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Assessing residual neck mobility when wearing a cervical orthosis: an application in patients with Motor Neurone Disease

A thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy

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Abstract

Severe weakness of the neck extensor muscles has been observed in neuromuscular pathologies, such as motor neurone disease (MND). This condition reduces the ability to perform daily activities and communicate, leading to the adoption of a cervical orthosis. However, commercially available devices are designed to immobilize the neck, which makes them uncomfortable and strenuous to wear for a long time. The lack of a device specifically designed for those patients led to the development of the Sheffield Support Snood (SSS) which enables to adjust the support given to the head, according to the task performed and to the disease progression. The following step toward the SSS commercialisation and adoption was an objective evaluation of its performance and the assessment with the end users, which was the aim of this thesis. To this purpose, an experimental protocol designed to quantitatively assess neck mobility when wearing cervical orthoses, has been developed. This protocol and the associated signal processing techniques proved to be suitable for the assessment of neck mobility through the measurement of head movements, both in laboratory and clinical settings. After having quantitatively assessed head movement limitation in MND patients, filling an existing gap in the current literature, the effects of the SSS were tested. Compared to controls, patients presented an overall impaired ability to perform head movements in terms of reduced velocity (mean values between 27% and 41% lower in movements performed reaching the maximum range of motion and between 34% and 48% lower in movements performed reaching the maximum angular velocity), reduced smoothness (mean values between 21% and 44% lower in movements performed reaching the maximum range of motion) and increased presence of coupled movements (mean values between 37% and 58% higher in movements performed reaching the maximum range of motion and between 44% and 53% in movements performed reaching the maximum angular velocity). The SSS was effective in facilitating the head movements in MND patients. Among those 9 individuals that were fitted with anterior or anterior plus lateral supports 5 of them had a reduced presence on coupled movements in at least one of the movements performed. However, a proper fitting of the orthosis appeared crucial and in the future it should be based on a quantitative approach similar to the one developed in this

thesis. This study paved the way for improvements in the SSS design and for future quantitative assessment of the characteristics of motor control and movement strategies in MND patients and of how these change when using a device aiming at compensating for functional impairments.

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Declaration

A substantial part of the material presented in this thesis is published work or is currently under revision:

- Part of the material presented in Chapter 3 has been included in:

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- Part of the material presented in Chapter 4 has been included in:

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Written permission was obtained from all the co-authors.

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List of abbreviations

MND: motor neurone disease

ALS: amyotrophic lateral sclerosis

ADL: activities of daily living

ALSFRS-R: ALS functional rating scale revised

MMT: manual muscle testing

HHD: hand held dynamometers

MVIC: maximum voluntary isometric contraction

QoL: quality of life

CROM: cervical range of motion

IMUs: inertial measurement units

ROM: range of motion

NJ: normalized jerk

F_T : technical sensor reference frame

F_G: global reference frame

F_A : anatomical reference frame

SSS: Sheffield Support Snood

AHM: active head movements

NP: neutral position

RMSE: root mean square error

HR: Headmaster orthosis

VA: Vista orthosis

E: extension

F: flexion

AR: axial rotation

LF: lateral flexion

RMS: root mean square

AP: Anterior-Posterior

V: Vertical

ML: Medio-Lateral

C_{SH}: attenuation coefficient between sternum and head

ICC: intraclass correlation coefficient

ω_m : mean angular velocity

ω_p: peak angular velocity

RMC: ratio of movement coupling

Z_{CS} : composite score

Chapter 1

Introduction

1.1 Motor Neurone Disease (MND)

Motor Neurone Disease (MND) is a degenerative disorder which causes progressive weakness of limb, bulbar and respiratory muscles. The disease is progressive and irreversible and leads to death typically in three to five years, most often due to respiratory failure [1]. MND is relatively rare with an annual incidence of 2 in 100 000 individuals and prevalence of 5-7 in 100 000 [2]. Motor neurons are specialized nerve cells, which are responsible for transmitting electrical signals from the nervous system to the muscles to generate movement. There are two types of motor neurons: upper and lower. Upper motor neurons start at the top of the brain (motor cortex) and travel down to the spinal cord to connect with the lower motor neurons. This second type of cells, lower motor neurons, travel down to the spinal cord (along arms and legs) and connect to the muscles. MND causes undergoing degeneration and death of upper, lower or both types of motor neurons with the result that the nervous system is no longer able to initiate and control muscle movements and muscles become weak [3]. The term MND can refer to several forms of disease. Amyotrophic lateral sclerosis (ALS) is the most common form and is characterized by a mixture of upper and lower motor neurone features [2]. The consequences of the disease for the motor function differ depending on the extent to which upper and/or lower motor neurons are affected by the degeneration [4]. It has been observed that MND has a relevant impact on both basic and instrumental activities of daily living (ADL) according to the level of severity of the disease [5]. The level of functional impairment in MND patients is commonly assessed in clinical practice using the ALS Functional Rating Scale revised (ALSFRS-R, Appendix A) which is a validated questionnaire-based scale that measures physical function in carrying out ADL [6]. The scale covers 12 items that encompass: gross motor tasks, fine motor tasks, bulbar functions and respiratory functions. The score is based on a self-reported assessment of the patient (or the caregiver, when the patient is not able to

communicate). The answer to each item is rated from 0 (complete dependence) to 4 (normal function), resulting in a total score ranging from 0 (maximum disability) to 48 (no disability). This scale is widely used because is easy to administer in clinics and has been recognized as a useful predictor of disease progression [7].

1.1.1 Quantification of motor impairment in people with MND

The main limitations of functional rating scales, as the ALSFRS-R, are to provide ordinal data, which may lack of sensitive in presence of small changes and to provide steps between grades which are not guaranteed to be qualitatively equivalent for each interval [8]. It has been observed that the ALSFRS-R scale doesn't take into account different levels of impairment between left and right extremities, often observed in ALS patients, and the score obtained is based on a self-assessment performed by the patient, which is subjective and prone to be altered by the presence of a cognitive impairment [9]. Furthermore, some authors have expressed their concerns about the validity of summing the ALSFRS-R items into a single score, suggesting that the mean scores from three different domains (bulbar, motor and respiratory functions) should be taken into account more than a global total score [10]. Although the ALSFRS-R remains a valid tool to broadly assess functional disturbances in ALS patients, measurements of muscular strength have been introduced as an indicator of motor loss and they represent an essential component of the evaluation of patients with neurological disorders. An accurate assessment of muscle strength can provide valuable information to clinical care to evaluate the patient's status, its changes over time and the efficacy of a therapeutic intervention [11] [12]. The use of manual muscle testing (MMT) is widely diffused among physicians, because is quick, simple to administer and doesn't require special equipment [8] [11]. In this test, the ability of the patient to move against gravity and the examiner resistance is evaluated and graded by the examiner. Muscle strength is usually assessed using the Medical Research Council scale, which scores from 0 to 5 (0 = no movement, 1 = flicker of movement, 2 = movement of the joint when the effect of gravity is eliminated, 3 = movement through full range of the joint, against gravity, 4 = movement of the joint, against gravity and against added resistance, 5 = full strength) [13]. However, primary limitations of MMT are similar to those observed in functional rating scales, as the test is evaluator

dependent and is reported to be scarcely sensitive to small changes, particularly in the higher grades [8] [11]. For example, it has been reported that in the above mentioned Medical research Council ordinal scale the grades of 4 and 5 can cover the 97% of muscle's expected strength [14]. This can cause the disease to progress for an extended period before it is detected by a change in the MMT score. Additional instruments have been then introduced to obtain a quantitative and more accurate assessment. When assessing the muscle strength, maximal isometric contraction, which represents the greatest amount of force a muscle can generate and hold in the muscle testing, is usually evaluated. Alternatively, eccentric contraction can be assessed instead and, in this case, the load on the muscle under testing is increased until it reaches a point where the external force is greater than the force the muscle can generate [12]. Hand-held dynamometers (HHD), are devices that are held by the examiner and applied on patient's specific locations, according to the muscle tested. They are portable, relatively inexpensive but the maximum force they can measure is limited by the strength of the examiner [8]. The evaluation of the maximal voluntary isometric contraction (MVIC) performed by using fixed force gauges, which are devices incorporating load cells, strain gauges or cable tensiometers, is also reported in literature [15] [16]. The additional information provided by those devices, compared to MMT and HHD, is the rate at which the muscle develops the force through the force-time curve [12]. On the other hand, its main limitations are the need for specialized equipment and trained operators [8]. Thanks to the capability to evaluate the force-time curve, this method has been used to assess also motor fatigue in ALS patients. By testing selected groups of muscles (elbow flexors, knee extensors and ankle dorsiflexors) Sanjak et al. [16] observed that fatigue was significantly greater in ALS patients compared to healthy subjects in all muscles, including those that were not considered as weak. When different muscle strength testing techniques were applied on ALS patients and compared, it was observed by the Great Lakes ALS Study Group [17] that the MVIC measured with fixed load cell tensiometers and the MMT were equivalent in terms of reproducibility, while Andres et al. [8] reported a high inter-rater reliability for both methods but a lower sensitivity to early changes for the MMT. In terms of precision, the MVIC measured with a strain gauge system and the HHD, in a strength range up to 20 kg, were reported to provide similar results [18]. However, the same authors highlighted that the HHD has the additional advantage, with respect to

the fixed force gauges, to be possibly used in wheelchair-bound patients and do not require patients with respiratory difficulties to take a supine position which can increase the degree of respiratory distress. The use of hand-grip dynamometers is also reported in studies with ALS patients [15] although they are extremely limited in terms of muscle group application, since they can measure hand-grip strength only. All those methods described above capture only isolated strength over specific joints and do not assess the overall limb function. In a study conducted by Vandervelde et al. [19] it was observed that, in patients with neuromuscular disorders, including patients with ALS, the correlation between motor impairments (evaluated through manual muscle testing, hand grip dynamometer and 10 meters walking test) and activity limitations (evaluated through a questionnaire) was moderate to poor, with the spontaneous gait speed showing the highest correlation. This suggests that patient's level of activity limitation can't be merely inferred from muscle strength measurements. In fact, the presence of muscle weakness can induce patients to develop compensatory strategies that allow them to complete the activities. On the other hand, other impairments such as fatigue, pain, contractures, respiratory or sensory impairments can affect patients' ability to perform daily activities. Furthermore, it has been hypothesized that there can be some critical levels at which a small decline in strength leads to a large functional loss [8]. Thus, an assessment based only on muscle strength evaluation can be inadequate to describe the actual level of progression of the disease.

To overcome the limitations of muscle strength evaluation, the use of a Kinect sensor, which allows measuring the 3D reachable workspace and assessing the residual upper limbs function, has been recently proposed by Oskarsson et al. [9]. Using the Kinect-based system it was observed that the reachable workspace relative surface area in ALS patients was significantly reduced compared to controls. Further advantages of this system were to be able to discriminate between asymmetric extremity dysfunctions, to transmit data electronically, so that patients' functional data could be collected in a home setting, and the possibility to have pre-registered instructions in order to reduce the reliance on clinical evaluators. The assessment of the 3D reachable workspace highlighted the need for quantitative measurement of the ALS patients' residual functional ability to perform a task, rather than the assessment of a muscle

group's strength. The proposed method could be extended to other body regions and other activities commonly performed in daily life.

Since the walking performance is considerably affected by the progression of ALS [20], gait characteristics have been also investigated. Through the use of force-sensitive insoles, which measure temporal gait parameters, Hausdorff et al. [21] observed that the walking ability of ALS patients was altered compared to healthy controls. In fact, gait in ALS patients was characterized by an increased stride time and stride to stride variability while, on the contrary, walking speed appeared reduced. ALS gait resulted also less steady and more temporally disorganized compared to healthy subjects. Furthermore, ALS patients with lower limb onset disease showed a significant reduction of speed compared to those with upper limb and bulbar onset [22]. Those studies underlined the importance of assessing alterations in the gait dynamics to determine disease severity, medication utility, fall risk and response to therapeutic interventions. Furthermore, using gait signals available from the Physionet database [23], gait dynamics was investigated in order to develop a classification scheme able to facilitate the discrimination between ALS and healthy subjects and to monitor of the disease progression [24] [25] [26].

1.1.2 Neck muscle weakness, consequences and treatments

The onset of ALS normally occurs in a particular group of muscles first. This is usually distally in one limb with an inevitable progression to other muscles within the limb and beyond over time. Eventually, bulbar and respiratory muscles are also affected as well as neck muscles which support and move the head. Neck muscles affected are commonly the neck extensors with or without the involvement of the neck flexors [27]. As muscle weakness increases, the head drops and this creates a condition of significant disability by exacerbating problems with breathing, swallowing and communicating. It has been observed that the reduced ability to support and move the head leads to a reduction of patients' quality of life (QoL) [28] and an increasing difficulty in performing the ADL which can significantly shorten the survival time in ALS patients [29]. Since at the moment there are no treatments that can slow, stop or reverse the progression of this condition, interventions offered to patients focus on preserving their independence and a good QoL [2]. Patients affected by neck muscle

weakness are thus advised to wear a cervical orthosis, in order to improve their neck posture and their social interaction [27].

1.2 Quantification of Cervical Movements

1.2.1 Anatomy and biomechanics of the cervical region

Although, throughout the study, the vertebrae that constitute the cervical region of the spine will be considered as a unique pivot joint, a brief description of the anatomy of the cervical region is here provided in order to enhance the comprehension of complex movements that the cervical spine is able to perform and justify the assumptions made in the study.

The cervical region is the most mobile region of the cervical spine and is made up of seven vertebrae (C1-C7, Figure 1-1).

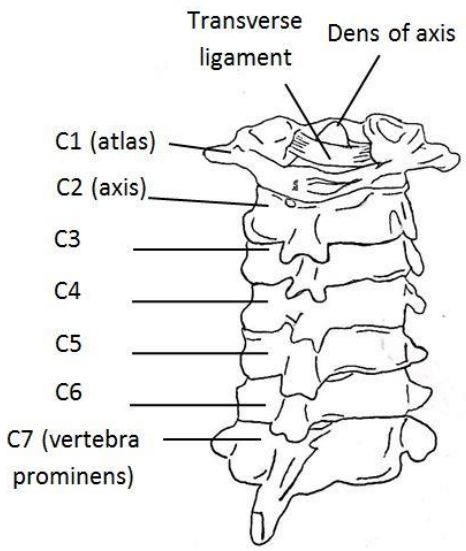


Figure 1-1 Cervical region of the spine

Its primary functions are to provide support and stability to the head, to allow its complex motion and to transfer the weight of the head to the trunk. Furthermore, it protects the carotid and vertebral arteries, the spinal cord, the anterior and posterior nerve roots, and, in its uppermost portion, the brain stem [30]. All these primary functions of the spine are achieved thanks to the presence of the vertebrae and the different structures that are often referred to as soft tissues of the cervical spine.

Those structures consist of the ligaments, the facet capsules and the intervertebral discs. The ligaments connect the vertebral bodies and the posterior elements of the cervical vertebrae and prevent, together with the paracervical muscles, motion between vertebrae which might injure the spinal cord or the nerve roots. The facet capsules connect the articular processes of the vertebrae while the intervertebral discs absorb the stress and shock the body incurs during movement and prevent the vertebrae from grinding against one another. These structures allow for movement between the cervical vertebrae and, together with muscles, control the overall motion of the head. The head movements enabled by the cervical vertebrae in the three main anatomical planes are referred to as extension/flexion (movements in the sagittal plane), axial rotation (movement in the transverse plane) and lateral flexion (movement in the frontal plane, Figure 1-2).

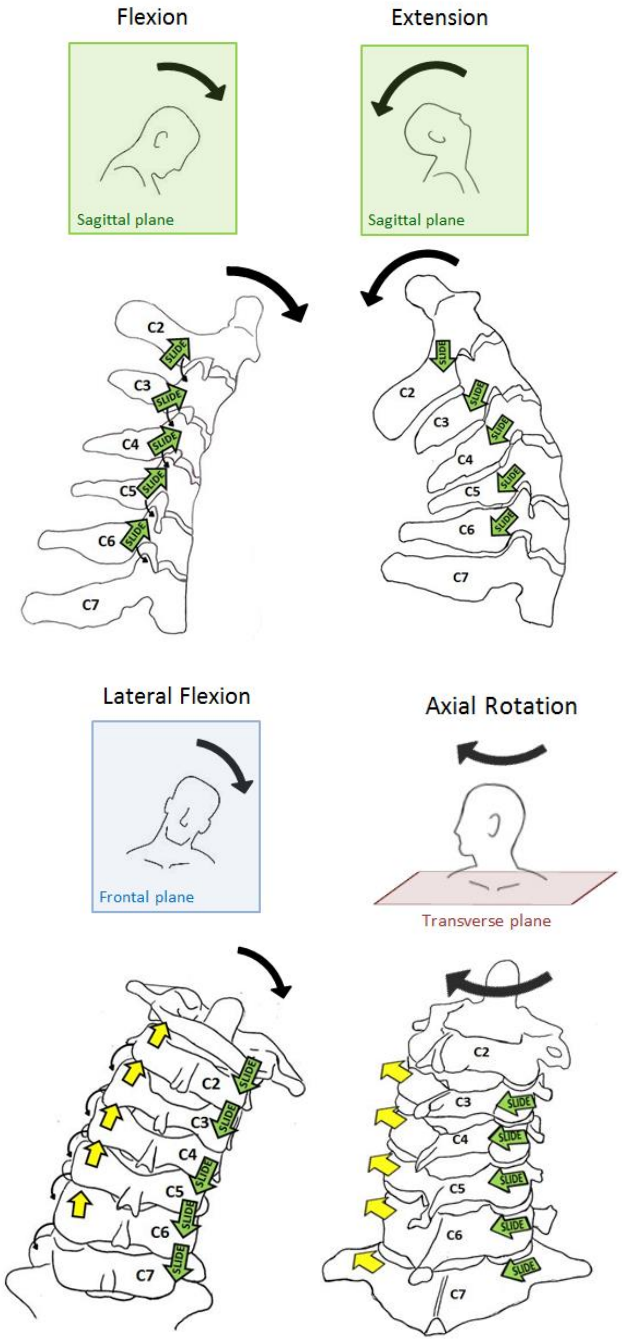


Figure 1-2 Head movements in the three main anatomical planes

Due to morphological and functional differences, the cervical region can be divided in two main segments: the upper and the lower cervical spine. The upper cervical spine consists of the occiput (C0) and the first two vertebrae (C1-C2), also known as atlas and axis, respectively. The atlas (Figure 1-3b) is characterized by an anterior and a posterior arch, paired lateral masses, and paired transverse processes onto which muscle

attachments are made. Differently from the other cervical vertebrae (Figure 1-3a), it has no pedicles, laminae or spinous process. The atlanto-occipital joint (C0-C1) is comprised of a pair of condyloid synovial joints, which allow for flexion-extension: the only physiological movement possible at this joint. A minimal degree of lateral flexion and axial rotation can be however obtained by artificially forcing the head while keeping the atlas fixed [31]. The flexion-extension movement is achieved because the C1 superior articular surfaces are concave whereas the occipital condyles are convex.

During flexion, the condyles roll forwards and slide backwards across the anterior walls of the notches while, during extension, a converse combination of movements is observed. The flexion movement is limited by the compression of the rim of the socket against the skull base, by the tension of the posterior muscles and capsules and by the contact of the submandibular tissues against the throat. The extension movement, on the other hand, is limited by the compression of the sub-occipital muscles against the occiput. Side to side movements are prevented by the sidewalls of the concave sockets of the atlas, anterior-posterior movements are prevented by the front and back walls while upward displacements are prevented by axial forces applied by the mass of the head and the muscles.

The axis (C2, Figure 1-3c and Figure 1-3d) is the largest cervical vertebrae. Similarly to the other vertebrae, it is characterized by a body and an arch but, additionally, it presents also the odontoid process, or dens, which protrudes from the cranial part of the body and articulates with the ventral arch of the atlas. Together with the weight bearing, the main function of the axis is to allow a large rage of axial rotation. In fact, the anterior arch of the atlas pivots and slides around the odontoid process of the axis and the inferior facet surfaces of the atlas slide across the large superior facet surfaces of the axis [31]. The articulation of the first and second vertebrae, which allows for the rotation movement to be performed, is called the atlanto-axial joint (C1-C2).

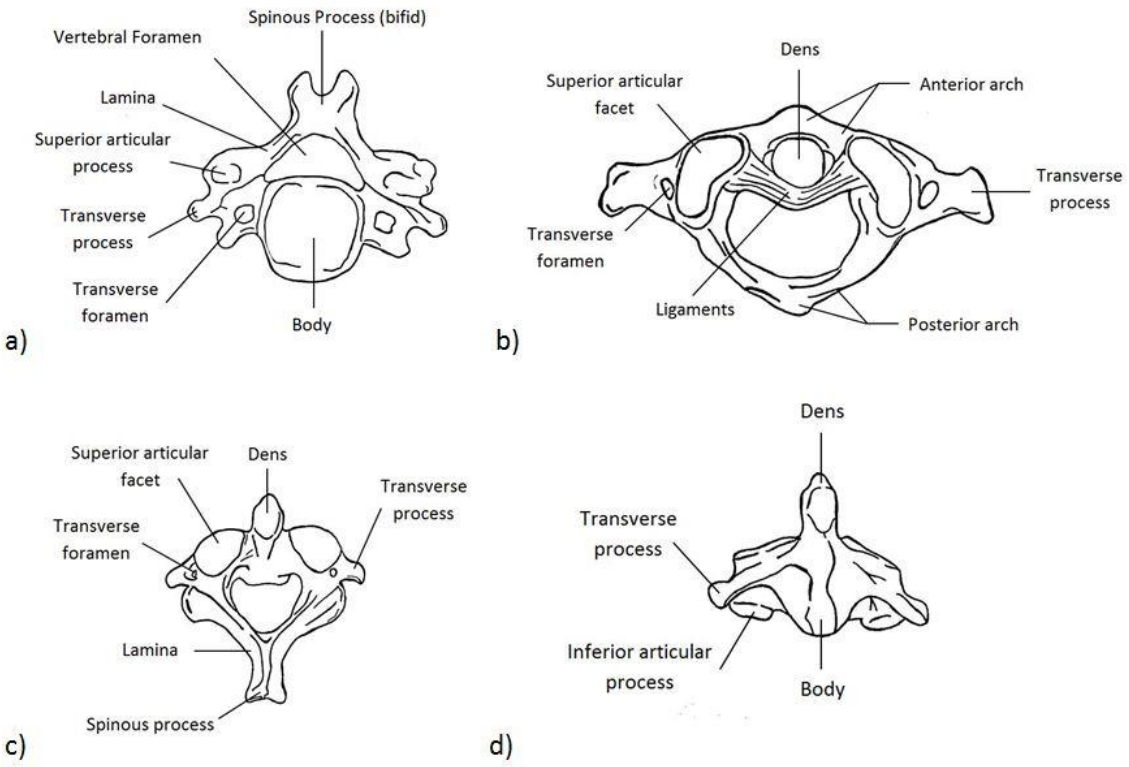


Figure 1-3 Cervical vertebrae; a) structure of a typical cervical vertebra; b) superior view of the atlas; c) superior view of the axis; d) anterior view of the axis.

The lower cervical spine comprises vertebrae from C3 to C7. Those vertebrae are characterized by a body and an arch which includes: two pairs of articular facets, a spinous process and two transverse processes. Those vertebrae are separated by intervertebral discs with a large cross sectional area, to bear the applied loads. They are characterized by an oblique orientation that allows them to support flexion-extension movement, which is the primary movement of this cervical segment. Also, since discs are thicker anteriorly than posteriorly, the cervical spine presents, in this segment, an anterior convex curve, known as cervical lordosis. Cervical interbody joints are described as saddle joints. The movement that occurs is predominantly a rocking movement, although translatory movements are also allowed. In the sagittal plane, the concave inferior surface of the cranial vertebra articulates with the convex superior surface of the caudal vertebra, created by the presence of a process called “uncinate”. In the frontal plane, conversely, convex inferior surface of the cranial vertebra articulates with the concave superior surface of the caudal vertebra. Due to the geometry of the vertebral bodies and the orientation of the facet joints, axial rotation movements are inexorably associated with lateral movements and vice versa. In fact,

whenever an axial rotation movement is performed, the inferior articular process rises up the slope of the superior facet of the vertebra below and a tilt to the side of rotation occurs.

1.2.2 Movement coupling

As mentioned in Paragraph 1.2.1, due to the morphology of the cervical spine, when gross rotation is performed, a lateral flexion to the same side occurs as well as when lateral flexion is the primary movement it is necessarily associated with ipsilateral rotation. This phenomenon is referred to as movement coupling [32]. Movement coupling has been investigated in-vivo through the analysis of x-ray films. In healthy subjects it was observed that when an axial rotation is performed, a lateral flexion occurs in the same direction as the axial rotation at the segments below C3-C4 level and in the opposite direction above the C2-C3 level. Furthermore, a flexion movement occurs in association with the axial rotation at the segments below the C5-C6 level, while an extension movement can be seen above the C4-C5 level [33]. A following study conducted through the use of an electromagnetic device, able to measure the orientation of the forehead relative to the C7 level of the spine, investigated the gender and age influence on movement [34]. It was seen that age affects the lateral flexion and extension movement associated to the axial rotation while no effects of gender on coupling movements have been observed. Results obtained in the study from Trott [34] are summarized in Table 1-1. A more recent study, conducted by Malmström et al. [35] using a 3D motion analyser based on ultrasounds, confirmed that coupled movements associated to axial rotation are affected by age. They observed also a variation in coupled movements associated to lateral flexion due to increasing age as well as a gender difference in coupled lateral flexion to primary axial rotation.

Table 1-1 Mean range of motion coupling associated to different groups of healthy subjects according to Trott [35]. Negative value denotes movement to the right side and extension.

Primary Motion	Range of Motion (deg)				
		Age groups (n=40 per group)			
Flexion		20-29	30-39	40-49	50-59
	Coupled Lateral Flexion	3.0	0.8	-0.8	-0.1
	Coupled Rotation	4.8	3.1	3.9	3.3
Extension					
	Coupled Lateral Flexion	13.2	4.2	5.5	9.2
	Coupled Rotation	-9.0	-2.7	-3.6	-5.7
Rotation (L)					
	Coupled Flexion/Extension	-13.8	-5.4	-6.8	-6.5
	Coupled Lateral Flexion	8.8	1.8	3.2	2.5
Rotation (R)					
	Coupled Flexion/Extension	-14.0	-6.1	-7.9	-7.7
	Coupled Lateral Flexion	-11.3	-1.3	-4.6	-2.9
Lateral Flexion (L)					
	Coupled Flexion/Extension	-2.5	-4.3	-2.7	1.6
	Coupled Rotation	5.1	8.1	9.9	8.3
Lateral Flexion (R)					
	Coupled Flexion/Extension	-11.4	-12.1	-10.1	-8.3
	Coupled Rotation	-7.0	-8.0	-13.1	-13.2

1.2.3 Measurement systems to assess the cervical motion

The term cervical motion can refer both to the movement of the cervical vertebrae in relation to each other and to the head with respect to a stationary reference system (often represented by the trunk). When referring to the first case, radiological analyses through the acquisition of lateral x-rays images, while the participant is performing head movements, are the gold standard to investigate vertebral motion [33] and instantaneous axis of rotation [36]. However, these techniques are largely invasive, since they expose the subject to radiation. Furthermore, there are errors associated with marker positioning and detection that

occur during X-ray elaboration, in particular when two radiographic projections are superimposed and homologous landmarks have to be detected in both of them [37]. In the context of treatment and rehabilitation, cervical motion commonly refers to the movement of the head with respect to the trunk. Movements of the head with respect to a fixed reference frame can be measured through different techniques including: goniometry, ultrasonography, electromagnetic tracking systems, optoelectronic stereophotogrammetric systems and inertial sensors.

The Cervical Range of Motion (CROM) device is an example of commercially available gravity goniometer. The CROM device consists of two independent inclinometers, one in the sagittal plane and one in the frontal plane attached on a head mounted frame. Those two inclinometers indicate the position of the head with respect to the gravity while a third sensor (compass) is positioned in the horizontal plane and indicates the position of the head in rotation, with respect to a reference position. A magnetic yoke is supplied which is rested over the front and back of the chest to reduce the influence of trunk rotations (Figure 1-4). Its validity and between day reliability has been assessed against an electromagnetic motion system [38] and a good test-retest reliability was observed in all the movements performed in the three main anatomical planes. The main advantages of CROM device are to be easy to use, relatively affordable and portable. This last feature allows it to be used in clinical settings. On the other hand, among its main limitations there are: the possibility to measure the movement only in the primary plane (coupled movements cannot be measured), the inability to isolate cervical motion from the upper thoracic segments so that head movements measured by the device might include a contribution from the trunk [39].

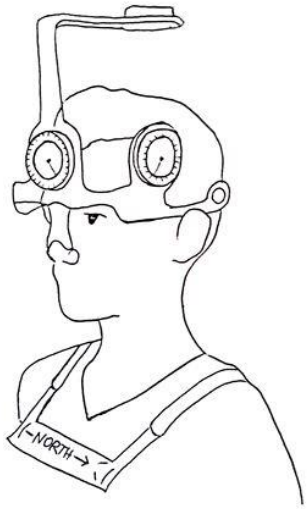


Figure 1-4 CROM device

The Zebris system is an ultrasonic three dimensional motion analysis device. Measurement is performed by determining the spatial coordinates of miniature ultrasound transmitters. The transmitters are arranged in two triads and attached to head and chest through plastic frames. Their position relative to a fixed system of three microphones is derived from the time delay between the ultrasound pulses, using triangulation. In fact, a measuring sensor mounted on a tripod detects the travel time of the ultrasonic signals and transmits the results to the basic unit. The system has been validated against X-rays taken while healthy participants were performing extension and flexion movements [40] and several studies report a high inter an intra examiner reliability [40] [41] [42] [43]. The resolution of the system is reported to be ± 0.1° [44]. Together with the high accuracy, the main advantages of the device are: the reduction of the examiner-bound error of measurement, the ability to record coupled movements, the calculation of higher-order displacement derivatives [45]. The main drawback of the system is represented by its cost. Furthermore, it requires accurate calibration and has a reduced portability.

The use of electromagnetic motion analysis is reported in literature in the form of two devices: the FASTRAK and Flock-of-Birds. Both devices work by tracking position of sensors electromagnetically relative to a source transmitter. Each sensor can measure data in three planes of joint motion, collecting the range of motion and speed over time. The disadvantage of those systems is the relative expense, the lack of portability and the need for substantial calibration procedures. Furthermore, they can be affected

by the presence of metals although no interaction with the commonly used orthopaedic alloy has been observed [46]. Positional and rotational errors for the system are reported to be less than 2%, when used in its optimal operating range (22.5-64 cm). The assessment of the inter and intra operator reliability for this system is reported in literature [47] as well as a comparison with the CROM device [39]. From the comparison between the two systems emerged that the electromagnetic system and the CROM device compared well in extension, flexion and rotation with the electromagnetic system showing a high intra-operator and a fair-to-high inter-operator reliability for the measurement of extremes of range of motion in all 3 planes tested. In addition, authors underlined the advantage of the electromagnetic tracking system with respect to the CROM device to exclude the contribution of the trunk by measuring only the cervical motion.

Optoelectronic stereophotogrammetric systems are designed to reconstruct the 3D position of light emitting or light reflective spherical objects, called active or passive markers, respectively. Their position is reconstructed according to the laboratory reference frame. The system is generally composed of a minimum of two cameras, and the position of each marker, reconstructed for each acquired frame, allows determining the trajectory of that marker [48]. Optoelectronic systems are extremely reliable and sensitive and have been extensively used to assess the cervical motion [49] [50] [37]. However, the main drawbacks of this system are to be expensive, cumbersome and have a definite measurement volume, within which the movement must take place. Those features make them challenging to be used outside a laboratory setting, thus unsuitable for a protocol translatable to a clinical context. In addition, well trained users are required and a further limitation is represented by point-marker emissions which may not be detected by the relevant sensors in case of interposition of other body segments [51].

Inertial Magneto Units (IMUs) have been recently demonstrated to be viable instruments to assess cervical motion [52]. They are characterized by the presence of a tri-axial accelerometer, a tri-axial gyroscope and a tri-axial magnetometer able to measure the linear acceleration, the angular velocity and the orientation of the sensor according to its own reference frame. The main advantages of the IMUs are to be easy to use, light to wear, relatively cheap and portable. This last feature allows them to be

easily used in clinical settings. IMUs characteristics and their application in measuring the cervical motion will be extensively described in Paragraph 1.3.6.

1.2.4 Parameters to evaluate the cervical motion

The assessment of cervical motion can be required in several different conditions: traumatic, degenerative, rheumatic, neurological or congenital. Since those conditions interest a wide range of population, several studies are reported in literature which investigated the human cervical motion and its alterations. The investigation of the cervical motion is usually performed by assessing the ability to execute head movements in the three main anatomical planes: flexion-extension in the sagittal plane, axial rotation in the transverse plane and lateral bending in the frontal plane.

Cervical motion does not include only the angular excursions of the head relative to the three major anatomical planes but also the first (velocity), second (acceleration) and third (jerk) derivatives of head displacement. In addition, coupled movements have attracted growing interest among clinicians.

Cervical motion has been widely assessed by measuring its range of motion (ROM) and it is commonly accepted that evaluation of ROM plays an important role in diagnosis, assessment of severity and assessment of treatment outcome, in the management of musculoskeletal conditions. Cervical ROM can be evaluated through active or passive techniques. Active techniques consist in participants performing the head movements without the assistance of the examiner while passive techniques are performed through the assistance of the examiner that evaluates when the full ROM is reached. Passive ROM is reported to be greater than the active ROM [53]. However, active movements are preferred when pathological conditions are investigated, since participants perform those movements within their pain limits and therefore in a safer way.

Among active techniques, two modes of movements' execution have been reported in literature: maximum amplitude and maximum speed. The first mode consists in asking the participants to move their head as far as possible from the initial reference position, until the end of the ROM in that direction is reached, but without causing

pain. The second mode consists in asking the participants to move their head as fast as possible, without causing pain. Some studies have attempted to provide reference data on the cervical ROM in adult healthy participants [50] and reference values measured in the two modes mentioned above are reported in Table 1-2.

Table 1-2 Mean ± SD of the cervical range of motion in healthy subjects according to Bonnechère [51]

Mode	Range of Motion (deg)			
	Extension	Flexion	Axial Rotation (total right and left)	Lateral Flexion (total right and left)
Max Amplitude	55±11	68±9	147±14	91±10
Max Speed	56±17	76±15	153±11	100±15

Effects of age and gender on ROM were also investigated by Trott et al. [34] in healthy individuals and a significant decrease of ROM with increasing age was observed, while no effects of gender were reported. It has been observed that in many pathologies of the cervical spine such as cervical dystonia [54], insidious neck pain and whiplash associated disorders [55] [56] [37] the ROM was significantly reduced with respect to healthy control, thus its evaluation could be an aid to the diagnosis and contribute to the assessment of changes over time in the disease. Cervical ROM was also taken to document baseline status and to evaluate the effects of treatments such as thrust manipulation [57] and arthrodesis surgery [58] [59].

Although the assessment of ROM through imposed movements is widely performed, both in research and clinics, some authors raised concerns regarding the ability of forced movements to be representative of what individuals perform in daily conditions. For this reason, cervical ROM was investigated by Bennett et al. [60] on individuals instructed to perform selected activities of daily living, to assess a baseline knowledge regarding the ROM required to perform ADL to understand the effects of motion loss on everyday activities. Starting from similar observations, Duc et al. [61] investigated unconstrained daily mobility with the aim of evaluating the actual cervical function in individuals that underwent an arthrodesis surgery.

Head movement angular velocity is another parameter which has been extensively examined when assessing the cervical kinematics. Reference values for a healthy adult

group are available in literature, both for movements performed reaching the maximum amplitude and the maximum speed (see values in Table 1-3) [50].

Table 1-3 Mean ± SD of the head movement speed in healthy subjects according to Bonnechère [51]

Mode	Movement angular velocity (deg/s)					
	Extension	Flexion	Axial Rotation		Lateral Flexion	
			Right	Left	Right	Left
Max Amplitude	149±35	143±35	361±262	348±261	115±36	115±37
Max Speed	362±86	371±100	625±239	609±226	328±96	308±76

For some pathological conditions such as insidious neck pain, whiplash associated disorders [55] and cervical dystonia [54] a significant reduction of movement velocity has been reported. In the study from De Beyl et al., it was shown that the reduction of movement velocity was the most robust characteristic observed in those patients. In addition, it was observed that the range of velocity reduction exceeded the range of movement reduction, suggesting that the investigation of movement velocity can add valuable information to the analysis of cervical motion.

Sjölander et al [55] observed that shaky and discontinuous movements are important sensorimotor symptoms and proposed the use of the jerk to quantify this motion. The jerk index, by measuring the variation of the acceleration, describes the stability and the smoothness of a motion. The parameter formulation commonly used in literature is the one proposed by Teulings [62]:

$$NJ = \sqrt{\left(\frac{1}{2}\frac{D^5}{L^2}\int J^2(t)dt\right)} \qquad (1\text{-}1)$$

where D is the duration of the movement, L is the length of the movement and J is the jerk, which is the first time derivative of the acceleration.

According to his formulation the jerk is normalized by the duration and the length of the movement since it has been observed that jerk levels depend on those two parameters [62]. Thanks to the applied normalization, movement patterns with different shape, size and duration can be compared.

Smoothness of cervical movements has been investigated in healthy individuals and it was observed that it is strongly related to the movement velocity: with fast movements being smoother and slow movements being jerkier. In addition,

movements of larger amplitude were reported to be less smooth than movements of smaller amplitude [63]. Movement smoothness was observed by Sjölander et al. [55] to be significantly reduced in cervical pathologies such as insidious neck pain and whiplash associated disorders. In this study it was noticed that jerky movements are important sensorimotor symptoms in chronic neck pain, of both traumatic and non-traumatic origin. Jerkier cervical movements compared to controls were observed also in individuals that underwent a fusion surgery [58]. Cattrysse et al. [58] suggested that the jerk index can be considered a valuable objective tool to estimate the quality of the motion and to investigate motor control strategies.

As discussed in Paragraph 1.2.2, different coupling mechanisms in the upper and lower cervical spine are intrinsic in the anatomy of the cervical region. However, it has been observed that, due to compensatory mechanisms, the presence of coupled movements can increase both in presence of a pathological condition [54] and with increasing age [35], causing changes in the quality of cervical kinematics that might affect the quality of functioning [58]. The presence of increased movement coupling has been investigated in conditions such as cervical dystonia [54] or after arthrodesis surgery [58]. In the study conducted on cervical dystonia patients, the higher presence of coupled movements was attributed to the co-contraction of cervical muscles. The alteration in the ability to control coordinated muscle contraction is, in fact, a recognized characteristic of cervical dystonia. In the group of patient treated with arthrodesis surgery the causes of increased movement coupling have not been investigated in depth. However, the authors underlined the importance of assessing qualitative changes in the cervical motion, such as the increased presence of movement coupling, in order to understand patients' limitation in performing ADL, to evaluate aspects related to QoL and to evaluate the efficacy of an intervention such as a fusion surgery.

1.3 Inertial sensors

1.3.1 Wearable inertial sensors: main features

Inertial sensors, also referred to as inertial measurement units (IMUs), use the property of bodies to maintain constant translation and rotational velocity, unless

disturbed by forces or torques, respectively. Practical inertial tracking is made possible by advantages in miniaturized and micromachined sensor technologies, particularly in silicon accelerometers and rate sensors. In fact, MEMS, acronym for Micro Electro Mechanical Systems, is the integration of mechanical elements, sensors, actuators, and electronics on a common silicon substrate through the utilization of microfabrication technology. The fundamental idea behind MEMS is to combining together silicon-based microelectronics with micromachining technology [64]. This kind of component is particularly suitable for human movement application because of their small size (they can be easily placed on body segments to be tracked) and inexpensive nature.
Gyroscopes measure the angular velocity, and, if integrated, the change in angle with respect to an initially known angle. Accelerometers measure acceleration, including gravitational acceleration g. However, in practice, noise and bias errors associated with small inexpensive sensors make it impractical to track orientation and position changes for long time periods if no compensation is applied (see Paragraph 1.3.5 for details) [65]. By combining the signals from the inertial sensors with aiding/complementary sensors, such as magnetometers, and using knowledge about their signal characteristics, drift and other errors can be minimized.

1.3.2 Accelerometer

A single axis accelerometer consists of a mass, suspended by a spring in a housing. Within their linear region, springs are governed by a physical principle known as Hooke's law. According to Hooke's law, a spring will exhibit a restoring force which is proportional to the amount it has been expanded or compressed, as described by the following equation:

$$F = -kx, \qquad (1\text{-}2)$$

where, K is spring constant, F is the force exert on the mass and x is the distance of compressed and stretched from the equilibrium position or the position of mass at zero force.

By taking into account Newton's second law, which states that force on mass (F) is directly proportional to the acceleration (a), if object's mass (m) remains constant:

$$F = ma, \tag{1-3}$$

the relation of acceleration caused by the force can be described in terms of displacement of mass as:

$$a = -\frac{kx}{m}. \tag{1-4}$$

Once that the displacement of a mass connected to a spring is observed, then its acceleration can be measured. There are various methods of sensing change in displacement which also define the type of sensor. In commercial devices it is possible to have piezoelectric, piezoresistive or capacitive components to convert the mechanical motion into an electrical signal, however, due to their ease of use, reliability and lack of temperature calibration requirements, capacitive components are currently the most widely used [66]. In order to measure multiple axes of acceleration, this system needs to be duplicated along each of the required axes.

