individuals (Chapter 3) and people with CA (Chapter 4). In this previous work, people with CA walk with reduced gait speed, increased step width and increased gait variability while postural symmetry and regularity are also impaired. Since these measures show sensitivity to disease severity and correlate with clinical measures of balance impairment, here we explore these variables in the context of a longitudinal study.

5.1.1. AIMS AND HYPOTHESIS

This study aimed to identify spatiotemporal and upper-body gait characteristics capable of objectively quantifying gait changes over 12 months period in people with CA and examine whether this relates to disease progression. A second follow-up visits was intended to be completed at 24 months to examine a longer disease course.

In our previous study (Chapter 4) many gait measures were sensitive to disease severity, therefore these variables may also show promise in measurement of disease progression. We hypothesise that spatiotemporal and upper body motion characteristics may be able to recognize disease progression in an ataxic cohort.

5.2. METHODS

5.2.1. STUDY INFORMATION

This longitudinal study of gait characteristics in cerebellar ataxia is incorporated by “Gait Analysis in Cerebellar Ataxia and Hereditary Spastic Paraparesis”, which is sponsored by the Sheffield Children’s Hospital. This project aims to detect subtle gait characteristics of ataxia. This study was conducted, according to the Declaration of Helsinki, and received ethical approval by the North West - Liverpool East Research Ethics Committee (REC: 16/NW/0343). Local approvals were obtained from the Sheffield Children’s Hospital as study sponsor and the Sheffield Teaching Hospitals Trust as the site of data collection (SCH2048 and STH19282). All testing took place at the Clinical Research Facility at the Northern General Hospital, Sheffield. All participants signed an informed consent form.

5.2.2. PARTICIPANTS

Ataxic participants enrolled in the Clinic-based gait analysis study (Chapter 4) were invited to attend follow-up assessments (1) 12-18 months after their baseline assessment and (2) a further 12-18 months after their 12 month follow-up if this occurred within the data collection period. If they were no longer able to complete the gait analysis tasks unaided, they did not complete in any further assessments. Follow-up assessments visits took place between November 2017 and December 2018. Therefore, some participants did not reach their follow-up assessment date within this time period. Details of participant attrition rate provided in section 5.3.1.

5.2.3. PROTOCOL

Follow-up assessments took place at 12-18 months later and at 24-28 months following baseline assessment. Participants underwent the same protocol as at baseline in order to be consistent in our gait assessment methods. Usual clinical care was not examined within this study and no change was made during the follow-up period to care received. A structured medical interview and clinical examination completed (Appendix 14) with recent falls history, and upper motor neuron signs of lower limb spasticity (clonus, spastic limbs, and hyperreflexia) were noted. Validated rating scales were also completed: Montreal Cognitive Assessment (MoCA, Nasreddine et al., 2005), Berg Balance Scale (BBS, Berg et al., 1995), and the Scale for Assessment of Ataxia (SARA, Schmitz-Hübsch et al., 2006). The $SARA_{Gait\&Posture}$ subscore was calculated (Lawerman et al., 2017). For individual changes in the SARA score, a minimal detectable change (MDC) considered as <3.5 (Schmitz-Hübsch et al., 2010).

Participants performed a short gait task, at a self-selected speed. The OptoGait photoelectric 5m gait analysis system with Boosted transmission bar was implemented (Microgate Corporation, Bolzano, Italy) while wearing five ADPM Opal triaxial inertial sensors (APDMInc, Portland, OR, USA) (see Section 4.2.4 for further information on equipment used).

5.2.4. EQUIPMENT

As discussed in Chapter 4, gait analysis was performed on participants using two gait analysis systems: the OptoGait LED array system (Microgate Corporation, Bolzano, Italy)

and the ADPM Opal system of triaxial inertial sensors (APDMInc, Portland, OR, USA). Equipment was set up in the same synchronised way as at baseline assessment (Chapter 4).

All data gathered for the purposes of the study was backed up to an encrypted external hard drive and stored in a locked cupboard within the Sheffield Institute for Translational Neuroscience, the University of Sheffield alongside completed study report forms. Signed consent forms were stored within the site file in the possession of Dr McNeill and lists of recruited participants maintained regularly.

5.2.5. DATA ANALYSIS

5.2.5.1. Spatiotemporal Gait Parameters

The gait events that were automatically detected by the OptoGait system were verified visually and trial results exported to Microsoft Excel. Only footfalls where both heel strike and toe-off were considered to begin within the system were included to ensure accurate detection of initial and final contact events for calculation of gait parameters.

Spatiotemporal gait parameters selected in Chapter 4 and therefore used here include measurement of speed (m/s), step width (cm), cadence asymmetry (steps/min), stride time asymmetry (s) and variability of a number of these measures (%CV). For further explanation of gait parameters, see Figure 1.1.

The within-person variability of spatiotemporal gait parameters was considered through the calculation of the coefficient of variation (CV, expressed as a percentage) (Equation 5.1).

Equation 5.1: $\text{Coefficient of Variation } (\%) = {}^{\text{S}}/_{\text{mean}} \times 100$

Meanwhile, computing left-right asymmetry (Equation 5.2) from absolute difference of mean gait measures recorded for left and right feet enables an appreciation of step to step differences (Godfrey et al., 2015).

Equation 5.2: $Asymmetry = \left[mean_{Left} - mean_{Right}\right]$

5.2.5.2. Upper body Motion Gait Parameters

As described previously, motion inertial data was analysed using MATLAB (Mathworks Inc., Natick, MA, USA) through custom computational programmes (Section 4.2.5.2). Trial data were segmented into single passes and gait events detected from the left and right ankle angular velocity signal following the method used by Salarian et al (2004).

A number of upper body motion variables were selected on the basis of univariate analysis of baseline gait results incorporating age, sex and baseline analysis as covariate factors (Chapter 4). Computational analysis of acceleration signals included: Root Mean Square (RMS) of accelerations (at each of the three levels) (Helbostad and Moe-Nilssen, 2003), Harmonic Ratio (Latt et al., 2008), RMS Jerk (also at the three levels, (Brodie et al., 2014, Fazio et al., 2013)). Auto-correlation coefficients for step and stride durations were computed for each pass for each walking trial (Moe-Nilssen and Helbostad, 2004). Details of the analysis of motion at the head, trunk and pelvis levels can be found in Table 4.1.

Descriptive analysis of upper-body gait parameters was then completed per participant in MATLAB prior to export in preparation for cohort statistical analysis.

5.2.6. STATISTICAL ANALYSIS

Descriptive analysis (average and standard deviation) was completed for demographic characteristics. Participant level summary of gait measures were assembled into a single data table for cohort level statistical analysis (SPSS Statistics (version 23, IBM)).

To appreciate changes in gait measures at 12 month follow-up, descriptive analysis was also completed for spatiotemporal gait characteristics and upper body measures to compare between study visits for the ataxia cohort. Normality of the datasets was tested using Shapiro Wilks tests, then between-visit differences assessed through paired t-tests and Wilcoxon non-parametric paired samples test. A significance level assumed at p value<0.05. The effect size was calculated based on the results of paired samples test as Cohen's *d* (Equation 5.3) where paired difference calculated as baseline – 12month result. The threshold thresholds of 0.1, 0.3, and 0.5 were recommended by Field (2018) for small, medium, and large effect sizes, respectively.

$$\text{Equation 5.3: Effect Size} = {}^{\text{Paired mean difference}}/_{\text{SD paired differences}}$$

Paired samples correlation coefficients are also reported to indicate agreement between partcipants. To explore how disease severity correlates with gait change over 12month period, paired samples correlation tests were completed for change in SARA and change in gait measures. For parameters that achieved a large effect size, individual results were plotted against SARA score at each timepoint.

Due to the small number of participants that completed 24 month follow-up, no formal analyses were completed. As an exploratory examination of the trends, the results for parameters that achieved a large effect size were plotted to appreciate any intra-individual differences.

5.3. RESULTS

5.3.1. PARTICIPANT RETENTION

Of the 27 ataxic participants recruited to the study at baseline, 16 completed their 12-month follow-up within the data collection period at 12.8±1.8months after baseline. Two participants were not able to complete gait tasks unaided due to disease progression, 1 participant was not well enough to attend so withdrew from further participation. Three participants chose not to return for follow-up assessment (n=3). For 5 participants recruited to the study, due to the timing of their baseline assessments, their 12-month follow-up visit was not due until following the end of the data collection period.

A subgroup of 5 participants also completed their 24month follow-up at 12.1±0.2months after their 12-month visit. No other participants reached their follow-up assessment date within the data collection period.

5.3.2. PARTICIPANT CHARACTERISTICS

The participant demographics for the individuals who completed at 12 month and 24month follow-ups are detailed in Table 5.1.

16 participants (7 female) completed 12-month follow-up assessments. 5 Participants also completed a 24month follow-up assessment (approx. 12 months following 2nd visit). No significant difference was observed in SARA, MoCA and BBS between visits 1 to 2 and visits 1 to 3. For individuals, change in SARA score greater than the MDC <3.5 did not occur in any of the individuals that completed 12 month or 24-month follow-up. Therefore, for the cohort on the whole, the disease status was stable within this time period and no disease progression occurred.

The 5 participants who were able to complete 24 month follow-up displayed a less severely affected subgroup of the cohort assessed at 12 month follow-up as indicate by a lower average SARA score and $SARA_{Gait\&Posture}$ subscore as well as better balance performance (higher BBS score).

Table 5.1: Individual participant details

Participant Number	Sex (Male/Female)	Age (years)	Height (cm)	Weight (kg)	Leg length (cm)	Right/Left handed	Alcohol (Units pw)	CA diagnosis	UMN signs present?	Diagnosis Duration (yrs)	Baseline					12mo Follow-up				24mo Follow-up			
											Falls history (Y/N)	SARA total (/40)	$SARA_{Gait\&Posture}$ (/18)	MoCA (/30)	BBS (/56)	SARA total (/40)	$SARA_{Gait\&Posture}$ (/18)	MoCA (/30)	BBS (/56)	SARA total (/40)	$SARA_{Gait\&Posture}$ (/18)	MoCA (/30)	BBS (/56)
P01	F	52	161	54	78	R	0	SCA6	N	6	N	14.5	6	29	53	11.5	3	30	40				
P03	M	54	174	70	77	R	5	SPG7	Y	21	N	14	4	26	43	11.5	3	29	46				
P04	M	51	162	82	78	L	0	•	Y		N	10	3	27	41	8.5	3	29	51				
P06	M	53	187	81	90	R	6	SPG7	N	3	N	6	1	25	56	6	1	26	54	9	2	27	48
P07	F	55	160	56	74	R	5	SCA6	N	21	Y	2	1	30	56	0	0	29	56	0	0	30	55
P08	M	52	180	90	83	R	2	ADFHx	Y	42	Y	13	5	26	31	14	6	27	28				
P10	M	52	175	91	73	R	23	SPG7	Y	16	N	8.5	4	30	39	12	4	28	46	9.5	2	28	44
P11	F	61	171	60	80	R	3	SCA6	N	4	Y	2.5	1	29	56	2.5	1	29	56	3	1	30	56
P13	M	65	186	105	87	L	30	SCA6	N	10	N	10	5	25	42	8	5	27	45	9	2	28	40
P14	F	57	161	41	84	R	0	SCA6	N	6	N	18	5	27	29	18	7	26	26				
P16	F	66	171	62	92	R	5	SPG7	N	0	N	4.5	2	24	44	2	2	24	44				
P17	M	65	181	63	75	L	5	•	N	10	N	10.5	4	28	51	9	4	29	48				
P18	M	37	175	73	73	R	0	•	N		N	11	3	25	41	12	3	23	40				
P20	M	53	175	73	83	R	0	SPG7	Y	7	Y	8.5	5	26	39	9	4	26	35				
P21	F	19	161	62	67	R	5	SCA6	N	0.5	N	11.5	4	28	47	8	3	27	45				
P22	F	63	131	68	79	L	5	SCA6	N	1.5	N	11.5	4	26	52	9	3	27	48				

Values for demographics characteristics and clinical rating scales as measured at baseline, 12 months & 24months. Abbreviations: M-Male, F-Female, cm-centimetre, SARA-Scale for Assessment and Rating of Ataxia, BBS-Berg Balance Scale, MoCA-Montreal Cognition Assessment

Table 5.2: Descriptive summary of participants that completed follow-up

a)	**Baseline (n=16, 7F)**	**12 month Follow-up (n=16, 7F)**	**p**
Age (years)	53.44 (11.71)		
Height (cm)	169.41 (13.62)		
Mass (kg)	70.64 (16.14)	71.03 (16.59)	0.60
Leg Length (cm) to floor	90.25 (5.54)		
Diagnosis subtype	7 SCA6, 5 SPG7, AD FHx		
Duration of diagnosis	10.57 (11.39)		
Time to follow-up	12.8±1.8months		
Falls history	12 Non-Fallers, 4 Fallers		
Alcohol intake	5.88 (8.47)		
SARA (/40)	9.75 (4.36)	8.81 (4.61)	0.06
$SARA_{Gait\&Posture}$ (/18)	3.56 (1.59)	3.25 (1.81)	0.26
BBS (/56)	45.0 (8.51)	44.25 (8.84)	0.40
MoCA (/30)	26.94 (1.88)	27.25 (1.95)	0.57
UMN signs	Present in 4 patients		
b)	**Baseline (n=5, 2F)**	**24 month Follow-up (n=5, 2F)**	**p**
Age (years)	57.20 (5.59)		
Height (cm)	175.80 (11.21)		
Mass (kg)	78.58 (20.69)	77.10 (19.57)	0.21
Leg Length (cm) to floor	90.6 (5.86)		
Diagnosis subtype	3 SCA6, 2 SPG7		
Duration of diagnosis	10.80 (7.73)		
Time to follow-up	12.1±0.2months		
Falls history	3 Non-Fallers, 2 Fallers		
Alcohol intake	13.40 (12.26)		
SARA (/40)	5.80 (3.55)	6.10 (4.34)	0.75
$SARA_{Gait\&Posture}$ (/18)	2.4 (1.95)	2.4 (1.82)	1.00
BBS (/56)	49.80 (8.56)	48.60 (6.91)	0.41
MoCA (/30)	27.80 (2.59)	28.60 (1.34)	0.60
UMN signs	Present in 4 patients		

a) 12 month follow-up and b) 24 month follow-up. Data reported as mean (SD). Statistical test: paired sampled T-Test. Abbreviations: n-number of patients, SARA- Scale for Assessment and Rating of Ataxia, BBS – Berg Balance Scale, MoCA – Montreal Cognitive Assessment, UMN – Upper Motor Neuron

5.3.3. GAIT ASSESSMENT

5.3.3.1. Baseline vs 12 months

Table 5.3 contains the results of gait assessment at baseline and 12 month follow-up with effect size and significance level from paired statistical-tests.

At 12 month follow-up, of the spatiotemporal gait parameters selected from baseline study, CA patients exhibit a significant increase in step width (mean difference (MD) =1.00cm, p=0.04, effect size (*d)*=-0.57). For the upper body motion gait characteristics selected based on baseline findings, lumbar HR_{ML} (MD=-0.2, p<0.01, *d*=0.86), and ML stride regularity (MD=-0.1, p=0.04, *d*=-0.38) as well as forehead HR_V (MD=-0.41, p=0.05, *d*=-0.36) and resultant step regularity (MD=-0.06, p=0.02, *d*=0.67) display significant differences and medium to large effect sizes compared with baseline. Insufficient adjacent steps were computed for 1 participant at 12-month followup to be able to compute upper body motion parameters. In addition, Stride time asymmetry, lumbar anteroposterior (AP) stride regularity and Trunk AP harmonic ratio show medium to large effect sizes. Therefore, this study may be underpowered to detect changes in these variables within 12 months.

Paired samples correlations indicate a measurement consistency across the cohort in many variables between baseline and 12-month follow-up. Notably, step width, lumbar HR_{ML} and forehead $AD1_R$ change significantly over time and have strong paired correlations with a good effect size (Figure 5.1).

No decline in SARA score occurred over the 12-month period, a significant correlation was only observed between intra-individual change in trunk HR_{ML} and SARA score but none of the other measures examined (Table 5.3, Figure 5.2). Since no significant change occurred in this measure over time this does not reflect any clinically relevant change over time. There does not appear to be much consistency in the responsiveness of the gait measures to the SARA on an individual level and how these changed between visits.

5.3.3.2. Baseline vs 24months

For the 5 participants that completed 24month follow-up, gait parameters with medium to large effect sizes at 12 months were examined visually (Figure 5.3). These individuals reflect a less severely disabled ataxia cohort and no consistent changes appear to be present in these variables at 12 months and 24 month follow-up. It is not possible to determine whether a decline of gait occurs in this small cohort. Since there is also no change in

disease severity or balance performance occurs, any trend observed in this subgroup may be a natural fluctuation and not a genuine progression of gait impairment.

Table 5.3: Baseline and follow-up results for gait variables in cerebellar ataxia.

						Correlation	
		Baseline (n=16, 7F)	**12 month follow-up (n=15/16, 7F)**	**p**	**Effect Size (Cohen's d)**	**Paired Samples**	**Δ variable vs Δ disease severity**
Spatiotemporal Measures							
Speed (m/s)		1.18 (0.18)	1.16 (0.24)	0.50	0.17	**0.80*** **	0.01
Step Width (cm)		15.86 (4.71)	16.86 (5.28)	**<0.05**	**-0.57**	**0.94*** **	-0.04
Asymmetry Measures							
Cadence (Steps per min)		1.32 [0.55, 1.99]	0.76 [0.36, 1.23]	0.23	-0.21	0.23	-0.30
Stride Time (s)		0.013 (0.009)	0.009 (0.005)	0.12	**0.41**	0.00	-0.34
Variability Measures							
Speed (%CV)		5.27 [4.21, 6.54]	4.89 [3.31, 7.13]	0.64	-0.08	0.53*	-0.09
Cadence (%CV)		3.49 [2.95, 5.81]	3.22 [2.67, 5.34]	0.72	-0.06	0.11	-0.09
Stride Time (%CV)		3.46 [2.97, 5.66]	3.18 [2.66, 5.33]	0.64	-0.08	0.18	-0.13
Step Time (%CV)		5.69 [4.20, 7.44]	5.90 [3.69, 7.50]	0.84	-0.04	0.10	0.01
Stride Length (%CV)		3.42 [2.53, 4.47]	4.72 [2.88, 6.24]	0.43	-0.17	**0.64****	-0.16
Step Length (%CV)		5.07 [4.14, 7.91]	6.94 [4.65, 9.09]	0.28	-0.16	**0.64****	0.03
Stance Time (%CV)		4.79 [4.05, 6.76]	5.19 [3.13, 6.68]	0.54	-0.11	0.26	-0.05
Lumbar							
Harmonic Ratio	AP	2.48 (0.53)	2.29 (0.75)	0.11	0.44	0.58*	0.42
	ML	2.02 (0.44)	1.82 (0.42)	**<0.01**	**0.86**	**0.60***	0.30
	V	2.65 [2.07, 3.17]	2.12 [1.80, 2.68]	0.17	-0.25	**0.69****	0.30
Step Regularity	AP	0.70 (0.16)	0.69 (0.12)	0.86	-0.05	**0.72****	0.29
	ML	-0.47 (0.17)	-0.41 (0.14)	0.45	-0.20	0.56*	-0.25
	V	0.70 (0.18)	0.66 (0.15)	0.67	0.11	0.59*	0.09
Stride Regularity	AP	0.74 (0.11)	0.70 (0.13)	0.17	**0.37**	**0.76*** **	0.11
	ML	0.52 [0.43, 0.65]	0.42 [0.38, 0.51]	**<0.05**	**-0.38**	**0.60***	-0.05
	V	0.70 (0.16)	0.67 (0.17)	0.69	0.10	**0.69****	-0.17
	R	0.69 (0.12)	0.64 (0.13)	0.27	0.30	**0.63***	-0.18
Trunk							
Harmonic Ratio	AP	1.75 (0.25)	1.54 (0.25)	0.06	**0.54**	0.49	0.11
	ML	2.46 [2.19, 3.39]	2.63 [2.04, 3.20]	1.00	0.00	**0.79*** **	**0.53***
	V	2.79 (0.64)	2.55 (0.77)	0.35	0.25	0.55*	0.45
Step Regularity	AP	0.48 (0.13)	0.44 (0.14)	0.39	0.23	0.58*	0.29
	V	0.74 (0.17)	0.73 (0.15)	0.90	0.03	**0.75****	-0.04
	R	0.60 (0.15)	0.55 (0.17)	0.51	0.18	0.45	0.11
Stride Regularity	AP	0.59 (0.12)	0.57 (0.16)	0.82	0.06	**0.61***	0.08
	V	0.76 (0.14)	0.72 (0.15)	0.29	0.28	**0.78*** **	-0.05
	R	0.65 (0.13)	0.61 (0.15)	0.51	0.18	0.59*	-0.03
Forehead							
Jerk (ms^{-3})	AP	21.71 (8.25)	32.23 (10.67)	0.72	-0.10	**0.83*** **	0.05
	ML	25.30 (9.47)	22.74 (5.58)	0.97	-0.01	**0.87*** **	-0.34
Harmonic Ratio	V	2.51 [2.06, 3.19]	2.10 [1.81, 2.53]	**<0.05**	**-0.36**	**0.63***	0.48
Step Regularity	V	0.71 (0.17)	0.67 (0.16)	0.34	0.26	**0.87*** **	0.27
	R	0.55 (0.18)	0.46 (0.17)	**<0.05**	**0.67**	**0.85*** **	0.12
Stride Regularity	AP	0.50 (0.10)	0.48 (0.18)	0.70	0.10	**0.68****	-0.15
	V	0.72 (0.16)	0.68 (0.16)	0.16	0.38	**0.86*** **	0.06

Results displayed as mean (SD) or median [IQR]. Also shown: effect size calculation; paired samples correlation coefficient; the correlation between change (Δ) in each gait variable and change (Δ) in disease severity (SARA score) at 12month follow-up. *p<0.05, **p<0.01, *** p<0.001. Missing data: Lumbar, Trunk and Forehead parameters – 12 month follow-up (n=15)

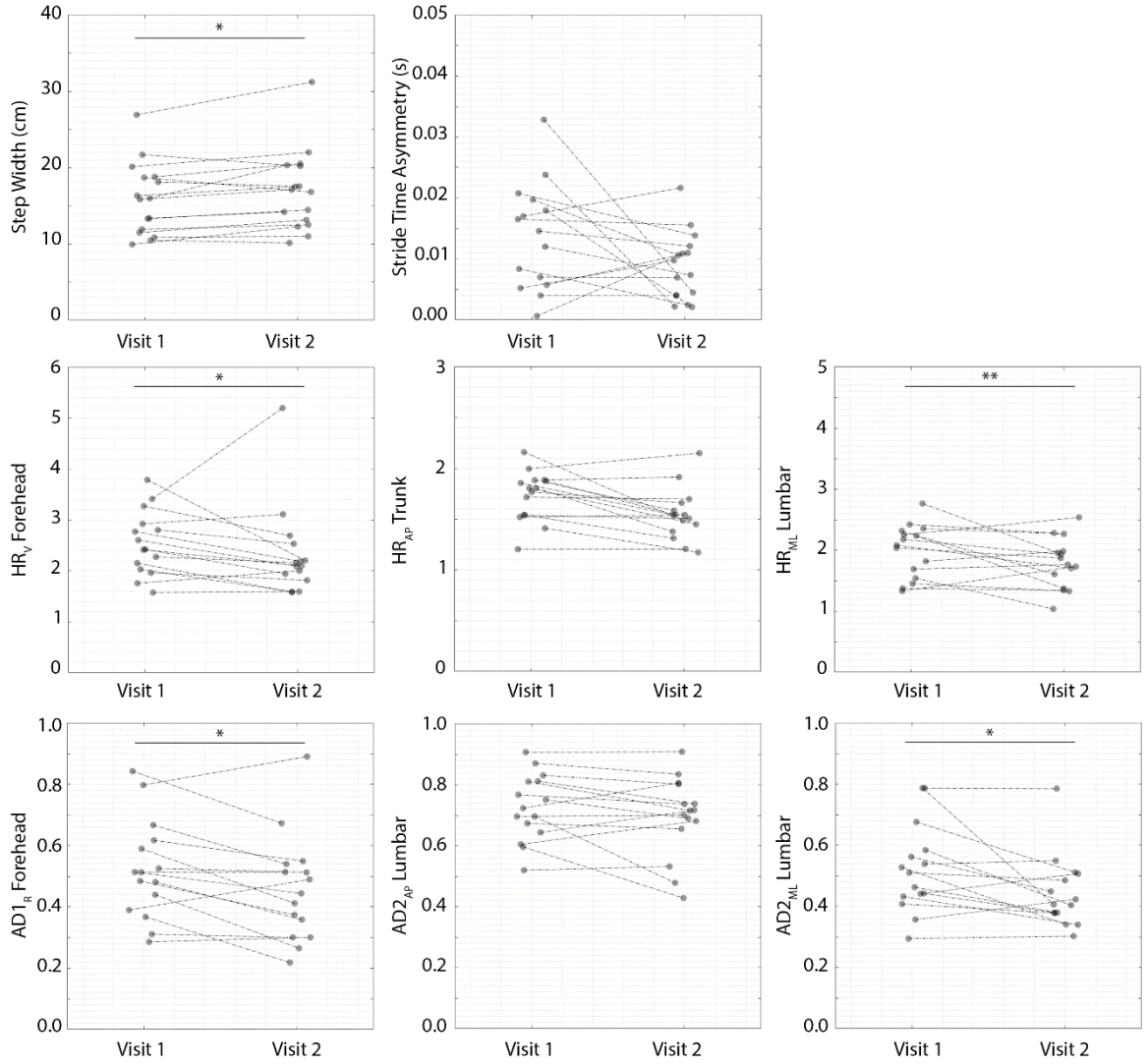

Figure 5.1: Follow-up results of selected variables.
Results for healthy controls at baseline and cerebellar ataxia at baseline, and 12 months follow-up with lines between individual CA participant results. Significant change indicated: * p<0.05, ** p<0.01 Missing data: Upper body motion parameters - visit 2 (n=15).

