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Quantitative assessment of upper limb motor impairments in people with neurological diseases

A dissertation
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Doctor of Philosophy

Federica Corona

Abstract

Individuals with neurological diseases often exhibit upper limb (UL) motor deficits, which can compromise their ability to perform basic activities of daily living (ADL). The clinical assessment of these impairments is commonly performed by clinicians using tests and scales that are not suitable to adequately characterize UL alterations in terms of duration, velocity and kinematics of a performed movement. However, in recent times, the research on motor dysfunctions has been taking advantage of the possibilities offered by quantitative motion analysis techniques (e.g. motion capture systems and wearable inertial sensors) which are able to provide objective information regarding UL movement abilities during the performance of functional tasks.

The aim of this thesis was to define and validate an experimental approach, based on the use of optoelectronic stereophotogrammetry, aimed to obtaining quantitative information about the kinematics of a specific functional motor task (hand to mouth, HTM) that are fully representative of important ADLs such as feeding and drinking. In particular, the study was focused on the assessment of the main spatio-temporal and kinematic parameters of the HTM task, providing in this way information about movement quality in order to better understand the control characteristics of impairment. Moreover, on the basis of the kinematic data associated with the main UL joint movements, a specific synthetic index (Arm Profile Score, APS) was formulated following an approach similar to the one that previously proposed to characterize the gait kinematics in a range of neurological conditions. In this way, the whole kinematic pattern can be summarized by a single value that can be easily interpreted by physicians (i.e. the larger the value, the more distant the movement pattern from those of unaffected individuals).

Experimental tests were performed in samples of individuals with Multiple Sclerosis (MS, n = 30), Parkinson's disease (PD, n = 16) and Dementia with Lewy Bodies (DLB, n = 10) and in 56 age- and gender-matched individuals (HC), who underwent a 3D kinematic evaluation of the HTM task using a motion capture system. A range of spatial-temporal parameters (e.g. total and phases' duration of the movement, velocity of the hand) and joint kinematics were calculated as well as the APS score. Differences between groups were investigated using one-way MANOVA, while a correlation analysis was performed to assess

the existence of a possible relationship with clinical tests and/or disability level assessed by specialized neurologists.

The results obtained suggest that the analysis of HTM task is suitable to objectively characterize UL functional motor performance. Moreover, the APS score succeeded in discriminating abnormal kinematic patterns with respect to a physiological movement. Furthermore, the existence of significant relationships between the synthetic indexes and the clinical scales scores (i.e. Expanded Disability Scale Score, EDSS, for MS, Hoehn & Yahr, H&Y, scale and Unified Parkinson's Disease Rating Scale, UPDRS, for basal ganglia disorders) suggests that these are suitable to represent the peculiar UL alterations associated with each condition. Thus, the use of quantitative synthetic measures is an effective way to quantify overall UL functions and compare motor impairments between clinical groups, features that are undetectable by standard clinical tests.

In summary, the quantitative assessment of UL impairments in people with neurological diseases during a functional task may effectively support and integrate the clinical evaluation through an accurate description of the movement features. This technique appears able to play an important role in supporting physicians in monitoring the individual's deficit progression and in planning suitable interventions for managing UL movement disorders.

Acknowledgments

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List of Abbreviations

AD	Alzheimer's Disease
ADL	Activities of Daily Living
AMPS	Assessment of the Motor and Process Skills
AP	Adjusting Phase
APS	Arm Profile Score
ARAT	Action Research Arm Test
AS	Adjusting Sway
AVS	Arm Variable Score
CNS	Central Nervous System
DASH	Disabilities of the Arm, Shoulder and Hand
DLB	Dementia with Lewy Bodies
EDSS	Expanded Disability Status Scale
FAB	Frontal Assessment Battery
FMA	Fugl-Meyer Assessment
FTD	Fronto-Temporal Dementia
GP	Going Phase

GPS	Gait Profile Score
H&Y	Hoehn & Yahr
HC	Healthy Controls
HGS	Hand Grip Strength
HTM	Hand to Mouth
ICF	International Classification of Functioning
IHA	Instantaneous helical axes
ISB	International Society of Biomechanics
ISG	International Shoulder Group
MAL	Motor Activity Log
MAM-36	Manual Ability Measure- 36
MAS	Modified Ashworth Scale
MMSE	Mini Mental State Examination
MS	Multiple Sclerosis
MSA	Multiple System Atrophy
NHPT	Nine Hole Peg Test
PD	Parkinson's
PDD	Parkinson's Disease Dementia
PwDLB	People with Dementia with Lewy Bodies
PwMS	People with Multiple Sclerosis
PwPD	People with Parkinson's Disease
RMS	Root Mean Square
ROM	Range of Motion
RP	Returning Phase
UL	Upper Limb
UPDRS	Unified Parkinson's Disease Rating Scale
WHO	World Health Organization

Chapter 1

Motion Analysis of Upper Limbs for Clinical Applications

In this chapter background information relevant for understanding the purposes is provided, the methods, the results and conclusions of this thesis. In particular, motion capture technologies and the use of motion capture system in clinical field are described. Then, the assessment of arm and hand movement is shown in clinical and laboratory settings, taking into account the previous studies carried out in this field. This dissertation focuses on characterizing upper limb (UL) motor functions and providing quantitative synthetic measures to quantify the deviation of arm movement in people with neurological diseases from normal pattern by means of 3D dimensional motion analysis techniques.

1.1 Motion analysis

1.1.1 Historical background

Human motion analysis provides applications that are relevant to an interdisciplinary and systematic field that involves several scientific subjects, such as engineering and medicine. Its aim is to provide quantitative information about the musculoskeletal system biomechanics during the performance of a motor task.

The early attempts to describe movements were done by Greek ancients, who were interested in both sport and human movement, as it can be seen in the kinematic representations of Greek athletics. The first book on human movement, "*De Motu Animalius*" (*About the Movements of Animals*), was written by the philosopher and kinesiologist Aristotle (384-322 B.C.), who described animal and human movement and muscles action. In the Renaissance, the interest about human movement and anatomy grew (Lu and Chang, 2012). Firstly, Leonardo da Vinci (1452-1519) described human body and motion as mechanical systems including soft tissue, joints, muscles, bones, ligaments, tendons, and cartilage. Few years later, Andrea Vesalius (1524-1564) published in 1543 "*De Humani Corporis Fabrica*" (*About the Structure of the Human Body*), the first book about anatomy. Galileo Galilei (1564-1643), father of the scientific method, was also interested in biomechanics and applied mechanical theory on animal movement's study. Following the principles set by Galileo, Giovanni Alfonso Borelli (1608- 1679) began his investigation into the science of animal movements and achieved important scientific results, such as the first experiments in gait analysis, the determination of the human center of gravity position, and the concept of the musculoskeletal system as a set of levers that magnified motion rather than force. These achievements were collected in his great treatise called, in honor of Aristotle's work, "*De Motu Animalium*" (*About the Motion of Animals*), and made him the "Father of Biomechanics" (Lu and Chang, 2012).

In the 19th century, photography and cinematography's advent gave the basis for the modern motion analysis. Among the notable characters of this period, we can find: the Weber brothers, Wilhelm Eduard (1804-1891) and Eduard Friedrich (1806-1871), who were the pioneers of today's gait analysis; Etienne-Jules Marey (1830-1904), who accurately recorded the progression of legs during walking using chronophotography; Eadweard Muybridge (1830-1904), known for having done worth improvement in the photography and having

recorded the motion of human and animal by camera; Carl Pulfrich (1858-1929), known for the stereophotogrammetry's development, the technique of measuring 3D coordinates; Christina Wilhelm Braune (1831-1892) and Otto Fisher (1861-1917), who conducted studies about human movement combining geometrical proprieties of central projection from multi-camera observations to estimate the 3D position from digitized image.

Starting from 20th century, biomechanics became a worldwide recognized discipline and, thanks to the advances in technology, it has constantly evolved to present days. In particular, video camera system, such as infrared camera, became a widespread used tool in clinical setting during the 1970's, in order to provide better medical services in prostheses design for amputees. In the following section, the main approaches used nowadays for human motion analysis are further described.

1.1.2 Motion analysis technologies

Several methods for tracking and analysing human movement are currently available. Generally, the process of movement recording of objects or people through technological instruments is known as Motion Capture (also known as *mo-cap*). Motion capture systems are based on various technologies and they are used for human movement studies in several applications, such as sport, ergonomics, entertainments and clinic.

Optical Motion Capture Systems

The most commonly used motion capture approach is based on optoelectronic devices. Optical motion capture systems depend on the data acquired by two or more calibrated cameras in order to compute the position of an object or a subject in a 3D space. Achieving this goal is possible by the conjunction use of cameras and specific markers, which are attached to specific points of body on subjects' skin and tracked by the cameras.

These markers can be passive or active. The former markers are coated with a spherical retro-reflective material and they are illuminated at regular intervals by light (generally in the infrared spectrum) generated by sources in correspondence to camera's lens and the reflection is captured by the camera that is coaxial with the light source. Al least two cameras captures images in which only the reflective markers appear as bright dots on a dark background, ignoring skin and fabric. By processing these images and using triangulations techniques it is possible to derive the 3D position of each marker in a calibrated volume. Since all markers

have the same aspect on the acquired images, this approach is often matter of problem of marker swapping, which can be partially reduced using proper software tools and manual clean-up of the data. Nevertheless, an accuracy of 1 mm with a limited number of cameras can be easy reached. An example of commercial passive marker-based motion capture systems is shown in Figure 1.1a.

In the active markers, the light source is placed directly on the markers, which often are LEDs, emitting visible or infrared light. The cameras infrastructure detects the markers correspondence in multiple images and triangulates the relative positions of each point. This approach is more reliable and stable because the light generated by LEDs can be tuned in order be easily picked up by cameras, enabling them to reach accuracies in the order of 0.1 mm within the calibrated volume. A commercial active-marker system for motion capture is shown in Figure 1.1b. The advantage of active marker-based system respects to the passive one is that each marker can transmit information at own predefined frequencies and this means that post-processing of localization of marker positions is minimized (Popat et al., 2009). On the other hand, active markers have often a large size, heavier and, therefore, they can make difficult the movement.

Lately, different techniques for reconstructing motion from images without the need of wearing special equipment for tracking have appeared. These systems, called marker-free systems, are based mostly on the use of structured light patterns (i.e., Kinect by Microsoft, WA, USA), stereoscopy or depth cameras. Although marker-less system are more affordable and flexible than the marker-based ones, the performance achieved by these methods is still not comparable with state of the art approaches.

(a) (b)

Figure 1.1 Motion capture systems: (a) a passive marker-based motion capture system by BTS Bioengineering (Italy, http://www.btsbioengineering.com); (b) an active marker-based optoelectronic system by PhaseSpace Inc. (CA, USA, http://www.phasespace.com).

In fact, marker-based optoelectronic system is considered the gold standard in motion capture because it is highly accurate, minimally intrusive, non-invasive and adaptable to different applications (i.e. sport and clinical fields) (Cappozzo et al., 2005). Generally speaking, the main disadvantages of this approach concern:

- the need of an external infrastructure and specifically trained personnel, which limits its usability in a non-structured environment;
- its complexity and high cost;
- the long time required for setup, calibration, and data cleaning procedures;
- the sensitivity to light conditions and occlusions, which can generate artefacts;
- the need to stay within the limited volume of space that the cameras can capture.

Once the 3D coordinates of the markers are known, the kinematics of the segments in which the markers are placed can be computed, thus velocity, acceleration and joint angles during the movement. More details about human motion analysis using optoelectronic stereophotogrammetry and reconstruction's algorithms are in the specialist literature (Cappozzo et al., 2005; Leardini et al., 2005; Della Croce et al., 2005).

Non-Optical Motion Capture Systems

Alternatives to optical motion capture systems are available, in which usually the tendency is to sacrifice some accuracy in favour of higher flexibility and usability. Some of the non-optical technologies used for motion capture are reported in Table 1.1, such as electromechanical (Figure 1.2a) and inertial (Figure 1.2b).

Optical and non-optical motion capture technologies aim at characterizing human motion from a kinematic point of view. Thus, they provide measures to describe body movements (displacement, velocity, joint angles, etc.) without considering its causes. In order to study also kinetic or muscular activity aspects of motion, other technologies, such as force platform (in particular for the study of gait or posture analysis) and electromyography technique, are employed in conjunction with motion capture systems.

Table 1.1 Description of the principal non-optical motion capture systems

Technologies	Description
Electromechanical	These kind of systems are real-time, relatively low-cost, free-of-occlusion, and highly-accurate but are also sensitive to soft tissue artefacts, can limit the user's movements, require to be calibrated for each subject, and have problems to reconstruct the motion of joints with multiple degree of freedom (i.e., shoulder or hip). An example is the exoskeleton (Figure 1.2a), which is worn by subject and it can directly provide measurements of joint angles and body relative motion through rods connected by potentiometers.
Optical Fibre	Flexible optical fibres are attached on clothes, such as gloves. The fibres are bent with the body movement and the movement amplitude is proportional to the induced attenuation in the light measured by the fibre-optic sensors. This technique permits real-time and inexpensive data acquisition, but it is generally suitable for capturing only the motion of limited body parts, such as the hands.
Electromagnetic	Magnetic motion capture systems use sensors placed on the body to measure the changing in the flux of a magnetic field (usually formed by three orthogonal coils) generated by a transmitter source. By measuring the relative intensity of the voltage or current of the three coils, it can be accurately measure the positions and the orientations of the sensors. The main limitations of this technology are the high cost and the interference problems caused by proximity of ferromagnetic materials in the environment.
Inertial	A variable amount of Inertial Measurement Units (IMUs), equipped with accelerometers, gyroscopes, and often magnetometers, are attached to rigid segments of the user's body, through Velcro straps or using specific Lycra suites. Using biomechanical models, the position and the orientation of segments can be derived, usually building a skeleton model of the subject. Inertial-based solutions are becoming the second most popular motion capture technology, after optical systems, especially because they allow to collect motion data in a variety of non-structured environments, they are self-contained, cost-effective, portable, and relatively easy-to-use. The main drawbacks of this approach are related to noise and drift phenomena, which can lower the accuracy of the measures on the long period. A commercial product for full-body inertial motion capture suite is shown Figure 1.2b.

(a) (b)

Figure 1.2 Non-optical motion capture systems: (a) the Gypsy 7 mechanical suite (CA, USA, http://metamotion.com) and (b) the Xsens MVN inertial motion capture suite (Xsens, Netherlands, http://www.xsens.com).

1.1.3 Clinical applications

Motion analysis systems have been used in clinical environment for several applications, such as the assessment of both normal and pathological movements, the planning and the monitoring of pharmacological and rehabilitation treatments and the evaluation of surgery interventions effectiveness (de los Reyes-Guzmán et al., 2014). Traditionally, clinician's focus in 3D motion analysis has been on the lower limbs and thereby this technique is widespread used in order to assess gait alterations. Conversely, the assessment of the arm movement kinematic by means of motion capture systems is not so common.

However, it has to be highlighted that using motion capture systems is not always feasible in clinical settings, especially given the high costs and complexity in use of these tools. In particular, environmental interferences and occlusion phenomena can occur and this results in very long post-processing and data cleaning operations. Moreover, trained personnel are required to run the acquisitions.

Subsequently in this chapter, the upper limb (UL) evaluation movement in clinic will be briefly described, with particular focus on the analysis of the 3D motion analysis of the UL motor characteristics. Details about UL dysfunctions and its assessment with clinical scales and with motion capture technology will be provided in the next chapters.

1.2 Arm and hand movement

1.2.1 Upper limb motor evaluation tools

Reaching or grasping with the arm and hand is a complex task that appears already in uterus, it is refined over the early years of life and is central to useful activities of daily living (ADL), such as feeding and grooming, during the all course of life (Morris and Whishaw, 2015).

Several neurological conditions, such as Multiple Sclerosis, Parkinson's disease, Stroke, Dementia and Cerebral Palsy, can affect the ability to perform UL movements and thus greatly impact the quality of life of the affected person. Thereby, deficits related to arm and hand functions are one of the most disabling motor conditions, given the huge impact that UL movements have in everyday ADL (Roh, 2013).

In clinical setting, motor abilities may be measured using several approaches and, in fact, many clinical outcome measures have been introduced to assess UL functionality during task performance (Roh, 2013).

A useful reference for the classification of the outcome measures used to address functionality and disability in people with UL motor impairments (Velstra et al., 2011; Lamers et al., 2014) was provided by the World Health Organization (WHO) through the International Classification of Functioning, Disability and Health, more commonly known as (ICF[1]).

The ICF categorizes the outcome measures into "Participation", "Body Functions and Structures", and "Activities" levels. According to the ICF, outcome measures of the "Participation" level assess the individual's restrictions in the involvement of a life situation. These outcome measures are influenced by UL functionality as well as by the ability to walk or independently perform a movement, and the cognitive functions.

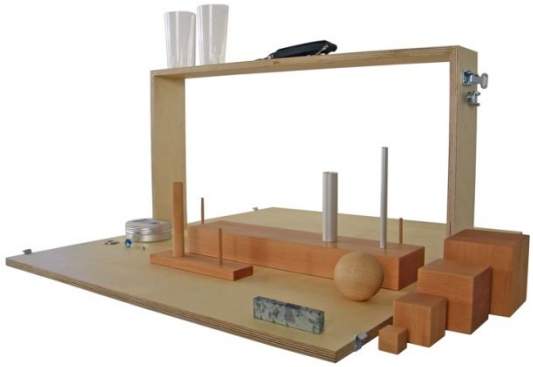
In contrast, the outcome measures of "Body Functions and Structures" level assess the physiological functions and anatomical parts of the body, while the outcome measures of "Activity" level are applied to understand the impairments related to ADL performance. In

[1] The International Classification of Functioning, Disability and Health, or ICF, (http://www.who.int/classifications/icf/en/) is a comprehensive framework of the World Health Organization (WHO) for classifying the describing functioning, disability and health in individuals with various kinds of diseases or condiction (i.e. stroke, tetraplegia, Multiple Sclerosis, Cerebral Palsy, etc.).

according to this latter level, clinicians are used to distinguish in motor capacity and motor performance evaluation (Young et al., 1996; Van Tuijl et al., 2002; Lamers et al., 2014).
The former is referred on motor function assessment of the maximal ability to perform a task that occurs under structured conditions (i.e. in clinical and laboratory settings), while the latter evaluates the motor function that occurs under unstructured environments (i.e. outside laboratory and clinical environments, such as home, work, social events, etc.).

The main goal of rehabilitation treatments is to improve motor capacity, with the assumption that it can lead to motor performance improvements too during real ADLs. However, several studies in rehabilitation field showed that the increase in motor capacity may not predict improvements in UL motor performance of ADLs (Gross et al., 2006; Rand et al., 2011; Cattaneo et al., 2017). Hence, both motor capacity and performance should be measured to accurately assess disability and/or recovery of UL motor functions.

To date, the most frequently used outcome measures in clinic for the UL assessment are a set of clinical scales, timed tests and questionnaires, on the basis of the motor aspect to assess. Some tools are used to evaluate ataxia and tremor (i.e. Fahn tremor rating scale, finger to nose testing), others to assess motor control (i.e. finger tapping, Fugl-Meyer Assessment, FMA), spasticity (like the Modified Ashworth Scale, MAS) or perceived UL performance (i.e. ABILHAND, Disabilities of the Arm, Shoulder and Hand, DASH, Manual Ability Measure- 36, MAM-36, Motor Activity Log, MAL) (Velstra et al., 2011; Lamers et al., 2014). Moreover, the UL capacity can be measured with outcome tools such as the Action Research Arm Test (ARAT, Figure 1.3a), the Box & Block (Figure 1.3b), the Hand Grip Strength (HGS) test with handle-dynamometer (Figure 1.3c), the Coin rotation task, the Nine Hole Peg Test (NHPT, Figure 1.3d), or the Purdue Pegboard test (Rudick et al., 2002; Platz et al., 2005; Aggarwal et al., 2006; Hobert et al., 2010; Severijns et al., 2015; Lin et al., 2016). Furthermore, other clinical tests applied to specific disorders are available. For instance, it can be possible mention the items of UPDRS Unified Parkinson's Disease Rating Scale – Part III (UPDRS-III) dedicated to UL evaluation in Parkinson's disease (Hoffman et al., 2011) or the Assessment of the Motor and Process Skills (AMPS), which are used in dementia (Hartman et al., 1999; Mori and Sugimura, 2007). The most used outcome measures abovementioned are reported in Table 1.2.



(a)

(b)

(c)

(d)

Figure 1.3 Clinical outcome tools for UL capacity assessment: (a) Action Research Arm Test (Reha-Stim Germany, http://www.reha-stim.de); (b) Box and Block (Reha-Stim, Germany); (c) handle-dynamometer for Hand Grip Strength (HGS) test (DynEx, MD Systems, OH, USA, https://www.mdsystems.com); (d) Nine Hole Peg Test (http://www.healthandcare.co.uk).

Overall, UL outcome tools include more objective measures, such as muscle strength, and more subjective measures, such as patient quality of life's perception (Lamers et al., 2013; Lamers et al., 2016), which are strongly influenced by each other (Cattaneo et al., 2017). For instance, HGS value has a critical role during the performance of ADL and it is an important outcome of evaluation of treatment effectiveness (Bohannon et al., 1991; Günther et al., 2008; Cattaneo et al., 2017).

The main advantage of these scales is their easy administration, because they generally require short time and little space for the evaluation and they can be used in clinical routine (Lamers et al., 2014). On the other hand, the main disadvantage is that they suffer from high subjectivity, because they strongly depend on the tester's evaluation (Jasper et al., 2009; Roh,

2013; de los Reyes-Guzmán et al., 2014), and from poor sensitivity to mild impairments (Carpinella et al., 2014).

Furthermore, another important limitation of clinical tools is that more attention is put on motor capacity, while rarely complete ADL tasks (i.e. drinking or moving the hand to the head for combing) are exhaustively assessed (Van Tuijl et al., 2002). This is due in part to the fact that a clinical test cannot easily capture the complexity and the nature of human movement that occurs during ADL outside clinic. In fact, when the ADL tasks are assessed with clinical tests (i.e. in some items of the ARAT), the movement is evaluated as a whole and no specific and detailed information are provided about the phases by which the movement is composed (i.e. reaching the object, grasping and manipulating it) (Carpinella et al., 2014).

Therefore, for all of these reasons, the clinical-based assessment seems insufficient to assess motor strategies used during ADL movements, and their use in combination with other more objective measures is needed (Roh, 2013).
In particular, the kinematic study of UL functions can provide accurate and objective information about motor strategies associated with the movement, thus a better understanding about the UL motor disability and, in the meanwhile, it can help in defining patient-based rehabilitation treatments and in monitoring the effectiveness of therapies for UL (de los Reyes-Guzmán et al., 2014).

Table 1.2 Description of some principal tools (capacity and perceived performance measures) used in clinic for UL functionality.

	Instrumental	Purpose and description of the test	Scoring Methods	Advantages	Disadvantages
Motor Capacity	**Action Research Arm Test (ARAT)**[1,2]	Measure of the unilateral ability to perform UL movement. 19-items for arm divided into four subtests: grasp, grip, pinch and gross movement.	4 scores for items from 0 (deficit) to 4 (competent). The maximum score is 57.	Easy to administrate. Evaluate different grasp, grip and pinch functions.	Ceiling effect in people with less UL motor impairments.
	Assessment of the Motor and Process Skills (AMPS)[3]	Detection of ability to perform ADL movements (i.e. washing dishes by hand or serving drink) with 36-items	4 scores from 1 (deficit) to 4 (competent). A higher score indicates normal abilities in ADL performance.	Specific for Dementia diseases	Ceiling effect in people with mild UL motor impairments.
	Box and Block test[1,2]	Measure of unilateral gross manual dexterity. People are asked to transport as many blocks, one at time, as possible from one box to another.	Number of blocks transferred in one minute.	Easy and quick to administrate.	Require ability to pick up a block.
	Hand Grip Strength test[4,5]	Detection of hand and forearm muscle strength. People are asked to squeeze the handheld dynamometer with much force as possible, being careful to squeeze only one for each measurement.	Maximum strength measured with handheld dynamometer	Easy and quick to administrate.	Reproducibility of the grip strength is influenced by exactly replacing the grip position.
	Nine Hole Peg Test (NHPT) [1,4]	Measure of the unilateral fine hand dexterity. People are asked to place and removes 9 pegs, one at time, as quickly as possible. Time to complete the task is recorded.	Time in seconds need to complete the test. Higher time indicates worse performance.	Easy to conduct. Normative values are available.	Require ability to pick up and manipulate small object with a single hand.
	Purdue Pegboard Test[1,6]	Measure of unilateral and bilateral fine manual dexterity. Persons are asked the place as many pegs or assemblies in one minute. Number of pegs is recorded.	Number of pins and assemblies in 60 seconds.	Easy and quick to administrate (~5 min for both arms).	Requires that person is able to pick up and manipulate small object.

(Lamers et al., 2014); [2](Platz et al., 2005); [3] (Hartman et al., 1999); [4](Kraft et al., 2014); [5] (Hamilton et al., 1992); [6](Hobert et al., 2010); [7](Fynlayson et al., 2013)

Table 1.2 Description of some principal tools (capacity and perceived performance measures) used in clinic for UL functionality. (continued)

	Instrumental	Purpose and description of the test	Scoring Methods	Advantages	Disadvantages
Perceived Performance	**ABILHAND**[1]	Questionnaire to examine self-perceived difficulties in performing 23 manual ADL tasks.	3-point ordinal scale (Impossible, Difficult, Easy). The score is transformed into linear measure using the psychometric Rasch model.	Easy and quick to administrate (~ 10 min to complete and score).	The included tasks are only complex bilateral ones.
	Disabilities of the Arm, Shoulder and Hand (DASH) [1,7]	Self-reported questionnaire to examine self-perceptions of UL functions in 30-items.	5-point ordinal from 0 (no difficulty) to 4 (unable). A higher score indicates worse functioning and symptoms.	Easy and quick to administrate (~ 15 min to complete and score).	Some of included tasks require good UL function and good balance.
	Manual Ability Measure – 36 (MAM-36) [1,7]	Self-reported questionnaire to examine self-perceptions of manual ability in 36-items.	5-point ordinal, from 0 (almost never do) to 4 (easy to do), A higher score indicates greater perceived manual ability.	Easy and quick to administrate (~ 15-20 min to complete and score).	None apparent.
	Motor Activity Log (MAL)[1]	Questionnaire about the quantity and quality of UL use in daily life during 30 ADL tasks.	6-point ordinal, form 0 (no ability and no use of the arm) to 5 (normal ability and use of the arm).	20 min for the administration and score. The MAL includes both unilateral and bilateral ADL tasks.	No Rasch-derived scores available.

[1](Lamers et al., 2014); [2](Platz et al., 2005); [3] (Hartman et al., 1999); [4](Kraft et al., 2014); [5] (Hamilton et al., 1992); [6](Hobert et al., 2010); [7](Fynlayson et al., 2013)

1.2.2 Three-dimensional motion analysis of the upper limbs

As described in *Paragraph 1.1.2*, 3D motion analysis offers an objective method for quantifying movement. The optoelectronic stereophotogrammetry is considered the gold standard in movement assessment and its potential is well-recognised for kinematic analysis of gait. In fact, 3D gait analysis is widespread utilized in biomechanical research and many clinical scenarios (Mackey et al., 2005; Mackey et al., 2008; Cimolin and Galli, 2014; Pau et al., 2016).