1.3.3 Gyroscope

Gyroscopes are instruments used to measure angular motion. According to Newton's second law, the angular momentum of a body will remain unchanged unless it is acted upon by a torque. The fundamental equation describing the behaviour of a gyroscope is:

$$\boldsymbol{\tau} = \frac{d\mathbf{L}}{dt} = \frac{d(I\boldsymbol{\omega})}{dt} = I\boldsymbol{\alpha} \tag{1-5}$$

,

where the vectors $\boldsymbol{\tau}$ and $\boldsymbol{L}$ are the torque on the gyroscope and its angular momentum, respectively. The scalar I is the momentum of inertia, the vector $\boldsymbol{\omega}$ the angular velocity and the vector $\boldsymbol{\alpha}$ the angular acceleration. There are mainly three different types of gyros available: rotary, vibrating and optical gyroscopes. Rotary and optical gyroscopes are not suitable for human motion analysis due to their large size and high costs. Vibrating mass gyroscopes, on the other hand, are small, inexpensive and have low power requirements, making them ideal for human movement analysis. A vibrating element (vibrating resonator) when rotated, is subjected to the Coriolis effect that

causes secondary vibration orthogonal to the original vibrating direction. By sensing the secondary vibration, the rate of turn can be measured. The Coriolis force is given by:

$$F_C = -2m(\boldsymbol{\omega} \times \mathbf{v}), \tag{1-6}$$

where m is the mass, ***v*** the momentary speed of the mass relative to the moving object to which it is attached and ***ω*** the angular velocity of that object.

Various micro-electromechanical machined geometries are available of which many use the piezo-electric effect for vibration.

1.3.4 Magnetometer

Magnetometers are devices that measure the strength and/or direction of a magnetic field. Because magnetic fields are defined by containing both a strength and a direction (vector fields), magnetometers that measure just the strength or direction are called scalar magnetometers, while those that measure both are called vector magnetometers. The detection of the magnetic field can be achieved by using different physical principles such as: super conductivity, magnetoresistivity, Hall effect and Lorentz force interaction. Among those, magnetometers based on Lorentz force are extremely attractive because they can resolve very weak magnetic fields down to nT, they require no special magnetic materials and they can thus be fabricated using standard micromachining techniques. Those sensors are generally composed by a central resonating mass which, in presence of an external magnetic field vibrates at resonance under the action of the Lorentz force. The displacement of this structure, usually in the out of plane direction, can then be measured with optical, piezoresistive or capacitive sensing techniques [67].

1.3.5 Inertial sensors inherent limitations

As mentioned above the IMUs are generally equipped with a tri-axial accelerometer and a tri-axial gyroscope, leading to a direct detection of the acceleration (which consists of the sum of gravitational and inertial linear accelerations) and of the angular velocity, respectively. A crucial parameter in

movement analysis that can't be directly measured by inertial sensors, but can be estimated using these systems, is the orientation of each unit, often referred to as "box". 3D accelerometer units can be used as an inclinometer in the absence of acceleration. Under this condition they measure the angle of the sensor unit with respect to gravity [68]. This method is appropriate if the magnitude of the acceleration can be neglected with respect to the gravity, however it will give unacceptable errors in many practical human movement recordings. Furthermore, accelerometer signals do not contain information about the rotation around the vertical and therefore do not give a complete description of orientation. The accuracy of inclination estimation is thus increased by using gyroscopes in addition to accelerometers. Change in orientation can be estimated by integrating the angular velocity directly measured by gyroscopes. However, the accuracy of this numerical integration might be highly compromised by errors that grow over time due to gyroscope bias drift [65]. The presence of even a relatively small offset on the gyroscope signal will lead to large integration errors, restricting the time of accurate measurement to few seconds. Moreover, if an absolute orientation is required instead of a change in orientation, a reference orientation has to be obtained at least once during a recording. The integration drift caused by noise and slow time-varying biases can be compensated by adding the information provided by the magnetometer. Magnetometers provide stability in the horizontal plane by sensing the direction of the magnetic field like a compass. Data from this complementary sensor can be used to eliminate the drift by continuous correction of the orientation obtained by rate sensor data. Techniques proposed so far to combine data obtained from different sensors use fusion algorithms, among which the most used is the Kalman filter based algorithm [69]. The key assumption when using magnetometers for orientation estimation is the presence of a homogeneous external magnetic field. The earth magnetic field is the most common external field, and it easily meets the homogeneity assumption. However, inside buildings, ferromagnetic objects or electrical appliances may introduce local distortions to the magnetic field which violate the above mentioned assumption and result in inaccurate orientation estimates when not properly accounted for [70]. In addition, instants of time where the velocity is known or preferably zero can be used to restrict the integration interval time and reset the velocity error, by applying the so called zero-velocity update [71].

Inertial sensors measure kinematics according to their own reference frame, also referred to as technical sensor frame (F_T), commonly aligned with the edges of the case. Each unit thus computes the orientation of the global reference frame (F_G) with respect to F_T. In order to estimate segmental and joints kinematics an IMU needs to be associated to each body segment under analysis using a procedure called anatomical calibration. The anatomical calibration allows determining the time-invariant registration between the sensors' F_T and the anatomical frame (F_A) of each bone, thus making possible the estimation of the anatomical frame pose relative to F_G for each instant of time [72]. First of all, the IMU fixation should be realized in order to minimize the so called soft tissue artefact, originated by the relative motion between the units attached to the skin surface and the underlying bones. Secondly, the IMU's case needs to be aligned with the anatomical planes and axes of the underling body segments. Alignment approaches reported in literature are: manual alignment, gravity alignment, functional approach, imposition of joint constraint and direct anatomical landmark identification. The easiest alignment procedure is the manual one, realized by visually identifying anatomical landmarks and axes. Although straightforward to perform, this procedure is highly inaccurate due to absence of planar surfaces in the body segments and the scarce repeatability of the positioning. The direction of gravity, while the segment is in a static known position, can be also used to initialize the joint kinematics. The main limitation of this approach is that angles around the vertical axis are not considered. The functional approach is realized using active and/or passive movements of the body segment about two of its anatomical axes [73]. The movements allow defining the anatomical frame axes by estimating the average angular velocity vector. One of the axes of the anatomical frame is assumed as coinciding with the direction of the 3D angular velocity vector measured by the IMU attached to the body segment while the segment is performing the calibration movement. The second axis of the anatomical frame is defined using the direction of gravity measured by the IMU during resting posture. The third axis is then defined in order to obtain a right-handed frame. The main limitation of this approach is represented by the ability of the subject to perform the procedure, which significantly affects the accuracy of the calibration and which can represent a relevant issue especially in presence of joint impairments. In addition, since movements planes and postures are subjective, the repeatability of the procedure is not guaranteed. The

imposition of joint constraints approach imposes specific movement to body segments in order to take into consideration the kinematic constraints offered by human joints. The main limitation of this approach is to be applicable only to joints characterized by a number of degrees of freedom lower than 3. Moreover, this approach is robust for hinge-like joints, like the knee joint, but is much less robust for nonparallel hinge joints, like the ankle joint. Finally, the direct anatomical landmark identification approach is based on the direct measure of the direction of anatomical axes by using palpable anatomical landmarks [74]. A calibration device which carries a IMU aligned with the axis passing through the tips of two pointers is used in this approach. By pointing two palpable anatomical landmarks, an anatomical axis is determined with respect to the technical frame of the IMU attached to the body. The main drawback of this approach is represented by the need of a calibration device. Methods which combine two or more than the above mentioned approaches are also reported in literature [75].

1.3.6 Assessment of cervical motion using inertial magneto units

Thanks to the numerous advantages of those sensors, IMUs have been widely used in both upper [76] [77] and lower limbs [78] to investigate their movement. The use of IMUs has been recently extended to the evaluation of cervical motion. Jasiewicz et al. [79] demonstrated that inertial sensors are suitable measurement systems for neck motion, by comparing their accuracy with a Fastrack motion analysis device. Different clinically identifiable anatomical landmark were investigated by Theobald et al. [52] to determine the most reliable position in order to assess cervical ROM. In fact, the ability of IMUs to acquire reliable human motion data is susceptible to artefacts from soft tissue movement and skin-sensor attachment, which may vary according to the different locations. From the results obtained in the study, sensors location on forehead and T4 gave the most reliable data. Duc et al. [59] proposed a methodology based on wearable inertial sensors to assess the cervical mobility in clinical settings and assessed the validity of their method against an optoelectronic reference system. In the protocol proposed, IMUs were attached to forehead and sternum of the participants and the sensors alignment to the anatomical frame was achieved through a functional calibration. The calibration procedure consisted of forward trunk flexions

associated to a period of static standing. In a later study they questioned the effectiveness of imposed movements in representing what patients perform in real life conditions and underlined the importance of analysing the mobility limitation during ADL. Therefore they proposed a methodology that uses IMUs to quantify cervical movement in real life conditions [61]. IMUs were located on the forehead and sternum of each participant and left there for four hours while they were doing free living activities. The use of inertial sensors is also reported in literature for the evaluation of different cervical manipulation techniques. In a study conducted by Williams et al. [80], by placing an inertial sensor on the forehead of the participants, the authors were able to observe different kinematics patterns associated to different manipulation techniques.

1.4 Cervical orthoses

1.4.1 Introduction to cervical orthoses

Cervical orthoses are medical devices designed to offer support and protection to the spinal cord. Several different cervical orthoses are currently available to compensate for neck muscles weakness. However, neck orthoses currently available on the market can be divided in two broad categories: soft orthoses and rigid orthoses. Soft orthoses (Figure 1-5a) are made from thick foam rubber, covered in cotton. They are minimally restrictive and allow the user a range of motion which is close to the unrestricted one. Soft orthoses are usually prescribed for patients with whiplash injuries and for those complaining of neck pain. Rigid orthoses (Figure 1-5b) are made from moulded plastic with added padded liners. They are usually used to immobilize the neck during recovery from a fracture or a surgery. The range of motion allowed by rigid orthoses is significantly lower compared to that allowed by soft orthoses. In healthy subjects, the ROM offered by the rigid orthosis is reported to be about 24 degrees in flexion, 14 degrees in extension, 43 degrees in lateral bending and 80 degrees in axial rotation lower than the ROM offered by the soft orthosis [81]. A recent study from Reed et al., investigated how MND patients, advised to wear a cervical orthosis as a consequence of increasing muscle weakness, perceived the support offered by those two types of orthoses [82]. Results from this study highlighted that

soft orthoses do not provide sufficient support, and are often unable to prevent the head from dropping. In a previous study conducted on healthy individuals by Whitcroft [83] it was observed that the soft orthosis reduced movement on average by 17.4% leading to an inadequate immobilization of the cervical spine, even when performing routine daily activities that require between the 30 and 50% of full ROM [83]. This last consideration is in contrast with the observations from Miller [84] that didn't observe any significant difference between the functional ROM values acquired during 13 out of 15 ADLs simulated both with a rigid and a soft cervical orthosis. Differently from the study conducted by Reed [82], the main limitation of both studies conducted by Whitcroft and Miller Is that they involved only healthy subjects with no damages to their neck muscle tone. On the other hand, rigid orthoses are prone to cause an over restriction of the range of motion, which leads to difficulties in performing daily activities. Studies from Plaisier [85], Rondinelli [86] and Karason [87]reported general discomfort issues, often suffered by patients, such as overheating, or more serious side effects such as pressure sores, increased intracranial pressure, dysphagia, and abnormal distraction within the upper spine. As a result, when worn for a long time, those orthoses become very uncomfortable and are often rejected by patients.

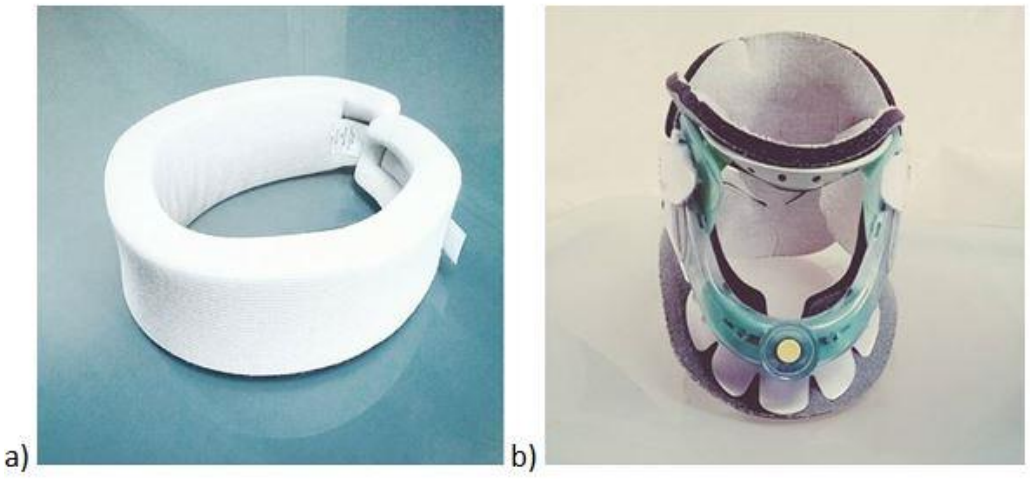


Figure 1-5 Soft and rigid cervical orthoses a) Soft orthosis (Stro II, Trulife, Dublin, Ireland); b) Rigid orthosis (Vista, Aspen Medical Products, Inc. Irvine, CA).

The MNDA (motor neurone disease association) has indicated a list of head supports available on the market for the treatment of neck weakness in patients with MND: Soft

collar, Headmaster Collar, wheelchair head supports, Hereford Collar neck support, MND Oxford Collar, Oxford Lees Head Support, Hensinger Head Support, Miami J Cervical Collar, Burnett vacuum head and neck supports, Marlin cervical collar (Motor Neuron Disease Association, Information Sheet No P1, Head supports for people with motor neurone disease, last rev.10/14). Among those orthoses there are examples of both soft (Burnett vacuum head and neck supports, Hereford Collar neck support, Soft Collar) and rigid (Marlin Cervical Collar, Miami J Cervical Collar) supports. The Headmaster (Figure 1-6) has also been included in the above mentioned list and represents an example of semi-rigid design, instead. This orthosis is characterized by a chin pad supported by a rigid frame that rests on the chest while a Velcro strap around the lower part of the neck keeps the device in position. Although widely used by MND patients, the main drawback of this type of orthosis is that they only prevent the head from dropping forward, without offering support in other directions.

Figure 1-6 Headmaster Collar (Symmetric Designs Ltd., Salt Spring Island, Canada)

A need exists for the modification of current cervical orthoses to reduce the painful or uncomfortable side effects associated with wearing them which would, in turn, increase the effectiveness of the support that the orthosis provides to the spine. In particular, problems related with the extended use of cervical orthoses are driving researchers to think new solutions to give MND patients a head support specifically designed for them. A recent work from Hansen et al. [88] proposed a new device to help people facing neck muscle weakness. This device is an elastic head support made by an elastic strap which connects the back of the patient's pants to the back of a

baseball cap. The main limitation of this orthosis is to support exclusively in the flexion/extension movement. Glazener [89] proposed a new neck brace able to support the head posteriorly with a diaphragm-assist strap secured around the lower abdominal area. The main advantage of this design is to avoid the support under the chin, which often causes difficulties in eating and communicating. Furthermore, since it is stabilized below the diaphragm, the brace doesn't restrict lung expansion, which is a crucial aspect for MND patients, often affected by respiratory muscles weakness as well. Although this brace is still a prototype and quantitative data on the ROM allowed were not provided by the author, it offers an interesting alternative design to support the head. The same will to address the unmet needs of people affected by neck muscle weakness inspired the creation of the Head-up project which led to the development of the Sheffield Support Snood orthosis.

1.4.2 The Head-up project and the Sheffield Support Snood

The 'Head-Up' project was conceived with the aim to develop a new orthosis which could satisfy the unmet needs of people affected by neck muscle weakness and in need to wear a cervical orthosis for a long time during the day. The project was funded by the Motor Neurone Disease Association (Northampton, UK), the National Institute for Health Research Devices for Dignity Healthcare Technology Cooperative (Sheffield, UK) and the National Institute for Health Research (NIHR). The "Head-up" is a collaboration between clinicians, engineers, creative designers, patients and carers who worked closely together to design a new cervical orthosis specifically designed for patients with MND and other neurodegenerative conditions causing neck muscle weakness. Thanks to this cooperation the Sheffield Support Snood (SSS) was developed. This new orthosis consists of a lightweight snood made of stretchable fabric that fits the neck of the user (Figure 1-7). It functions as a scaffold allowing for additional lightweight polymer support structures to be added or removed. Four support structures are available with the snood: shoulder supports to prevent lateral tilt, A-shape frontal supports, to support the head to the chin, straight supports of different sizes and stiffness to sustain the posterior region of the neck and jaw Z-shape supports to sustain the head to the rear of the jaw (Figure 1-7a). The support structures can be adjusted to be patient-specific and this enables the degree of

support to be varied when needed: either when performing specific tasks in a day, or as support requirements change with disease progression [28]. Since it is made of fabric, the snood is also quite thin and can be easily worn under clothes. Following an initial fitting appointment with a clinician, during which patients and carers are instructed about how to fit the orthosis, the SSS can be independently adjusted by the users.

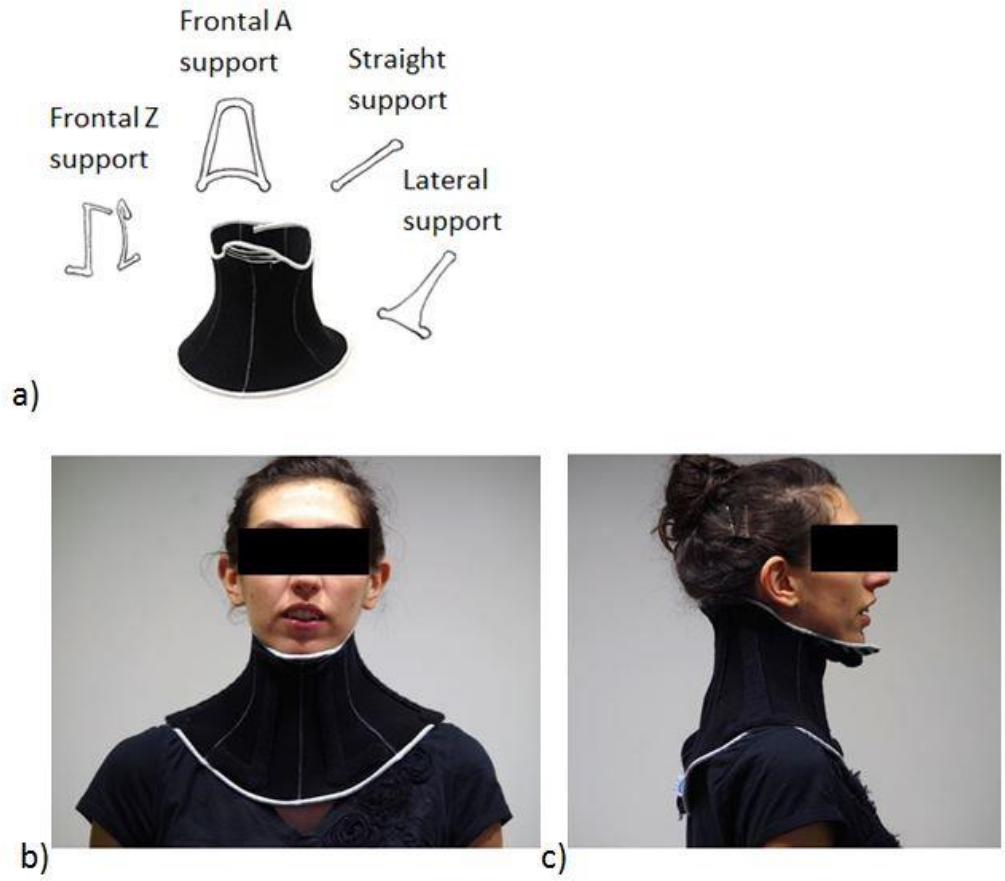


Figure 1-7 Sheffield Support Snood a) Sheffield Support Snood orthosis with supports; b) Sheffield Support Snood frontal view; c) Sheffield Support Snood lateral view.

1.4.3 Assessment of cervical motion while wearing a cervical orthosis

More often than to compensate for neck muscle weakness, cervical orthoses are used in the management of patients following cervical spine injury or surgery, to provide stability and protection to the spinal cord by reducing cervical motion. Since those conditions involve a large number of individuals, there is a great interest in assessing the different supports currently available. A summary of the studies conducted to compare the effectiveness of different orthoses is reported in Table 1-4.

Table 1-4 Studies comparing different cervical orthoses

Study	Technique	Outcome measures
Aker et al., 1991 [90]	Spinal Rangiometer	Cervical ROM
Plaiser et al., 1994 [85]	Electropneumatic sensor	Interface pressure in the occiput, chin and mandible areas, comfort
Gavin et al., 2003 [91]	Optoelectronic motion measurement system, Video fluoroscopy	Cervical and intervertebral ROM
James et al., 2004 [92]	Electromagn. tracking device	Time, total linear distance, total angular displacement during application, cervical ROM
Zhang et al., 2004 [93]	3 cameras optoelectronic stereoph. system	Cervical ROM
Quinlan et al., 2006 [81]	Zebris ultrasonic 3-dimensional motion analysis system	Cervical ROM
Schneider et al., 2007 [94]	3-dimensional digital tracking sensor, fluoroscopic images	Cervical and intervertebral ROM, comfort
Tescher et al., 2007 [95]	CROM device, XSENSOR X2 System	Cervical ROM and occipital tissue-interface pressure
Miller et al., 2010 [84]	Dynamic motion analysis system (electrogoniometer and torsiometer)	Cervical ROM
Whitcroft et al., 2011 [83]	CROM goniometer	Cervical ROM
Evans et al., 2013 [96]	8 cameras optoelectronic stereoph. system	Cervical ROM
Karason et al., 2014 [87]	Goniometer, micro-catheter	Cervical ROM, Jugular venous pressure, comfort

In the majority of the applications the main task of the orthosis is to immobilize the neck. As a consequence, almost all the studies reported in the table aimed at assessing the ability to restrict motion by comparing the maximum physiological ROM reached in the sagittal, transverse and frontal plane without orthosis, with the maximum ROM allowed, in the same planes, by each orthosis. Different measurement systems have been used to achieve this aim: goniometric [90] [97] [95] [83] [84] [87], electromagnetic [92], optoelectronic [91] [96], ultrasound [81] and fluoroscopy [94] [91]. Subjects recruited were healthy adults (18-55) although a few studies [95] [94] [83] involved also older participants, with age up to 60, 61 and 67 years, respectively. No studies were found involving participants over 70 years of age. Furthermore, no studies were found involved participants presenting a pathological condition and all data collections described in the papers reported in Table 1-4 were executed in a laboratory setting. Movements performed by participants were flexion, extension, axial rotation and lateral flexion while sitting, except a few studies where only flexion or flexion/extension was evaluated [90] [91]. James et al. [92] investigated the same movements (flexion, extension, axial rotation and lateral flexion) while the subjects were lying supine and Schneider et al [94] also while the subjects were in an upright position. Miller et al. [84] observed that maximum ROM is rarely used in performing ADL. In their work they tested soft and rigid supports while the participants were performing 15 daily activities suggesting that the measurement of ROM used while performing ADL (functional ROM) would provide more clinically useful information about how the orthosis function in everyday life.

Apart from the measurement of the ROM, only a few studies investigated also different aspects related to the use of the head supports. The works from Plaiser [85] and Tescher [95] considered the occurrence of pressure ulcers as a common side effect of wearing rigid cervical orthoses for an extended period of time and aimed at investigating the interface pressure exerted by different types of support in the occiput, chin and mandible areas. Bell et al. [98] investigated also the consequences of ill fitted orthoses in restricting the cervical movements in the three main anatomical planes. In fact, because of limited availability, emergency applications, limited number of sizes available from the manufacturer, limited training/experience of the operator and financial constraints, a patient might be fitted with a cervical orthosis that is not

optimal for his/her size and body type. The study shed light on the importance of understanding the effects of ill-fitting orthoses and considering them when applying supports in clinical settings, since improperly sized and fitted supports may increase the incidence of complications such as the development of skin lesions. The consequences of rigid orthosis settings, and in particular of the frontal support height, have been investigated by Miller et al. [99]. By measuring the maximum ROM while performing movements in the three main anatomical planes and functional ROM while doing 15 different daily activities, they observed that differences in neck positioning larger than 3cm may substantially alter the efficacy of the orthosis in inhibiting motion. The study emphasizes the importance of properly fitting each patient with an orthosis that restricts motion without placing the neck into excessive extension. Although motion restriction is the first aim of a head support, patient's compliance with wearing it is also an important factor in the success of the intervention. Patient's compliance is largely affected by the comfort perceived by the individual while wearing the orthosis. Starting from those considerations a few studies also investigated the comfort perceived by the users [87] [85] [94]. In those studies, participants were asked to grade the orthoses according to how comfortable they were to wear, using a scale where the highest score was associated to the most comfortable support.

In this study, the rational for looking at head movements in the context of cervical orthoses is related to its primary aims, which are to assess the effects of MND on the ability of patients to perform head movements and to investigate whether this ability is affected by the use of a cervical orthosis. As mentioned above, the main purpose of a cervical orthosis is to restrict motion. In case of neck injuries or neck pain this restriction has to be as higher as possible in order to prevent damages to the cervical spine or pain. However, when cervical orthoses are used by people affected by neck muscle weakness due to neurological diseases, such as MND, different user needs need to be considered. Those patients often develop difficulties in performing only some head movements because only some neck muscles are impaired due to the disease. The most common case is the severe damage of extensor muscles which causes the head to drop forward. As a consequence, a suitable orthosis for those patients is the one that gives substantial support to those movements that are highly compromised while keeping other movements free to be performed. In order to

evaluate an orthosis which is meant to be used by neurological patients, together with the ability to provide support, by restricting range of motion, its ability to sustain only desired movements, by restricting range of motion in desired directions while enhancing better movements in others directions, should be evaluated. Accordingly to that, cervical movements performed by participants and parameters investigated in this study were chosen not only in order to evaluate the restriction offered by the devices, but also to assess those aspects of cervical motion related to the quality and quantity of residual movements.

The protocols proposed in papers reported in Table 1-4 have been used to design the experimental protocol developed in this study (see Paragraph 2.2.1), although some modifications were required to adapt to a clinical setting and to individuals affected by MND. The performance of three movements: flexion/extension, axial rotation and lateral flexion was deemed as satisfactory to describe motion ability in each direction and suitable to be performed by MND patients in a clinical setting. The sitting position was assumed as the most appropriate for patients since many of them may have difficulties in keeping a steady standing position or use wheelchairs. In papers reported in Table 1-4 orthoses tested were on average four (two in [90], four in [97], four in [85], four in [91], four in [92], four in [93], three in [81], seven in [94], four in [95], two in [84], two in [83], four in [96], four in [87]). This number was considered as appropriate to test orthoses in a group of healthy individuals, however, when the protocol was administered to MND patients, since those patients are easily fatigable, the number of orthoses tested was reduced to shorten the experimental protocol. Considerations expressed from Miller et al. about the opportunity to test cervical orthoses when performing ADL were reckoned as valuable and included in the protocol, as well as the collection of feedbacks from the participants in order to record the overall participants' perceptions about the orthoses tested.

1.5 Conclusions

In conclusion, from the analysis of the literature it appears clear that neck muscle weakness significantly reduces the QoL of patients affected by MND. The necessity for an orthosis able to meet the needs of these patients in terms of comfort and support offered also clearly emerged from the literature analysis. This led to the development

of the SSS, a customisable orthosis which should allow overcoming the limitations of the currently available devices. In order to evaluate whether the use of the SSS is indeed able to improve MND patients' ability to perform head movements and to overcome the difficulties related to head dropping, a patient's ability to initiate and control head movements, while wearing a cervical orthosis, needs to be quantitatively assessed. The literature analysis also highlighted that several different techniques are available to assess cervical motion through the measurement of head movements, among which inertial sensors seems to be the most promising for the context of this project, thanks to the possibility to be used in a routine clinical context. This thesis will hence focus on developing a method for the assessment of head and neck mobility based on the use of these sensors.

1.6 Aim and objectives

The aim of this study was to quantitatively assess the changes in the neck mobility through the assessment of head movements associated to the use of the SSS, a newly developed cervical orthosis specifically designed for patients affected by neck muscle weakness due to neurological conditions, such as MND.

In order to achieve this aim, it has been necessary to: a) evaluate the new device, b) characterize the end users for what concerned the aspects of interest to the problem, and c) to assess the interaction between them. This translated into four main objectives described below together with the relevant main practical steps:

1. To design a protocol to assess head movements while wearing a cervical orthosis, which could be performed by people affected by MND.
    - selection of the measurement system and of its setting
    - identification of the tasks to be performed by the participants
    - evaluation of the data processing to obtain relevant parameters to investigate cervical motion
2. To evaluate the performance of the SSS and of other alternative devices in terms of potential support provided to the user.
    - identification of one or more parameters suitable to describe the restriction to cervical motion offered by an orthosis

- assessment of the support offered by the SSS against different cervical orthoses available in the market through the measurement of chosen parameter/s

3. To characterize the group patients for whom the device was developed, by investigating how MND impacts on their ability to perform head movements.
   - selection of one or more parameters suitable to describe the ability of patients to initiate and control head movements
   - comparison of the parameter/s measured in the patients' group and in a control group of healthy subjects
4. To assess how the new cervical orthosis affects a patient's ability to perform head movements.
   - quantitative evaluation of the SSS on the ability to initiate and control head movements
   - qualitative evaluation of patients' perception of performing head movements and ADL while wearing the SSS

1.7 Outline of the study

In order to provide a clearer picture of the overall outline of this work, a diagram which resumes the main steps of the thesis is presented below.

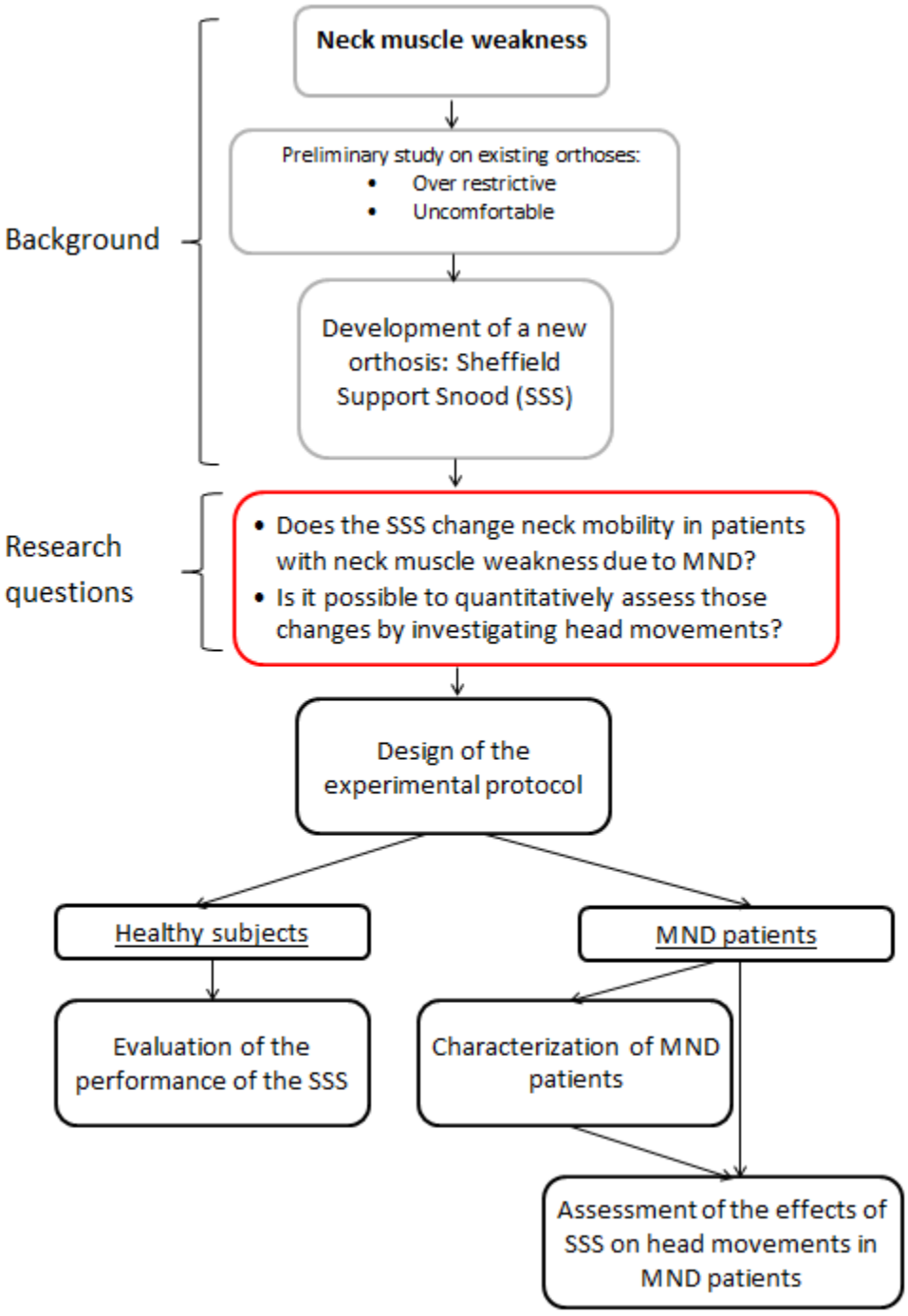


Figure 1-8 Outline of the study

This thesis is constituted of five Chapters of which this is the first.

Chapter 1 provides a general background of the study. In particular, an extended review of motor neuron disease, cervical spine, cervical motion analysis and cervical orthoses topics is presented. Through the analysis of the literature the need for further investigations emerged which are discussed in this chapter and represent the aim of this project.

Chapter 2 presents the design of the experimental method which was later adopted in the studies described in Chapters 3, 4 and 5. The development of the experimental protocol, through the selection of the experimental tasks and measurement system, is presented. Data processing is extensively described and details about its validation are also provided. Finally, a preliminary investigation conducted on a small sample of volunteers, in order to evaluate the experimental protocol developed, is presented and discussed.

Chapter 3 describes the study conducted on healthy individuals to quantitatively assess the biomechanical features of the Sheffield Support Snood. The investigation is conducted by comparing the biomechanical features of the SSS with two other cervical orthoses available on the market and using the experimental protocol described in Chapter 2. Results obtained from the study are presented and discussed. A revision of the experimental protocol presented in Chapter 2 is also proposed.

Chapter 4 presents the first study conducted on MND patients and aiming to assess their ability to execute head movements. The experimental protocol presented in Chapter 2 and amended according to the results obtained in Chapter 3 is used. The characterization of the group of patients, obtained through the comparison with a control group of age-matched individuals, is presented and discussed.

Chapter 5 presents the second study involving MND patients. The ability of the SSS to facilitate head movements in MND patients is investigated through the use of the experimental protocol described in Chapter 2 and refined in the two previous studies detailed in Chapters 3 and 4. Results obtained in the study are reported and discussed together with future prospects opened by those results.

Chapter 6 highlights the conclusion and future prospects of the project. The main findings of this work together with future scope and advanced application of the experimental protocol developed are discussed.

Appendix A presents the Amyotrophic Lateral Sclerosis functional rating scale revised, mentioned in Chapters 4 and 5.

Appendix B contains most relevant information regarding ethics approval obtained for the studies on healthy individuals and patients.

Appendix C presents the questionnaire administered to patients during the study described in Chapter 5.

Chapter 2

Design of the experimental protocol

2.1 Introduction

Looking at the literature several studies aiming at testing cervical movements/cervical orthosis could be found, however none of them at the same time quantitatively investigated cervical movements while wearing a cervical orthosis, used a methodology suitable for a clinical application and involved patients with MND. Table 2-1 summarizes the main studies that could be found in literature and clearly shows the lack of a protocol suitable for this study.

Table 2-1 Summary of the main studies reported in literature. Studies selected on the basis of one or more of the following characteristics: being a quantitative assessment, involving patients with MND, investigating cervical movements, using a methodology suitable for clinical applications, testing cervical orthoses. Y=Yes. N=No.

	Quantitative	MND	Cervical movement	Methodology suitable for clinical application	Cervical orthosis
Goonetilleke, 1994 [100]	✓ Y	✓ Y	✗ Muscular strength (no neck muscles)	✓ Dynamometer	✗ N
Andres, 1996 [8]	✓ Y	✓ Y	✗ Muscular strength (no neck muscles)	✗ TQNE technique	✗ N
Hausdorff, 2000 [21]	✓ Y	✓ Y	✗ Gait	✓ Foot switch system	✗ N
Duc, 2013 [59]	✓ Y	✗ N	✓ Y	✓ Inertial sensors	✗ N
Evans, 2013 [96]	✓ Y	✗ N	✓ Y	✗ Motion capture cameras	✓ Y
Schneider, 2007 [94]	✓ Y	✗ N	✓ Y	✓ 3d digital tracking sensor	✓ Y
Miller, 2010 [84]	✓ Y	✗ N	✓ Y	✓ Electrogoniometer and torsiometer	✓ Y
Glazener P, 2014 [89]	✓ Y	✓ Y	✗ N	✓ TUG, FVC, questionnaires	✓ Y

Therefore, the initial part of the project was focused on designing an experimental method to assess head movements while wearing a cervical orthosis and which could be performed by people affected by MND.

The study from Duc [59] was used as a reference to design the experimental protocol used to assess cervical motion. Studies from Evans [96], Schneider [94] and Miller [84] were used as a reference to design the experimental protocol used to evaluate cervical motion while wearing a cervical orthosis. However, as mentioned in Paragraph 1.4.3, since none of those studies involved individuals affected by MND, the experimental protocol was modified in order to be suitable for administration on neurological patients and to be performed in a clinic and/or a domestic environment.

The first step was the selection of the tasks to be performed by the participants and the measurement system to be used in order to investigate cervical moments with and without wearing an orthosis. Then the procedures for the post processing of data coming from the selected sensors were defined. To verify the accuracy of the data processing adopted to estimate the sensors orientation, a validation study using a stereophotogrammetric system was conducted. Finally, to test the feasibility of the proposed experimental protocol, a preliminary test was performed with a small group of healthy subjects. Feedback from this pilot study was used to further refine the protocol.

2.2 Methods

2.2.1 Experimental protocol

A first experimental protocol which comprised three phases was initially designed. The first phase involved active head movements (AHM), the second phase involved activities of daily living (ADLs) and the third phase involved gait analysis.

Phase 1: assessment of the primary components of motion

In the first phase the primary components of motion were evaluated asking participants to perform active maximum flexion, extension, lateral flexion (both left

and right side) and axial rotation (both left and right side). Participants were requested to wear the orthosis and to sit on a chair with a backrest that provided support for their thoracic spine but with no arm supports. They were asked to keep their feet flat on the floor, their arms comfortably by their side and to sit upright, looking straight ahead. This was referred to as initial neutral position (NP). After the recording of data in an initial neutral posture, participants were asked to perform the above listed head movements trying to move the head as far as possible from the NP, without experiencing neck pain. The same movements were repeated asking the participants to move their head as fast as possible. For each movement, participants started from the NP, moved to one direction, moved to the opposite direction and came back to NP. Participants were required to look at the same reference point in front of them, both at the beginning and at the end of the movement, to help them assume always the same NP. Each movement was repeated three times. Time requested to instruct the participants was about 10 minutes, while time requested to perform the movements was about 5 minutes.

Phase 2: ADLs Assessment

In the second phase the participants were required to perform five common activities of daily living (drinking, eating, typing on a laptop, washing hands and rising from a chair). Activities were chosen starting from previous studies involving the use of daily activities to evaluate different types of orthoses and different orthosis settings [84] [99] .

1. *Typing a sentence on a keyboard*. Participants were requested to sit on an ordinary chair with firm seat and backrest in front of a desk and to assume the previous described NP. A laptop was placed on the desk and participants were requested to type a sentence on the keyboard before returning to the NP.

2. *Rising from sitting position*. Participants sat on an ordinary chair with firm seat and backrest. Starting from the NP they were required to stand up and then come back to NP.

3. *Bringing food to the mouth***.** Participants were requested to sit on an ordinary chair and assume the NP. A spoon and a plate with food on were placed on the desk. Starting from the NP participants were required to take the food with the spoon and bring it to their mouth, then place the spoon back on the desk and return to NP.

4. *Drinking a glass of water*. Participants were requested to sit in front of a desk and assume the NP. A glass of water was placed on the desk. Starting from NP participants were asked to take the glass, bring it to their mouth in order to drink, then put it back on the table and come back to NP.

5. *Washing hands*. Participants were requested to stand in front of a sink keeping their arms by their side and looking straight forward. This was assumed as initial position. Starting from this position they were asked to turn on the tap and wash their hands, then turn it off and return to the initial position.

Time requested to instruct subjects was approximately 10 minutes while time requested to perform the activities was approximately 6 minutes.

Phase 3: Walking Assessment

Participants were asked to perform a 30 m walk test at a self-selected walking speed and to climb one flight of stairs up and down. Time requested to instruct subjects was approximately 10 minutes while time requested to perform the tasks was approximately 6 minutes.