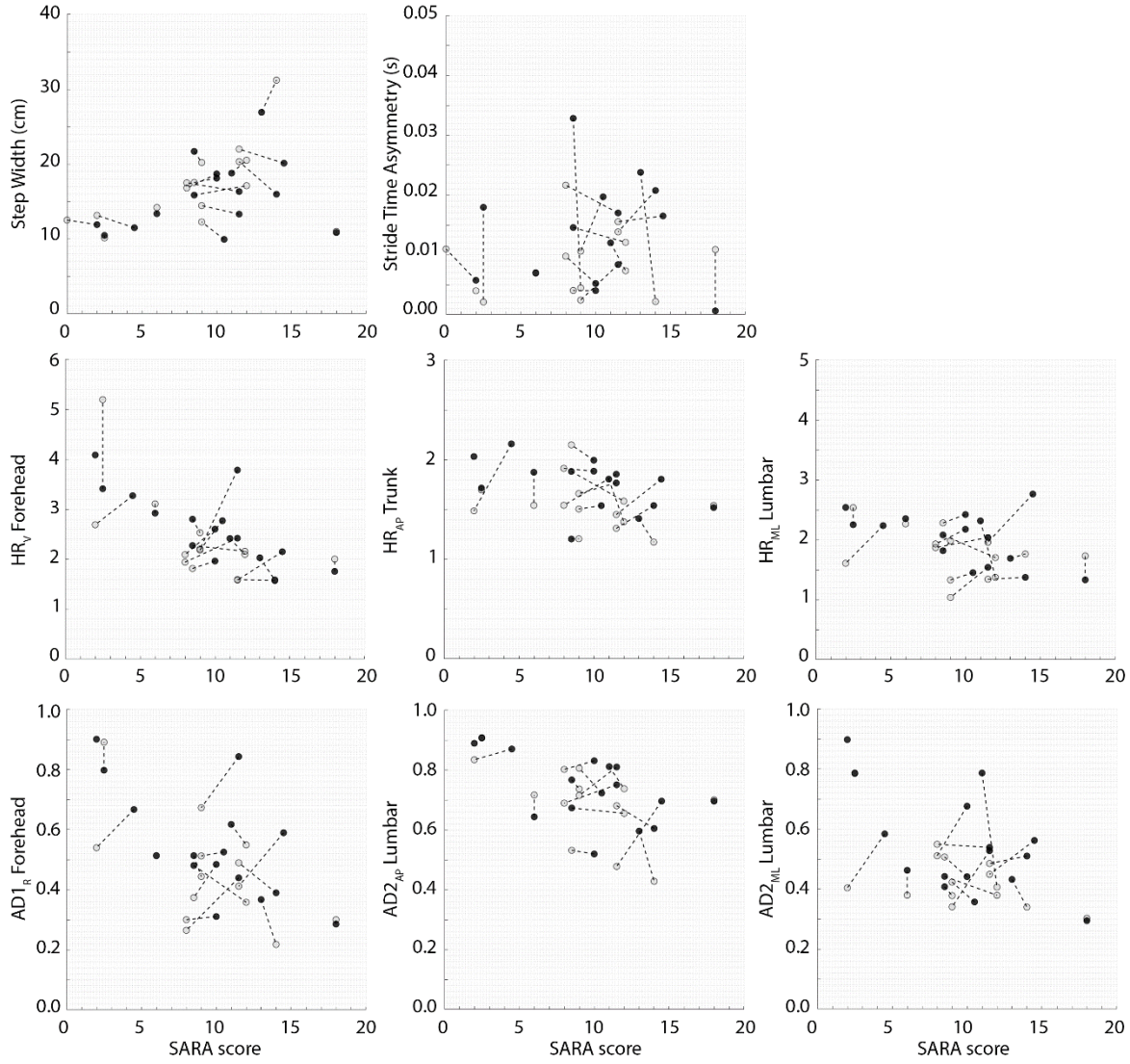

Figure 5.2: Results for selected gait variables plotted against SARA score
Indicates the change over time and the relationship between disease severity (SARA /40) and gait abnormality. Black circles: baseline measure compared with baseline SARA score, Grey circles: 12 month gait measure compared with 12 month SARA score, ---- individual change in gait measure and SARA score. Missing data: Upper body motion parameters - visit 2 (n=15).

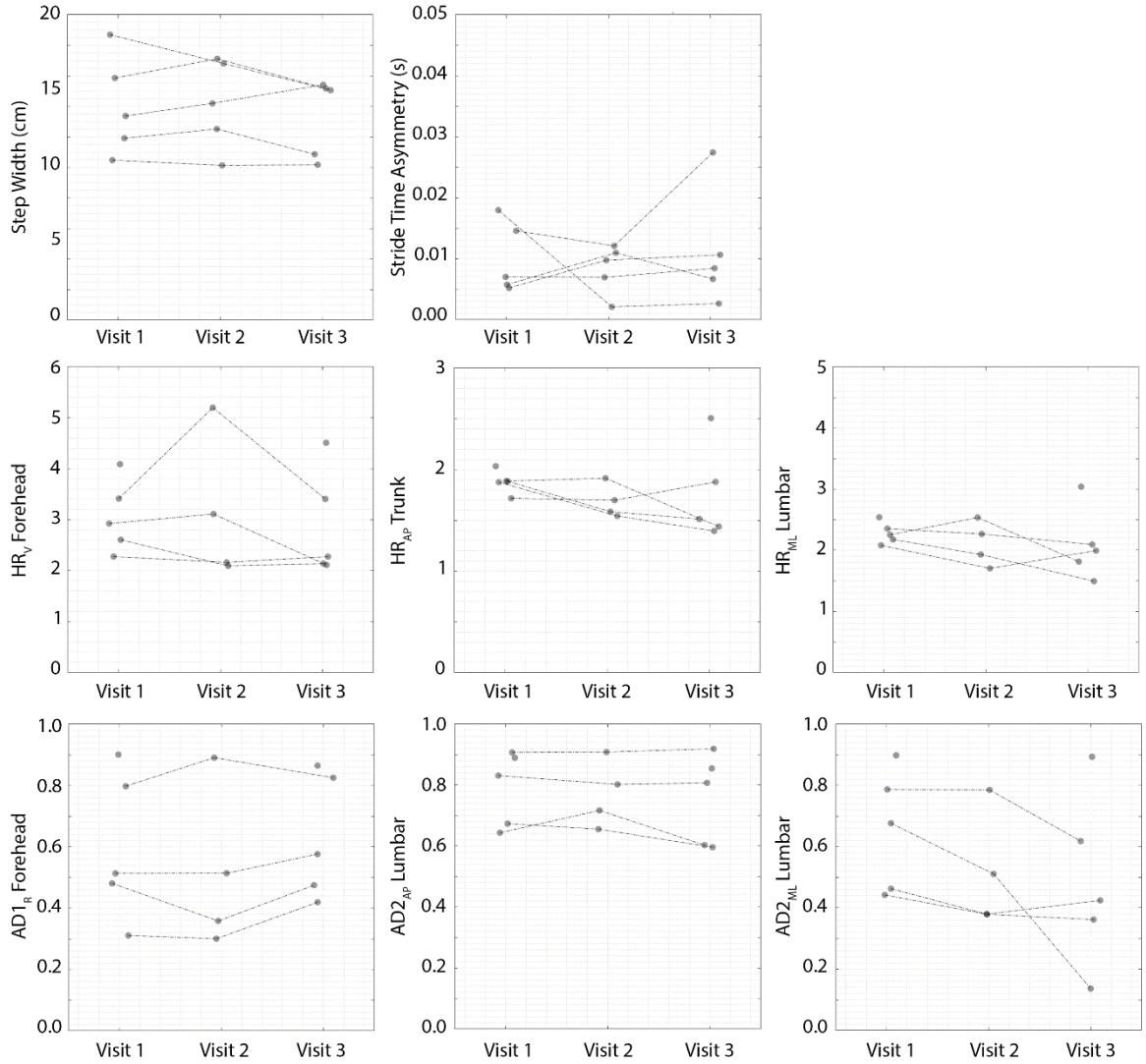

Figure 5.3: Results for participants that completed 24month follow-up for selected variables. Results for cerebellar ataxia at baseline, 12 months and 24months follow-up with lines between individual CA participant results. Missing data: Upper body motion parameters - visit 2 (n=4).

5.4. DISCUSSION

5.4.1. PARTICIPANT CHARACTERISTICS

Follow-up was completed in 16 participants, 12 months after their baseline assessment. Diagnosis duration and age are comparable to those who only completed baseline assessment (Chapter 4). No significant difference was observed between baseline and either 12month follow-up in disease severity and none of the participants exhibited a change greater than the minimal detectable change (SARA score, <3.5pts). Individual changes in balance performance were also not within a clinically relevant range (BBS <8pts). For the subgroup of 5 participants who also complete 24months within the data collection period, no longitudinal change in disease severity or balance performance occurred. While the subgroup of participants that completed 12-month follow-up are similar to those recruited to the study population at baseline in terms of disease severity and frequency of ataxia subtypes, the 5 participants who completed 24-month follow-up exhibited a more mild phenotype than the cohorts at previous timepoints.

5.4.2. GAIT ASSESSMENT

In the present cohort, after 12 months, a significantly increased step width, reduced rhythmicity (HR_{ML} at pelvis and HR_V forehead), and reduced regularity (resultant forehead step regularity and ML component of lumbar stride regularity) were detected with good statistical power. These measures showed a strong significant paired correlation over time. However, none of the participant showed a deterioration in disease severity, balance performance or gait speed in this time period. No significant correlations were observed between change in SARA score and these gait measures. Also, in the small subgroup of participants that completed the 24month follow-up, no clear trends are apparent in these selected gait measures.

The change in these measures was also small, for instance, the increased step width, was approximately 1cm over 12 months. Although this could be considered to reflect a compensation mechanism for impaired balance (Serrao et al., 2012), since this change is within the limit of agreement for the OptoGait system (Table 3.11), it is not likely to be a genuine change. As this adjustment of step width over time was only slight, it may not provide considerable additional gait control later in the disease process. A previous study of

gait in ataxia over a 4-year period did not identify any significant progression in step width over time (Serrao et al., 2017a).

None of the spatiotemporal gait variability or asymmetry variables investigated showed significant change over time in the present study. Left step length variability has previously been identified as increasing over time in a cohort of patients with ataxic gait (Serrao et al., 2017a).

At the lower back and forehead, harmonic ratio (ML and V axis respectively) was able to distinguish between gait assessment visits. Recent studies have explored the harmonic ratio as a marker of disease severity in CA (Caliandro et al., 2019, Ilg et al., 2019). Meanwhile, the changes in the ML component of stride regularity at the lower back, and resultant step regularity at the forehead are also significantly different over time. Previous studies have indicated the potential of step and stride regularity as a measure of postural control (Matsushima et al., 2015). Shirai et al. (2019) also recently reported that over a 1.5yr period, Spinocerebellar Degeneration (SCD) is associated with impaired ML amplitude of accelerations which complements our findings. Previous studies have indicated that lateral balance and adjustment of step width reflects instability more than step length (Collins and Kuo, 2013). Therefore, this alteration in the ML asymmetry over time may complement these findings.

However, since these selected measures do not exhibit consistent deterioration in the same direction or trunk segment which would indicate a specific change in gait pattern and gait strategy over time. This infers that, the participants in this study may not exhibit a genuine worsening of postural control within 12months. These variables that have been identified may be able to detect subtle gait changes that are not evident when using clinical rating scales and un-instrumented walk tests but also could be a result of random fluctuations. Since the SARA scores did not show significant progress in the present cohort either and the effect size was small for these variables in the present study, it is likely that there were too few heterogeneous patients in this study to corroborate this finding. The intra-individual change in SARA was small in this time frame so although for many gait measures, a worse result is clearly associated with a worse SARA score, the correlation between changes in gait measures and changes in SARA scores was inconsistent. With a longer follow-up where

genuine change in function is detected it will be possible to better stratify rate of disease progression in CA depending on the extent to which an individual's gait pattern changes.

Our estimate of the statistical power of these acceleration variables in objectively measuring gait impairment over time indicates that each of these variables had a medium to large effect size. Although this could indicate that a sufficient number of individuals participated in the follow-up to detect impairment in this cohort, due to the heterogeneity of the cohort and lack of consistency between the gait domains, this may also give weight to the conclusion that these changes in the gait pattern are not specific to disease progression in ataxia. This may also be related to the small sample size and short follow-up duration.

5.4.3. LIMITATIONS

The main restraint within this study is the limited number of participants that completed follow-up. Firstly, of the 27 participants that took part in the baseline study, only 16 were able to be included in the follow-up assessment. Of those that did not complete follow-up (n=11), the reasons included: disease progression so that gait tasks could not be completed unaided, illness and disinterest in returning. The remaining participants were not approached for follow-up as the data collection period was closed prior to scheduling. Further, only 5 participants completed follow-up assessment at 24 months as the remaining participants had not reached the appropriate timepoint within the data collection period. Therefore, few conclusions can be drawn from this additional time point. Further, as the 5 participants that completed follow-up at 24months had a mean SARA score that was approx. 4 points lower than the 12 month follow-up cohort. Therefore, this subset represents a milder phenotype than those that completed the 12-month follow-up only.

In addition it is important to consider that this cohort included individuals with different types of cerebellar ataxia, (SCA6, SPG7, AD FHx and other forms of ataxia) and there may be some heterogeneity in their disease course depending on the genotypes (Marsden and Harris, 2011). Whilst SCA6 and SPG7 are both associated with slowly progressing ataxia, other features of the disease such as spasticity and weakness contrast and may influence the gait pattern differently over time and with treatment (Ashizawa et al., 2013, Jacobi et al., 2012). Therefore, further work is required to confirm whether longitudinal gait changes are subtype specific.

Sex disparity was not controlled in the invitation to follow-up or explored in analysis. However, the cohorts retained an approximate female: male ratio between baseline (10/27 female, 37.0%), 12 month follow-up (7/16 female, 43.8%) and 24month follow-up (2/5 female, 40.0%) and was comparable to the sex split in previous literature (44.12% female, Table 2.1). However, in light of the aforementioned differences between sexes in gait characteristics and considering that hereditary ataxias are not more prevalent in a specific sex, future study should endeavour to control for this within recruitment strategies.

In this study, individual participant's usual care was not altered and not detailed extensively. In this disease cohort, symptoms such as spasticity and vertigo are treated through medication and many people undergo physiotherapy and undertake regular exercise. It is therefore possible that changes to their usual care implemented by their treating physician could impact a participant's gait performance within a 12-month period. However, since no disease modifying therapy exists for ataxia, this impact was likely minimal.

Limitations of the gait analysis systems selected also contributed to these results. For instance, for 1 participant algorithms were unable to accurately identify every gait event in the walking bout so the walking bout was too short to provide multiple adjacent strides. The algorithms were then unable to compute the upper body motion parameters reliably and so their upper body characteristics were excluded from follow-up analysis but spatiotemporal measures included. Therefore, further disease specific adaptation of the algorithms may be necessary to ensure data is not lost.

It is also important to consider that by pre-selecting variables on the basis of baseline disease severity and ability to differentiate CA from HC, some features of the gait pattern may have been missed. It is possible that there may be gait measures that are sensitive to disease progression despite not meeting the criteria implemented here. Therefore, further appraisal of gait changes with disease progression is needed to confirm the potential of gait measures as a biomarker.

5.5. CONCLUSION

There is a considerable interest in the use of postural control as a biomarker for monitoring of CA. Here we report, the results of a longitudinal assessment of gait in a cohort of adults with CA gait. Our findings indicate that although accelerometery measures reflecting

rhythmicity and regularity of gait display statistically significant changes at 12month follow-up, as no disease progression occurred during this time period, these may not be generalisable to the wider population. The small degree of change within short follow-up period for a heterogeneous cohort indicate that the trend of gait decline in CA may not reflect a genuine functional change.

Further study in people with homogenous ataxia phenotype over a longer follow-up period, is necessary to further explore the gait changes that were detected here as the present study may be underpowered to detect change in these measures. Future studies should explore postural changes during gait in a larger cohort as it may be possible to identify further measures of gait progression and to validate those recognised here as biomarkers of disease progression.

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Chapter 6. GENERAL DISCUSSION

6.1. REVIEW OF AIMS & OBJECTIVES AND PRINCIPAL FINDINGS

Chapter 2: Aimed to completion of a systematic review to summarise and meta-analyse the reported gait characteristics of cerebellar ataxia (CA). Critical appraisal and quality assessment was planned to summarise previously reported results. The gait characteristics differentiating between CA and controls were identified. An estimation of the objective gait pattern in CA was completed and sample size estimation completed.

Following our searches and subsequent scrutiny of the literature from the last 20 years, twenty-six studies were identified that considered spatiotemporal gait characteristics in individuals with cerebellar ataxia (CA), as measured by instrumented analysis techniques during preferred paced steady-state walking.

During preferred paced walking, there is strong evidence that CA patients display the following gait differences against healthy controls:

- reduced walking speed and cadence
- reduced step length, stride length, and swing phase
- increased base width, stride time, step time, stance phase and double limb support phase
- increased variability of step length, stride length, and stride time.

The gait parameters that were greatest affected in CA were speed, double limb support phase duration (%cycle) and stride time variability followed by step length variability and step length.

Unfortunately, due to limitations of the dataset, it is not possible to formally explore the influence of distinct confounding influences such as ataxia diagnosis type separately from equipment used, the correlations between upper body and spatiotemporal gait parameters, or the effect of changing velocity or disease progression on gait characteristics.

Sample size estimation indicated that between 2-47 individuals can be recommended for studies of gait in CA. However, since estimating sample size from meta-analyses results can lead to an overestimation of statistical power, a more conservative estimation should be considered for most gait parameters evaluated.

Chapter 3: An in-house validation was planned to compare the proposed gait analysis equipment (Microgait OptoGait photoelectric walkway and APDM Opal inertial sensors) against the gold-standard of gait analysis (Vicon 3D motion capture). This intended to ensure the accurate measurement of spatiotemporal parameters and confirm the synchronisation of data capture.

A group of healthy control participants were recruited to the study and completed preferred speed walking trials. The Vicon 3D motion capture system was the reference device/gold standard. This experiment lead to the development of algorithms to process the OptoGait output.

Examination of the agreement and consistency of the three system measurements and algorithm identified that statistically differences are present for gait event detection by the OptoGait system and ADPM Opal sensors, these are small and agreement was good. There was a larger but still not substantially higher systematic bias for the detection of final contact than initial contact timing. There was a minimal impact of this on the calculations if step and stride duration but stance and swing durations correlated more weakly for the OptoGait system and APDM Opal sensors but systematic differences were small. The step and stride length estimation by the OptoGait system showed excellent correlations and negligible systematic bias. However, step width estimation by the Optogait system was associated with a systematic bias between systems and a generally poor level of agreement. This is likely due to the differing parameters definitions between the systems.

Also, the participant gait speed was not correlated with the accuracy of the gait analysis systems. However, being a healthy control cohort, the range of gait speeds captured were not reflective of potential pathological cohorts.

Taken together, thresholds for valid measurements can be inferred from limits of agreement in preparation for interpretation of clinical gait assessments (Table 3.11).

Chapter 4: An observational gait analysis study was completed to assess the gait characteristics of people with CA (n=27) compared with a healthy age-matched control population (n=27). The association between upper-body motion and spatiotemporal gait parameters as well as the influence of disease severity and walking speed were explored.

Spatiotemporal gait parameters and upper-body motion characteristics were measured concurrently and additional validation in a CA cohort completed. This indicated that in a pathological cohort, during longer walking trials, a similar level of agreement and precision are possible to that estimated in a young healthy cohort (Chapter 3).

Here ataxic gait pattern is characterised by an attempt to compensate for excessive sagittal, lateral and vertical oscillations despite insufficient coordination between the upper and lower body segments. Speed, step width, gait variability as well as step to step asymmetry, step regularity and stride regularity are able to differentiate between disease severity subgroups independent of changes in gait speed. Therefore, these variables show promise as biomarkers for severity of gait ataxia. This corroborates findings from Chapter 2, while also quantifying ataxic gait in terms of measures of trunk motion.

Comparison of gait characteristics against clinical measures of disease severity (Scale for Assessment and Rating of Ataxia (SARA) and balance performance (Berg Balance Scale, BBS) was completed. Indeed, objectively measured gait changes in CA, differentiate patients with a pre-symptomatic/mild CA phenotype from more severely affected patients and healthy controls independent of age, sex and gait speed. This indicates their potential as gait biomarkers for disease severity.

Since in people with CA, spatiotemporal gait changes may be a form of compensation for loss of balance, assessing the two aspects of gait in synchronisation is highly advantageous. In addition, since step variability, stride variability and step width negatively correlate with postural asymmetry, stride regularity and step regularity, further work could explore whether spatiotemporal gait parameters are interchangeable with upper body motion variables in the monitoring of CA. Further work is also required to examine differences between disease diagnoses and falls history.

Chapter 5: Follow up assessments of gait in the study population was planned to be completed after a 12 month and after 24-month interval. While the majority of the study cohort completed 12 month follow-up, many were did not complete either 12 month or 24 month follow-up visits as: they were no longer able to complete the gait tasks due to disease progression; they were recruited towards the end of the data collection period so were not due to complete their follow-up visit in time; they chose not to take part for other

reasons. Therefore, the 24 month follow-up can only give an estimation of the trends within the small cohort.

In order to reduce the number of variables, a 37 gait measures were selected to be implemented that had shown sensitivity to disease severity in baseline assessments. Following clinical assessment of disease severity, balance performance, gait tasks were completed in the same way as at baseline to objectively measure whether the gait pattern changes over time in CA and how. This would provide evidence for the use of the instrumented gait tasks to detection of disease progression. I hypothesised that spatiotemporal and upper body motion characteristics may be able to recognize disease progression in an ataxic cohort.