The use of motion capture systems is valuable to provide additional objective information also about UL movement abilities, such as accuracy, efficiency of movement, joint angles trajectory and spatio-temporal parameters (Chang et al., 2005; de los Reyes-Guzmán et al., 2014). Results from kinematic analysis of UL movements may be used to discriminate between healthy and pathological motor pattern, to identify maladaptive strategies employed by people with neurological impairments during the task performance, and for helping in the decision making in the clinical settings. For instance, kinematic analysis of UL movement can identify how movements of the trunk and proximal arm were used to compensate for distal arm impairment during reaching and grasping tasks in adults post stroke event (Michaelsen et al., 2001; Murphy et al., 2011).

Over the years, many kinematic studies have been performed in research settings with the aim to quantitatively characterize the UL kinematics during ADL in healthy people in order to provide a normative data (Murphy et al., 2006; Petuskey et al., 2007; Coluccini et al., 2007; Van Andel et al., 2008; Caimmi et al., 2015), while in people affected by neurological pathologies, the most frequently analysed movements were functional tasks, related to reaching and pointing (Alberts et al., 2000; Wenzelburger et al., 2000; Ferrarin et al., 2005; Menegoni et al., 2008; van der Noort et al., 2017). The conditions mostly investigated were stroke (Michaelsen et al., 2001; Michaelsen et al., 2004; Caimmi et al., 2008; Murphy et al., 2011; Aprile et al., 2014) and Cerebral Palsy (Mackey et al. 2005; Ricken et al. 2005; van der Heide et al. 2005; Mackey et al., 2008; Jasper et al., 2009; Cimolin et al., 2012; Butler et al., 2012).

Nonetheless, compared to gait analysis, 3D motion analysis of UL kinematics in clinic appears considerably more complex and over the years different approaches have been adopted to assess the movement kinematics. The complexity of the UL kinematic analysis in clinical environment is mainly due to the non-cyclic nature of UL movements and the lack of

a single most relevant task. In other words, the variety of possible functional tasks makes it complicated to standardize procedures for UL kinematic assessment and, hence, the different studies in this field have investigated different motor tasks (Jasper et al., 2009; de los Reyes-Guzmán et al., 2014). Another reason, more technical, concerns the anatomical complexity of motion at the shoulder joint (van Andel et al., 2008).

However, as aforementioned, the studies regarding 3D UL movement analysis have been used different methodological approaches, marker-set configurations, study set-ups and UL tasks. In literature, most of the used models employed markers placed on bony landmarks (Rab et al., 2002; Mackey et al., 2006; Ricken et al., 2005; Leardini et al., 2011; Cimolin et al., 2012), but also rigid clusters (CAST-methods, Cappozzo et al., 1995) have been adopted (Coluccini et al., 2007; van Andel et al., 2008; Chen et al., 2010; De Baets et al., 2017), even though with different marker sets.

Another important issue when estimating the UL movements is how to represent UL kinematics. Overall, an arm consists of three joints (the shoulder, the elbow and the wrist) and three segments (the upper arm, the forearm and the hand). On the basis of the accuracy needed, the shoulder and wrist joints are represented as a spherical joint, while the elbow as a hinge joint (Rab et al., 2002; Wu et al., 2005; Jasper et al., 2009). However, the shoulder girdle is known as the shoulder complex, which involves a series of joints (sterno-clavicular, scapula-thoracic, acromion-clavicular and glenohumoral) with greater mobility than any other human joint (Wu et al., 2005).

Although the International Society of Biomechanics (ISB) and some authors have suggested to use a different rotation sequence for the shoulder movements taking into account also the glenohumeral and scapular movements (Wu et al., 2005; Coluccini et al., 2007; Kontaxis et al., 2009), in clinical practice seems appropriate and easy to understand the use of the rotation sequence of flexion-abduction-axial rotation (Rab et al., 2002). Accordingly, it has been proven that this sequence rotation and the ISB recommendations for the shoulder lead to identical results (Rab et al., 2008). Moreover, although scapula movement seems to be clinically relevant to better understand the complexity and the abnormal movements of the shoulder joint (De Baets et al., 2017), the mostly used biomechanical shoulder models restricted shoulder movements to a simplified movement between the humerus and the trunk, omitting the scapula and, hence, simplifying the shoulder girdle with a single joint (Rab et al., 2002; Mackey et al., 2006; Coluccini et al., 2007; Petuskey et al., 2007).

Another important aspect regarding the shoulder model entails the calculation of the shoulder joint center of rotation. In literature, different techniques have been described to identify the shoulder joint rotation center, such as regression analysis (Meskers et al., 1998), calculation of the pivot point of instantaneous helical axes (IHA) (Veeger et al., 2000; Wu et al., 2005) or as an offset from external landmark positions (van der Helm et al., 1992; Rab et al., 2002). The ISB recommends the IHA method (Wu et al., 2005), but most studies here considered, represented the shoulder joint rotation center as an offset from external markers (Rab et al., 2002; Coluccini et al., 2007; Petuskey et al., 2007; Menegoni et al., 2008) or even as an external marker itself (Ricken et al., 2005).

For these reasons, the need to standardize the protocol for 3D UL motion has been pointed out by several authors (Rab et al., 2002; Jaspers et al., 2009; Kontaxis et al., 2009; de los Reyes-Guzmán et al., 2014). Despite the proposed protocols and recommendations of some authors (Rab et al., 2002; Kontaxis et al., 2008) and ISB (Wu et al., 2005) for UL biomechanical model, a standardization has not yet been used in studying UL movement characteristics because of clinic scenario's needs.

1.3 Thesis overview

Given the lack of standardized protocol for motion analysis during important UL daily activities, this thesis focuses on characterizing UL abilities in people with neurological diseases during the performance of an ADL task, the hand to mouth movement (HTM), by means of 3D motion analysis technique. In particular, the HTM involves all major joints of the UL and simulates an ADL task (i.e. feeding) and, thereby, it appears feasible and challenging enough to identify motor deficits in people with movement disorders (Menegoni et al., 2008). Indeed, the HTM task is representative of typical important ADL such as feeding and drinking (Bohannon et al., 1991; Menegoni et al., 2008; Mackey et al., 2005) and has been widely used to assess UL functions in individuals affected by neurological diseases (Mackey et al., 2008; Caimmi et al., 2008; Cimolin et al., 2011; Caimmi et al., 2015).

The aim of the dissertation is to provide quantitative information regarding the performed HTM task, such as duration, velocity and accuracy of the movement as well as the associated joint kinematics. Moreover, this dissertation wants to provide quantitative synthetic measures to quantify the deviation of arm movement from normal motor pattern, which may be suitable both for research and clinical applications.

Also, it can be noteworthy understanding if the quantitative synthetic measures approach is appropriate enough for effectively quantifying UL kinematic functions regardless the health status or the specific disease.

For this reason, in this dissertation, this approach is applied in different pathologies, which are totally different from each other:

- Multiple Sclerosis, which is the most common immune-mediate inflammatory diseases, characterized by demyelination of axon in different degrees, mainly diagnosed in young and middle-age adults (20-40 years (Haussleiter et al., 2009; Finlayson et al., 2013).
- Parkinson's disease, which is a progressive neurological disease, which affect older adults (>50 years), characterized by a degeneration of dopaminergic neurons in the area of the brain called substantia nigra (Politis and Niccolini, 2015).
- Dementia with Parkinsonism, known as Dementia with Lewy Bodies, which is a common neurodegenerative dementia in older people, characterized by the presence of cytoplasmic clumps, called Lewy Bodies, in the substantia nigra (Vann Jones et al., 2014; Gomperts et al., 2016).

Even if these three pathologies have different etiology, their main common feature depends on their neurodegenerative nature. In fact, the progression of the disease over time could produce significant motor (i.e. balance, gait or UL motor deficits) and non-motor disability (i.e. cognitive impairments). The UL motor impairments, especially, may negatively affect carrying on daily activities and, hence, impact on patient's independence. However, objective information about UL movement deficits during functional task in each of these pathologies is still limited. A way to quantify the motor impairments is essential for neurological rehabilitation, thus, it seems interesting to provide a useful understanding of the impact of the pathologies on UL motor abilities, quantitatively characterizing the UL motor features of each of them during a basic HTM task.

Thus, this dissertation is structured as follows:

- *Chapter 2: Experimental protocol for Hand to Mouth task evaluation.* In this chapter, it is described the task procedure, the biomechanical model, the marker-set and the data analysis.

- *Chapter 3: Quantitative assessment of Hand to Mouth Task in Multiple Sclerosis.* The technical approach described in the Chapter 2 for the HTM task, is proposed for assessing the movement abilities in a group of people affected by Multiple Sclerosis. Some of the results presented in this Chapter have been published in an international journal and Conference proceedings.
- *Chapter 4: Quantitative assessment of Hand to Mouth Task in Parkinson's disease.* The approach proposed for characterizing people with Multiple Sclerosis, is used for assessing the HTM task of a convenient group of people with Parkinson's disease. The relative results are described in details.
- *Chapter 5: Quantitative assessment of Hand to Mouth Task in Dementia with Parkinsonism.* In agreement with previous chapters, the approach is proposed for the assessment of UL functions in people who suffer from dementia with Lewy Bodies. In order to understand how Parkinsonism motor signs and cognitive decline may influence the HTM performance, a comparison between people with dementia and Parkinson is also performed.
- *Conclusions and future work.* The findings of the dissertation are summarized and , finally, recommendations for future work are made, including a discussion on possible improvements as well as the potential further uses of this work.

The introduction and the methods sections within the Chapter 3, 4 and 5 may contain information redundant to the Chapter 1 and Chapter 2.

Chapter 2

Experimental protocol for Hand to Mouth task evaluation

'If you cannot measure it, you cannot improve it' – W. Thomson, Lord Kelvin

The focus of this chapter is to describe the protocol of assessment of the UL kinematics during a functional task representative of daily living, the hand to mouth (HTM). In particular, the task procedure and the marker setup used for the task acquisition are presented in detail. Then, the biomechanical model and the data processing are described, as well as the movement features which will be used in the study described in next chapters for characterising the upper limbs abilities in presence of neurological diseases. Details about participants and used clinical tools are provided in the following chapters.

2.1 Introduction

As mentioned in *Chapter 1*, in clinical settings the motor limitation assessment in different pathologies should be performed by analysing functional goal-oriented tasks. In particular, each task should represent a movement involved in ADL, such as feeding and dressing, and it should be simple enough to allow the goal achievement by patients affected by different pathologies. Moreover, it should be difficult enough to allow the description of the functional limitation of patient affected by different pathologies and it may be linked to movements usually proposed in clinical measures (Butler et al., 2010; Lamers et al., 2016). Finally, in order to use it in clinic settings it should provide a detailed movement description to permit repeatability and standardization.

As already mentioned in the *Chapter 1*, the tools typically employed in clinical setting may not be enough to assess what kinds of motor strategies of UL are used during functional movements. It appears suitable using them in combination with other measures such as kinematics which provides accurate and objective information about associated motor strategies. Whereas functional movements such as pointing and reaching have been largely investigated in neurological diseases, UL kinematics during ADL appears less analysed (Menegoni et al., 2008; Butler et al., 2010; Kim et al., 2011; Cimolin et al., 2012).

This work would like to establish the usefulness of 3D kinematic analysis as an outcome measure to assess performance of an everyday functional activity, the HTM task. This task, which resembles the act of eating and drinking (Bohannon et al., 1991; Menegoni et al., 2008; Mackey et al., 2005), has been used to assess UL functions in individuals affected by Stroke (Mackey et al., 2008; Caimmi et al., 2015) and Cerebral Palsy (Cimolin et al., 2011).

2.2 Experimental design

2.2.1 Hand to mouth task

The HTM task was performed having participants comfortably and safely sat on a chair with a comfortable seatback in the centre of video-capture's volume area. The chair was positioned in front of a table which was adjusted in height so that when the participants placed their hand palms on the table, the shoulders and the wrists assumed a neutral position, with the elbows flexed at approximately 90° and the forearm prone, as described in previous

similar studies (Caimmi et al., 2008; Menegoni et al., 2009; Mackey et al., 2005; Cimolin et al., 2011).

Participants were then instructed to perform the HTM task at a self-selected pace as follows: from starting position, following a verbal signal, they moved their hand to touch their mouth with the palm and then, returned to the starting position (Figure 2.1). The movement was repeated at least six times for each arm in a single acquisition, which took approximately 10 minutes.

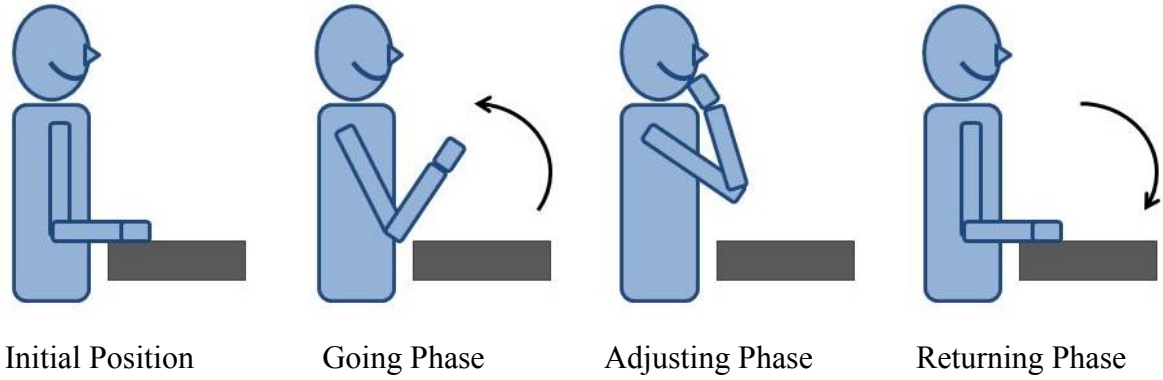


Figure 2.1 Representation of the several phases of the hand to mouth movement.

2.2.2 Participants

In this thesis, people with neurological disorders (Multiple Sclerosis, Parkinson's disease and Dementia with Lewy Body) and healthy age- and gender-matched volunteers were recruited for a cross-sectional study. The sample size for each study is similar to those of previous similar studies in the field. Each participant was informed about the study purposes and signed a written informed consent in accordance with Helsinki's Declaration. Groups' characteristics as well as clinical assessment tools used to assess movement disabilities will be extensively described in the next chapters (*Chapter 3, Chapter 4* and *Chapter 5*).

2.2.3 Marker positions and model

Retro-reflective markers (14 mm diameter) were positioned with double-sided adhesive tape on the superficial bony landmarks (Table 2.1, Figure 2.2) to reduce the effect of marker movement artefact due to skin tissue (Leardini et al., 2005) and to facilitate the marker replacement in repeated testing, following ISB recommendations (Wu et al., 2005), already employed in other kinematics studies (Rab et al., 2002; Murphy et al., 2006; Petuskey et al., 2007; Cimolin et al., 2012).

The three dimensional UL model consisted on eight segments (head, trunk with the shoulder girdle, right and left upper arm, right and left forearm, right and left hand). These segments were assumed to be rigid and non-deformable bodies, defined by three markers, generally representing a proximal and distal point of the segment and a third non-collinear marker to allow rotational orientation (Rab et al., 2002). This has allowed determining embedded coordinate frames for each segment from three associated non-collinear points.

Markers were placed bilaterally on the acromion (RSHO and LSHO), lateral epicondyle (RELB and LELB), ulnar (RULNA and LULNA) and radial (RRADIUS and LRADIUS) styloid processes, on third metacarpal head (RHAND and LHAND) in order to identify the position and orientation of the arm, forearm and hand segments. The head and trunk positions were estimated by placing markers respectively on the zygomatic (RHEAD and LHEAD) and nasion (NASION) processes and mouth (head), right and left acromion (RHSO and LSHO), clavicular (CLAV) notch and spinous processes of the C7 and T8 vertebrae (trunk).

The marker on the chin was then removed after the acquisition of a rest trial in order to avoid interference with the fingernail marker during the acquisition of the HTM movement.

Table 2.1 List of bony landmarks that were used in the study.

Bony landmarks	**Description**
Head	
NASION: nasion process	Head centre on the
HEAD: zygomatic process	On right and left frontal bone
MOUTH: chin	Under the bottom lip, between mouth and chin
Trunk	
C7: processus spinous of 7th cervical vertebra	Most dorsal point
T8: spinous process of the 8th thoracic vertebra	Most dorsal point
CLAV: incisura jugularis	Deepest point of the suprasternal notch
Upper arm	
SHO: acromion	Most dorsal point on the right and left acromionclavicular joint
ELB: lateral epicondyle	Most caudal point on right and left lateral epicondyle
Forearm	
ULNA: ulnar styloid process	Most caudal-lateral point of the right and left ulna
RAD: radial styloid process	Most caudal-lateral point of the right and left radius
Hand	
HAND: 3rd metacarpal head	Most dorsal point on dorsal side of the hand
FING: distal phalanx	On the right and left fingernail

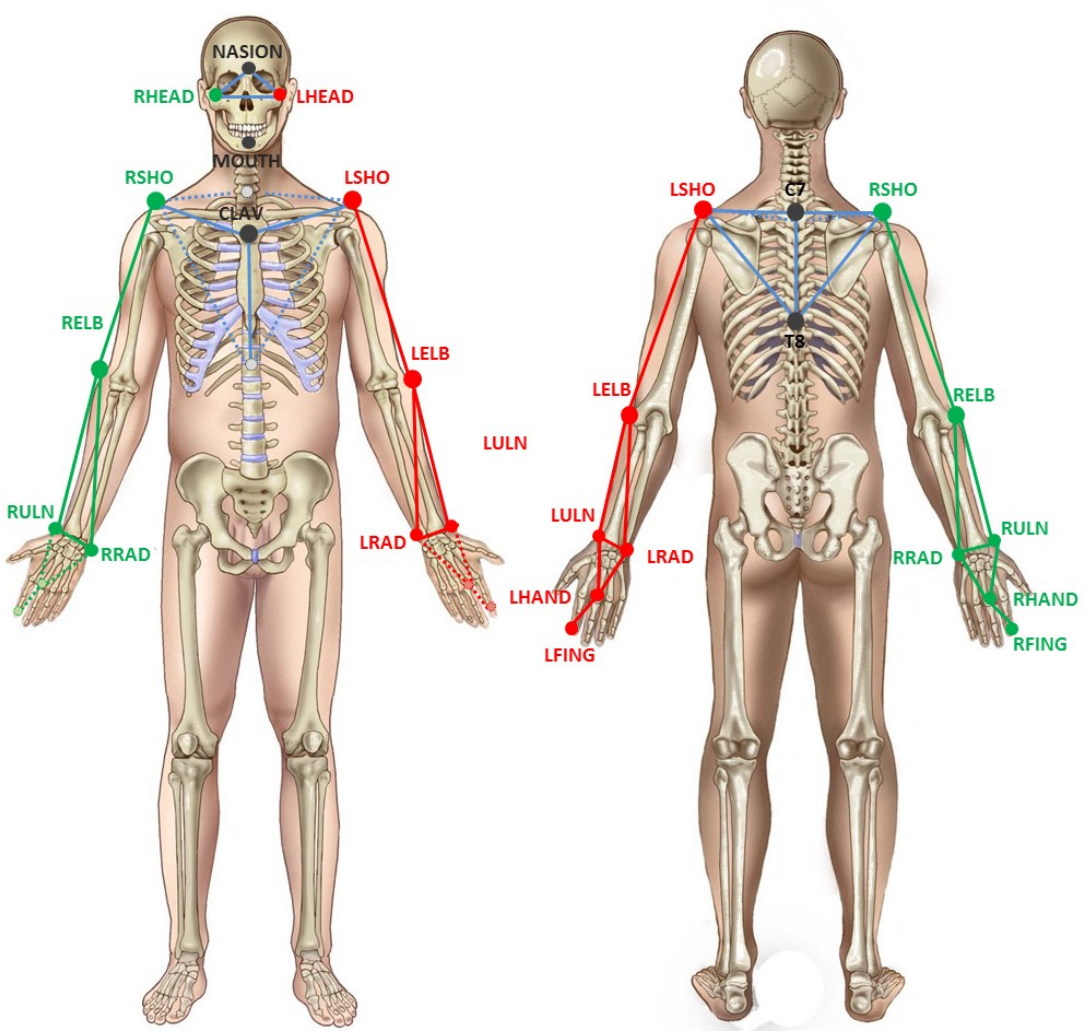


Figure 2.2 Frontal and posterior view of the marker setup and relative stick diagram for kinematic analysis of upper limbs. Markers of the left side are reported in red, markers of the right side in green, while the others are represented in black. The MOUTH marker (placed on the chin, above to the mouth) was removed after a static trial.

2.2.4 Data acquisition

The 3D motion analysis of the HTM task was performed using a motion capture system based on passive markers equipped with 8 infrared cameras set at a sampling rate of 120 Hz (SMART-D, BTS Bioengineering, Italy). Two digital video cameras (BTS Vixta, Bioengineering, Italy), integrated with the motion capture system, recorded the movement in frontal and sagittal planes for documentation purposes.

Prior to data collection, the cameras were calibrated to a measurement volume of almost 75x75x65 cm (Murphy et al., 2006; Murphy et al., 2011) and the markers visibility throughout the task was verified with a person sitting in the measurement area. The global

coordinate system was defined with X-axis directed laterally to the right, Y-axis directed forward (anteriorly) and Z-axis directed upward (superiorly).

2.2.5 Data processing

After kinematic data collection, each trial was checked in the Smart Tracker environment (BTS Bioengineering, Italy), where markers were labelled in according with the biomechanical model (Figure 2.2) and their entire 3D trajectory was reconstructed as a function of time.

Then, the raw data was processed by means of a custom code implemented in the Smart Analyzer environment (BTS Bioengineering, Italy). The 3D trajectories data was filled using a cubic-spline and low-pass filtered before further calculations (4^{th} order zero-lag Butterworth filter, cut-off frequency of 6 Hz). Then velocity and acceleration of each marker were computed through numerical differentiation (D'Amico and Ferrigno, 1992).

According to previous studies (Menegoni et al., 2008; Cimolin et al., 2011; Rigoldi et al., 2012), the HTM movement was segmented into three main phases, as represented in Figure 2.1:

- Going phase (GP): identifies the hand movement from the table to the mouth;
- Adjusting phase (AP): dedicated to precisely locating the mouth;
- Returning phase (RP): the hand is moved back to the initial position.

The starting and ending time of different phases were automatically detected by setting a threshold value for the velocity of the hand marker equal to 10% of the peak velocity of the hand calculated on the whole trial (Topka et al., 1996; van der Heide et al., 2005; Murphy et al., 2006; Coluccini et al., 2007; Carpinella et al., 2014). Following the same criteria, the starting and ending time of the AP, which corresponds to the end of the GP and the start of the RP, were defined. The finger-target distance was computed too, in order to identify the instant in which the subject touches his mouth, which was the time of minimum distance of the finger from the mouth. In Figure 2.3 is reported an example of the 3 task's phases computed taking into consideration the velocity profile of the marker positioned on the hand.

The three phases above described for the HTM movement are summarized in Table 2.2.

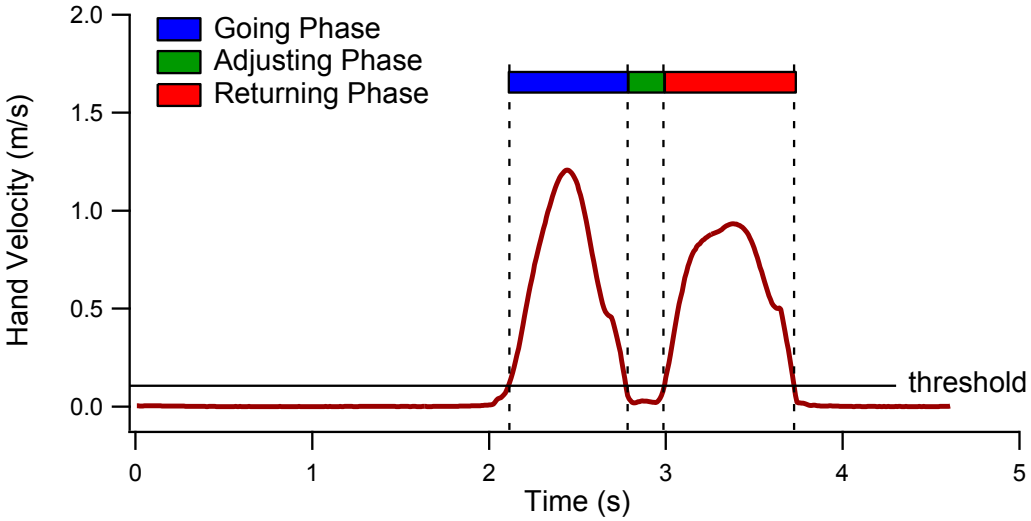
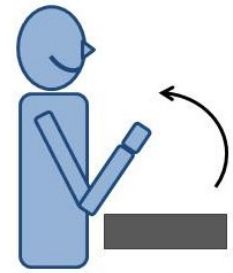
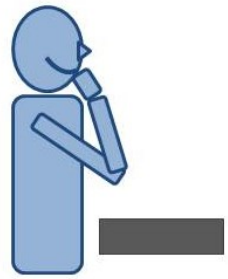
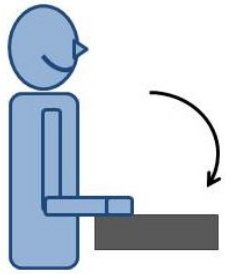


Figure 2.3 Hand velocity during the HTM task: representation of the phases' definition.

Table 2.2 Phase definitions for the HTM movement cycle.

	Phase name	Start	End
	**Going Phase (GP)**	**Hand movement begins:** hand's marker velocity exceeds the velocity-threshold.	**Hand begins to move towards the mouth:** elbow is in his maximal flexion. Hand velocity drops velocity-threshold.
	**Adjusting Phase (AP)**	**Hand moves towards the mouth:** hand's velocity drops velocity-threshold.	**Hand begins to move back to initial position:** hand's velocity exceeds above the velocity-threshold.
	**Returning Phase (RP)**	**Hand moves back to initial position:** hand velocity exceeds above the velocity-threshold.	**Hand is back resting in initial position:** elbow is in his maximal extension. Hand velocity drops below the velocity-threshold.

As regard UL model, the computation of UL joint centers of shoulder, elbow and wrist was carried out from anthropometric offsets of markers on the skin (van der Helm et al., 1992; Veeger et al., 1997; Rab et al., 2002).

UL coordinate systems were established at each joint on the basis of the method proposed by the Standardization and Terminology Committee of the International Shoulder Group (ISG) of the ISB (Meskers et al., 1998; Wu et al., 2005), as described by Rab et al. (2002).

Eulerian angles (X-Y-Z sequence that corresponds to flexion, abduction and axial rotation) were used for arm joint angles, according with the joint coordinate system. In particular:

- Joint flexion – extension was measured about medio-lateral axis: positive value represents the flexion, while negative value the extension (0°: neutral position for the shoulder; in the elbow movement 0° represents the maximal extension physiologically possible);
- Joint abduction – adduction was measured about the anterior-posterior axis: positive value represents the adduction, while negative value the abduction;
- Joint internal – external rotation was measured about longitudinal axis: positive value represents the internal rotation, while negative value the external rotation (0°: neutral position).