2.2.2 Measurement system

As mentioned in Paragraph 1.2.3 several different measurement systems could be used to assess cervical motion: CROM device, ultrasonic three-dimensional motion analysis device, electromagnetic motion analysis systems, optoelectronic systems and inertial magneto units. CROM device was deemed as not suitable for the purposes of this study since it provides information only about the angle performed by the subject (no additional information about kinematic quantities that can describe the motion, such as accelerations and angular velocities). Furthermore it provides the measurement only in a single plane, so that coupled movements cannot be measured. Additionally, movements of the trunk, which are likely to happen while performing head movements, are hard to detect and isolate. Ultrasonic three-dimensional motion analysis device was excluded because the system is cumbersome and presents a reduced portability which makes it unpractical to be used in clinical and domestic environments. Electromagnetic motion analysis systems were deemed as not suitable since they are quite cumbersome. In particular, they are not wireless and it was

believed that the presence of cables might get more difficult or at least less spontaneous the movement of individuals that present significant impairments. Furthermore, the system can be affected by the presence of metal, which makes it inappropriate for a use in a clinical setting. Optoelectronic cameras system, although being extremely reliable and sensitive was excluded due to the reduced portability of the cameras and the reduced space available in clinics for data collection, about 4 m^2. Furthermore, to apply the markers, participants are required to take off their upper body clothes which could constitute a further bother for patients.

Inertial measurement units (IMUs) were thus chosen due to a series of features that make them suitable for a study involving MND patients.

1. IMUs don't require a laboratory setting. Since MND patients often develop mobility problems, it is fundamental to have the opportunity to collect data in a clinical setting or even at the patients' home, without asking participants to come to the laboratory.

2. IMUs are relatively small, light to wear and are applied through double side tape or elastic bands, thus they don't interfere with the participants' movements and cause them a minimum discomfort.

3. IMUs require a short time (approximately 10 minutes) to be set up. MND patients easily experience fatigue and it is important to reduce the duration of the protocol as much as possible.

The system used in this study was the APDM Opal (APDM Inc., Portland, OR) described in details in the next Paragraph. Number and location of the sensors were chosen according to a configuration proposed and validated in a previous study by Duc et al [61]. Therefore, during phase 1 and 2, two IMUs were applied on the subject, one on the forehead and one on the sternum using proper straps/dermatological patches. During phase 3, three additional IMUs were located on ankles and on pelvis.
As mentioned in Paragraph 1.3.5, inertial sensors measure kinematics according to their own reference frame. To evaluate head movements with respect to the trunk it was hence necessary to align the sensors' frame to an anatomical frame, which is a bone-embedded frame rigidly associated with the anatomy of the bone [101]. A

manual alignment of the two IMUs couldn't be performed due to the absence of planar surfaces both in the sternum and in the frontal bones. A functional calibration, initially proposed for the knee joint and upper extremities [73] [102] and then adapted to the neck joint by Duc et al [61], was used instead.

2.2.2.1 Opal inertial measurement units

The APDM movement monitoring system (APDM Inc., Portland OR) is composed by: a docking station, a wireless access control point and up to 6 Opal sensors, also known as monitors. The docking station is used to configure, charge, and download data from the sensors. The wireless access control point allows for wireless communication between the host computer and Opal monitors, as well as synchronization with external third party hardware. The Opal sensors are IMUs that consist of a tri-axial accelerometer, tri-axial gyroscope and tri-axial magnetometer. Each Opal sensor is about the size of a wristwatch (48.4×36.1×13.4 mm, see Figure 2-1a) and weighs 22 grams. The accelerometers can be configured in a high 6g mode or a low 2g mode, depending on the target application. The main characteristics of the Opal sensors are that they can collect data for up to 8 hours when using the wireless streaming mode and up to 16 hours when using the asynchronous logging mode, they have wireless connectivity, latency recovery and 16 GB of on-board storage [103] . Data can be transmitted to a computer or be recorded directly on board and be viewed once a wireless connection is detected. The on board data can be accessed once the sensors are connected to the docking station. The Motion Studio software (APDM Inc., Portland, OR) can be used to view the IMU data in real-time and save the data as HDF5 or CSV file format. HDF5 is an open format for storing structured, binary data. Files are more compact than their CSV counterparts and can be opened directly in a number of analysis software packages, including MATLAB. CSV is a plain-text format that can be opened in spreadsheet software applications, such as Excel or OpenOffice. Thanks to those features Opal sensors can be used outside a laboratory setting and during persons' activities of daily living. Furthermore, Opal sensors can be synchronized with third-party systems, such as optical motion capture systems, EMG or gait mats. As explained in Paragraph 1.3.5 inertial sensors measure kinematics according to their

own reference frame (F_T). In the case of the Opals sensors F_T is defined as shown in Figure 2-1.

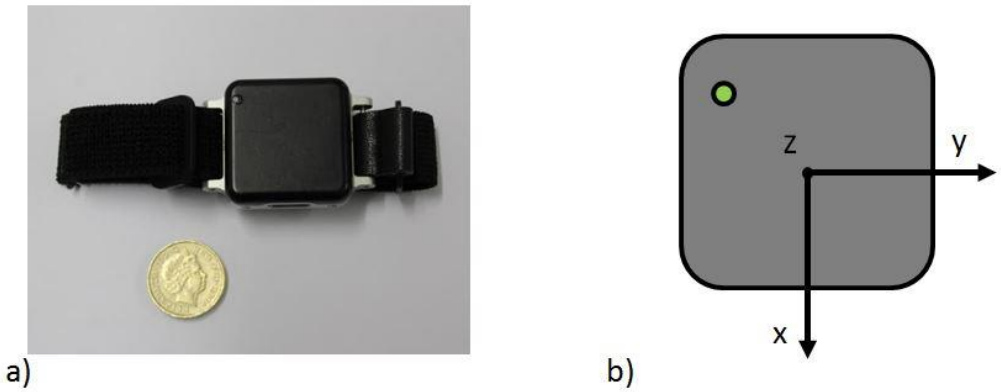


Figure 2-1 Opal inertial magneto unit (IMU). a) Opal sensor, b) Opal unit reference frame (technical reference frame, F_T).

2.2.3 Functional calibration

The functional calibration is a procedure used to align the IMU reference frame to a body segment anatomical frame (Figure 2-2). This entails determining the rotation matrix that aligns the sensor technical frame (xyz, F_T) to the anatomical frame (XYZ, F_A). In order to perform the functional calibration, participants were asked to sit on a chair, stay in a natural, still posture looking forward for about 10s and then perform 5 trunk flexions. The anatomical reference systems were built on the sternum and forehead according to the ISB definition [104]: with X pointing anteriorly, Y pointing upward and Z pointing to the right.

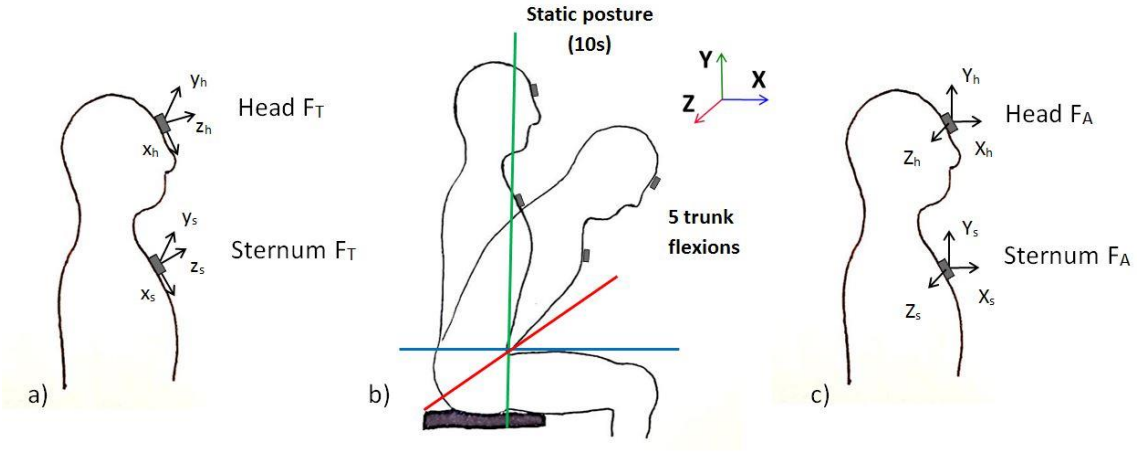


Figure 2-2 Functional calibration approach. a) Initial orientation of the sensors' technical frame; b) Functional calibration tasks; c) Final orientation of the sensors' frame according to the anatomical reference frame built through the functional calibration tasks.

Vertical axis (Y) was defined through the mean value of the acceleration ($\bar{a}_S$) measured by the sensor during the standing posture of the functional calibration:

$$Y = \frac{\overline{a_S}}{\left\|\overline{a_S}\right\|}. \qquad (2\text{-}1)$$

Anterior-posterior axis (X) was defined through the mean value of the angular velocity ($\overline{\omega_f}$) measured during trunk flexions:

$$X = Y \times \frac{\overline{\omega_f}}{\left\|\overline{\omega_f}\right\|}; \qquad (2\text{-}2)$$

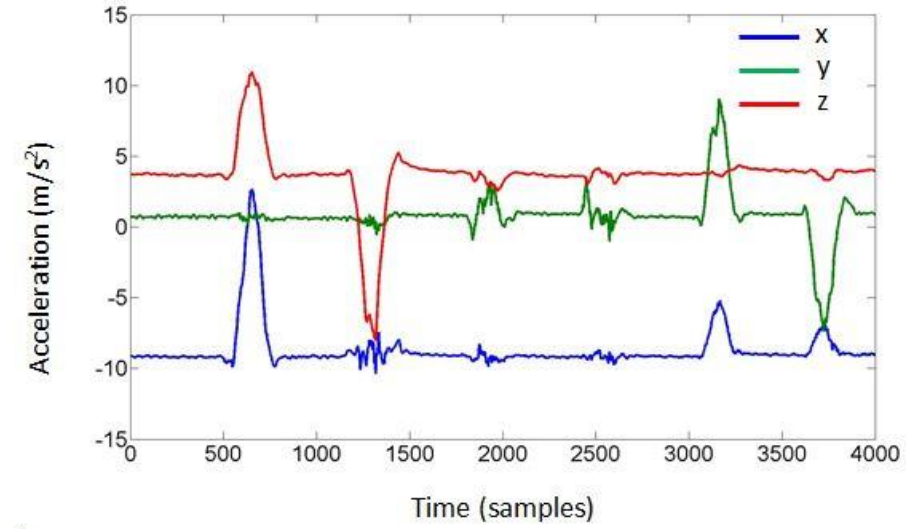
where × denotes the cross product.

Medio-lateral axis (Z) was defined in order to obtain a right-handed orthogonal frame:

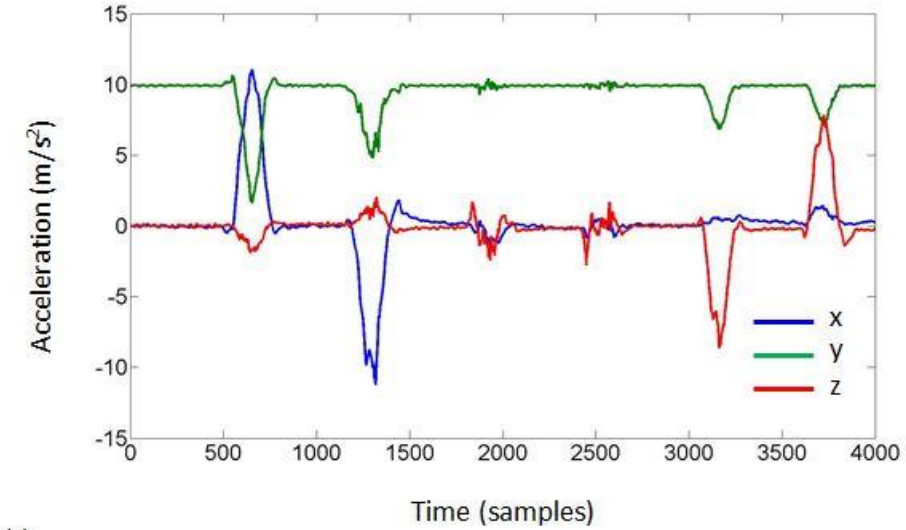
$$Z = X \times Y \qquad . \qquad (2\text{-}3)$$

In the walking task, a different procedure, which uses the IMU's quaternion output to provide a global reference frame, was adopted to re-orientate the sensors' reference frames to a common global reference frame. The sensors acting as the global reference were placed with their vertical component aligned to the earth's vertical axis, the anterior-posterior direction aligned to the direction of the participant's

walking direction and the medio-lateral axis was defined according to a right-handed reference frame [105]. Four IMUs were used so that the average of values they measured could be calculated and a better estimate of the orientation could be obtained. Thereafter, the local reference frame of each sensor (head, sternum, pelvis and ankles) was reoriented for each time sample to the newly established global reference frame. Figure 2-3 shows the raw acceleration signal as it is recorded by the inertial sensor placed on the forehead (Figure 2-3a, axes are oriented according to the IMU's reference frame) and after the reorientation performed through the functional calibration procedure (Figure 2-3b).



a)



b)

Figure 2-3 Active head movements performed by a healthy individual. Raw acceleration signal as recorded at the head level prior to the application of the functional calibration procedure (a) and after (b).

2.3 Data processing

As mentioned in Paragraph 2.2.2.1 the Opal system was equipped with a tri-axial accelerometer and a tri-axial gyroscope, leading to a direct detection of the acceleration (which consists of the sum of gravitational and inertial linear accelerations) and of the angular velocity, respectively. A crucial parameter in movement analysis that can't be directly measured by inertial sensors, but can be estimated using these systems, is the orientation of each IMU. This could be theoretically achieved by using, together with the gyroscope and the accelerometer, the tri-axial magnetometer, which is also embedded in each sensor. However, as mentioned in Paragraph 1.3.5 the accuracy of the magnetometer has been observed to be negatively influenced by the presence of ferromagnetic material and electronic devices in the environment. The scarce reliability of magnetometer data was checked by performing three static data collection in three different days, both in a laboratory and a clinical setting. As the sensor was not moving during the recording, the magnetic field measured by the device was expected to be constant throughout the trial. As can be observed from Figure 2-4, in a laboratory setting the magnetic field measured by the sensor was constant during the trial section and among different sections. On the contrary, in the clinical setting the magnetic field was differently affected in different days (see days 2 and 3) by devices and/or ferromagnetic material present in the environment. As a consequence, since the protocol was meant to be executed in a clinical and a domestic setting, it was decided to use only data measured by the gyroscope and the accelerometer to estimate the orientation.

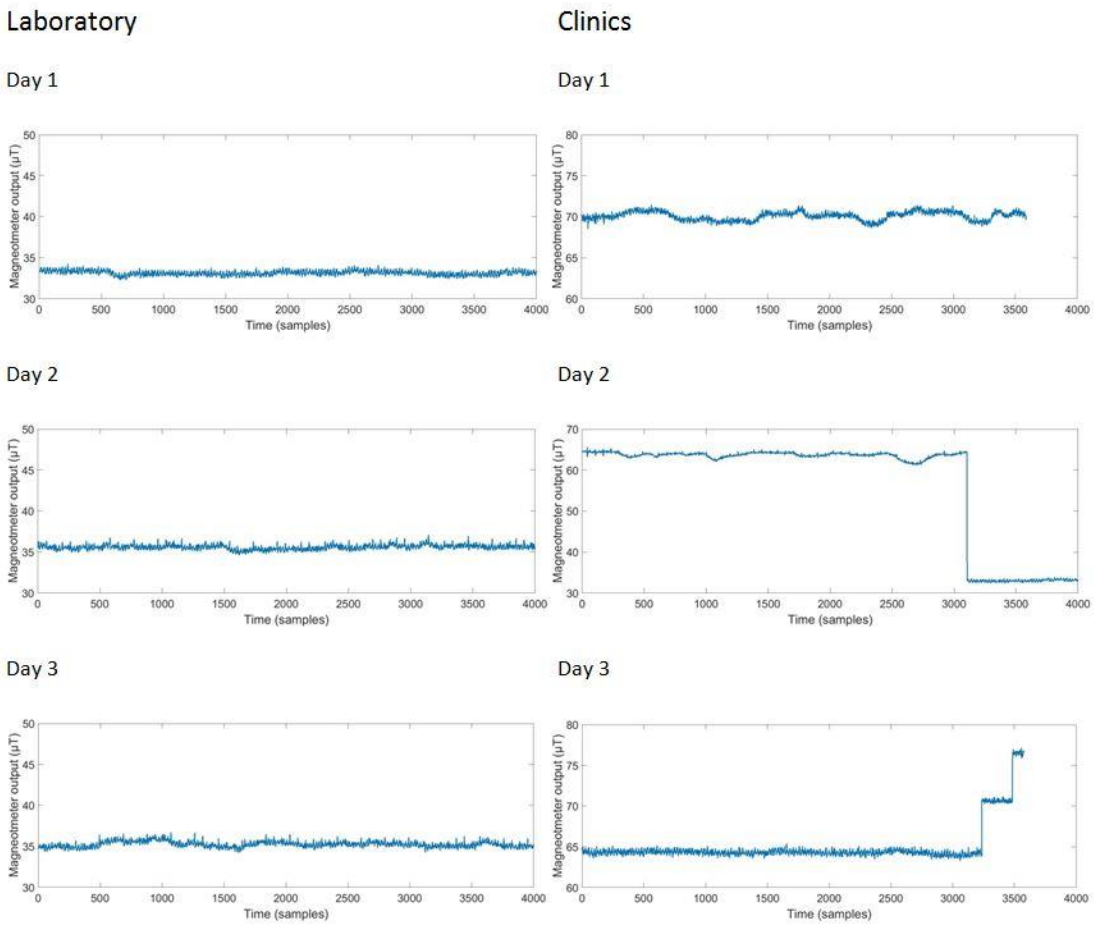


Figure 2-4 Output measured by the magnetometer (sum of the three components along the x,y and z axes) in a laboratory and clinical setting. Data collected on three different days during a static test.

2.3.1 Estimate of the sensor orientation

Once the two sensors (placed on head and sternum, respectively) were aligned to the anatomical reference frame, their orientation was computed using a method proposed by Favre et al. [106]. The method is based on the fusion of the 3D gyroscope with the 3D accelerometer in order to estimate orientations and uses quaternions to represent rotations because they are compact, don't suffer from gimbal lock and can easily be interpolated. Prior to explaining in details the fusion algorithm used, a brief description of quaternions and their properties is given to facilitate its comprehension.

2.3.1.1 Quaternions

The most common way to represent the attitude of a rigid body is a set of three Euler angles. These are popular because they are easy to understand and to use. Some

sets of Euler angles are so widely used that they have names that have become part of the common language, such as: roll (φ), pitch (θ), and yaw (ψ) of an airplane. However, the main disadvantages of Euler angles are: (1) that they are less accurate than unit quaternions when used to integrate incremental changes in attitude over time, (2) that certain important functions of Euler angles have singularities. In fact, Euler angles also introduce the problem of "Gimbal lock" or a loss of one degree of rotational freedom. Gimbal lock happens when a series of rotations at 90 degrees is performed; suddenly, the rotation doesn't occur due to the alignment of the axes.

The above limitations in the adoption of the Euler angle representation have led researchers to use unit quaternions as a parametrization of the attitude of a rigid body. The relevant functions of unit quaternions don't have singularities and the representation is well-suited to integrating the angular velocity of a body over time. The main disadvantages of using unit quaternions are: (1) that the four quaternion parameters do not have intuitive physical meanings, (2) that a quaternion must have unity norm to be a pure rotation. The unity norm constraint is particularly problematic if the attitude parameters are to be included in an optimization, as most standard optimization algorithms cannot encode such constraints [107].

Quaternions are generally represented in the form:

$$a + bi + cj + dk; \tag{2-4}$$

where a, b, c, and d $\in \Re$ and i, j, and k are the fundamental quaternion units, such as:

$$i^2 = j^2 = k^2 = ijk = -1 \tag{2-5}$$

and

$$ij = k = -ji,\ jk = i = -kj,\ ki = j = -ik. \tag{2-6}$$

Alternatively, they can be represented as:

$$[w, \mathbf{v}]\ ; \tag{2-7}$$

where **v** = (x, y, z) is a vector and w is a scalar.

Basic operations using quaternions are summarized in Table 2-2.

Table 2-2 Basic operations that may be applied on quaternions

Addition	$q+q'=[w+w',v+v']$
Multiplication	$qq'=[ww'-v\cdot v',vxv'+wv'+w'v]$ with · dot product and x cross product Note: $qq'\neq q'q$
Conjugate	$q^*=[w,-v]$
Norm	$N(q)=w^2+x^2+y^2+z^2$
Inverse	$q^{-1}=q^*/N(q)$
Unit Quaternion	q is a unit quaternion if $N(q)=1$ and $q^{-1}=q^*$
Identity	[1,(0,0,0)] when involving multiplication [0,(0,0,0)] when involving addition
Vector Rotation	$p'=qpq^{-1}$ with $p=(p_x, p_y, p_z)$ and p' the new position vector
Quaternion Product	$n=q\otimes r=n_0+in_1+jn_2+kn_3$

If a unit quaternion is described by using the following notation:

$$q = q_0 + iq_1 + jq_2 + kq_3; \tag{2-8}$$

Euler angles can be obtained from the quaternion through these relations:

$$\begin{bmatrix}\phi\\ \theta\\ \psi\end{bmatrix} = \begin{bmatrix}\arctan\dfrac{2(q_0q_1+q_2q_3)}{1-2(q_1^2+q_2^2)}\\ \arcsin(2(q_0q_2-q_3q_1)\\ \arctan\dfrac{2(q_0q_3+q_1q_3)}{1-2(q_2^2+q_3^2)}\end{bmatrix}; \tag{2-9}$$

2.3.1.2 Fusion algorithm

Assuming XYZ to be the fixed reference frame and xyz the mobile reference frame, the initial orientation q(0) of the forehead and sternum segments in the fixed reference frame (XYZ) can be calculated and expressed using a quaternion notation. If

segments are considered in a static posture at the beginning of the acquisition, the acceleration measured at that moment is equal to the gravity and gives the vertical axis Y. θ corresponds then to the inclination of z at time 0 and XYZ is defined as the rotation of xyz (0) around the horizontal axis V(0) that aligns z with Z.

$$\theta(0) = \cos^{-1}(-a(0) \cdot Y) = \cos^{-1}(-a_y(0)); \quad (2\text{-}10)$$

where · is a dot product.

$$V(0) = -a(0) \times Y = [a_z(0), 0, -a_x(0)]; \quad (2\text{-}11)$$

where × denotes the cross product.

Using the quaternion notation, the initial orientation of the segment q(0) in XYZ can be expressed as:

$$q(0) = \left[\frac{cos(\theta(0))}{2}, \frac{sin(\theta(0))}{2} \cdot \left[\frac{V(0)}{\|V(0)\|}\right]\right]; \quad (2\text{-}12)$$

The orientation of the further samples (*i*=1,2…n) relative to the fixed reference frame is then obtained through a quaternion-based time integration. For each segment, the orientation q(i) at each sample time (*i*) is computed using the orientation at the previous time sample (i-1) and the angular velocity ω(*i*).

$$\Omega(i) = q(i-1) \otimes \left(\frac{\omega(i)}{f}\right) \otimes q(i-1)^{-1}. \quad (2\text{-}13)$$

The new orientation q(*i*) is calculated assuming that the sample frequency (f) is sufficiently high to have small rotation and a constant angular velocity between two consecutive samples:

$$q(i) = \left[\frac{\cos\|\Omega(i)\|}{2f}, \sin\left(\frac{\|\Omega(i)\|}{2f}\right) \cdot \frac{\Omega(i)}{\|\Omega(i)\|}\right] \otimes q(i-1) \quad (2\text{-}14)$$

where Ω(*i*) is the angular velocity vector expressed in the fixed reference frame and ⊗ is the product operator associated with quaternions.

Finally, the orientation of the head relative to the thorax is obtained by multiplying the quaternion of the two segments.

$$D = q_t{}' \otimes q_h. \qquad (2\text{-}15)$$

Last step is the computation of the forehead orientation relative to the sternum through the ZYX Euler sequence.

2.3.1.3 Drift correction

Inaccuracy in the estimation of the orientation, mentioned in Paragraph 1.3.5 and caused by drift and accumulated error due to the sensor noise, is inevitable when evaluating orientation by integrating the rotational rates measured by the gyroscopes (Figure 2-5). In order to reduce this inaccuracy, a drift correction was applied. Since the use of the magnetometer was excluded due to its scarce reliability in clinical settings (see Figure 2-4), the correction was attained through a quaternion-based algorithm proposed by Sabatini [108]

The algorithm imposes equal conditions at the beginning and at the end of the acquisition and uses a spherical linear interpolation procedure (SLERP) to compensate for the error due to the influence of the gyroscope bias, as explained in details below. Since it is undeniable that the chosen correction method introduces a certain approximation, thus a certain error, its accuracy was tested against an optoelectronic system (see Paragraph 2.4). To make easier for participants to assume the same neutral position at the beginning and at the end of each movement, they were given a reference point in front of them to look at, at the beginning and at the end of each movement (see Paragraph 2.2.1).

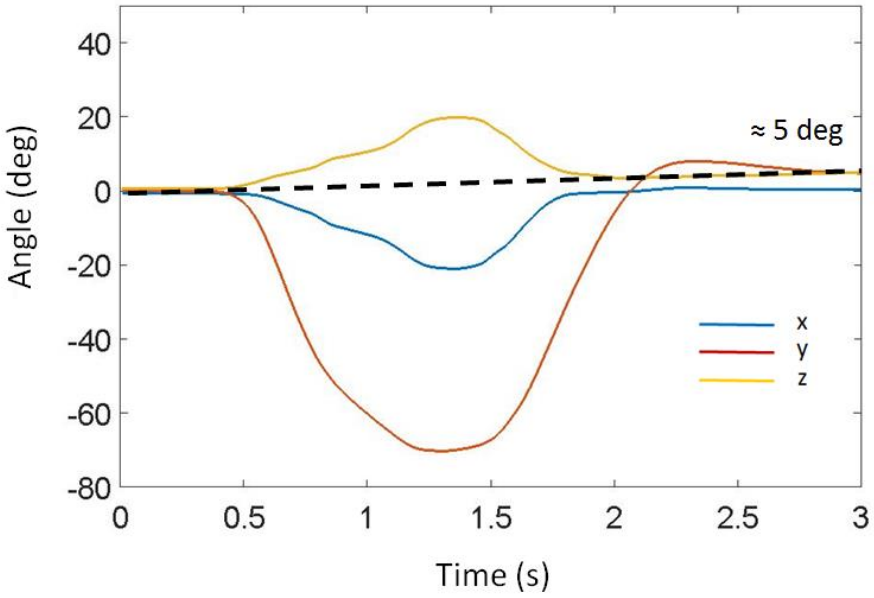


Figure 2-5 Axial Rotation movement. Angles estimated without drift correction.

Spherical Linear Interpolation (SLERP)

Unit quaternions represent directions in a four-dimensional space thus they represent points on a 4D sphere of radius one (see white points in Figure 2-6). The path between two orientations can be considered to be moving from one direction to another on the surface of this 4D sphere. Linear interpolation of quaternion values would then give unequal rotation increments (black points in Figure 2-6).

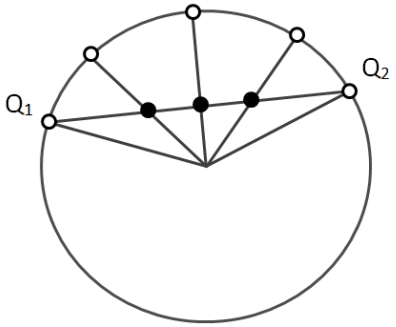


Figure 2-6 Spherical (white points) vs linear (black points) interpolation

In order to obtain an equal increment along the arc connecting two quaternions on the spherical surface it was necessary to apply a spherical interpolation.

$$slerp(Q_1,Q_2,u) = Q_1 \frac{sin((1-u)\Omega)}{sin\,\Omega} + Q_2 \frac{sin(\Omega u)}{sin(\Omega)}; \qquad (2\text{-}16)$$

with $0 \leq u \leq 1$.

Due to the fact that Q and –Q represent the same rotation, interpolation can take the "long path" (Figure 2-7) when the angle between the quaternions is bigger than 90º. Thus if the 4-vector dot product between the two quaternions is less than zero, then the long path will be taken. To prevent this, one of the quaternions is negated before interpolating.

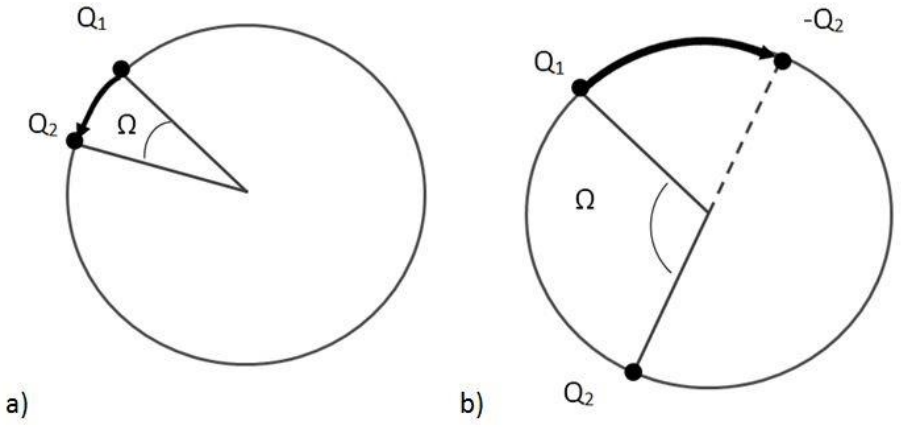


Figure 2-7 Spherical linear interpolation. a) Angle between quaternions smaller than 90°; b) Angle between quaternions greater than 90°.

Drift correction algorithm

An algorithm proposed by Sabatini [108], which assumes that the conditions at the beginning and at the end of the movement are equal and that is due to the error growth process if they are actually different, was implemented. Considering T_S the system's sampling interval and $T=NT_S$ the time instant when the integration terminates, the error quaternion q^e is introduced as:

$$\vec{\boldsymbol{q}}^{\boldsymbol{e}} = \vec{\boldsymbol{q}}_0 \otimes \vec{\boldsymbol{q}}_N^{-1} = [q_0{}^{e}, \vec{\boldsymbol{e}}^{\boldsymbol{e}}]^T; \qquad (2\text{-}17)$$

where $\otimes$ is the product operator associated with quaternions and $\vec{\boldsymbol{q}}_0$ and $\vec{\boldsymbol{q}}_N$ are normalized quaternions. This is necessary prior to the application of the SLERP

procedure to make sure they represent rotation on the unit sphere. $\vec{q}^{e}$ defines the transformation that aligns $\vec{q}_N$ to $\vec{q}_0$. The SLERP procedure is thus applied:

$$\begin{cases} \vec{q}_k^{\,i} = \dfrac{\vec{q}_0^{\,i}\sin[(1-\rho_k)\Omega] + \vec{q}^{\,e}\sin[\rho_k\Omega]}{\sin\Omega} \\ \vec{q}_0^{\,i} = [1,0,0,0]^T \end{cases}; \qquad (2\text{-}18)$$

with ρ_k=k/N k=0, …N and Ω=arcos(q_0^e).

The normalized quaternion $\vec{q}^{\,i}$ moves on the unit sphere along the arc connecting $\vec{q}_0^{\,i}$ to $\vec{q}_N^{\,i} = \vec{q}^{\,e}$ and the interpolated quaternion that fulfils the initial and final conditions is obtained for each stride:

$$\vec{q}_k^{\,u} = \vec{q}_k^{\,i} \otimes \vec{q}_k; \qquad (2\text{-}19)$$

with K=0,1,…N.

Figure 2-8 presents all the steps employed to obtain the angle estimation starting from the raw linear acceleration and angular velocity signals recorded by the IMUs.

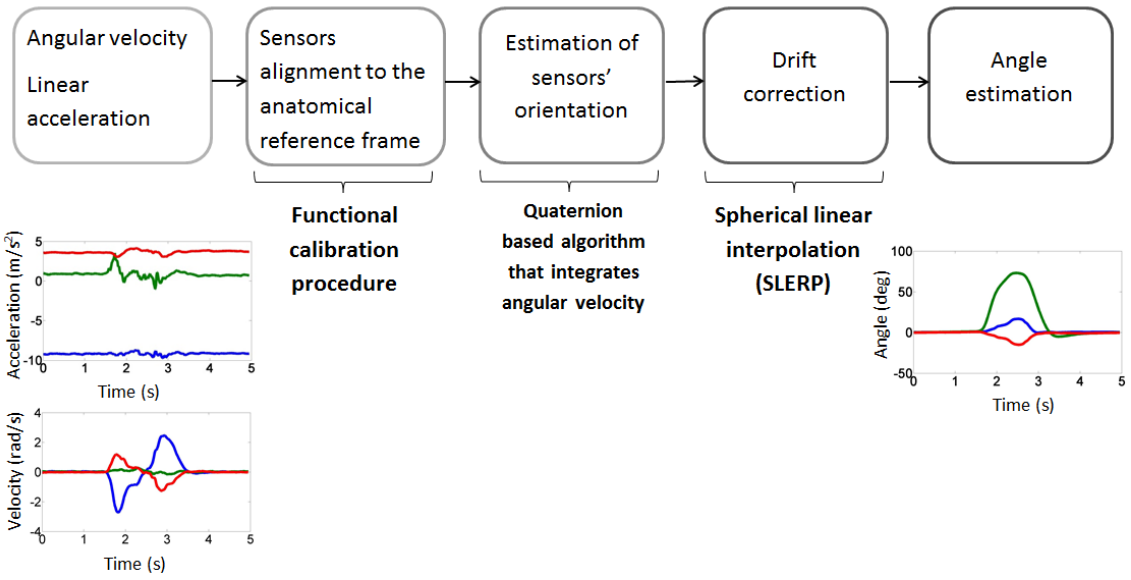


Figure 2-8 Data processing performed to obtain the angle estimation starting from the raw linear acceleration and angular velocity signals recorded by the IMUs

2.4 Validation of the sensor orientation estimate

2.4.1 Procedure for the validation

The above described approach to estimate the sensor orientation and hence the neck ROM has been previously validated using a stereophotogrammetric system [59]. Eventual errors induced by the alternative method implemented to correct the drift and by the use of a different system of IMUs than the one adopted in [59] were however verified on ad hoc trials. Three participants (1 female, 2 males, age 26±2 years, body mass index 26±4 kg/m2) were asked to perform the entire set of AHM (Phase 1, Paragraph 2.2.1). Three reflective markers were attached to each of the IMUs using double-sided tape (Figure 2-9 Inertial Magneto Units with reflective markers.Figure 2-9) and a 10-camera stereophotogrammetric system (Vicon T160 Camera, Oxford Metrics Ltd, Oxford, UK) was used to measure their trajectories.

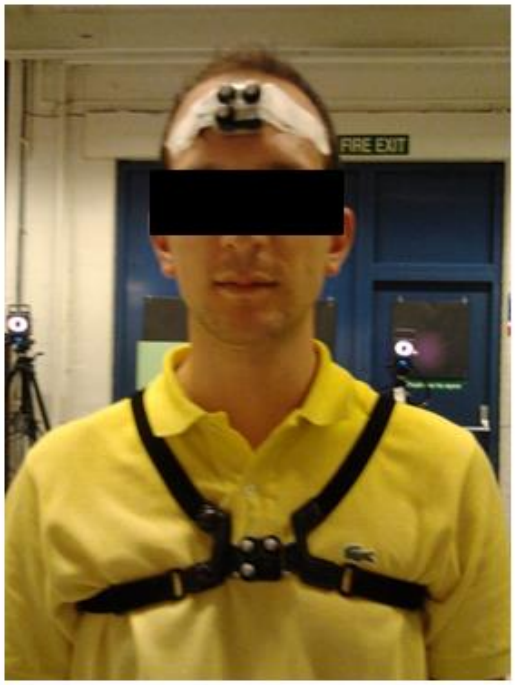


Figure 2-9 Inertial Magneto Units with reflective markers. Sensors attached on the forehead and sternum of the participant.

Signals provided by the sensors were filtered using a bidirectional 4^{th} order Butterworth filter with cut-off frequency of 5Hz, after having checked the frequency content of signals collected. The Butterworth filter was chosen to smooth signals since it is optimally flat in its pass band and, therefore, often the filter of choice when

working on movement data [109]. This filter produces a weighted average of data from several time points and the weight on each time point determines the cut-off. This process of averaging time points prior to the time of interest causes the filtered data to "lag" behind the raw with respect to time. To correct for this lag and to produce filtered data that are properly aligned in time, a bidirectional filter is applied. To make a bidirectional or zero-lag filter, the data are passed through the filter twice (once in the forward direction and once in reverse). In addition to correcting for lag, the second filtering in the reverse direction creates a sharper cut-off. In this study, the cut-off frequency was chosen on the basis of the following analysis.

Figure 2-10 shows an example of the frequency content of the angular velocity signal recorded by the sensor placed on the forehead while the participant was performing the AHM. As can be seen from the graph there is a strong component of the signal below 5Hz, while in the rest of the frequency spectrum, only noise is observed.

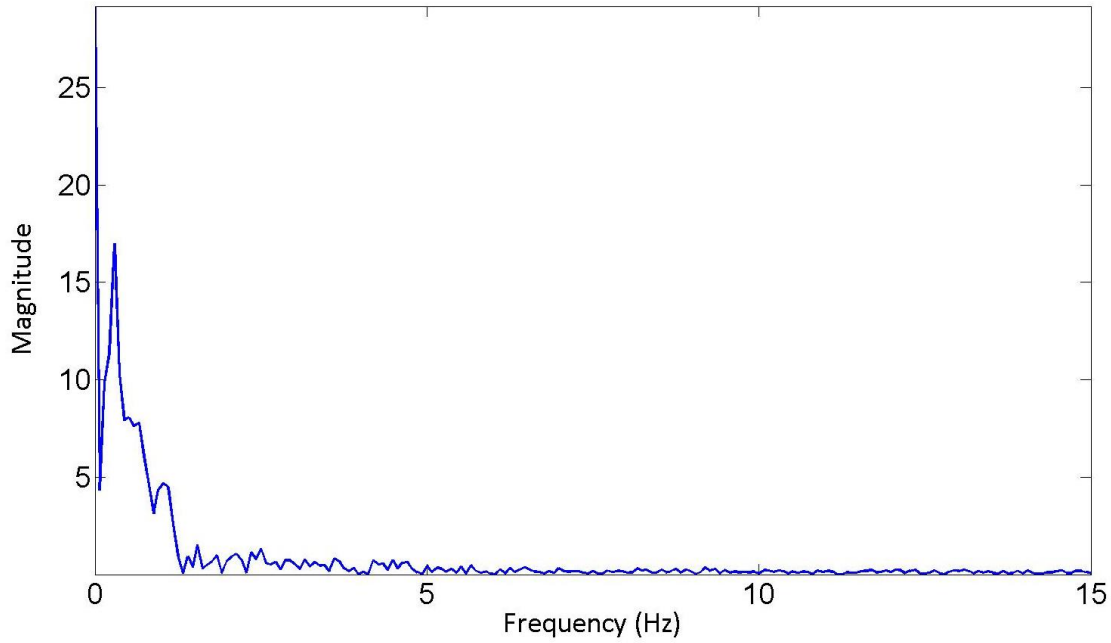


Figure 2-10 Single side magnitude spectrum of an angular velocity signal. Signal recorded by the sensor placed on the forehead while the participant was performing the active head movements (AHM).

For the sake of clarity in Figure 2-10 only part of the signal (extension movement) is analyzed, before (Figure 2-11a) and after (Figure 2-11b and Figure 2-11c) the application of the filter. In Figure 2-11b a 4^{th} order Butterworth filter with a cut-off frequency of 5 Hz has been applied to the raw angular velocity signal recorded by the

sensor placed on the forehead. The signal appears smoother compared to Figure 2-11a, although its main features seem mostly preserved. It can be observed that the shape of the signal is minimally altered, although the negative peak of the y component in Figure 2-11a is -1.822 rad/s while in Figure 2-11b is -1.807 rad/s. The signal appears also shifted after the application of the filter; in fact, in Figure 2-11a, the negative peak occurs at 1.703 seconds while, in Figure 2-11b, it occurs at 1.68 seconds. Figure 2-11c shows the same signal after the application of a 4th order Butterworth filter with a cut-off frequency of 2 Hz. In this case, the shape of the signal is significantly altered. Furthermore, the value of the negative peak of the y component is -1.779 rad/s and occurs at 1.828 seconds. Similarly, different orders for the Butterworth filter were analysed, as shown in Figure 2-12. Figure 2-12a shows the same angular velocity signal after the application of a 2nd order filter while in Figure 2-12b and Figure 2-12c the effects of a 4th and 6th order filter are shown, respectively. The 4th order filter seemed to better preserve the content of the signal, compared to the original raw signal (Figure 2-11a). In fact, the negative peaks of the y component were recorded at -1.801 rad/s, -1.807 rad/s and -1.805 rad/s, in Figure 2-12 a, b and c, respectively.

An analogous analysis was conducted on signals recorded at the sternum level and led to the adoption of a 4th order Butterworth filter with a cut-off frequency of 5 Hz. However, in practice, since a bidirectional filter was applied, the cut-off frequency used was reduced to approximately 4 Hz. This frequency was calculated by using the equation proposed by Gordon et al [109]:

$$f_{Bw}^{*} = f_{Bw} \times \frac{1}{\sqrt[4]{2^{\frac{1}{n}} - 1}} \qquad (2\text{-}20)$$

where f^{*}_{Bw} is the cut-off frequency adjusted to produce the requested cut-off. f_{Bw} is the requested cut-off and n is the number of filter passes.