Over a 12 month period, people with CA did not show significant progression in disease severity or balance performance. In preferred speed self-paced walking gait tests, the cohort, exhibited an increased step width and reduced rhythmicity and regularity. However, the small cohort of participants had a heterogeneous disease pathology, the follow-up period short and changes detected were within the previously established limit of agreement for the gait analysis systems. Therefore, it is likely that these changes do not reflect a genuine change of function. Due to small numbers of participants that completed the 24month follow-up, these findings could not be analysed formally at a longer follow-up period in this study. A longer follow-up period of assessment in a larger more homogeneous cohort is required to detect true disease progression in people with CA.

6.2. UNDERLYING GAIT CHANGES

Here I examined the spatiotemporal and upper body motion characteristics that characterise CA and how these are changed with disease severity. I also assessed whether the gait pattern in cerebellar ataxia changes over 12-month follow-up and if instrumented gait tests can objectively measure these changes. Taken together, the ataxic walking gait pattern corroborates the characteristics reported in the literature: slow and highly variable footfall with a wide base of support that is also associated with uncontrolled regularity of lateral motion and reduced rhythmicity of trunk rotation as well as more jerky head motion. Here I recognise that despite a relatively mild severity of ataxia present in the recruited cohort, it is possible to distinguish between healthy controls, very mild ataxia, and more moderate ataxia. Due to the nature of the walking tasks, it was not possible to explore gait

in people who require a walking aid at all times. Therefore, these results are limited to people with a lower level of disability.

Further, stratifying patients on the basis of their disease severity enabled the identification of gait changes that occur in mild/presymptomatic ataxia compared with a more severe ataxia phenotype. The mild ataxia cohort also exhibits an intermediate gait phenotype compared with the other cohorts, which is characterised particularly by temporal variability, and rhythmicity of pelvis rotation. These gait changes that distinguish mild ataxic gait from healthy controls may have diagnostic benefit. In the more moderately affected ataxia cohort, these features are exacerbated, and other aspects of the gait pattern are additionally impacted.

Since no disease progression was observed in the people recruited to this study, although changes were identified in selected variables, these are not likely to reflect genuine disease progression. The variables that exhibit an ability to differentiate CA and healthy controls and disease severity subgroups and were also able to characterise 12-month follow-up in ataxia were gait speed, step width, asymmetry, variability, postural symmetry, and regularity measures.

6.3. NOVEL FINDINGS

These features of ataxic gait require instrumented gait analysis tests in order to be objectively measured. Current non-instrumented clinical assessments of gait changes require a subjective rating and previous experience to rate ataxic gait severity. The key outcomes of existing performance tests such as the timed up and go and six-minute walk test include submaximal exercise capacity and gait speed. Reduced gait speed is a common feature of gait impairment and loss of balance confidence (Fritz and Lusardi, 2009). Therefore, while poor performances on these tests can be indicative of gait disability, they cannot determine specific gait pattern deficiencies. Here we provide a thorough description of gait impairment in cerebellar ataxia that cannot be discerned from non-instrumented tests. Our findings also provide evidence of speed-independent gait impairment in cerebellar ataxia.

This offers the potential to use gait variables as quantitative biomarkers for disease severity and disease progression. This in turn opens the possibility of using gait measures including upper body motion as outcomes in clinical trials in cerebellar ataxia to establish treatment

effects. Further detailed studies are required to fully characterise the gait phenotype in relation to clinical and molecular features of cerebellar ataxia such as genetic and neuro-imaging findings in preparation for this purpose.

In terms of instrumentation, the OptoGait is not widely used in clinical settings. However, it enables a portable method of detection spatiotemporal gait characteristics so can be implemented in a wide range of settings. The system is quick to set up and provides feedback reports for participants. It is also possible to synchronise recordings between systems through an external trigger signal. Here, I have validated the OptoGait system in a healthy control cohort and an ataxia cohort within clinical and laboratory settings. Although, previous studies have explored the different settings for the LED filter thresholds (Healy et al,. 2019), the use of the perpendicular bar to assess step width has rarely been reported in the literature to my knowledge. Therefore, our estimation of the agreement between the OptoGait and reference system for step width indicates that further work is required to improve the accuracy and precision of this measurement.

6.4. STRENGTHS AND LIMITATIONS

The strengths and limitations of this work have been discussed in the previous chapters. To summarise however, there are factors to consider when interpreting these findings.

By examining the existing literature in a systematic review and meta-analysis it was possible to create a thorough summary of the previous understanding while fully assessing the methodological quality of all included studies. It provided an estimation of the usual recruitment targets and by pooling data it was possible to better calculate the statistical power possible in a large CA cohort. Although this may have led to an under-estimation of the number of participants required for a single study, it was clear that there is consistency between studies despite within-study variability and heterogeneous cohorts.

Throughout this work, healthy individuals have been used as control participants. Our findings therefore indicate there may be a diagnostic value of gait analysis. While this was intended to reduce the impact of possible comorbidities on measurements, further work differentiating ataxia from other disease cohorts is also necessary to establish a disease-specific gait signature. In preparation for this work, validation calculations for the OptoGait system and APDM Opal sensors were completed in data from the young healthy, older healthy and cerebellar ataxia cohorts in laboratory and clinical settings. Further validation

of step width measurements is recommended since there were short comings to the approach taken here. Namely the use of two marker set placement meant that the lateral markers were inconsistent between participants and not able to be included in the model of the foot placement. This led to an inherently different strategy for determining step width than the OptoGait system implements. The incorporation of force platforms in future validation studies would also improve the reliability of foot placement estimations.

The main restraint within this study is the limited number of participants that were recruited at baseline and those completed follow-up. Of the 27 participants that took part in the baseline study, only 16 were able to be included in the 12-month follow-up assessment and only 5 participants that completed follow-up at 24months. The main reason for these missing assessments was data collection period was closing prior to scheduling of visits. As indicated in results of the systematic review, these recruitment numbers are similar to those recruited in the previous literature. Also since sample size estimation based on the meta-analysis results indicate that between 2-14 participants is necessary to achieve statistical power. However, effect size was calculated for each of the statistical tests completed to indicate the probability that sufficient statistical power was achieved for each comparison.

Further, the recruited cohort of people with CA included individuals with different types of cerebellar ataxia, (SCA6, SPG7, AD FHx and others), there may be heterogeneity in their clinical characteristics, and disease progression. This was not accounted for in either the baseline or follow-up analyses reported here, but further work is underway to explore this. The difference between SCA6 and SPG7 for instance will confirm whether these gait contributions are related to ataxia or confounded by spasticity which is common in SPG7.

As discussed, an individual participant's usual care was not altered as part of this study. Therefore, changes to usual care may have occurred during the study period. Since no disease modifying therapy is available in this disease cohort, symptomatic treatment is often implemented. Spasticity is treated through used of muscle relaxants and to combat weakness many patients undertake regular physiotherapy and exercise. Therefore, it is possible that changes to a participant's usual care could impact gait performance within a 12-month period. As this was not explored in detail in this study, this potential confounding

factor will be considered in design of future protocols and careful interpretation of these findings should occur in light of this.

In systematic review of the previous literature and these primary studies, the use of walking aids was not considered. Given the nature of the walking tests, participants with a low disease burden and disability are commonly recruited to such studies. However, since use of walking aids is a common aspect of daily life for many people with CA, it is important to consider how this can affect walking gait, and balance performance. As a result, our findings cannot be generalised to people with more severe ataxia or to walking while using a walking aid.

In this study, recruitment was not controlled on the basis of sex. Although there is no conclusive indication of sex influencing ataxia onset and symptoms since mechanics is impacted by body structure, this may have influenced the between-cohort differences. This should be considered in future work through matching specific controls to specific patient participants. However, to account for this, supplementary analysis where age, sex and gait speed were included as covariate factors was completed in and our key findings are reported independent of these factors.

Walking gait characteristics reliant of gait speed. From a technical point of view, slow walking can interfere with the accuracy of gait event detection using inertial sensors (Feng et al., 2017). Since the CA cohort, adopt a slower preferred walking pace, it was important to verify the validity of gait event detection in HC and CA between the OptoGait system and APDM Opals sensors. Bland-Altman plots did not indicate that ataxia cohort membership leads to inaccurate gait event detection and gait parameter calculation compared with age-matched healthy controls. Gait strategies during different walking speeds was not explicitly explored here. Instead the difference in gait speed between HC and CA was accounted for in univariate analyses and the correlation between speed and gait measures reported. Further work may explore the influence of speed changes on the gait pattern as the study protocol included fast and slow speed self-paced walking trials. From the literature, it is expected that an individuals' preferred walking pace reflects their most comfortable and energy efficient gait strategy, while slow and fast paced walking provide a challenging task that requires an altered gait strategy.

Similarly, as walking gait parameters are inherently interdependent, it is essential to subsume gait measures where possible. For the systematic review of the literature, gait measures assessed were dependent on the data provided in the articles. However, an effort was made to calculate supplementary metrics where necessary to reduce the number of measures overall and increase the amount of data included in each meta-analysis. For instance, where gait cycle and phase duration were reported such as single support time, the percentage of each phase with respect to the gait cycle was calculated. Therefore these results could be combined to provided a larger dataset for meta-analysis. For the clinical studies, in order to appreciate the full gait pattern, additional gait measures were reported. However, informed by the results of baseline assessments and the knowledge of the interrelated gait parameters a short-list of 37 gait measures was selected for appraisal of the longitudinal gait changes in CA. In a larger cohort, multi linear regression analysis would be a better approach to outline the essential gait measures to be included in a model gait in CA.

For the clinical studies, despite completing visual checks at the time of assessment and taking precautions to ensure data validity, some issues with the technique persisted, particularly for the OptoGait. Issues with the detection of the gait events by the OptoGait occasionally occurred. For instance, occasional steps were identified as having an invalid flight time and other steps were overlooked by the built-in algorithm. This was considered to be related to differences in footwear and gait speed. Issues with synchronisation of the systems were also occurred which may pose an issue if data is to be segmented by gait events detected by another system. However, testing was quick to complete, lasting a maximum of 1.5 hours for patient participants, which indicating a low fatigue burden.

6.5. Recommendations For Future Work

While the studies discussed in this thesis largely conclude the planned activity for the clinical study “Gait Analysis in Cerebellar Ataxia and Hereditary Spastic Paraparesis”, there are a number of recommendations for future developments of the work that will enable the findings to be widely taken up into clinical practice.

6.5.1. Clinical Gait Analysis for Research

Despite the advantages of implementing the OptoGait system into a clinical study, in order to be used more reliably further validation is necessary. Most importantly, the inaccuracy of

step width estimation has been discussed in previous sections. Since different estimation methods employed between the OptoGait system and the Vicon 3D motion capture system future studies should be wary of this measurement until further validation is completed. Researchers should consider whether incorporation of an offset is necessary to correct the systematic bias detected here.

Further, position of step detection and labelling of left/right footfalls, can occasionally be incorrectly identified by the built-in algorithm, therefore it is important to minimise issues wherever possible through proper configuration and by monitoring recurring problems. Although visual checks at the time of data collection is recommended, since people with pathological gait may be prone to fatigue, repeating of trials, is not always possible. A semi-automated method of assessing validity of the data capture has been established to ensure correct labelling of data and to remove data that is incorrectly captured. Use of this system all restricted the walkway length to the length of the bars and the amount of support that could be provided to participants. A longer walkway enables participants to achieve a true steady state walking pace in the centre portion of a walking bout. Here, to avoid confounding results with the influence of acceleration/deceleration periods of gait, the steps outside of the system were not considered. However, this restricts the assessment space to 4 m x 1 m and therefore the number of gait events captured within this is limited.

For this study, the OptoGait system was used to compute the temporal and spatial features of gait. However, since the temporal gait parameters can be accurately obtained from acceleration and angular velocity signals, these measures were arguably redundant. Therefore, with the development of reliable approaches to measure spatial gait parameters, future studies could implement just IMU and avoid the need for an external gait analysis system. This exclusive use inertial sensors would provide additional flexibility to protocols.

Meanwhile, our findings indicate the importance of control of the upper trunk and forehead in control of gait in CA. Therefore, a holistic view of the gait pattern through spatiotemporal and acceleration variables are useful, the addition of the trunk and or forehead sensor to protocols should be considered in future studies in CA. In addition, there appears to be overlap in the information provided by spatiotemporal gait variables and postural control parameters. Therefore, with additional research in a larger cohort,

multivariate regression analysis can be completed to identify the variables best able to classify CA and distinguish from other neurological gait disorders.

6.5.2. Cerebellar Ataxia Subtype Stratification

Although, genetic forms of ataxia are associated with heterogeneity of symptoms, here many CA subtypes were assumed to be homogeneous in the interest of exploring the influence of symptom severity and progression. Of the participants recruited to the clinical studies, while some participants had previously received a diagnosis of a "pure" cerebellar ataxia (e.g. SCA6), others exhibited a more complex gait impairment with spasticity and weakness involved (e.g. SPG7). Combining these cohorts may mask the differences that are inherent to the clinical features, (Coarelli et al., 2019). Therefore, further work is underway to explore the differences between these specific genotypes. In future, recruitment of a larger cohort of each will be necessary to confirm the diagnostic value of instrumented gait tests in this situation. To assist with this effort, the inclusion of genetic testing and magnetic resonance imaging (MRI) would allow a better stratification of ataxia subtypes by allowing accurate genotyping and assessment of neurological degeneration.

6.5.3. Longitudinal Gait Changes

As discussed previously, in the present cohort, no disease progression appears to have occurred within the study period. Since progression of CA, changes over a longer period than 12months, to assess whether ataxic gait pattern reflects longitudinal disease progression, further characterisation in a larger, better-defined cohort and in comparison, to other disease groups over a longer follow-up interval is required.

Since no disease progression occurred in this time point, it is not possible to determine whether the pre-selected variables implemented here would be sensitive to disease progression. As these were selected on the basis of baseline disease severity and ability to differentiate CA from HC, some features of the gait pattern may have been missed due tp the criteria implemented. Further work is needed to assess the gait changes in a hypothesis free manner and to develop a model of gait in CA. This will help establish gait measures as biomarkers for disease progression in addition to stratifying for disease severity.

6.5.4. MACHINE LEARNING

Through the use of machine learning techniques, it may be possible to identify gait parameters and patterns that might be most effective at distinguishing between healthy controls and individuals with ataxia. Machine learning algorithms group data points based upon statistical similarity rather than testing pre-specified hypotheses. These techniques can involve a phase of training based on previous datasets before testing new datasets to find and recognise patterns.

In this way, the classification of participants by analysing gait data using machine learning techniques could improve generalisability to a wider population and identification of patterns unique to specific disease groups. It is important to balance sensitivity and specificity in order to appropriately diagnose ataxic gait without falsely classifying healthy gait as a disease.

Automated pattern recognition systems such as an artificial neural network (ANN) and support vector machine (SVM) methods have previously been implemented to classify neurological gait disorders using data from the GaitRite pressure-sensitive carpet (Pradhan et al., 2015). Researchers successfully classified spatiotemporal gait patterns of phobic postural vertigo, CA, progressive supranuclear palsy (PSP), bilateral vestibulopathy (BVP), and healthy participants with high sensitivity. This study also indicated the relevance of the difference between gait patterns when selecting a machine learning method since high false-negative rates were present for BVP and PSP depending on the method used.

Using the full gait signals to classify gait rather than predetermined variables, may permit finer resolution of gait abnormalities and reveal novel biomarkers of disease progression. However, it is vital to establish the essential gait and postural information required to distinguish healthy from ataxic gait and between movement. For instance, if classification can be made based on a single sensor-based approach to gait analysis, then it may be quicker and easier to capture and process gait data while being minimally intrusive to participant gait. In addition, these requirements could be improved by identifying gait tasks most likely to distinguish the gait of healthy individuals and different disease subgroups such as fast-paced walking, tandem walking, simulated activity tasks or dual-task gait conditions. These gait tasks have not been explored in this thesis but can add value to studies of gait in neurodegenerative gait disorders.

6.5.5. REAL WORLD GAIT ANALYSIS IN HEREDITARY CEREBELLAR ATAXIA

Observation and test conditions can influence the behaviour being measured (McCambridge et al., 2014). This is in part due to the considerable differences in observed gait in a clinical or laboratory setting and that seen in daily life (Storm et al., 2016). Indeed, inconsistencies between average daily gait speed and average in-laboratory gait speed have been identified (Takayanagi et al., 2019).

Further, even in healthy individuals, the physical activity level is sensitive to changing abilities. For instance, older adults demonstrate a decreased energy expenditure and physical activity (Meijer et al., 2001), and display a tendency to spend a higher proportion of daily life in lower intensity activities than younger healthy controls (Copeland and Esliger, 2009).

Recent studies have shown the importance of capturing real-life physical activity in pathological cohorts. Remote monitoring of physical activity has been shown to be feasible in many neurological conditions including ataxia and offer the ability to quantify walking gait and falls in daily life (Block et al., 2016, Ilg et al., 2018). However, a single study has explored physical activity in individuals with CA (Subramony et al., 2012). This study reported that during home-based gait monitoring in Spinocerebellar Ataxia (SCA) physical activity correlated with disease duration and participant's functional stage. More recently, gait has been measured during "supervised free walking" and "real-life walking" conditions in ataxia where stride time variability and harmonic ratio AP distinguished subgroups during lab-based walking (Ilg et al., 2019).

In future, we hope to corroborate these findings in our cohort of participants. Therefore, a subset of participants (n=11) within the present observational study of gait in CA (Chapter 4, Chapter 5), completed week-long physical activity monitoring using the Dynaport Movemonitor (MM+, McRoberts, The Hague, The Netherlands) in a subset of participants in addition to their within-clinic gait analysis tests. These participants wore the Dynaport MM+ using an elastic belt alongside the ADPM Opal sensors during clinic-based gait analysis to enable validation of gait event detection. Then by wearing the sensor over a seven-day period, data on the participants' gait and movement in the home environment to will provide a measure of their gait in a "natural" setting.

As well as using the proprietary processing platform (MyMcRoberts) to generate physical activity monitoring reports relating to physical activity type, raw triaxial accelerometry data will be processed to compute spatiotemporal and upper body motion gait characteristics over the seven-day period. This will use similar processing methods to that described in Chapter 4 and Chapter 5. Since participants were asked to complete the physical activity diary, a validation of the activity types completed during this time, and the length of time each activity was performed for can be provided. This will enable us to determine which laboratory gait parameters correlate best with real-life activity levels and assess gait characteristics during free walking periods for comparison against those captured during laboratory testing.

6.5.6. ACCEPTABILITY STUDY

At present, there are no guidelines regarding the use of gait analysis in the diagnosis of CA or diagnostic values and thus, they have not been implemented into clinical practice. For gait analysis to be truly feasible in a clinical setting it should provide real-time clinical feedback and provide a tangible improvement on the current gait assessment methods. Equipment with real clinical potential will need to be simple to use, provide easy to interpret results, relatively cheap, and appropriate to the setting in which assessment will occur. To encourage healthcare providers to invest and make them part of standard practice, it is also essential that their use in a clinical setting is tolerated well by patients and clinicians.

Therefore, in future, a mixed methods patient and clinician centred acceptability study should be completed to enable feedback to be gathered about how well this equipment would be accepted in a clinical setting and at home for monitoring of real-life gait. A small number of studies have been completed in individuals with Multiple Sclerosis (Newland et al., 2016), Parkinson's disease (Cancela et al., 2014) and stroke survivors (Taylor-Piliae et al., 2016) to explore the acceptability of using in-home and wearable sensor technology for fall risk detection and continuous remote monitoring of symptoms.

Since gait has real potential as a novel biomarker, a similar acceptability study for assessment of gait in a clinical or real-life setting would support our findings and emphasise the benefit that gait analysis could provide to patient care and clinical assessment. In this

way, health trusts and services can potentially be encouraged to invest in the equipment and resources required to incorporate gait assessment techniques into clinical practice.

6.6. Overall Conclusion

Instrumented gait analysis tests have the potential to identify and diagnose cases of movement disorders by capturing subtle characteristics more accurately than present methods. Motion analysis techniques have been shown to be comparable to the current gold standard of movement assessment in Parkinson's Disease: the UPDRS ptIII (Parisi et al., 2015). An early attempt by Ferrarin et al. (2005) in the context of CA, demonstrated moderate to good correlations between the results of kinematic analysis and the equivalent ICARS items.

Our systematic review of the literature and our validation and longitudinal gait analysis study, indicate the diagnostic ability to differentiate HC from in CA. This project has also identified gait variables that correlate well with SARA and BBS scores at baseline in CA and discriminate ataxic gait pattern from Healthy gait and between CA subgroups stratified for disease severity. No disease progression occurred over a 12 month period in the CA cohort therefore, although some variables exhibit significant changes over time this may not reflect a genuine functional change. Further work is required in order to establish whether the objective measurement of the CA gait pattern can provide a novel biomarker for disease progression. Since gait analysis variables appear to be superior to present methods of examination in the monitoring of gait changes over time, our findings contribute to the body of literature suggesting the value of gait measures in clinical practice and research (Gordt et al., 2018).

In future, as well as confirming our findings in larger cohorts, continuing real-life monitoring, examination of the gait patterns specific to different movement disorders and ataxia subtype is essential. This will enable the future use of gait measures as endpoints in clinical trials, and objective methods of monitoring disease progression.

Routine gait analysis in the UK, is restricted to expensive 3D motion capture techniques. The uptake of more portable gait analysis systems such as wearable sensors might provide valuable data to clinicians regarding patient physical activity and gait impairment. Since this vital information can be captured in a more realistic setting than a clinical gait analysis lab, this has potential to be more clinically relevant and widespread than motion capture. This

could enable the accurate characterisation of gait, and measurement of falls occurrence, physical activity, and real-world gait impairment. There is potential to save time and money for the NHS and patients by reducing the amount of time spent in clinic. For instance, in future, clinician's may be able to refer patients to physical activity monitoring or gait analysis tests prior to a care review in order to discuss recent gait impairment and treatment effects more reliably than is possible with current subjective methods. Taken further, clinicians could review a patient's progress to avoid unnecessary clinic visits in stable patients and prompt further clinic visits for individuals most in need.

These results indicate that gait measures are able to differentiate between healthy controls and disease severity subgroups in CA. Although further work is needed to clarify whether the gait changes occur in CA in line with disease severity, instrumented gait tests have potential in the monitoring of disease progression in CA. This will make it possible to accurately monitor intervention effects, and produce evidence for rehabilitation and treatment options that are available to patients and clinicians.

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APPENDIX

Chapter 2 (Systematic Review) supplementary material

Appendix 1: Literature Search Strategies.