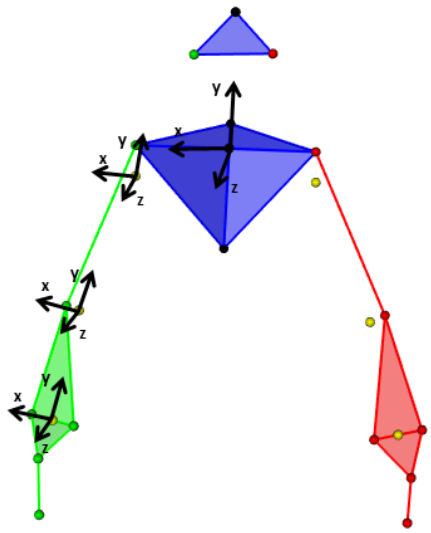


Figure 2.4 Upper limb model used to compute kinematics: segmental coordinate systems are displayed for the trunk and right upper limb. Joint centers are displayed with yellow circle/cross.

In agreement with clinical convention, shoulder angle movements were representing by movements between upper arm and trunk segments. Glenohumeral and scapulothoracic joint motions as shoulder movement contribution were ignored for the HTM movement, and it was taken into account only the acromion-clavicular joint. Elbow motion was assumed uniplanar (flexion-extension) and, so, it was computed as angle movement between forearm and upper arm. Lastly, wrist angle motion was defined by movements between hand and forearm segments.

Trunk motion was calculated relatively to the fixed coordinate system of laboratory (0°: trunk upright; positive value: flexion or forward rotation; negative value: extension or backward rotation). Finally, forearm pronation and supination were modelled as rotation about the longitudinal axis of forearm, which connected the elbow and ulna markers (0°: fully supine; positive value: pronation).

2.2.6 Kinematic features of movement

Spatiotemporal and angular kinematic variables used to evaluate the task are the most considered for analysing the UL movement performance (de los Reyes-Guzmán et al., 2014). The spatiotemporal variables were divided into temporal, velocity and smoothness parameters (Table 2.3). Movement features are following described.

Table 2.3 Description of spatiotemporal and kinematic variables.

Parameter	Name	Unit
Time	Total movement time	S
Time	Going Phase (GP)	s, %
Time	Adjusting Phase (AP)	s, %
Time	Returning Phase (RP)	s, %
Velocity	Mean velocity	m/s
Smoothness	Tremor	Hz
Stability	Adjustment sway (AS)	-
Kinematics	Range of Motion	°
Kinematics	Arm Profile Score (APS)	°
Kinematics	Arm Variable Scores (AVS)	°

Time parameters

Movement time was computed as the time required completing the HTM task, so it is the time between the start and the end of movement (s).

Moreover, the single phases of the movement (GP, AP and RP) were expressed in seconds and as a percentage of the total movement cycle (Menegoni et al., 2008).

Velocity parameters

Velocity parameters include mean and peak velocity, as computed form the speed profile of the hand marker during the GP. Increase in velocity parameters generally indicates an improvement in task performance (Chang et al., 2005).

Tremor parameter

Movement smoothness was assessed using frequency of change in direction of the hand. In fact, the presence of confounding hand displacements originated by tremor was assessed by calculating the frequency of changes in direction of the hand trajectory during the movement as a smoothness measure (Quintern et al., 1999; Menegoni et al., 2009). To this end, a digital band-pass filter (2-10 Hz) was used to separate voluntary movements (0-2 Hz) from tremor (2-12 Hz). The analysis of tremor, so, was performed by digital band-pass filtering on unfiltered fingertip marker data.

Stability parameter

Movement stability was estimated in terms of adjustment sway (AS, in mm), which represents the overall length of the 3D trajectory followed by the fingertip during the AP phase (Figure 2.5). It measures the adjustments made to precisely reach and touch the mouth (Feng et al., 1997; Menegoni et al., 2008). Thus, AS decreases as movement precision increases.

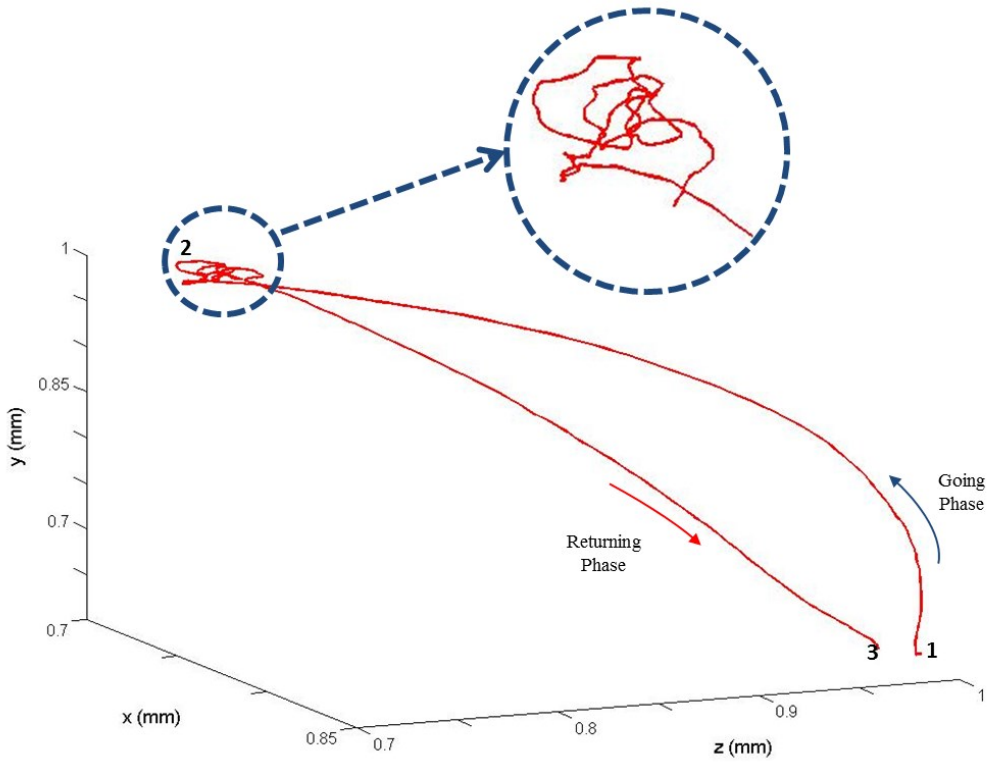


Figure 2.5 Representation of the 3D fingertip trajectory during the HTM task. The hand starts from the top of the table located in front of the person (point 1) and then it moves towards the mouth (Going Phase, GP). During the Adjusting Phase (AP, area 2), the hand touches the mouth, and it moves back (Returning Phase, RP) to end position (point 3). In the circle is highlighted the 3D sway path described by fingertip during the AP, namely Adjusting Sway (AS).

Joint and segment kinematic parameters

Upper arm and forearm kinematics were assessed by means of joint (shoulder, elbow and wrist) motion curves which were time-normalized and plotted as a function of the movement time. Similarly, trunk flexion-extension and forearm pronation-supination were assessed.

Dynamic range of motion (ROM, in degrees) at the shoulder, elbow and wrist were calculated as the difference between the highest and lowest joint angle value on the sagittal plane (shoulder, elbow and wrist) and on the frontal plane (shoulder) during the task. In Figure 2.6 is reported an example of dynamic ROM calculation referring to shoulder abduction-adduction during the HTM movement.

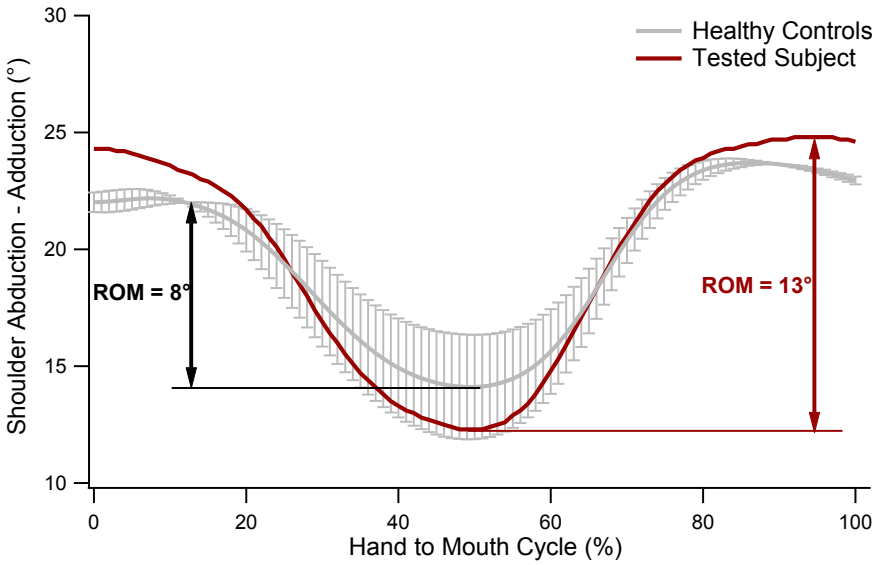


Figure 2.6 Examples of dynamic Range of Motion (ROM) calculation for Shoulder Abduction-Adduction. It is reported the ROM for a tested subject (ROM=13°) and the relative value for healthy subjects (ROM=8°).

Kinematic synthetic measures

Several measures have been proposed to provide a single score able to quantify the overall severity of gait disorders (Cimolin and Galli, 2014), such as Gillet Gait Index (Schuttle et al., 2000), the Gait Deviation Index (Schwartz and Rozumalski, 2008) and the Gait Profile Score (GPS) (Baker et al., 2009). Using similar approaches, researches have proposed synthetic measures of UL kinematics. In particular, this was done to assess arm swing during gait (Riad et al., 2011; Frykberg et al., 2014) and to quantify UL deviations from normal movement pattern during reach to grasp (Jasper et al., 2011; Butler et al., 2012) and hand to head or hand to shoulder movements (Jasper et al., 2011; Salvia et al., 2015).

In particular, the Arm Profile Score (APS) is a synthetic index based on UL kinematic data recently proposed for children with motor limitations (Jasper et al., 2011), with the purpose to describe the deviation from a physiological pattern of a given UL movement associated to several functional tasks (i.e. reach to grasp, hand to head, hand to shoulder). In accordance with the basis of the mathematical construction of GPS developed by Baker et al. (2009) to characterize gait, the APS is defined as the root mean square (RMS) deviation between the individual's kinematic data and an average reference value calculated over a whole movement cycle in a population of healthy individuals. Similarly to GPS, APS has the peculiarity to be independent from the pathology, so it can be calculated directly from the data of one individual and the average data of a range of healthy people.

In the present study, instead of using the 13 variables considered by Jaspers et al. (2011), the APS was expressed as combination of a restricted subset of 7 relevant variables (Arm Variable Score, AVS), considered relevant for the HTM task, and associated with the following movements: trunk flexion-extension, shoulder rotation, shoulder abduction-adduction, shoulder flexion-extension, elbow flexion-extension, forearm pronation-supination and wrist flexion-extension. This APS will hereafter be referred to APS_7.

The APS here proposed differs from the one proposed by Jasper et al. (2011) for two reasons. Firstly, the APS_7 assesses UL motion during a single functional UL task, the hand to mouth, unlike during four to eight different tasks in children with CP (Jasper et al., 2011; Salvia et al., 2015). Secondly, the APS_7 considers only the trunk flexion-extension because HTM basically does not require trunk axial rotation and obliquity.

Each AVS is calculated as the RMS difference across time between the joint motion curve of an individual and that same angle mean curve of the reference healthy dataset.

Thus, AVS is given by the equation below, where T is the number of instants into which the movement cycle has been divided:

$$AVS_i = \sqrt{\frac{1}{T}\sum_{t=1}^{T}(x_{i,t} - x_{i,t}^{-ref})^2}$$

The value $x_{i,t}$ is the i-esim kinematic variable computed on a specific instant of the movement cycle t, and $x_{i,t}^{-ref}$ is the mean value of the same variable on the same instant referred to the healthy population.

The APS_7 (expressed in degrees) can be thus obtained by the following relationship:

$$APS_7 = \sqrt{\frac{1}{N}\sum_{i=1}^{N} AVS_i^2}$$

where N = 7 (the set of movements considered and previously listed). A higher APS_7 value implies a larger deviation from a physiological movement.

Figure 2.7 shows an example of AVS calculation referring to elbow flexion-extension during the HTM manoeuvre for two individuals with Multiple Sclerosis characterized by different

level of disability, as reported by their Expanded Disability Status Scale (EDSS) scores.[2] Impairments in UL movement and the application of these measures to Multiple Sclerosis will be described in detailed in *Chapter 3*.

As it can be seen on the graph, a more severe impairment leads to a greater distance between patients' curves and the reference curve calculated for healthy subjects. Correspondingly, as it will be presented in *Chapter 3*, the larger deviation from the hypothetical normal movement of the individual with higher EDSS score should result in a higher AVS value.

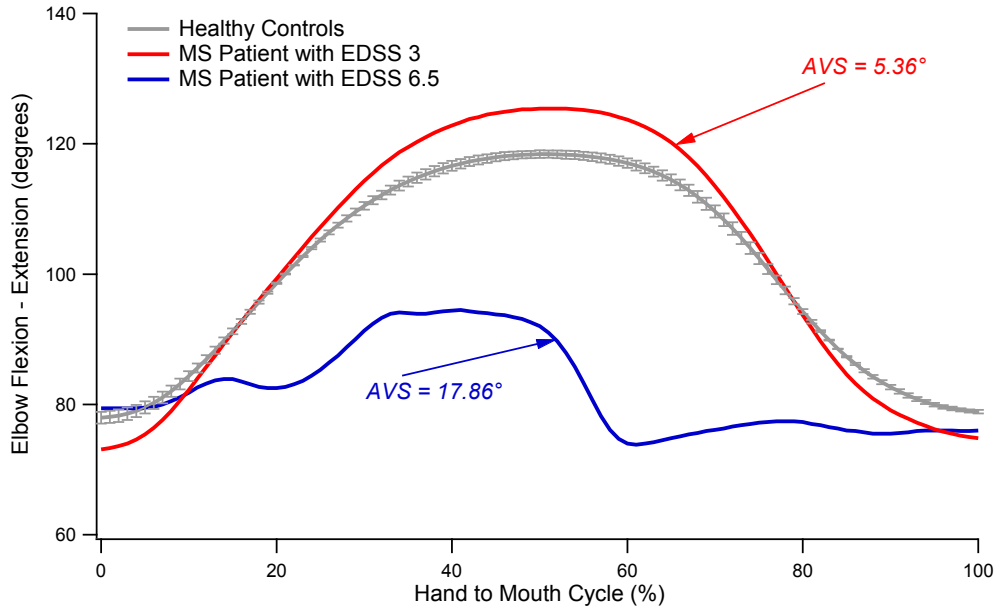


Figure 2.7 Examples of Arm Variable Score (AVS) calculation for Elbow Flexion-Extension. The larger deviation from physiological movement of the individual with higher EDSS results in a higher AVS value.

2.2.7 Statistical analysis

The Statistical Package for Social Sciences (SPSS Statistics, IBM) was used for data analysis. The level of significance was set at $p < 0.05$. Data analysis will be described in detailed in each chapter, according with the characteristics of the investigated pathology.

Generally, demographic data, clinical and kinematics characteristics were firstly described with descriptive statistics, using mean and standard deviation. Differences between groups for the investigated features as well as relationships between clinical scores and kinematic

[2] The Expanded Disability Status Scale (EDSS) is the gold standard scale used to evaluate disability in Multiple Sclerosis, in both daily clinical practice and trials. An EDSS score equal to 3 corresponds to a moderate motor disability, while an EDSS score of 6.5 corresponds to a severe overall impairment.

values were assessed with parametric or non-parametric tests, in accordance with the data distribution.

Chapter 3

Quantitative assessment of Hand to Mouth Task in Multiple Sclerosis

'MS is always in the back of your mind. If there is something you want to do, you always wonder if the MS will allow you do to it' – Darlene, living with MS for 22 years

Multiple Sclerosis (MS) is one of the most disabling chronic disease in young and middle age population. Upper limb (UL) dysfunctions, besides walking disability, fatigue and cognitive deficits, are quite widespread and have a great negative impact on daily living activities (Kraft et al., 2014; Lamers et al., 2014). Quantitative measurements of the impairments of UL functions could give further information about disability level of people with MS (pwMS) with respect to clinical outcomes and contribute to better planning patient-based rehabilitation treatments. In this chapter, a quantitative assessment of the UL kinematics during a Hand to Mouth task in pwMS is presented. Moreover, synthetic measures based on kinematic data and able to represent UL deviation movement from physiological pattern are described and experimentally investigated.

3.1 Introduction

3.1.1 Multiple Sclerosis

Multiple Sclerosis (MS) is a chronic, neurological and progressive disease of the Central Nervous System (CNS). It is characterized by neuronal demyelination and axonal degeneration, leading to cumulative heterogeneous disability over time. MS is mainly diagnosed in young and middle-age people (20-40 years) and its prevalence in women is twice as high as in men (Haussleiter et al., 2009). The cause of MS is still unknown, but it appears that it is required a combination of genetic susceptibility and environmental factors for its development (Dendrou et al., 2015; Monti et al., 2016).

The pathology appears rather unpredictable (Goldenberg, 2012) and, on the basis of the MS type, it could be characterized by episodes of reversible neurological deficits (Relapsing-Remitting MS), which could be followed by progressive neurological deterioration over time (Primary or Secondary Progressive MS) (Finlayson et al., 2013). Moreover, the MS impairments are disabling and may affect many ADL such as eating, typing, using the shower and toilet, dressing and writing, reducing functional independence, productivity and quality of life as well as socioeconomic status (Cattaneo et al., 2017).

Some of the most common symptoms are walking deficit, which has been reported in up to 90% of people with MS (pwMS) (Bethoux et al., 2011). Other disabling symptoms in MS include: fatigue, a kind of exhaustion which is out of all proportion to task undertaken; unusual feeling in the skin such as numbness; slowed thinking; visual problems; muscle dysfunctions, such as muscle weakness, spasticity, lack of selective motor control (Kister et al., 2013). Even if UL dysfunctions are also common in pwMS, their importance is underestimated with respect to walking impairments (Kraft et al., 2014). In fact, recent studies reported a high prevalence of UL disability, especially in progressive stage, and the self-reported limitations were confirmed by clinical outcome measures of arm performance (Lamers et al., 2016). Approximately 50% of pwMS exhibits sensory-motor UL dysfunctions such as impaired sensation (i.e. reduced sensibility, pain), motor impairments (i.e. reduced arm strength and manual dexterity), cerebellar symptoms (i.e. tremor, ataxia, dysmetria) and motor fatigue (McDonald et al., 2006; Holper et al., 2010; Kraft et al., 2014; Bertoni et al., 2015). These dysfunctions involve either one or both limbs (Johansson et al., 2007; Bertoni et

al., 2015), and can be present even since early stages of the disease (Lamers et al., 2014; Bertoni et al., 2015).

In particular, a recent study, conducted by Bertoni et al. (2015), evidenced the prevalence of symptoms causing UL dysfunctions in 105 pwMS. They found that about 68% and 44% of pwMS had bilaterally impaired tactile sensitivity and muscle weakness, 28% and 30% of pwMS presented bilaterally intention tremor and ataxia, while spasticity and decreased range of motion in wrist extension were only bilaterally present in 5% and 4% of the studied population.

A careful neurological examination of the symptoms in each patient is required to make a diagnosis the MS. When the diagnosing of MS is verified, pharmacological treatments are chosen ad hoc for the patient. However, the pharmacological therapies are currently focused on reducing the duration of inflammatory events, decreasing the frequency of acute exacerbations and manage MS symptoms, but they cannot cure the disease nor restore functionality (Pellegrino et al., 2015). Moreover, together with drugs, a relevant rule is given by the rehabilitation of motor functions, which is widely employed to manage the functional impairments and recovery the lost abilities in MS.

To provide a useful understanding of the impact of MS on motor abilities and, consequently, in defining patient-focused therapies, it could be worthwhile to extensive investigate not only the walking and balance impairments but also the UL abilities in pwMS.

3.1.2 Clinical motor assessment

The clinical assessment of MS deficits seems somehow to neglect the importance of the UL limitations with respect to lower limbs deficits (i.e. balance and walking) (Lamers et al., 2016). However, it is important to note that typical UL impairments might negatively affect a wide range of ADL like eating, dressing, grooming, manipulating of small object, even in the early stages of MS (McDonald et al., 2006; Yozbatiran et al., 2006; Johansson et al., 2007; Kraft et al., 2014). Moreover, UL impairments are relevant especially in individuals with greater levels of disability, because the ability to use walking aids may be affected by them (Kraft et al., 2014; Lamers et al., 2016). Concurrently, given their negative impact, UL dysfunctions are important predictors of social participation restriction (Kierkegaard et al., 2012; Cattaneo et al., 2017).

The less importance given to the assessment of UL limitations compared to lower limb dysfunctions is reflected on the most frequently used measure of disability in MS, the Expanded Disability Scale Score (EDSS)[3], which is a scale substantially based on the assessment of change in walking ability (Kurtzke, 1983), especially from score 4.0 upwards.

On the other hand, a composite outcome measure that takes into consideration the total body functions (lower body, upper limbs and cognitive functions) is the MS Functional Composite (MSFC) (Fisher et al., 2001). Indeed, the MSFC's components are the Timed 25-Foot walk, the Nine Hole Peg Test (NHPT) and the Paced Auditory Serial Addition Test (PASAT). However, the MSFC is used as a research tool, while the EDSS remains the common standard tool used to identify the disability level of MS by the time.

Given the lack of clinical approach oriented to assess UL in MS, it is important to carefully analyze the UL motor functions features in MS in order to evaluate the progression of the disease and plan suitable rehabilitation strategies in order to maintain the functional status or manage the symptoms (Lamers et al., 2016).

Several reviews on UL motor assessment (Rudick et al., 2002; Lamers et al., 2014; Kraft et al., 2014; Lamers et al., 2016) confirmed that the clinical assessment of UL motor impairments is usually performed using different rating scales, timed tests and strength test (Finlayson et al., 2013). Some of the standard assessment tools used for UL motor abilities in pwMS are reported in *Chapter 1, Paragraph 1.2.1*. Moreover, in MS the presence of tremor and dysmetria of UL could be measured in clinical settings with finger to nose testing, where the person is asked to touch his nose with his fingertip, alternating right and left side. Another tool used to assess tremor severity of UL is the Fahn Tremor Rating Scale (Hooper et al., 1998).

Given that the importance of motor impairments of manual dexterity and hand grip strength (HGS) in ADL, the NHPT and the HGS tests are often used in clinical settings for evaluating UL motor deficits in MS (Bertoni et al., 2015; Cattaneo et al., 2017). In particular, the NHPT

[3] EDSS scale ranges from 0 (no disability) to 10 (higher levels of disability) in 0.5 unit increments. Scoring is based on an examination by a neurologist.
EDSS steps 1.0 to 4.5 refer to people with MS who are able to walk without any aid and is based on measures of impairment in eight functional systems: (1) pyramidal – weakness or difficulty moving limbs; (2) cerebellar – ataxia, loss of coordination or tremor; (3) brainstem – problems with speech; (4) sensory – numbness or loss of sensations; (5) bowel and bladder function; (6) visual function; (7) cerebral (or mental) functions; (8) other.
Each functional system is scored on a scale of 0 (no disability) to 5 or 6 (more severe disability).
EDSS steps 5.0 to 9.5 are defined by the impairment to walking.
Although the scale takes account of the disability associated with advanced MS, most people will never reach these scores.

is the most used test of UL function used for research and clinical practice in MS (Finlayson et al., 2013; Kraft et al., 2014; Feys et al., 2017), even if it is a primary measure of hand dexterity and could provide information about UL coordination. The NHPT requires the individuals to pick up the nine pegs one at time from a box, put them into nine holes of a pegboard in any order till all of the holes are filled, and then remove the peg one at a time and return them from the pegboard to the box as quickly as possible. Subjects are scored on the basis of the amount of time (in seconds) passed since they have touched the first peg and placed the last one in the box (Kellor et al., 1971). Alternatively, the score can be expressed in terms of number of pegs moved per second (Feys et al., 2017).

Instead, the HGS by means of dynamometer is a simple and standard procedure commonly used by clinicians to determine the forearm and hand disability ratings in terms of muscle strength (Hamilton et al., 1992; Günther et al., 2008). Moreover, the grip strength may influence the performance of a functional task like HTM (Bohannon et al., 1991) and may also be useful for identifying motor fatigue in pwMS (Kraft et al., 2014).

However, clinical tools suffer from some serious limitations. In fact, they are poorly sensitive to mild impairments and unable to accurately capture changes in motor skills in response to intervention (Rosti-Otajarvi et al., 2008) and they are influenced by rater's subjectivity (Carpinella et al., 2014). Also, all the above mentioned tests evaluate each task as a whole and cannot provide detailed and clinically important information about the duration of the different movement phases (i.e. reaching, manipulation, transport and release) and the associated kinematics variables (i.e. joints angles, displacements, velocities and accelerations).

For these reasons, it appears important to integrate the information obtained from clinical tests with those supplied by other instruments such as the quantitative methods of motion capture systems or inertial sensors during simple everyday tasks such as drinking from a glass (Finlayson et al., 2013). Such techniques are potentially able to objectively assess UL dysfunctions associated with the execution of tasks typical of ADL (Hooper et al., 1998; Alusi et al., 2000; Feys et al, 2002; de los Reyes-Guzmàn et al., 2014; Lamers et al., 2014).

3.2 Quantitative assessment of UL functions in MS

In the last two decades, only few studies investigated alterations in UL movements in pwMS during functional tasks (i.e. pointing or grasping) using quantitative tools such as sensor-glove for finger tapping (Bonzano et al., 2013), virtual peg board (Lambercy et al.,

2013), inertial sensors (Carpinella et al., 2014), robot-assisted training in virtual reality environment (Carpinella et al., 2009; Vergaro et al., 2010) or optoelectronic system (Quintern et al., 1999; Menegoni et al., 2008). Despite the limited amount of available data, their results demonstrated good capabilities of quantitative techniques in effectively assess motor performance and subtle, yet clinically meaningful, changes in arm and hand functionality (Carpinella et al., 2014). So far, the use of motion capture systems to characterize the kinematics of UL alterations in pwMS is still scarce (Quintern et al., 1999; Menegoni et al., 2008; Corona et al., 2017; Corona et al., 2018). This looks quite surprising, given that motion capture systems based on optoelectronic stereophotogrammetry represent the gold standard in human movement analysis and it has been extensively applied in other neurological diseases, such as Cerebral Palsy (CP) (Mackey et al., 2005; Ricken et al., 2005; Mackey et al., 2008; Rigoldi et al., 2012; Butler et al., 2010), stroke (Caimmi et al., 2008; Murphy et al., 2011; Aprile et al., 2014) or in ataxic people (Ferrarin et al., 2005; Menegoni et al., 2009).

Possible reasons for the limited use of motion capture systems in MS can be found in the intrinsic complexity of the data they usually provide (Cameron and Wagner, 2011). For example, the analysis of movement kinematics would require physician or physical therapists to interpret a large number of curves (which represent angles and trajectories of specific anatomical landmarks or articular joints) associated with the investigated movements. Moreover, the few quantitative studies on MS with motion capture system have been conducted mainly on the lower limbs, probably because walking impairment is a benchmark symptom of MS that is reported up to 90% of pwMS (Bethoux et al., 2011), and it leads to increased financial costs. From a kinematic point of view, another reason is due to the existence of standard protocols for gait analysis makes relatively simpler a comparison with the healthy individuals (Pau et al., 2014).