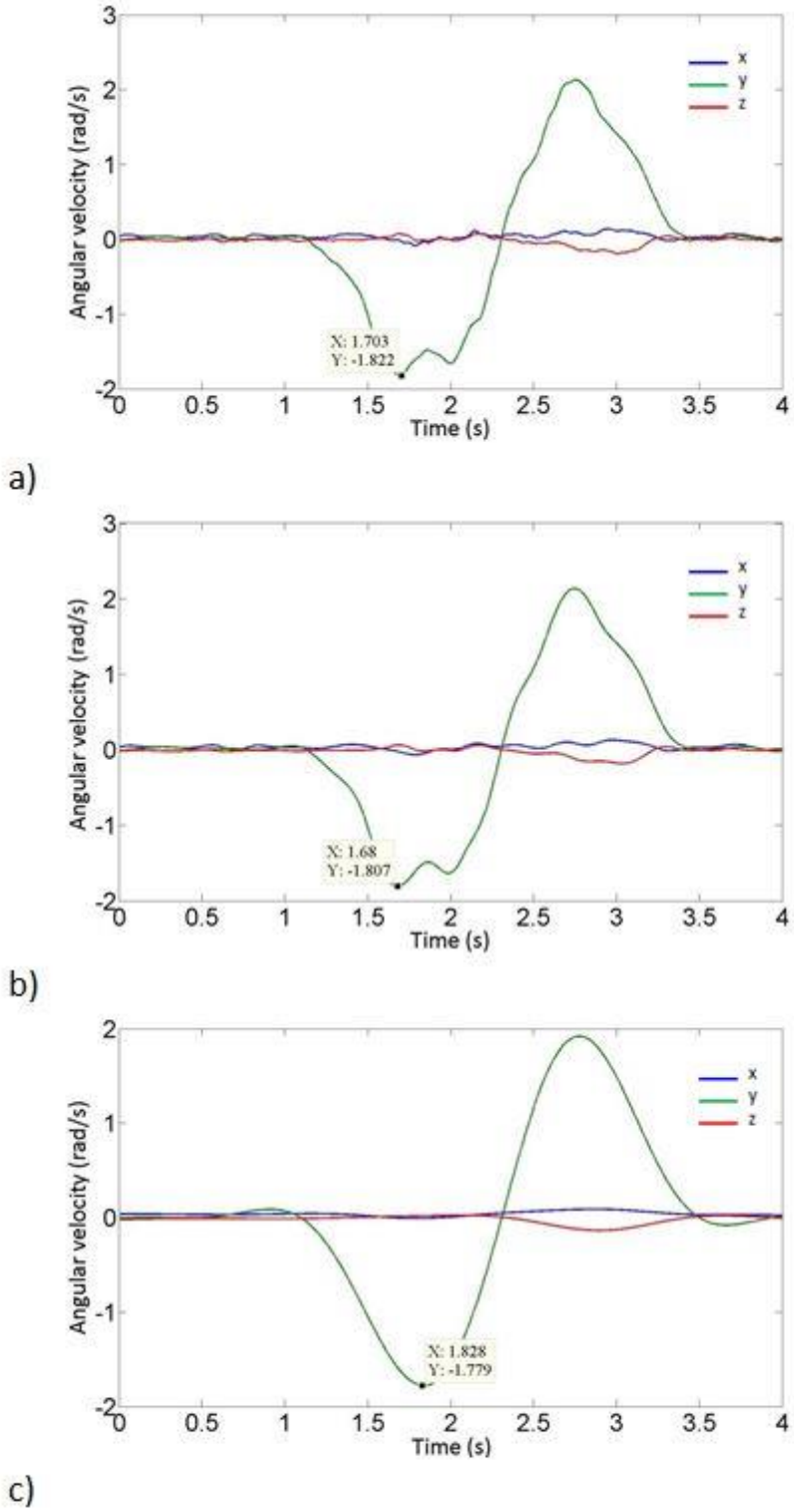
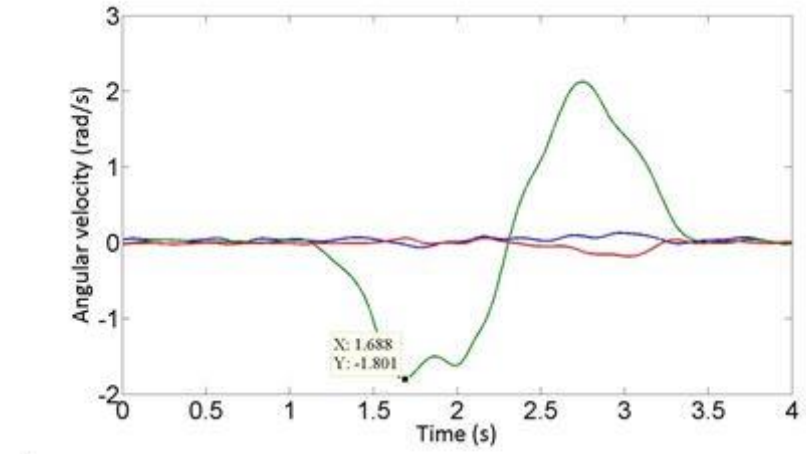
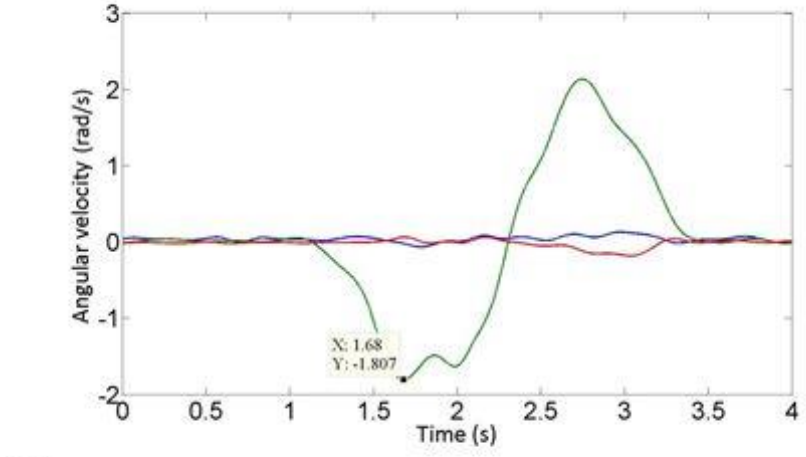


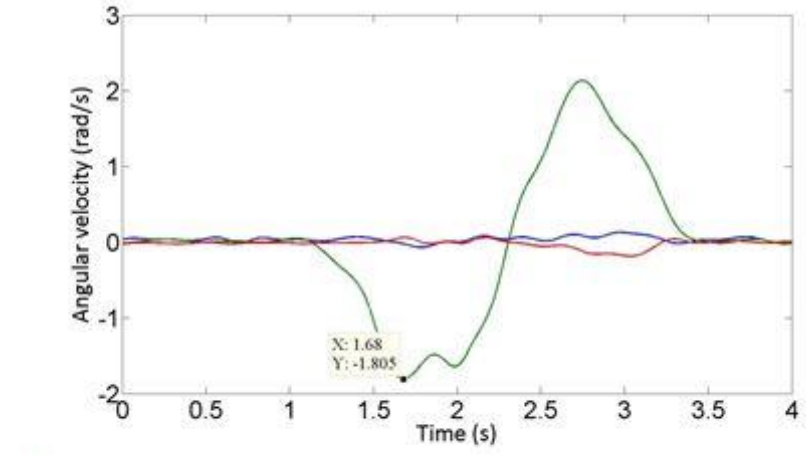
Figure 2-11 Angular velocity signal recorded at the head level while the participant was performing an extension movement. Signal prior to the application of any filter (a) and after the application of a 4th order Butterworth filter with a cutoff frequency of 5 Hz (b) and 2 Hz (c).



a)



b)



c)

Figure 2-12Angular velocity signal recorded at the head level while the participant was performing an extension movement. Signal after the application of a 2nd order (a), 4th order (b) and 6th order (c) Butterworth filter.

Pre-processing was performed using Vicon Nexus 1.8.5 while the orientation of the segments was calculated using MATLAB R2013a. In order to synchronize Vicon and

OPAL systems a dedicated cable was made. The cable was made following the instructions given by the manufacturers and it synchronized the two systems by using the 5V signal from the Vicon as a trigger for the OPALS. For the cameras, a reference frame was defined and used to describe a set of three orientations equivalent to those obtained from the IMUs, after the realignment of the two reference systems. The matrix that rotates the camera's technical frame to the segment anatomical frame was defined through a functional calibration identical to the one used to align the IMUs' frames and described in Paragraph 2.2.3. Participants were asked to look straight ahead for 10 seconds and then perform 5 trunk flexions.

The inferior-superior axis (Y') was defined through the vertical vector (v_s) measured by the cameras during the standing posture of the functional calibration.

$$Y' = \frac{v_s}{\|v_s\|}. \qquad (2\text{-}21)$$

The anterior-posterior axis (X') was defined through the mean of the helical angle (α) measured during the trunk flexions [59]. Helical angle was preferred rather than the angular velocity obtained through differentiation to avoid errors that could come from the differentiation.

$$X' = Y' \times \frac{\bar{\alpha}}{\|\bar{\alpha}\|} \quad ; \qquad (2\text{-}22)$$

where × denotes the cross product.

The medio-lateral axis (Z') was defined in order to obtain a right-handed orthogonal frame

$$Z' = X' \times Y'. \qquad (2\text{-}23)$$

The orientation of the segments in the cameras reference frame was then rotated to the segment anatomical frame. Stereophotogrammetric and IMUs' data were compared in terms of ROM, correlation and root mean square error (RMSE).

2.4.2 Results of the validation

The comparison with the data obtained from the camera's system showed the suitability of the methods chosen to estimate the IMUs' orientations for the purposes

of this study. In Figure 2-13 a comparison between the angle curves measured by the IMUs and the cameras systems for the same movement is shown.

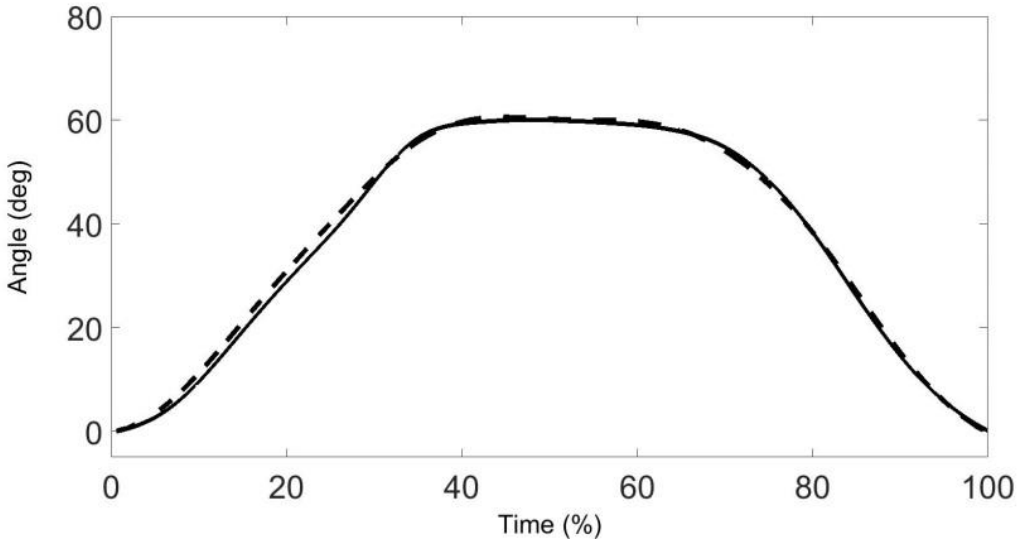


Figure 2-13 Results for the head axial rotation movement performed by a typical participant reaching the maximum amplitude toward the left side. The angles measured by the IMUs system (plain line) and by the camera system (dashed line) are reported.

Table 2-3 shows the results obtained for the comparison between the angles measured by the IMUs and the cameras system reported in terms of correlation (Pearson correlation coefficient, ρ), ROM absolute difference and RMSE. As can be seen from the table, the correlation was higher than 0.9 in all the movements, both in trials performed at maximum amplitude and maximum speed. In the trials at maximum amplitude the difference between the measured ROMs was less than 5° for the extension/flexion movement (corresponding to 4.5% of the maximum ROM), less than 3° for the axial rotation movement (corresponding to 2.5% of the maximum ROM) and less than 4° for the lateral flexion (corresponding to 4% of the maximum ROM), respectively. These values were equivalent to those found in the trials performed at maximum speed (Table 2-3), except for the lateral flexion movement, where the measured difference was less than 5°, which corresponded approximately to the 5.5% of the maximum measured ROM. The RMSE associated with the movements performed at maximum amplitude was less than 4° for the flexion/extension and the lateral flexion and less than 3° for the axial rotation. Equivalent values were measured in the trials performed at maximum speed (Table 2-3).

Table 2-3 Comparison between angles estimated with the IMUs and the cameras' systems. Comparison performed in terms of correlation, mean(SD), difference in ROM measured, mean(SD) and RMSE, mean(SD) for each movement: flexion/extension, axial rotation and lateral flexion. Max ROM as measured by the IMUs system is also reported.

		Max ROM (deg)	ρ	Difference in ROM (deg)	RMSE (deg)
Flexion/ Extension	Max Amplitude	99 (18)	0.98 (0.02)	4.4 (3.2)	3.2 (1.8)
	Max Speed	98 (13)	0.98 (0.02)	4.6 (1.7)	3.3 (1.1)
Axial Rotation	Max Amplitude	130 (6)	1.00 (0.00)	2.9 (2.6)	2.1 (0.9)
	Max Speed	131 (6)	0.99 (0.00)	2.4 (1.5)	2.4 (0.7)
Lateral Flexion	Max Amplitude	75 (7)	0.96 (0.03)	3.1 (1.7)	3.4 (1.0)
	Max Speed	77 (6)	0.99 (0.01)	4.2 (1.1)	2.5 (0.6)

2.4.3 Conclusions

The method proposed to estimate the angles using the IMUs, where the drift was corrected assuming no difference in the position of the subject's head at the beginning and at the end of each movement, was certainly limited by the fact that it cannot be excluded that these positions might be slightly different. For this reason, the accuracy of the angles estimated was tested against a stereophotogrammetric reference system during a series of AHM. A satisfactory concordance between the angle curves measured by the two systems was observed. This concordance between the two motion patterns was confirmed with the overall correlation between the two curves, both in trials at maximum amplitude and maximum speed. Also values measured for the RMSE and difference in ROM confirmed the close correspondence between the two measurement systems (see Table 2-3). The values measured were consistent with those reported in literature. In fact, by placing the sensors in the same location and asking participants to perform the same movements Theobald et al. obtained a RMSE of 6.93±0.14, 7.99±4.85 and 6.31±2.16, in flexion/extension, axial rotation and lateral flexion, respectively [52]. The same author reported a difference in ROM of 5±4, 3±2 and 4±3 degrees in flexion/extension, axial rotation and lateral flexion respectively. Furthermore, the difference between the two systems represents the 4%, 2% and 4%

of maximum ROM in flexion/extension, axial rotation and lateral flexion, respectively; therefore, in further studies differences among trials, lower than those values will be not deemed as significant. For these reasons, the error introduced by the use of the drift correction method was deemed to be acceptable for our investigation.

2.5 Pilot study

2.5.1 Subjects and protocol

Six subjects (age 25±2.4 years, BMI 25.2±3 kg/m^2) without any history of cervical disorder or pain were enrolled in a pilot study. This preliminary investigation was conducted in order to evaluate the designed protocol. Participants were asked to perform the experimental protocol described above without wearing any cervical support and while wearing different cervical orthoses. Two devices available on the market were selected for this purpose and tested together with the SSS (Figure 2-14). The entire experimental protocol was repeated by the participants with each orthosis. The study was approved by the ethical committee of the Department of Mechanical Engineering of the University of Sheffield (see the letter of approval in Appendix B). Participants were informed about the protocol and signed a consent form prior to the experimental session.

2.5.2 Orthoses

As well as the SSS, the two additional orthoses chosen were those most commonly used by people affected by serious neck weakness, according to the experience of patients in care at the Royal Hallamshire Hospital (Sheffield, UK). Orthoses selected were the Headmaster (Symmetric Designs Ltd., Figure 2-14c) and the Vista (Aspen Medical Products, Figure 2-14d). Since the SSS can have different configurations, according to the number and the position of supports used (Figure 2-14b), a decision was made to test it in two different settings. Configurations were chosen in order to provide the lowest and the higher support possible. The first configuration was characterized by only one straight support applied on the frontal part of the snood, in order support the chin. The second configuration was characterized by six supports:

two frontal jaw supports, two lateral shoulder supports (one per side) and two straight supports applied on the back of the snood.

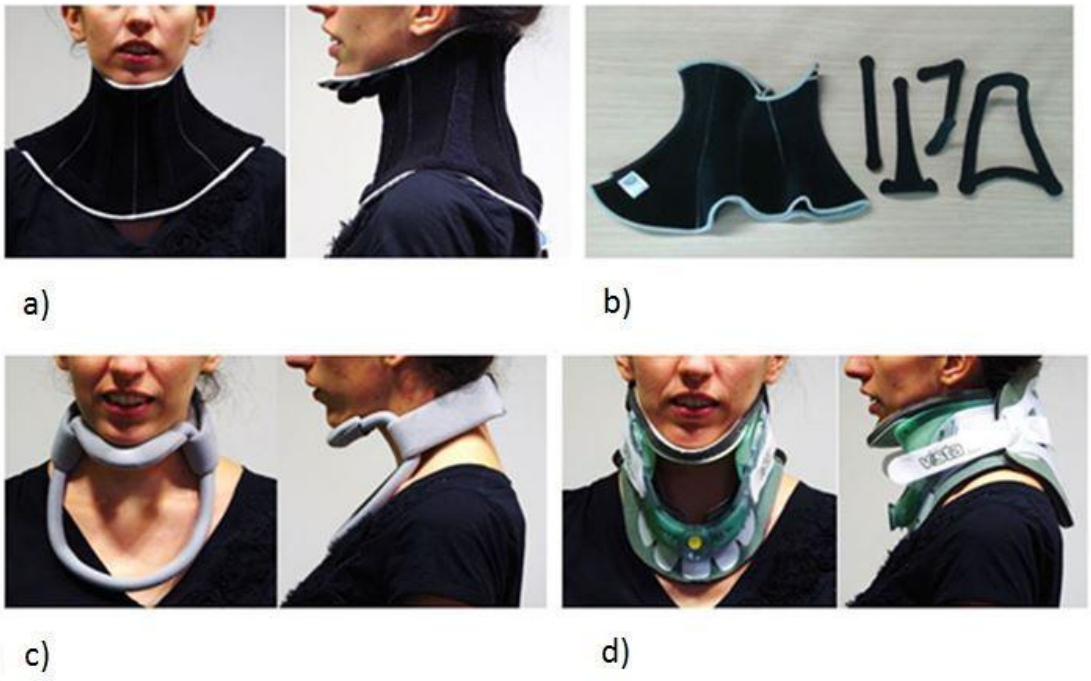


Figure 2-14 Tested orthoses. a) Sheffield Support Snood; b) Sheffield Support Snood with supports (from left to right: straight support, lateral support, jaw support and A-shape support); c) Headmaster cervical orthosis; d) Vista cervical orthosis.

2.5.3 Pilot study results

Phase 1 (Active Head Movement): Cervical angles were estimated relative to the three major anatomical axes. Although the algorithm implemented appeared to be appropriate for the signal processing and gave the required data, the obtained curves were affected by a significant drift. It is commonly known that the accuracy of time-integration methods is affected by errors that grow over time. This is mainly due to the gyroscope bias drift (see Paragraph 1.3.5). In this case the absence of a pause between the flexion and extension, as well as between axial rotation and lateral flexion on the two sides, was identified as the issue to be solved to be able to adopt no orientation correction. Data related to the trials with the SSS with only one support were deemed not reliable due to the instability of the configuration. Putting only one, narrow (1cm wide) support led to an inadequate support of the head, due to a significant difficulty

in maintaining the initial setting of the orthosis. A minimal rotation of the snood around the neck could cause the lack of support under the chin.

Phase 2 (ADLs): The standardisation of the washing task was deemed as not satisfactory. This led to highly different signals between participants that made the comparison not meaningful. Typing appeared to be poorly informative since a really low inclination of the head was necessary to perform the task so differences between the orthoses were hard to detect.

Phase 3 (Gait): No lacks in the protocol emerged from the analysis of the data collected in this phase.

2.5.4 Pilot study conclusions

On the basis of the results obtained in the preliminary study, it could be concluded that the use of inertial sensors was suitable for the purpose of this study and the algorithm implemented was appropriate for the signal processing. Nevertheless, the following modifications to the experimental protocol were applied in order to improve the proposed method:

- SSS configuration with one support was modified. The straight support was replaced by an A support in order to give more stability.
- In the active head movement tasks a pause was introduced between two consecutive movements to reduce the drift error.
- Washing and typing tasks were excluded from the protocol.

Chapter 3

Quantification of the biomechanical features of the Sheffield Support Snood and comparison with two existing cervical orthoses

3.1 Introduction

The SSS is a Class 1 medical device (C.E. Self Certified to 93/42/EEC as amended by 2007/47/EC by Sheffield Teaching Hospitals NHS Foundation Trust, the registered manufacturer). The SSS (Figure 2-14a) is a new orthosis specifically designed for people affected by progressive neck muscle weakness caused by neurological diseases such as MND or muscular dystrophy. A key feature of its design is to be customisable to increase or decrease head support as required, by configuring the support provided appropriately for individual users. The main requirements of an orthosis to be used for such individuals are linked to the need of keeping the head in an upright position without further degrading the muscle tone from restricted movement. The main limitation of many commercially available orthoses is that they are designed for trauma use and completely immobilize the neck, resulting in them being uncomfortable to wear and overly restrictive in planes where muscle strength remains strong. The SSS has been designed with the goal of overcoming these limitations. The orthosis is characterized by a minimally-bulky structure, which is adaptable due to the incorporation of adjustable supports (Figure 2-14b), according to the task performed and to the subject's level of functional limitation. However, these biomechanical features of the SSS have not been previously objectively quantified either in healthy or pathological users. The aim of this study was to characterize and quantify the biomechanical features of the SSS and compare them to those of two other

commercial neck orthoses, widely used by people affected by neck muscle weakness: the Headmaster (HR, Figure 2-14c) and the Vista (VA, Figure 2-14d).

The assessment of neck orthoses is typically based on the assessment of the full, active head or intervertebral ROMs that are allowed by the orthoses during the execution of movements along the three principal anatomical axes [109] [96] [91] [93] [90] [83] [97] [94]. Furthermore there are studies in which, together with the full active ROMs, the functional ROMs, allowed by the cervical orthoses in some selected activities of daily living, are also investigated [84] [99]. Head and/or intervertebral residual range of motion have been classically investigated through different techniques: radiographic measurements [109] [91] [94], motion capture systems [96] [91] [93], goniometric techniques [90] [83] [97] [94] [84] [99] and measurement systems based on ultrasound pulses [81]. As mentioned in the previous chapters, although motion capture is the gold standard in movement analysis, it cannot be performed outside a laboratory and requires very cumbersome procedures, which make it unsuitable for a protocol translatable to a clinical context. Recently, IMUs have been recognized as a valid instrument to assess the range of movements of the neck in healthy participants [52] and in post-surgery evaluations [61] [59]. They were chosen as measurement system in this study for the reasons explained in Paragraph 2.2.2 and after a successful validation against an optoelectronic system (see Paragraph 2.4 for details). Within this study, the aimed characterization of the SSS and the comparison of the chosen orthoses were then performed using IMUs and the protocol described in Chapter 2.

3.2 Materials and Methods

3.2.1 Participants and protocol

Twelve healthy participants (5 females, 7 males, age 26±2 years, body mass index 23±3 kg/m^2) without any history of neck disorder or pain were involved in the study, which was approved by the Ethical Committee of the University of Sheffield (Sheffield, UK). Participants were informed about the protocol and signed a consent form prior to the acquisition sessions. The number of participants was chosen on the basis of a power analysis (probability 0.05, power level 95%) conducted using the values of ROM

measured in the pilot study in which the same protocol was performed with and without orthoses by 6 healthy participants (see Paragraph 2.5 for details).

The experimental protocol used is extensively described in Paragraph 2.2.1 and included: active head movements (AHM: extension (E), flexion (F), axial rotation (AR) and lateral flexion (LF)), some activities of daily living (ADLs: drinking, eating and rising from sitting position) and gait tasks (30 m walk and stairs climbing up and down). According to the results obtained in the pilot study, while executing the AHM participants performed the head movement in one direction, came back to the reference position and maintained it for about three seconds before performing the movement in the opposite direction. Each movement was repeated six times: three asking the participants to reach the maximum amplitude and three to reach the maximum speed. The first condition was used to evaluate participants' ability to perform head movements while they endeavoured to reach their maximum range of motion in each direction, but still in a controlled state. The second condition was used to evaluate participants' ability to perform head movements in a less controlled state. Only the data from the trial in which the highest value of amplitude/speed respectively was reached, among the three repetitions, were retained for further analysis. Each ADL was repeated three times. Since participants weren't given a goal (e.g. perform the task as faster as possible) the "best" repetition out of three couldn't be selected and the average of values obtained in the three repetitions was retained for further analysis, after having checked the repeatability of the trials. Walking and stairs climbing tasks were performed only once. Before the actual data collection, participants performed the whole range of head movements at least once to familiarize themselves with the test procedure and to stretch the neck muscles.

The entire protocol was repeated by each participant while wearing each of the three investigated orthoses (SSS, HR and VA) and without wearing any orthosis to have a reference measure. Since the SSS can have several different configurations, according to the number of supports used it was tested in the two configurations that more closely resemble the VA (which offers frontal, lateral and posterior supports) and the HR (which offers only a frontal support), respectively. The SSS was hence tested both in its most supportive (with six supports: two frontal, two lateral and two posterior) and less supportive configuration (with one A-shape frontal support). Participants were allowed to rest whenever needed and both orthoses and movements orders were

randomized to minimize fatigue or learning related effects. Two IMUs were used in the study and placed on the participants as per the experimental protocol developed (see Paragraph 2.2.2). The signals were recorded at a sampling frequency of 128 samples/s.

3.2.2 Data processing

The acquired acceleration and angular velocity signals were low pass filtered using a 4th order Butterworth filter with a cut-off frequency of 5Hz, after having analysed the frequency content of signals collected, using a procedure analogous to the one described in Paragraph 2.4.1. Data processing was performed using custom procedures written in MATLAB R2013a. The sensor orientation was then computed using the functional calibration approach and the quaternion-based algorithm presented in Paragraphs 2.2.3 and 2.3.1.2, respectively.

The differences between AHM performed with and without orthoses were quantified for each orthosis and each movement using the ROM calculated from the sensor rotation angles, as estimated using the above mentioned techniques. In addition, its percentage variation from the values obtained without orthosis was calculated as:

$$\%ROM_{NC} = \frac{ROM_C}{ROM_{NC}} \cdot 100; \qquad (3\text{-}1)$$

where ROM_c and ROM_{NC} are the ROM measured with and without cervical orthosis, respectively.

As mentioned in Paragraph 1.3.5, although it is possible to estimate the sensor orientation using the data from the wearable sensors, the procedure has some limitations. A recent article from Bergamini et al [65] illustrates the state of art of orientation estimation through inertial sensors and underlines that time duration, measurement volume and presence/absence of phases during which the sensor is stationary are crucial factors that considerably affect the accuracy of the estimation. Due to those limitations, it wasn't possible to calculate the ROM in activities of phases 2 (ADLs) and 3 (walking), characterized by longer time duration, larger measurement volume and the absence of stationary stances.

To evaluate the participants' movements during phase 2, it was thus decided to look at those parameters computed directly from the measured linear acceleration and angular velocity. Both for acceleration and angular velocity the root mean square

(RMS), as opposed to the peak value, was taken into consideration. RMS is a measure of dispersion of data relative to zero and this value provides information on the average value of acceleration and angular velocity in each direction during a complete task, thus can describe movements better than an instantaneous value.

The RMS related to daily activities was calculated by subtracting the contribution of the sternum from the head after having aligned the two sensors to the anatomical frame using the functional calibration procedure described in Paragraph 2.2.3. RMS was investigated separately along the three main anatomical axes (AP: anterior-posterior, V: vertical, ML: medio-lateral). In addition, its percentage variation from the values obtained without orthosis was calculated as:

$$\%RMSx_{NC} = \frac{RMSx_C}{RMSx_{NC}} \cdot 100; \qquad (3\text{-}2)$$

where RMS_c and RMS_{NC} are the RMS measured with and without cervical orthosis and x is substituted by a or ω when the RMS is calculated on the acceleration or angular velocity values, respectively.

In phase 3, i.e. during the locomotion task, both spatio-temporal parameters (stride frequency, average walking speed) and head and trunk accelerations were investigated. RMS of the acceleration was calculated, but, in order to account for the effects of walking speed, for the locomotion tasks, it was normalized using the mean walking speed, as computed for the central strides. RMS was then used to evaluate the walking task through the attenuation coefficient (C_{SH}) [110]. In young individuals the oscillation of the upper body during level walking is characterized by an attenuation of the linear acceleration, going from pelvis to head level. C_{SH} was used to investigate the ability to attenuate the acceleration between sternum and head in participants that were performing the walking task with and without orthoses. The coefficient was computed using the following equation [110]:

$$C_{SH} = 1 - \frac{RMS_H}{RMS_S} \cdot 100; \qquad (3\text{-}3)$$

where RMS_H and RMS_S are the root mean square values for head and sternum, respectively. The coefficient was evaluated along the three main anatomical axes.

3.2.3 Statistical analysis

A first analysis was carried out in order to check the repeatability of the movements performed by the participants. A reliability analysis was performed using the intra-class correlation coefficient (ICC) [111] to estimate, for each movement, the level of agreement between the repeated tests. The significance of ICC was interpreted as: good, ICC > 0.75; moderate, 0.40 < ICC < 0.75; poor, ICC < 0.40 [112].

To identify any differences among AHM, ADLs and gait tasks performed with and without orthoses a statistical analysis was carried out using a one-way repeated measure ANOVA with a post-hoc Tukey analysis. The significance level p was set at 0.05. A second level of analysis involved those orthoses and movements for which significant variations were observed from the reference condition. In order to investigate the inter-orthosis differences a one-way repeated measure ANOVA with a post-hoc Tukey analysis was performed between the values measured with those orthoses and expressed as a percentage of the values obtained without any orthosis. Also in this second analysis the significance level p was set at 0.05.

Finally, Cohen's d was chosen as an indicator of the effect size. According to Cohen's definition an effect size of 0.2 was considered as small, an effect size of 0.5 was considered as medium and an effect size of 0.8 or greater as large [113].

3.3 Results

3.3.1 Reliability of the assessment protocol

Table 3-1 shows the ICC values obtained for the AHM. As can be seen from the table, in trials at maximum amplitude the ICC was above 0.8 in all the tasks except in the axial rotation performed without orthosis where the ICC was 0.65. Similar results were obtained in trials where movements were performed at self-selected maximum speed.

Table 3-1 ICC of the ROM. Coefficient calculated in three trials for each movement: extension (E), flexion (F), axial rotation (AR) and lateral flexion (LF) with orthoses (HR= Headmaster, SSS –A support= SSS with the A support, SSS –6 supports= SSS with six supports, VA= Vista) and without orthoses.

ICC (ROM)		*Trials without orthosis*	*HR*	*SSS A support*	*SSS 6 supports*	*VA*
E	Max Amplitude	0.88	0.86	0.88	0.89	0.82
	Max Speed	0.84	0.92	0.86	0.97	0.94
F	Max Amplitude	0.92	0.90	0.96	0.85	0.93
	Max Speed	0.87	0.93	0.94	0.97	0.94
AR	Max Amplitude	0.65	0.94	0.98	0.95	0.94
	Max Speed	0.59	0.92	0.95	0.96	0.87
LF	Max Amplitude	0.91	0.85	0.96	0.94	0.92
	Max Speed	0.92	0.92	0.94	0.97	0.98

To check the repeatability of ADLs performed by the participants, the ICC of the RMS of the acceleration was calculated for the three trials executed for each ADL and for each orthosis. Results obtained are shown in **Error! Reference source not found.**. ICC was calculated for the three components of the RMS along the three anatomical axes. ICC for drinking and eating activities was moderate to good with all the orthoses and along all the axes. A moderate to good ICC for RMS was observed also in the rising from a chair activity, except along V axis when the activity was performed with the Vista orthosis (ICC=0.36). Values obtained along this axis, for this task and orthosis were excluded from further analysis. Differently, for all the other tasks, axes and orthoses the values obtained in the three repetitions were averaged and retained for further analysis. Similar results were obtained for the ICC calculated on the RMS of the angular velocity and data were post-processed as explained above.

Table 3-2 ICC of the RMS of the acceleration (RMSa). Coefficient calculated in three trials for each daily activity with orthoses (HR= Headmaster, SSS –A support= SSS with the A support, SSS –6 supports= SSS with six supports, VA= Vista) and without orthoses. AP= anterior-posterior, V=vertical, ML= medio-lateral.

ICC (RMSa)		*Trials without orthosis*	*HR*	*SSS A support*	*SSS 6 supports*	*VA*
Drinking	AP	0.84	0.67	0.70	0.86	0.69
	V	0.72	0.64	0.64	0.70	0.81
	ML	0.93	0.83	0.72	0.82	0.92
Eating	AP	0.84	0.87	0.82	0.89	0.91
	V	0.46	0.71	0.51	0.53	0.69
	ML	0.89	0.84	0.85	0.82	0.91
Rising from a chair	AP	0.64	0.48	0.62	0.84	0.73
	V	0.54	0.53	0.52	0.41	0.36
	ML	0.60	0.78	0.71	0.69	0.87

3.3.2 Comparison between the orthoses

Active head movements

Figure 3-1 shows a typical signal recorded while a healthy participant is performing a full series of AHM reaching the maximum amplitude and without wearing any orthosis. Signals presented in the two graphs are the acceleration and the angular velocity recorded at the forehead level. The three components of each signal are shown after the alignment with the external reference frame built using the functional calibration procedure.

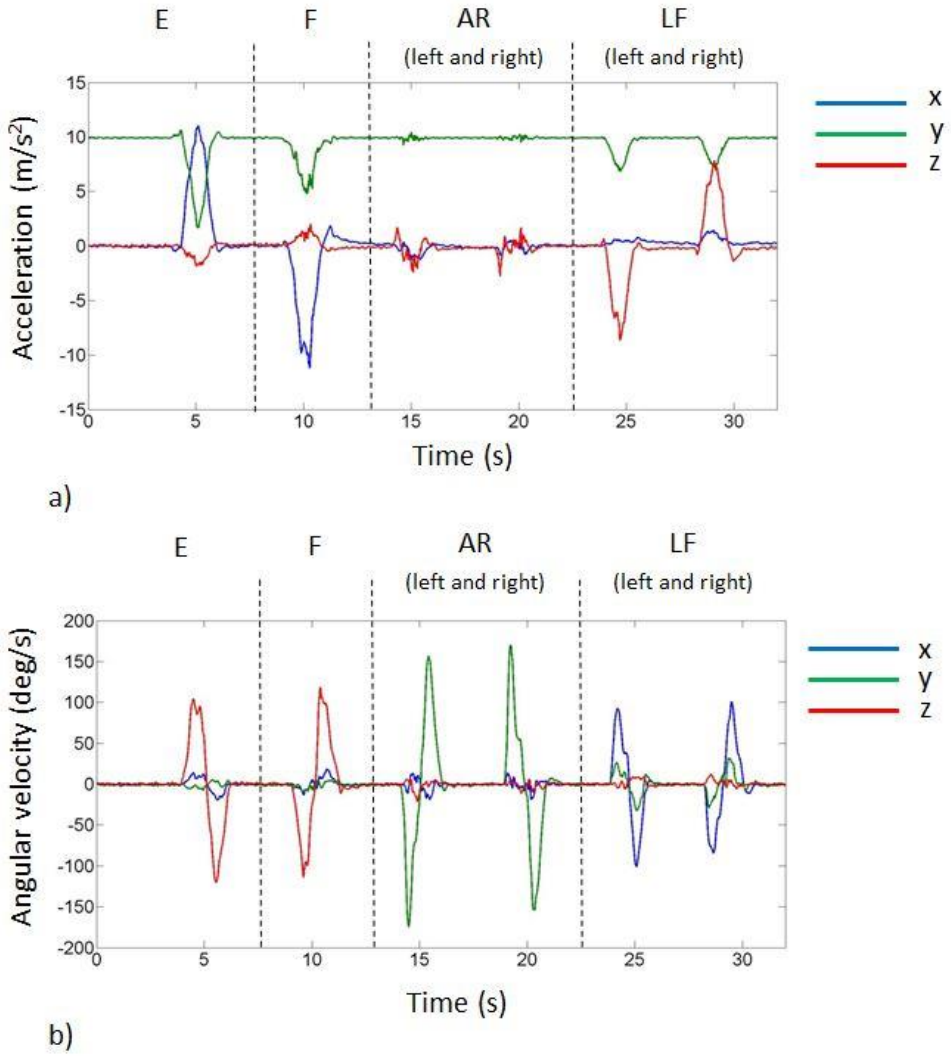


Figure 3-1 Acceleration (a) and angular velocity (b) signals recorded by the sensor placed on the forehead. Signals recorded when a healthy participant was performing: extension (E), flexion (F), axial rotation (AR, left and right side) and lateral flexion (LF, left and right side) movements reaching the maximum amplitude and without wearing any orthosis. Components along the three axes (x, y and z) are shown after being aligned to a common reference frame defined using a functional calibration procedure.

Table 3-3 shows the ROMs obtained for the different orthoses. In the trials performed at maximum amplitude, the ROM measured with the HR was significantly reduced (52(9) ° vs 28(13) °, p<0.001, d=0.7) with respect to the trials without orthosis, but only in the flexion movement. A significant reduction in both flexion (52(9) ° vs 36(13) °, p<0.05, d=0.6) and axial rotation (145(12) ° vs 101(30) °, p<0.05, d=0.7) was observed for the SSS with the A support. Finally, significant reductions of the angles were observed for all the movements when performed with the VA (see values in Table 3-3, p<0.05 and d>0.5) and the SSS with six supports (see values in Table 3-3, p<0.05 and

d>0.5). These results were confirmed in the trials at maximum speed, except for the flexion movement, where no significant differences were found between the values measured with the SSS with the A support and without orthosis.

Table 3-3 Mean (SD) values for the ROM. Values reached performing extension (E), flexion (F), axial rotation (AR) and lateral flexion (LF) with orthoses (HR= Headmaster, SSS –A support= SSS with the A support, SSS –6 supports= SSS with six supports, VA= Vista) an and without orthoses. (*) Level of significance for the difference with "trials without orthosis" is $p<0.05$. (**) Level of significance for the difference with "trials without orthosis" is $p<0.01$.

Max ROM (deg)		*Trials without orthosis*	*HR*	*SSS A support*	*SSS 6 supports*	*VA*
E	Max Amplitude	54 (13)	50 (12)	43 (7)	35 (10)**	35 (7)**
	Max Speed	51 (9)	47 (10)	46 (9)	39 (13)*	35 (9)**
F	Max Amplitude	52 (9)	28 (13)**	36 (13)*	36 (12)*	27 (10)**
	Max Speed	52 (11)	30 (14)**	40 (13)	37 (12)*	32 (11)**
AR	Max Amplitude	145 (12)	116 (21)	101 (30)**	96 (33)**	77 (30)**
	Max Speed	143 (15)	117 (23)	105 (35)*	105 (32)*	81 (29)**
LF	Max Amplitude	80 (12)	70 (13)	67 (11)	60 (18)*	61 (15)*
	Max Speed	82 (14)	72 (13)	71 (15)	63 (18)*	62 (16)*

The second level of analysis focused only on the data obtained for those orthoses and movements for which significant variations were observed from the reference condition (without orthosis), in order to allow for an inter-orthosis comparison. The results of this analysis are shown in Figure 3-2 and Figure 3-3, where the ROMs measured with each orthosis are plotted as a percentage of the corresponding values obtained without orthosis in the maximum amplitude and maximum speed trials, respectively.

In both trials at maximum amplitude (Figure 3-2) and at maximum speed (Figure 3-3) the percentage of ROM reached with the HR was significantly different from the reference condition only in the flexion movement where a reduction in the ROM respectively of 47% and 43% was observed. However, the values measured with the HR were not significantly different from the values measured with the other orthoses ($p>0.05$, $d<0.4$). In the trials at maximum amplitude the percentage of ROM achieved

with SSS with six supports was not significantly different (p > 0.05, d < 0.4) from the one achieved with VA in none of the movements performed. The use of SSS with six supports and VA led to a reduction in the ROM respectively between 25% and 34% and between 24% and 47%. These results were confirmed in trials at maximum speed where the use of SSS with six supports and VA led to a reduction in the ROM respectively between 24% and 29% and between 25% and 43%. No statistically significant difference (p>0.05, d<0.1) was observed between the SSS with the A support and the SSS with six supports in the values measured for the axial rotation movement: both orthoses led to a reduction in ROM around 30% in trials performed reaching the maximum amplitude and around 25% in trials performed at maximum speed.