Psycinfo via OvidSP:	Medline via OvidSP:
1. cerebellar ataxia.ti,ab.	1. cerebellar ataxia.ti,ab.
2. gait Ataxia.ti,ab.	2. exp Cerebellar Ataxia/
3. exp ataxia/	3. gait Ataxia.ti,ab.
4. 1 or 2 or 3	4. exp Gait Ataxia/
5. (measur* or assess*).ti,ab.	5. 1 or 2 or 3 or 4
6. (evaluat* or examin*).ti,ab.	6. (measur* or assess* or analysis or analyse or
7. (analysis or analyse or analyze).ti,ab.	analyze).ti,ab.
8. Biomechanic.ti,ab.	7. (evaluat* or examin*).ti,ab.
9. exp biomechanics/	8. Biomechanic.ti,ab.
10. kinematic.ti,ab.	9. kinematic.ti,ab.
11. instrumented.ti,ab.	10. instrumented.ti,ab.
12. gait analysis.ti,ab.	11. gait analysis.ti,ab.
13. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	12. 6 or 7 or 8 or 9 or 10 or 11
14. exp Walking/	13. exp Walking/
15. (walk or walks).ti,ab.	14. (walk or walks).ti,ab.
16. gait.ti,ab.	15. gait.ti,ab.
17. exp Gait/	16. exp Gait/
18. exp Locomotion/	17. exp Locomotion/
19. locomotion.ti,ab.	18. locomotion.ti,ab.
20. 14 or 15 or 16 or 17 or 18 or 19	19. 13 or 14 or 15 or 16 or 17 or 18
21. 4 and 13 and 20	20. 5 and 12 and 19

PubMed:

(((((((((Walking[Title/Abstract]) OR walk[Title/Abstract]) OR walks[Title/Abstract]) OR gait[Title/Abstract]) OR Locomotor[Title/Abstract]) OR Locomotion[Title/Abstract]))
AND ((((((((measur* [Title/Abstract]) or evaluat*[Title/Abstract]) or examin*[Title/Abstract]) OR assess* [Title/Abstract]) OR analysis[Title/Abstract]) OR analyse[Title/Abstract]) OR analyze[Title/Abstract]) OR Biomechanic[Title/Abstract]) OR kinematic[Title/Abstract]) OR instrumented[Title/Abstract]) OR gait analysis[Title/Abstract]))
AND ((((cerebellar ataxia[Title/Abstract]) OR cerebellar/ataxic[Title/Abstract]) OR ataxia/cerebellar[Title/Abstract]) OR gait ataxia[Title/Abstract])

IEEExplore (metadata only):

(Walking OR walk OR walks OR gait OR Locomotor OR Locomotion)
AND (Measur* OR assess* OR analysis or evaluat* or examin*OR analyze OR analyse OR Biomechanic OR kinematic OR instrumented OR gait analysis)
AND (cerebellar ataxia OR gait ataxia)
Web of Science Core Collections:
TS=(Measur* OR assess* OR analysis OR analyze OR analyse or evaluat* or examin* OR Biomechanic OR kinematic OR instrumented OR gait analysis)
AND TS=(Walking OR walk OR walks OR gait OR Locomotor OR Locomotion)
AND TS=(cerebellar ataxia OR gait ataxia)

Scopus:

(TITLE-ABS-KEY (walking OR walk OR walks OR gait OR locomotor OR locomotion)
AND TITLE-ABS-KEY (measur* OR assess* or evaluat* or examin* OR analysis OR analyze OR analyse OR biomechanic OR kinematic OR instrumented OR gait analysis)
AND TITLE-ABS-KEY (cerebellar ataxia OR gait ataxia))
Cochrane trials database:
(Walking or walk or walks or gait or Locomotor or Locomotion):ti,ab
AND (Measur* or assess* or evaluat* or examin* or analysis or analyze or analyse or Biomechanic or kinematic or instrumented or gait analysis):ti,ab
AND (cerebellar ataxia or gait ataxia):ti,ab

The strategy comprised of three key levels of search terms and was adapted for each of the databases searched.

Appendix 2: Inclusion & Exclusion Criteria for Article Screening.

	Inclusion Criteria	**Exclusion Criteria**
Participants/ Population:	Adult (Age 18yrs Or Older), Diagnosis of Cerebellar Ataxia, Human	Animal, Robot, Amputee, Inpatient, Freezing of Gait, Heart, Blood, Cardiac Related Study, Women or Men Only
Intervention(s), Exposure(s):	Assessed During Walking on a Treadmill or Overground but are not required to undergo any type of intervention	Gait Assessed Via Observation or Rating Scale or Single Muscle Kinetics Analysis or Activity Monitoring
Comparator(s)/ Control:	Control population (no known morbidities, age & gender matched)	
Outcome(s):	Spatiotemporal characteristic measured	
Study Types:	All designs.	Not English, review, earlier than 1996

To be applied to screening of Title, Abstract and Full Texts.

Appendix 3: Quality Assessment Scale.

When assessing an article, for each question give rating of: Yes (Y); No (N); cannot determine (CD); not applicable (NA); not reported (NR). Then at the reviewer's discretion a rating of "Good", "Fair" or "Poor" should then be assigned to judge whether the article has a low, some or high risk of bias respectively.
1. Was the research question clearly stated?
2. Were the inclusion and exclusion criteria clearly stated?
3. Was the study population clearly specified and defined?
4. Were the subjects in the study representative of the pathological population?
5. Were all the subjects selected or recruited from the same or similar populations (including the same time period)?
6. Did control group's age and gender match those of the pathological group?
7. Was a sample size justification via power analysis provided?
8. Were the main findings of the study clearly described?
9. Were the spatiotemporal gait parameters well defined?
10. Were trial instructions clearly stated and uniformly applied to all participants?
11. Was the walking protocol appropriate to measure spatiotemporal gait parameters?
12. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?
13. Were the outcome assessors blinded to the exposure status of participants?

Adapted from NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (QATOCCS).

Appendix 4: Full Study Information.

Reference	Participants	Clinical assessment at baseline (average ± SD or median (range))	Research Question	Publication Type	Study Design	Gait Analysis Protocol	Gait parameter reported	Country of Study	Quality Assessment Result
Caliandro et al. (2015)	Mixed CA: 19, 10F Control: 15, 8F		Maintenance of dynamic balance	1	3	3D Motion Capture System; 10m walking; barefoot; preferred speed.	Stance, swing time, DLS%, speed, step length, step width + kinematic joint features	ITL	G
Chini et al. (2016)	Mixed CA: 16, 5F Control: 16, 5F	ICARS: 22.5±12.6 No. Falls (1yr): 3.0±6.1	Local stability with STPs and falls history	1	3	Inertial sensor; 20m walkway; 16 passes; preferred (CA) and slow (HS) speed; barefoot.	Cadence, DLS%, Speed, Stance%, Stride Length, Stride Time, Swing%	ITL	G
Conte et al. (2014)	Mixed CA: 16, 5F Controls: 16, 5F	Brain Atrophy: 5*Mild, 6*Moderate, 5*Severe ICARS: 25.1±18.8	Upper body kinematics	1	3	3D Motion Capture System; 8m walkway; barefoot; comfortable and slow (HS) speed.	Cadence, DLS%, Speed, Stance%, Step Length, Step Length CV, Step Width, Stride Time, Swing%	ITL	G
Ebersbach et al. (1999)	Mixed CA: 20, 7F Control: 30, 3F		Step length-speed relationship in preferred pace walking	1	3	Pulley system via optical recording device; 10m walking; 10 passes; normal, slow, fast, very slow, very fast speed.	Cadence, DLS%, Speed, Step Length CV, Stride Time CV, Sway Path	AT	F
Gouelle et al. (2013)	FRDA: 14 adults, 9F (of 31 total) Control: 123, 65F	FAPS: 88.9±11.9 ICARS: 28.4±8.5 PGD: 13.3±4.8	Development of gait variability index	1	3	Pressure Sensitive Mat; comfortable speed; bare-foot; 488, 610 or 732 cm mat with 2m run-up and 2m exit; min. 3 trials. (data taken from assessments at	SLS Time, Speed, Stance Time, Step Length, Step Time, Stride Length, Stride Time, Swing Time	FR	F

						6month intervals over 2 year follow-up period)			
Ienaga et al. (2006)	All Ataxia: 18, 7F MSAc: 8, 3F SCA6: 4, 1F 16qADCA: 6, 3F Control: 6, 3F	ICARS	Dynamic imbalance and irregular stepping	1	3	3D Motion Capture System + insole pressure sensors; preferred speed; 6 consecutive steps.	Cadence, Speed, Stance Time, Step Width, Stride Length, Swing Time	JP	F
Ilg et al. (2007)	Mixed CD: 13, 5F Control: 9, 3F	ICARS: 23.4±11.0	STPs vs variability of joint coordination	1	3	3D Motion Capture System, self-selected pace; barefoot; 8-12 gait cycles from 2-3 trials.	Speed, Step Length, Step Width, Stride Time, Sway Path, Swing Time	DE	F
Ilg et al. (2009)	All Ataxia: 16, 8F CA: 10, 5F AA: 6, 3F	SARA: 16.4±6.0 ICARS: 45.1±9.0	Effectiveness of 4-week coordinative training programme	1	4	3D Motion Capture System; self-selected pace; barefoot; 12-15 gait cycles from 3 trials; examination at 4 time points (incl. 8 weeks before and after training).	Speed, Step Length, Step Width, Sway Path	DE	G
Im et al. (2016)	Mixed CA: 19, 12F	ICARS: 34.2±6.8	Rehabilitation in CA via 12-week training programme	1	4	3D Motion Capture System; preferred & slow speeds; 6m walkway; examination before, and after training and at 3month follow-up;	COM Displacement, COM Velocity, SLS Time, Step Length, Step Width	KR	F
Martino et al. (2014)	Mixed CA: 19, 5F Control: 20, 7F	ICARS: 16.7±7.8	Muscle activation patterns & kinematics, kinetics vs pathology severity	1	3	3D Motion Capture System & Surface EMG; ~7m walkway; barefoot; preferred, fast (CA) & slow (HS) speed; min. 15 trials.	Speed, Stance Time, Step Width, Stride Length, Stride Time	ITL	G
Matsushima et al. (2015)	Mixed CA: 51, 27F Control: 56, 28F	SARA: 8.6±3.6 (1-16) SARA G+S: 3.9±2 (0-8)	Usefulness of triaxial accelerometer with 6 month follow-up	1	3	Inertial sensor; 10m walkway; 12 repeats; comfortable speed, 6 month follow-up	Cadence, Speed, Step Length	JP	F

Milne et al. (2014)	FRDA: 13, 1F	FARS: 57.3±12.3 (34-76.5) 25FWT: 6.7±1.5 (5.3-9.1)	STPs at different walking speeds	1	3	Pressure Sensitive Mat; 830cm mat + 80cm run-up and exit; 6 trials; preferred, fast & slow speed	Base of Support, Cadence, DLS%, Speed, Stride Length, Swing%	AU	F
Mondal et al. (2015)	Mixed SCA: 23, 9F		Influence of cognitive load on gait	2	3	Pressure Sensitive Mat	Base of Support, Cadence, Speed	IN	CD
Palliyath et al. (1998)	Mixed CD: 10, 1F Control: 10, 1F	HMCS Balance: 1.8±1.1 HMCS Gait: 2.4±1.3	Quantitative Analysis in CA	1	3	3D Motion Capture System & Force plates; barefoot; self-selected speed; 0.606x2.24x2.04 volume 6-10 trials	Cadence, Heel Off Time, Speed, Stance Time, Step Length, Step Length Asymmetry, Step Length CV, Step Time, Step Width, Step Width Asymmetry, Step Width CV, Stride Length, Stride Length Asymmetry, Stride Length CV, Stride Time, Stride Time CV, Swing Time, Toe off Time	USA	F
Rochester et al. (2014)	SCA6: 18, 13F Preclinical SCA6: 6, 4F Control: 25, 17F	(HS vs Clin) ICARS: 3 (1, 3) vs 20.5 (13.8, 20.5) (HS vs Pre-Clin vs Clin) ABCS: 96±3.7 vs 86.3±8.1 vs 59.2±24.3 No. Falls (3mo): 0/25, 1/6, 4/18	Pre-symptomatic gait	1	3	Pressure Sensitive Mat; 7m mat within 12m walkway; 4 trials; comfortable speed	Cadence, Speed, Step Length, Step Length Asymmetry, Step Length CV, Step Time Asymmetry, Step Width, Step Width CV	UK	G
Schmitz-Hübsch et al. (2016)	SCA14: 8, 3F Control: 9, 6F	INAS (3.1 (1-6)), SARA (10.7 (6.5-14.5))	Features of SCA14	1	3	Pressure Sensitive Mat; 5.1m mat within 8m walkway; 10 trials; comfortable, slow, very slow, fast, max speeds	Base of Support, Cadence, Speed, Step Length CV, Stride Length, Stride Length CV, Stride Time, Stride Time CV, Walk Ratio	DE	G
Schniepp et al. (2014)	Mixed CA: 48, 22F	SARA: 10 (3,20) BBS: 4 (2,8) FGA: 17,(6,30)	Gait variability and falls in CA	1	3	Pressure Sensitive Mat; 6.7m mat with 1.5m run-up and 1.5m exit; preferred, slow, fast speeds	Base of Support, Base of Support CV, Cadence, DLS%, Speed, Stride Length, Stride	DE	G

		No. Falls (6mo): 0=21/48, 1=10/48, >2=17/48					Length CV, Stride Time, Stride Time CV		
Seidel and Krebs (2002)	Mixed CD: 32, 13F Control: 34, 18F		Neuro impairments and base of support with free and paced walking	1	3	3D Motion Capture System, Force plates & LED array; 10m walkway; barefoot; preferred speed and paced; two trials in each condition (free vs metronome (120bpm))	Base of Support, Speed	USA	F
Serrao et al. (2012)	All Ataxia: 16, 8F SCA1/2: 8, 2F FRDA: 8, 6F Control: 15, 7/8F	ICARS: 23±10.8	Global and segmental features of gait in hereditary ataxias	1	3	3D Motion Capture System & Force plates; barefoot; comfortable speed, 4m examined from 10m walkway; 10 gait cycles from 5 trials	DLS%, Stance%, Step Length, Step Width, Stride Time, Swing Velocity	ITL	G
Stephenson et al. (2015)	FRDA: 8, 2F Control: 8, 2F	BBS: P<0.05 LOS Test: 48±1.3 (44-56)	Gait in FRDA	1	3	Pressure Sensitive Mat; comfortable & fast speed; 7.93m mat with 1m run-up and >1m exit; 5 trials for each speed	Cadence, DLS%, Speed, Stance%, Step Length, Stride Length, Stride Length CV, Swing%	USA	G
Wuehr et al. (2013)	Mixed CA: 11, 8F Control: 11, 8F	(HS Vs CA) FES: 19.2±2.3 vs32.5±8.3 ABCS: 94.0±12.3 Vs 57±16.3 SARA: 14.0±5.8 FGA: 29.0±-3.1 Vs 16.7±5.6	Variability with speed	1	3	Pressure Sensitive Mat & Pressure Sensitive Treadmill; 6.7m mat with 1.5m run-up and 1.5m exit; preferred and max speed; 2 trials at each speed; five 5min trials on treadmill at Preferred, & 20%, 40%, 70%, 80% of Max. speed	Base of Support CV, Stride Length CV, Stride Time CV	DE	F

Full details of study information including quality assessment results. Abbreviations: F-Female, SD-standard deviation, 1 - Journal Article, 2 - Conference Abstract; 3 - Prospective Observational, 4 - Intervention, ITL - Italy, AT - Austria, FR - France, JP - Japan, DE - Germany KR - South Korea, AU - Australia, IN – India, G-good, F-fair, CD-cannot determine.

Appendix 5: Full Quality Assessment Results

	Caliandro, P., et al. (2015).	Chini, G., et al. (2016).	Conte, C., et al. (2014).	Ebersbach, G., et al. (1999).	Gouelle, A., et al. (2013).	Ienaga, Y., et al. (2006).	ilg, W., et al (2009)	Ilg, W., et al. (2007).	Im, S. J., et al. (2016).	Martino, G., et al. (2014).	Matsushima, A., et al. (2015).	Milne, S. C., et al. (2014).	Mondal, B., et al. (2015).	Palliyath, S., et al. (1998).	Rochester, L., et al. (2014).	Schmitz-Hubsch, T., et al. (2016).
Overall Rating (Good, Fair, Poor)	**G**	**G**	**G**	**F**	**F**	**F**	**F**	**G**	**F**	**G**	**F**	**F**	**CD**	**F**	**G**	**G**
1. Was the research question clearly stated?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
2. Were the inclusion and exclusion criteria clearly stated?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
3. Was the study population clearly specified and defined?	CD	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
4. Were the subjects in the study representative of the pathological population?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y
5. Were all the subjects selected or recruited from the same or similar populations (including the same time period)?	CD	Y	Y	Y	CD	Y	Y	Y	Y	Y	Y	Y	CD	Y	Y	Y
6. Did control group's age and gender match those of the pathological group?	Y	Y	Y	Y	N	Y	N/A	Y	N/A	Y	Y	N/A	CD	Y	Y	Y
7. Was a sample size justification via power analysis provided?	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
8. Were the main findings of the study clearly described?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
9. Were the spatiotemporal gait parameters well defined?	Y	Y	N	N	Y	N	Y	Y	N	Y	Y	Y	N	Y	Y	Y
10. Were trial instructions clearly stated and uniformly applied to all participants?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	CD	Y	Y	Y
11. Was the walking protocol appropriate to measure spatiotemporal gait parameters?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	CD	Y	Y	Y
12. Were key potential confounding variables measured and adjusted statistically for their impact	Y	Y	Y	Y	N	Y	N	Y	N	Y	N	Y	CD	Y	Y	Y

Y, Yes; N, No; CD, cannot determine; NA, not applicable; NR, not reported

Appendix 6: Full Study Results.

All data extracted from the 21 included articles. (Green= data collected within a protocol where patients and controls were matched for speed, Blue = result standardised/normalised to height or leg length, orange=variability measured as combined Left/Right standard deviation, yellow=results calculated from subgroup results following cochrane review guidelines)

i) Demographic characteristics of each cohort from the included studies

cohort	no._total	no._female	no._male	age_mean (yrs)	age_SD	Height_mean (cm)	Height_sd	Mass_mean (kg)	Mass_SD	leglength_mean (cm)	leglength_SD	BMI_mean	BMI_SD	diseaseduration_mean (months)	diseaseduration_sd
Caliandro_2016_CA	19	10	9	50.5											
Caliandro_2016_HC	15	8	7	54.5											
Chini_G_2016_CA	16	5	11	50.5	8.9									14.3	6.8
Chini_G_2016_HC	16	5	11	49.8	8.8										
Conte_C_2014_CA	16	5	11	51.0	10.7	165.8	8.4	69.7	7.9			24.4	3.0	10.9	6.4
Conte_C_2014_HC	16	5	11	51.5	11.9	168.5	9.1	69.1	7.1			22.6	2.8		
Ebersbach_G_1999_CA	20	7	13	41.4	14.2	169.2	8.1								
Ebersbach_G_1999_HC	30	11	19	60.9	9.0	171.8	9.1								
Gouelle_A_2013_CA	14	9	5	20.5	1.9	166.0	8.3			85.0	4.0				
Gouelle_A_2013_HC	123	65	58	32.3	12.8	167.9	8.3			87.0	4.0				
Ienaga_Y_2006_CA	18	7	11	61.6	6.4									45.9	44.9
Ienaga_Y_2006_CA_ADCA	6	3	3	62.5	6.6									36.8	32.0
Ienaga_Y_2006_CA_MSAc	8	3	5	61.3	7.8									27.8	24.6
Ienaga_Y_2006_CA_SCA	4	1	3	61.0	4.2									96.0	62.7
Ienaga_Y_2006_HC	6	3	3	58.3											
Ilg_W_2007_CA	13	5	8	50.4	14.4										

Ilg_W_2007_HC	9	3	6	48.1	13.8										
ilg_W_2009_CA	16	8	8	61.4	11.2									12.9	7.8
ilg_W_2009_CA_AA	6	3	3	56.2	12.9									17.7	5.4
ilg_W_2009_CA_CA	10	5	5	64.6	9.4									10.0	7.8
Im_S_J_2016_CA	19	12	7	53.2	13.8									4.5	5.4
Martino_G_2014_CA	19	5	14	48.5				68.0	8.0	78.0	6.0			11.0	7.1
Martino_G_2014_HC	20	7	13	52.0				70.0	14.0	80.0	5.0				
Matsushima_A_2015_CA	51	27	24	60.3	10.4									8.7	6.5
Matsushima_A_2015_HC	56	28	28	57.2	14.1										
Milne_S_C_2014_CA	13	1	12	32.0	12.9	173.2	7.8	70.1	18.5			23.1	4.9	11.6	4.9
Mondal_B_2015_CA	23	9	14	47.2	12.1										
Palliyath_S_1998_CA	10	1	9	45.5	13.9	175.3	7.7	79.5	3.5			26.4	5.0		
Palliyath_S_1998_HC	10	1	9	46.0											
Rochester_L_2014_CA	18	13	5	61.5	8.5	165.0	8.0	78.8	12.5			28.6	3.7	3.7	3.2
Rochester_L_2014_HC	25	17	8	50.2	12.2	167.0	9.0	74.1	13.7			26.6	4.6		
Schmitz-Hübsch_T_2016_CA	8	3	5	53.0		172.0		81.0				27.4		216.0	
Schmitz-Hübsch_T_2016_HC	9	6	3	50.0		173.0		78.0				26.1			
Schniepp_R_2014_CA	48	22	26	64.3	17.8	171.0	6.0	76.3	8.6			26.1		54.8	32.3
Seidel_B_and_D_E_Krebs_2002_CA	32	13	19	45.0	13.2							33.9	6.7		
Seidel_B_and_D_E_Krebs_2002_HC	34	18	16	46.9	15.0							25.0	3.5		
Serrao_M_2012_CA	16	8	8	40.1	15.8									132.8	113.5
Serrao_M_2012_CA_FRDA	8	6	2	33.1	18.5									121.5	82.0
Serrao_M_2012_CA_SCA	8	2	6	47.1	9.2									144.0	143.6
Serrao_M_2012_HC	15	7	8	40.0	15.8										
Stephenson_J_2015_CA	8	2	6	29.4	9.0	174.3	13.8	75.8	19.2			25.0		9.9	3.8
Stephenson_J_2015_HC	8	2	6	29.6	9.1	174.0	12.5	75.2	16.9			24.8			
Wuehr_M_2013_CA	11	8	3	47.0	9.4	176.9	6.7			91.2	6.2				
Wuehr_M_2013_HC	11	8	3	46.1	17.8	168.8	17.8			90.5	7.1				

ii) gait variables reported in each cohort from the included studies

Cohort	BaseWidth_ave (m)	BaseWidth_sd	Cadence_ave (no. steps/min)	Cadence_sd	DLSPhase_perc_cycle_ave (% Gait Cycle)	DLSPhase_perc_cycle_sd	DLSPhase_perc_cycle_Var_ave (%CV)	DLSPhase_perc_cycle_Var_sd	Speed_ave (m/s)	Speed_sd	Speed_Var_ave (%CV)	Speed_Var_sd	Stance_Phase_perc_cycle_ave (% Gait Cycle)	Stance_Phase_perc_cycle_sd	Stance_Phase_perc_cycle_var ave (%CV)	Stance_Phase_perc_cycle_var sd	Step_Length_ave (m)	Step_Length_sd
Caliandro_2016_CA	0.2	0.1			19.2	10.4			0.6	0.3			68.5	10.1			0.3	0.1
Caliandro_2016_HC	0.2	0.0			11.1	1.6			1.0	0.2			60.9	1.6			0.6	0.1
Chini_G_2016_CA			100.6	20.2	15.5	4.6			1.1	0.3			65.3	4.6				
Chini_G_2016_HC			96.9	17.3	14.6	3.4			0.9	0.2			64.7	3.5				
Conte_C_2014_CA	0.2	0.0	52.3	4.9	13.7	3.2	16.0	8.1	0.8	0.3	8.7	6.5	63.5	3.3	3.8	1.7	0.4	0.1
Conte_C_2014_HC	0.2	0.0	43.5	5.7	13.9	2.1	9.4	5.3	0.8	0.2	10.2	15.4	63.9	2.1	2.2	0.6	0.5	0.1
Ebersbach_G_1999_CA			93.1	11.1					0.7	0.2								
Ebersbach_G_1999_HC			98.5	7.3					1.0	0.1								
Gouelle_A_2013_CA	0.1	0.1	97.3	14.2	24.8	6.6	18.5	11.6	1.0	0.2	12.6	8.5	62.3	4.4	9.1	6.1	0.6	0.1
Gouelle_A_2013_HC	0.1	0.0	117.3	7.0	21.5	2.0	7.5	1.8	1.3	0.1	2.9	0.8	60.6	1.0	2.6	0.5	0.7	0.1
Ienaga_Y_2006_CA	0.2	0.0	93.6	15.3					0.8	0.2								
Ienaga_Y_2006_CA_ADCA	0.2	0.0	89.2	8.7					0.7	0.2								
Ienaga_Y_2006_CA_MSAc	0.2	0.0	98.8	12.7					0.8	0.2								
Ienaga_Y_2006_CA_SCA	0.1	0.1	89.6	26.2					0.6	0.3								
Ienaga_Y_2006_HC	0.1	0.0	113.6	4.9					1.3	0.1								
Ilg_W_2007_CA	0.1	0.0							0.8	0.2							0.5	0.1
Ilg_W_2007_HC	0.1	0.0							1.2	0.1							0.6	0.1
ilg_W_2009_CA									0.8	0.1								
ilg_W_2009_CA_AA									0.7	0.1								
ilg_W_2009_CA_CA									0.9	0.1								