In order to reduce the complexity of the large amount of kinematic data originated by 3D movement analysis, it has recently been proposed to use synthetic indexes to summarize the whole dataset of kinematic data into few (or even only one) scores (Cimolin and Galli, 2014). In the case of MS, such approach has mainly been applied in investigating gait alterations with encouraging results (Pau el al., 2014, 2015; Morel et al., 2017) but, in recent times, researchers have employed it even to investigate UL movements in other pathologies, such as Cerebral Palsy and hemiplegia (Jaspers et al, 2011; Butler et al., 2012). Given the encouraging results of the use of synthetic measures in gait, appears worth of interest to apply

the same method to quantify also the UL deviation from normal patterns during a functional task in pwMS.

3.2.1 Purposes of the study

As previously mentioned, it appears essential to have available quantitative and sensitive tools to evaluate UL disorders in MS and to monitor the possible effects of the applied treatments. In fact, taking into account that these impairments are involved in many essential activities and may be reflected in other functions, influencing the person's quality of life, it is noteworthy the investigation of UL movement abilities.

For these reasons, the main purpose of this analysis was to objectively evaluate with a motion capture system the UL dysfunction in MS and to verify the feasibility of use of the synthetic quantitative indexes to characterize UL kinematics during a functional task, the HTM, in a sample of pwMS, by comparing their values with those of a group of unaffected individuals. Moreover, the relationship between synthetic indexes, individual disability (assessed through Expanded Disability Status Scale, EDSS) and results of clinical tools like HGS and NHPT was investigated.

The application of the quantitative synthetic measure might result useful in supporting physicians in identifying subtle, yet clinically relevant, changes in UL function associated with the disease progression or pharmacologic treatments. It would also be helpful in defining and measuring the outcomes of rehabilitation protocols.

3.3 Experimental set-up

3.3.1 Participants

A convenience sample of 30 pwMS (14 male, 16 female; age 46.7 ± 11.2 years) with EDSS score ranging from 1 to 6.5 (mean value 4.1 ± 2.2) currently followed at the Regional Multiple Sclerosis Centre of Cagliari (Italy) and at Don Gnocchi Foundation of Milan (Italy) was enrolled for this study. The main inclusion criteria were a definitive diagnosis of MS according to 2005 McDonald criteria (Polman et al., 2005), a current EDSS score < 9, absence of relapses in the last 3 months prior the study, no severe cognitive impairments (i.e. Mini Mental State Examination, MMSE, score > 24), and absence of visual or hearing

impairments able to interfere with the protocol. Twenty-seven pwMS declared to be right-handed, while 3 pwMS declared to be left-handed.
A same size group of healthy individuals (16 male, 14 female; age 49.4 ± 19.9 years) with no history of documented musculoskeletal and neurological disorders was enrolled as control group (HC). As regards hand dominance, 28 HC declared to be right-handed and 2 left-handed.

All participants received detailed information about the purposes of the study and signed an informed consent form. The study was approved by the Ethics Committee of each participating center. The main demographic and clinical characteristics of the pwMS are reported in Table 3.1.

Table 3.1 Demographic data and clinical features of MS participants. Values are expressed as mean (SD).

Status	Participants # (M,F)	Age (years)	Dominant hand, R/L	EDSS
MS	30 (14 M, 16 F)	46.7 (11.2)	27/3	4.2 (2.4)
HC	30 (16 M, 14 F)	49.4 (19.9)	28/2	-

MS: Multiple Sclerosis, HC: Healthy Controls, R: right hand, L: left hand, EDSS: Expanded Disability Status Scale.

3.3.2 Clinical assessment

Manual dexterity of both limbs in pwMS was assessed using the Nine Hole Peg Test, NHPT (Kellor et al., 1971; Mathiowetz et al., 1985). PwMS performed two consecutive trials with the dominant hand and then with the non-dominant hand. The mean time for hand and of the all 4 NHPT trials (in seconds) was used (Fisher et al., 2001). The most affected limb, considered for the subsequent analysis (Carpinella et al., 2014), was identified as the one that exhibit the worst performance.

Maximal HGS was measured using a digital handheld dynamometer (DynEx, MD Systems, Westerville OH, USA). The participants were seated comfortably on a chair without rest arms with their forearm leaning on a table in neutral position, shoulder adducted and neutrally rotated, elbow flexed at 90°, and wrist between 0° and 30° of extension (Fess et al., 1992). From this position, they were asked to squeeze the dynamometer with as much force as possible, while receiving a verbal encouragement (Mathiowetz et al., 1984). Three trials on

each side, interspersed by approximately 20 s of rest and alternating sides were usually performed. However, if the difference in score among the 3 trials was found higher than 3 kg, the test was repeated.
The final score was represented by the maximal grip score calculated from all six valid trials.

Given that EDSS is a scale strongly based on the assessment of walking and not on UL functions, in this study pwMS were stratified into two classes according to their manual disability level, using an approach similar to previous study which took NHPT scores into consideration (Carpinella et al., 2014):

- Class 1: low-mild manual disability (NHPT 18.3 - 30.0 s, n = 17)
- Class 2: moderate-severe manual disability (NHPT 31.5 - 71.2 s, n = 13).

In Table 3.2 are reported clinical scores obtained by pwMS.

Table 3.2 Clinical assessment of pwMS. Values are expressed as mean (SD).

	Entire Sample		**MS Class 1**		**MS Class 2**	
	Most Affected	**Less Affected**	**Most Affected**	**Less Affected**	**Most Affected**	**Less Affected**
NHPT (s)	30.9 (12.5)	25.8 (8.6)	23.8 (4.0)	21.0 (2.5)	41.9 (13.4)	33.8 (8.5)
HGS (kgf)	20.8 (13.9)	22.8 (14.5)	27.2 (15.1)	33.5 (12.8)	15.0 (6.4)	15.9 (13.0)

NHPT: Nine Hole Peg Test, HGS: Health Grip Strength.

3.3.3 Quantitative analysis of movement features

All participants were asked to perform the HTM movement (described on Chapter 2, Paragraph 2.2). The kinematic analysis of the HTM movement was carried out in part at the "Laboratory of Movement Analysis" (Biomedical Technology Department, Don Gnocchi Foundation of Milan, during the period October-December 2015) and in part at the "Laboratory of Biomechanics and Industrial Ergonomics" (Department of Mechanical, Chemical and Materials Engineering, University of Cagliari), using the same motion capture system equipped with 8 infrared cameras set at a sampling rate of 120 Hz (SMART-D, BTS Bioengineering, Italy).

Spatio-temporal parameters (i.e. duration phases, velocity during the GP, movement precision index), dynamic ROM at the shoulder, elbow and wrist, and the synthetic kinematic indexes for a set of 7 movements of interest (AVS) and for the whole task (APS_7) were taken into account for analyzing the motor abilities in pwMS. Details about the used marker-set, protocol and feature extraction can be found on *Chapter 2*.

3.3.4 Statistical analysis

Characteristics of the participants (demographic data, clinical scores and kinematic features) were mainly presented with number, mean and standard deviation (SD) and sometimes range. Statistical analyses were performed using the Statistic Package SPSS Statistics v.20 software (SPSS IBM, Armonk, NY, USA).

Before any comparisons, data was tested for normality, homogeneity and presence of outliers. When the data was not normally distributed, variables were log transformed to achieve normally distributed and homogeneous residuals. Comparison between groups in order to investigate the possible differences in the movement features, kinematic parameters and AVS/ APS_7 scores caused by the presence of MS were assessed using one-way multivariate analysis of variance (MANOVA). In all cases the independent variables were the individual's status (HC or MS Class 1 or 2) and, the dependent variables were the 7 kinematic parameters previously listed, the dynamic ROM of shoulder, elbow and wrist, the 7 AVSs and the APS_7. The level of significance was set at $p = 0.05$ and effect sizes were assessed using the eta-squared coefficient (η^2). Follow-up analyses were conducted using one-way ANOVAs for each dependent variable, setting the level of significance at $p = 0.007$ (0.05/7) for kinematic parameters, $p = 0.0125$ (0.05/4) for dynamic ROM and $p = 0.006$ (0.05/8) for AVS/APS_7 scores after a Bonferroni adjustment for multiple comparisons.

Given the non-linear distribution of the data, Spearman's rank correlation analysis was performed to explore the relationship in pwMS between the kinematic parameters, level of disability and manual capacity, on the basis of EDSS, NHPT and HGS values. Also in this case, significant differences were set at $p = 0.05$. The rho values of 0.1, 0.3, and 0.5 represent small, moderate, and large correlations respectively, according to Cohen's guidelines (Cohen, 1988; Cohen, 1992).

3.4 Results

All participants were able to successfully complete the HTM task according to the protocol previously described. A preliminary analysis performed on unaffected individuals showed no significant differences in all investigated parameters between dominant and non-dominant arm and, similarly, no differences were found in pwMS grouped considering most vs. less affected limb. The same findings were found when each MS class was taken into account.

In Figure 3.1 is reported as example the profile of the hand-mouth distance of the most and less affected side for pwMS (expressed as percentage of the maximal distance) during the HTM movement. It can be seen that in both cases the curves appear quite similar, smooth and bell-shaped.

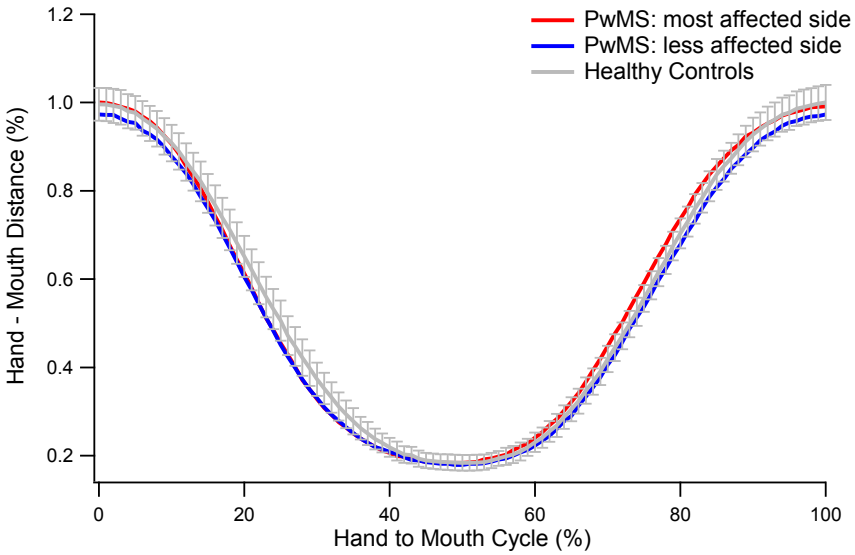


Figure 3.1 Profiles of the hand-mouth distance, expressed as percentage of the distance. The red and blue curves represent respectively the most and less affected side of the whole MS sample, while in grey is reported the normative profiles of the healthy controls.

On the basis of these findings, the analysis was performed considering the dominant arm for HC group and the most affected arm (worst performance at NHPT) for pwMS, in agreement with the approach used in this pathology by Carpinella et al. (2014). Following this criterion, the most affected side coincided with the dominant side for fourteen pwMS (47%) and with the non-dominant arm for 16 pwMS (53%). All pwMS exhibited NHPT scores higher than the threshold value typical of healthy individuals of comparable age (18.8 ± 0.8 s, Oxford Grice et al., 2003).

3.4.1 Kinematic features

The kinematic parameters calculated for the different groups are summarized in Table 3.2. MANOVA revealed a main significant effect of the individual's status on spatio-temporal parameters [$F(14,104) = 2.68$, $p=0.003$, Wilks $\lambda = 0.54$, $\eta^2 = 0.27$]. In particular, when all the pwMS were considered as a single group regardless their disability level, the follow-up analysis showed that during the execution of the movements, pwMS spent more time in the AP (MS: 9.11%, HC: 5.43%, $p<0.005$). Furthermore, pwMS exhibit a less smooth movement in terms of frequency of direction changes (MS: 4.32 Hz, HC: 3.42 Hz, $p=0.004$). Considering the disability level, the follow-up tests detected significant differences between HC and MS Classes for some of the investigated parameters and the main differences were found between MS Class 2 and HC (Figure 3.2). In particular, whereas when the entire MS group was considered no differences were found in terms of velocity during the GP and AS, when the disability level was considered they appears significantly higher in the MS Class 2 than HC ($p < 0.005$).

As regards dynamic ROM, MANOVA failed to detect significantly differences between MS Classes and HC were found [$F(8,108) = 1.929$, $p=0.063$, Wilks $\lambda = 0.76$, $\eta^2 = 0.125$].

Table 3.2 Spatio-temporal and kinematic parameters of the hand to mouth task in pwMS and healthy controls. Values are expressed as mean (SD).

	HC	MS		
		Entire sample	**Class 1**	**Class 2**
Spatio-temporal parameters				
Total Movement duration (s)	1.36 (0.27)	1.63 (0.08)	1.48 (0.59)	**1.83 (0.40)** [a]
GP duration (%)	46.63 (3.18)	45.60 (0.68)	45.25 (1.75)	46.03 (6.35)
AP duration (%)	5.43 (3.18)	**9.11 (0.90)** [a]	6.94 (3.92)	**11.95 (7.66)** [a]
RP duration (%)	44.22 (12.37)	46.25 (1.74)	47.89 (3.67)	44.09 (5.55)
Velocity during GP (m/s)	0.59 (0.09)	0.50 (0.02)	0.53 (0.12)	**0.46 (0.09)**[a]
AS (mm)	2.94 (0.60)	4.73 (0.57)	3.29 (2.52)	**6.61 (3.33)** [a, b]
Frequency of direction changes (Hz)	3.42 (1.12)	**4.32 (0.21)** [a]	**4.55 (1.18)** [a]	4.02 (1.17)
Range of Motion				
Shoulder Abduction-Adduction (°)	10.35 (3.54)	11.92 (6.71)	10.28 (5.06)	11.51 (4.46)
Shoulder Flexion - Extension (°)	22.34 (11.78)	19.44 (11.62)	23.94 (9.96)	18.31 (11.55)
Elbow Flexion - Extension (°)	56.02 (14.27)	60.72 (21.53)	52.81 (20.70)	28.76 (17.07)
Wrist Flexion-Extension (°)	17.38 (5.71)	20.23 (7.22)	14.54 (4.27)	22.50 (7.41)

MS: Multiple Sclerosis group, HC: Healthy Controls, GP: Going Phase, AP: Adjusting Phase, RP: Returning Phase, AS: Adjusting Sway.
[a] Significant differences vs. Healthy Controls (HC), [b] Significant differences vs. MS Class 1 after Bonferroni correction ($p<0.007$ for Spatio-temporal parameters, $p<0.0125$ for Range of Motion)

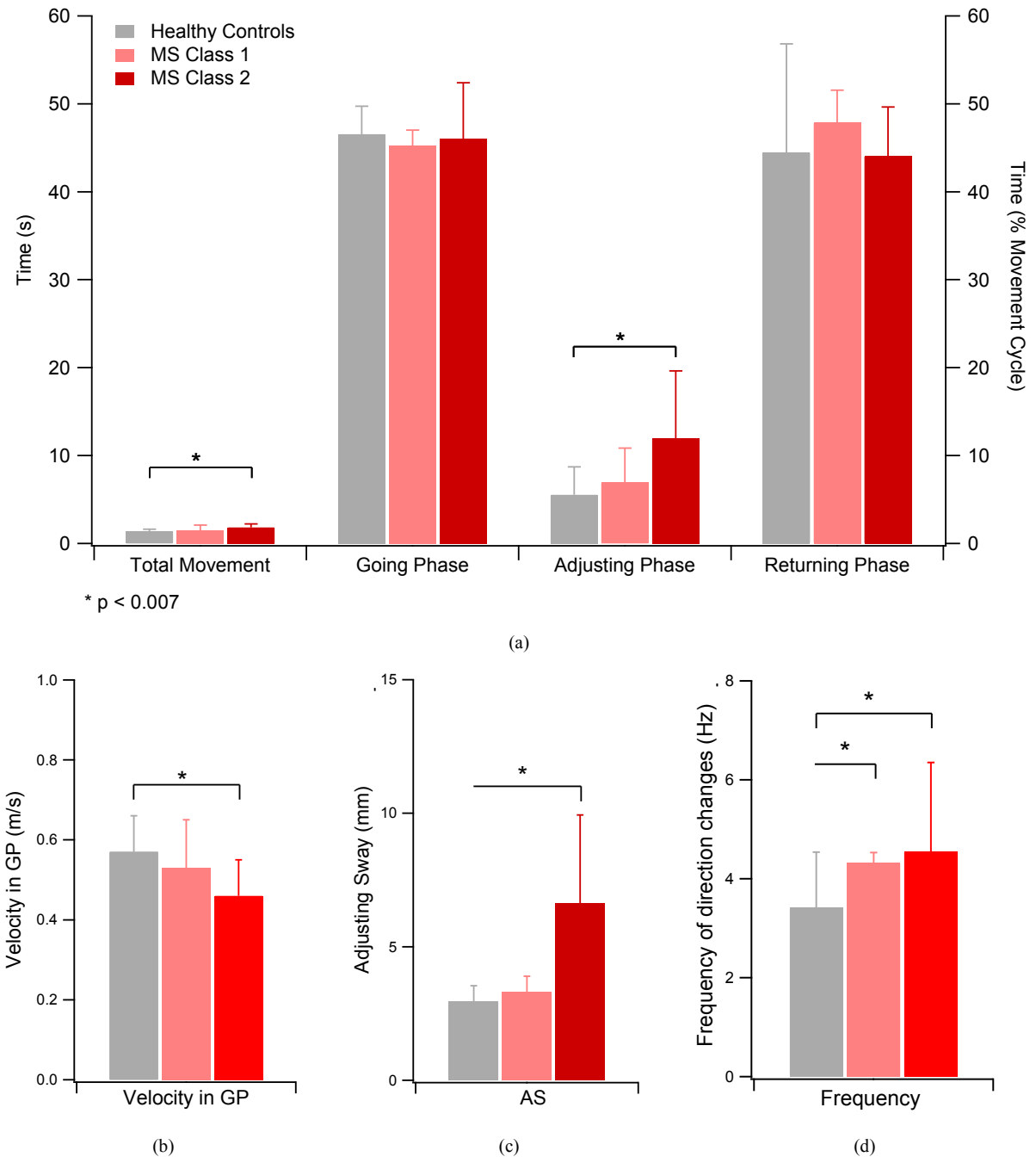


Figure 3.2 Main quantitative results about spatio-temporal parameters calculated during the hand-to-mouth task (mean ± standard deviation). Displayed in (a) are the movement durations, in (b) the hand velocity during the Going Phase (GP), in (c) the adjusting sway (AS) during the Adjusting Phase (AP) and in (d) the frequency of direction changes of the hand. * denotes statistical significant differences ($p < 0.007$) between Healthy Controls, MS Class and MS Class 2.

3.4.2 Kinematic profiles of UL movements

The diagrams in Figure 3.3 report the kinematic curves for each articular joint of interest during the HTM task. All variables were normalized to task duration time (Figure 3.3).

The last part of the movement (dedicated to the RP) and the first part (dedicated to the GP) are almost similar in all kinematic graphs for each group. UL kinematic patterns of the MS Class 1 and Class 2 demonstrated some differences with respect to HC during the HTM movement, such as greater than one standard deviation from the HC means curves. Although movement patterns of MS Class 2 were almost similar to those of MS Class 1, some exceptions were found because some pwMS had their elbow near to the body (adducted arm) and others away from body (more abducted arm) at the starting point and during the whole movement.

Similar patterns were found in MS groups for elbow and shoulder movements in sagittal plane. Elbow angle graph demonstrated a characteristic smooth movement pattern in pwMS with a maximal elbow flexion when the hand reached the mouth, during the AP (50% of the cycle). An initial flexion was followed by a second movement phase in which the elbow was extended again to return the hand to the initial position.
Shoulder flexion approached the maximum angle in the end of the GP, and peaked shortly during the AP.
Also shoulder abduction trends were similar for MS Class 1 and 2, with a small peak in the middle of GP, indicating a thin half-circular arm movement in GP, and with a maximal adduction when the hand achieved the mouth. It can be seen also the tendency to more supinate the forearm when the mouth was reached, as a compensatory strategy to increase wrist flexion. Trajectories of MS Class 1 and 2 appeared smooth and almost continuous as well as HC's one, indicating an almost good coordination between elbow and shoulder joint during the HTM task.

Some differences emerged between MS Class 1 and Class 2. Class 2 pwMS showed increased tendency to abduct the arm during the task and to actively externally rotate the shoulder and increase forearm supination during the AP compared to MS Class 1, likely due to the fact that Class 1 pwMS demonstrated decreased tendency to flex their wrist during the task. Moreover, Class 1 pwMS sat with trunk more flexed and increased their shoulder external rotation at the beginning of the GP compared to MS Class 2.

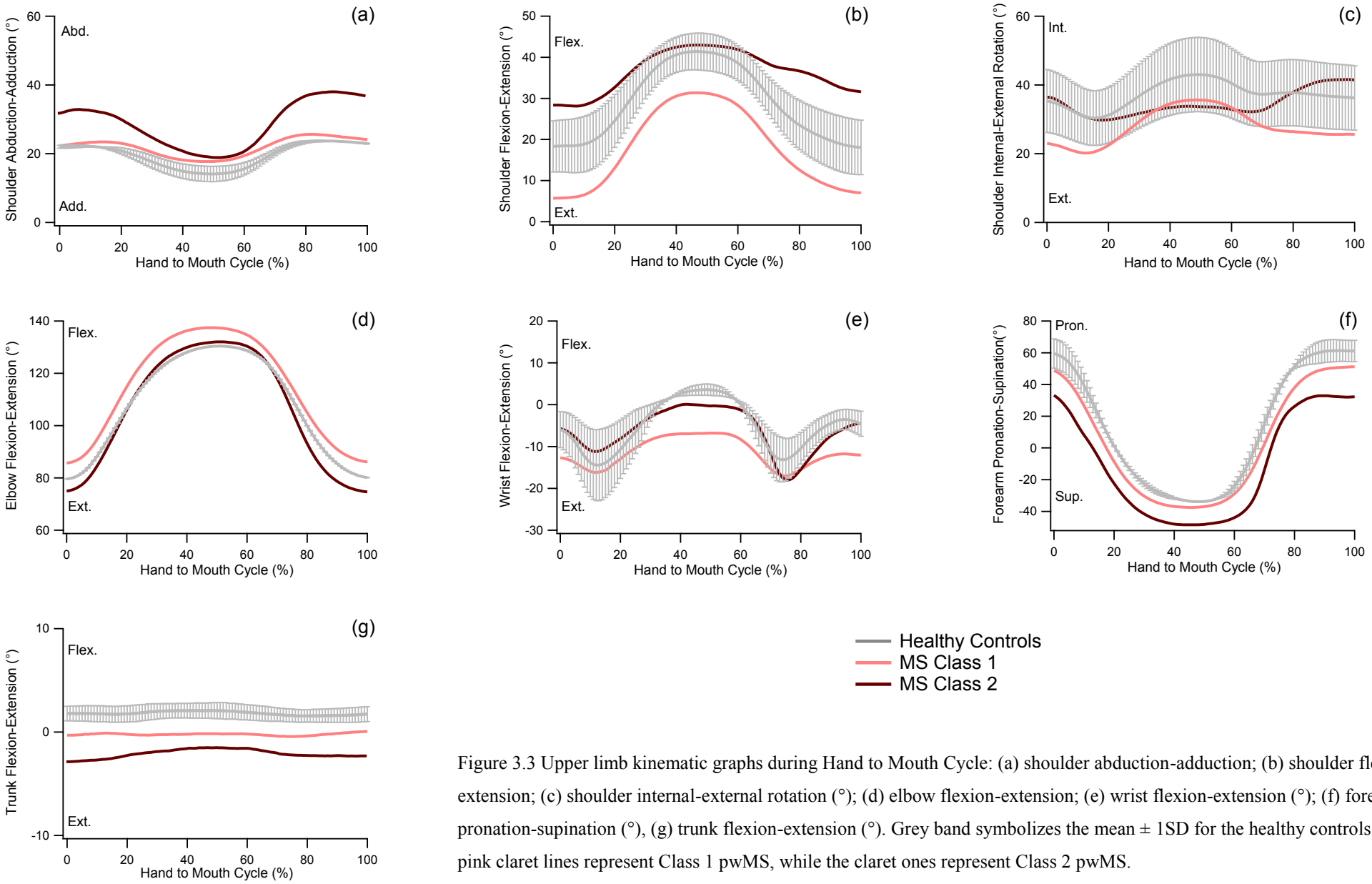


Figure 3.3 Upper limb kinematic graphs during Hand to Mouth Cycle: (a) shoulder abduction-adduction; (b) shoulder flexion-extension; (c) shoulder internal-external rotation (°); (d) elbow flexion-extension; (e) wrist flexion-extension (°); (f) forearm pronation-supination (°), (g) trunk flexion-extension (°). Grey band symbolizes the mean ± 1SD for the healthy controls; the pink claret lines represent Class 1 pwMS, while the claret ones represent Class 2 pwMS.

3.4.3 AVS and APS scores

MANOVA revealed a significant effect of the individual's status on APS_7/AVS indexes [$F(16,10) = 9.03$, $p<0.001$, Wilks $\lambda= 0.17$, $\eta^2 = 0.59$]. In particular, the subsequent follow-up analysis revealed significant differences between HC and MS Class 1 and 2 for APS_7 ($p < 0.001$) and most of AVS scores ($p < 0.005$). In particular, Class 1 and 2 exhibited higher APS than HC (1.8-2.3 times larger than HC) and AVS of shoulder flexion-extension (1.9-2.3 times higher than HC, $p < 0.001$) and pronation-supination (1.6-2.4 times higher than HC, $p < 0.006$). Class 1 showed significantly higher elbow flexion-extension respect to HC and reduced shoulder abduction-adduction with respect Class 2. Significantly higher shoulder rotation was found in Class 2 with respect HC, as well as trunk flexion-extension.

In Table 3.3 is reported the results of the follow-up ANOVA and the AVS and APS scores for the entire MS and the HC groups, while these findings when the disability level was considered are showed in Figure 3.4.

Table 3.3 Comparison between APS and AVS values in individual with MS (pwMS) and healthy controls (HG) during the hand to mouth task. Values are expressed as mean (SD).

		HC	MS		
			Entire sample	Class 1	Class 2
	APS_7 (°)	7.55 (2.49)	**15.12 (3.73)** [a]	**13.77 (3.34)** [a]	**16.89 (3.56)** [a]
AVS (°)	**Trunk Flexion-Extension**	2.41 (1.76)	**5.24 (6.32)** [a]	3.79 (2.92)	**7.13 (2.84)** [a]
	Shoulder Abduction-Adduction	5.85 (4.17)	8.68 (6.18)	6.09 (4.16)	**12.05 (6.88)** [a, b]
	Shoulder Flexion-Extension	7.78 (4.76)	**16.22 (7.98)** [a]	**15.15 (8.76)** [a]	**17.61 (6.89)** [a]
	Shoulder Rotation	6.72 (3.44)	**10.25 (5.67)** [a]	8.11 (3.92)	**13.05 (6.50)** [a]
	Elbow Flexion-Extension	8.52 (5.82)	**12.84 (5.17)** [a]	**14.18 (5.38)** [a]	11.09 (4.48)
	Forearm Pronation-Supination	12.25 (6.83)	**23.92 (10.52)** [a]	**20.06 (10.53)** [a]	**28.97 (8.42)** [a]
	Wrist Flexion-Extension	7.46 (4.44)	11.57 (7.37)	12.32 (7.76)	10.57 (7.01)

MS: Multiple Sclerosis group, HC: Healthy Controls, APS: Arm Profile Score, AVS: Arm Variable Score.
[a] Significant differences vs. Healthy Controls (HC), [b] Significant differences vs. MS Class 1 after Bonferroni correction ($p<0.006$).