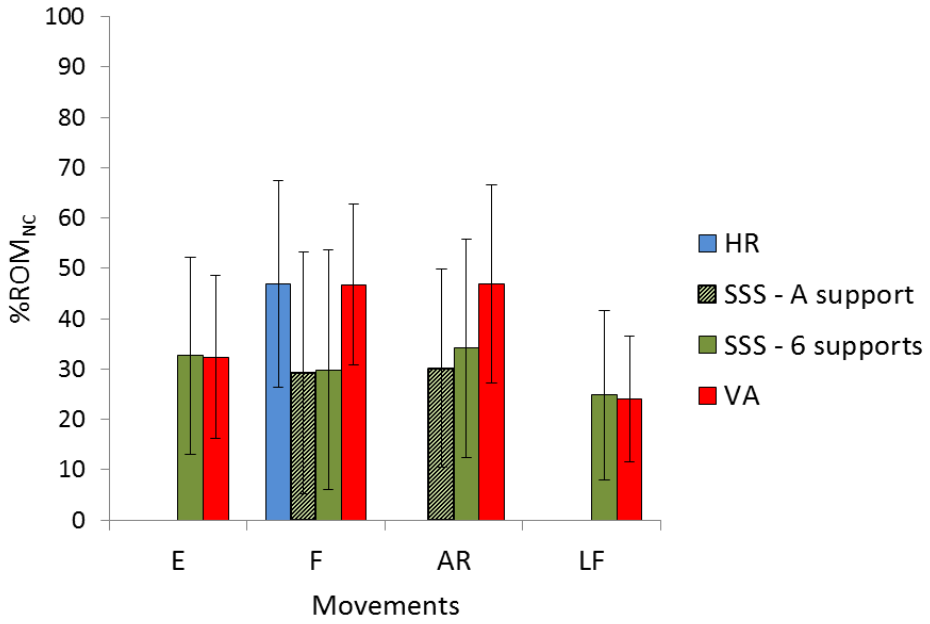


Figure 3-2 Trials performed reaching the maximum amplitude. Mean (SD) values for the percentage of ROM reached performing extension (E), flexion (F), axial rotation (AR) and lateral flexion (LF) with orthoses (HR= Headmaster, SSS –A support= SSS with the A support, SSS –6 supports= SSS with six supports, VA= Vista) with respect to trials performed without any orthoses. Values are reported only when significantly different from those measured in the trials performed without orthosis (as per Error! Reference source not found.**). (*) p < 0.05. Statistical comparison is not reported since the ifferences were never significant.**

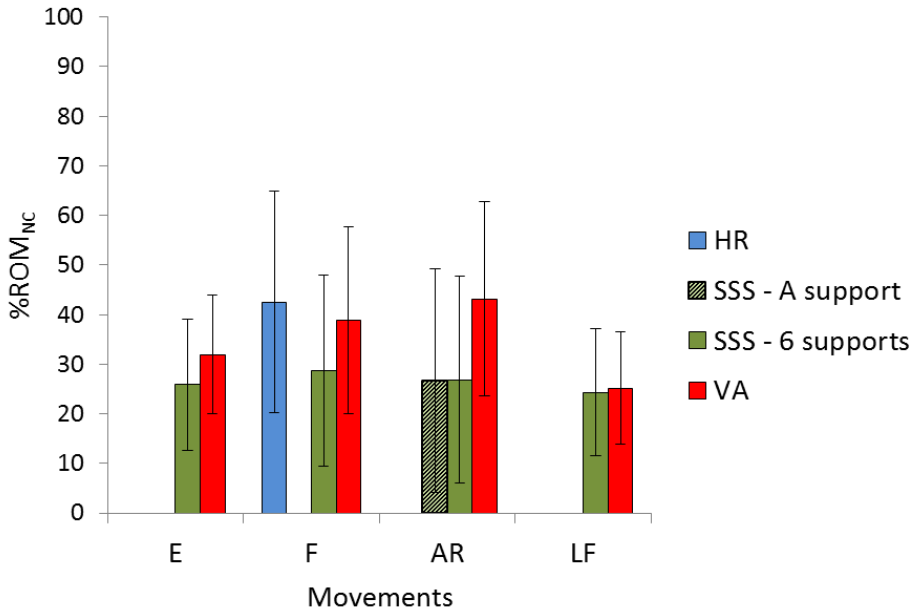


Figure 3-3 Trials performed reaching the maximum speed. Mean (SD) values for the percentage of ROM reached performing extension (E), flexion (F), axial rotation (AR) and lateral flexion (LF) with orthoses (HR= Headmaster, SSS –A support= SSS with the A support, SSS –6 supports= SSS with six supports, VA= Vista) with respect to trials performed without any orthoses. Values are reported only when significantly different from those measured in the trials performed without orthosis (as per Error! Reference source not found.**). (*) *p*<0.05. Statistical comparison is not reported since the ifferences were never significant.**

Activities of daily living

Figure 3-4 shows a typical signal recorded while a participant was executing the eating task. Only the eating task performed without orthosis is presented, for the sake of conciseness. Signals presented in the two graphs are the acceleration and the angular velocity recorded at the forehead level. The three components of each signal are shown after being aligned to the external reference frame built using the functional calibration procedure.

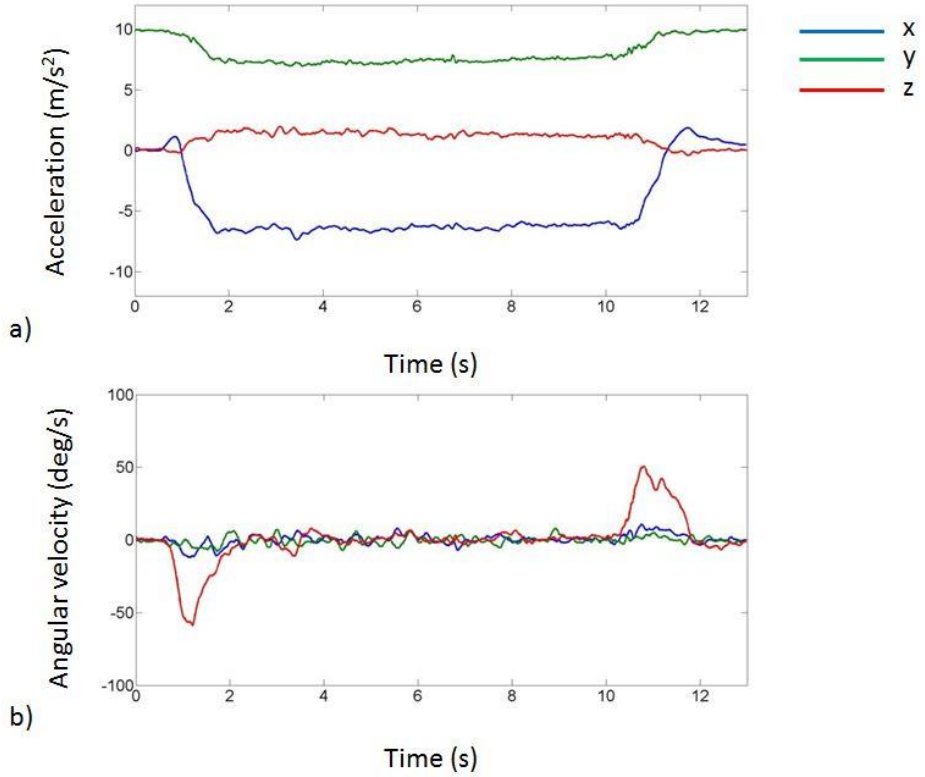


Figure 3-4 Acceleration (a) and angular velocity (b) signals recorded by the sensor placed on the forehead when a healthy participant is performing the eating task. Components along the three main axes (x, y and z) are shown after being aligned to a common reference frame defined using a functional calibration procedure.

Figure 3-5 shows the results related to the eating task. Graphs show the three components of the RMS of the quantities under observation, along the three main anatomical axes. Looking at the acceleration values (Figure 3-5a) no significant difference was found between the tasks performed with and without orthoses. Looking at the angular velocity values (Figure 3-5b), it can be observed that along the AP axis only VA gave a value significantly different from the one obtained without orthosis while, along the vertical axis, all the orthoses gave values significantly lower than the one obtained without orthosis. However, as can be seen from Figure 3-6, there wasn't any significant difference among the orthoses and the reduction in angular velocity along the vertical axis was assessed between 30% and 45%, compared to trials without orthosis.

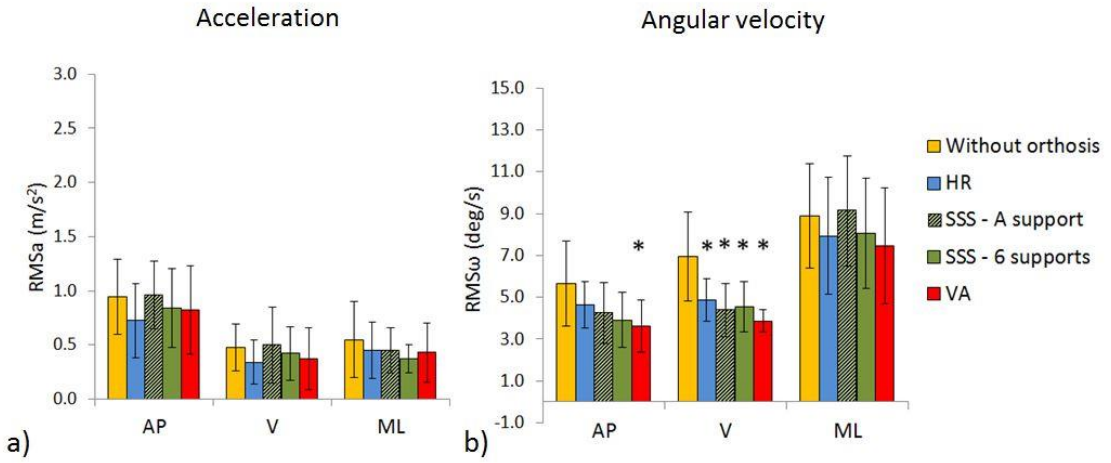


Figure 3-5 Eating. Mean (SD) values of the RMS of the acceleration (RMSa, Figure a) and angular velocity (RMSω, Figure b). Values measured with orthoses (HR= Headmaster, SSS with A support, SSS with six supports, VA= Vista) and without orthosis. Components along the three main anatomical axes (AP=anterior-posterior, V=vertical, ML=medio-lateral) are shown in both graphs. (*) *p*<0.05 compared to trials without orthosis. Statistical comparison between different orthoses is not reported since the differences were never significant.

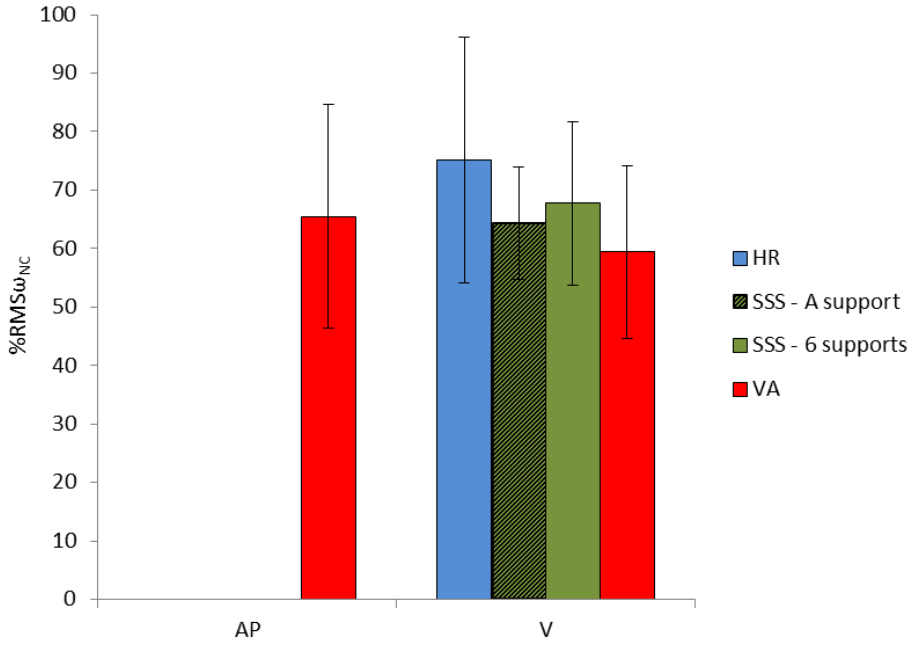


Figure 3-6 Eating. Mean (SD) values for the percentage of the RMS of angular velocity (RMSω). Values measured in trials with orthoses (HR= Headmaster, SSS with A support, SSS with six supports, VA= Vista) with respect to trials without orthosis. Components along the anatomical axes anterior-posterior (AP) and vertical (V) are shown. Values are reported only when significantly different from those measured in the trials performed without orthosis (as per Error! Reference source not found.**). *) *p*<0.05. Statistical comparison is not reported since the differences were never significant.**

Figure 3-7 shows the results related to the drinking task. In terms of acceleration (Figure 3-7a) trials performed with the SSS with the A support, SSS with six supports and VA gave values significantly lower with respect to trials executed without orthosis, along ML. The reduction in the acceleration was assessed between 35% and 40%, however no significant difference among different orthoses was observed (Figure 3-8a). Angular velocity values measured in the drinking task (Figure 3-7b) gave results analogous to those observed for the eating task. Along AP, only VA gave a value significantly lower from trials performed without orthosis; while, along V, all orthoses presented values significantly lower from those measured when the task was executed without orthosis. Similarly to what was found for the eating task, no significant difference was observed among different orthoses and the angular velocity reduction along V was assessed between 30% and 40% (Figure 3-8b).

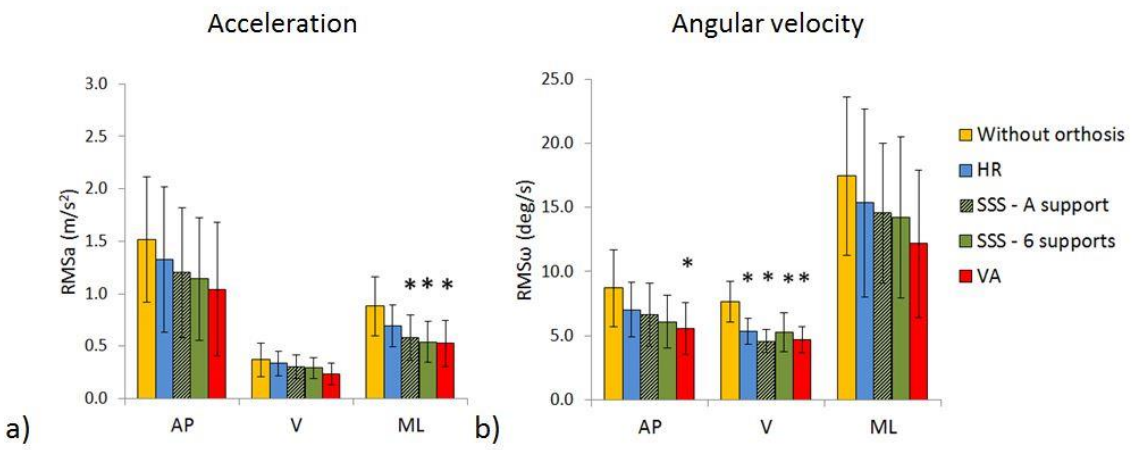


Figure 3-7 Drinking. Mean (SD) values of the RMS of the acceleration (RMSa, Figure a) and angular velocity (RMSω, Figure b). Values measured with orthoses (HR= Headmaster, SSS with A support, SSS with six supports, VA= Vista) and without orthosis. Components along the three main anatomical axes (AP=anterior-posterior, V=vertical, ML=medio-lateral) are shown in both graphs. (*) p<0.05 compared to trials without orthosis. Statistical comparison between different orthoses is not reported since the differences were never significant.

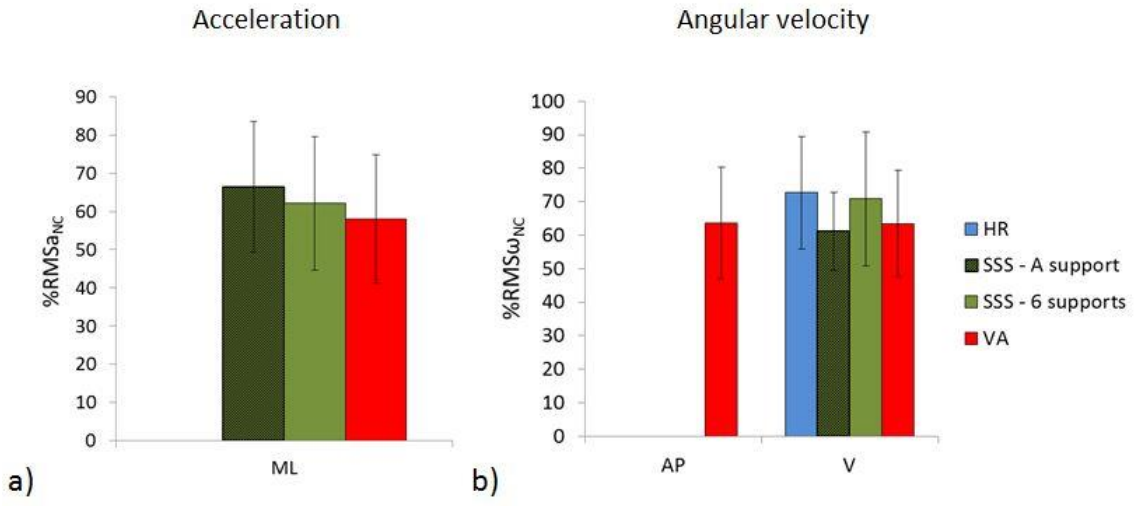


Figure 3-8 Drinking. Mean (SD) values for the percentage of the RMS of the acceleration (RMSa, Figure a) and angular velocity (RMSω, Figure b). Values measured in trials with orthoses (HR= Headmaster, SSS with A support, SSS with six supports, VA= Vista) with respect to trials without orthosis. Components along the anatomical axes: anterior-posterior (AP), vertical (V) and medio-lateral (ML) are shown. Values are reported only when significantly different from those measured in the trials performed without orthosis (as per Error! Reference source not found.**). (*) *p*<0.05. Statistical omparison is not reported since the differences were never significant.**

Data obtained when participants were asked to rise from a chair didn't show any statistically significant variation between the task performed with and without orthoses, both in terms of acceleration and angular velocity values. They also didn't highlight any significant difference among different orthoses.

Gait tasks

Figure 3-9 and Figure 3-10 show the spatio-temporal parameters related to the walking task. As can be seen from the graph, the average speed value was about 1.3 m/s. No significant difference was observed between the task performed with and without orthosis. Similarly, for the step frequency, no significant difference was found between values obtained when participants were wearing the orthoses and when they were free from them. The average value of the step frequency was about 1.2 steps/s.

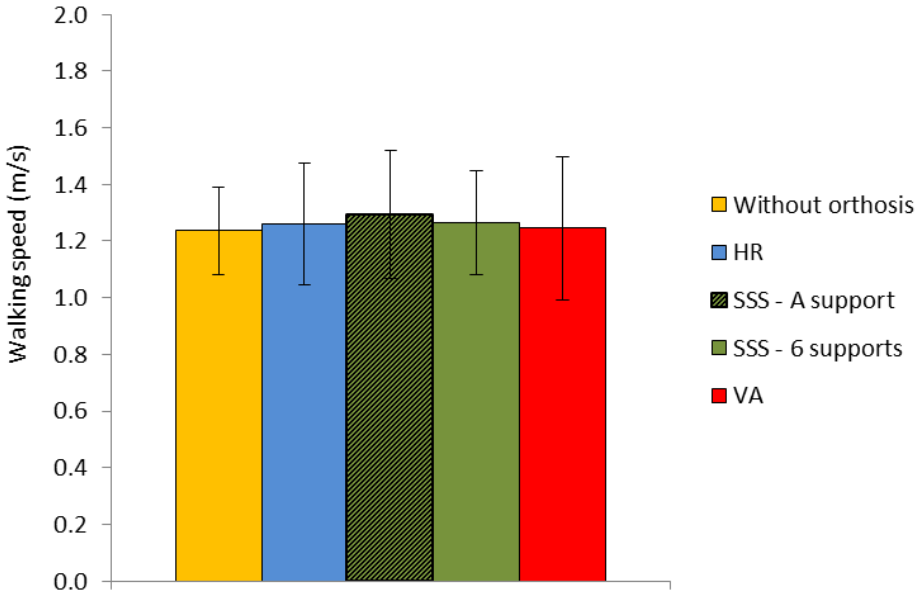


Figure 3-9 Walking. Mean (SD) values for the walking speed. Values measured while wearing the orthoses (HR= Headmaster, SSS with A support, SSS with six supports, VA= Vista) and without orthosis. (*) p<0.05 with respect to trials without orthosis. Statistical comparison between different orthoses is not reported since the differences were never significant.

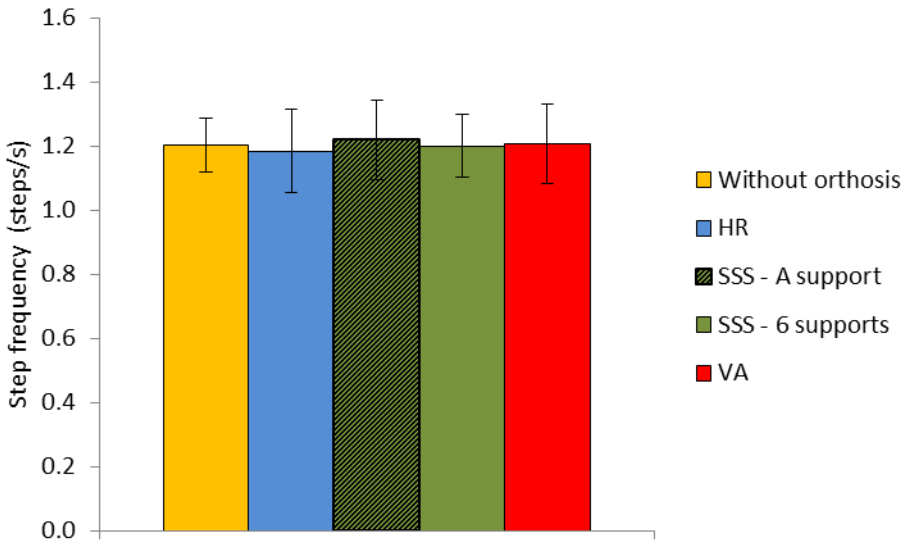


Figure 3-10 Walking. Mean (SD) values for the step frequency. Values measured while wearing the orthoses (HR= Headmaster, SSS with A support, SSS with six supports, VA= Vista) and without orthosis. (*) p<0.05 with respect to trials without orthosis. Statistical comparison between different orthoses is not reported since the differences were never significant.

Figure 3-11 shows the attenuation coefficient related to the three major axes calculated during the walking task. As can be seen from the graph, no significant difference was observed between values measured with and without orthoses.

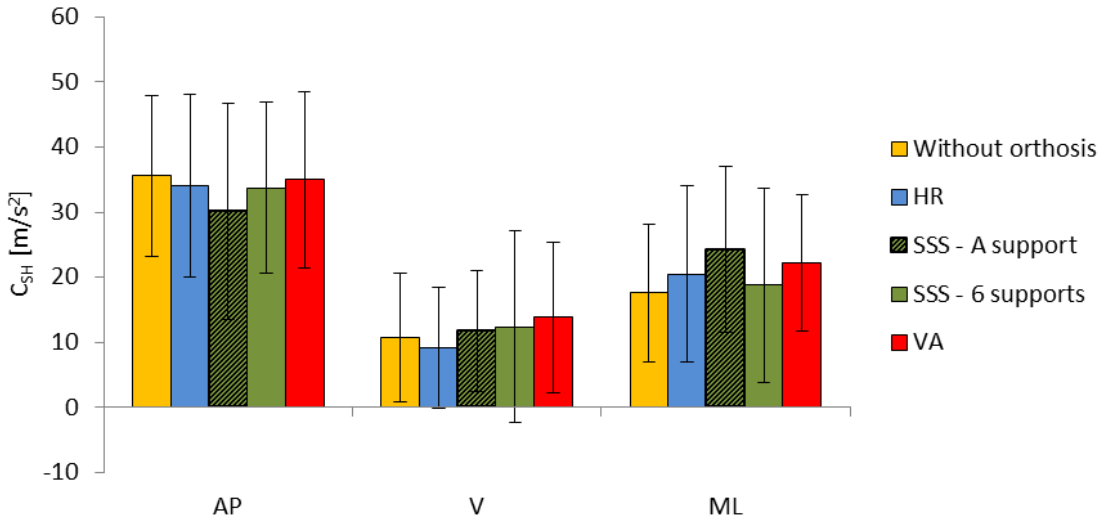


Figure 3-11 Walking. Mean (SD) values of the attenuation coefficient (C_{SH}). Values measured along the three main anatomical axes (AP=anterior-posterior, V= vertical, ML=medio-lateral) with orthoses (HR= Headmaster, SSS with A support, SSS with six supports, VA= Vista) and without orthosis. (*) p<0.05. Statistical comparison between different orthoses is not reported since the differences were never significant.

Figure 3-12 shows the average speed measured when participants were asked to climb a flight of stairs. As can be observed, average speed was about 0.28 m/s when participants were going up and about 0.32 m/s when going down the stairs. No significant difference in the values obtained with and without the orthoses was found, as well as differences among the orthoses. Figure 3-13 and Figure 3-14 show the normalized RMS of the forehead acceleration calculated respectively when participants were going up and down stairs. No significant difference between the tasks performed with and without orthoses was found.

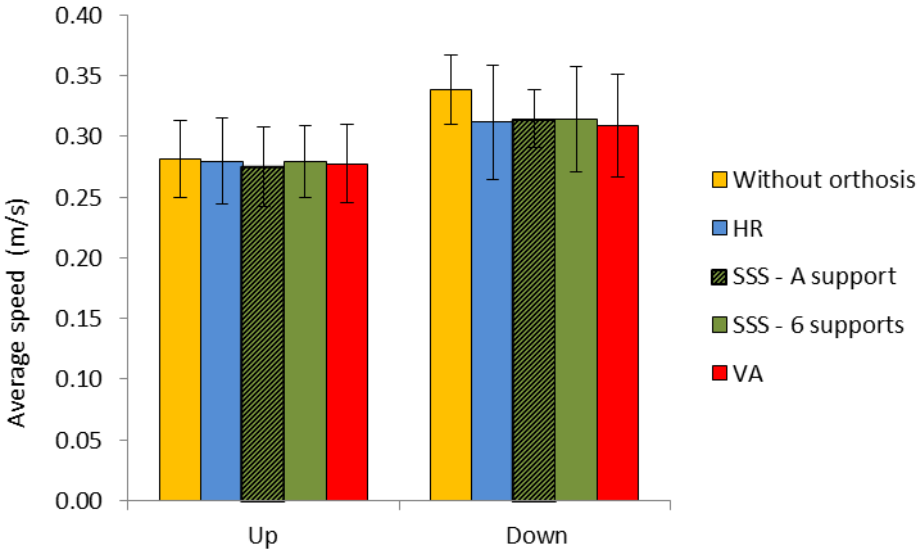


Figure 3-12 Mean (SD) values for the average speed measured when participants were going up and down stairs. Values measured while wearing the orthoses (HR= Headmaster, SSS with A support, SSS with six supports, VA= Vista) and without orthosis. (*) *p*<0.05. Statistical comparison between different orthoses is not reported since the differences were never significant.

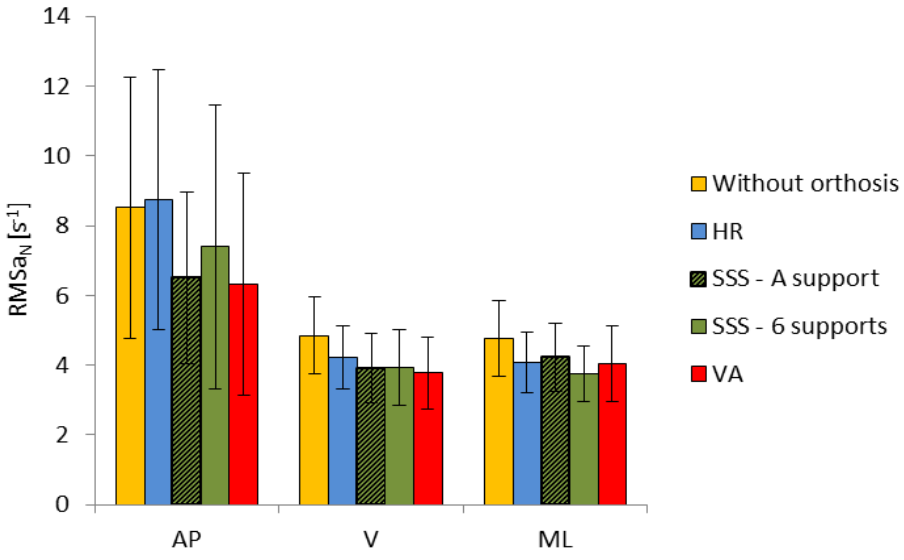


Figure 3-13 Participants going up stairs. Mean (SD) values of the normalized RMS of the three acceleration components (AP=anterior-posterior, V=vertical, ML=medio-lateral). Values measured with orthoses (HR= Headmaster, SSS with A support, SSS with six supports, VA= Vista) and without orthosis. (*) *p*<0.05. Statistical comparison between different orthoses is not reported since the differences were never significant.

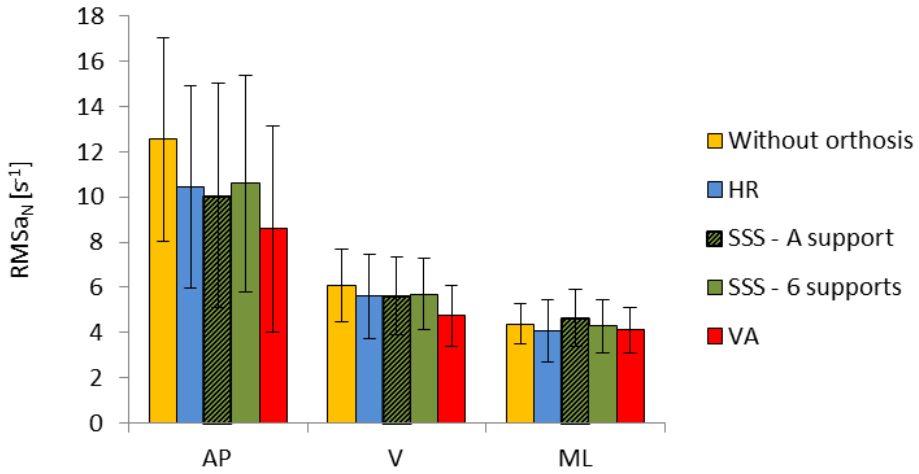


Figure 3-14 Participants going down stairs. Mean (SD) values of the normalized RMS of the three acceleration components (AP=anterior-posterior, V=vertical, ML=medio-lateral). Values measured with orthoses (HR= Headmaster, SSS with A support, SSS with six supports, VA= Vista) and without orthosis. (*) p<0.05. Statistical comparison between different orthoses is not reported since the differences were never significant.

3.4 Discussion

The aim of this study was to test a cervical orthosis specifically designed for people affected by neck muscle weakness, the Sheffield Support Snood, and to compare it to two other orthoses, the Headmaster and the Vista, by assessing their performances in providing support and limit the neck motion in desired directions. A protocol based on the use of wearable sensors has been proposed to this purpose, which is easily translatable to a clinical context. Significant differences in the participants' neck motion were detected when performed with and without orthoses and the experimental results were highly informative in the characterization of different orthoses' performance.

In performing the active head movements, although for each participant the highest value among the three tests was considered in the analysis, the level of agreement between the three repetitions was checked for each movement using the intra-class correlation coefficient (ICC) in order to verify if, when the movements were performed repeatedly under the same conditions, it was possible to record the same values. In addition, it was hypothesized that the limitations imposed by the orthoses could increase the repeatability of the task. The ICC obtained was overall high indicating a

good reproducibility. The worst results corresponded to the movements performed without orthosis, likely due to the absence of the constraint offered by the device, which reduces an individual's capability of performing the movement. It is important to note, however, that the repeatability obtained in those trials was still satisfactory, being good in the flexion-extension and lateral flexion and moderate in the axial rotation. The reliability value found for the axial rotation, lower than that reported by other authors [47] [59], might be due to the fact that this movement does not involve against gravity actions and might have hence be executed by the participants in a more confident manner, which might have led to more variable movement. Further studies are needed to test this hypothesis.

The results reported in this study demonstrated that the ROM measured with the Headmaster was significantly reduced compared to the trials without orthosis only in the flexion movement. Furthermore, the reduction in movement offered by the Headmaster was not significantly different from the reduction in movement observed with the other orthoses.

The ROMs measured with the SSS in its stiffer configuration and the Vista were significantly lower than those observed in the trials performed without orthosis in all the tasks and no significant differences were observed between them showing that the SSS with six supports is comparable to the Vista in terms of support provided, even though its structure is much less bulky than that of the latter. The same results were obtained in the trials at maximum speed, confirming the capability of the new orthosis to effectively reduce the movement in the desired direction, even in presence of a movement causing higher mechanical stimuli. These results, despite having been obtained from a limited sample of healthy participants, are extremely encouraging in relation to the use and utility of the SSS in patients with neck muscle weakness.

One of the main innovative features in the design of the SSS is that the device is intended to facilitate the movements about selected anatomical axes by providing a more robust support and limiting the excessive range of motion that could be generated by weakness of specific neck muscles, but without limiting the movements in the other planes. This is achieved by changing the number and location of the additional supports. Despite the limitation that the orthosis was only tested in two of its' possible configurations, the reported results seem to confirm the achievement of this design goal. The ROM measured with the SSS with the A support was significantly

reduced compared to the trials without orthoses only in the flexion and the axial rotation movements. This indicates that the SSS provides support under the chin without affecting the capability to perform extension and lateral flexion. In addition, no significant differences in the axial rotation values were observed between the SSS using solely the A support, aiming at limiting only flexion, and the SSS using all six supports (two frontal, two lateral and two posterior), aiming at limiting all movements apart from axial rotation. Further studies, are certainly needed to confirm these encouraging results. One other aspect to consider in future studies is that the healthy participants were applying loadings actively against the orthosis during short time spans (either at preferred velocity or maximal achievable velocity). With regard to the capabilities of each orthosis to support and control the head of an individual with neck muscle weakness, the loading generated is more typically due to passive gravitational loading resulting from the failure of the muscle or muscles to generate or maintain sufficient activation to support the head.

Also for the ADLs, the level of agreement between the three repetitions performed by the participants was checked for each task. The ICC of the RMS of the acceleration was calculated to this purpose. Values obtained were moderate to good and data measured in the three trials were averaged and retained for further analysis. Similar results were obtained for the ICC calculated for the RMS of the angular velocity and data were thus subjected to the same procedure. Acceleration values obtained performing the eating task didn't allow us to discriminate between different orthoses. In the drinking task, acceleration values of the SSS with the A support, SSS with six supports and Vista appeared to be significantly reduced only along the medio-lateral axis and values observed were not significantly different among different orthoses. Furthermore, both in the eating and in the drinking task only exercises performed with the Vista showed a significant reduction of angular velocity along the anterior-posterior axis while the reduction of angular velocity along the vertical axis was significant for all the orthoses but comparable among them. One possible reason for the absence of significant differences between ADLs performed with and without orthoses, in terms of acceleration and angular velocity, might be the small value assumed by those two quantities when performing the selected tasks. As can be observed in Figure 3-5, acceleration and angular velocity involved in performing the

eating task were significantly lower (about half the value) of those involved in the head movements executed reaching the maximum amplitude (Figure 3-1). Similar considerations apply to the drinking and rising tasks. In view of developing a protocol easily translatable to a clinical context and which minimizes the effort and the time required to make the orthoses assessment, results obtained in this study suggest that ADLs might be removed from the protocol. The performance of the ADLs would require patients a significant work and increase the duration of the protocol without giving adequate information to characterize the orthoses or discriminate among them. In order to evaluate the performance of an orthosis while executing ADLs, which remains a crucial aspect of everyday life, the employment of alternative methods, such as the use of questionnaires, should be considered.

Looking at the gait tasks, both in walking and in stairs climbing no significant difference was observed in the spatio-temporal parameters. This suggests that the ability to walk and climb stairs was not affected by the presence of the orthoses. Looking at the values obtained for the attenuation coefficient, no significant difference in the ability to attenuate the acceleration between sternum and head was observed when participants were wearing the orthoses. Similar considerations as those suggested in the ADLs apply to the gait tasks, which should be removed from the protocol in view of a clinical application.

Among the limitations of this study there is the reduced number of orthoses tested. Including more orthoses would have caused the protocol to become extremely long for participants. Furthermore, the number of orthoses compared is consistent with other studies reported in literature as already discussed in Paragraph 1.4.3. To minimize this limitation a careful selection of the orthoses (based on the experience of patients in care at the Royal Hallamshire Hospital (Sheffield, UK) and the consultation of a neurologist) was made in order to include those that are more likely to be used by patients affected by neck muscle weakness.

3.5 Conclusions

This study demonstrated that the SSS is effectively adaptable to different tasks, offering the possibility to limit neck movement in a selected direction without affecting

the ability to move in other directions. The SSS offered a support comparable to the Headmaster in flexion movements both performed at maximum amplitude and maximum speed in its more supportive configuration and in movements performed at maximum amplitude even in its less supportive configuration. Furthermore, the SSS in its stiffer configuration offered a support comparable to the Vista in all the tasks performed, both at maximum amplitude and maximum speed, although its structure was much less bulky and cumbersome compared to that of the Vista.

When performing activities of daily living Vista and SSS appeared to have comparable performances except along the anterior-posterior axis where only tasks performed with Vista appeared to be significantly different from those performed without orthosis. Furthermore, the presence of the orthoses didn't affect the ability of the participants to walk and climb stairs. The protocol proposed in this study was effective in assessing different orthoses. The execution of active head movements proved to be highly informative in the characterization of the orthoses. On the contrary, activities of daily living were not useful to discriminate between orthoses. In order to improve the protocol and in view of a future application on patients, those tasks were removed from the protocol. Also tasks related to the gait analysis were removed from the protocol, since they didn't give any significant information to evaluate the orthoses and to discriminate between tasks performed with and without them.

Results obtained and the definition of a reliable clinically-translatable protocol pave the way for further testing in patients with neck muscle weakness.

Chapter 4

Ability to perform head movements in individuals with neck muscle weakness due to MND: a quantitative assessment

4.1 Introduction

As more extensively discussed in Chapter 1, motor neurone disease is a degenerative disease primarily of motor neurones that leads to progressive muscle weakness. The consequences in terms of motor function differ depending on the extent to which upper and lower motor neurons are affected by the degeneration [2]. The onset of MND tends to be focal with weakness presenting in a particular group of muscles first. This is usually distally in one limb before spreading to other muscles within this limb and beyond over time. Bulbar and respiratory muscles are also affected, as are the muscles in the neck which support the head and enable its motion. Muscle weakness in the neck usually affects the neck extensor muscles, with or without the involvement of the neck flexors [27]. In those cases, a consequent head drop exacerbates problems with swallowing, communicating and breathing, causing significant disability and difficulties in social interactions. It has been reported that in MND patients head drop affects quality of life [28] and, in order to improve their posture and overcome those difficulties, patients are advised to wear a cervical orthosis [28] [29]. It has also been recently shown that neck muscle weakness leads to an increasing difficulty in performing the ADL and is negatively associated with survival time in MND patients [29].

A quantification of the interaction between neck muscle weakness due to MND and consequent functional limitation, to the author's knowledge, has only been performed

by testing muscle weakness with a manual muscle test and by assessing the ability to perform ADL using a clinical scale [29]. The main limitations of both functional rating scales and manual muscle testing (MMT) are that they are evaluator-dependent, provide ordinal data, which may lack sensitivity in the presence of small changes, and that they provide steps between grades which are not guaranteed to be qualitatively equivalent for each interval [8]. This can cause the disease to progress for an extended period before it is detected by a change in the MMT score. Furthermore, it has been proposed that there can be some critical levels at which a small decline in strength leads to a large functional loss [8]. Additional instruments, such as hand-held dynamometers (HHD), have been introduced in clinical practice to obtain a quantitative and more accurate assessment. These devices are portable, easy to use and relatively inexpensive. Nevertheless, they evaluate only isolated strength over specific muscle groups and do not provide an assessment of the overall function of a joint [9]. Thus, an assessment based only on muscle strength evaluation conveys limited information with regard the actual level of progression of the disease and there is a need for the development of tools that enable a more function based objective quantitative assessment of execution of movement. In the specific case of the assessment of functional neck impairment in MND patients, since currently used MND clinical scales do not take into account any measure of neck function and MMT and HHD techniques usually only evaluate neck extensor muscles, there is a need for a better outcome measure.

In an attempt to investigate the ability of different cohorts of participants to perform head movements, a number of researchers have measured both the velocity and the smoothness of these movements [54] [114] [115] [116]. The reduction of the velocity of head movements has been demonstrated to be a feature characteristic of individuals with chronic neck pain [114] and a marker of neck pathologies, such as cervical dystonia [54]. The fluidity, or smoothness, of a movement is often used as an indicator of unimpaired movement control and coordination. Several studies, in fact, have recognised that a lack of coordination, due to advanced age [115] or pathological conditions is typically associated with reduced smoothness [116]. Since impaired coordination and poor muscle control are primary consequences of altered muscle strength [117], it is reasonable to hypothesise that the assessment of movement smoothness, together with the measurement of velocity parameters, could allow the

quantitative evaluation of a patient's ability to perform head movements and provide valuable information to inform clinical care.