Im_S_J_2016_CA																		
Martino_G_2014_CA	0.4	0.1							1.1	0.1			65.0	2.6				
Martino_G_2014_HC	0.3	0.0							1.1	0.1			64.9	2.6				
Matsushima_A_2015_CA			111.7	11.4					0.9	0.3	29.6						0.5	0.1
Matsushima_A_2015_HC			117.0	7.8					1.3	0.1	9.4						0.7	0.1
Milne_S_C_2014_CA	0.1	0.1	105.6	7.6	24.7	5.8	1.4	0.8	1.2	0.2	5.2	2.1						
Mondal_B_2015_CA																		
Palliyath_S_1998_CA	0.1	0.0	102.2	15.9					0.5	0.2	5.7	2.2					0.3	0.1
Palliyath_S_1998_HC	0.2	0.1	111.0	7.6					0.9	0.4	3.8	4.5					0.5	0.2
Rochester_L_2014_CA	0.2	0.1	101.2	18.3					1.0	0.3							0.5	0.2
Rochester_L_2014_HC	0.1	0.0	119.0	9.2					1.5	0.2							0.8	0.1
Schmitz-Hübsch_T_2016_CA	0.2	0.0	111.6	9.8	25.9	4.5			1.0	0.2								
Schmitz-Hübsch_T_2016_HC	0.1	0.0	107.1	8.3	23.5	4.0			1.3	0.2								
Schniepp_R_2014_CA	0.1	0.1	102.0	15.0	31.0	9.0			0.9	0.3								
Seidel_B_and_D_E_Krebs_2002_CA	0.2	0.1							1.0	0.2								
Seidel_B_and_D_E_Krebs_2002_HC	0.2	0.0							1.3	0.2								
Serrao_M_2012_CA	0.2	0.0			13.5	0.5	9.9	1.1	1.1	0.1	4.7	0.6	67.7	2.7	5.7	0.6	0.6	0.1
Serrao_M_2012_CA_FRDA	0.2	0.0			13.3	0.5	10.6	1.1	1.1	0.1	4.3	0.5	67.9	2.3	5.4	0.6	0.6	0.0
Serrao_M_2012_CA_SCA	0.2	0.0			13.8	0.6	9.1	0.4	1.0	0.1	5.1	0.3	67.5	2.8	6.0	0.5	0.7	0.1
Serrao_M_2012_HC	0.1	0.0			7.7	0.3	4.4	0.9	1.4	0.1	3.7	0.9	60.4	2.0	2.4	0.7	0.7	0.0
Stephenson_J_2015_CA			78.3	18.6	31.0	6.8			0.7	0.3			65.6	3.4			0.5	0.1
Stephenson_J_2015_HC			112.2	8.6	21.5	2.1			1.4	0.1			60.4	1.1			0.7	0.1
Wuehr_M_2013_CA	0.1	0.1							1.0	0.2								
Wuehr_M_2013_HC	0.1	0.0							1.2	0.2								

iii) Further gait variables reported in each cohort from the included studies

cohort	Step_Length_Var_ave (%CV)	Step_Length_Var_sd	Step_Time_ave (secs)	Step_Time_sd	Step_Width_Var_ave (%CV)	Step_Width_Var_sd	Stride_Length_ave (m)	Stride_Length_sd	Stride_Length_Var_ave (%CV)	Stride_Length_Var_sd	Stride_Time_ave (secs)	Stride_Time_sd	Stride_Time_Var_ave (%CV)	Stride_Time_Var_sd	Swing_Phase_perc_cycle_ave (% Gait Cycle)	Swing_Phase_perc_cycle_sd	Swing_time_ave (secs)	Swing_time_sd
Caliandro_2016_CA															30.3	9.8		
Caliandro_2016_HC															39.2	1.6		
Chini_G_2016_CA							1.1	0.2			1.3	0.3			34.6	4.5		
Chini_G_2016_HC							1.3	0.2			1.3	0.3			35.4	3.6		
Conte_C_2014_CA	5.6	2.9			5.2	2.7					1.2	0.1	6.6	6.8	36.5	3.3	0.5	0.3
Conte_C_2014_HC	4.2	2.9			3.2	1.7					1.4	0.2	4.0	2.1	35.1	4.1	0.5	0.1
Ebersbach_G_1999_CA	7.7	5.5											4.8	2.1				
Ebersbach_G_1999_HC	2.8	1.2											2.3	1.2				
Gouelle_A_2013_CA	11.2	7.3	0.6	0.1			1.2	0.3	8.7	6.0	1.3	0.2	7.0	5.0	37.2	3.6		
Gouelle_A_2013_HC	2.1	0.4	0.5	0.0			1.4	0.1	1.7	0.4	1.0	0.1	2.0	0.5	39.4	1.0		
Ienaga_Y_2006_CA	11.0	6.8					0.4	0.3										
Ienaga_Y_2006_CA_ADCA	9.7	4.7					0.2	0.0										
Ienaga_Y_2006_CA_MSAc	7.5	3.4					0.6	0.1										
Ienaga_Y_2006_CA_SCA	15.8	11.6					0.1	0.1										
Ienaga_Y_2006_HC	4.0	2.7					0.9	0.1										
Ilg_W_2007_CA											1.2	0.1					0.4	0.0
Ilg_W_2007_HC											1.0	0.2					0.4	0.1
ilg_W_2009_CA																		
ilg_W_2009_CA_AA																		
ilg_W_2009_CA_CA																		

Im_S_J_2016_CA																	
Martino_G_2014_CA							1.5	0.2			1.1	0.1					
Martino_G_2014_HC							1.6	0.1			1.2	0.1					
Matsushima_A_2015_CA	25.1																
Matsushima_A_2015_HC	8.6																
Milne_S_C_2014_CA							1.3	0.2							37.5	2.9	
Mondal_B_2015_CA																	
Palliyath_S_1998_CA	7.2	4.3	0.6	0.1	12.5	5.1	0.6	0.1	6.1	3.4	1.2	0.2	4.3	2.7			0.4	0.1
Palliyath_S_1998_HC	3.2	2.1	0.5	0.0	9.5	4.1	1.0	0.4	2.0	1.5	1.1	0.1	3.0	2.5			0.4	0.1
Rochester_L_2014_CA			0.6	0.2													
Rochester_L_2014_HC			0.5	0.0													
Schmitz-Hübsch_T_2016_CA							0.6	0.1	5.5	2.4	1.1	0.1	5.0	1.9			
Schmitz-Hübsch_T_2016_HC							0.8	0.0	2.2	0.7	1.1	0.1	2.0	1.0			
Schniepp_R_2014_CA							1.0	0.2	6.1	3.5	1.2	0.5	5.2	4.1			
Seidel_B_and_D_E_Krebs_2002_CA																	
Seidel_B_and_D_E_Krebs_2002_HC																	
Serrao_M_2012_CA	7.8	1.6			13.3	2.6					1.2	0.1	5.8	1.1			
Serrao_M_2012_CA_FRDA	7.0	1.2			15.5	0.5					1.2	0.1	4.9	0.3			
Serrao_M_2012_CA_SCA	8.7	1.7			10.7	0.9					1.3	0.1	6.8	0.7			
Serrao_M_2012_HC	3.4	0.9			2.9	0.9					1.0	0.0					
Stephenson_J_2015_CA							1.0	0.3							34.0	3.4	
Stephenson_J_2015_HC							1.4	0.1					2.2	0.6	39.2	1.1	
Wuehr_M_2013_CA							1.1	0.2			1.2	0.3					
Wuehr_M_2013_HC							1.3	0.1			1.0	0.1					

Appendix 7: Correlation analysis between gait parameters and disease severity

Results of non-parametric bivariate correlation analysis between gait parameters and disease severity where data were available. Correlation r >0.6 and r<-0.6 = bold, significance p<0.05 = *, p<0.01=**. n= number of articles reporting feature.

a) Results for CA cohort

i) Correlation between demographics and gait parameters

	Walkway length	ICARS score	SARA score	Disease Severity	Age	Height	Mass	BMI	Disease Duration
ICARS score	-0.553, n=9								
SARA score	**-0.671**, n=5								
Disease Severity	-0.404, n=13	**0.725***, n=9	**0.866**, n=5						
Age	-0.178, n=20	0.167, n=9	-0.200, n=5	0.098, n=13					
Height	-0.315, n=10			**0.655**, n=6	-0.248, n=10				
Mass	0.049, n=8	0.500, n=3			0.310, n=8	0.179, n=7			
Leg Length	**0.866**, n=3			**0.866**, n=3	-0.500, n=3				
BMI	0.179, n=8				0.333, n=8	-0.250, n=7	**0.857***, n=7		
Disease Duration	-0.028, n=13	0.071, n=7	0.400, n=4	-0.261, n=10	0.022, n=13	0.257, n=6	0.214, n=7	-0.086, n=6	
Base/Step Width	-0.042, n=11	**-0.800**, n=4	-0.500, n=3	**-0.612**, n=7	0.109, n=11	-0.314, n=6	**0.800**, n=4	**0.800**, n=5	0.543, n=6
Cadence	-0.150, n=10		-0.500, n=3		0.261, n=10	0.262, n=8	0.371, n=6	0.029, n=6	0.143, n=7
DLS perc.	-0.206, n=7				0.126, n=7	0.154, n=5	0.316, n=4	0.316, n=4	-0.410, n=5
Speed	0.352, n=16	-0.500, n=5	-0.200, n=5	-0.311, n=9	-0.209, n=16	-0.183, n=9	-0.200, n=6	0.036, n=7	0.200, n=9
Speed var.	0.258, n=4				0.400, n=4				
Step Length	0.401, n=7	0.000, n=4			-0.393, n=7	-0.500, n=3			0.400, n=4
Step Length var.	0.507, n=6				0.086, n=6				
Step Time	0.500, n=3				-0.500, n=3	-0.500, n=3			
Stride Length	**0.655**, n=6			0.000, n=3	-**0.657**, n=6	-0.100, n=5			-**0.600**, n=4
Stride Length var.	0.500, n=4				-**0.632**, n=4	-**0.632**, n=4	-**0.866**, n=3	-**0.866**, n=3	
Stride Time	0.348, n=7	0.500, n=3	-0.500, n=3	-0.393, n=6	-0.414, n=7	-**0.700,** n=5			
Stride Time var.	**0.676**, n=6				-0.486, n=6	-**0.700**, n=5	-0.500, n=3	-0.500, n=3	-0.500, n=3
Swing perc.					-0.400, n=4	-0.500, n=3			

ii) Correlation between gait parameters

	Base/ Step Width	Cadence	DLS perc.	Speed	Speed var.	Stance perc.	Step Length	Step Length var.	Stride Length	Stride Length var.	Stride Time
Cadence	0.257, n=6										
DLS perc.	**-0.657**, n=6	-0.410, n=5									
Speed	-0.036, n=11	0.515, n=10	-0.342, n=7								
Speed var.		0.500, n=3		-0.400, n=4							
Stance perc.			-**0.600**, n=4	-0.400, n=4							
Step Length	-0.300, n=5	-0.400, n=4	-0.400, n=4	**0.893**,** n=7		-0.400, n=4					
Step Length var.		0.400, n=5		**0.600**, n=6	**0.800**, n=4						
Stride Length	-0.300, n=5	0.500, n=5	-**0.949**, n=4	**0.829***, n=6			0.500, n=3	**0.866**, n=3			
Stride Length var.		-**0.949**, n=4	-0.500, n=3	-0.316, n=4							
Stride Time	-0.200, n=6		0.000, n=4	-0.108, n=7	**0.866**, n=3				0.500, n=3	**0.949**, n=4	
Stride Time var.	-0.400, n=4	-0.200, n=5	-**0.600**, n=4	**0.714**, n=6	0.500, n=3					**0.632**, n=4	**0.667**, n=5
Swing perc.	-0.500, n=3		0.200, n=4								

b) Results for HC cohort

i) Correlation between demographics and gait parameters

	Age	Height	Mass	Leg Length	BMI
Height	-0.250, n=7				
Mass	-**0.800**, n=5	**0.600**, n=4			
Leg Length	-0.500, n=3				
BMI	0.000, n=5	-0.400, n=4	0.400, n=4	0.500, n=3	
Base/ Step Width	0.071, n=8	**0.800**, n=4			
Cadence	-0.190, n=8	-**0.600**, n=5			0.500, n=3
DLS perc.	-0.154, n=5	0.000, n=3			
Speed	-0.266, n=12	-0.257, n=6			0.400, n=4
Stance perc.	**0.800**, n=4				
Step Length	-0.286, n=7	-0.500, n=3			
Step Length var.	0.314, n=6				
Step Time	-0.500, n=3				
Stride Length		0.500, n=3			
Stride Time	0.348, n=6	0.500, n=3			
Stride Time var.	0.100, n=5	0.000, n=4			
Swing perc.	-0.500, n=3				

ii) Correlation between gait parameters

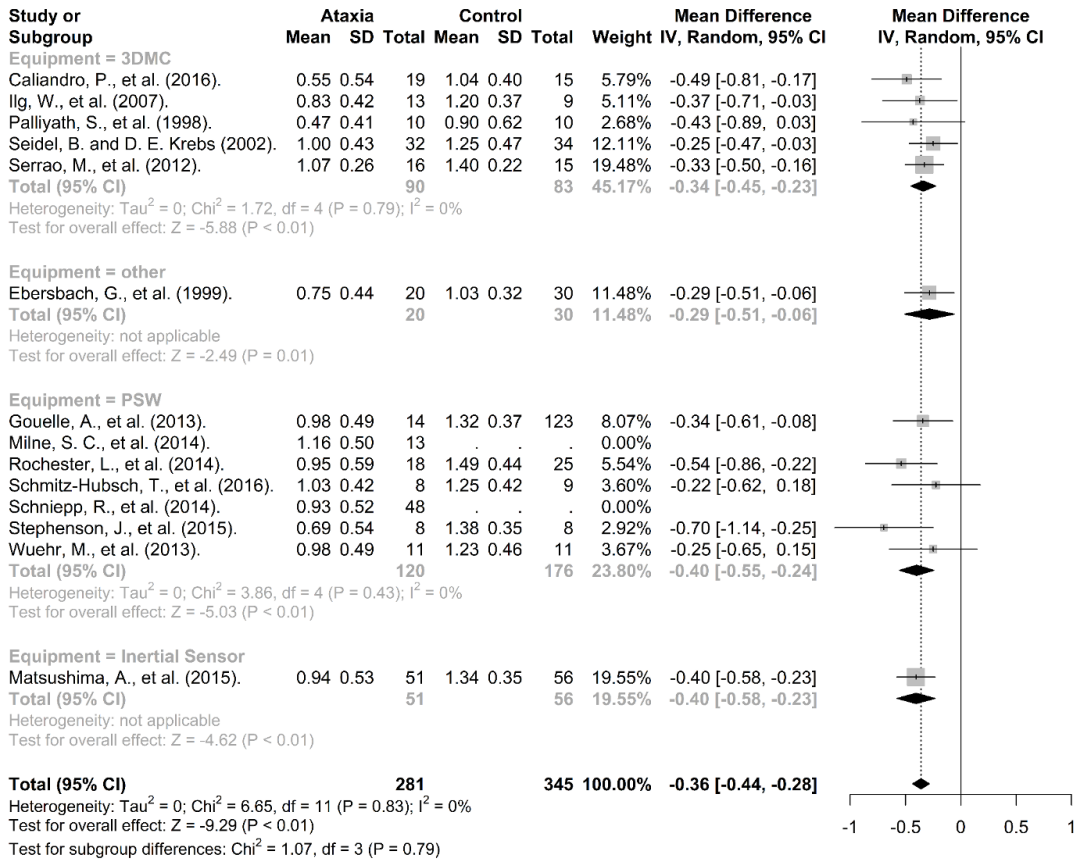
	Base/ Step Width	Cadence	DLS perc.	Speed	Speed var.	Stance perc.	Step Length	Step Length var.	Stride Length var.	Stride Time
DLS perc.	-0.600, n=4	-0.866, n=3								
Speed	-0.310, n=8	0.750, n=7	-0.359, n=5							
Speed var.		-0.500, n=3		0.000, n=4						
Stance perc.	0.500, n=3		-0.211, n=4	-0.800, n=4						
Step Length	-0.300, n=5	0.200, n=4	0.211, n=4	0.964**, n=7	0.500, n=3					
Step Length var.		0.000, n=5	-1.000, n=2	0.500, n=5	0.800, n=4		0.500, n=3			
Stride Length var.				-0.500, n=3						
Stride Time	-0.462, n=5			-0.348, n=6	0.500, n=3		-0.500, n=3	-0.500, n=3		
Stride Time var.		-0.200, n=5	-0.866, n=3	-0.600, n=5					-0.500, n=3	-0.500, n=3
Swing perc.			0.866, n=3	0.500, n=3		-0.500, n=3	0.500, n=3			

Appendix 8: Equipment & diagnosis subgroups analysis

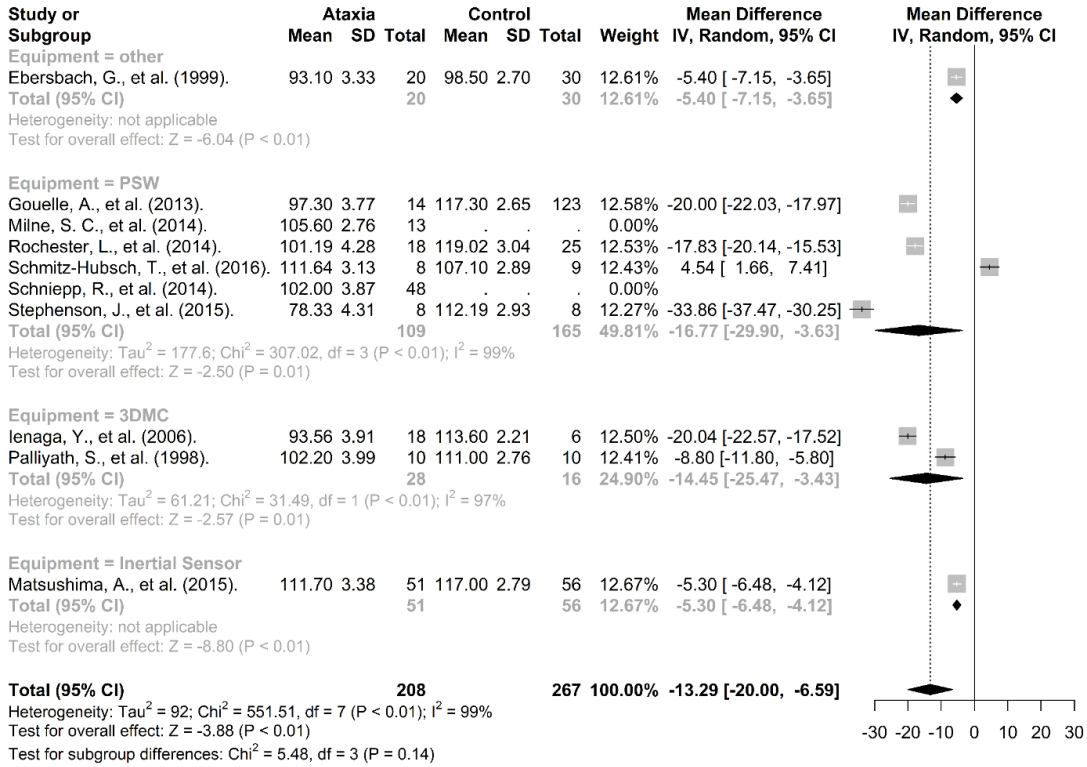
Forest plots for supplementary equipment and disease diagnosis subgroup analysis.

a) Equipment subgroup meta-analysis. Abbreviations: 3DMC – 3D motion capture, PSW – pressure sensitive walkway

Speed

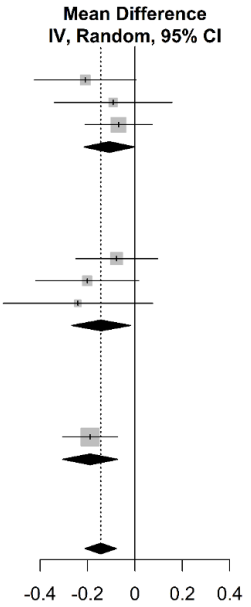


Cadence



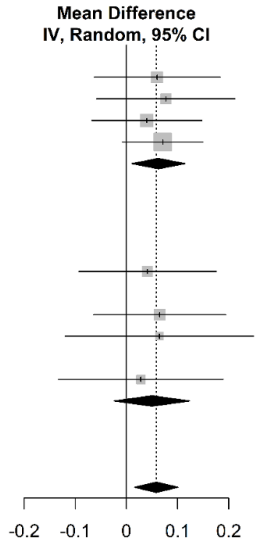
Step Length

Study or Subgroup	Ataxia Mean	Ataxia SD	Ataxia Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Equipment = 3DMC								
Caliandro, P., et al. (2016).	0.34	0.37	19	0.55	0.26	15	9.57%	-0.21 [-0.43, 0.01]
Ilg, W., et al. (2007).	0.48	0.31	13	0.57	0.28	9	7.21%	-0.09 [-0.34, 0.16]
Serrao, M., et al. (2012).	0.64	0.24	16	0.71	0.16	15	22.01%	-0.07 [-0.21, 0.07]
Total (95% CI)			48			39	38.80%	-0.11 [-0.21, 0.00]
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 1.17$, df = 2 (P = 0.56); $I^2 = 0\%$								
Test for overall effect: Z = -1.98 (P = 0.05)								
Equipment = PSW								
Gouelle, A., et al. (2013).	0.60	0.32	14	0.68	0.23	123	14.91%	-0.08 [-0.25, 0.10]
Rochester, L., et al. (2014).	0.55	0.40	18	0.75	0.29	25	9.31%	-0.20 [-0.42, 0.02]
Stephenson, J., et al. (2015).	0.50	0.36	8	0.74	0.27	8	4.45%	-0.24 [-0.56, 0.07]
Total (95% CI)			40			156	28.68%	-0.14 [-0.27, -0.02]
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 1.21$, df = 2 (P = 0.55); $I^2 = 0\%$								
Test for overall effect: Z = -2.25 (P = 0.02)								
Equipment = Inertial Sensor								
Matsushima, A., et al. (2015).	0.50	0.35	51	0.69	0.24	56	32.52%	-0.19 [-0.31, -0.07]
Total (95% CI)			51			56	32.52%	-0.19 [-0.31, -0.07]
Heterogeneity: not applicable								
Test for overall effect: Z = -3.18 (P < 0.01)								
Total (95% CI)			139			251	100.00%	-0.14 [-0.21, -0.08]
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 3.39$, df = 6 (P = 0.76); $I^2 = 0\%$								
Test for overall effect: Z = -4.25 (P < 0.01)								
Test for subgroup differences: $Chi^2 = 1.01$, df = 2 (P = 0.60)								