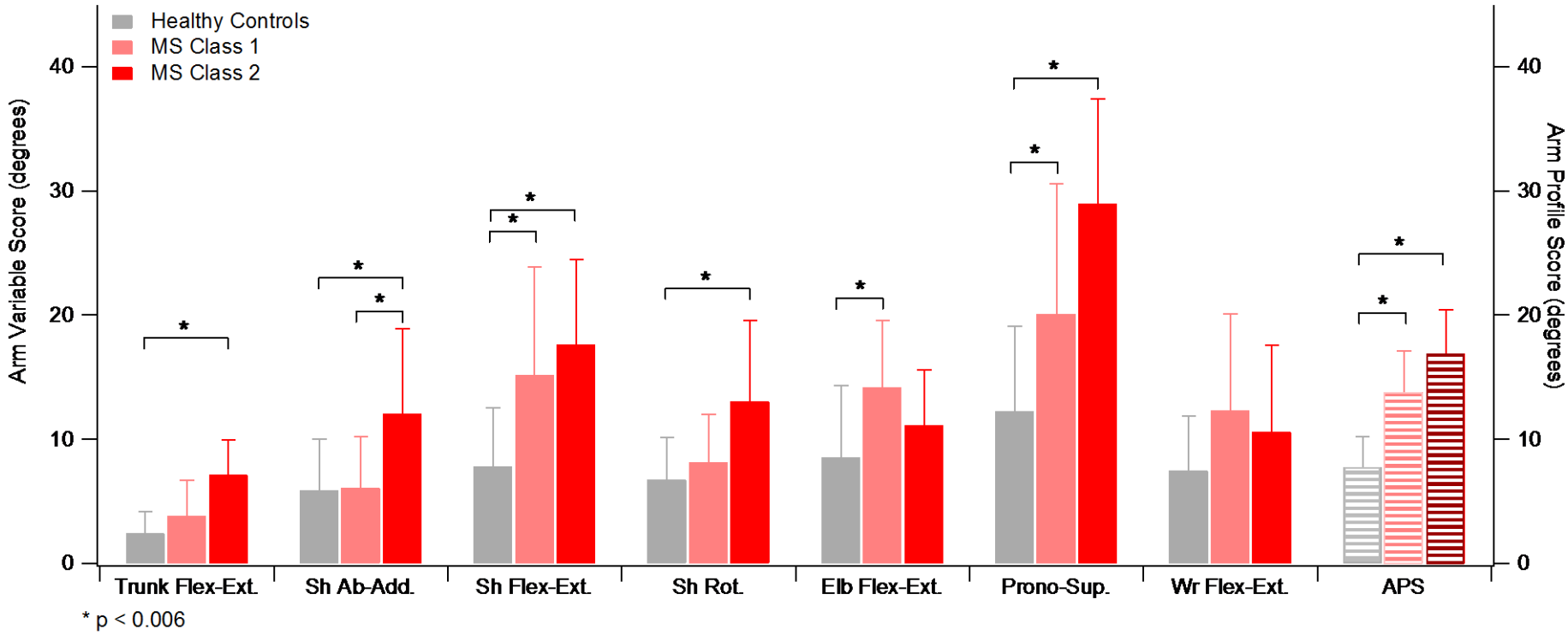


Figure 3.4 The Arm-Movement Analysis over the hand-to-mouth task: Arm Variable Score (AVS) values (Trunk Flex-Ext.: Trunk Flexion-Extension; Sh Ab-Add.: Shoulder Abduction-Adduction; Sh Flex-Ext.: Shoulder Flexion-Extension; Sh Rot.: shoulder Rotation; Elb Flex-Ext.: Elbow Flexion-Extension; Prono-Sup.: Pronation-Supination; Wr Flex-Ext.: Wrist Flexion-Extension) and Arm Profile Score (APS) are reported for the three groups (Healthy Controls, MS Class 1 and MS Class 2). * denotes significantly differences ($p < 0.006$).

3.4.4 Correlation between clinical scores and kinematic variables

Tables 3.4, 3.5, 3.6 show the Spearman's rank correlation coefficient rho between the measures of motor impairment in pwMS and the UL parameters (spatio-temporal and APS_7/AVS values). When considering all the pwMS grouped, a significant positive correlation was found between motor impairment scores and some of UL kinematic variables, such as the correlations found between AS value and the EDSS (rho = 0.520 $p<0.01$) and NHPT scores (rho = 0.384 $p<0.05$). Instead, when the stratified groups were considered, we found a large correlation only with the EDSS score (rho=0.578) in MS Class 2.

Significant large to moderate correlations were found between EDSS and APS_7 index (rho = -0.530 $p<0.05$) and three AVS, namely shoulder abduction-adduction (rho = 0.407 $p <0.05$), shoulder rotation (rho =0.369 $p<0.05$) and forearm pronation-supination (rho = 0.438 $p<0.05$). The analysis for stratified groups showed that for pwMS of Class 2 only APS_7 was found significantly correlated with EDSS (rho = -0.593).

Table 3.4 Spearman's rank correlation coefficients between EDSS scores and the UL parameters in pwMS.

	Parameters	All MS	MS Class 1	MS Class 2
Spatio-temporal parameters				
	Total Movement duration (s)	**0.526** §	0.120	0.092
	GP duration (%)	-0.167	-0.042	**-0.731**§
	AP duration (%)	**0.464**§	0.220	**0.696**§
	RP duration (%)	**-0.364**§	-0.047	-0.348
	Velocity during GP (m/s)	-.202	0.036	0.423
	AS (mm)	**0.520**§	0.270	**0.578**†
	Frequency of direction changes (Hz)	-0.266	-0.199	-0.053
Synthetic kinematic indexes				
	APS_7 (°)	**-0.530** †	0.151	**-0.593**†
AVS (°)	**Trunk Flexion-Extension (°)**	0.319	0.350	-0.328
	Shoulder Abduction-Adduction (°)	**0.407** †	0.095	-0.288
	Shoulder Flexion-Extension (°)	-0.209	0.123	0.314
	Shoulder Rotation (°)	**0.369** †	-0.130	0.256
	Elbow Flexion-Extension (°)	-0.320	-0.021	-0.138
	Forearm Pronation-Supination (°)	**0.438** †	-0.076	0.503
	Wrist Flexion-Extension (°)	0.060	0.037	0.414

EDSS: Expanded Disability Status Scale, APS: Arm Profile Score, AVS: Arm Variable Score. † $p < 0.05$, § $p < 0.01$

Large to moderate correlations were also found when all pwMS was considered, between NHPT score and the APS_7 (rho = 0.577 $p<0.05$) and three AVS scores, namely trunk flexion-extension (rho = 0.391 $p<0.05$), shoulder abduction-adduction (rho = 0.550 $p<0.05$) and forearm pronation-supination (rho = 0.493 $p<0.05$). Large correlations to these parameters were found also for participants belonging to MS Class 2.

Table 3.5 Spearman's rank correlation coefficients between NHPT and the UL parameters in pwMS.

	Parameters	All MS	MS Class 1	MS Class 2
Spatio-temporal parameters				
	Total Movement duration (s)	**0.492** [§]	0.099	0.225
	GP duration (%)	0.101	0.326	-0.214
	AP duration (%)	0.317	-0.113	0.47
	RP duration (%)	**-0.385**[†]	0.065	-0.478
	Velocity during GP (m/s)	-.299	0.015	-0.055
	AS (mm)	**0.384**[§]	-0.15	0.368
	Frequency of direction changes (Hz)	-0.148	0.292	-0.303
Synthetic kinematic indexes				
	APS_7 (°)	**0.577**[†]	0.434	**0.533**[†]
	Trunk Flexion-Extension (°)	**0.391**[†]	0.437	**0.593**[†]
	Shoulder Abduction-Adduction (°)	**0.550**[†]	0.249	**0.577**[†]
AVS (°)	**Shoulder Flexion-Extension (°)**	0.255	0.213	0.363
	Shoulder Rotation (°)	0.355	-0.158	0.137
	Elbow Flexion-Extension (°)	-0.316	-0.264	0.148
	Forearm Pronation-Supination (°)	**0.493**[†]	0.020	0.412
	Wrist Flexion-Extension (°)	0.075	0.394	0.126

NHPT: Nine Hole Peg Test, APS: Arm Profile Score, AVS: Arm Variable Score. [†] $p<0.05$, [§] $p<0.01$

As regards HGS, moderate to large correlations were found with the APS_7 index (rho = -0.486 $p<0.05$) and two AVS scores of trunk flexion-extension (rho = -0.415 $p<0.05$) and forearm pronation-supination (rho = -0.662 $p<0.05$), which was the only one parameter correlated with HGS also in MS Class 2.

Table 3.6 Spearman's rank correlation coefficients between HGS and the UL parameters in pwMS.

	Parameters	All MS	MS Class 1	MS Class 2
Spatio-temporal parameters				
	Total Movement duration (s)	-0.182	0.303	0.227
	GP duration (%)	0.022	**-0.720**§	**0.736**§
	AP duration (%)	-0.217	0.363	-0.318
	RP duration (%)	**0.417**†	0.220	0.191
	Velocity during GP (m/s)	0.020	-0.267	-0.591
	AS (mm)	-0.217	0.407	-0.300
	Frequency of direction changes (Hz)	-0.266	0.132	-0.478
Synthetic kinematic indexes				
	APS_7 (°)	**-0.486**†	-0.418	-0.318
	Trunk Flexion-Extension (°)	**-0.415**†	-0378	-0.291
	Shoulder Abduction-Adduction (°)	-0.294	0.335	-0.445
	Shoulder Flexion-Extension (°)	0.106	0.192	0.400
AVS (°)	**Shoulder Rotation (°)**	-0.211	-0.082	0.173
	Elbow Flexion-Extension (°)	0.175	-0.044	0.373
	Forearm Pronation-Supination (°)	**-0.622**†	-0.527	**-0.709**†
	Wrist Flexion-Extension (°)	0.054	-0.264	-0.027

HGS: Hand Grip Strength, APS: Arm Profile Score, AVS: Arm Variable Score. † $p<0.05$, § $p<0.01$

3.5 Discussion

The aim of this study was to investigate UL kinematics during an ADL task in pwMS with different level of manual disability using a quantitative technique and to verify the existence of relationships between kinematic parameters and motor impairment clinical scores. Generally speaking, our results indicate that pwMS experience difficulties in effectively performing the HTM task, as demonstrated by the significantly higher values that they exhibited in most spatio-temporal parameters. PwMS of Class 1 exhibit performance similar to HC. Moreover, all parameters increased with manual disability level and this may be due to progressive deterioration of proprioceptive and cerebellar systems (Quintern et al., 1999; Casadio et al., 2008).

PwMS of Class 1 and 2 performed the task with slower and more hypermetric movements. In particular, the most relevant alteration was found among pwMS of Class 2 with respect to unaffected individuals as regards time required to precisely locate the mouth (AP). This suggests that pwMS need more adjustments than healthy individuals to accomplish this task, based on the available visual or proprioceptive information (Casadio et al., 2008). Such a loss of accuracy is likely due to cerebellar impairment such as ataxia (Topka et al., 1998) or loss of proprioceptive feedback, not corrected by visual feedback (Quintern et al., 1999), considering that the mouth is not visible during the task. These findings are consistent with previous studies on UL impairments in pwMS (Quintern et al., 1999; Menegoni et al., 2008; Carpinella et al., 2014; Corona et al., 2018).

In pwMS of Class 2, the GP phase was characterized by slower velocity in comparison with HC. This phenomenon may reflect the impairment of the pyramidal system in MS. The pyramidal dysfunction leads to hyposthenia thus reducing movement fluency and speed. Moreover, the slower velocity can be considered a strategy: as pwMS perceive difficulties in precisely locating the target (mouth) they reduce the velocity in an attempt to increase accuracy of the movement. The same behaviour was previously observed in pwMS in several types of UL movements (Quintern et al., 1999; Menegoni et al., 2008; Pellegrino et al., 2015; Corona et al., 2017; Corona et al., 2018), even in the early stage of the disease (Casadio et al., 2008).

PwMS of Class 1 exhibited a significantly higher frequency of direction changes, consistent with previous observations on ataxic individuals (Menegoni et al., 2009). This denotes the

presence of tremor in the final part of the movement in pwMS, characteristic of proprioceptive or cerebellar ataxia. This is in keeping with findings reported by Rinker et al. (2015), who estimated a prevalence of tremor ranging from 45% to 46.8% of the whole MS population and showed that 5.5-5.9% of pwMS exhibit severe tremor, which impacts the quality of life.

As regards dynamic ROM, in contrast with other conditions like stroke (Aprile et al., 2014) and Cerebral Palsy (Butler et al., 2011), pwMS showed no reduction in the ROM (Corona et al., 2018), thus implying that muscle spasticity does not play a role in the UL limitations, as suggested by Bertoni et al. (2015), who reported almost no increase in normal muscle tone when assessed with a clinical test.

As regards synthetic measures proposed for characterizing the whole movement, significant differences were found between pwMS and HC (Corona et al., 2018). In particular, the results showed that APS_7 is higher in pwMS with respect to unaffected individuals, thus indicating significantly larger deviations from physiological UL motion. This suggests that this index is able to summarize the UL impairments and alterations associated with the presence of the disease, thus discriminating in an immediate and clear way motor performance limitations of pwMS from those of HC.

When the single AVS scores were analyzed, significantly higher values were found in pwMS, thus indicating a deviation from a physiologic movement pattern which occurs both proximally and distally, supported also by the joint curves' analysis (Corona et al., 2018). UL kinematic curves of elbow and shoulder reported here are consistent with typical pattern of cerebellar limb ataxia (Topka et al., 1998) and provide information regarding functional disorders present in MS. For instance, pwMS of Class 2 showed an increased tendency to externally rotate and flex the shoulder and supinate the forearm when reaching the mouth and pronate the forearm when returning to initial position.

The more significant differences between pwMS and HC were found in the more proximal joints and trunk flexion-extension, which appear practically doubled with respect to HC, with exception of the shoulder abduction-adduction. This may be partly due to the movement targeted by the functional system and it is consistent with the results of Carpinella et al. (2014), who investigated the HTM task using wearable inertial sensors, finding that in the different disability stages not only fine movements and hand dexterity (Bonzano et al., 2013) but also subtle proximal arm alterations are present in pwMS (Carpinella et al., 2014). This

also suggests that alterations observed during the execution of the functional test (i.e. NHPT) may be due to impairments in proximal and/or distal segments. The use of quantitative measure is useful in concurrently assessing abnormal arm and trunk movements so as to understand the impact of UL disorders on different functional tasks and to provide interventions tailored to subject's specific needs.

Even if EDSS is more indicated for the assessment of walking ability, its use is widespread in MS clinical settings to identify the overall disability level of the individual. For its importance in MS clinical evaluation, the correlation between kinematic indexes and EDSS score was investigated as well. Our findings showed that the APS_7 correlated well with the EDSS score and seemed to be sensitive to disability level. Thus, it is reasonable to hypothesize that this index is somehow representative of the overall disability of the individual and suitable for identifying the progressive motor impairments associated with increasing disability (Corona et al., 2018), even though EDSS is mainly constructed considering the ambulatory functions. Similarly, good correlations were found between the APS_7 and AVS of shoulder abduction-adduction with the NHPT score, although the HTM targets gross movements, while NHPT targets fine manual dexterity (Feys et al., 2017) and is unable to detect proximal weakness (Yozbatiran et al., 2006). However, a good relationship was found in MS group with higher disability, indicating that our sample presented both proximal and distal alterations.

The existence of such a relationship would suggest that the APS_7 index is a suitable tool for identifying overall impairment of UL motor function in pwMS related to proximal and distal impairments due to different functional systems (namely pyramidal, sensibility, cerebellar and visual). Indeed, ataxia is one of the key features captured by the system, as partly confirmed by the significantly higher values of the parameters associated with the GP and AP duration and AS (i.e. in proximity of the target) observed in pwMS (Quintern et al., 1999; Menegoni et al., 2009).

3.6 Conclusions

The aim of the analysis was to perform an extensive kinematic characterization of the UL functional limitations of pwMS with different disability levels during the execution of a task representative of ADL. In particular, the feasibility of the application of the spatio-temporal indexes and Arm Profile Score (APS_7) for immediate quantification of the degree of UL

impairments in pwMS during the HTM task was investigated. This task was chosen among those proposed in previous similar studies (i.e. reaching, pointing, etc.) because is feasible to be performed in pwMS with motor deficits and it is complex enough to highlight specific limitations associated with the presence of MS.

Some limitations of the study should be acknowledged. Firstly, the sample was quite small, and thus further analyses should be done to confirm these preliminary results. Secondly, this was a cross-sectional study, and it should be integrated with longitudinal studies that would allow determining if the APS_7/AVS scores are sensitive enough to monitor the disease progression in terms of UL impairments. At last, it must be considered the intrinsic nature of the APS_7/AVS indexes that suffer from some limitations. In fact, these measures are only based on kinematic variables (i.e. joint kinematics) neglecting spatio-temporal as well as smoothness and precision parameters. Furthermore, their values (expressed in degrees) do not provide any indication about the direction of the movement deviation (i.e. the same values of AVS of elbow may indicate either a hyper-flexed or extended elbow). For these reasons, APS_7 and AVS should be supported by the kinematic graphs as well as by the joints ROMs for a complete knowledge of the level of alteration in the UL motor pattern (Jasper et al., 2011; Butler et al., 2012; Pau et al., 2014).

Moreover, in order to fully explain the motor strategies employed by pwMS to perform goal-oriented daily tasks, it would be interesting to integrate kinematic analysis of movement with joint synergies assessment, as it has been done with different pathologies such as stroke (Michaelsen et al., 2001). In particular, interjoint coordination analysis during the HTM task should be performed to support kinematic analysis here presented and better clarify what mechanisms are involved in MS to control arm joint interactions during a multi-joint movement.

Chapter 4

Quantitative assessment of Hand to Mouth Task in Parkinson's Disease

'The moment I understood this – that my Parkinson's was the one thing I wasn't going to change – I started looking at the things I could change, like the way research is funded' – Michael J. Fox

We have previously shown that the kinematic analysis of UL movements and in particular the use of synthetic indexes APS/AVS has the potential to effectively characterize functional task such as hand to mouth movement. However, it appears important to understand how this approach can be extended to completely different neurologic pathologies. Thus, in this chapter the application of the kinematic analysis to HTM task to individuals affected by Parkinson's disease is presented.

4.1 Introduction

4.1.1 Parkinson's Disease

Parkinson's Disease (PD) is a chronic and progressive neurodegenerative disorder and it is considered the second most common neurodegenerative disorder in elderly population, after Alzheimer's disease (De Lau et Breteler, 2006). Indeed, PD affects about 0.3% of the people worldwide, with a high prevalence in older adults and with a 4% in people under 50 years (De Lau and Breteler, 2006). PD is attributed by a progressive degeneration of dopaminergic neurons located mostly in the *substantia nigra* and other non-dopaminergic system of basal ganglia and other areas of the CNS (Politis and Niccolini, 2015).
A detailed description of the symptoms of PD was first published by James Parkinson in 1817 (Parkinson, 1817). Since early stages of the disease, people with PD (pwPD) show a gradual loss of motor and non-motor functions, such as depression, anxiety, dementia and many others. The motor disorders, such as tremor, limb and muscle rigidity, ideomotor apraxia, gait and balance instability, slowness of movement, reduced movement amplitude and dysrhythmia, have a huge impact on ADL and may lead to limitations in functionality and (Mazzoni et al., 2012).

In particular, rest and action tremor are common manifestation of basal ganglia pathologies (Louis et al., 2001). In fact, the tremor at rest is the most common symptom of the disease, prominent in distal part of an extremity and characterized by a frequency about 4-5 Hz (Heida et al., 2013). Although less recognised with respect to tremor at rest, also the tremor in action could be present in the disease that appears during voluntary muscle contraction, with a frequency around 4-9 Hz (Wenzelburger et al., 2000; Heida et al., 2013). Rigidity is characterized by increased resistance to externally imposed movement due to stiffness of movement due to difficulty in planning, initiating and executing movements.

Among the aforementioned motor symptoms, UL disorders can restrict daily lives of pwPD and have a huge impact on their overall quality of life. Activities such as dressing, self-care, eating and writing are often hindered or even impossible to perform with a less functional hand. Good arm and hand functions are therefore important for an independent life.
Moreover, pwPD exhibit a number of dysfunctions to movement organization, such as difficulties in simultaneous or sequential movements or movement components.

A careful examination of each patient is required to detect motor symptoms and to diagnose the presence of PD. When the disease has been diagnosed, a patient-centric therapy is required to maximize the efficacy of medications and minimize its complications. The typical management of the motor symptoms is based on the use of dopaminergic drugs, such as Levodopa and dopamine agonist, which are able to strongly control most of the motor symptoms (Cossu and Pau, 2017). However, medications and standard treatments have the side effect (i.e. dyskinesia and motor fluctuations, which can even be worsen the dysfunctions induced by the PD itself) to decrease its efficacy over time. So, when drug medications are not sufficient or related side effects are too severe, Deep Brain Stimulation (DBS), which is a surgical procedure in which implanted electrodes stimulate specific brain areas, can be considered as an option for managing motor symptoms (Cossu and Pau, 2017).

Therefore, to adequately study the PD motor symptoms and the fluctuation over time as well as to define an effective and patient-focused therapy, it is worthy of interest to find an accurate, continuous and quantified monitoring of these motor symptoms, in order to define an effective and patient-focused therapy.

4.1.2 Clinical motor assessment in PD

Even though limited clinical guidelines for evaluating UL functions and activities in PD exist, different standardized and semi-quantitative evaluation scales have been introduced to support clinicians in achieving a more objective analysis of motor symptoms in PD (Proud et al., 2015). Above all, the Hoehn & Yahr (H&Y) scale (Hoehn and Yahr, 1967) is the most used scale to define how the disability symptoms progress in PD. It originally included stages 1 (unilateral involvement only usually with minimal or no functional disability) through 5 (wheelchair bound or bedridden unless aided) (Hoehn and Yahr, 1967), but then a modified H&Y scale was proposed with the addition of stages 1.5 (unilateral and axial involvement) and 2.5 (mild bilateral disease) to help describe the intermediate course of the disease (Goetz et al., 2004). Although this scale can be easily applied whether or not patient is receiving medications, it is also limited because it focuses on issues of unilateral versus bilateral disease and the presence or not of postural reflex impairments, while other motor deficit aspects are leaving.

For this reason, in clinical examination to rate motor impairments in PD, clinicians use the Movement Disorder Society - Unified Parkinson's Disease Rating Scale (UPDRS) (Goetz et

al., 2008). The UPDRS aims to follow the longitudinal course of the disease and define specific tasks to assess different aspects of the disorder. In particular, it focuses on the evaluation of four sections, each of them with several items:

1. Part I: non-motor experiences of daily living (13 items);
2. Part II: motor experiences of daily living (13 items);
3. Part III: motor examination (18 items);
4. Part IV: motor complications (6 items).

Each item is evaluated providing a discrete score from 0 (no impairments) to 4 (severe impairments which affect the performance of the task). In particular, UPDRS – Part III (UPDRS-III) is mostly used in order to assess motor signs (Stebbins and Coetz, 1998) as well as bradykinesia of UL (Stewart et al., 2009) and it is composed of 27 items. In particular, hand movement assessment is an important part of the UPDRS-III and includes items for bradykinesia, hand tremor at rest or in action and rigidity (Goetz et al., 2008; Stewart et al., 2009). Total scores range from 0 to 108, with higher scores representing higher levels of motor dysfunction (Stebbins and Coetz, 1998).

However, the clinical scales are inherently subjective due to its reliance on the physician's visual assessment of impairments in pwPD and in general it is difficult to convey a concise score, especially when several movement components (i.e. speed, hesitation, amplitude) should be taken into account for the evaluation. For instance, bradykinesia (which results from impairments in speed and amplitude of movement), akinesia (inability to initiate movement or extreme poverty of it) and hypokinesia (reduction in movement amplitude) are frequently considered together and are not separately measured by UPDRS-III (Proud et al., 2015). Moreover, it may not detect small changes as all items are scored on five-point scale (van Den Noort et al., 2017). So, even if these clinical tests and scales are the most used and standardized tools to evaluate motor functions, it may appears useful support clinical outcome measures with detailed quantitative information about UL impairments in PD (Proud et al., 2015).

4.2 Quantitative assessment of UL functions in PD

In contrast to what observed for other neurologic disease like MS, objective and quantitative assessment of PD hand motor symptoms has been investigated by several studies over time,

especially using inertial sensors and optoelectronic systems (Hasan et al., 2017). However, some typical limitations about UL motor assessment have emerged, and they concern the complexity of the symptoms, the inability to measure all of them in one shot or to apply in patients as well as the not easily applicability of the quantitative systems in clinical settings (Van den Noort et al., 2017).

Some authors investigated the kinematics in PD during functional tasks, such as reaching and grasping using optoelectronic system (Bonfiglioli et al., 1998; Castiello et al., 2000; Alberts et al., 2000; Camarda et al., 2005; Khandwala et al., 2015), while others have quantitatively investigated the performance of some items of UPDRS-III scale (i.e. finger tapping, hand grasping, pronation-supination) using inertial sensors (Salarian et al., 2007; Delrobaei et al., 2016).

The results of such studies agreed to describe the UL movements of pwPD as asymmetric (Castiello et al., 2000; Delrobaei et al., 2016) and often variably disrupted, with coordination impairments, especially in terms of elbow-shoulder coordination (Alberts et al., 2000; Leiguarda et al., 2000; Fradet et al., 2009) and arm-hand and arm-trunk coordination (Bertram et al., 2005; Wang et al., 2006; Rand et al., 2010).
High correlation between quantitative kinematic measures and clinical scores, such as UPDRS-III scores, were found, especially in terms of movement speed, amplitude of movement and rhythm (Salarian et al., 2007; Delrobaei et al., 2016). These results demonstrated good capabilities in effectively assess motor performance and UL motor signs hardly detectable with typical clinical scores (Delrobaei et al., 2016; Hasan et al., 2017).

Although different studies investigated UL abilities in pwPD during functional task, in our knowledge, no studies reported an analysis of HTM movement in pwPD. In addition, no one has employed synthetic indexes to summarize the whole dataset of UL kinematic data into few scores (Jasper et al., 2011; Butler et al., 2012) during a functional task in PD yet. As regards this point, the synthetic kinematic measures (Cimolini and Galli, 2014) have mainly used in investigating gait alterations in pwPD with encouraging results (Speciali et al., 2014; Pau et al., 2016; Corona et al., 2016), so appears worth of interest to employ them also in PD in order to describe deviation of UL movement from normal patterns.

4.2.1 Purposes of the study

The aforementioned evidences show that a quantitative and objective assessment of the UL motor features in PD is crucial to characterize PD motor dysfunctions during ADL task and to verify the efficacy of medications and treatments.