An additional feature of potential interest for a quantitative assessment of specific residual abilities is the so-called coupling of the movements [35]. Pure neck flexion-extension, axial-rotation and lateral flexion are movements executed in the sagittal, transverse and frontal planes, respectively. However, whilst the orientation of the cervical vertebral bodies allow for pure flexion-extension, they impede pure lateral flexion, and a simultaneous axial rotation is typically observed [35]. The out of plane movement resulting from this combination is often described as a coupling of the primary (lateral flexion) and the secondary (axial rotation) movements. Similar physiological movement couplings can, of course, also occur in other planes and for the other movements. Coupled mechanisms of the upper cervical spine have been shown to be significantly increased in pathological conditions such as cervical dystonia, likely due to the co-contraction of the cervical muscles which is known to occur in this condition [54] and with increasing age [35]. In patients with MND, the presence of increased coupled movements of the neck could be expected as a result of neighbouring muscles being employed to compensate for muscle weakness. Its quantification may hence add useful information for the functional assessment of these patients. Since radiological examinations, in order to directly investigate the motion of the cervical spine, couldn't be performed, coupled movements of the neck were investigated through the assessment of the movements of the head with respect to the trunk.

The aim of the study described in this chapter was to quantitatively characterise head movements with regard to velocity, smoothness and coupling in MND patients compared to aged matched controls.

4.2 Methods

4.2.1 Participants

A cohort of thirteen individuals affected by neck muscle weakness due to MND (6 females, 7 males, age range 45-74 years) participated in the study. The severity of

the disease was assessed in patients by using the MND Functional Rating Scale-Revised (ALSFRS-R, Appendix A). The ALSFRS-R is a validated ordinal scale, commonly used in clinics to estimate a patient's degree of functional impairment [6]. The scale ranges from 0 (worst) to 48 (best). The participating patients' characteristics (age, ALSFRS-R score at the time of recording and time course from diagnosis to recording) together with the trials performed are summarized in Table 4-1 Inclusion criteria were: ability to understand instructions and give informed consent, definite diagnosis of MND accordingly to the modified El Escorial criteria [118]; absence of comorbidities and presence of neck muscle weakness, as observed by a physician, as well as the presence of residual muscle strength to enable the performance of the test procedure. Individuals that were not able to lift their head at all from their chest were excluded from the study. Thirteen age-matched healthy individuals (6 females, 7 males, age range 44-75 years) were also enrolled. Inclusion criteria for healthy individuals were: the absence of symptoms or history of cervical spine disorders. All the participants were informed about the protocol through an information sheet and signed a consent form prior to their inclusion in the study. The study was reviewed and approved by the NRES Committee North East- Newcastle and North Tyneside (REC project number STH18733).

Table 4-1 Patients' characteristics. y= yes, the patient was able to execute the trial, n= no, the patient was not able to execute the trial.

Participant	Age (years)	ALSFRS-R score	Time from diagnosis (months)	Trials at Max Amplitude	Trials at Max Speed
1	69	30	11.5	y	y
2	74	13	49	y	n
3	69	44	1.5	y	y
4	63	18	36.5	y	y
5	58	43	34.5	y	y
6	53	22	2.5	y	n
7	69	23	18	y	n
8	53	34	10	y	y
9	65	19	36	y	n
10	74	17	59	y	y
11	50	23	57	y	y
12	45	18	36	y	y
13	63	36	45	y	y

4.2.2 Protocol

The assessment was performed using two IMUs (sampling frequency 128 samples/s), following the protocol described in Chapter 2 and modified according to the results obtained in the study presented in Chapter 3. The two IMUs were firmly attached on the forehead and sternum of each participant using double sided tape and the functional calibration approach described in Paragraph 2.2.3 was implemented. The sensor attached to the forehead was used to record the movements of the head while the sensor attached to the sternum was used to detect undesired movements of the trunk.

Each participant was asked to sit on a chair and perform the following active head movements (AHM): flexion (F), extension (E), axial rotation (AR, toward their left and right side) and lateral flexion (LF, toward their left and right side), starting from their own neutral position (NP) and looking ahead. To make sure they were well familiarized with the protocol, all participants were asked to practise the sequence of movements before the acquisition session started. All movements were performed first reaching the maximum amplitude (i.e. the participants were asked to move their head as far as possible from the neutral position), then at maximum speed (i.e. the participants were asked to move their head as fast as possible). Each movement was repeated three times. The participants with MND were asked to perform the movements at maximum speed only if they felt comfortable with doing it. The assessment took approximately 30 minutes.

4.3 Data Processing

4.3.1 Main issues and amendment to the data processing developed for the healthy subjects

Figure 4-1 shows the acceleration signal recorded at the forehead level when the AHM reaching the maximum amplitude were executed by a participant from the control group (Figure 4-1a) and a patient (Figure 4-1b). Signals are shown after the functional calibration procedure was applied.

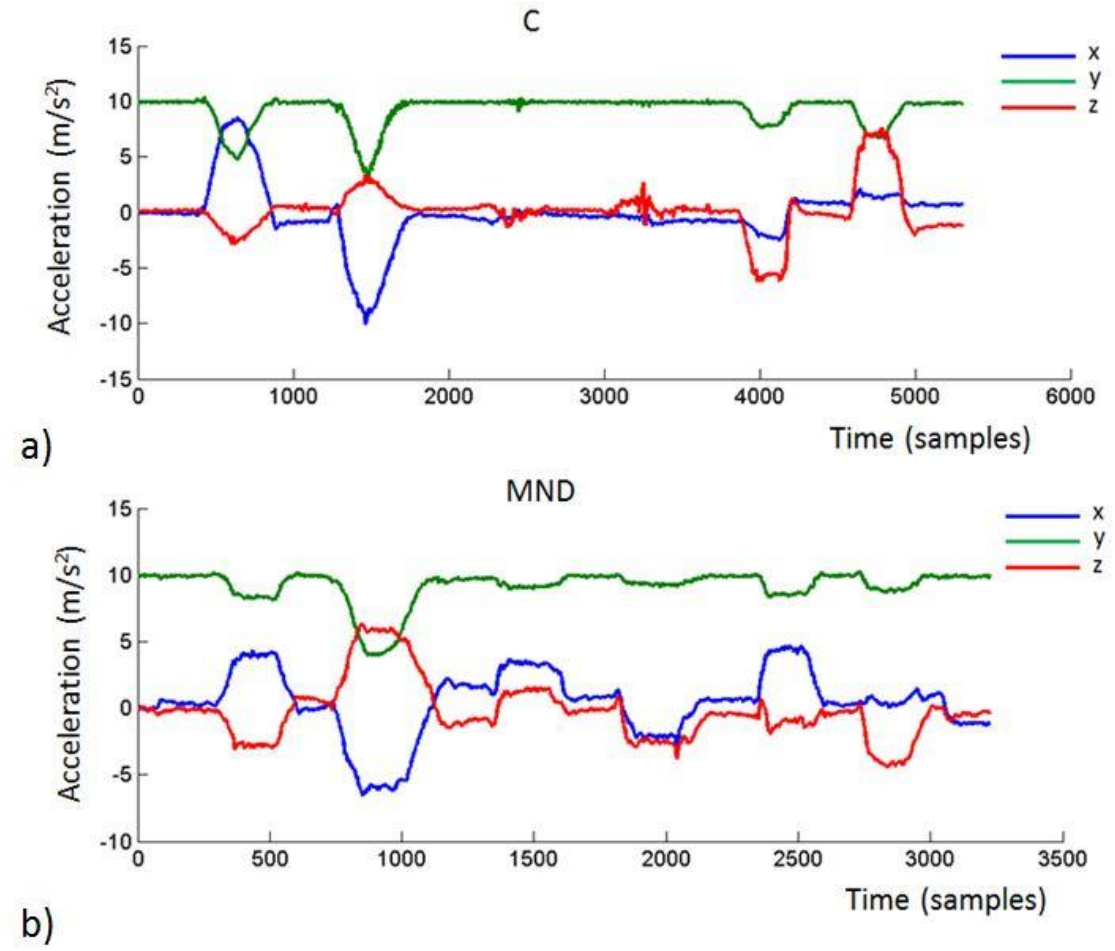


Figure 4-1 Acceleration signal recorded at the forehead level while performing active head movements reaching the maximum amplitude. a) Participant from the control group (C); b) MND patient (MND).

From an initial comparison, it was observed that healthy participants were able to come back to the initial reference position, after having performed the head movements (Figure 4-2a). On the contrary, MND patients seemed to have difficulties in getting back to the initial position (Figure 4-2b)

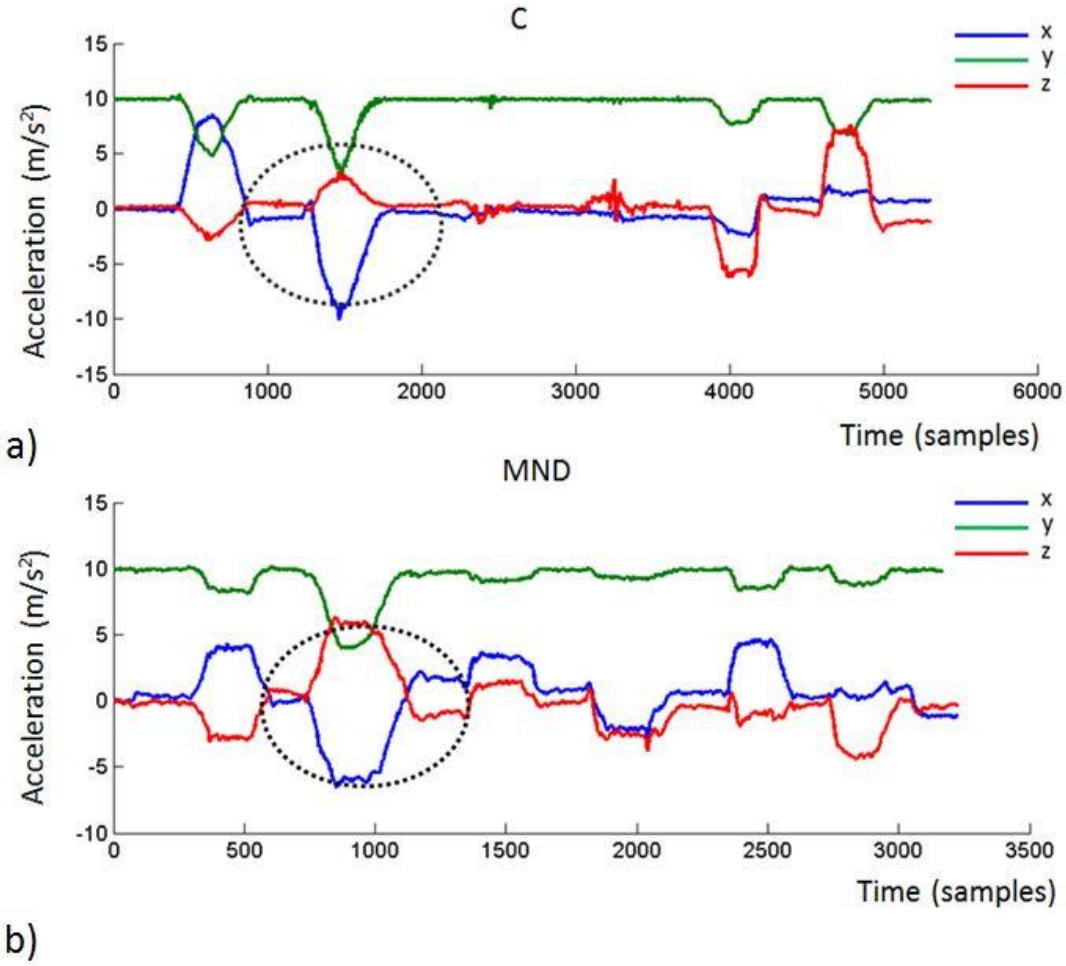


Figure 4-2 Acceleration signal recorded at the forehead level while performing active head movements reaching the maximum amplitude. a) Participant from the control group (C); b) MND patient (MND). The portion of signal highlighted by the circle corresponds to the flexion movement. In graph a) the value of the three components of the acceleration before and after the execution of the movement is similar while in graph b) is significantly different.

Furthermore, healthy participants showed a good stability of the head while executing AR (Figure 4-3a). In fact, since AR is a movement which is not performed against gravity, no relevant variation in the value of the three acceleration components is expected to be observed while executing it. However, looking at typical acceleration signals recorded from a MND patient (Figure 4-3b), a significant variation in the acceleration, especially along the x and z axes, was observed.

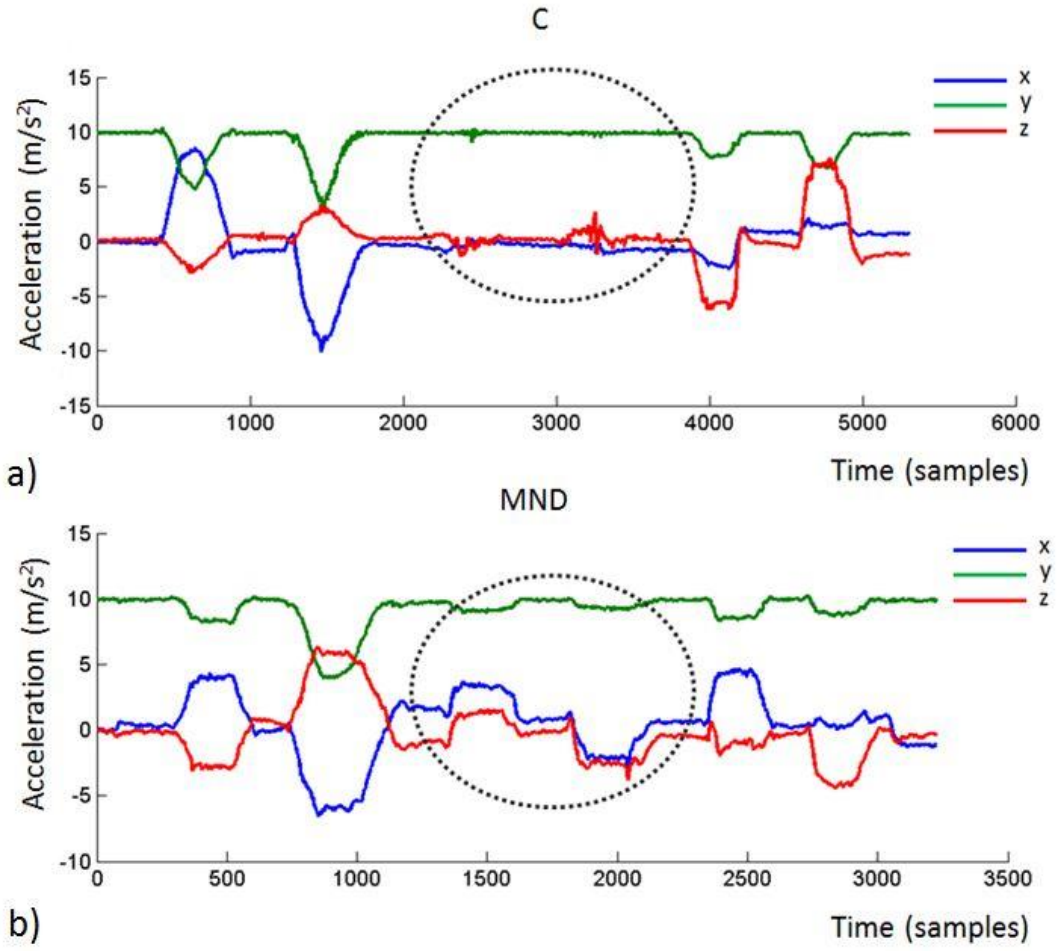


Figure 4-3 Acceleration signal recorded at the forehead level while performing active head movements reaching the maximum amplitude. a) Participant from the control group (C); b) MND patient (MND). The portion of signal highlighted by the circle corresponds to the axial rotation movement (AR). In graph a) there is a very small change in the value of the three components of the acceleration during the execution of AR. In graph b) there is a significant variation in the value of the three components of the acceleration (especially along the x and z axes) during the execution of AR.

Due to the observed poor control of head movements and the consequent inability to come back to the reference position, the drift correction presented in Paragraph 2.3.1.3 couldn't be reliably applied to these signals. Furthermore, since signals were recorded in a clinical setting the use of the magnetometer output was precluded as well, since excessive ferromagnetic disturbances and a variable external magnetic field were present in the recording area. As a consequence, the estimation of angles was significantly affected by the drift introduced by the gyroscope (see Paragraph 1.3.5 for further details) and it was deemed as not acceptable for the purposes of this study. Alternative parameters, directly computed from the measured linear acceleration and

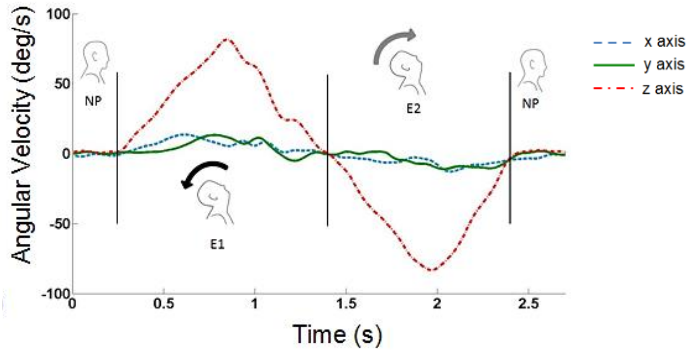
angular velocity and potentially reflecting the clinical characteristics described in the introduction, were thus selected to investigate differences between head movements performed by healthy participants and by patients with MND.

4.3.2 Data analysis and parameters

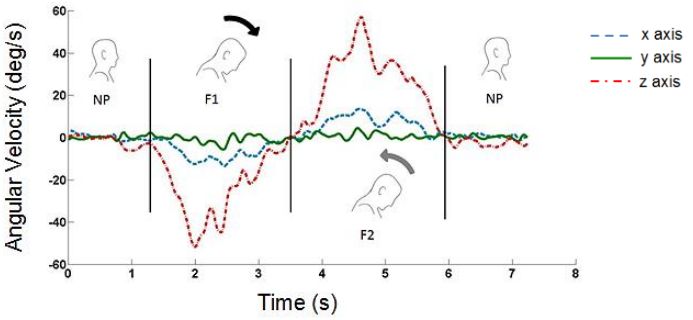
Data were analysed using custom procedures written in MATLAB R2015a. Prior to the analysis, the signals were filtered using a 4th order zero-lag Butterworth filter. The cut-off frequency value was then conservatively set to 10 Hz, after having analysed the frequency content of signals collected, using a procedure similar to the one presented in Section 2.4.1. Thereafter, the reference frames of the sensor placed on the forehead and on the sternum were aligned following the results of the functional calibration, in order to remove the orientation errors associated to their manual placement. Once the two sensor reference frames were aligned, the accelerations and the velocities recorded at the sternum level were subtracted from those recorded at the head level. This enabled movements of the head arising from a movement of the trunk to be isolated and removed [119].

Every movement (M) was sub-divided in two phases: movement away from neutral position (M1) and movement back to neutral position (M2), as they involve different groups of muscles. For each movement the end of the first phase was detected when the angular velocity first crossed the zero (from positive to negative or vice versa, according to the movement), which coincided with the moment when the direction of the movement is reversed (Figure 4-4).

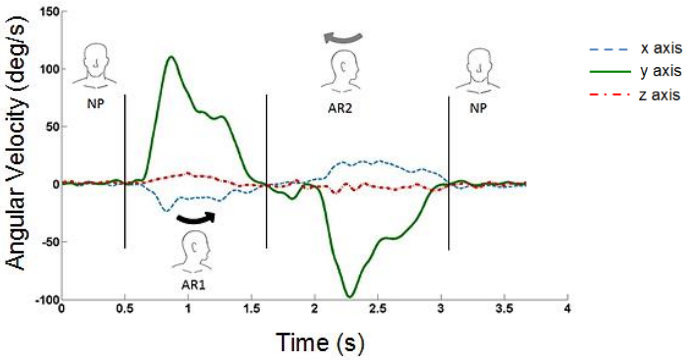
a)



b)



c)



d)

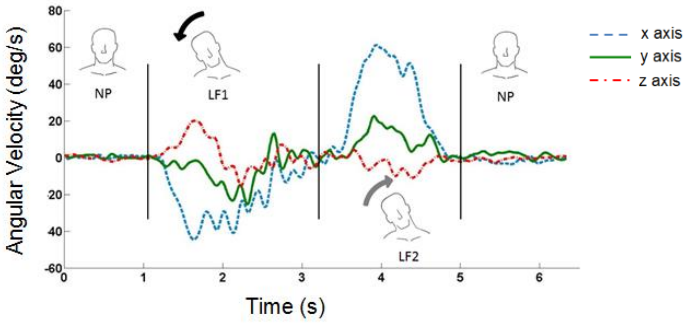


Figure 4-4 Exemplifying angular velocity graphs as measured during head movements in one patient with MND. a) Head extension: the movement starts from the neutral position (NP), then the head is moved backward (E1), from the NP until the neck is fully stretched, and finally forward (E2), back to the initial NP. Corresponding graphs for other movements: b) flexion (F), c) axial rotation (AR), d) lateral flexion (LF).

The following parameters were used to quantify the head movements: mean angular velocity (ω_m), peak angular velocity (ω_p), normalized jerk (NJ), and ratio of movement coupling (RMC). ω_m and ω_p were calculated using the signal recorded by the tri-axial gyroscope. To calculate ω_m the signal was averaged through the duration of the movement while, to evaluate ω_p, its peak value was considered.

The jerk (J) was initially computed as the first time derivative of the linear acceleration measured by the tri-axial accelerometer. Then, a time-integrated squared jerk was calculated and normalized with respect to the mean absolute acceleration and duration of the movement, using the following equation [120]:

$$NJ = \sqrt{\frac{1}{2}\frac{T}{\bar{a}^2}\int J^2(t)dt} \quad , \qquad (4\text{-}1)$$

where T is the duration of the movement and $\bar{a}$ is its mean absolute acceleration. By definition, lower values of NJ are associated with smoother movements [120].

As described in the introduction, a pure primary movement would entail a rotation in only one of the three main anatomical planes. In this case, the direction of the angular velocity would coincide with the direction of the main anatomical axis perpendicular to the anatomical plane in which the movement is performed and the relevant angular velocity signal would be the highest among the three recorded ones. The presence and amount of coupled movements, on the contrary, entails higher values also of the other angular velocity components. The presence of coupled movements was hence quantified using the following ratio:

$$RMC = \frac{A_j + A_k}{A_i}, \qquad (4\text{-}2)$$

where *i* is the axis around which the primary movement is performed, *j* and *k* are the other two main anatomical axes and A_i, A_j, and A_k are the areas under the angular velocity time-curves measured along those axes.

Finally, in order to evaluate the deviation of each specific parameter measured in patients from the reference data obtained in the control group, a Z-score was used, calculated as [119]:

$$Z_{Pi} = \begin{cases} \dfrac{\overline{P_C} - P_i}{\sigma_C} \; for \quad P = RMC, NJ \\ \dfrac{P_i - \overline{P_C}}{\sigma_C} \; for \quad P = \omega_m, \omega_p \end{cases} ; \qquad (4\text{-}3)$$

where P is the parameter of interest, i is the participant and $\overline{P_C}$ and σ_C are the mean and the standard deviation values of the parameter P measured in the control group.

By summing all the scores obtained for different parameters, a composite score (Z_{CS}) was calculated for each patient, as associated to the performance of a specific movement:

$$Z_{CSi} = \sum_P Z_{Pi} \; . \qquad (4\text{-}4)$$

As can be deducted from its formulation, the lowest the Z-score, the more the participant differs from the control group reference value calculated for that movement.

4.4 Statistical analysis

A reliability analysis was performed to check, for each movement and for each parameter, the level of agreement between the repeated tests. A two-way random interclass correlation coefficient (ICC (2, 1)) for a single measurement was used [111]. According to the literature [112], ICC values were interpreted as: good > 0.75, moderate 0.4-0.75, poor < 0.4. For those parameters that showed levels of agreement ranging from moderate to good, values obtained in the three repetitions of the various movements were averaged and retained for further analysis.

Normality of the data was verified for each parameter and movement using a Shapiro-Wilk test and parametric (independent t-test) or non-parametric (Mann-Whitney U-test) tests were then consistently adopted to quantify differences between the two groups. In both cases, statistical significance was set at an alpha level of 0.05. Cohen's d was also computed and used as an indicator of the effect size. According to the interpretation scale reported in literature [113], the effect size was judged as negligible if $d \leq 0.2$, small if $0.2 < d \leq 0.5$, medium if $0.5 < d \leq 0.8$ and large if $d > 0.8$.

Finally, Spearman's rank correlation coefficient (ρ) was calculated to evaluate the relationship between the Z-scores computed for each patient and his/her ALSFRS-R score. Statistical significance for the correlation between the Z-score and the ALSFRS-R score was set at an alpha level of 0.05.

4.5 Results

All participants performed the head movements to reach the maximum amplitude. Among the 13 MND participants, only a subgroup of 9 (5 females, 4 males, age range 45-74 years, ALSFRS-R score 29±11) was able to perform the head movements when asked to reach their maximum speed (See Table 4-1).

ICC values obtained for all movements, in trials performed at both maximum amplitude and maximum speed, are given in Table 4-2 and Table 4-3, respectively. ICC was moderate to good in all movements and for most parameters. In the MND patients the only exceptions were observed for the NJ in extension from neutral position (E1) and in flexion back to neutral position (F2), when performed at maximum speed. In the controls, NJ in the extension from the neutral position (E1) showed a poor agreement, when performed at maximum speed. Those parameters were excluded from further analysis.

Table 4-2 ICC values for mean (ω_m) and peak (ω_p) angular velocity, normalized jerk (NJ) and ratio of movement coupling (RMC). ICC calculated for both MND patients and controls (C) in the Extension (E), Flexion (F), Axial Rotation (AR) and Lateral Flexion (LF) movements performed at maximum amplitude. 1: movement from neutral position; 2: movement back to neutral position.

ICC	Amplitude							
	ω_m		ω_p		NJ		RMC	
	C	MND	C	MND	C	MND	C	MND
E1	0.68	0.57	0.81	0.61	0.41	0.54	0.78	0.78
E2	0.68	0.66	0.63	0.63	0.64	0.56	0.87	0.88
F1	0.71	0.65	0.48	0.65	0.48	0.42	0.87	0.92
F2	0.63	0.59	0.67	0.53	0.52	0.83	0.85	0.94
AR1	0.56	0.61	0.66	0.61	0.74	0.53	0.53	0.92
AR2	0.83	0.69	0.82	0.62	0.57	0.45	0.50	0.69
LF1	0.87	0.69	0.81	0.72	0.84	0.63	0.83	0.57
LF2	0.90	0.87	0.86	0.72	0.65	0.87	0.80	0.78

Table 4-3 ICC values for mean (ω_m) and peak (ω_p) angular velocity, normalized jerk (NJ) and ratio of movement coupling (RMC). ICC calculated for both MND patients and controls (C) in the Extension (E), Flexion (F), Axial Rotation (AR) and Lateral Flexion (LF) movements performed at maximum speed. 1: movement from neutral position; 2: movement back to neutral position.

ICC	Speed							
	ω_m		ω_p		NJ		RMC	
	C	MND	C	MND	C	MND	C	MND
E1	0.69	0.55	0.67	0.79	< 0.40	< 0.40	0.44	0.90
E2	0.76	0.82	0.76	0.88	0.42	0.54	0.96	0.94
F1	0.42	0.65	0.74	0.59	0.48	0.70	0.65	0.89
F2	0.83	0.85	0.80	0.77	0.44	< 0.40	0.67	0.93
AR1	0.63	0.82	0.64	0.82	0.75	0.57	0.65	0.65
AR2	0.59	0.77	0.62	0.78	0.41	0.41	0.50	0.73
LF1	0.84	0.80	0.89	0.80	0.46	0.58	0.67	0.63
LF2	0.94	0.89	0.89	0.82	0.75	0.67	0.57	0.76

A comparison between the typical signals obtained from a control individual and a MND patient (participant Nr 3 in Table 4-1) is shown in Figure 4-5, which illustrates data from an extension of the head from the neutral position (E1), when asked to reach the maximum amplitude. Table 4-4 shows the results obtained for both groups and for all the maximum amplitude movements. ω_m was significantly lower in the patient group in the extension and in the axial rotation both from (E1 and AR1, p=0.012, d>0.8 and p=0.003, d>0.8, respectively) and back (E2 and AR2, p=0.010, d>0.8 and $p < 0.001$, d>0.8, respectively) to the neutral position and also in the lateral flexion back to neutral position (LF2, p=0.009, d>0.8). Similar results were observed in the ω_p, where significantly lower values were measured in the MND group, for the same movements (p<0.05, d>0.8) and for the lateral flexion from neutral position (L1, p=0.048, d=0.8). A significant reduction of movement smoothness was observed in MND patients in the extension (E1: p=0.001, d>0.8 and E2: p=0.034, d>0.8), flexion back to neutral position (F2, p=0.013, d=0.8) and lateral flexion (LF1: p=0.031, d=0.8 and LF2: p=0.016, d>0.8) movements. A higher presence of coupled movements was observed in the MND group in all movements (p<0.05, d≥0.8), except for the lateral flexion from neutral position. As highlighted in Figure 4-6, the inter-patient variability of the RMC values differed between movements, consistently with the variability of the pathology progression.

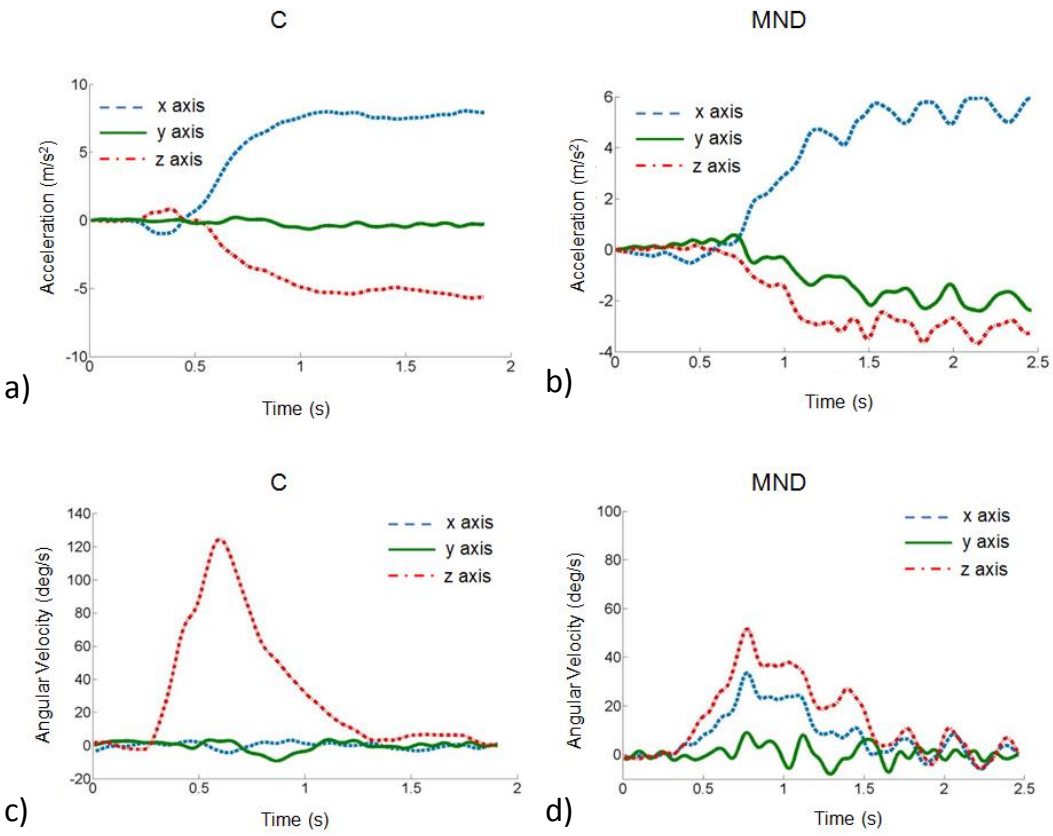


Figure 4-5 Extension from neutral position performed reaching the maximum amplitude. a) and b) Acceleration recorded when the movement was performed by the control individual (C) and the MND patient (MND), respectively. c) and d) Angular velocity recorded when the movement was performed by the control individual (C) and the MND patient (MND), respectively.

Table 4-4 Movements at maximum amplitude. Mean (SD) values for mean (ω_m) and peak (ω_p) angular velocity, normalized jerk (NJ) and ratio of movement coupling (RMC). Values obtained from both MND patients and controls (C) in the Extension (E), Flexion (F), Axial Rotation (AR) and Lateral Flexion (LF) movements. 1: movement from neutral position; 2: movement back to neutral position. (*) Level of significance for the difference between MND and C <0.05. (**) Level of significance for the difference between MND and C <0.001.

Movements Max Amplitude	Mean Ang. Velocity (deg/s)		Peak Ang. Velocity (deg/s)		NJ		RMC	
	C	MND	C	MND	C	MND	C	MND
E1	31 (12)	20 (8)*	67 (27)	46 (20)*	2.1 (0.3)	3.8 (2.2)*	0.25 (0.09)	0.45 (0.26)*
E2	40 (11)	29 (10)*	75 (23)	58 (16)*	2.3 (0.5)	2.9 (0.8)*	0.24 (0.08)	0.43 (0.20)*
F1	36 (11)	34 (17)	77 (22)	73 (33)	2.5 (0.6)	3.0 (1.4)	0.23 (0.09)	0.48 (0.30)*
F2	42 (8)	34 (13)	86 (25)	69 (27)	2.1 (0.4)	3.0 (1.5)*	0.22 (0.06)	0.44 (0.19)*
AR1	49 (14)	32 (11)*	110 (33)	73 (20)*	5.1 (2.6)	5.5 (2.2)	0.26 (0.11)	0.48 (0.20)*
AR2	61 (20)	36 (10)**	109 (34)	74 (16)*	5.3 (1.8)	5.6 (2.1)	0.23 (0.09)	0.55 (0.42)*
LF1	29 (12)	23 (9)	68 (25)	51 (20)*	3.1 (1.0)	4.1 (1.4)*	1.08 (0.70)	1.22 (0.38)
LF2	40 (15)	27 (10)*	77 (28)	52 (16)*	2.6 (0.8)	3.6 (1.2)*	0.84 (0.50)	1.33 (0.73)*

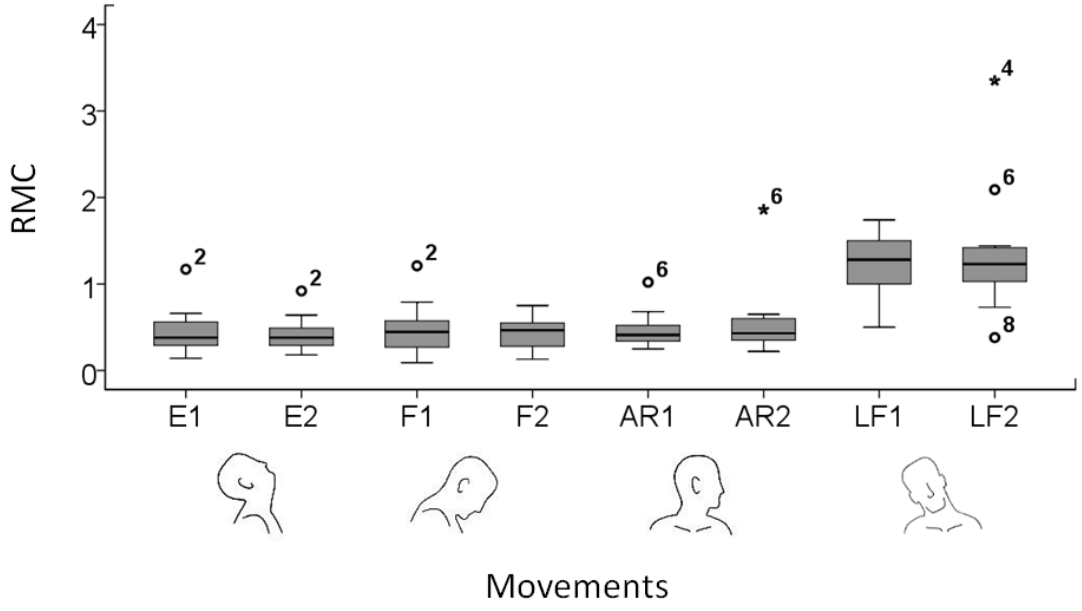


Figure 4-6 Ratio of movement coupling (RMC) values measured in movements executed by MND patients reaching the maximum amplitude. Movements performed: Extension (E), Flexion (F), Axial Rotation (AR) and Lateral Flexion (LF). 1: movement from neutral position; 2: movement back to neutral position. Values are presented through the median, upper and lower quartiles and whiskers. The whiskers extend from the upper and lower edge of the box to the highest and lowest values which are no greater than 1.5 times the interquartile range. Outliers (cases with values between 1.5 and 3 times the interquartile range) and extreme outliers (cases with values more than 3 times the

interquartile range) are represented by circle and stars, respectively. Number above the outlier indicates the patient associated to that value.

The results concerning the trials performed reaching the maximum speed, are shown in Table 4-5 for both groups. The ω_m and ω_p were significantly lower (p<0.05, d>0.8) in the MND group in extension, axial rotation and lateral flexion from the neutral position (see values in Table 4-5). The most significant difference was observed in the axial rotation from and back to the neutral position, where values measured in MND were almost half those measured in the control group, both for the ω_m and the ω_p. Movement performed by the MND group did not show a significant reduction (p>0.05) of movement smoothness in none of the movements performed, while the presence of coupled movements was significantly higher (p<0.05, d>0.8) in the flexion and in the axial rotation movements, both from and back to the neutral position.

Table 4-5 Movements at maximum speed. Mean (SD) values for mean (ω_m) and peak (ω_p) angular velocity, normalized jerk (NJ), and ratio of movement coupling (RMC). Values obtained from both MND patients and controls (C) in the Extension (E), Flexion (F), Axial Rotation (AR) and Lateral Flexion (LF) movements. 1: movement from neutral position; 2: movement back to neutral position. (*) Level of significance for the difference between MND and C <0.05. (**) Level of significance for the difference between MND and C <0.001.

Movements Max Speed	Mean Ang. Velocity (deg/s)		Peak Ang. Velocity (deg/s)		NJ		RMC	
	C	MND	C	MND	C	MND	C	MND
E1	80 (28)	45 (12)*	163 (55)	93 (26)*	-		0.26 (0.11)	0.42 (0.17)
E2	87 (28)	57 (20)*	170 (58)	108 (44)*	2.3 (0.5)	2.1 (0.3)	0.24 (0.13)	0.37 (0.13)
F1	91 (16)	77 (25)	176 (35)	147 (37)	2.5 (0.4)	2.5 (0.4)	0.24 (0.09)	0.49 (0.35)*
F2	87 (36)	63 (25)	159 (59)	123 (48)	2.3 (0.5)	-	0.22 (0.06)	0.47 (0.27)*
AR1	136 (40)	73 (17)*	263 (68)	147 (27)*	3.9 (1.7)	3.4 (0.5)	0.24 (0.06)	0.45 (0.12)**
AR2	122 (30)	63 (20)**	223 (58)	121 (34)**	3.6 (0.6)	3.8 (0.9)	0.25 (0.05)	0.45 (0.11)*
LF1	64 (28)	39 (13)*	131 (53)	84 (27)*	3.2 (0.8)	3.3 (0.5)	1.05 (0.53)	1.30 (0.59)
LF2	66 (28)	44 (16)	126 (49)	86 (26)	2.8 (0.6)	3.3 (0.9)	0.91 (0.47)	1.20 (0.55)

Figure 4-7a exemplifies the Z_{CS} values obtained for the E1 movement in the maximum amplitude task. Figure 4-7b shows the Z_{CS} obtained for each patient in E1, performed reaching the maximum amplitude, as a function of the patient's ALSFRS-R scores. The evident absence of a correlation between the two quantities was confirmed by the non-significance (p=0.548) of the Spearman correlation coefficient.