Base Width

Study or Subgroup	Ataxia Mean	Ataxia SD	Ataxia Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Equipment = 3DMC								
Caliandro, P., et al. (2016).	0.22	0.22	19	0.16	0.14	15	11.87%	0.06 [-0.06, 0.18]
Ilg, W., et al. (2007).	0.14	0.22	13	0.07	0.09	9	9.87%	0.08 [-0.06, 0.21]
Seidel, B. and D. E. Krebs (2002).	0.20	0.23	32	0.16	0.21	34	15.69%	0.04 [-0.07, 0.15]
Serrao, M., et al. (2012).	0.19	0.13	16	0.12	0.09	15	29.41%	0.07 [-0.01, 0.15]
Total (95% CI)			80			73	66.83%	0.06 [0.01, 0.11]
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.26$, df = 3 (P = 0.97); $I^2 = 0\%$								
Test for overall effect: Z = 2.36 (P = 0.02)								
Equipment = PSW								
Gouelle, A., et al. (2013).	0.13	0.25	14	0.09	0.15	123	10.02%	0.04 [-0.09, 0.18]
Milne, S. C., et al. (2014).	0.14	0.26	13	.	.	.	0.00%	
Rochester, L., et al. (2014).	0.15	0.24	18	0.09	0.16	25	10.84%	0.07 [-0.06, 0.19]
Schmitz-Hubsch, T., et al. (2016).	0.16	0.22	8	0.10	0.16	9	5.32%	0.06 [-0.12, 0.25]
Schniepp, R., et al. (2014).	0.13	0.22	48	.	.	.	0.00%	
Wuehr, M., et al. (2013).	0.12	0.23	11	0.10	0.14	11	6.99%	0.03 [-0.13, 0.19]
Total (95% CI)			112			168	33.17%	0.05 [-0.02, 0.12]
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.16$, df = 3 (P = 0.98); $I^2 = 0\%$								
Test for overall effect: Z = 1.33 (P = 0.19)								
Total (95% CI)			192			241	100.00%	0.06 [0.02, 0.10]
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.50$, df = 7 (P = 1.00); $I^2 = 0\%$								
Test for overall effect: Z = 2.69 (P < 0.01)								
Test for subgroup differences: $Chi^2 = 0.08$, df = 1 (P = 0.78)								

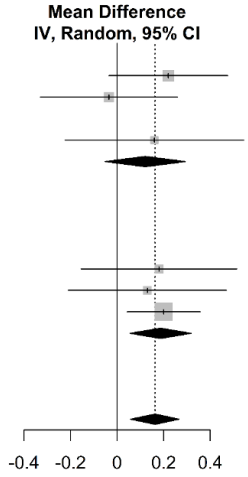


Step Time

Study or Subgroup	Ataxia Mean	Ataxia SD	Ataxia Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Equipment = PSW								
Gouelle, A., et al. (2013).	0.63	0.32	14	0.51	0.17	123	49.12%	0.12 [-0.05, 0.29]
Rochester, L., et al. (2014).	0.63	0.47	18	0.51	0.20	25	26.69%	0.12 [-0.11, 0.35]
Total (95% CI)			32			148	75.81%	0.12 [-0.02, 0.26]
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0$, df = 1 (P = 1.00); $I^2 = 0\%$								
Test for overall effect: Z = 1.74 (P = 0.08)								
Equipment = 3DMC								
Palliyath, S., et al. (1998).	0.61	0.33	10	0.54	0.20	10	24.19%	0.07 [-0.17, 0.31]
Total (95% CI)			10			10	24.19%	0.07 [-0.17, 0.31]
Heterogeneity: not applicable								
Test for overall effect: Z = 0.57 (P = 0.57)								
Total (95% CI)			42			158	100.00%	0.11 [-0.01, 0.23]
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.13$, df = 2 (P = 0.94); $I^2 = 0\%$								
Test for overall effect: Z = 1.80 (P = 0.07)								
Test for subgroup differences: $Chi^2 = 0.13$, df = 1 (P = 0.72)								

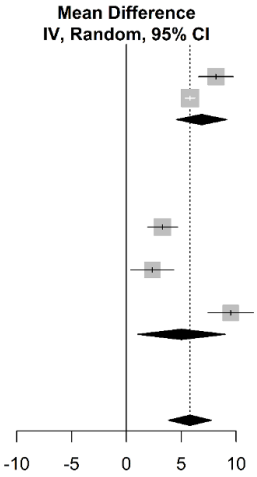
Stride Time

Study or Subgroup	Ataxia Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Equipment = PSW								
Gouelle, A., et al. (2013).	1.25	0.48	14	1.03	0.24	123	16.70%	0.22 [-0.03, 0.47]
Schmitz-Hubsch, T., et al. (2016).	1.08	0.30	8	1.12	0.32	9	12.48%	-0.04 [-0.33, 0.26]
Schniepp, R., et al. (2014).	1.23	0.69	48	.	.	.	0.00%	
Wuehr, M., et al. (2013).	1.18	0.57	11	1.02	0.30	11	7.40%	0.16 [-0.22, 0.54]
Total (95% CI)			81			143	36.58%	0.12 [-0.05, 0.29]
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 1.7$, df = 2 (P = 0.43); $I^2 = 0\%$								
Test for overall effect: Z = 1.37 (P = 0.17)								
Equipment = 3DMC								
Ilg, W., et al. (2007).	1.20	0.30	13	1.02	0.45	9	9.69%	0.18 [-0.15, 0.51]
Palliyath, S., et al. (1998).	1.21	0.47	10	1.08	0.28	10	9.42%	0.13 [-0.21, 0.47]
Serrao, M., et al. (2012).	1.21	0.26	16	1.01	0.17	15	44.31%	0.20 [0.04, 0.36]
Total (95% CI)			39			34	63.42%	0.19 [0.06, 0.32]
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.14$, df = 2 (P = 0.93); $I^2 = 0\%$								
Test for overall effect: Z = 2.80 (P < 0.01)								
Total (95% CI)			120			177	100.00%	0.16 [0.06, 0.27]
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 2.19$, df = 5 (P = 0.82); $I^2 = 0\%$								
Test for overall effect: Z = 3.06 (P < 0.01)								
Test for subgroup differences: $Chi^2 = 0.36$, df = 1 (P = 0.55)								



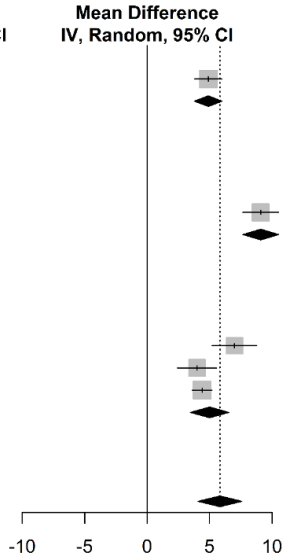
DLS % cycle

Study or Subgroup	Ataxia Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Equipment = 3DMC								
Caliandro, P., et al. (2016).	19.21	3.23	19	11.05	1.25	15	19.92%	8.16 [6.58, 9.74]
Serrao, M., et al. (2012).	13.50	0.71	16	7.70	0.55	15	22.62%	5.80 [5.36, 6.24]
Total (95% CI)			35			30	42.53%	6.85 [4.55, 9.15]
Heterogeneity: $Tau^2 = 2.43$; $Chi^2 = 7.91$, df = 1 (P < 0.01); $I^2 = 87\%$								
Test for overall effect: Z = 5.84 (P < 0.01)								
Equipment = PSW								
Gouelle, A., et al. (2013).	24.80	2.57	14	21.50	1.41	123	20.59%	3.30 [1.93, 4.67]
Milne, S. C., et al. (2014).	24.72	2.41	13	.	.	.	0.00%	
Schmitz-Hubsch, T., et al. (2016).	25.88	2.11	8	23.52	2.00	9	18.63%	2.36 [0.40, 4.32]
Schniepp, R., et al. (2014).	31.00	3.00	48	.	.	.	0.00%	
Stephenson, J., et al. (2015).	31.00	2.61	8	21.50	1.44	8	18.25%	9.50 [7.43, 11.57]
Total (95% CI)			91			140	57.47%	5.02 [1.03, 9.00]
Heterogeneity: $Tau^2 = 11.53$; $Chi^2 = 29.95$, df = 2 (P < 0.01); $I^2 = 93\%$								
Test for overall effect: Z = 2.47 (P = 0.01)								
Total (95% CI)			126			170	100.00%	5.79 [3.83, 7.75]
Heterogeneity: $Tau^2 = 4.39$; $Chi^2 = 45.33$, df = 4 (P < 0.01); $I^2 = 91\%$								
Test for overall effect: Z = 5.78 (P < 0.01)								
Test for subgroup differences: $Chi^2 = 0.61$, df = 1 (P = 0.43)								



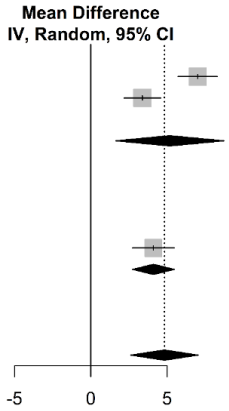
Step Length Variability

Study or Subgroup	Ataxia Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Equipment = other								
Ebersbach, G., et al. (1999).	7.70	2.35	20	2.80	1.10	30	20.87%	4.90 [3.80, 6.00]
Total (95% CI)			20			30	20.87%	4.90 [3.80, 6.00]
Heterogeneity: not applicable								
Test for overall effect: Z = 8.73 (P < 0.01)								
Equipment = PSW								
Gouelle, A., et al. (2013).	11.20	2.70	14	2.10	0.63	123	19.78%	9.10 [7.68, 10.52]
Total (95% CI)			14			123	19.78%	9.10 [7.68, 10.52]
Heterogeneity: not applicable								
Test for overall effect: Z = 12.56 (P < 0.01)								
Equipment = 3DMC								
Ienaga, Y., et al. (2006).	11.01	2.61	18	4.01	1.66	6	18.36%	7.00 [5.21, 8.79]
Palliyath, S., et al. (1998).	7.20	2.07	10	3.20	1.45	10	19.23%	4.00 [2.43, 5.57]
Serrao, M., et al. (2012).	7.80	1.26	16	3.40	0.95	15	21.76%	4.40 [3.62, 5.18]
Total (95% CI)			44			31	59.35%	5.01 [3.48, 6.54]
Heterogeneity: $Tau^2 = 1.33$; $Chi^2 = 7.64$, df = 2 (P = 0.02); $I^2 = 74\%$								
Test for overall effect: Z = 6.42 (P < 0.01)								
Total (95% CI)			78			184	100.00%	5.83 [4.09, 7.58]
Heterogeneity: $Tau^2 = 3.49$; $Chi^2 = 39.17$, df = 4 (P < 0.01); $I^2 = 90\%$								
Test for overall effect: Z = 6.54 (P < 0.01)								
Test for subgroup differences: $Chi^2 = 23.68$, df = 2 (P < 0.01)								



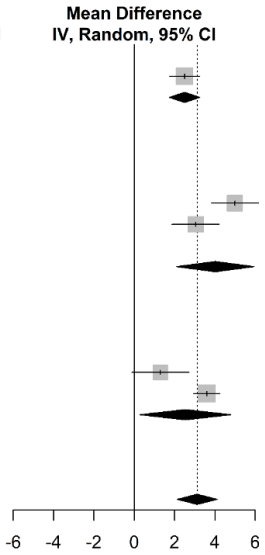
Stride Length Variability

Study or Subgroup	Ataxia Mean	Ataxia SD	Ataxia Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Equipment = PSW								
Gouelle, A., et al. (2013).	8.70	2.45	14	1.70	0.63	123	33.33%	7.00 [5.71, 8.29]
Schmitz-Hubsch, T., et al. (2016).	5.54	1.54	8	2.17	0.84	9	33.84%	3.37 [2.17, 4.57]
Schniepp, R., et al. (2014).	6.10	1.87	48	.	.	.	0.00%	
Total (95% CI)			**70**			**132**	**67.17%**	**5.18 [1.63, 8.73]**
Heterogeneity: $Tau^2 = 6.17$; $Chi^2 = 16.29$, df = 1 ($P < 0.01$); $I^2 = 94\%$								
Test for overall effect: $Z = 2.86$ ($P < 0.01$)								
Equipment = 3DMC								
Palliyath, S., et al. (1998).	6.10	1.84	10	2.00	1.22	10	32.83%	4.10 [2.73, 5.47]
Total (95% CI)			**10**			**10**	**32.83%**	**4.10 [2.73, 5.47]**
Heterogeneity: not applicable								
Test for overall effect: $Z = 5.86$ ($P < 0.01$)								
Total (95% CI)			**80**			**142**	**100.00%**	**4.82 [2.62, 7.02]**
Heterogeneity: $Tau^2 = 3.36$; $Chi^2 = 17.62$, df = 2 ($P < 0.01$); $I^2 = 89\%$								
Test for overall effect: $Z = 4.29$ ($P < 0.01$)								
Test for subgroup differences: $Chi^2 = 0.31$, df = 1 ($P = 0.58$)								



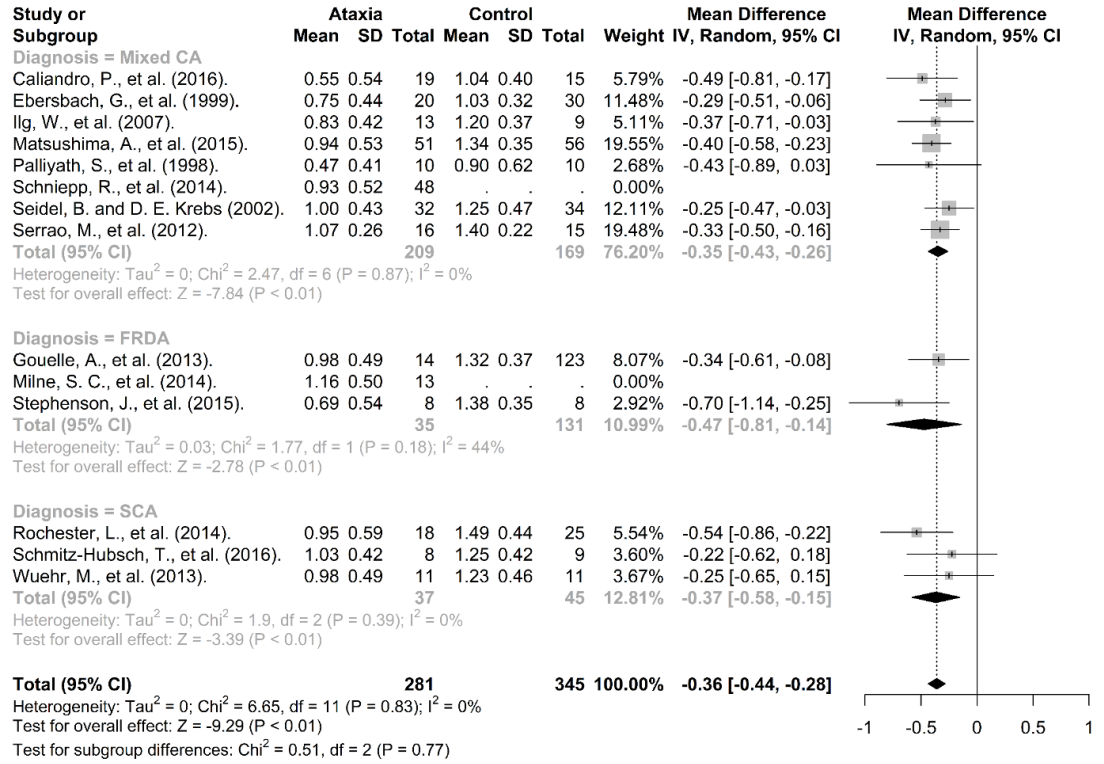
Stride Time Variability

Study or Subgroup	Ataxia Mean	Ataxia SD	Ataxia Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Equipment = other								
Ebersbach, G., et al. (1999).	4.80	1.45	20	2.30	1.10	30	22.40%	2.50 [1.75, 3.25]
Total (95% CI)			**20**			**30**	**22.40%**	**2.50 [1.75, 3.25]**
Heterogeneity: not applicable								
Test for overall effect: $Z = 6.57$ ($P < 0.01$)								
Equipment = PSW								
Gouelle, A., et al. (2013).	7.00	2.24	14	2.00	0.71	123	18.78%	5.00 [3.82, 6.18]
Schmitz-Hubsch, T., et al. (2016).	5.04	1.39	8	1.99	1.00	9	18.89%	3.05 [1.88, 4.21]
Schniepp, R., et al. (2014).	5.20	2.02	48	.	.	.	0.00%	
Total (95% CI)			**70**			**132**	**37.67%**	**4.02 [2.10, 5.94]**
Heterogeneity: $Tau^2 = 1.55$; $Chi^2 = 5.35$, df = 1 ($P = 0.02$); $I^2 = 81\%$								
Test for overall effect: $Z = 4.11$ ($P < 0.01$)								
Equipment = 3DMC								
Palliyath, S., et al. (1998).	4.30	1.64	10	3.00	1.58	10	16.79%	1.30 [-0.11, 2.71]
Serrao, M., et al. (2012).	5.80	1.05	16	2.20	0.77	15	23.14%	3.60 [2.95, 4.25]
Total (95% CI)			**26**			**25**	**39.93%**	**2.54 [0.29, 4.79]**
Heterogeneity: $Tau^2 = 2.33$; $Chi^2 = 8.41$, df = 1 ($P < 0.01$); $I^2 = 88\%$								
Test for overall effect: $Z = 2.21$ ($P = 0.03$)								
Total (95% CI)			**116**			**187**	**100.00%**	**3.13 [2.14, 4.11]**
Heterogeneity: $Tau^2 = 0.98$; $Chi^2 = 20.83$, df = 4 ($P < 0.01$); $I^2 = 81\%$								
Test for overall effect: $Z = 6.23$ ($P < 0.01$)								
Test for subgroup differences: $Chi^2 = 2.12$, df = 2 ($P = 0.35$)								

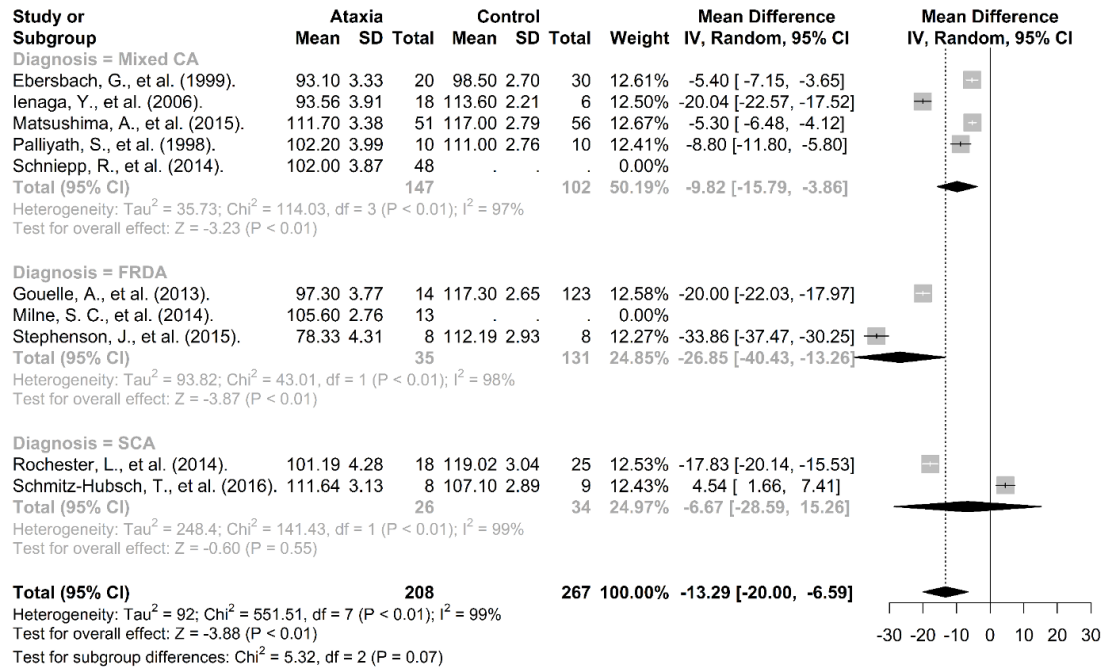


b) Disease subgroup meta-analysis. Abbreviations: CA – Cerebellar Ataxia, FRDA – Friedreich'sAtaxia, SCA – spinocerebellar ataxia

Speed

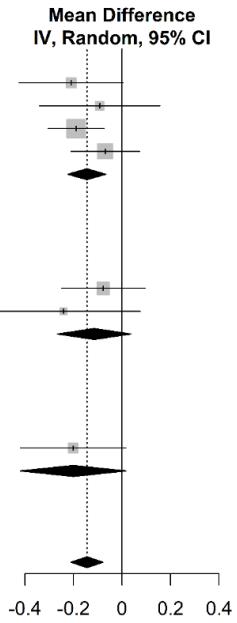


Cadence



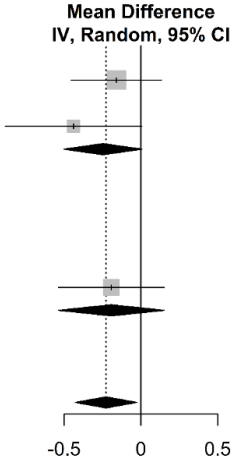
Step Length

Study or Subgroup	Ataxia Mean	Ataxia SD	Ataxia Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Diagnosis = Mixed CA								
Caliandro, P., et al. (2016).	0.34	0.37	19	0.55	0.26	15	9.57%	-0.21 [-0.43, 0.01]
Ilg, W., et al. (2007).	0.48	0.31	13	0.57	0.28	9	7.21%	-0.09 [-0.34, 0.16]
Matsushima, A., et al. (2015).	0.50	0.35	51	0.69	0.24	56	32.52%	-0.19 [-0.31, -0.07]
Serrao, M., et al. (2012).	0.64	0.24	16	0.71	0.16	15	22.01%	-0.07 [-0.21, 0.07]
Total (95% CI)			99			95	71.32%	**-0.14 [-0.22, -0.07]**
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 2.18$, df = 3 (P = 0.54); $I^2 = 0\%$								
Test for overall effect: Z = -3.61 (P < 0.01)								
Diagnosis = FRDA								
Gouelle, A., et al. (2013).	0.60	0.32	14	0.68	0.23	123	14.91%	-0.08 [-0.25, 0.10]
Stephenson, J., et al. (2015).	0.50	0.36	8	0.74	0.27	8	4.45%	-0.24 [-0.56, 0.07]
Total (95% CI)			22			131	19.37%	**-0.11 [-0.27, 0.04]**
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.8$, df = 1 (P = 0.37); $I^2 = 0\%$								
Test for overall effect: Z = -1.49 (P = 0.14)								
Diagnosis = SCA								
Rochester, L., et al. (2014).	0.55	0.40	18	0.75	0.29	25	9.31%	-0.20 [-0.42, 0.02]
Total (95% CI)			18			25	9.31%	**-0.20 [-0.42, 0.02]**
Heterogeneity: not applicable								
Test for overall effect: Z = -1.81 (P = 0.07)								
Total (95% CI)			139			251	100.00%	**-0.14 [-0.21, -0.08]**
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 3.39$, df = 6 (P = 0.76); $I^2 = 0\%$								
Test for overall effect: Z = -4.25 (P < 0.01)								
Test for subgroup differences: $Chi^2 = 0.41$, df = 2 (P = 0.81)								



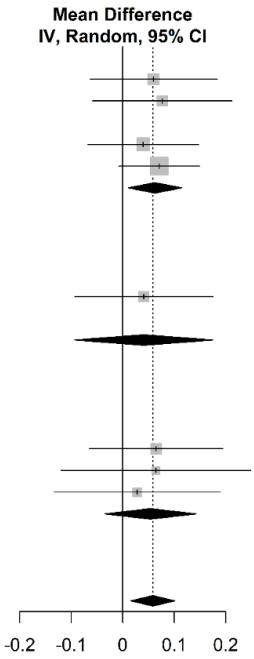
Stride Length

Study or Subgroup	Ataxia Mean	Ataxia SD	Ataxia Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Diagnosis = FRDA								
Gouelle, A., et al. (2013).	1.21	0.55	14	1.36	0.32	123	46.17%	-0.16 [-0.45, 0.13]
Milne, S. C., et al. (2014).	1.32	0.48	13	.	.	.	0.00%	
Stephenson, J., et al. (2015).	1.00	0.51	8	1.44	0.39	8	20.19%	-0.44 [-0.88, 0.01]
Total (95% CI)			35			131	66.36%	**-0.25 [-0.50, 0.01]**
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 1.06$, df = 1 (P = 0.30); $I^2 = 5\%$								
Test for overall effect: Z = -1.91 (P = 0.06)								
Diagnosis = Mixed CA								
Schniepp, R., et al. (2014).	0.96	0.48	48	.	.	.	0.00%	
Wuehr, M., et al. (2013).	1.14	0.47	11	1.33	0.34	11	33.64%	-0.19 [-0.54, 0.15]
Total (95% CI)			59			11	33.64%	**-0.19 [-0.54, 0.15]**
Heterogeneity: not applicable								
Test for overall effect: Z = -1.10 (P = 0.27)								
Total (95% CI)			94			142	100.00%	**-0.23 [-0.43, -0.03]**
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 1.11$, df = 2 (P = 0.57); $I^2 = 0\%$								
Test for overall effect: Z = -2.23 (P = 0.03)								
Test for subgroup differences: $Chi^2 = 0.06$, df = 1 (P = 0.80)								