The focus of this analysis was to evaluate the UL motor abilities during the HTM task by means of an optoelectronic system and, in particular, to verify if the synthetic kinematic measures were suitable to characterize the level of UL impairments in pwPD. For doing that, the UL kinematic parameters of pwPD were compared with those of healthy age- and gender-matched individuals. Secondly, relationships between individual's disability (assessed by H&Y and UPDRS-III scores), HGS scores and synthetic indexes were investigated. It is clear that a tool which allows physicians to pursue a non-invasive and objective assessment of UL motor abilities of pwPD during an ADL movement, would overcome the majority of the limitations of current clinical evaluation methods.

4.3 Experimental Set-Up

4.3.1 Participants

Sixteen patients with PD (12 male, 4 female, age 68.7 ± 10.5 years, duration of the disease 9.8 ± 6.1 years), followed at "G. Brotzu" General Hospital (Cagliari, Italy) were enrolled for this study. All patients declared to be right-handed. They were treated with Levodopa and were evaluated on 'on' state to diminish the effects of elemental motor deficits such as rigidity and dyskinesia (Leiguarda et al., 2000). The main inclusion criteria were as follow:

- diagnosis of PD according to the UK Brain Bank criteria (Gibb et al., 1988);
- mild-to-moderate disability assessed by means of the modified H&Y staging scale ($1.5 \leq H\&Y \leq 3$);
- being able to understand the task instructions; absence of significant cognitive impairment (MMSE > 24; Frontal Assessment Battery (FAB) > 13);
- absence of psychiatric or severe systemic illness.

Furthermore, a same size group of age and gender-matched healthy individuals without history of head or physical injuries, neurological and orthopaedic diseases was included as

benchmark (HC). The main demographic and clinical characteristics of the participants are reported in Table 4.1.

The local ethics committee approved the study, which was conducted according to Declaration of Helsinki principles. All participants signed a written informed consent prior to participation.

Table 4.1 Demographic data and clinical features of PD participants. Values are expressed as mean (SD).

Status	Participants # (M,F)	Age (years)	Most Affected Arm	H&Y	UPDRS-III	HGS (kgf)
PD	16 (13 M, 3 F)	71.6 (9.9)	10 R / 6 L	1.9 (0.4)	20.3 (9.6)	29.3 (9.8)
HC	16 (12 M, 4 F)	68.8 (6.3)	-	-	-	-

PD: Parkinson's Disease, HC: Healthy Controls, R: right hand, L: left hand, H&Y: Hoehn and Yahr Scale, UPDRS-III: Unified Parkinson's Disease Rating Scale – Part III overall score, HGS: Hand Grip Strength.

4.3.2 Clinical assessment

Clinical evaluation of the pwPD was performed by a clinician expert in PD. The modified H&Y scale was used to assess the severity progression of the disease on one of the seven levels of the scale (Hohen and Yahr, 1967; Goetz et al., 2004). In particular, the modified H&Y scale is as follow (Goetz et al., 2004):

- H&Y score 0: no sign of disease, asymptomatic;
- H&Y score 1.0: very mild symptoms and unilateral involvement only;
- H&Y score 1.5: unilateral and axial involvement;
- H&Y score 2.0: bilateral involvement without impairment of balance;
- H&Y score 2.5: mild bilateral disease with recovery on pull test:
- H&Y score 3.0: mild to moderate bilateral disease with physically independent;
- H&Y score 4.0: severe disability, but still ability to walk or stand unassisted;
- H&Y score 5.0: wheelchair bound or bedribben unless aided.

The motor dysfunctions were quantified using UPDRS-III, and so, clinicians assigned the patient an integer score between 0 and 4. In particular:

- UPDRS-III score equal to 0 corresponds to no motor dysfunctions;

- UPDRS-III score 1 is assigned when the motor symptoms are slight (for instance when rigidity is detectable only with activation manoeuver);
- UPDRS-III score 2 is given in presence of mild motor signs (for instance when rigidity is detectable without activation manoeuver but the range of motion is easily achieved);
- UPDRS-III score 3 is assigned with moderate deficits (for instance when the range of motion is achieved with efforts);
- UPDRS-III score 4 is given when the patient shows severe motor signs (for instance, subject cannot perform the task).

Given that the manual strength has an important role in the completion of the HTM task (Bohannon et al., 1991), HGS of pwPD was measured by means of a digital handheld dynamometer (DynEx, MD Systems, Westerville OH, USA). The test position was standardized (Fess et al., 1992) with shoulder adducted and neutrally rotated, elbow flexed at 95°, forearm and wrist in neutral position. As described (see *Chapter 3 - Paragraph 3.3.2*), participants squeezed the dynamometer as stronger as possible (Mathiowetz et al., 1984) and three trials on each side were registered and the final score was the maximal grip strength calculated from all six valid trials.

Generally, clinical evaluations (Table 4.1) showed that most of the recruited pwPD exhibited a unilateral impairment (10 individuals showed impairment on the right side and 6 on the left side), while no one displayed a bilateral involvement.

4.3.3 Quantitative analysis of movement features

All participants underwent a kinematic analysis of the HTM movement (see *Chapter 2, Paragraph 2.2*). The acquisition was performed at the "Laboratory of Biomechanics and Industrial Ergonomics" of the Department of Mechanical, Chemical and Materials Engineering, University of Cagliari (Italy), using an optoelectronic system composed by 8 infrared Smart-D cameras (BTS Bioengineering, Italy) set at a frequency of 120 Hz.

Spatio-temporal parameters (i.e. duration phases, velocity during the GP, movement precision index), dynamic ROM at the shoulder, elbow and wrist, and the synthetic kinematic indexes for a set of 7 movements of interest (AVS) and for the whole task (APS_7) were calculated.

The biomechanical marker-set, the acquisition protocol and the movement parameters extraction are described in details on *Chapter 2*.

4.3.4 Statistic analysis

The Statistical Package for Social Sciences (SPSS Statistics v. 20, IBM, Armonk, NY, USA) was used for data analysis.

Descriptive statistics, normality tests, homogeneity and outlier's presence analysis were performed before made any comparison. Given the small size of the sample, residual patterns were also analysed. In fact, especially the normal quantile plot (Normal-QQ plot) could be a good way to verify if the normality hypothesis can be assumed. When the normality assumption could not considered acceptable, variable were log transformed to achieve this hypothesis.

A preliminary analysis was performed to test possible differences between most affected and less affected limbs. Comparisons between groups were carried out with multivariate analysis of variance (MANOVA) in order to evidence possible differences in movement features originated by the presence of the disease. The independent variables were the individual's status (HC or PD) and, the dependent variables were the 7 kinematic parameters previously listed, the dynamic ROM of shoulder, elbow and wrist, the 7 AVSs and the APS_7. The level of significance was set at $p = 0.05$ and effect sizes were assessed using the eta-squared coefficient (η^2). Follow-up analyses were conducted using one-way ANOVAs for each dependent variable, adjusting the level of significance with the Bonferroni formula for post-hoc analyses (p value = 0.05 / n comparison).

Correlation between clinical and kinematic assessment variables were evaluated too. Also in this case, significant differences were set at $p = 0.05$.

4.4 Results

All subjects successfully completed the HTM movement. A preliminary analysis performed on elderly HC showed no significant differences in all investigated parameters between most affected and less affected arm ($p > 0.05$), as well as previously found in young healthy people which participated as healthy controls group for the analysis in pwMS (see *Chapter 3*). Similarly, no differences were found in pwPD considering the two limb side ($p > 0.05$).

In Figure 4.1 is reported the distance profile between hand and mouth (expressed as percentage of the distance) during the HTM movement. Figure 4.1b reports the hand velocity's profile in the GP of the most and less affected side for pwPD. Both curves appear quite similar, smooth and bell-shaped. Moreover, no significant differences were found between HC and pwPD in the profile of the hand-mouth distance.

On the basis of these results, the analysis was performed considering the most affected arm for the PD group and the dominant arm for the HC one. So, the right side was more affected in 10 pwPD and the left side in 6 pwPD.

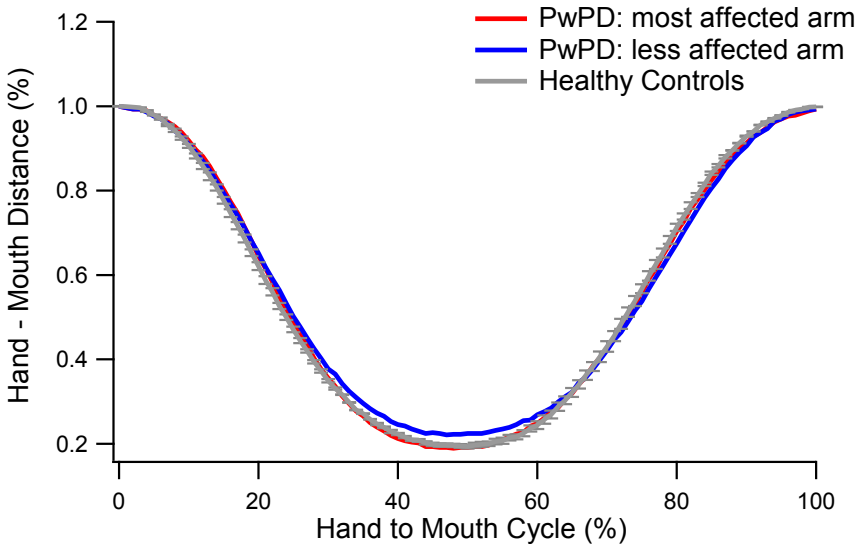


Figure 4.1 Profiles of the hand-mouth distance, expressed as percentage of the distance. The red and blue curves represent respectively the most and less affected side of pwPD, while in grey is reported the normative profiles of the healthy controls.

4.4.1 Kinematic features

The kinematic parameters calculated are summarized in Table 4.2.
MANOVA revealed a main significant effect of the individual's status on spatio-temporal parameters [$F(7,56) = 2,395$, $p = 0.03$, Wilks $\lambda = 0.77$, $\eta^2 = 0.23$].

The follow-up analysis showed that during the execution of the movements, pwPD exhibited a less smooth movement in terms of frequency of direction changes (PD: 5.40 ± 0.70 Hz, HC: 4.51 ± 1.25 Hz, $p = 0.001$). Instead, after Bonferroni correction, no differences were found in the movement duration phase ($p > 0.007$), AS and in velocity ($p > 0.007$).

As regards dynamic ROM, MANOVA failed to detect significantly differences between pwPD and HC were found [$F(4,59) = 1.322$, $p=0.272$, Wilks $\lambda = 0.92$, $\eta^2 =0.08$].

Table 4.2 Spatio-temporal and kinematic parameters of the hand to mouth task in pwPD and healthy controls. Values are expressed as mean (SD).

	HC	PD	*P – value*
Spatio-temporal parameters			
Total Movement duration (s)	1.39 (0.26)	1.67 (0.54)	0.012
GP duration (%)	45.71 (3.72)	43.52 (5.85)	0.078
AP duration (%)	7.53 (5.55)	12.04 (9.99)	0.029
RP duration (%)	46.36 (3.96)	46.25 (5.64)	0.119
Velocity during GP (m/s)	0.59 (0.09)	0.52 (0.11)	0.008
AS (mm)	3.08 (2.16)	5.30 (4.91)	0.022
Frequency of direction changes (Hz)	4.51 (1.25)	**5.41 (0.70)** [a]	**0.001**
Range of Motion			
Shoulder Abduction-Adduction (°)	8.39 (3.88)	9.67 (5.09)	0.261
Shoulder Flexion - Extension (°)	21.41 (12.33)	23.52 (12.24)	0.493
Elbow Flexion - Extension (°)	62.72 (14.37)	54.23 (18.54)	0.045
Wrist Flexion-Extension (°)	18.73 (5.16)	18.24 (6.71)	0.747

PD: Parkinson's Disease group, HC: Healthy Controls, GP: Going Phase, AP: Adjusting Phase, RP: Returning Phase, AS: Adjusting Sway.
[a] Significant differences vs. Healthy Controls (HC) after Bonferroni correction ($p<0.007$ for Spatio-temporal parameters, $p<0.0125$ for Range of Motion)

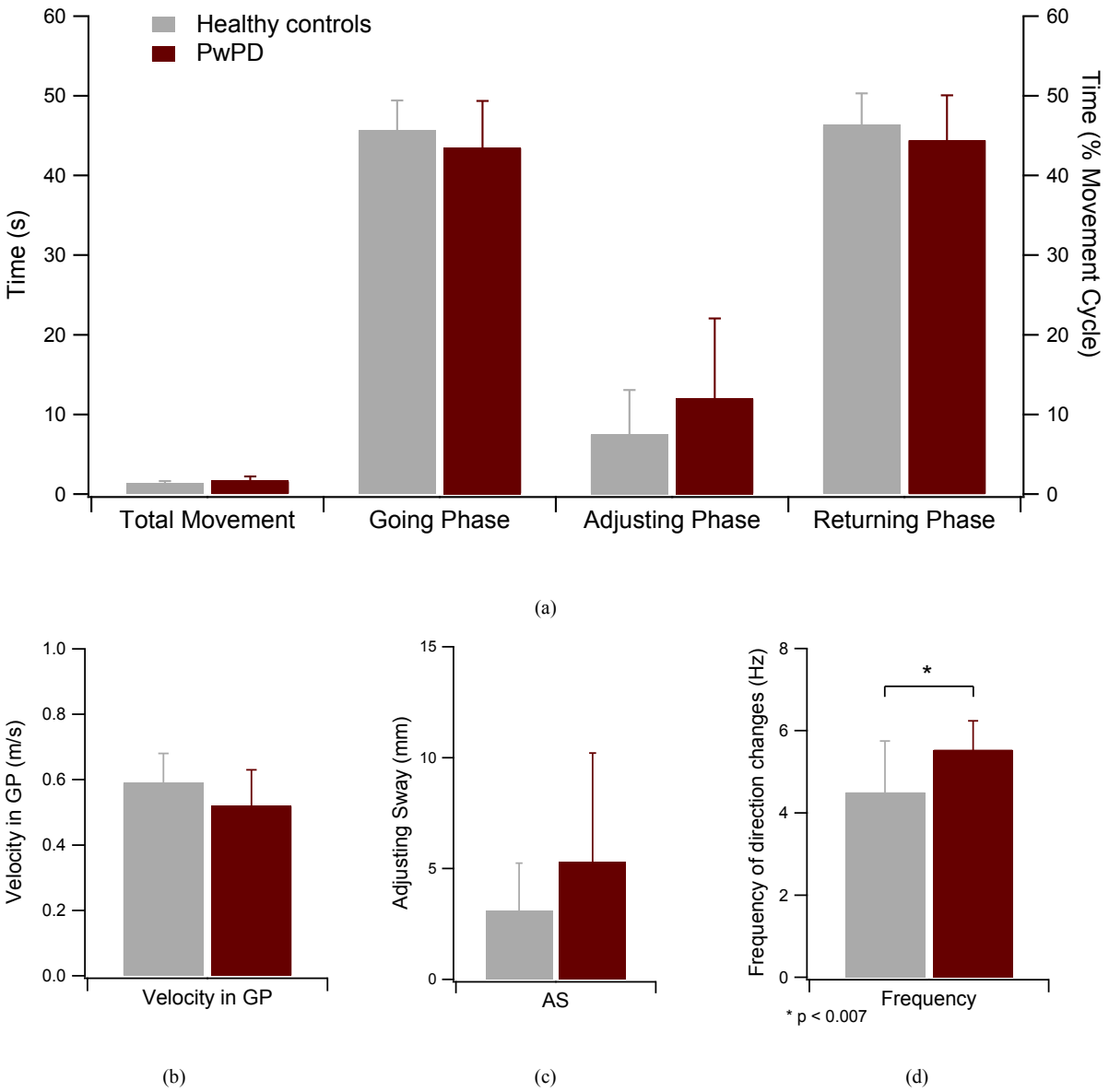


Figure 4.2 Main quantitative results about spatio-temporal parameters calculated during the hand-to-mouth task (mean ± standard deviation). Displayed in (a) are the movement durations, in (b) the hand velocity during the Going Phase (GP), in (c) the adjusting sway (AS) during the Adjusting Phase (AP) and in (d) the frequency of direction changes. * denotes statistical significant differences ($p < 0.007$) between Healthy Controls and people with PD after Bonferroni correction.

4.4.2 Kinematic profiles of UL movements

Kinematic joint graphs during the HTM movement were normalized to task duration time (Figure 4.3).

In each group, the last part of the movement (dedicated to the RP) and the first part (dedicated to the GP) are almost similar in all of kinematic graphs. Some differences in joint trajectories of pwPD were found with respect to those of HC during the HTM cycle. Although the trend is quite similar, some exceptions were found because some pwPD had their elbow near or away from the body (so, respectively their arm was more adducted or abducted) during the performance.

Trajectories of pwPD appeared smooth and almost continuous as well as HC's one, and, in particular, these findings in shoulder and elbow movements indicated an almost good coordination between joints during the HTM task.

Shoulder in pwPD started with a flexion of the shoulder almost equal to 10.3°±2.5° and it approached the maximum flexion angle in the AP. PwPD demonstrated the tendency to abducted the arm during the AP compared to HC, likely due to the fact that pwPD showed a decreased tendency to flex their wrist during the task. Shoulder abduction movement in pwPD presented a peak at ~20% (in the GP) and at ~82% (in the RP) of the cycle, whit a maximal adduction at ~50% of cycle (in the AP).
Elbow angle trajectory demonstrated a smooth curve both in pwPD and in HC with a maximal elbow flexion at the ~50% of the cycle (instant belonging to AP).
Forearm pronation-supination of pwPD looked quite similar to that of HC, while differences in wrist flexion-extension were clearer. Both HC and pwPD showed an extension of the wrist during the whole movement.

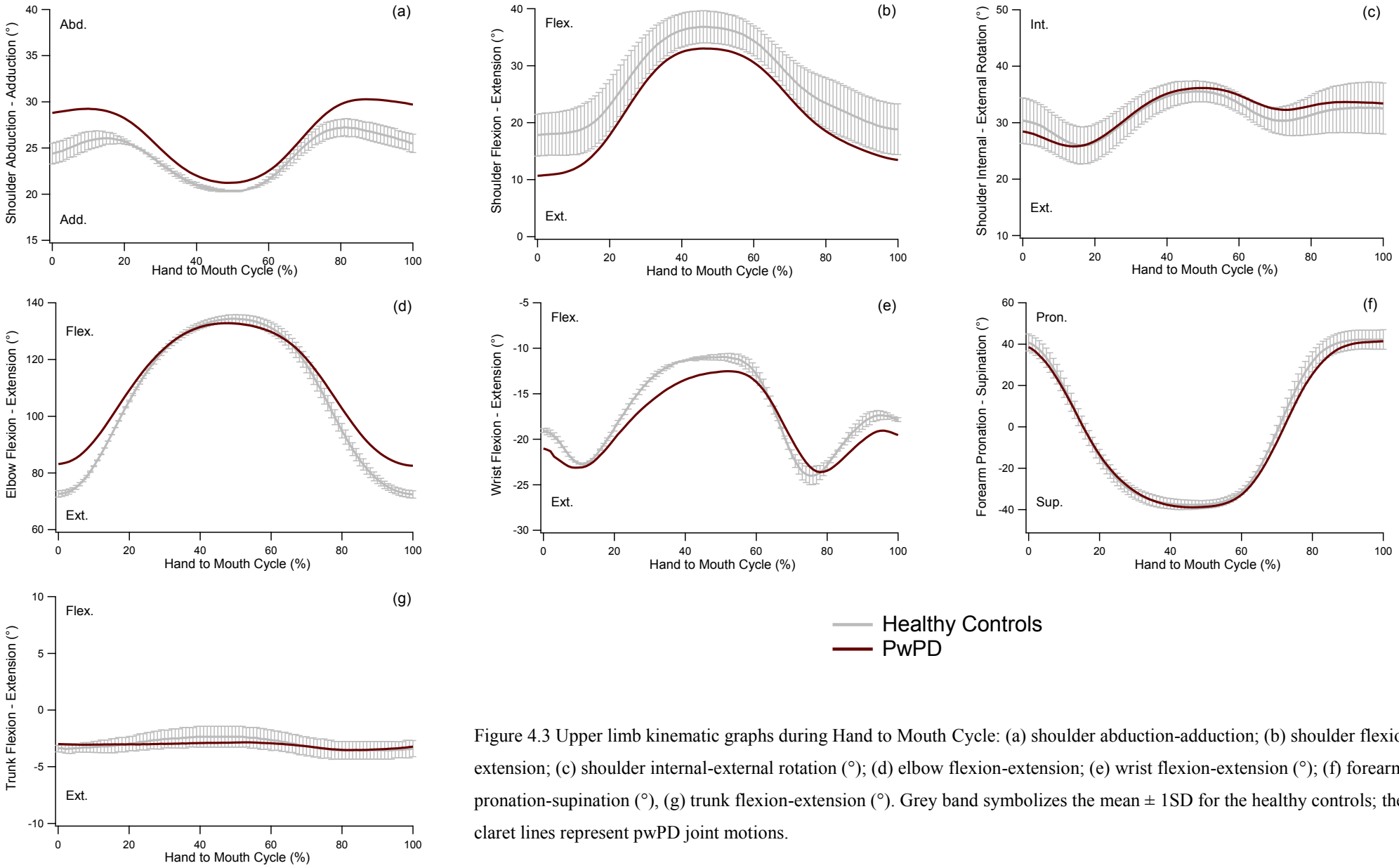


Figure 4.3 Upper limb kinematic graphs during Hand to Mouth Cycle: (a) shoulder abduction-adduction; (b) shoulder flexion-extension; (c) shoulder internal-external rotation (°); (d) elbow flexion-extension; (e) wrist flexion-extension (°); (f) forearm pronation-supination (°), (g) trunk flexion-extension (°). Grey band symbolizes the mean ± 1SD for the healthy controls; the claret lines represent pwPD joint motions.

4.4.3 AVS and APS scores

MANOVA revealed a significant influence of the individual's status on APS_7/AVS indexes [$F(8,55) = 2.86$, $p<0.001$, Wilks $\lambda= 0.17$, $\eta^2 = 0.59$]. The subsequent follow-up analysis revealed significant differences between HC and pwPD for APS_7 ($p < 0.001$) and only one of AVS scores, namely Forearm Pronation-Supination ($p = 0.002$).

In Table 4.3 is reported the results of the follow-up ANOVAs and the AVS and APS scores for the PD and the HC groups, and their values are showed in Figure 4.4.

Table 4.3 Comparison between APS and AVS values in individual with PD (pwPD) and healthy controls (HG) during the hand to mouth task. Values are expressed as mean (SD).

		HC	PD	*P - value*
	APS_7 (°)	9.70 (3.33)	**13.67 (3.36)** [a]	**< 0.001**
	Trunk Flexion-Extension	2.98 (1.78)	4.97 (3.72)	0.066
	Shoulder Abduction-Adduction	5.75 (3.97)	8.55 (5.35)	0.021
	Shoulder Flexion-Extension	9.35 (6.31)	12.31 (5.84)	0.056
AVS (°)	**Shoulder Rotation**	7.18 (3.46)	9.72 (7.14)	0.075
	Elbow Flexion-Extension	9.65 (7.12)	13.55 (7.37)	0.035
	Forearm Pronation-Supination	12.69 (6.96)	**19.14 (8.79)** [a]	**0.002**
	Wrist Flexion-Extension	9.69 (6.11)	12.56 (8.09)	0.131

PD: Parkinson's Disease group, HC: Healthy Controls, APS: Arm Profile Score, AVS: Arm Variable Score.
[a] Significant differences vs. Healthy Controls (HC) after Bonferroni correction ($p<0.006$).

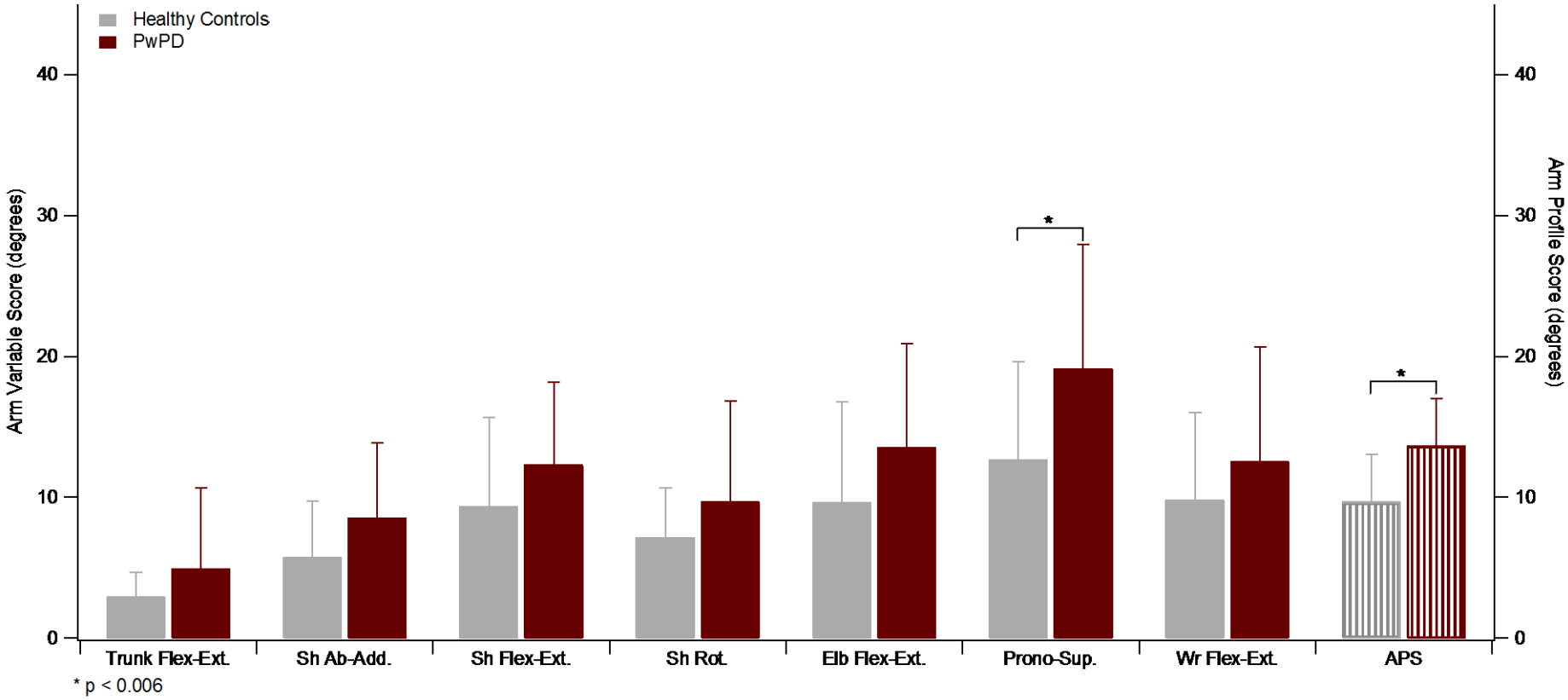


Figure 4.4 The Arm-Movement Analysis over the hand-to-mouth task: Arm Variable Score (AVS) values (Trunk Flex-Ext.: Trunk Flexion-Extension; Sh Ab-Add.: Shoulder Abduction-Adduction; Sh Flex-Ext.: Shoulder Flexion-Extension; Sh Rot.: shoulder Rotation; Elb Flex-Ext.: Elbow Flexion-Extension; Prono-Sup.: Pronation-Supination; Wr Flex-Ext.: Wrist Flexion-Extension) and Arm Profile Score (APS) are reported for the Healthy Controls and the PD groups. * denotes significantly differences ($p < 0.006$) for Bonferroni correction.