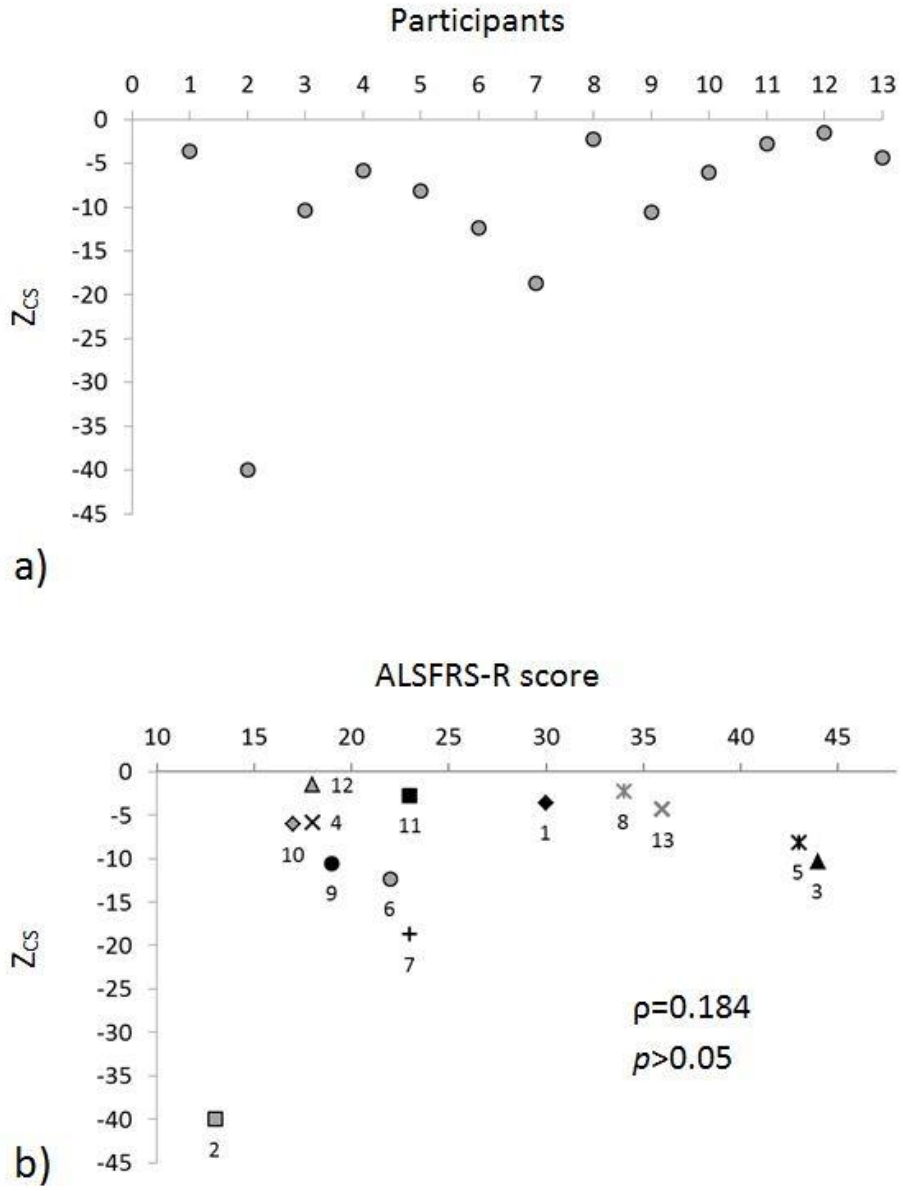


Figure 4-7 Composite score (Z_{CS}). a) Z_{CS} calculated during the extension from neutral position (E1) movement, reaching the maximum amplitude. b) Z_{CS} calculated in E1 movement plotted against the ALSFRS-R score given to participants at the time of recording. Numbers close to the markers indicate the participant associated to those Z and ALSFRS-R scores. ρ= Spearman's rank correlation coefficient. Level of significance for the correlation between Z_{CS} and ALSFRS-R score: $p<0.05$.

4.6 Discussion

The aim of this study was to quantitatively characterise head movements with regard to velocity, smoothness and coupling in MND compared to aged matched controls.

The new protocol specifically developed to evaluate the ability to perform head movements and validated on healthy individuals proved to be suitable to be applied also in a clinical contest. IMUs were easily placed on patients and didn't limit them in performing the experimental protocol. Tasks selected appeared suitable to be executed in a clinical setting and were highly informative.

Despite the relatively small number of participants enrolled in this study, reported results demonstrated a reduced ability of patients tested to perform head movements. In particular, the observed movements in MND, when performed at a self-selected speed, appeared to be characterized by a reduced mean and peak velocity and a reduced smoothness in a subset of movements and a higher presence of coupling movements in almost all the movements, compared to controls. In order to generalize the encouraging results obtained in the small sample of patients tested and draw stronger conclusions on the clinical meaning of the proposed method, further studies involving a larger number of patients are needed.

Despite their limited ability, the patients managed to perform the chosen tests, which were minimally invasive for them. The level of agreement between the three repetitions performed for each movement and parameter was satisfactory overall, with ICC values ranging from moderate to high, except in a few cases. This is a very encouraging result and supports progression towards the definition of a reliable quantitative approach to overcome the current limitations of the MMT and HHD, reported in the introduction. In addition, the proposed approach might be used to measure specific neck muscle impairment, currently not provided by clinical scales such as the ALSFRS-R, which could be used in the longitudinal assessment of changes or to drive personalised intervention, such as the choice of a cervical orthosis.

Mean and peak velocities were significantly reduced in the MND group in a subset of movements in trials at maximum amplitude and in trials at maximum speed. Those results confirmed that angular velocity is a viable parameter to identify and quantify movement impairment in MND patients, as previously reported in patients affected by cervical dystonia [54]. The reduction of velocity is likely to be multi-factorial, relating to both muscle weakness and tone change. In addition, compensatory movement strategies developed to avoid the loss of cervical stability, using an avoidance

behaviour similar to that observed in individuals affected by chronic musculoskeletal pain, may be occurring [121]. Further studies are needed to understand better the degree and relative impact of muscle weakness and tone change and to investigate these hypotheses.

The movements performed by the MND patients, when reaching the maximum amplitude, were significantly less smooth in extension, flexion back to neutral position and lateral flexion, as illustrated by the curves presented in Figure 4-5a and Figure 4-5b. These data highlight how the acceleration signal is more jagged when the movement is performed by a patient with MND and confirm the presence of impaired movement coordination. The overall jerkier movements observed in patients with MND were similar to those reported previously for other neurological conditions such as Parkinson's disease [62] and multiple sclerosis [119]. In MND patients that participated in this study reduced coordination was, on average, only observed in a subset of movements, possibly providing an indication of the group of muscles that were more compromised. Results obtained from the participants were consistent with a significant functional deterioration of neck extensor muscles, as reported in literature for patients with MND [27]. Results obtained support the hypothesis that jerkier movements could be associated with motor control strategies characterized by continuous feedback corrections, caused by an alteration of the proprioceptive input or of the feedforward control mechanisms [55]. This seems to be compatible with the nature of MND, the major impact of which is a reduced ability to initiate and control muscle movements. Additional studies, possibly involving also upper and lower limbs movements, would help to further investigate these hypotheses.

The smoothness results obtained in trials performed reaching the maximum amplitude were not confirmed in trials performed reaching the maximum speed. The presence of lower jerk values in movement performed at higher speed was consistent with experimental values found in previous studies [122]. The different results obtained could be also attributable to the different level of ability of the MND patients that performed the faster movements (see Table 4-1), who were considered to be less impaired, compared to those that were able to perform only movements at maximum amplitude. An independent objective quantification of the residual patient ability,

however, was not available and further studies are hence needed to verify this hypothesis.

Values obtained for the RMC in trials at maximum amplitude showed a higher presence of coupled movements when the exercises were performed by MND patients, as can be observed by comparing two typical angular velocity signals from a control individual and an MND patient (Figure 4-5c and Figure 4-5d, respectively). Increased coupled movements could be caused by an alteration of central motor control and/or by the degenerative process that involves neck muscles with a consequent adoption of compensating movement strategies to maintain the orientation of the head. Both the alteration of the central motor control and the degeneration of neck muscles, in fact, have been previously reported in MND patients [123]. The variability of these degenerative processes might indeed be directly associated with the observed RMC inter-patient variability. The absence of a significant difference between MND patients and the control group in lateral flexion from the neutral position is most likely due to the characteristics of the movement itself, which has been shown to be associated with an axial rotation movement also in healthy participants [124] [56]. The trials at maximum speed were performed similarly by the two groups, except for the flexion and the axial rotation movements. This may well be due to the fact that only the patients with less severe deficits managed to perform these tests.

In addition, looking at Figure 4-6, it can be noticed that some of the patients presented different abilities in performing different movements. An example is represented by patient 2, who presented a poor control in performing the extension and the flexion movements which was not observed in performing the axial rotation and the lateral flexion. On the contrary, axial rotation and lateral flexion performed by patient 6 were characterized by a high presence of coupled movements which was not observed in extension and flexion. The high intra-patient variability observed in the group tested supports the need for a personalized intervention able to sustain different movements in different subjects.

The composite Z score here proposed can be used for comparison between participants and also to quantify the (dis)similarity between the quantities measured in

patients and the reference values obtained for the control group. Using this score, for example, it was possible to clearly classify patients according to their ability to perform the extension movement (E1, Figure 4-7a). Although, for the sake of conciseness, only the result for one movement are shown, the score here proposed might be used to objectively rate and classify patients according to their ability to control their head movements and monitor relevant changes in time and/or after an intervention. Further studies, including longitudinal data from larger groups, are indeed needed to build a larger reference dataset and validate this approach. From the comparison between the Z-score and the ALSFRS-R score the absence of a correlation emerged. The ALSFRS-R score has been proved to be adequate to catch the overall condition of patients [6] but, due to its design, it has also been shown as inadequate to accurately describe functional loss in performing arm movements [9]. The somehow expected lack of correlation between the Z-score and the ALSFRS-R score shows that the latter cannot be used to quantify functional loss in head movements. Although, the small sample size limits the possibility to draw general conclusions, this result supports the need for a quantitative clinical scale able to detect small but potentially significant functional loss in patients with MND and paves the way for further research in this direction.

The main limitation of this study is represented by the small group of patients involved. This is a drawback of working with patients affected by a rare disease. In addition, not all patients affected by MND develop neck muscle weakness which further reduces the number of individuals matching the including criteria. The recruitment of 13 patients required approximately six months. To overcome this limitation a multi-centre study could be conducted. This was beyond the purposes of this project but it can represent a further development of this study and will be included and discussed in a later section about future research (Chapter 6).

4.7 Conclusions

The reported results demonstrate that head movements in MND patients, compared to age–matched controls, are characterized by reduced smoothness and velocity and by increased presence of coupling movements, which are consistent with weakness of neck extensor muscles. The ratio of movement coupling described in this

study is a viable functional parameter and paves the way for future investigations to quantify functional impairment in other body areas (e.g. upper and lower limbs). Further work involving different body areas and correlation with existing methods of evaluating neuromuscular function, such as dynamometry and EMG, is needed to explore the use of this approach as a marker of disease progression in MND. Finally, the high intra-patient variability observed in the group tested, supported the need for a personalized intervention able to compensate for specific functional loss developed by each patient. The next step of the work was then to investigate whether a customizable device, such as the Sheffield Support Snood, was able to satisfy the specific needs of each patient and to help compensate for those functional losses observed in this study. In order to perform this assessment, the same protocol used in this study was performed by the same group of patients while wearing the newly developed orthosis. Since head movements executed at maximum speed required a significant effort to patients without providing additional information with respect to movements performed reaching the maximum amplitude, they were removed from the protocol. Similarly, since the evaluation of mean and peak angular velocities provided analogous results only the assessment of mean angular velocity was considered in the successive study, which is extensively described in Chapter 5.

Chapter 5

Efficacy of the Sheffield Support Snood in facilitating functional head movements in patients with Motor Neurone Disease

5.1 Introduction

As observed in the study described in Chapter 4, patients with MND tend to execute head movements at a slower velocity and in a less smooth fashion compared to age-matched healthy subjects. In addition, in these patients, the movements of flexion-extension, axial-rotation and lateral flexion of the neck are characterized by a high presence of “coupled movements”.

Patients affected by MND that experience neck muscle weakness are advised to wear a cervical orthosis in order to improve their posture, their ability to communicate and to perform daily activities. However, most commonly adopted cervical orthoses are inadequate to offer the proper support and are often rejected by the patients [82]. The main drawback of those orthoses is that they have been designed for different pathological conditions. This makes them, either not supportive enough, or too much restrictive and thus uncomfortable when worn for a long time. The results reported in Chapter 4 highlighted a high inter and intra-patient variability in the ability to perform the various movements, which suggests the need for personalized interventions. The devices currently available, however, do not allow for much customization. They often come in two/three different sizes (small, medium, large) and their configuration can’t be modified according to the anatomy or functional needs of the specific patient.

The Sheffield Support Snood is a cervical orthosis which has been specifically developed for neurological patients affected by neck muscle weakness. The orthosis consists of a snood-like base, made of stretchable fabric, on which various support structures can be attached. These structures can be placed in any position in order to adapt the support offered according to the task performed and to the patients' level of functional limitation [28].

The assessment of the SSS described in Chapter 3, was the first attempt to objectively quantify the amount of support that the orthosis can provide. That study showed, in particular, that the SSS is effective in supporting selected targeted head movements without limiting the others and that it can provide a mechanical support comparable to that of bulkier orthoses commonly used by MND patients [125]. The acceptability of the SSS has also been evaluated through questionnaires by a group of patients with MND, who reported among its main beneficial features the ability to provide support while allowing a satisfactory range of motion, the flexibility in use, the appearance and the comfort offered [28]. However, the effectiveness of the SSS in improving the quality of the head movements for MND patients has not been quantitatively investigated yet.

The aim of the study presented in this Chapter was to perform a quantitative evaluation of the effects of the SSS on the ability to perform head movements in patients affected by neck muscle weakness due to MND. In particular, leveraging on the results obtained from the quantification of the MND related movement limitations observed in Chapter 4, this study aimed to establish whether the new orthosis was able to facilitate more controlled and less coupled movements of the head, without limiting the natural velocity at which movements were performed or decreasing the smoothness of the movements.

5.2 Methods

5.2.1 Participants

The same group of patients involved in the work described in Chapter 4 was included in this study. All the participants were informed about the protocol through

an information sheet and provided written consent prior to the participation in the study, which was approved by the local ethics committee (REC project number STH18733).

5.2.2 Experimental Protocol

Participants were asked to perform a series of AHM following the protocol presented in Chapter 2 and amended according to the successive studies. They were instructed to start from a neutral position (NP, maintaining an upright head position and looking forwards), then perform an extension (E), a flexion (F), an axial rotation (AR, both on the left and right side) and a lateral flexion (LF, both on the left and right side) of the head, moving it as far away as possible from the neutral position. Before the actual acquisition session, participants performed the whole range of head movements at least once in order to familiarize themselves with the test procedure and to stretch the neck muscles. Movements were performed while wearing the SSS. The orthosis was fitted by a trained operator, according to the needs of each patient and to their instructions (see Table 5-1 for details). The patients were allowed to try different configurations of the SSS until when they felt that the orthosis was offering the support they needed. Data were collected in the same session where the measurements without orthosis were taken (Chapter 4).

Participants were asked to perform three repetitions of each movement, if able to, otherwise to stop once they felt too tired to complete the task. Finally, patients with a safe swallow were asked to perform three activities of daily living: eating, drinking and washing hands, while wearing the SSS. Those who were not able to eat and/or drink by themselves were helped by the operator or by a caregiver. A summary of the main characteristics of patients has already been reported in Table 4-1, while a summary of the orthosis used and the activities performed by each subject is shown in Table 5-1.

Table 5-1 Participants' characteristics. Orthosis currently used (NA: no orthosis used at the time of recording), number and type of SSS supports used, head movements and daily activities performed, reported in table. All= participant performed: extension, flexion, axial rotation and lateral flexion. y= yes, the patient was able to perform the task, n= no, the patient wasn't able to perform the task.

Participant (P)	Cervical orthosis currently used	SSS: number and type of supports used	Head movements	Eating	Drinking	Washing
1	Soft Orthosis	2 frontal	All	y	y	y
2	SSS	2 frontal, 2 lateral	All	n	n	n
3	Headmaster	2 frontal	All	y	y	y
4	NA	2 posterior	All	y	y	n
5	NA	2 frontal	All	y	y	y
6	Headmaster	2 frontal, 2 lateral	All	y	y	n
7	Soft Orthosis	2 frontal	All	n	n	n
8	Soft Orthosis	no supports, only snood	All	y	y	n
9	Soft Orthosis	2 frontal	All	n	y	n
10	Soft Orthosis	2 posterior	All	n	n	n
11	Soft Orthosis	2 frontal	No flexion without orthosis	y	n	n
12	NA	2 frontal	All	y	y	n
13	NA	no supports, only snood	All	y	y	y

As per the previous experiments, two IMUs were firmly attached to the forehead and sternum of each participant, using double-sided tape and a functional calibration procedure, was performed to ensure proper alignment of the reference system (Chapter 2).

After the recording session, participants were asked to fill three short questionnaires (see Appendix C for details) to give their feedback about aspects of the orthosis tested. The first questionnaire assessed the participants' perception about performing head movements and daily activities with the SSS. It was made up of six statements. Participants were asked to express their level of agreement to each statement using a 7-point scale, ranging from "strongly disagree" to "strongly agree". The second questionnaire compared the SSS with the orthosis the participant was currently using, if applicable. It was made up of 4 statements and used a five-point scale ranging from "much worse than with the device I'm currently using" to "much better than with the device I'm currently using". The third questionnaire compared the participants' perception about performing head movements and daily activities with the SSS and without any orthosis. It was made up of 4 statements and used a five-point scale

ranging from “much worse than in the no-collar condition” to “much better than in the no-collar condition”. Questionnaires were designed on purpose for this study.

5.2.3 Data Processing

All data were processed using custom procedures written in MATLAB R2015a. Data were filtered using a 4th order zero-lag Butterworth filter with a cut-off frequency of 10 Hz, conservatively selected after having examined the frequency content of the recorded signals, using a procedure analogous to the one described in Paragraph 2.4.1. The accelerations and angular velocities recorded at the sternum were subtracted from those recorded at the head, to identify and exclude from the analysis those movements of the head that were only a consequence of movements of the trunk.

Every movement was sub-divided in two phases: phase 1, from neutral position NP until the neck had reached the end of the possible range of movement and phase 2, from the end position back to NP, following the same procedure described in Chapter 4. Those two phases were identified and analysed separately since they typically involve different group of muscles. For example, if the extension movement is considered, the primary muscles responsible for the first phase of the head extension (E1) are the trapezius, the splenius cervicis and the spinalis and semispinalis capitis. Secondary muscles are the small short muscles of the head and neck known as the intrinsic neck muscles. The muscle primarily responsible for the second phase of the extension movement (E2), which can be assimilated to a flexion movement, is the sternocleidomastoid muscle together with the trapezius, longus colli, longus capitis and anterior rectus capitis [126]. These observations can be extended to the flexion, axial rotation and lateral flexion movements. As a consequence, 1 and 2 can be considered two different movements that could be differently affected by the use of a support. For each movement the two phases were identified by detecting the instant when the angular velocity crossed the zero value, which coincided with the moment when the direction of the movement was reversed (see Figure 4-4).

The mean angular velocity (ω_m) was calculated by averaging the signal recorded by the tri-axial gyroscope over the duration of the movement. The normalized jerk (NJ) was

calculated using the equation (4-1) while the ratio of movement coupling (RMC) was calculated using the equation (4-2).

In addition, the Z score associated to the performance of each specific movement was calculated using equation (4-3) for each of the parameters considered in the analysis ($\omega_{m,}$ NJ and RMC). By summing all the scores obtained for the different parameters, a composite score (Z_{CS}) was calculated using equation (4-4).

5.2.4 Statistical analysis

The repeatability of the ω_m, NJ and RMC values over the three trials was verified, for both conditions, by using a two-way random interclass correlation coefficient (ICC (2, 1)) for a single measurement [111]. According to the literature, ICC values were interpreted as: good > 0.75, moderate 0.4-0.75 and poor < 0.4 [112].

To assess the effect of the orthosis, a first level of analysis was performed by averaging, for each movement, the values obtained in its three repetitions. Differences between the parameter measured with and without the SSS were assessed by using a paired samples t-test or a Mann-Whitney U-test according to the normality or non-normality of data, as verified using a Shapiro-Wilk test. Cohen's d was also calculated as an indicator of the effect size. The effect size was considered negligible when $d \leq 0.2$, small when $0.2 < d \leq 0.5$, medium when $0.5 < d \leq 0.8$ and large when $d > 0.8$ [113]. A second level analysis was carried out by looking in details at the RMC values measured during the three repetitions for each subject and for each movement.

Finally, levels of agreement or disagreement with statements given in the questionnaires were evaluated. To this purpose, participants' answers related to their perceptions were coded from 0 (worst perception) to 7 (best perception) for the first questionnaire and from 0 (worst perception) to 5 (best perception) for the second and the third questionnaires.

5.3 Results

The adopted configuration of the SSS was different among participants, ranging from a minimally restrictive (only snood) to a highly supportive setting (2 frontal and 2

lateral supports). The most frequently used supports were the two frontal Z-supports, chosen by 9 participants. All participants were able to perform the head movements, nine of them were able to perform also the eating and the drinking activities and four of them were able to perform also the washing task.

Scores based on the participant's perceptions about the SSS are summarized in Table 5-2 and Table 5-3**Error! Reference source not found.**. The SSS was reported to offer support (mean score 6.5 out of 7) without restricting the natural breathing (mean score 6.5 out of 7) and the natural swallowing (mean score 6.5 out of 7) and without impeding eating (mean score 6.4 out of 7) and drinking (mean score 6.3 out of 7). A slightly lower score (mean: 5.9 out of 7) was observed when participants rated the range of head movements allowed by the orthosis, although no negative feedback was registered (range 5-7). The feedback was positive when participants were asked to compare the SSS to the orthosis they were using at the time of the study (Table 5-3), especially in performing the head movements (score 4.6 out of 5). Finally, a positive but lower score was associated both to head movements and daily activities performed wearing the SSS when compared to the same tasks performed without the orthosis (see values in Table 5-3).

Table 5-2 Statements related to the overall participants' perceptions about the SSS. Mean and range values for the score obtained by each statement, according to the coding explained in the legend.

Statement	n	Mean score	Range score
SSS offered support	13	6.5	(6-7)
SSS allows a completely free range of head movement	13	5.9	(5-7)
SSS caused no restrictions to natural breathing	13	6.5	(6-7)
SSS caused no difficulties eating a meal	9	6.4	(5-7)
SSS caused no problems drinking	9	6.3	(3-7)
SSS caused no restrictions to natural swallowing	12	6.5	(6-7)

Score legend:
7 Strongly Agree
6 Agree
5 Agree Somewhat
4 Neither Agree or Disagree
3 Disagree Somewhat
2 Disagree
1 Strongly Disagree

Table 5-3 Statements related to the comparison between the SSS and the orthosis currently used by the participant and between movements performed with the SSS and without any orthosis. Mean and range values for the score obtained by each statement, according to the coding explained in the legends.

Statement	n	Mean score	Range score	n	Mean score	Range score
Performing the head movements with the SSS was:	9	4.6	(4-5)	13	3.8	(2-5)
Performing the eating task with the SSS was:	5	4.3	(3-5)	9	3.4	(2-5)
Performing the drinking task with the SSS was:	5	3.8	(2-5)	9	3.4	(2-4)
Performing the washing task with the SSS was:	2	4.0	(3-5)	5	3.2	(2-4)
	Score legend: 5 Much better than with the device I currently use 4 Better than with the device I currently use 3 Almost the same as with the device I currently use 2 A little worse than with the device I currently use 1 Much worse than with the device I currently use			Score legend: 5 Much better than without orhtosis 4 Better than without orhtosis 3 Almost the same as without orhtosis 2 A little worse than without orhtosis 1 Much worse than without orhtosis		

For ω_m, a moderate to good ICC was observed (Table 5-4). ICC for the NJ was moderate to good in all movements except in E2, where a poor correlation was observed. Consequently, data from this parameter in this movement were excluded from further analysis. ICC for the RMC was good in all movements except in AR2 and LF1, where a moderate ICC was found.

Table 5-4 ICC values for the mean angular velocity (ω_m), normalized jerk (NJ) and ratio of movement coupling (RMC). ICC measured with the SSS in the Extension (E) Flexion (F), Axial Rotation (AR) and Lateral Flexion (LF) movements. 1: movement from neutral position; 2: movement back to neutral position.

ICC			
	ω_m	NJ	RMC
E1	0.72	0.49	0.85
E2	0.52	<0.4	0.88
F1	0.87	0.72	0.95
F2	0.55	0.63	0.97
AR1	0.76	0.76	0.92
AR2	0.71	0.55	0.83
LF1	0.80	0.54	0.68
LF2	0.80	0.45	0.83

Figure 5-1 shows the results obtained for the angular velocity ω_m. The calculated data were normally distributed, and differences between the two groups were hence assessed using a t-test. For each movement, the average value among the three

repetitions performed by each patient was considered in the analysis. As can be observed from the graph, no evident trend could be observed and no significant differences were found between the two groups.

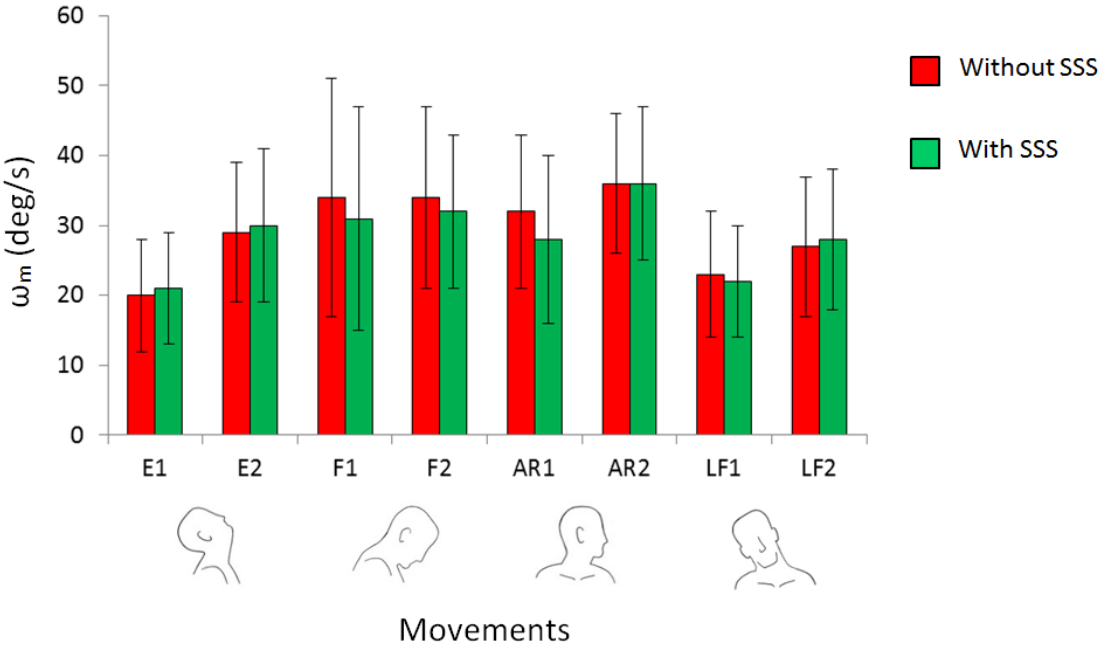


Figure 5-1 Mean angular velocity (ω_m) measured when movements were performed without and with the SSS. Values measured in the Extension (E) Flexion (F), Axial Rotation (AR) and Lateral Flexion (LF) movements (1: movement from neutral position; 2: movement back to neutral position). Values are presented through their mean and standard deviation. Statistical comparison is not reported since the differences were never significant. Values measured without orthosis were taken from the study described in Chapter 4.

Figure 5-2 shows the results obtained for the normalized jerk. The calculated data were not normally distributed, thus differences between the two groups were assessed using the Mann-Whitney U-test. For each movement, the average value among the three repetitions performed by each patient was considered in the analysis. As can be observed from the graph, no significant differences were found between the two groups in any of the movements performed.

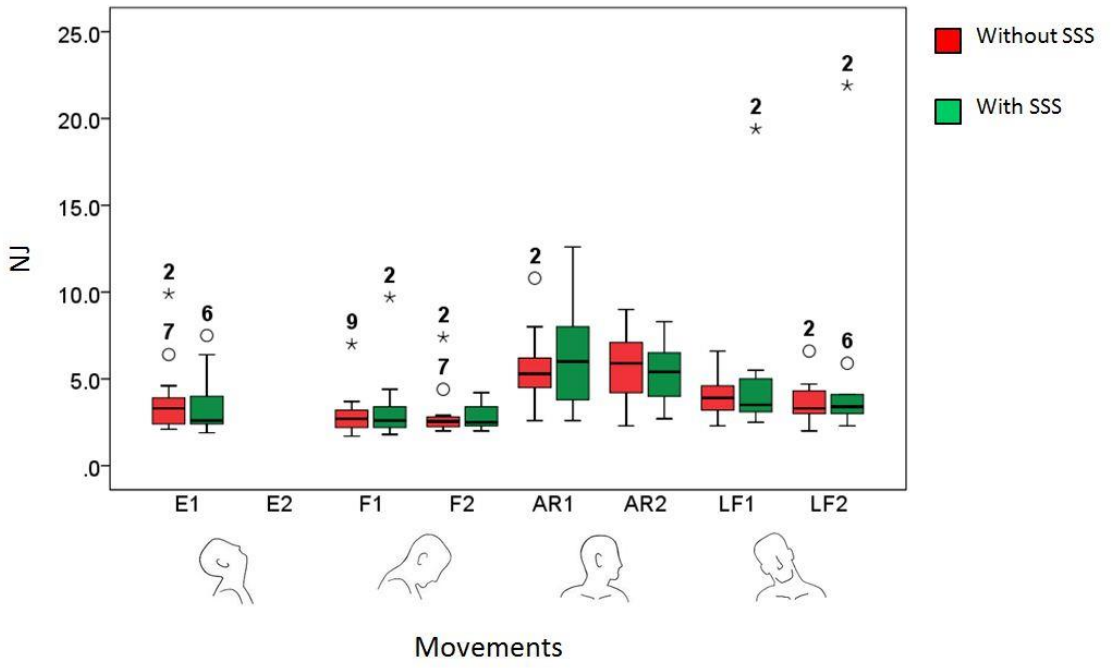


Figure 5-2 Normalized jerk (NJ) measured when movements were performed without and with the SSS. Values measured in the Extension (E) Flexion (F), Axial Rotation (AR) and Lateral Flexion (LF) movements (1: movement from neutral position; 2: movement back to neutral position). Values are presented through the median, upper and lower quartiles and whiskers. The whiskers extend from the upper and lower edge of the box to the highest and lowest values which are no greater than 1.5 times the interquartile range. Outliers (cases with values between 1.5 and 3 times the interquartile range) and extreme outliers (cases with values more than 3 times the interquartile range) are represented by circle and stars, respectively. Number above the outlier indicates the patient associated to that value. (*) Level of significance for the difference between trials performed without and with the SSS <0.05. Values measured without orthosis were taken from the study described in Chapter 4.

Figure 5-3 shows the average value of RMC among three repetitions, calculated when the movements were performed with and without the SSS. Data were not normally distributed thus differences between the two groups were assessed using the Mann-Whitney U-test. A reduced number of outliers was observed in movements executed with the SSS, except in the axial rotation. A significant reduction of coupled movements was observed in lateral flexion back to the neutral position (L2, p=0.013, d=0.72).

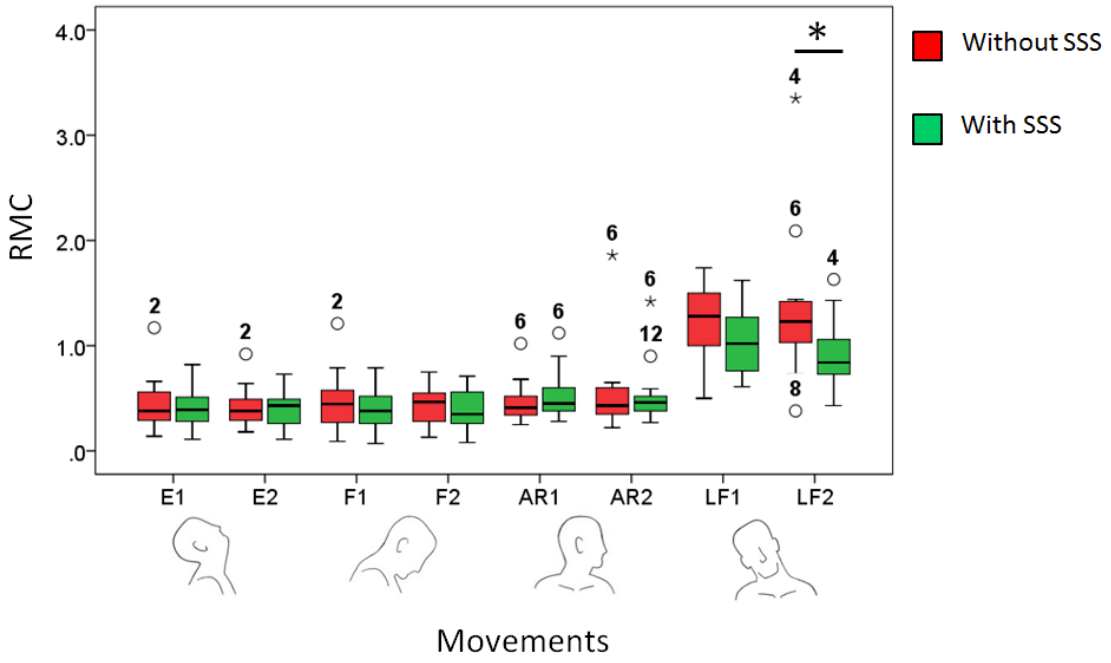


Figure 5-3 Ratio of movement coupling (RMC) measured when movements were performed with and without the SSS. Values measured in the Extension (E) Flexion (F), Axial Rotation (AR) and Lateral Flexion (LF) movements (1: movement from neutral position; 2: movement back to neutral position). Values are presented through the median, upper and lower quartiles and whiskers. The whiskers extend from the upper and lower edge of the box to the highest and lowest values which are no greater than 1.5 times the interquartile range. Outliers (cases with values between 1.5 and 3 times the interquartile range) and extreme outliers (cases with values more than 3 times the interquartile range) are represented by circle and stars, respectively. Number above the outlier indicates the patient associated to that value. (*) Level of significance for the difference between trials performed without and with the SSS <0.05. Values measured without orthosis were taken from the study described in Chapter 4.

In order to highlight in more details the effects of the use of specific supports, Figure 5-4 shows the RMC values measured with and without the SSS only for those participants (P) who needed the orthosis to be fitted with two frontal Z-shape supports (i.e. the most common configuration) and only for those movements that were expected to be affected by these supports, namely frontal and lateral flexion. Not all patients managed to perform three repetitions of each movement, mainly due to excessive fatigue.

The use of the SSS was beneficial for P5 and P12. For them, out of plane movements were reduced when performing F1. Similarly, while wearing the orthosis, P12 showed improved control of the head movement also in performing F2. The positive support

offered by the SSS to the execution of the flexion movement was particularly significant for P11, who was able to perform both F1 and F2 only with the orthosis. Only P1, on the contrary, had a higher RMC, and hence worse head control, in both F1 and F2 when performed with the SSS.

Concerning the head lateral flexion, a lower RMC was found in P9 and P12 when performing LF1 with the SSS, while a higher value was observed in P7 in the same condition. Finally, P9, P11 and P12 showed an improvement toward the reduction of out of plane movements, when performing LF2 with the SSS.

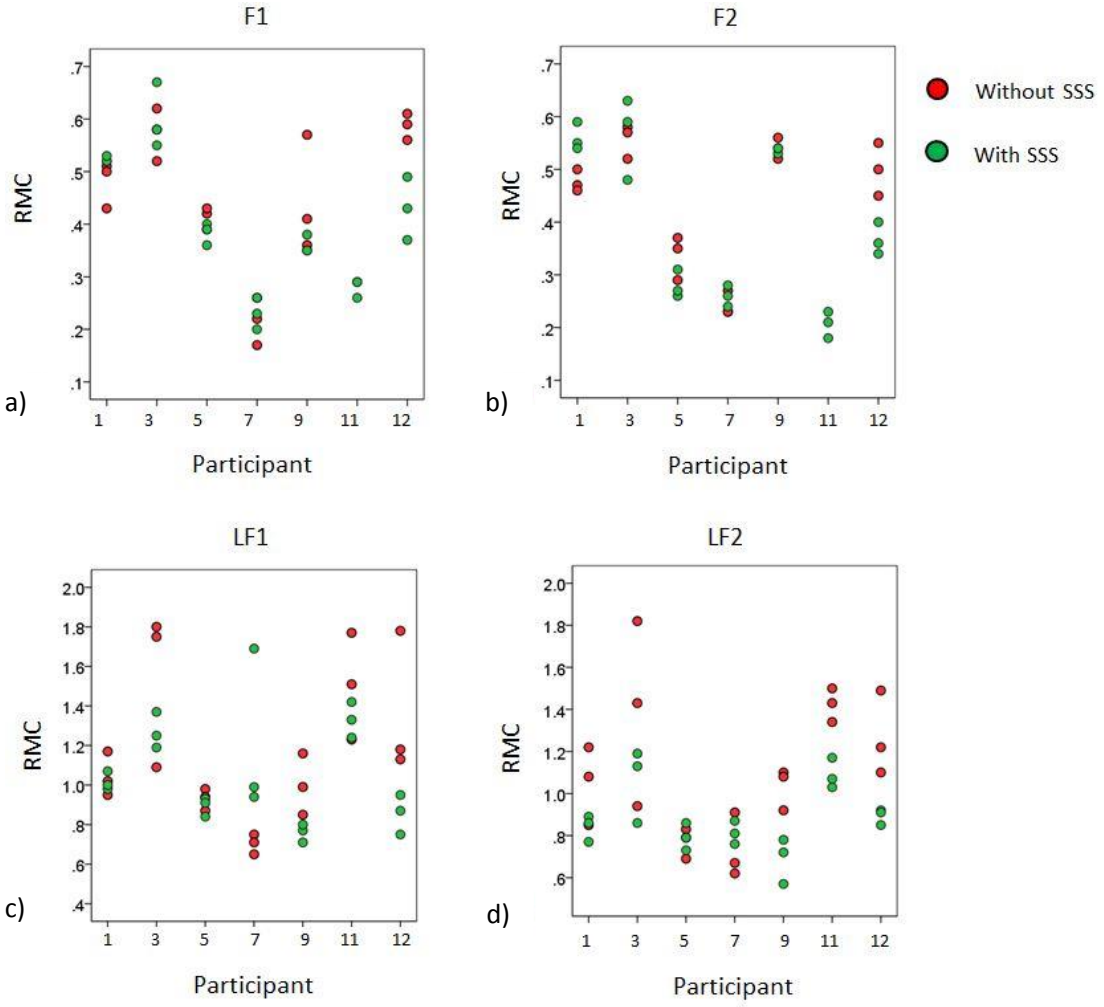


Figure 5-4 Ratio of movement coupling (RMC). Values measured in the three trials performed without orthosis (red circles) and the three trials performed with the SSS with two frontal Z-shape supports (green circles). Movements reported are Flexion (F): from neutral position (a) and back to neutral position (b) and Lateral Flexion (LF): from neutral position (c) and back to neutral position (d).

Figure 5-5 shows the RMC values measured with and without the SSS only for those participants (P) who needed the orthosis to be fitted with two posterior straight supports. Only the extension movement, which was expected to be affected by these supports, is analysed. A higher RMC was observed in both participants when performing E1 with the SSS. P10 showed a higher presence of coupled movements also when performing E2 with the SSS.

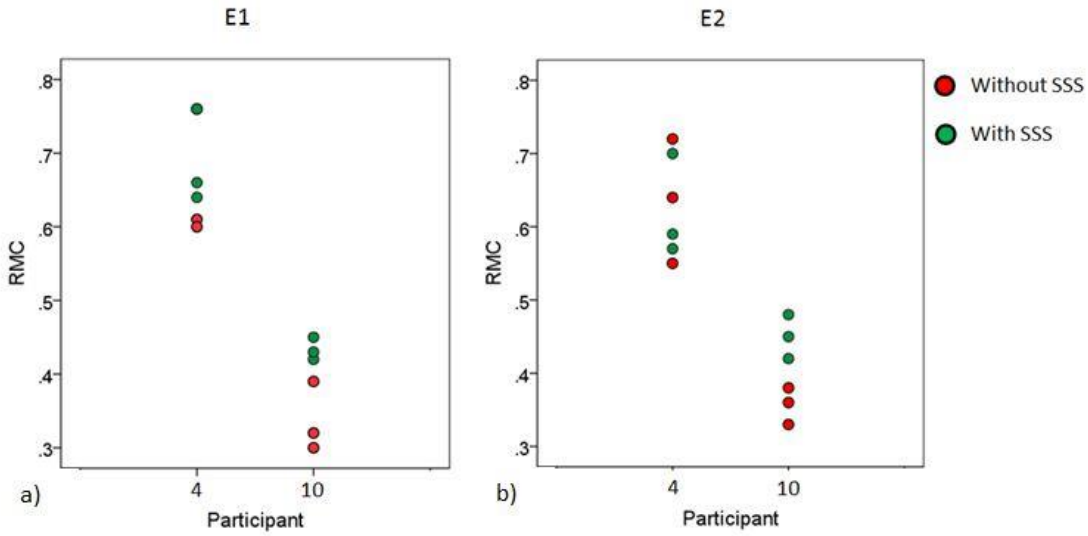


Figure 5-5 Ratio of movement coupling (RMC). Values measured in the three trials performed without orthosis (red circles) and the three trials performed with the SSS with two posterior straight supports (green circles). Movements reported are Extension (E): from neutral position (a) and back to neutral position (b).

Figure 5-6 shows the RMC values measured with and without the SSS only for those participants (P) who needed the orthosis to be fitted with two frontal Z-shape and two lateral supports. Only the frontal and later flexion movements, which were expected to be affected by these supports, are analysed. P2 showed a reduced presence of coupled movements when using the SSS, only in performing F1, while P6 showed a lower amount of coupled movements in F2, LF1 and LF2 when using the orthosis.