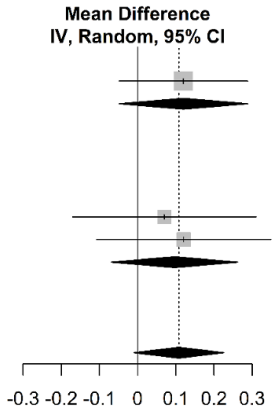
Base Width

Study or Subgroup	Ataxia Mean	Ataxia SD	Ataxia Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Diagnosis = mixed CA								
Caliandro, P., et al. (2016).	0.22	0.22	19	0.16	0.14	15	11.87%	0.06 [-0.06, 0.18]
Ilg, W., et al. (2007).	0.14	0.22	13	0.07	0.09	9	9.87%	0.08 [-0.06, 0.21]
Schniepp, R., et al. (2014).	0.13	0.22	48	.	.	.	0.00%	
Seidel, B. and D. E. Krebs (2002).	0.20	0.23	32	0.16	0.21	34	15.69%	0.04 [-0.07, 0.15]
Serrao, M., et al. (2012).	0.19	0.13	16	0.12	0.09	15	29.41%	0.07 [-0.01, 0.15]
Total (95% CI)			128			73	66.83%	0.06 [0.01, 0.11]
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.26$, df = 3 (P = 0.97); $I^2 = 0\%$								
Test for overall effect: Z = 2.36 (P = 0.02)								
Diagnosis = FRDA								
Gouelle, A., et al. (2013).	0.13	0.25	14	0.09	0.15	123	10.02%	0.04 [-0.09, 0.18]
Milne, S. C., et al. (2014).	0.14	0.26	13	.	.	.	0.00%	
Total (95% CI)			27			123	10.02%	0.04 [-0.09, 0.18]
Heterogeneity: not applicable								
Test for overall effect: Z = 0.60 (P = 0.55)								
Diagnosis = SCA								
Rochester, L., et al. (2014).	0.15	0.24	18	0.09	0.16	25	10.84%	0.07 [-0.06, 0.19]
Schmitz-Hubsch, T., et al. (2016).	0.16	0.22	8	0.10	0.16	9	5.32%	0.06 [-0.12, 0.25]
Wuehr, M., et al. (2013).	0.12	0.23	11	0.10	0.14	11	6.99%	0.03 [-0.13, 0.19]
Total (95% CI)			37			45	23.14%	0.05 [-0.03, 0.14]
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.14$, df = 2 (P = 0.93); $I^2 = 0\%$								
Test for overall effect: Z = 1.19 (P = 0.23)								
Total (95% CI)			192			241	100.00%	0.06 [0.02, 0.10]
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.50$, df = 7 (P = 1.00); $I^2 = 0\%$								
Test for overall effect: Z = 2.69 (P < 0.01)								
Test for subgroup differences: $Chi^2 = 0.10$, df = 2 (P = 0.95)								



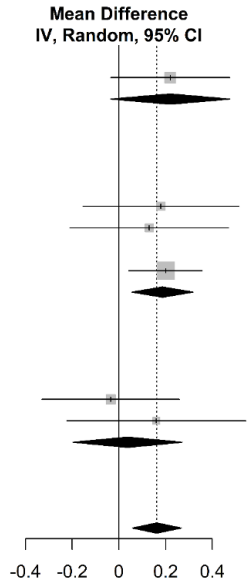
Step Time

Study or Subgroup	Ataxia Mean	Ataxia SD	Ataxia Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Diagnosis = FRDA								
Gouelle, A., et al. (2013).	0.63	0.32	14	0.51	0.17	123	49.12%	0.12 [-0.05, 0.29]
Total (95% CI)			14			123	49.12%	0.12 [-0.05, 0.29]
Heterogeneity: not applicable								
Test for overall effect: Z = 1.40 (P = 0.16)								
Diagnosis = Mixed CA								
Palliyath, S., et al. (1998).	0.61	0.33	10	0.54	0.20	10	24.19%	0.07 [-0.17, 0.31]
Rochester, L., et al. (2014).	0.63	0.47	18	0.51	0.20	25	26.69%	0.12 [-0.11, 0.35]
Total (95% CI)			28			35	50.88%	0.10 [-0.07, 0.26]
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.09$, df = 1 (P = 0.76); $I^2 = 0\%$								
Test for overall effect: Z = 1.15 (P = 0.25)								
Total (95% CI)			42			158	100.00%	0.11 [-0.01, 0.23]
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.13$, df = 2 (P = 0.94); $I^2 = 0\%$								
Test for overall effect: Z = 1.80 (P = 0.07)								
Test for subgroup differences: $Chi^2 = 0.04$, df = 1 (P = 0.85)								



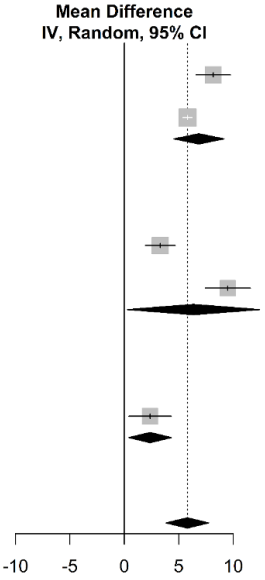
Stride Time

Study or Subgroup	Ataxia Mean	Ataxia SD	Ataxia Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Diagnosis = FRDA								
Gouelle, A., et al. (2013).	1.25	0.48	14	1.03	0.24	123	16.70%	0.22 [-0.03, 0.47]
Total (95% CI)			14			123	16.70%	0.22 [-0.03, 0.47]
Heterogeneity: not applicable								
Test for overall effect: Z = 1.69 (P = 0.09)								
Diagnosis = Mixed CA								
Ilg, W., et al. (2007).	1.20	0.30	13	1.02	0.45	9	9.69%	0.18 [-0.15, 0.51]
Palliyath, S., et al. (1998).	1.21	0.47	10	1.08	0.28	10	9.42%	0.13 [-0.21, 0.47]
Schniepp, R., et al. (2014).	1.23	0.69	48	.	.	.	0.00%	
Serrao, M., et al. (2012).	1.21	0.26	16	1.01	0.17	15	44.31%	0.20 [0.04, 0.36]
Total (95% CI)			87			34	63.42%	0.19 [0.06, 0.32]
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.14$, df = 2 (P = 0.93); $I^2 = 0\%$								
Test for overall effect: Z = 2.80 (P < 0.01)								
Diagnosis = SCA								
Schmitz-Hubsch, T., et al. (2016).	1.08	0.30	8	1.12	0.32	9	12.48%	-0.04 [-0.33, 0.26]
Wuehr, M., et al. (2013).	1.18	0.57	11	1.02	0.30	11	7.40%	0.16 [-0.22, 0.54]
Total (95% CI)			19			20	19.88%	0.04 [-0.20, 0.27]
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.63$, df = 1 (P = 0.43); $I^2 = 0\%$								
Test for overall effect: Z = 0.31 (P = 0.75)								
Total (95% CI)			120			177	100.00%	0.16 [0.06, 0.27]
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 2.19$, df = 5 (P = 0.82); $I^2 = 0\%$								
Test for overall effect: Z = 3.06 (P < 0.01)								
Test for subgroup differences: $Chi^2 = 1.43$, df = 2 (P = 0.49)								



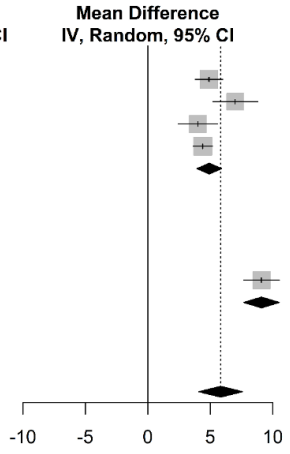
DLS % cycle

Study or Subgroup	Ataxia Mean	Ataxia SD	Ataxia Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Diagnosis = Mixed CA								
Caliandro, P., et al. (2016).	19.21	3.23	19	11.05	1.25	15	19.92%	8.16 [6.58, 9.74]
Schniepp, R., et al. (2014).	31.00	3.00	48	.	.	.	0.00%	
Serrao, M., et al. (2012).	13.50	0.71	16	7.70	0.55	15	22.62%	5.80 [5.36, 6.24]
Total (95% CI)			83			30	42.53%	6.85 [4.55, 9.15]
Heterogeneity: $Tau^2 = 2.43$; $Chi^2 = 7.91$, df = 1 (P < 0.01); $I^2 = 87\%$								
Test for overall effect: Z = 5.84 (P < 0.01)								
Diagnosis = FRDA								
Gouelle, A., et al. (2013).	24.80	2.57	14	21.50	1.41	123	20.59%	3.30 [1.93, 4.67]
Milne, S. C., et al. (2014).	24.72	2.41	13	.	.	.	0.00%	
Stephenson, J., et al. (2015).	31.00	2.61	8	21.50	1.44	8	18.25%	9.50 [7.43, 11.57]
Total (95% CI)			35			131	38.84%	6.35 [0.27, 12.42]
Heterogeneity: $Tau^2 = 18.42$; $Chi^2 = 23.99$, df = 1 (P < 0.01); $I^2 = 96\%$								
Test for overall effect: Z = 2.05 (P = 0.04)								
Diagnosis = SCA								
Schmitz-Hubsch, T., et al. (2016).	25.88	2.11	8	23.52	2.00	9	18.63%	2.36 [0.40, 4.32]
Total (95% CI)			8			9	18.63%	2.36 [0.40, 4.32]
Heterogeneity: not applicable								
Test for overall effect: Z = 2.36 (P = 0.02)								
Total (95% CI)			126			170	100.00%	5.79 [3.83, 7.75]
Heterogeneity: $Tau^2 = 4.39$; $Chi^2 = 45.33$, df = 4 (P < 0.01); $I^2 = 91\%$								
Test for overall effect: Z = 5.78 (P < 0.01)								
Test for subgroup differences: $Chi^2 = 8.92$, df = 2 (P = 0.01)								



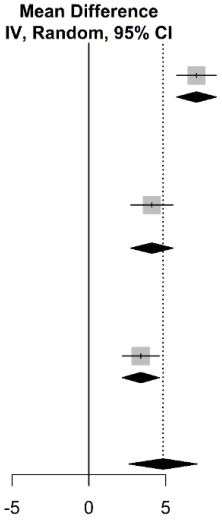
Step Length Variability

Study or Subgroup	Ataxia Mean	Ataxia SD	Ataxia Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Diagnosis = Mixed CA								
Ebersbach, G., et al. (1999).	7.70	2.35	20	2.80	1.10	30	20.87%	4.90 [3.80, 6.00]
Ienaga, Y., et al. (2006).	11.01	2.61	18	4.01	1.66	6	18.36%	7.00 [5.21, 8.79]
Palliyath, S., et al. (1998).	7.20	2.07	10	3.20	1.45	10	19.23%	4.00 [2.43, 5.57]
Serrao, M., et al. (2012).	7.80	1.26	16	3.40	0.95	15	21.76%	4.40 [3.62, 5.18]
Total (95% CI)			64			61	80.22%	4.92 [3.93, 5.92]
Heterogeneity: $Tau^2 = 0.61$; $Chi^2 = 7.76$, df = 3 (P = 0.05); $I^2 = 61\%$								
Test for overall effect: Z = 9.70 (P < 0.01)								
Diagnosis = FRDA								
Gouelle, A., et al. (2013).	11.20	2.70	14	2.10	0.63	123	19.78%	9.10 [7.68, 10.52]
Total (95% CI)			14			123	19.78%	9.10 [7.68, 10.52]
Heterogeneity: not applicable								
Test for overall effect: Z = 12.56 (P < 0.01)								
Total (95% CI)			78			184	100.00%	5.83 [4.09, 7.58]
Heterogeneity: $Tau^2 = 3.49$; $Chi^2 = 39.17$, df = 4 (P < 0.01); $I^2 = 90\%$								
Test for overall effect: Z = 6.54 (P < 0.01)								
Test for subgroup differences: $Chi^2 = 22.33$, df = 1 (P < 0.01)								



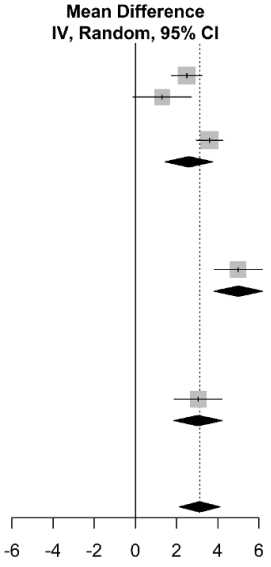
Stride Length Variability

Study or Subgroup	Ataxia Mean	Ataxia SD	Ataxia Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Diagnosis = FRDA								
Gouelle, A., et al. (2013).	8.70	2.45	14	1.70	0.63	123	33.33%	7.00 [5.71, 8.29]
Total (95% CI)			14			123	33.33%	7.00 [5.71, 8.29]
Heterogeneity: not applicable								
Test for overall effect: Z = 10.65 (P < 0.01)								
Diagnosis = Mixed CA								
Palliyath, S., et al. (1998).	6.10	1.84	10	2.00	1.22	10	32.83%	4.10 [2.73, 5.47]
Schniepp, R., et al. (2014).	6.10	1.87	48	.	.	.	0.00%	
Total (95% CI)			58			10	32.83%	4.10 [2.73, 5.47]
Heterogeneity: not applicable								
Test for overall effect: Z = 5.86 (P < 0.01)								
Diagnosis = SCA								
Schmitz-Hubsch, T., et al. (2016).	5.54	1.54	8	2.17	0.84	9	33.84%	3.37 [2.17, 4.57]
Total (95% CI)			8			9	33.84%	3.37 [2.17, 4.57]
Heterogeneity: not applicable								
Test for overall effect: Z = 5.51 (P < 0.01)								
Total (95% CI)			80			142	100.00%	4.82 [2.62, 7.02]
Heterogeneity: $Tau^2 = 3.36$; $Chi^2 = 17.62$, df = 2 (P < 0.01); $I^2 = 89\%$								
Test for overall effect: Z = 4.29 (P < 0.01)								
Test for subgroup differences: $Chi^2 = 17.62$, df = 2 (P < 0.01)								



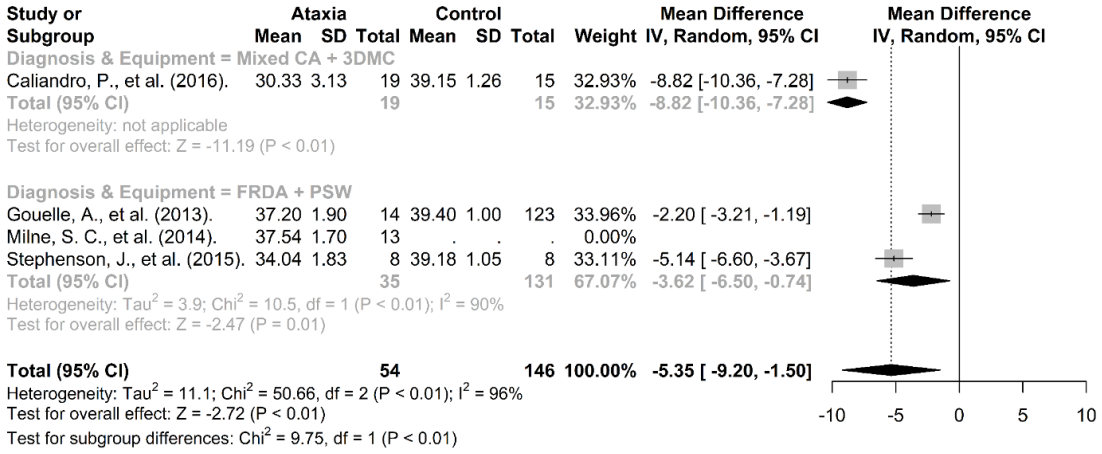
Stride Time Variability

Study or Subgroup	Ataxia Mean	Ataxia SD	Ataxia Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Diagnosis = Mixed CA								
Ebersbach, G., et al. (1999).	4.80	1.45	20	2.30	1.10	30	22.40%	2.50 [1.75, 3.25]
Palliyath, S., et al. (1998).	4.30	1.64	10	3.00	1.58	10	16.79%	1.30 [-0.11, 2.71]
Schniepp, R., et al. (2014).	5.20	2.02	48	.	.	.	0.00%	
Serrao, M., et al. (2012).	5.80	1.05	16	2.20	0.77	15	23.14%	3.60 [2.95, 4.25]
Total (95% CI)			94			55	62.33%	2.60 [1.45, 3.76]
Heterogeneity: $Tau^2 = 0.81$; $Chi^2 = 10.51$, df = 2 (P < 0.01); $I^2 = 81\%$								
Test for overall effect: Z = 4.42 (P < 0.01)								
Diagnosis = FRDA								
Gouelle, A., et al. (2013).	7.00	2.24	14	2.00	0.71	123	18.78%	5.00 [3.82, 6.18]
Total (95% CI)			14			123	18.78%	5.00 [3.82, 6.18]
Heterogeneity: not applicable								
Test for overall effect: Z = 8.32 (P < 0.01)								
Diagnosis = SCA								
Schmitz-Hubsch, T., et al. (2016).	5.04	1.39	8	1.99	1.00	9	18.89%	3.05 [1.88, 4.21]
Total (95% CI)			8			9	18.89%	3.05 [1.88, 4.21]
Heterogeneity: not applicable								
Test for overall effect: Z = 5.12 (P < 0.01)								
Total (95% CI)			116			187	100.00%	3.13 [2.14, 4.11]
Heterogeneity: $Tau^2 = 0.98$; $Chi^2 = 20.83$, df = 4 (P < 0.01); $I^2 = 81\%$								
Test for overall effect: Z = 6.23 (P < 0.01)								
Test for subgroup differences: $Chi^2 = 9.13$, df = 2 (P = 0.01)								

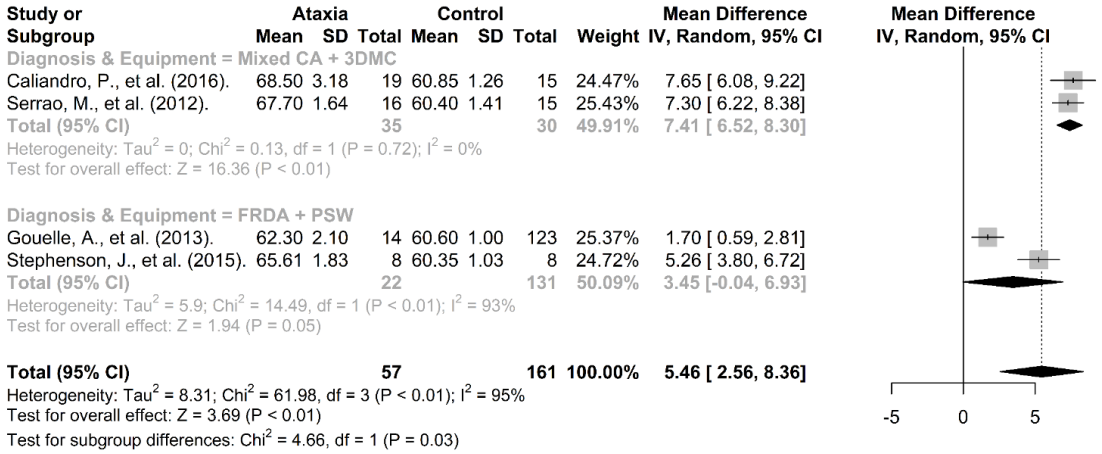


c) Subgroup meta-analysis for variables where diagnosis and subgroup could not be extracted from each other. CA – Cerebellar ataxia, 3DMC – 3D motion capture, FRDA – Friedreich's Ataxia, PSW – Pressure Sensitive Walkway

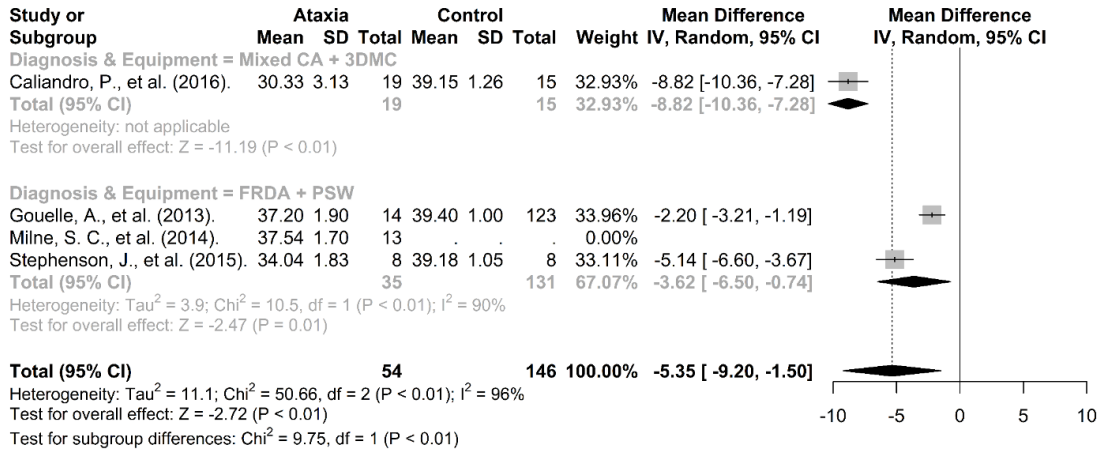
Swing % cycle



Stance % cycle



Speed Variability



Chapter 3 (Validation Study) supplementary material

Appendix 9: Structured proforma

GAIT ANALYSIS APPOINTMENT FORM

Participant Identification number: Participant Initials:

Date of Assessment: Consent form signed? Info Sheet signed?

DOB: __/__/____ Height (cm):

Gender: M/ F Weight (kg):

Handedness: R/ L Leg length (cm) To Ankle:

To Floor:

Medications:

Medical history:

Trial order:

1. Static Trial
2. Gait analysis (Preferred walking speed) * 10

Data collection:

Programs required: Vicon Nexus, OPTOgait, Motion studio and SWING.

Participant into position, Execute trial in OPTOgait, open streaming menu in Motion Studio, Start "recording" in Nexus (will trigger optogait and opals to record).

Instruct participant to stand still for 10 secs, at start and end of recording, before stop recording in Nexus, checking data in Motion Studio and saving data in Optogait.

Trial Comments

Appendix 10: Synchronization configuration gpo files.