4.4.4 Correlation between clinical scores and kinematic variables

Tables 4.4 and 4.5 show the Spearman's rank correlation coefficient rho between the measures of motor scales in pwPD (H&Y scale, UPDRS-III score and its subscores referred to hand movements assessment), the HGS and the UL parameters (spatio-temporal and APS_7/AVS values).

As it can be seen in Table 4.4, significant moderate correlations were found between UPDRS-III overall score and total movement duration (rho = 0.376 $p<0.05$), RP duration (rho = -0.401 $p<0.05$) and AS (rho = 0.355 $p<0.05$). The analysis for UPDRS-III items showed a negative correlation between the UPDRS-III postural tremor of hands and GP duration (rho = -0.460 $p<0.05$) and frequency of change direction (rho = -0.346 $p<0.05$). As regards synthetic indexes, only UPDRS-III Hand Movements score was found significantly correlated with two AVS scores, namely elbow flexion-extension (rho = -0.593 $p<0.05$) and trunk flexion-extension (rho = 0.418 $p<0.05$). Lastly, UPDRS-III prono-supination of hands was found moderate correlated only with AVS score of trunk flexion-extension (rho = 0.407 $p<0.05$).

Table 4.4 Spearman's rank correlation coefficients between UPDRS-III scores and its items regarding hand tasks and the UL parameters in pwPD.

	Parameters	UPDRS-III	UPDRS-III Postural tremor of hands	UPDRS-III Hand movements	UPDRS-III Prono-supination of hands
Spatio-temporal parameters					
	Total Movement duration (s)	**0.376†**	0.261	-0.094	0.313
	GP duration (%)	0.007	**-0.460†**	0.289	0.156
	AP duration (%)	0.320	0.287	-0.208	0.215
	RP duration (%)	**-0.401†**	0.131	0.153	**-0.421†**
	Velocity during GP (m/s)	-0.014	0.206	0.244	-0.059
	AS (mm)	**0.355†**	**0.296**	-0.116	0.267
	Frequency of direction changes (Hz)	-0.125	**-0.346†**	-0.057	0.031
Synthetic kinematic indexes					
	APS_7 (°)	0.172	-0.194	-0.057	**0.251**
AVS (°)	**Trunk Flexion-Extension (°)**	0.321	-0.051	**-0.418†**	**0.407†**
	Shoulder Abduction-Adduction (°)	0.159	-0.061	0.046	0.123
	Shoulder Flexion-Extension (°)	0.097	-0.264	0.161	0.118
	Shoulder Rotation (°)	-0.046	-0.187	0.077	0.188
	Elbow Flexion-Extension (°)	-0.141	-0.203	**0.351†**	-0.166
	Forearm Pronation-Supination (°)	0.102	0.111	-0.187	0.143
	Wrist Flexion-Extension (°)	-0.112	-0.105	0.229	-0.080

UPDRS-III: Unified Parkinson's Disease Rating Scale - Part III, APS: Arm Profile Score, AVS: Arm Variable Score. † $p<0.05$

Moderate positive correlations were also found between H&Y score and the total movement duration (rho = 0.416 $p<0.05$), the APS_7 (rho = 0.356 $p<0.05$) and the AVS score of the shoulder abduction-adduction (rho = 0.455 $p<0.05$).

As regards HGS, moderate correlations were found with AP duration (rho = -0.380 $p<0.05$), frequency of change direction (rho = 0.385 $p<0.05$) and the AVS score of wrist flexion-extension (rho = 0.370 $p<0.05$).

Table 4.5 Spearman's rank correlation coefficients between H&Y, HGS scores and the UL parameters in pwPD.

	Parameters	H&Y	HGS
Spatio-temporal parameters			
	Total Movement duration (s)	-0.039	-0.039
	GP duration (%)	0.178	0.178
	AP duration (%)	**-0.380†**	**-0.380†**
	RP duration (%)	**0.331†**	**0.331†**
	Velocity during GP (m/s)	-0.062	0.062
	AS (mm)	**-0.342†**	**-0.342†**
	Frequency of direction changes (Hz)	**0.385†**	**0.385†**
Synthetic kinematic indexes			
	APS_7 (°)	**0.356†**	0.137
	Trunk Flexion-Extension (°)	**0.331†**	0.036
	Shoulder Abduction-Adduction (°)	**0.455†**	-0.082
AVS (°)	**Shoulder Flexion-Extension (°)**	0.016	-0.242
	Shoulder Rotation (°)	0.270	-0.134
	Elbow Flexion-Extension (°)	-0.249	-0.061
	Forearm Pronation-Supination (°)	0.294	0.096
	Wrist Flexion-Extension (°)	0.048	**0.370†**

H&Y: Hoehn & Yahr scale, HGS: Hand Grip Strength, APS: Arm Profile Score, AVS: Arm Variable Score. † $p<0.05$

4.5 Discussion

The purpose of this study was to investigate UL kinematics during an ADL task, the HTM movement, in pwPD using an optoelectronic system and verify the relationship between kinematic parameters and motor clinical scores. The results indicate that UL kinematics during the HTM task was similar for pwPD and HC, suggesting that high level motor programming is preserved in PD and not compromised (Tresilian et al., 1997). First of all, as regards spatio-temporal parameters, no statistically differences were found between pwPD and HC, consistent with previous evidences (Bonfiglioli et al., 1998).

PwPD exhibited only a significantly higher frequency of direction changes, as previous observed (Heida et al., 2013). This denotes the presence of tremor in our sample of pwPD, in keeping with the subscales of the UPDRS-III scale, which showed that all patients exhibited postural and action tremor of the arm. The velocity was found to be normal ($p>0.05$), as also described by others (Bonfiglioli et al., 1998). On the other hand, others described that in presence of tremor the velocity in pwPD is faster than HC, with the result that the patients tend to overshoot the target (Berardelli et al., 1996).

Even if bradykinesia is a common feature in pwPD (Proud et al., 2015), our findings seem to demonstrate that our sample of pwPD is not bradykinetic. In fact, bradykinesia is reflected by lower velocity and longer movement time in pwPD (Khandwala et al., 2012), while we found no differences with respect to healthy subjects for these parameters. This could be due to the type of movement performed, the HTM: in fact, generally bradykinesia does not appear in simple and automatic task (Bonfiglioli et al., 1998).
The findings suggest that the absence of differences between PD and HC group might be explained by the tendency of pwPD to compensate for a series of motor symptoms, such as rigidity, resting tremor, bradykinesia (Bonfiglioli et al., 1998). Moreover, our pwPD are treated with Levodopa, which induced beneficial effects on movement performance, because seems to improve the sequential and simultaneous movements, such as the HTM task, while the isolated one (i.e. pointing) seems to be influenced by (Pottër-Nerger et al., 2013). It results also in shorter total movement duration and increased velocity during the GP (Castiello et al., 2000).

Furthermore, as regards the synthetic measures proposed for characterizing the whole movement, some significant differences were found between pwPD and HC. In particular, the

results showed that APS_7 is higher in pwPD with respect to healthy subjects, thus indicating significantly larger deviations from physiological UL motion. This suggests that this index is able to summarize the UL impairments and alterations associated with the presence of the disease, thus discriminating in an immediate and clear way motor performance limitations of patients with PD from normal motor pattern.

When the single AVS scores were analysed, only the one referred to forearm pronation-supination was found significantly higher ($p < 0.006$) in pwPD, thus indicating a deviation from a physiologic movement pattern only for this movement. Thus, taking a look at kinematic graphs, PD's curves appeared smooth and similar to HC's. This feature could be explained with medication and DBS employment (Pottër-Nerger et al., 2013; Khandwala et al., 2015), which improve the distal kinematics. Even if no reflections in proximal kinematics is generally displayed (Khandwala et al., 2015), simultaneous coordination of proximal and distal joint movements are required to move the hand to the mouth, so it can represent a connection between motor functions of basal ganglia circuit and its putative relationship (Kurlan, 2004).

The APS_7 and the AVS scores of trunk flexion-extension and shoulder abduction-adduction correlated well with the H&Y score. Thus, it can hypothesize that these indexes may be somehow representative of the overall disability of the individual. Thereby, the use of these synthetic measures can be suitable for identifying the UL progressive motor impairments associated with increasing disability, even though H&Y scale is mainly constructed considering the overall disability level. Moreover, a moderate correlation with the UPDRS-III pronation-supination of hands score seems to confirm that this index may be sensitive to this impairment. Similarly, good correlations were found between the AVS of trunk flexion-extension with the UPDRS-III scores referred to hand movements and pronation-supination of hands. This relationship suggests that our sample presented alterations both some proximal (with respect to trunk flexion-extension) and distal (with respect to hand deficits).

When the relationship between spatio-temporal parameters and motor clinical scores were investigated, some good correlations were found. In particular, the presence of tremor evidenced by the analysis well fits with the UPDRS-III score of the postural tremor of hands, the H&Y score and with the HGS value. We also found a moderate correlation between AS and clinical scores, indicating that this parameter is able to describe the some deficit somehow evidenced by the scales.

However, pwPD exhibit different behaviour with respect to healthy subject in performing the task. For this reason, it appears worthwhile to point out that our follow-up ANOVAs were conducted using Bonferroni correction, which is a conservative procedure that reduces the number of false positives when multiple pairwise tests are performed on a single data set. Despite this, it is interesting to note that our results showed that the performances of pwPD were worst with respect to those of HC. This suggests that, increasing the sample size, the significance could be reached for more parameters.

In particular, it could be interesting to point out that pwPD have already exhibited higher total time to complete the task (+20%, $p = 0.012$) and required more time in AP in order to achieve the mouth (+60%, $p = 0.029$). This influenced the velocity and the AS too, which respectively decreases (-12%, $p = 0.008$) and raises (+72%, $p = 0.022$). The loss of dopamine leads to disrupt the balance of direct and indirect pathways of motor circuit and precise localization deficits, which then may interfere with the movement performance and reduce the abilities to specify the motor plan (Alberts et al., 2000). This is likely responsible to irregular movement paths of pwPD when the reaching a target. In fact, when pwPD have to perform an accurate task (as the precise localization of the target), they often show problems with implementation of precise motor commands (Albert et al., 2000).

As regards synthetic measures proposed here, increasing the sample size other two AVS scores might be significantly difference from HC. In fact, pwPD have already showed a higher deviation from normality for shoulder abduction-adduction (PD: 5.55°±0.83° vs. HC: 5.75° ±0.83°, $p = 0.021$) and elbow flexion-extension (PD: 13.55°±0.1.28° vs HC: 9.65° ±1.28°, $p = 0.035$). This suggests that people with basal ganglia deficits could show irregular movement, with dissimilar variation in elbow and shoulder movements (that means abnormal joint coordination), while healthy subjects show a coordinated coupled joints motions, with a smooth and linear relationship of angle-angle variations (Leiguarda et al., 2000). In fact, disorders of sequential patterns of muscle activity could influence and increase the presence of joint coordination deficits (Leiguarda et al., 2000).

Summing up, our sample of pwPD showed movement performance similar from those of healthy individuals, in term of spatio-temporal parameters as well as in terms of joint kinematics. We claim that these characteristics depend mostly on the sample size, but they could depend also on the medication that pwPD use (Castiello et al., 2000; Khandwala et al., 2015) and in part may be due to the mild-to-moderate UL impairments of pwPD we recruited.

4.6 Conclusion

The aim of this chapter's study was to carry out a quantitative characterization of UL motor abilities in pwPD during the performance of a HTM task, representative of ADL, using an approach that can take several kinematic indexes into account. In particular, the focus was to investigate the feasibility of the application of Arm Profile Score (APS_7) for immediate quantification of the degree of UL impairments in pwPD during the HTM task.

Our results suggest that in our group of PD the UL kinematic abilities are preserved, as no differences between patients with PD and normal subjects were found. Nonetheless, the APS_7 index appears a useful tool for identifying overall impairment of UL motor function in pwPD related to basal ganglia dysfunction, and it seems to be able to discriminate motion patterns of different clinical conditions. Therefore, the use of quantitative measure may be useful in concurrently assessing altered arm and trunk movements in pathological individuals. Moreover, quantitative analysis can help in analysing of the impact of UL deficits on functional tasks and seems to be able to discriminate motion patterns of different clinical conditions. In the meanwhile, quantitative kinematic measures can accurately quantify velocity, amplitude and rhythm to aid in development of novel therapies in PD (Helmed et al., 2011).

Despite this, it should be underline that the results presented in this Chapter are still preliminary and belong to a cross-sectional study. Moreover, further investigations are needed to confirm their capability. In fact, in order to have more meaningful results from a statistical point of view, additional tests on a larger convenient sample of individuals would be performed.

Moreover, the same limitations described in *Chapter 3* should be reported, especially as regards the nature of the APS_7/AVS indexes that should be backed up by the kinematic graphs as well as by other UL parameter (i.e. spatio-temporal data) for a full understanding of the alteration level in the UL motor pattern (Jasper et al., 2011; Butler et al., 2012; Pau et al., 2016) in PD. In addition, also in this case, to fully describe the motor strategies employed by pwPD to perform goal-oriented daily tasks, it would be interesting to integrate kinematics with joint compensatory evaluation (Alberts et al., 2000; Leiguarda et al., 2000; Michaelsen et al., 2001). This should clarify what the exact mechanisms are involved in PD to control arm joint interactions during a HTM movement.

Chapter 5

Quantitative assessment of Hand to Mouth Task in Dementia with Parkinsonism

'What is dementia? Imagine feeling thirsty but not being able to get a drink. Imagine losing the ability to do the simplest everyday tasks.' – Unknown

It appears of some interest to verify how the analysis of UL motor patterns during the HTM task may result useful in other kind of neurologic diseases such as dementia, whose motor symptoms have been rarely investigated with quantitative techniques. To this purposes, in this chapter, a preliminary analysis of the HTM task in a sample of people with Dementia with Lewy Bodies (pwDLB), which is a dementia with Parkinsonism signs, is reported. In particular, the analysis here reported is focused on the comparison of the task performance between pwDLB and pwPD, in order to verify if dementia with Parkinsonism is characterized by different features, in terms of UL motor performance with respect to idiopathic PD.

5.1 Introduction

5.1.1 Dementia with Parkinsonism

Dementia is a progressive mental decline condition that involves multiple higher brain dysfunctions like hallucinations, attention and mental alertness disorders, and it is also characterized by memory impairment, which persists and degenerates over time (McKeith et al., 2017).

Dementia occurs predominantly in older adults and can be categorized in two different subtypes, namely Alzheimer's Disease (AD) and dementia with Parkinsonism (Vann Jones et al., 2014). The Dementia with Lewy Bodies (DLB), which belongs to the latter category, is a common neurodegenerative dementia in older people, second only to AD (Zaccai et al., 2005; Gomperts, 2016). DLB is caused by the presence of cytoplasmic clumps, known as Lewy bodies, in the brain (Gomperts et al., 2016) which were described for the first time by Dr. Frederich Lewy (1912) in the *substantia nigra* of pwPD, and which cause gradual degeneration of body functions. Lewy bodies are observed not only in DLB and in idiopathic PD, but also PD dementia (PDD) and multiple system atrophy (MSA).

The clinical diagnosis of DLB is based on McKeith criteria (McKeith et al., 2005) that include as essential feature a progressive cognitive decline capable to interfere with daily living. Also, the diagnosis should be considered if the individual is characterized by fluctuating cognitive symptoms with variations in attention, repeated visual and non- visual (hearing, smell, touch) hallucinations, rapid eye movement sleep behaviour disorder, depression and extrapyramidal motor impairments (e.g. Parkinsonism, McKeith et al., 2005; McKeith et al., 2017).

Thus, individuals affected by dementia are not only cognitively impaired but they suffer from limitations in primary motor functions are impaired (Scherder et al., 2008; Suzumura et al., 2016). Moreover, the decline in motor functions is related to cognitive decline (Suzumura et al., 2016) and, thus, it is a predictor of functional disability in elderly people (Scherder et al., 2008). In particular, it is well-known that UL motor function, especially HGS, decreases with aging and its decline is higher in presence of cognitive deficits (Ranganathan et al., 2001; Carmeli et al., 2003). Moreover, the decline of UL motor abilities appears to have a huge

negative impact on ADL performance (i.e. moving an object, eating, dressing, cooking) and person's independence (Scherder et al., 2008; de Paula et al., 2016).

As regards Parkinsonism motor signs, pwDLB usually exhibit bilateral impairments, and signs such as bradykinesia and rigidity are more common than rest tremor (Gomperts, 2016). This range of symptoms makes DLB similar to idiopathic PD (Walker et al., 2016). Moreover, a common feature of basal ganglia disorders (PD, DLB) is the apraxia disorder that is the difficulty of transforming motor planning in performed task (Zadikoff and Lang, 2005), common in other dementia subtypes too, such as AD, PDD, MSA and Fronto-Temporal Dementia (FTD).

Given that DLB management is challenging, non-pharmacological strategies (i.e. cognitive and motor training) and pharmacological interventions (i.e. antidepressants, antipsychotics) are usually used in combination (Walker et al., 2016; McKeith et al., 2017). As regards motor signs' management, pwDLB are poorly responsive to dopaminergic therapies such as Levodopa than pwPD (Gompers et al., 2016), and thus they are likely to increase the risk of psychosis and confusion (McKeith et al., 2017).

The relationship between DLB and idiopathic PD or PDD has not yet well-established (McKeith et al., 2017). However, it appears important to point out that, even though some clinical features are common in both DLB and PDD (i.e. hallucinations and Parkinsonism signs), the diagnosis of these disorders can be established on the basis of the different temporal onset of motor and cognitive deficits (Walker et al., 2015). In fact, a diagnosis of PDD is established when cognitive impairments develop on the context of well-established PD, while in DLB the cognitive decline develops before or within one year of spontaneous Parkinsonism (Walker et al., 2015; Gomperts, 2016). Thus, given the substantial overlapping of clinical and pathologic features, the accurate diagnosis of the DLB may be sometimes quite difficult (Zaccai et al., 2016), and, for this reason, diagnostic markers for dementia, such as cerebrospinal fluid, brain pathology and cognitive markers, are used to distinguish DLB to other dementia subtypes (Gillain et al., 2009).

In this context, a detailed assessment of UL motor abilities might help clinicians to establish a more accurate diagnosis for the various subtype of dementia (Scherder et al., 2008). Thus, in order to understand if some differences in motor abilities are noticeable, it appears worthy of attention to quantitatively characterize the movement pattern in pwDLB and pwPD.

5.1.2 Clinical motor assessment in DLB

As previously mentioned, the clinical assessment in pwDLB is performed assessing cognitive impairments and Parkinsonism signs (McKeith et al., 2017). Cognitive deficits in dementia are usually evaluated using tools such as MMSE (MMSE score < 24/30 corresponds to a state of mental decline), which, though, do not provide any information on ADL performance functions (Folstein et al., 1975).

Given that dementia can affect person's abilities to perform ADL (McKeith et al., 2005; McKeith et al., 2017), it is crucial to assess also physical motor skills, in particular UL functions (Scherder et al., 2008). Suitable tools for evaluating UL motor functions in dementia, especially as regards hand impairments, are the finger tapping task test (Muller et al., 1991; Hobert et al., 2010; Fritz et al., 2016), Purdue Pegboard test (Hobert et al., 2010; Aggarwal et al., 2006; Lin et al., 2016), and 3D motion analysis (Camarda et al., 2007).

Another clinical tool for the evaluation of the motor performance and the process skills to execute a movement is the Assessment of the Motor and Process Skills (AMPS), which is able to detect ADL deficits (i.e. washing dishes by hand or serving drink) since early stages of dementia (Hartman et al., 1999; Mori and Sugimura, 2007).

As regards Parkinsonism signs' assessment, the motor assessment is performed using typical clinical tools used in PD (McKeith et al., 2005; Walker et al., 2015; McKeith et al., 2017), such as H&Y and UPDRS-III scales (see *Chapter 4, Paragraph 4.1.2*). Moreover, given that reductions in muscular strength are predictor of cognitive decline, another clinical tool used in dementia to evaluate the hand and forearm functions is the HGS test (Scherder et al., 2008; Boyle et al., 2009; Jang and Kim, 2015).

However, it is important to note that the available clinical scales are subjective or partially objective methods (Pan et al., 2014) that may not adequately and quantitatively reflect the disease severity. Thus a reliable objective tool is necessary for appropriate assess impairments in clinical practice (Pan et al., 2014).

5.2 Quantitative assessment of UL functions in DLB

While the UL motor abilities in pwPD have been quantitatively investigated in several studies (Bonfiglioli et al., 1998; Castiello et al., 1999; Espay et al., 2009; Pötter-Nerger et al., 2013; Hasan et al., 2017), only few studies have quantitatively assessed motor functions in

dementia. As regards lower limbs deficits, gait analysis has been proposed as potential clinical biomarkers for dementia (Merory et al., 2007; Gillain et al., 2009; Nakardi et al., 2009), showing that instrumental quantitative assessment of gait impairments can be useful to support the prediction of mild cognitive impairments as well as dementia subtypes (Nadkarni et al., 2009; Anang et al., 2014; Lin et al., 2016).

On the other hand, UL motor evaluation using a quantitative approach did not receive the same attention, even though research pointed out the importance to quantitatively characterize hand and arm dysfunctions in order to provide rehabilitative care for dementia (Scherder et al., 2008; Suzumura et al., 2016; Kragh et al., 2017).

However, the studies performed so far have investigated the UL motor skills mostly in people with AD (Ott et al., 1995; Camarda et al., 2007; Scherder et al., 2008; de Paula et al., 2016; Lin et al., 2016; Suzumura et al., 2016), while UL motor impairments in DLB appear still not extensively investigated. Generally speaking, motor programming dysfunctions, which are typical in people to dementia, are reflected in the worse performance of motor task compared to healthy subjects (Ott et al., 1995; Goldman et al., 1999; Camarda et al., 2007; de Paula et al., 2016). People with dementia, especially individuals with AD, require longer times to prepare movements, perform more slowly the task and exhibit altered UL velocity during it (Ott et al., 1995; de Paula et al., 2016) with less accurate movement execution, especially when corrective adjustments are required (Camarda et al., 2007). As regards DLB, the few existing evidences showed that hand dexterity impairments are higher in pwDLB with respect to PD and AD people (Fritz et al., 2016).
However, given that few studies have investigated UL motor abilities in dementia and none of them has quantitatively characterized UL movements in DLB, it appears interesting to perform a kinematic analysis of UL motor task in pwDLB.

Indeed, the suitability of this technique has already pointed out for the assessment of gait impairments in dementia (Nadkarni et al., 2009; Anang et al., 2014; Lin et al., 2016) and, thereby it can be employed also for the UL motor assessment in dementia (Pan et al., 2014).

5.2.1 Purposes of the study

On the basis of the aforementioned evidences, it appears crucial characterizing motor dysfunctions during ADL in dementia with Parkinsonism and providing information that can overcome the limitations of current clinical evaluation tools in this pathology. In particular, it

seems worthy of interest to use an objective and accurate technique which allows physicians to characterize UL kinematic abilities of pwDLB.

For this reason, the focus of this analysis was to establish the UL movement features during the HTM task using an optoelectronic system and to verify if the synthetic measures previously described were suitable to characterize UL kinematics in pwDLB. To this aim, firstly the UL kinematic parameters of pwDLB were compared with those of healthy age- and gender-matched individuals and secondly with those of a sample of pwPD. Then, relationships between individual's disability (assessed by H&Y and UPDRS-III scores), HGS scores and UL movement parameters were investigated.

5.3 Experimental Set-Up

5.3.1 Participants

Ten patients with DLB (6 male, 4 female, age 74.8 ± 4.2 years, duration of the disease 9.8 ± 6.1 years), currently followed at the Department of Neurology, Azienda Universitaria-Ospedaliera of Cagliari (Italy), were enrolled for this study. The main inclusion criteria were diagnosis of DLB according to clinical criteria established by McKeith et al. (2005); presence of cognitive impairments (MMSE ranged from 10 to 24); spontaneous Parkinsonism and absence of any other neurological or orthopedic condition.

Furthermore, a same size group of pwPD (8 male, 2 female, age 72.8 ± 9.1 years, duration of the disease 9.8 ± 6.1 years) was recruited. Each PD participant was matched with one DLB participant by H&Y score in order to have similar disease severity levels in both groups. The main inclusion criteria for pwPD were the same used in *Chapter 4* (see *Paragraph 4.3.1*): diagnosis of PD according to the UK Brain Bank criteria (Gibb et al., 1988); being able to understand the task instructions and absence of psychiatric or cognitive impairment (MMSE > 24).

All pathological subjects were right-handed and characterized by a bilateral UL impairment. A same size of healthy and age and gender-matched individuals without history of head or physical injuries, neurological and orthopaedic diseases was included as control group (HC). The local ethics committee approved the study and all participants signed a written informed consent about the study's purposes prior to participation.

The main demographic and clinical characteristics of the participants are reported in Table 5.1.

Table 5.1 Demographic data and clinical features of participants. Values are expressed as mean (SD).

Status	Participants # (M,F)	Age (years)	Impairment side	H&Y	UPDRS-III	HGS (kgf)
DLB	10 (6 M, 4 F)	74.8 (4.2)	2 R/ 4 L (4 Bilateral)	2.5 (1.0)	34.7 (15.6)	29.3 (9.8)
PD	10 (8 M, 2 F)	72.2 (9.1)	7 R / 4 L	2.1 (0.4)	25.1 (7.0)	29.5 (9.2)
HC	10 (6 M, 4 F)	70.4 (5.8)	-	-	-	-

R: right hand, L: left hand, H&Y: Hoehn and Yahr Scale, UPDRS-III: Unified Parkinson's Disease Rating Scale – Part III overall score, HGS: Hand Grip Strength.

5.3.2 Clinical assessment

Clinical evaluation of the pwDLB was carried out by a neurologist expert in dementia assessment.

Given the presence of Parkinsonism signs both in DLB and PD, H&Y and UPDRS-III scales were used to assess the disability level of the pwDLB and pwPD. In particular, the disease severity was evaluated using the modified H&Y scale (Hohen and Yahr, 1967; Goetz et al., 2004), while the UPDRS-III scale was used to quantify the motor impairments (Goetz et al., 2008).

The evaluation of hand function and UL muscle tone in pwDLB and pwPD was performed by HGS test (Bohannon et al., 1991), using a digital handheld dynamometer (DynEx, MD Systems, Westerville OH, USA). The test position was standardized (Fess et al., 1992) with shoulder adducted and neutrally rotated, elbow flexed at 95°, forearm and wrist in neutral position. Participants squeezed the dynamometer as stronger as possible (Mathiowetz et al., 1984) and three trials on each side were registered and the final score was the maximal grip strength calculated from all the valid trials.

Overall, clinical evaluations (Table 5.1) showed that most of the recruited pwDLB were characterized by bilateral impairment, while pwPD exhibited unilateral impairment.

5.3.3 Quantitative analysis of movement features

The kinematic analysis of the HTM movement (see *Chapter 2, Paragraph 2.2*) was carried out at the "Laboratory of Biomechanics and Industrial Ergonomics" of the Department of Mechanical, Chemical and Materials Engineering, University of Cagliari (Italy), using an optoelectronic system composed by 8 infrared Smart-D cameras (BTS Bioengineering, Italy) set at a frequency of 120 Hz. The biomechanical marker-set, the acquisition protocol and the movement parameters extraction are described in details on *Chapter 2*.