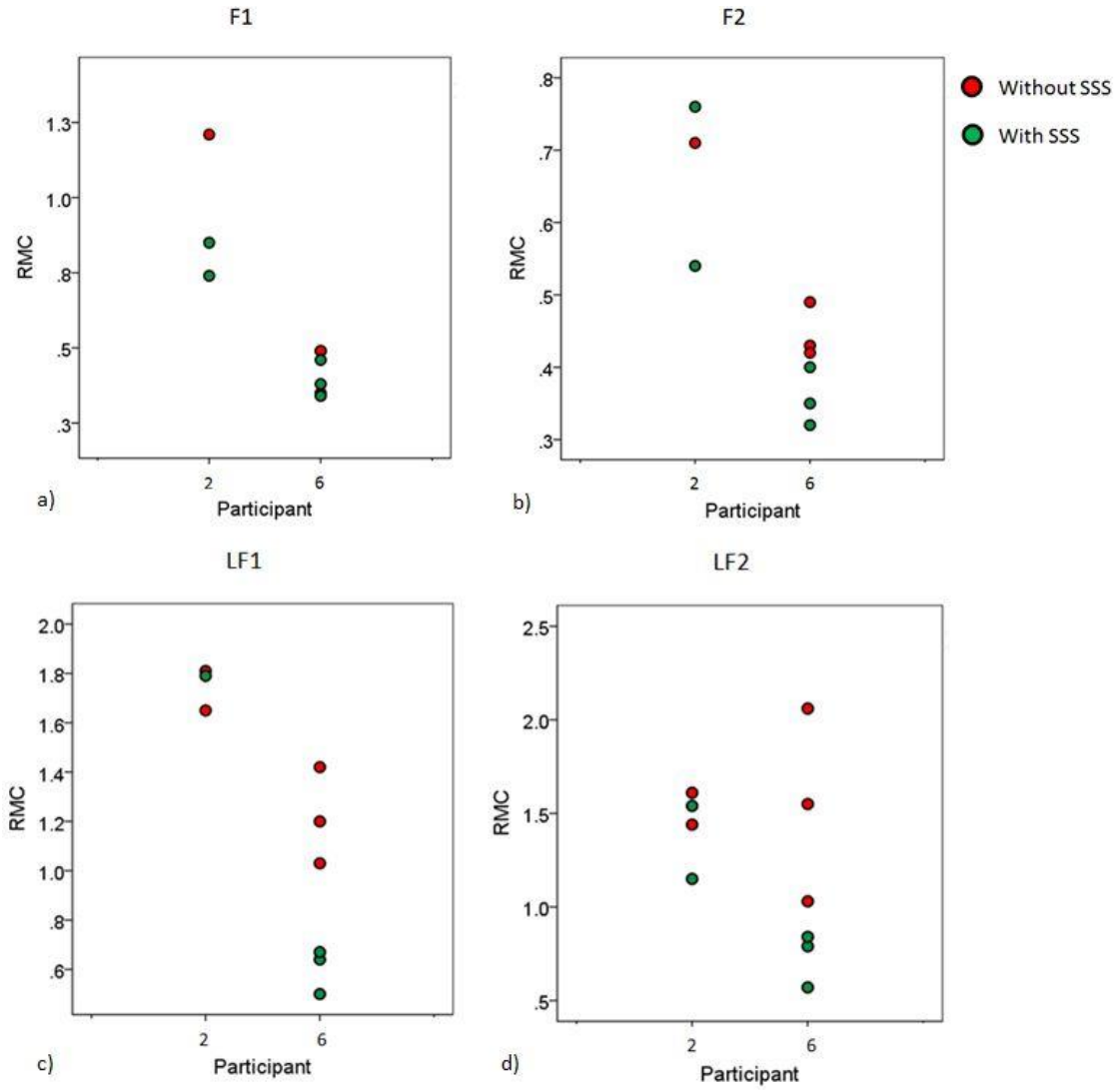


Figure 5-6 Ratio of movement coupling (RMC). Values measured in the three trials performed without orthosis (red circles) and the three trials performed with the SSS with two frontal Z-shape and two lateral supports (green circles). Movements reported are Flexion (F): from neutral position (a) and back to neutral position (b) and Lateral Flexion (LF): from neutral position (c) and back to neutral position (d).

Figure 5-7 shows the Z_{CS} values obtained for the E1 movement. Z score was calculated both when the movement was performed with the SSS (green circles) and without (red circles). As per its formulation, the lower is the Z score the further the patient's movement performance is from the reference value given by the control group.

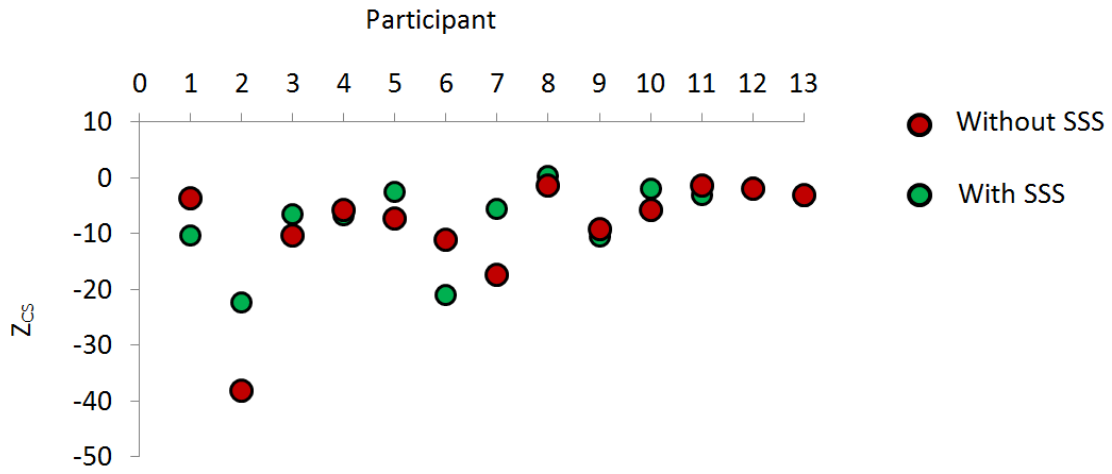


Figure 5-7 Composite score (Z_{CS}) calculated by summing the Z scores obtained for the mean angular velocity, normalized jerk and ratio of movement coupling. Z_{CS} calculated during the extension from neutral position movement (E1).

5.4 Discussion

Poor control of head movements was previously observed in patients with MND by observing and quantifying a series of parameters which were: angular velocity, normalized jerk and ratio of coupled movements (Chapter 4). The aim of the work described in this chapter was to verify whether the use of a cervical orthosis, specifically designed for people affected by neck muscle weakness as a result of MND, could compensate for the observed poor control, without limiting the natural movement velocity and without affecting the smoothness of the movement. This was achieved through quantitative observations. Furthermore, the participants' perceptions, as recorded through questionnaires, were added to the evaluation. The reported results, despite having been obtained from a relatively small number of participants, were encouraging in relation to the use of the SSS in patients affected by neck muscle weakness.

Results obtained through the quantitative functional evaluation approach performed in this study reinforced what observed in the previous study about the high heterogeneity that characterized the investigated group of patients. Participants in this study showed different RMC values when performing the head movements, although they had similar ALSFRS-R score, as can be observed in P3 and P5 (see Table 4-1 and Figure 5-4 Ratio of movement coupling (RMC).). In addition, different levels of impairment were detected for the same patient in performing different movements.

An example was represented by P11: although having a good control of the movement in lateral flexion (Figure 5-4c and Figure 5-4d), P11 was not able to perform the flexion movement without being supported by the SSS (Figure 5-4a and Figure 5-4b). This heterogeneity in muscle weakness and functional compromise was consistent with that described more generally within the wider MND population [2]. It also reinforced the need for personalized interventions, aimed at offering support, according to the specific need of the individual. The approach here proposed can be readily performed in a clinical setting, which paves the way for the development of clinical evaluation methods aimed at monitoring the disease progression and/or the effectiveness of an intervention.

The natural velocity of the movements was not affected by the snood; with the angular velocity remaining as high as when the movements were performed without it. This can be certainly regarded as a positive result since it has been recognized that the velocity of head motion has a significant functional relevance. In fact, this parameter has been often assessed to investigate kinematic characteristics of neck motion in presence of neck pathologies such as chronic neck pain [127] [55]. In addition, it has been observed that movement velocity might affect the smoothness of the movement, with slow movement being jerkier than fast one [63].

The smoothness of the movements was not reduced by the presence of the SSS. Values obtained from the assessment based on the quantification of the movement coupling (RMC) showed that the major improvement associated with wearing the SSS was in the improved control of the lateral flexion movement when returning to the neutral position. The positive impact of the SSS on this movement was likely generated by the frontal supports, characterized by a “z” shape and attached below the jaw (Figure 1-7a). These supports were designed to sustain and guide the head while performing a frontal flexion while offering a lateral support base, below the jaw, that facilitates the lateral flexion. Looking into more details at the trials performed by the seven participants who adopted the two Z-shape supports, it can be observed that the SSS enabled one of them to perform an otherwise impossible movement and improved the quality of the flexion in three additional ones, whereas no improvements were observed for the remaining three. The addition of lateral supports was beneficial for P6 who showed a lower presence of coupled movements in performing lateral flexion.

The same positive result wasn't observed in P2. Indeed, the fitting of the orthosis was based only on the patients' feedback and, as a consequence, some participants were given supports that they might not have really needed according to the experimental experience and to the actual observed movements. P7, for example, asked for frontal supports although his ability to perform frontal and lateral flexion movements was not compromised (Figure 5-4). This observation was confirmed also for other configurations and movements: P4, for example, asked for posterior supports although she seemed to be significantly impaired in performing lateral flexion (Figure 5-3) and might have benefited more from the use of supports placed under the jaw. Similarly, P10 asked for posterior supports although he showed a low presence of coupled movements when performing extension from and back to the neutral position without supports. Finally, P2 did not ask for posterior supports although he exhibited poor control when performing the extension movement (Figure 5-3). These results and considerations clearly indicate that a fitting of the orthosis based on a quantitative functional assessment of the patients rather than on their feedback would likely further improve the efficacy of the intervention. Additional studies are of course needed to verify this hypothesis.

The analysis of the composite Z score allowed a comparison between participants' performance in movement execution and the reference values for the same parameters, observed in a reference group of healthy individuals. Results obtained in this study seemed to confirm the hypothesized (Paragraph 4.6) viability of the use of the Z score to monitor the efficacy of an intervention. In fact, from Figure 5-7, those patients (2 and 7) that improved the performance of the movement and thus benefited from the intervention and those (1 and 6) that, on the contrary, had a decreased performance in the execution of the movement, due to the use of the orthosis, were easily detectable. Also in this Chapter, for the sake of conciseness, only the analysis of one movement is reported (extension from neutral position), although the investigation should involve all the movements performed by the participants for a more exhaustive analysis.

The results from this may also guide design modifications of the SSS itself. None of the patients seemed to benefit from the SSS in terms of reduction of coupled movements associated with axial rotation. This might be explained by the design of the supports,

which are not shaped to guide the head through the execution of this movement. The development of additional supports able to sustain and direct the head through axial rotation might be considered as a design target for further improvement of the SSS.

As already discussed in Chapter 4 (Paragraph 4.6), the main limitation of this study is represented by the small group of patients involved. The significant between-subjects variability observed in patients included in this study represents another limitation, since general consideration couldn't be drawn from the group data. To overcome this limitation, a patient by patient analysis was performed. In addition, a validation of the questionnaires used in this study was not performed, and this represents a further limitation, especially if results obtained from the interviews need to be related to other measurement taken on the participants. However, the designed questionnaires were easy to understand for patients and simple to administer. They didn't have any diagnostic aim but were meant to be used only to get an overall feedback about the sensations perceived by patients while using the SSS, thus they were deemed as appropriate for the purposes of this work. In case of further investigations aiming at correlating the score obtained in those interviews with different questionnaires and/or quantitative measurement, a validation of the proposed questionnaires needs to be performed.

5.5 Conclusions

The Sheffield Support Snood enabled the patients to perform more controlled head movements. Patients expressed satisfaction about head movements and daily activities performed with the orthosis. A key factor for the effectiveness of the intervention appeared to be the need for a fitting based on the functional assessment of the patients rather than the preference of the patient. The functional assessment methods used (angular velocity, normalized jerk and ratio of movement coupling) have been shown to have value in evaluating the functional limitations of neck movement and in evaluating the benefit of an orthosis. This approach may have value when applied in other areas of the body to evaluate an individual level of impairment and effectiveness of any intervention.

Chapter 6

Conclusions and future research

This thesis has been the first study providing a functional objective quantification of head movements in patients affected by MND and allowing for the quantitative assessment of the effects of a cervical orthosis. The reported results showed the achievement of the following four main objectives of the thesis:

- To design a protocol to assess head movements while wearing a cervical orthosis, which could be performed by people affected by MND.
- To evaluate the performance of the SSS in terms of support provided to the user.
- To characterize the group of patients for whom the device was developed, by investigating how MND impacts on their ability to perform head movements.
- To assess how the new cervical orthosis affects patients' ability to perform head movements.

The proposed experimental protocol provided repeatable and reliable information about the execution of head movements. It allowed gaining quantitative information about motion restriction associated with the use of different orthoses and discriminating among them. Having tested the designed protocol on healthy individuals prior to its use in the final clinical context allowed the protocol to be revised and refined up to the point of being able to translate it into a clinical context: the patients were able to perform the required movements and the chosen measurement system, in the defined configuration, proved to be suitable for a reliable data collection in the clinics.

Through the use of the proposed experimental approach and the chosen movement parameters, a quantitative assessment of the ability to execute head movements was obtained also when in the presence of patients with a significant motor impairment. Furthermore, the performed quantitative analysis detected important characteristics

of the patients' movement strategy which were not caught by the traditional qualitative assessments. Future research opened by the development of this quantitative assessment approach to investigate head movements involves its application in different pathologies. In fact, the importance of quantitative assessments has already been underlined by the interest in head movement velocity and presence of coupled movements shown in patients with Cervical dystonia [54]. However, neck muscle weakness has been reported also in neurological diseases different from MND and Cervical dystonia, such as: Parkinson, Multiple system atrophy, Postpolio syndrome, Cervical myelopathy, Chronic inflammatory polyneuropathy, tardive dyskinesia [128]. Therefore, there is a range of pathologies that would benefit from the application of the quantitative assessment approach proposed in this study and get an objective evaluation of consequences of neck muscle weakness. Patients affected by MND showed a reduced ability to perform head movements in terms of reduced velocity, reduced smoothness and increased presence of coupled movements. They presented also a significant inter and intra patient variability which suggests a dramatic need for personalized interventions. This work paves the way for further quantitative investigations on functional impairment in patient affected by MND involving different body areas and longitudinal studies. In particular, the assessment of coupled movements presented in this study should be extended to different joints to investigate the presence of analogous mechanisms when executing different tasks.

The Sheffield Support Snood was able to offer a support comparable to bulkier orthoses when tested on healthy individuals. It also proved to be adaptable to different tasks, offering the possibility to reduce the movement in a selected direction without affecting the ability to perform movements in others directions. The Sheffield Support Snood enhanced the execution of the head movements also in MND patients, although it was clearly highlighted that a correct fitting of the orthosis remains a crucial aspect and in the future it should be based on objective evaluations.

Future research concerns the improvement of the design of the SSS on the basis of the results obtained in this study. In fact, the need for a higher support in the execution of the axial rotation movement emerged from its quantitative assessment in patients. Furthermore, results obtained in this study suggest that the functional assessment of

patients' residual movement ability needed to better fit the Sheffield Support Snood might be obtained using the approach proposed in this thesis. This consideration could be extended to different orthosis/interventions, the efficacy of which could be investigated by looking at their objective effects when fitted accordingly to a quantitative functional assessment rather than to patients' perceptions. This approach might be extremely useful, especially when treating patients with cognitive impairments. Considerations drawn from this study pave the way for further research in this direction. Inertial sensors are easy and quick to apply, even for non-technical staff (physiotherapists, nurses, physicians, etc). They can be used in any environment and are easy to carry. Therefore, the experimental method proposed in this study can be applied in several contests to guide in prescribing and fitting a device. The development of a procedure and relative codes to analyse data may represent the next step of this project in order to make the data collection and data processing independently usable by clinicians.

More in general, the extension of the quantitative assessment approach presented in this study to a larger sample of patients would allow quantitatively investigating the characteristics of motor control and movement strategies in patients with MND and how they change in presence of a device aiming at compensating for functional impairments. On the basis of the experience gained in this study, the design of a multi-centre project seems to be necessary to obtain a larger sample due to the rarity of the disease and the occasional occurrence of neck muscle weakness. In fact, following this initial study a bigger project was launched involving several MND care centres (Sheffield, Oxford, Liverpool, London, Cambridge, Preston, Salford, Glasgow, Edinburgh and Dublin) with the aim of recruit 100 people with MND who experience neck weakness and 50 people who have neck weakness linked to another condition, such as muscular dystrophy or after having a stroke, to test out the latest design of the SSS. A contribution given from this work to the new project might be represented by the addition to the assessment of the orthosis of a quantitative functional assessment of patients' ability to perform movements, following the protocol proposed in this study.

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Appendix A

ALS Functional rating scale – revised (ALSFRS-R)

1. SPEECH

4 pts: Normal speech process

3 pts: Detectable speech disturbance

2 pts: Intelligible with repeating

1 pt: Speech combined with non-vocal communication

0 pts: Loss of useful speech

2. SALIVATION

4 Normal

3 pts: Slight but definite excess of saliva in mouth; may have night time drooling

2 pts: Moderately excessive saliva; may have minimal drooling

1 pt: Marked excess of saliva with some drooling

0 pts: Marked drooling

3. SWALLOWING

4 pts: Normal eating habits

3 pts: Early eating problems – occasional choking

2 pts: Dietary consistency changes

1 pt: Needs supplemental tube feeding

0 pts: NPO (exclusively parenteral or enteral feeding)

4. HANDWRITING

4 pts: Normal

3 pts: Slow or sloppy: all words are legible

2 pts: Not all words are legible

1 pt: No words are legible, but can still grip pen

0 pts: Unable to grip pen

5a. CUTTING FOOD AND HANDLING UTENSILS: Patients without gastrostomy

4 pts: Normal

3 pts: Somewhat slow and clumsy, but no help needed

2 pts: Can cut most foods (> 50%), although slow and clumsy; some help needed

1 pt: Food must be cut by someone, but can still feed slowly

0 pts: Needs to be fed

5b. CUTTING FOOD AND HANDLING UTENSILS: Patients with gastrostomy

4 pts: Normal

3 pts: Clumsy, but able to perform all manipulations independently

2 pts: Some help needed with closures and fasteners

1 pt: Provides minimal assistance to caregiver

0 pts: Unable to perform any aspect of task

6. DRESSING AND HYGIENE

4 pts: Normal function

3 pts: Independent; Can complete self-care with effort or decreased efficiency

2 pts: Intermittent assistance or substitute methods

1 pt: Needs attendant for self-care

0 pts: Total dependence

7. TURNING IN BED AND ADJUSTING BED CLOTHES

4 pts: Normal function

3 pts: Somewhat slow and clumsy, but no help needed

2 pts: Can turn alone, or adjust sheets, but with great difficulty

1 pt: Can initiate, but not turn or adjust sheets alone

0 pts: Helpless

8. WALKING

4 pts: Normal

3 pts: Early ambulation difficulties

2 pts: Walks with assistance

1 pt: Non-ambulatory functional movement only

0 pts: No purposeful leg movement

9. CLIMBING STAIRS

4 pts: Normal

3 pts: Slow

2 pts: Mild unsteadiness or fatigue

1 pt: Needs assistance

0 pts: Cannot do

10. DYSPNOEA

4 pts: None

3 pts: Occurs when walking

2 pts: Occurs with one or more of the following: eating, bathing, dressing (ADL)

1 pt: Occurs at rest: difficulty breathing when either sitting or lying

0 pts: Significant difficulty: considering using mechanical respiratory support

11. ORTHOPNOEA

4 pts: None

3 pts: Some difficulty sleeping at night due to shortness of breath does not routinely use more than two pillows

2 pts: Needs extra pillows in order to sleep (more than two)

1 pt: Can only sleep sitting up

0 pts: Unable to sleep without mechanical assistance

12. RESPIRATORY INSUFFICIENCY

4 pts: None

3 pts: Intermittent use of BiPAP

2 pts: Continuous use of BiPAP during the night

1 pt: Continuous use of BiPAP during day & night

0 pts: Invasive mechanical ventilation by intubation or tracheostomy

Appendix B

Ethical approval

B.1 Study involving healthy individuals

The University Of Sheffield.

Department Of Mechanical Engineering.

- APPLICATION IS APPROVED WITH SUGGESTIONS -

****

21 February 2014

Ms Silvia Pancani

Department of Mechanical Engineering

Dear Ms Pancani,

PROJECT TITLE: 'Comparative assessment of different neck collars in healthy individuals'

On behalf of the University ethics reviewers who reviewed your project, I am pleased to inform you that on 21 February 2014 the above-named project was **approved** on ethics grounds, on the basis that you will adhere to the following document that you submitted for ethics review:

- University research ethics application form (30/01/14)
- Example of Questionnaire (31/01/2014)
- Participant consent form (31/01/2014)

However, the ethics reviewers have suggested that you consider the following amendments, which you can choose to follow or to ignore:

(i) The ethics form and consent form state the data will be kept confidential and is anonymised but the feedback forms require the subject's name. Suggest that subjects are given a code e.g. "Participant no. xxx" when they fill out the consent form and then they use this on any other feedback forms. This will make storage of paper forms less risky.

If during the course of the project you need to deviate from the above-approved document please inform me. Written approval will be required for significant deviations from or significant changes to the above-approved document. Please also inform me should you decide to terminate the project prematurely.

Yours sincerely

[redacted]

Ethics Administrator

The Queen's Anniversary Prizes

1998 2000 2002

B.2 Amendment to include elderly individuals

The University Of Sheffield.

Downloaded: 22/10/2016
Approved: 02/12/2015

Silvia Pancani
Registration number: 130243777
Mechanical Engineering
Programme: NA

Dear Silvia

PROJECT TITLE: Assessment of neck movements in adults and elderly subjects
APPLICATION: Reference Number 006886

On behalf of the University ethics reviewers who reviewed your project, I am pleased to inform you that on 02/12/2015 the above-named project was **approved** on ethics grounds, on the basis that you will adhere to the following documentation that you submitted for ethics review:

- University research ethics application form 006886 (dated 16/11/2015).
- Participant information sheet 1013523 version 2 (16/11/2015).
- Participant information sheet 1013521 version 2 (16/11/2015).
- Participant consent form 1013524 version 1 (16/11/2015).
- Participant consent form 1013522 version 1 (16/11/2015).

The following optional amendments were suggested:

With the data recorders, one is on the sternum. Does the participant need to undress at all for this? Please give details either way, that they do or don't or what they can wear for it. In the document 'scheda informativa' I would be more specific about the ethics committe and add "Questo studio Ã© stato revisionato dal Comitato Etico di Ricerca della Facolta` di ..... dell' Univesita` di Sheffield, United Kingdom" The supporting documents should include the name of the supervisor as well or another permanent person in the group as a contact. Through the consent form you should ask participants to declare they are not aware of having any mobility or general pathological conditions that might introduce risk of harm to patients when asked to perform the tasks of the experimental protocol

If during the course of the project you need to deviate significantly from the above-approved documentation please inform me since written approval will be required.

Yours sincerely

[redacted]
Ethics Administrator
Mechanical Engineering

B.3 Study involving patients with MND

NHS
Health Research Authority
NRES Committee North East - Newcastle & North Tyneside 1
Jarrow Business Centre
Jarrow REC Centre
Room 001
Rolling Mill Road
Jarrow
NE32 3DT

Telephone: 0191 428 3565

2 February 2015

Dr Christopher J McDermott
Clinical Senior Lecturer
Sheffield Institute for Translational Neuroscience
University of Sheffield
385a Glossop Rd
Sheffield
S10 2HQ

Dear Dr McDermott

Study title:	**Assessment of the effects of Sheffield Support Snood in patients with MND**
REC reference:	**15/NE/0037**
Protocol number:	**STH18733**
IRAS project ID:	**170201**

The Proportionate Review Sub-committee of the NRES Committee North East - Newcastle & North Tyneside 1 reviewed the above application on 27 January 2015.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact the REC Manager Ms Gillian Mayer, nrescommittee.northeast-newcastleandnorthtyneside1@nhs.net. Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Ethical opinion

On behalf of the Committee, the sub-committee gave a **Favourable** ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Additional Conditions specified by the REC:

1. Include a sentence in the information sheet to inform that participants may not be able to keep the Snood, so as not to disappoint participants.

2. Include a sentence to specify that the project is being undertaken as part fulfilment of an educational qualification.

Recommendations: Consultation with a statistician is recommended with particular emphasis on the sample size and the use of descriptive statistics in the analysis.

You should notify the REC in writing once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. The REC will acknowledge receipt and provide a final list of the approved documentation for the study, which can be made available to host organisations to facilitate their permission for the study. Failure to provide the final versions to the REC may cause delay in obtaining permissions.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from NRES. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of

the study (see "Conditions of the favourable opinion").

Summary of discussion at the meeting

Social or scientific value; scientific design and conduct of the study

The Committee noted that the first reviewer mentions the need to have standard operating procedures to deal with potential adverse reactions like breathing problems or choking but then suggests no changes to protocol. The application form refers to immediate termination if there are breathing problems. Further details were requested.

It was explained that patients will be seen in a Neurology clinic with sufficient medical cover in the unlikely event that a patient does have an adverse effect and that Sheffield Teaching Hospital is a large teaching hospital with emergency facilities if required.

It was also noted that the first reviewer also mentions that the same person is delivering intervention and measuring outcomes, which could introduce bias, but suggested no changes – it was queried if this had been considered.

It was noted that the researchers disagreed with the reviewer about this comment, since the measuring outcomes are objective in their nature, being based on an instrumented quantitative assessment.

The Committee noted that the sample size calculation was not reproducible and limited information was provided. Further clarification was requested regarding the calculation.

It was explained that the sample size calculation was made on the basis of the results of a previous study conducted on 12 healthy subjects. In the study subjects performed the active head movements described in the protocol (extension, flexion, axial-rotation and lateral bending) both with the Sheffield Support Snood and without any collar and the ROM reached in the two conditions was measured. The two values measured with the collar and without it were compared for each movement and the statistical significance of the difference in the ROM was assessed using a one way ANOVA analysis. The probability used in the study was 0.05 and the power level 95%. You provided details of the values you had obtained in the study and used to calculate the sample size.

Further clarification was requested regarding the actual outcome measures which were not clearly stated.

It was noted that the outcome measures will be: Range of motion (ROM), Muscle activation times and signal amplitude (RMS). The range of motion performed for each movement will be measured using the inertial sensors. A calculation of the angle performed by the subjects in each direction will be undertaken using an algorithm that integrates the angular velocity measured by the sensor. Once the angles performed during the entire movement have been estimated the researchers will be able to calculate the ROM performed by the subject by calculating the difference between the maximum and the minimum angle performed by the subject in the same direction. Muscle activation times and signal amplitude (RMS) will be calculated by analysing the signals measured with the surface EMG system

Care and protection of research participants; respect for potential and enrolled participants' welfare and dignity

The application form only notes NHS indemnity but the investigators are all noted to be from Sheffield University and clarification was requested if any of the investigators also has an NHS contract.

It was confirmed that you have an honorary contract with the NHS Trust.

Informed consent process and the adequacy and completeness of participant information

The information sheet should state that the researcher is a PhD student and it might be useful to inform participants what will happen after the study has ended and whether they can keep the Snood if they find it comfortable. It also needs to be clarified that direct quotations would be anonymised to reduce the chance of identification. The consent form should specify that 'quotes' is indicated at point 4, rather than the vague reference to "some data".

It was noted that the student investigator would need to consult with yourself as chief investigator regarding what will happen at the end of the study and the Snood collar being kept by participants if they find it comfortable. A revised information sheet was provided to clarify that direct quotations would be anonymised and a revised consent form was also provided as requested.

Suitability of supporting information

In the evaluation form, it was noted that participants may not understand the phrase 'maximum amplitude' and an explanation for this should be given.

A revised document was provided accordingly.

The Sub-Committee was satisfied with the responses given to the issues raised and also the revised documentation provided.

Approved documents

The documents reviewed and approved were:

Document	*Version*	*Date*
Instructions for use of medical device [IFU Clinical]	1	17 January 2012
Letters of invitation to participant	1	01 December 2014
Non-validated questionnaire	2.0	27 January 2015
Other [ISR Lead Review]		
Other [ISR Second Review]		
Other [IFU daily user guide]	1	17 January 2012
Other [Response to issues]		
Other [Info]		
Participant consent form	2.0	27 January 2015
Participant information sheet (PIS)	2.0	27 January 2015
REC Application Form [REC_Form_21012015]		21 January 2015
Research protocol or project proposal	1	12 November 2014
Summary CV for Chief Investigator (CI)	1	09 March 2011
Summary CV for student	1	15 January 2015
Summary CV for supervisor (student research)	C. MazzÃ	01 January 2015

Membership of the Proportionate Review Sub-Committee

The members of the Sub-Committee who took part in the review are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for

Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

With the Committee's best wishes for the success of this project.

15/NE/0037	**Please quote this number on all correspondence**

Yours sincerely

[redacted]

[redacted]

[redacted]

Email: nrescommittee.northeast-newcastleandnorthtyneside1@nhs.net

Enclosures: *List of names and professions of members who took part in the review*

'After ethical review – guidance for researchers'

Copy to: *Ms Samantha Heaton – Clinical Research Office, Royal Hallamshire Hospital, Sheffield*

NRES Committee North East - Newcastle & North Tyneside 1

Attendance at PRS Sub-Committee of the REC meeting on 27 January 2015 in correspondence

Committee Members:

Name	*Profession*	*Present*	*Notes*
[redacted]	Clinical Trials Statistician	Yes	
[redacted]	Consultant Clinical Psychologist (Retired)	Yes	
[redacted]	Professor of Periodontology & Consultant in Restorative Dentistry	Yes	

Also in attendance:

Name	*Position (or reason for attending)*
[redacted]	REC Manager

Appendix C

Patients Questionnaire

headup

Patients Questionnaire

Subject: _____

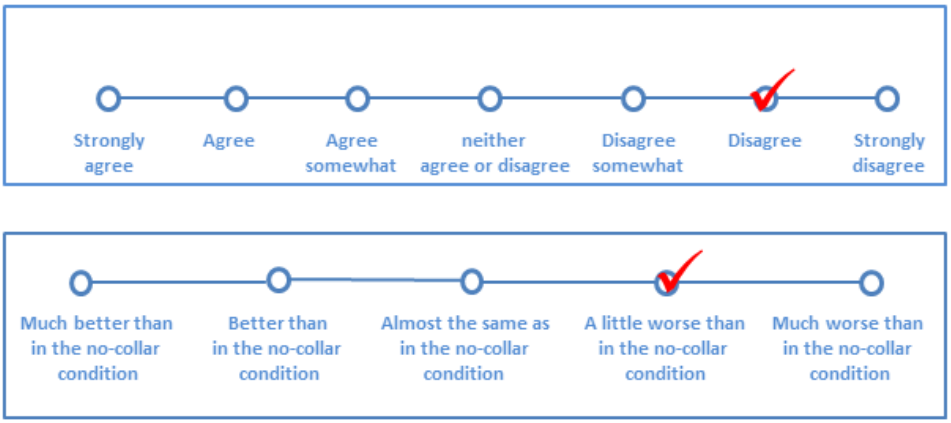
Age : _____

Gender: _____

Device currently used: _____

Instructions:

Please read the following statements and place a mark on the circle you feel best describes your response, as shown in the example below,



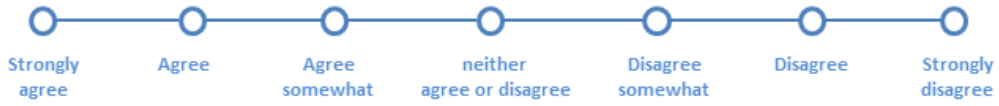
If you performed only phase 1 please answer questions related to Active Head Movements. If you performed both phases 1 and 2 please answer questions related to the Activities of Daily Living too.

Patients Questionnaire - v 2.0 - 27/01/2015

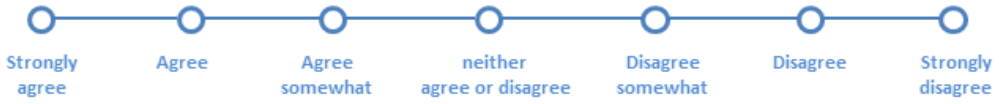
Sheffield Support Snood evaluation

Phase 1: Active Head Movements

I felt that this collar offered support.

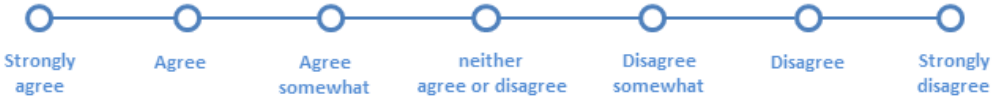


I have a completely free range of head movement wearing this collar.

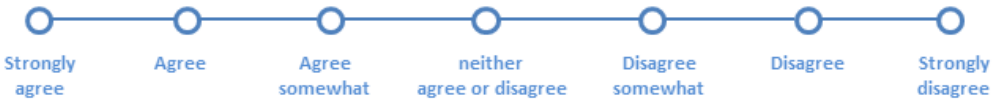


Phase 2: Activities of Daily Living (if applicable)

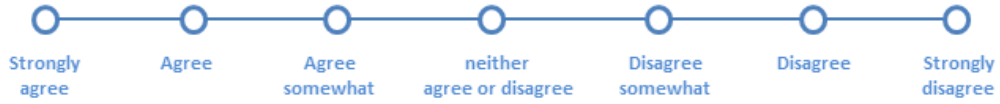
This collar caused no restriction to my natural breathing.



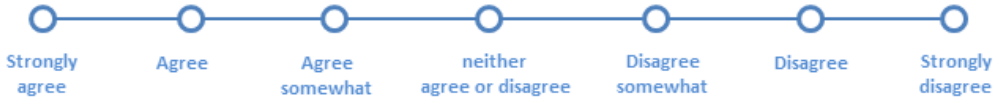
I experienced no difficulties eating a meal whilst wearing this collar.



I experienced no problems drinking whilst wearing this collar.



This collar caused no restriction to my natural swallowing.



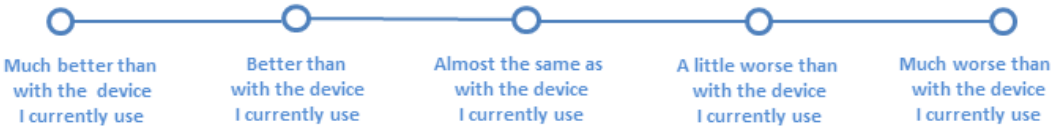
Comparison Sheffield Support Snood and device currently used

Phase 1: Active Head Movements

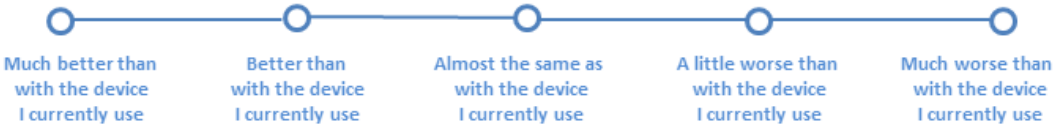
I felt performing the head movements while I was wearing this collar was:

Phase 2: Activities of Daily Living (if applicable)

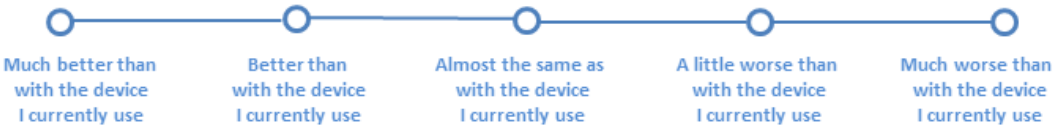
I felt performing the eating task while I was wearing this collar was:



I felt performing the drinking task while I was wearing this collar was:



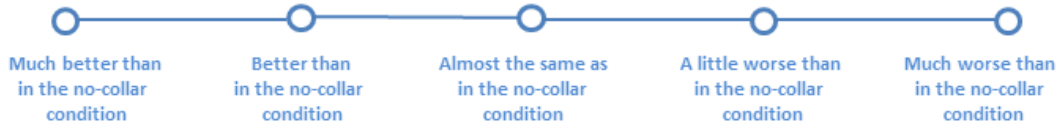
I felt performing the washing task while I was wearing this collar was:



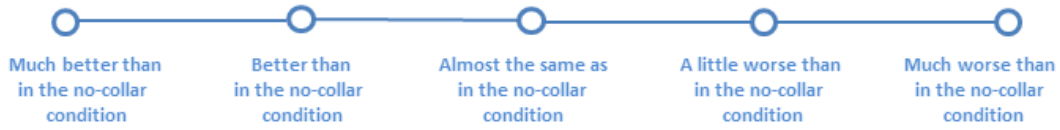
Comparison Sheffield Support Snood and no-collar condition

Phase 1: Active Head Movements

I felt performing the head movements trying to explore the maximum range of motion in each direction while I was wearing this collar was:

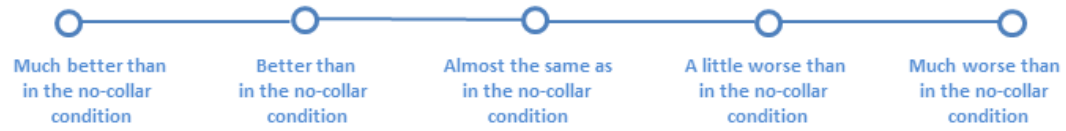


I felt performing the head movements at maximum speed while I was wearing this collar was:

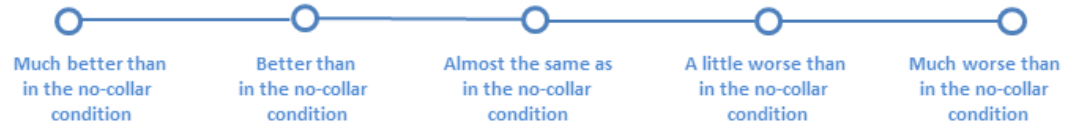


Phase 2: Activities of Daily Living (if applicable)

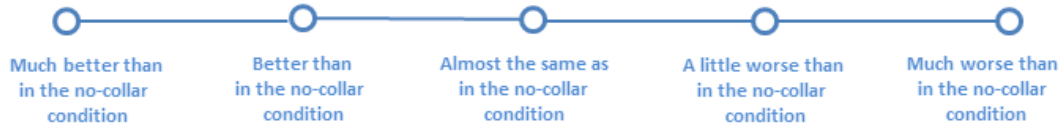
I felt performing the eating task while I was wearing this collar was:



I felt performing the drinking task while I was wearing this collar was:



I felt performing the washing task while I was wearing this collar was:



Do you have any comments or observation regarding your experience of wearing this collar?

We would like to take this opportunity to thank you for the valuable input you have provided.

Publications and short abstracts

- S. Pancani, J. Rowson, W. Tindale, N. Heron, J. Langley, A. D. McCarthy, A. Quinn, H. Reed, A. Stanton, P. J. Shaw, C. J. McDermott and C. Mazzà, “Assessment of the Sheffield Support Snood, an innovative cervical orthosis designed for people affected by neck muscle weakness”, *Clinical Biomechanics,* vol. 32, pp. 201-206, 2016.

- S. Pancani, W. Tindale, P. J. Shaw, C. J. McDermott, C. Mazzà, “Assessment of coupled movements in head movements performed by patients with Motor Neurone Disease”, Conf. Proc. *Gait & Posture*, vol. 49, S22, 2016.

- S. Pancani, W. Tindale, P. J. Shaw, C .J. McDermott, C. Mazzà, “An objective functional characterisation of head movement impairment in individuals with neck muscle weakness due to Amyotrophic lateral sclerosis”, *PLoS One*, under revision.

- J. Langley*, S. Pancani*, K. Kilner, H. Reed, A. Stanton, N. Heron, S. Judge, A. McCarthy, S. Baxter, C. Mazzà, C. J. McDermott, “A comfort assessment of existing cervical orthoses”, *Ergonomics*, under revision.

- S. Pancani, W. Tindale, P. J. Shaw, C. Mazzà, C. J. McDermott, ” Efficacy of the Sheffield Support Snood in facilitating functional head movements in patients with Amyotrophic Lateral Sclerosis”, in preparation for *PloS One*.

- S. Pancani, C. J. McDermott, J. Rowson, W. Tindale, C. Mazzà, "Assessment of an innovative collar designed for people affected by neck weakness", 25th ISB Congress, July 12-16, 2015, Glasgow, UK. Abstract accepted as oral presentation.

- S. Pancani , J. Rowson, W. Tindale, N. Heron, J. Langley, A. D. McCarthy , A. Quinn, H. Reed, A. Stanton, P. J. Shaw, C. J. McDermott and C. Mazzà,"Assessment of a new cervical orthosis using Inertial Magneto Units", 16th SIAMOC Congress, September 30 – October 3, 2015, Padua, IT - Abstract accepted as poster presentation.

- S. Pancani, C. J. McDermott, W. Tindale, P. J. Shaw, C. Mazzà, “Assessment of active head movements in patients with neck muscle weakness due to Motor Neurone Disease”, 22nd ESB, July 10 - 13, 2016, Lyon, FR- Abstract accepted as oral presentation.

- S. Pancani, W. Tindale, P. J. Shaw, C. J. McDermott, C. Mazzà “Assessment of coupled movements in head movements performed by patients with Motor Neurone Disease”, 17th SIAMOC Congress, October 5 – 8, 2016, Milan, IT - Abstract accepted as oral presentation.