Custom gpo file for Vicon Nexus to trigger OptoGait photoelectric system to begin recording (Microgate Inc.).

```
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</AllPrograms>
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Chapter 4 (Gait analysis Study) supplementary material

Appendix 11: Participant Information Sheets
Participant information sheet for people with Cerebellar ataxia (v1.6 02/05/2018) and Healthy Controls (v1.6 02/05/2018).
i) Participant information sheet for Cerebellar ataxia

Sheffield Children's NHS
NHS Foundation Trust

PATIENT INFORMATION SHEET - CEREBELLAR ATAXIA

V1.8 02/05/2018 IRAS ID 197883

Gait analysis in cerebellar ataxia and hereditary spastic paraparesis.

We would like to invite you to take part in a research study. Before you decide whether to participate or not it is important for you to understand why the research study is being done and what it will involve. Please take time to read the following information carefully and to decide whether or not you wish to take part. If you have any further questions after reading the information, please contact a member of the research team (contact details at end of information sheet).

1. What is the purpose of this study?

Our study will examine the ability of gait analysis and activity monitoring techniques to help in the assessment of cerebellar ataxia. Cerebellar ataxia causes poor coordination of movement, balance problems, and difficulty with speaking. It can affect both the arms and the legs. Some of the most disabling symptoms of cerebellar ataxia are related to difficulties with walking. By studying the way in which people with cerebellar ataxia walk we will better understand this disabling aspect of the disease. Ultimately we hope that we will be able to use gait analysis as a marker of early and late stage cerebellar ataxia. This would provide an objective marker of how severe the cerebellar ataxia is in an individual patient. Such objective markers would be useful in treatment trials; i.e.: to see if a treatment is having an effect on a person's gait. At the moment the severity of gait impairment is judged by individual doctors based upon their observations of the patient (i.e. it based on the doctor's opinion rather than a test).

2. Why have I been invited?

You have been invited to take part in this study because you have been diagnosed with cerebellar ataxia by your doctor and undergone genetic testing to diagnose the cause.

3. Do I have to take part?

No. It is up to you to decide whether or not to take part. A member of the research team

will discuss the project with you and give you the chance to ask questions before deciding to take part. You are free to withdraw at any time and without giving a reason. If you decide to take part we will ask you to sign a consent form indicating your willingness to participate in the study. Any current or future healthcare that you receive will not be affected by deciding whether or not to take part in the study. Taking part in the study is voluntary.

4. What will happen if I take part?

If you decide to take part, you will first be assessed by a member of the research team. They will perform a standard neurological assessment so that the research team has a record of your health. This will involve a questionnaire to test your memory and document what symptoms of cerebellar ataxia you have (if any) and a neurological examination (this will test the power and co-ordination in your limbs). These results will not be given to you, but will be kept in our confidential research files. After this the gait analysis will be performed by the research team.

The gait analysis involves wearing small sensors on your ankles, trunk and head. The sensors will be attached using Velcro strips and this is a painless and non-invasive process. We will then ask you to walk a defined distance (5 metres) through the gait analysis system (this is called the OptoGait). This consists of a series of infrared beams (like on TV remote control) which are broken as you walk, this gives very detailed information on your walking pattern. You will be asked to walk through this system 3 times. At slow, normal and fast speed as selected by you. All data is recorded anonymously on a computer. The gait analysis is painless and non-invasive.

We also wish to assess the ability of a new sensor we have made to analyse gait data. This sensor (called SWING) is worn on a Velcro strap on the shoe. It detects the timings and spacing of foot movements. We will compare the results from this to the results from the Optogait system to check the new SWING sensor works. You can participate in other parts of the study without wearing the SWING sensor if you wish.

We also wish to gather data on how Cerebellar Ataxia patients walk and move in their natural, home environment. This will involve wearing a small movement sensor for 7 days. This sensor is worn on a strap around the lower back, and is comfortable to wear and will be removed while bathing or swimming or in bed. We ask you to keep an activity diary in this period and to go about your routine day to day tasks as you always would. At the end of seven days you will need to return the equipment to us (by post). At the end of

this leaflet there is a picture of the gait analysis and activity monitoring equipment so you can get an idea of what it looks like. If you wish to participate in the gait analysis part of the project but not wear the activity monitor, then this is possible.

We want to see if the changes in gait can measure worsening of ataxia. To do this we would like you to come back and have the clinical examination, gait analysis and physical activity monitor repeated at 12 and 24 months after the initial assessment. We will retain your personal information (name and contact details) for the purpose of contacting you again for these assessments. This data will be held in password protected University of Sheffield computers and encrypted files in locked University of Sheffield offices.

We also wish to see if we can detect changes in certain blood chemicals in people with ataxia compared to people without. If you consent we would take about 5 mL (a teaspoon) of blood from a vein in your arm, just like would happen at the GP. The blood sample would be tested for the levels of certain chemicals in a university research laboratory. Since it is a research test a result will not be given to you. This part of the study is optional and you can take part in the gait analysis study without giving blood.

5. What do I have to do?

Firstly, take time to read this information sheet and decide if you would like to take part in the research project. If you have any questions you would like answered before deciding you can contact one of the study team (contact details at end of the leaflet). If you decide to participate you should sign the enclosed form and return it to us. The gait analysis and clinical assessment will occur in the Clinical Research Facility at the Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield. We will provide you with details of how to find this. On the day a medical doctor who is part of the research team will spend 30-45 minutes speaking to you, getting you to sign a consent form and examining you (if needed). The gait analysis will then take place (this should take around 20-40 minutes).

6. Expenses and payments.

If you incur travel expenses in order to attend especially for the project this extra appointment will be reimbursed on request. We can only reimburse expenses incurred for travelling to the Hospital for purposes of the research project.

7. What are the benefits of taking part?

You will not directly benefit from taking part in this study but the information we get from

this study will help improve future treatment of people with Cerebellar Ataxia.

8. What are the possible risks of taking part?

All techniques are safe and non-invasive. We do not anticipate any risks. The gait analysis equipment is manufactured and CE marked to standards for a medical device.

9. Will my taking part be kept confidential?

All patient information is stored on password protected computer databases and in locked filing cabinets and will only be accessible to the research team and regulatory authorities for auditing and monitoring purposes. You will be allocated a unique study number and staff not directly involved with you will know you only by this number. When the results of the study are reported, individuals who have taken part will not be identified in any way. Responsible members of the University of Sheffield or the local Hospital NHS Trust may be given access to data for monitoring or audit of the study to ensure we are complying with regulations. You will be asked if you would like to be contacted for future research projects; if you choose this option some personal information will be stored by us to allow us to contact you again in future.

10. What if I change my mind about taking part?

If you decide to withdraw from the study, your standard of care will not be affected. You will still be asked to attend the routine follow-up clinics required by your doctor and hospital as part of your standard care. These follow up clinics will not be part of the study.

If you withdraw from the study, all samples and clinical information that we have obtained up to the point of you coming out of the study will continue to be used for the purpose of the study unless you ask us to remove them.

11. Will my GP be informed of my participation in the study?

No. This research study will not alter your medical management in any way so we will not contact your GP.

12. What will happen to any samples I give?

No samples will be taken from you. The data we gather from you will be stored on password protected University of Sheffield computers.

13. What will happen to the results of the study?

We plan to publish the results in a health journal so others can read about and learn from the results of the study. You will not be identifiable from the published results.

14. Who is organising and funding the research?

The INSIGNEO institute for *in silico* medicine at the University of Sheffield and Sheffield Institute for Translational Neuroscience (SiTRAN).

15. Who has reviewed this study?

This study has been reviewed by the local research ethics committee and also by the research and development team at Sheffield Childrens Hospitals NHS Foundation Trust.

16. Further Information

Please contact Dr Alisdair McNeill (Senior Clinical Fellow).

SiTRAN.
385a Glossop Road,
Sheffield,
South Yorkshire.
S10 2HQ
Telephone: 0114 222 2230
Email: a.mcneill@sheffield.ac.uk

17. Complaints

Please contact Dr Alisdair McNeill, Chief Investigator, in the first instance.
If this cannot resolve the issue then please contact the PALS team at Sheffield Childrens Hospital:

Linda Towers
Telephone: 0114 271 7954
Email: linda.towers@sch.nhs.uk

In person:

Sheffield Children's Hospital, Western Bank, Sheffield. S10 2TH.

(the PALS team office is located just inside the main entrance)

The picture above shows the patient activity monitor to be worn by study participants.

The picture above shows a man wearing the small sensors which are worn by study participants during the gait analysis.

The picture above shows a man walking through the Optogait 5m system.

ii) Participant information sheet for Healthy Controls

Sheffield Children's NHS
NHS Foundation Trust

PATIENT INFORMATION SHEET - CONTROLS

V1.6 02/06/2018 IRAS 197883

Gait Analysis in Cerebellar Ataxia and Hereditary Spastic Paraparesis.

We would like to invite you to take part in a research study. Before you decide whether to participate or not it is important for you to understand why the research study is being done and what it will involve. Please take time to read the following information carefully and to decide whether or not you wish to take part. If you have any further questions after reading the information please contact a member of the research team (contact details at end of information sheet).

1. What is the purpose of this study?

Our study will examine the ability of gait analysis and activity monitoring techniques to help in the assessment of cerebellar ataxia. Cerebellar Ataxia causes poor coordination of movement, balance problems, and difficulty with speaking. It can affect both the arms and the legs. Some of the most disabling symptoms of cerebellar ataxia are related to difficulties with walking. By studying the way in which people with cerebellar ataxia walk we will better understand this disabling aspect of the disease. Ultimately we hope that we will be able to use gait analysis as a marker of early and late stage cerebellar ataxia.

2. Why have I been invited?

You have been invited to take part in this study because you are not affected by a neurological disease and you would be a suitable healthy "control". We need to study the gait patterns of people *without* Cerebellar Ataxia so we can understand how the gait patterns of Cerebellar Ataxia patients differ from healthy people.

3. Do I have to take part?

No. It is up to you to decide whether or not to take part. A member of the research team will discuss the project with you and give you the chance to ask questions before deciding to take part. You are free to withdraw at any time and without giving a reason. If you decide to take part, we will ask you to sign a consent form indicating your willingness to participate in the study. Any current or future healthcare that you receive will not be affected by

deciding whether or not to take part in the study. Taking part in the study is voluntary.

4. What will happen if I take part?

If you decide to take part you will first be assessed by a member of the research team. They will perform a standard neurological assessment so that the research team has a record of your health. This will involve a questionnaire to test your memory and document what symptoms of cerebellar ataxia you have (if any) and a neurological examination (this will test the power and co-ordination in your limbs). After this the gait analysis will be performed by the research team.

The gait analysis involves wearing small sensors on your ankles, trunk and head. The sensors will be attached using Velcro strips and this is a painless and non-invasive process. We will then ask you to walk a defined distance (5 metres) through the gait analysis system (this is called the OptoGait). This consists of a series of infrared beams (like on TV remote control) which are broken as you walk, this gives very detailed information on your walking pattern. You will be asked to walk through this system 3 times. At slow, normal and fast speed as selected by you. All data is recorded anonymously on a computer. The gait analysis is painless and non-invasive.

We also wish to gather data on how Cerebellar Ataxia patients walk and move in their natural, home environment. This will involve wearing a small movement sensor for 7 days. This sensor is worn on a strap around the lower back, and is comfortable to wear and will be removed while bathing or swimming or in bed. We ask you to keep an activity diary in this period and to go about your routine day to day tasks as you always would. At the end of seven days you will need to return the equipment to us (by post). At the end of this leaflet there is a picture of the gait analysis and activity monitoring equipment so you can get an idea of what it looks like. If you wish to participate in the gait analysis part of the project but not wear the activity monitor then this is possible. We want to see if the changes in gait can measure worsening of ataxia. To do this we would like you to come back and have the clinical examination, gait analysis and physical activity monitor repeated at 12 and 24 months after the initial assessment. We want to see if the changes in gait can measure worsening of ataxia. To do this we would like you to come back and have the clinical examination, gait analysis and physical activity monitor repeated at 12 and 24 months after the initial assessment. We will retain your personal information (name and contact details) for the purpose of contacting you again for these assessments. This

data will be held in password protected University of Sheffield computers and encrypted files in locked University of Sheffield offices.

It is important to realise that none of the research questionnaires or gait analysis are diagnostic tests. The results of these will not enable us to diagnose you with a particular neurological condition. We need to administer the research questionnaires and gait analysis to people without a neurological condition so that we understand the "scores" obtained from these in people without a neurological condition and can compare the "scores" from people with ataxia to these.

We also wish to see if we can detect changes in certain blood chemicals in people with ataxia compared to people without. If you consent we would take about 5 mL (a teaspoon) of blood from a vein in your arm, just like would happen at the GP. The blood sample would be tested for the levels of certain chemicals in a university research laboratory. Since it is a research test a result will not be given to you. This part of the study is optional and you can take part in the gait analysis study without giving blood.

5. What do I have to do?

Firstly, take time to read this information sheet and decide if you would like to take part in the research project. If you have any questions you would like answered before deciding you can contact one of the study team (contact details at end of the leaflet). If you decide to participate you should sign the enclosed form and return it to us. The gait analysis and clinical assessment will occur in the Clinical Research Facility at the Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield. We will provide you with details of how to find this. On the day a medical doctor who is part of the research team will spend 30-45 minutes speaking to you, getting you to sign a consent form and examining you (if needed). The gait analysis will then take place (this should take around 20-40 minutes).

6. Expenses and payments.

If you incur travel expenses in order to attend especially for the project this extra appointment will be reimbursed on request. We can only reimburse expenses incurred for travelling to the hospital for purposes of the research project.

7. What are the benefits of taking part?

You will not directly benefit from taking part in this study but the information we get from this study will help improve future treatment of people with Cerebellar Ataxia.

8. What are the possible risks of taking part?

All techniques are safe and non-invasive. We do not anticipate any risks. The gait analysis equipment is manufactured and CE marked to standards for a medical device.

9. Will my taking part be kept confidential?

All patient information is stored on password protected computer databases and in locked filing cabinets and will only be accessible to the research team and regulatory authorities for auditing and monitoring purposes. You will be allocated a unique study number and staff not directly involved with you will know you only by this number. When the results of the study are reported, individuals who have taken part will not be identified in any way. Responsible members of the University of Sheffield or the local Hospital NHS Trust may be given access to data for monitoring or audit of the study to ensure we are complying with regulations. You will be asked if you would like to be contacted for future research projects; if you choose this option some personal information will be stored by us to allow us to contact you again in future.

10. What if I change my mind about taking part?

If you decide to withdraw from the study, your standard of care will not be affected. You will still be asked to attend the routine follow-up clinics required by your doctor and hospital as part of your standard care. These follow up clinics will not be part of the study.

If you withdraw from the study, all samples and clinical information that we have obtained up to the point of you coming out of the study will continue to be used for the purpose of the study, unless you ask us to remove them.

11. Will my GP be informed of my participation in the study?

No. This research study will not alter your medical management in any way so we will not contact your GP.

12. What will happen to any samples I give?

No samples will be taken from you. The data we gather from you will be stored on password protected University of Sheffield computers.

13. What will happen to the results of the study?

We plan to publish the results in a health journal so others can read about and learn from the results of the study. You will not be identifiable from the published results.

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The INSIGNEO institute for *in silico* medicine at the University of Sheffield and Sheffield Institute for Translational Neuroscience (SiTRAN).

15. Who has reviewed this study?

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16. Further Information

Please contact Dr Alisdair McNeill (Senior Clinical Fellow).

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385a Glossop Road,
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17. Complaints

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Linda Towers
Telephone: 0114 271 7954
Email: linda.towers@sch.nhs.uk
In person:

Sheffield Children's Hospital, Western Bank, Sheffield. S10 2TH.

(the PALS team office is located just inside the main entrance)

The picture above shows the patient activity monitor to be worn by study participants.

The picture above shows a man wearing the small sensors which are worn by study participants during the gait analysis.

Optogait 5m system through which participants will be asked to walk.

Appendix 12: poster advert for clinical study of gait analysis in cerebellar ataxia.

SITraN
Sheffield Institute for Translational Neuroscience

Sheffield Children's NHS
NHS Foundation Trust

VOLUNTEERS NEEDED TO TAKE PART IN A STUDY OF GAIT ANALYSIS IN PEOPLE WITH CEREBELLAR ATAXIA.

At the moment the severity of gait impairment is judged by individual doctors based upon their observations of the patient. People with different types of cerebellar ataxia or spastic paraparesis often display very similar symptoms so it can be difficult for doctors to identify the cause based on physical examination alone. There are also no tests which can measure progression and worsening of ataxia.

Some of the most disabling symptoms of cerebellar ataxia are related to difficulties with walking. In this study we will explore the ability of gait analysis and activity monitoring techniques to distinguish between a type of cerebellar ataxia which causes only ataxia (called SCA6) and a type of ataxia which causes spasticity and ataxia (SPG7).

We need adults with genetically confirmed cerebellar ataxia (SCA6 or SPG7) or hereditary spastic paraparesis (SPAST) as well as healthy people to help establish whether or not gait analysis is a useful technique to help in the diagnosis and assessment of ataxia.

If you decide to take part, during the initial assessment, a medical doctor will perform a standard neurological assessment (involving questionnaires to test your memory and to document what symptoms you have (if any) and a neurological examination to test the power and co-ordination in your limbs). After this the gait analysis will be performed by the research team which involves wearing small sensors on your ankles, trunk and head, and having movements recorded whilst you walk a certain short distance. Clinical assessment will occur in the clinical research facility at the Royal Hallamshire Hospital or Northern General Hospital, Sheffield and will take no longer than 60-90 minutes. If you incur travel expenses in order to attend especially for the project this extra appointment will be reimbursed on request. After this we will follow the participants up at around 12 and 24 months after their initial visit which may help us determine if gait analysis can detect changes in ataxia symptoms over time.

Ultimately we hope that we will be able to use gait analysis as a marker of early and late stage cerebellar ataxia. This would provide an objective marker of how severe the cerebellar ataxia is in an individual patient.

If you would like more information about the study or would like to participate, please contact, Dr Alisdair McNeill, by email at a.mcneill@sheffield.ac.uk

Thank you for taking the time to read this information.

Appendix 13: Written informed consent forms

The written informed consent forms for people with i) Cerebellar ataxia (v1.3 23/03/2018) and ii) Healthy Controls (v1.2 23/03/2018).

i) Cerebellar ataxia cohort Informed Consent form

Consent Form v1.3 23.03.2018

Sheffield Children's NHS
NHS Foundation Trust

CONSENT FORM

Title of Project: **Gait analysis in cerebellar ataxia and hereditary spastic paraparesis. v1.3 23.03.2018 IRAS 197883**

Name of Researcher: Dr Alisdair McNeill PhD MRCP (UK) Senior Clinical Fellow

Ellen Buckley MSc Research Technician

Please initial each box

1. I confirm that I have read and understand the information sheet dated [02/05/2018] (version [1.6]) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by responsible individuals from the research team at Sheffield Institute of Translational Neuroscience (SITraN), University of Sheffield or from regulatory authorities or the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I would like to be contacted about relevant future studies carried out by SITraN. This is optional – please initial either Yes or No.
   Yes ☐
   No ☐

5. I consent to gait analysis ☐

6. I consent to wear the physical activity monitor (optional part of study) ☐

Gait analysis in cerebellar ataxia and hereditary spastic paraparesis. v1.3 23/03/2018

7. I agree to be contacted by telephone to be invited for the 12 month and 24 month follow up visits ☐

8. I agree to take part in the above study. ☐

9. I agree to wear the SWING sensor (optional part of study) ☐

10. I agree to have a blood sample taken (optional) ☐

Name of Participant	Date	Signature
Name of Person taking consent.	Date	Signature
Name of Person witnessing consent.	Date	Signature

1 copy of consent to be given to participant, 1 to be retained by researcher and 1 placed in medical notes

ii) Healthy Control cohort Informed Consent form

Consent Form v1.2, 23.03.2018

Sheffield Children's NHS
NHS Foundation Trust

CONSENT FORM

Title of Project: **Gait analysis in cerebellar ataxia and hereditary spastic parapalegia. 1.2, 23.03.2018**

Name of Researcher: **Dr Alisdair McNeill PhD MRCP (UK) Senior Clinical Fellow**

Ellen Buckley MSc Research Technician

Please initial each box

1. I confirm that I have read and understand the information sheet dated [02/05/2018] (version [1.5]) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by responsible individuals from the research team at **Sheffield Institute of Translational Neuroscience (SITraN), University of Sheffield** or from regulatory authorities or the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I would like to be contacted about relevant future studies carried out by SITraN. This is optional – please initial either Yes or No.
   Yes ☐
   No ☐

5. I consent to gait analysis ☐

6. I consent to wear the physical activity monitor (optional part of study) ☐

7. I agree to be contacted by telephone to be invited for the 12 month and 24 month follow up visits ☐

8. I agree to take part in the above study. ☐

9. I agree to have a blood sample taken (optional part of study) ☐

Name of Participant	Date	Signature
Name of Person taking consent.	Date	Signature
Name of Person witnessing consent.	Date	Signature

Appendix 14: structured medical interview proforma

Form and checklist intended to be used at all study visits with participants to ensure all essential data are captured.

Date: Participant Identification Number:

Visit number: Participant Initials:

GAIT ANALYSIS APPOINTMENT FORM (w/ PAM)

Consent given?

DOB: __/__/____ Height (cm):

Gender: M/ F Weight (kg):

Handedness: R/ L Leg length (cm) To Ankle:

To Floor:

Alcohol intake (units per week):

Medications:

Medical history:

Patients Only:

Date of Diagnosis (approx. year or duration):

Genetic diagnosis:

Falls history:

On examination (eliminate as needed):

Spastic?	Yes/ No	Clonus present?	Yes/ No
Plantars?	Up/ Down	Reflexes?	Hyper/ Hypo/ Normal

Other comments:

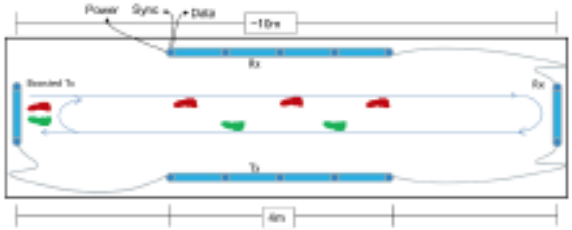
Functional Assessment Summary

SARA:

MoCA:

Berg Balance Score:

GAIT ANALYSIS 6x ~10m, 5m OPTOgait in 2D formation w/ Boosted Tx bar.
Sync requires dark green banana to green socket and yellow/green banana to black socket with 6pin DIN to Access Point.



OPAL sensor no's: Right Foot = 1624, Left Foot = 1629, L5 = 1627, C7 = 2410/1628, Forehead = 1631

Optogait Test = GAIT TEST 2D NORMAL - ataxia study - synced

Trial order: 1= Preferred walking speed, 2 = Fast walking speed, 3 = Slow walking speed.

OPTOgait Patient name = Participant no. E.g. ATAXIA01 **MotionStudio File Name**: Participant No. Test name. E.g. ATAXIA01 Fast

Movemonitor: Project= Ataxia **Subject** = Participant no. **Visit** = Visit no.
Set Movemonitor to record throughout. **Start**: Now, **Duration**: 1 hour
For each trial, get participant into position, Execute trial in OPTOgait, Start "recording" in OPALs in MotionStudio. Instruct participant to stand still at start for 10 secs, then walk with head straight, turn around at end and return. Don't step out of system and remain within parallel bars. 6 passes within each trial. One trial at each speed. Rest as needed between trials. Once trial finished ask participant to stand still for 10secs again, then stop recording in MotionStudio and save data in Optogait. Plug in Movemonitor to stop (Don't change visit number).
Transfer data file and reset Movemonitor for 7day recording. **Start**: Next day (__/__/__) 5am, **Duration**: 7days

Trial Comments

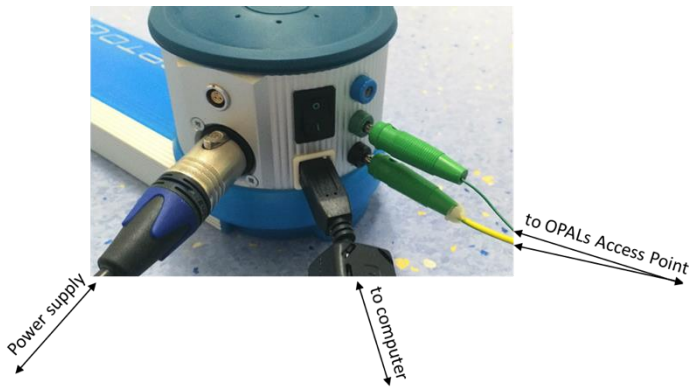
After analysis

- Movemonitor data uploaded. And reattached to participant. Provide activity diary.
- Phone number: Movemonitor no.
- Movemonitor to be return in 7days. Pre-paid envelope? **Posted back after** __/__/____.
- Sensors Cleaned, Docked and Data uploaded?
- Optogait data saved and system returned to storage?
- Any parking/taxi / expenses receipts?

Appendix 15: Custom-made cable for synchronisation between OptoGait system and ADPM Opal sensors access point.

A custom solution cable has been manufactured to enable a direct trigger signal to be transmitted between Motion Studio software and the OptoGait software.

a) OptoGait end: Green banana plug->Green socket
Yellow/Green plug->Black socket (Earth)



b) ADPM Opal sensors end: 6 pin digital I/O connector