5.3.4 Statistic analysis

Descriptive statistics, normality tests, homogeneity and outlier's presence analysis were applied before made any comparison. Given the small size of the sample, residual patterns were also analysed. In fact, especially the normal-quantile plot (Normal-QQ plot) could be a good way to verify if the normality hypothesis can be assumed. When the normality assumption could not considered acceptable, variable were log transformed to achieve this hypothesis.

A preliminary analysis was performed to test possible differences between most affected and less affected limbs. Comparisons between groups were carried out with multivariate analysis of variance (MANOVA) in order to detect possible differences in movement features originated by the presence of the disease. The independent variables were the individual's status (HC, DLB or PD) and, the dependent variables were the 7 UL kinematic parameters (i.e. total movement time, phases duration, hand velocity, adjusting sway, frequency of change in direction of the hand trajectory), the dynamic ROM of shoulder, elbow and wrist, the 7 AVSs and the APS_7. The level of significance was set at $p = 0.05$ and effect sizes were assessed using the eta-squared coefficient (η^2). Follow-up analyses were conducted using one-way ANOVAs for each dependent variable, adjusting the level of significance with the Bonferroni formula for post-hoc analyses (p value = 0.05 / n comparisons).

Correlation between clinical and kinematic assessment variables were evaluated using Spearman's correlation coefficient. In particular, it was investigated the association between the measurement parameters described above and the severity of motor impairments assessed by UPDRS-III, H&Y and HGS scores. Even in this case, significant differences were set at p

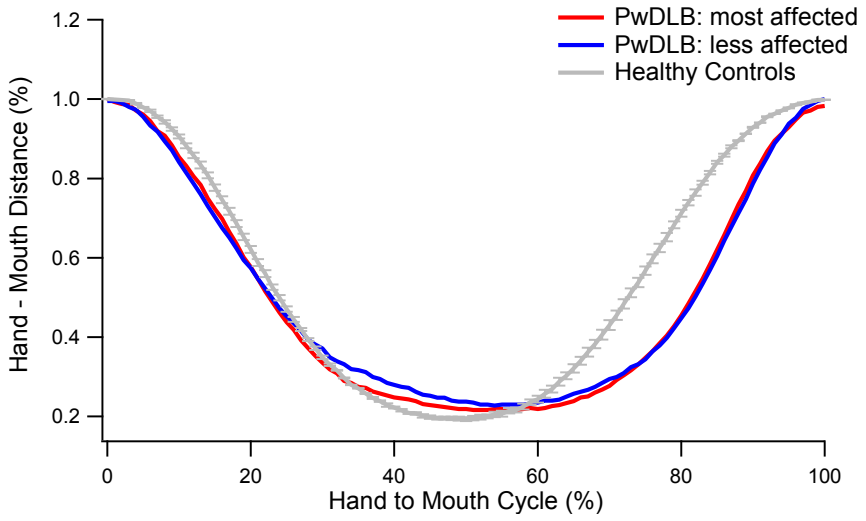
= 0.05. All the analyses were performed using SPSS Statistics v. 20 (IBM, Armonk, NY, USA).

5.4 Results

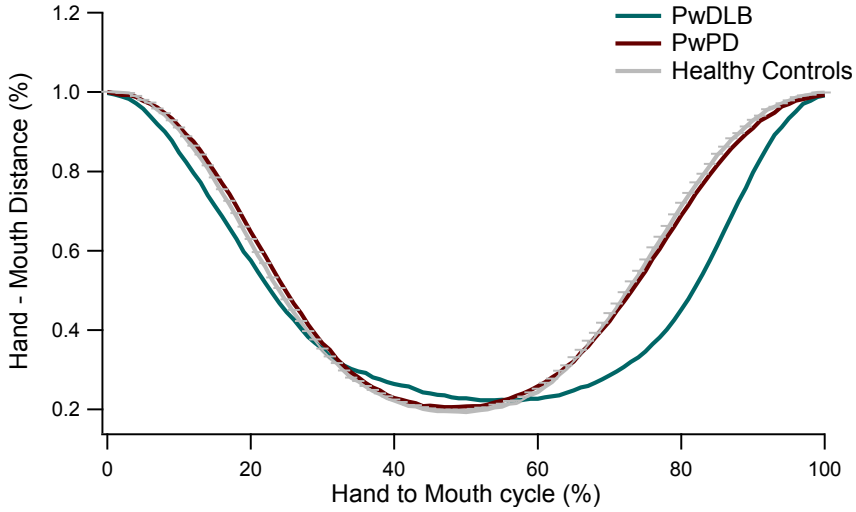
All participants successfully completed the HTM movement. Similarly to what found for pwMS (see *Chapter 3*) and pwPD (see *Chapter 4*), a preliminary analysis showed no significant differences in all investigated parameters between most affected and less affected side in pwDLB.

Figure 5.1 shows the diagrams which report the trend of the distance between hand and mouth during the HTM movement: in particular, Figure 5.1a shows the hand-mouth distance of both most and the less affected arm in pwDLB, while Figure 5.1b shows the comparison between pwDLB, pwPD and HC. It can be observed that both most and less affected arm curves appear quite similar in pwDLB (Figure 5.1a), while some differences between HC and pwDLB are visible in the profile of the hand-mouth distance. Moreover, the curve which refers to pwDLB differs from those of HC and pwPD. In particular, it can be seen that pwDLB reached the mouth (that corresponds to the minimum of the hand-mouth distance) later during the movement cycle (around at 60%).

On the basis of these results, it was decided to include both limbs for all the participants in the subsequent analysis.



(a)



(b)

Figure 5.1 (a) Profiles of the hand-mouth distance of pwDLB and HC, expressed as percentage of the hand-mouth distance. The red and blue curves represent respectively the most and less affected side of pwDLB, while in grey is reported the normative profiles of the healthy controls. (b) Profiles of the hand-mouth distance of pwDLB, pwPD and HC (a), expressed as percentage of the hand-mouth distance. The claret and dark green curves represent respectively the average of the hand-mouth distance of pwPD and pwDLB, while in grey is reported the normative profiles of the healthy controls.

5.4.1 Kinematic features

Table 5.2 reports the calculated kinematic parameters. MANOVA revealed a main significant effect of the individual's status on spatio-temporal parameters [$F(14,120) = 4.36$, $p < 0.001$, Wilks $\lambda = 0.44$, $\eta^2 = 0.337$]. The follow-up analysis showed that pwDLB required a longer time to complete the task compared to HC and pwPD ($p < 0.001$) and especially to precisely locating the mouth ($p<0.001$), with lower velocity in GP ($p < 0.001$) and higher AS ($p<0.001$). Furthermore, during the execution of the movements, pwDLB exhibited a less smooth movement in terms of frequency of direction changes with respect to HC (DLB: 5.53 ± 0.85, HC: 4.66 ± 1.32, $p = 0.001$).

As regards the dynamic ROM, MANOVA detected significantly differences between pwDLB, pwPD and HC [$F(10,126) = 3.21$, $p=0.001$, Wilks $\lambda = 0.631$, $\eta^2 =0.205$].The follow-up analysis showed statistically differences between DLB and PD group for the ROM of shoulder abduction-adduction (DLB: 6.53 ± 2.74, PD: 10.82 ± 5.38, $p = 0.006$) and shoulder flexion-extension (DLB 12.62 ± 5.87, PD: 24.65 ± 12.27, $p = 0.002$).

The comparison between pwPD and HC is consistent with what previously observed in *Chapter 4*: pwPD exhibited during the execution of the movements less smooth movement in terms of frequency of direction change (PD: 5.42 ± 0.79, HC: 4.66 ± 1.32, $p = 0.001$) and no differences were found in the movement duration phases, AS and hand velocity during the GP ($p > 0.007$).

Table 5.2 Spatio-temporal and kinematic parameters of the hand to mouth task in individuals with DLB (pwDLB), people with PD (pwPD) and healthy controls. Values are expressed as mean (SD).

	HC	PD	DLB
Spatio-temporal parameters			
Total Movement duration (s)	1.36 (0.33)	1.78 (0.61)	**2.76 (1.30)** [a,b]
GP duration (%)	45.69 (4.07)	42.77 (6.52)	41.85 (10.11)
AP duration (%)	7.36 (6.03)	14.52 (10.88)	**21.31 (13.48)** [a,b]
RP duration (%)	46.51 (4.16)	42.71 (5.43)	**36.61 (8.30)** [a,b]
Velocity during GP (m/s)	0.59 (0.09)	0.50 (0.13)	**0.40 (0.12)** [a,b]
AS (mm)	3.05 (2.43)	6.37 (5.43)	**17.06 (9.22)** [a,b]
Frequency of direction changes (Hz)	4.66 (1.32)	**5.42 (0.79)** [a]	**5.53 (0.85)** [a]
Range of Motion			
Shoulder Abduction-Adduction (°)	8.00 (4.17)	10.82 (5.38)	**6.53 (2.74)** [b]
Shoulder Flexion - Extension (°)	20.94 (12.28)	24.65 (12.27)	**12.62 (5.87)** [a,b]
Elbow Flexion - Extension (°)	62.75 (14.30)	50.89 (17.29)	62.83 (12.05)
Wrist Flexion-Extension (°)	18.68 (5.35)	17.99 (7.27)	19.14 (7.01)

HC: Healthy Controls, PD: Parkinson's Disease group, DLB: Dementia with Lewy Bodies, GP: Going Phase, AP: Adjusting Phase, RP: Returning Phase, AS: Adjusting Sway. [a] Significant differences vs. Healthy Controls (HC), [b] Significant differences vs. DLB after Bonferroni correction ($p<0.007$ for Spatio-temporal parameters, $p<0.0125$ for Range of Motion).

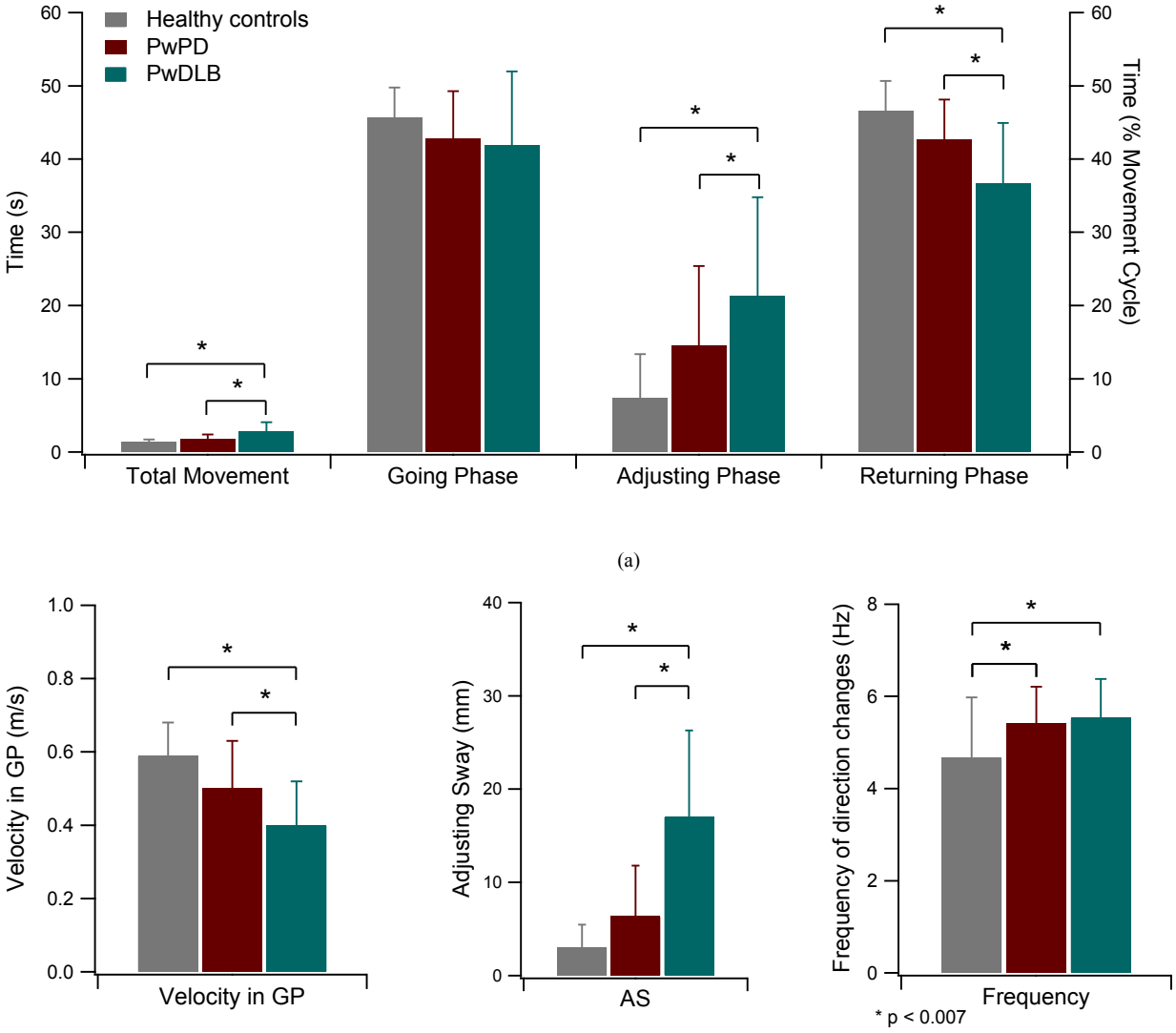


Figure 5.2 Main quantitative results about spatio-temporal parameters calculated during the hand-to-mouth task (mean ± standard deviation): (a) movement durations, (b) hand velocity during the Going Phase (GP), (c) adjusting sway (AS) during the Adjusting Phase (AP), (d) the frequency of direction changes. * denotes statistical significant differences between the groups after Bonferroni correction ($p < 0.007$).

5.4.2 Kinematic profiles of UL movements

The diagrams which show the joint angles during the HTM movement, which were normalized to task duration time, are reported in Figure 5.3.

Whereas the joint trajectory profiles of pwPD and HC are quite similar during the HTM cycle, pwDLB showed a different behaviour. In particular, joint angle trends of pwDLB did not appear smooth and continuous as pwPD and HC's ones. In fact, pwDLB tended to keep their arms stuck during the whole HTM performance, while in pwPD the excursions in movement appear similar to physiological pattern (see *Chapter 4, Paragraph 4.4.2*).

PwDLB started the movement with abducted arm similarly to HC, but they did not present adduction during the AP, while pwPD and HC exhibited a maximal adduction at ~50% of cycle (in the AP). PwDLB started the task with their shoulder flexed of approximately 30.0° and then approached their maximum shoulder flexion around 35.5° in the AP. Moreover, pwDLB exhibited a higher internal rotation at the beginning of the cycle (around 45°), with a decrease in value in the AP, showing a profile that is completely different from that of pwPD and HC.

As regards elbow and forearm angle trajectories, the three groups demonstrated a quite similar smooth profile with a maximal elbow flexion and maximal supination at approximately 50% of the cycle (instant belonging to AP).

Differences in wrist flexion-extension movement appear among all groups in the AP, and in particular pwDLB exhibited a jerky and lower flexion of the wrist.

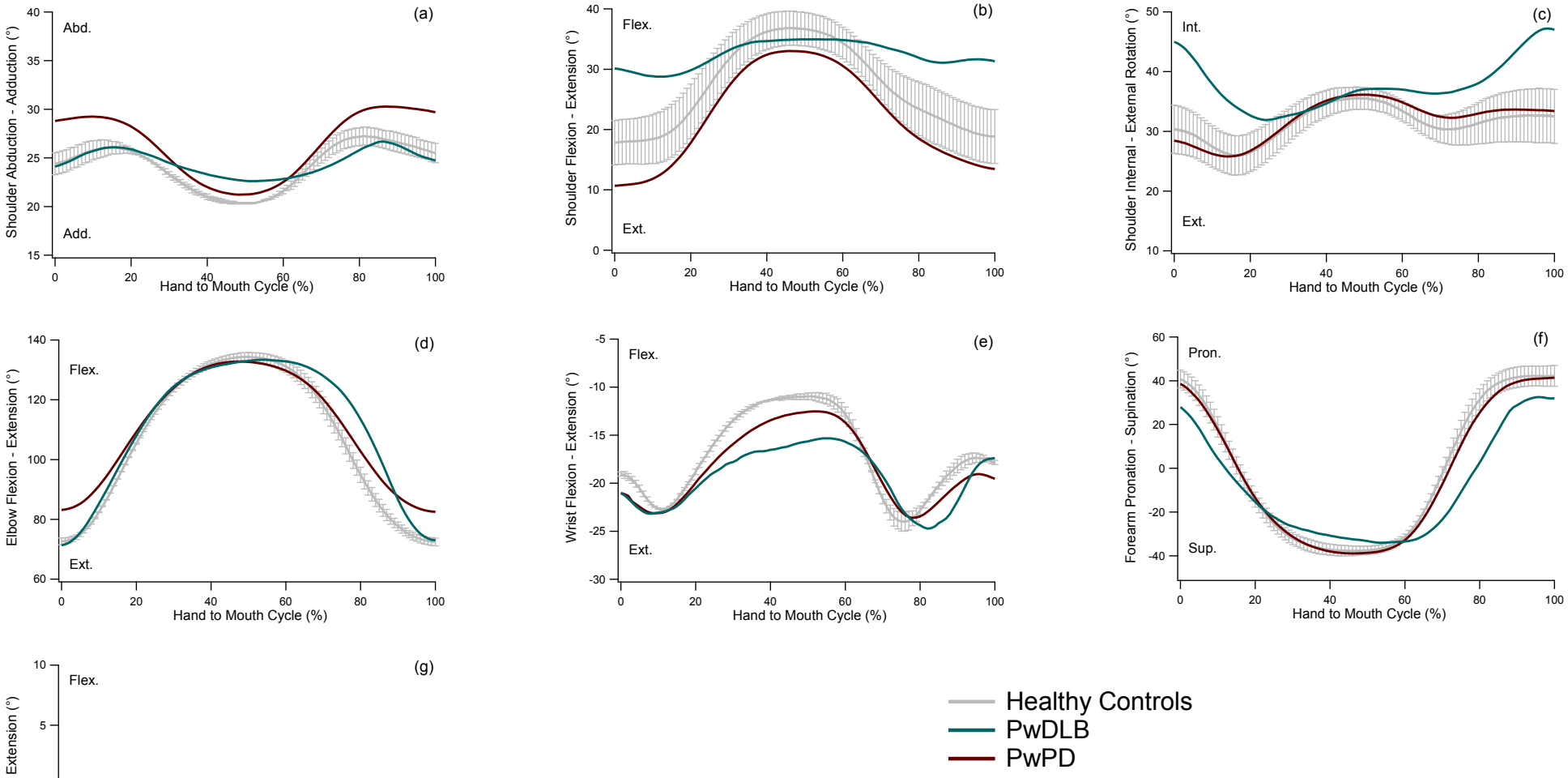


Figure 5.3 Upper limb kinematic graphs during Hand to Mouth Cycle: (a) shoulder abduction-adduction; (b) shoulder flexion-extension; (c) shoulder internal-external rotation (°); (d) elbow flexion-extension; (e) wrist flexion-extension (°); (f) forearm pronation-supination (°), (g) trunk flexion-extension (°). Grey band symbolizes the mean ± 1SD for the healthy controls; the claret lines represent pwPD joint motions while the dark blue-green lines represent pwDLB.

5.4.3 AVS and APS scores

MANOVA revealed a significant influence of the individual's status on the synthetic indexes [$F(16,120) = 2.61$, $p = 0.001$, Wilks $\lambda = 0.546$, $\eta^2 = 0.261$]. The subsequent follow-up analysis revealed significant differences between HC and pwDLB for APS_7 ($p = 0.002$) only for the Forearm Pronation-Supination AVS ($p = 0.002$). No significant differences were found between pwDLB and pwPD for the APS_7 and AVS scores.

In Table 5.3 are reported the results of the follow-up ANOVAs and the AVS and APS_7 scores for the HC, PD and DLB groups, and their values are showed in Figure 5.4.

Table 5.3 Comparison between APS and AVS values in individual with PD (pwPD) and healthy controls (HG) during the hand to mouth task. Values are expressed as mean (SD).

		HC	PD	DLB
	APS_7 (°)	9.09 (3.19)	**14.34 (3.02)** [a]	**12.85 (4.72)** [a]
	Trunk Flexion-Extension	3.07 (1.81)	5.70 (6.62)	5.71 (6.74)
	Shoulder Abduction-Adduction	5.39 (3.75)	8.45 (5.76)	5.96 (3.43)
	Shoulder Flexion-Extension	9.37 (6.60)	12.66 (6.43)	12.70 (6.78)
AVS (°)	**Shoulder Rotation**	7.56 (3.86)	9.10 (6.59)	10.16 (4.45)
	Elbow Flexion-Extension	9.33 (7.26)	13.07 (8.09)	13.03 (4.76)
	Forearm Pronation-Supination	11.55 (5.14)	**20.18 (8.88)** [a]	**20.18 (10.94)** [a]
	Wrist Flexion-Extension	8.51 (4.55)	13.93 (8.71)	9.28 (7.62)

HC: Healthy Controls, PD: Parkinson's Disease group, DLB: Dementia with Lewy Bodies, APS: Arm Profile Score, AVS: Arm Variable Score. [a] Significant differences vs. Healthy Controls (HC), [b] Significant differences vs. DLB after Bonferroni correction ($p<0.006$).

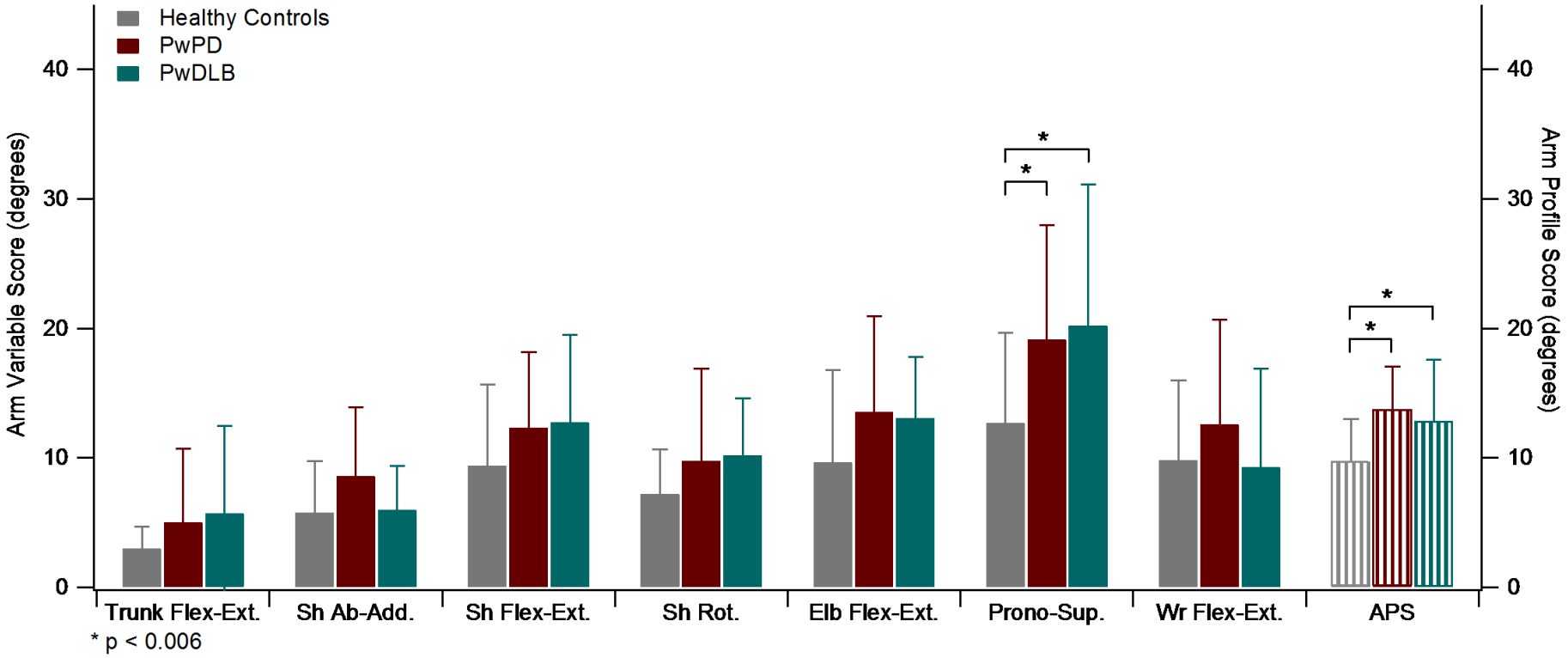


Figure 5.4 The Arm-Movement Analysis over the hand-to-mouth task: Arm Variable Score (AVS) values (Trunk Flex-Ext.: Trunk Flexion-Extension; Sh Ab-Add.: Shoulder Abduction-Adduction; Sh Flex-Ext.: Shoulder Flexion-Extension; Sh Rot.: shoulder Rotation; Elb Flex-Ext.: Elbow Flexion-Extension; Prono-Sup.: Pronation-Supination; Wr Flex-Ext.: Wrist Flexion-Extension) and Arm Profile Score (APS) are reported for the Healthy Controls, the PD and DLB groups.
* denotes significantly differences for Bonferroni correction ($p < 0.006$).

5.4.4 Correlation between clinical scores and kinematic variables

Tables 5.4 shows the Spearman's rank coefficient calculated for the correlations between the clinical scales scores (H&Y scale and UPDRS-III), the HGS, the MMSE score and the UL parameters (spatio-temporal and APS_7/AVS values) in pwDLB.

The correlation analysis detected significant moderate positive correlations only between the AVS score of the shoulder flexion-extension and UPDRS-III score (rho = 0.556 $p<0.05$), and H&Y score (rho = 0.479 $p<0.05$). As regards HGS, moderate negative correlations were found with APS_7 (rho = -0.481 $p<0.05$), and the AVS score of shoulder flexion-extension (rho = -0.532 $p<0.05$).

The MMSE score was found moderately correlated with total movement duration (rho = -0.524 $p<0.05$), the phase RP (rho = 0.515 $p<0.05$) and velocity during the GP (rho = 0.738 $p<0.05$). No significant correlations were found between MMSE score and synthetic indexes.

Table 5.4 Spearman's rank correlation coefficients between UPDRS-III, H&Y and HGS scores and the UL parameters in pwDLB.

	Parameters	UPDR-III	H&Y	HGS	MMSE
Spatio-temporal parameters					
	Total Movement duration (s)	0.380	0.255	-0.401	**-0.524**†
	GP duration (%)	-0.259	-0.341	0.338	-0.208
	AP duration (%)	0.210	0.218	-0.367	-0.160
	RP duration (%)	-0.136	-0.101	0.290	**0.515**†
	Velocity during GP (m/s)	-0.166	-0.127	0.098	**0.738**†
	AS (mm)	0.195	0.157	-0.253	-0.346
	Frequency of direction changes (Hz)	0.250	0.297	-0.248	0.089
Synthetic kinematic indexes					
	APS_7 (°)	0.248	0.179	**-0.481**†	-0.317
	Trunk Flexion-Extension (°)	0.195	0.179	-0.093	0.421
	Shoulder Abduction-Adduction (°)	0.110	0.140	-0.248	0.305
AVS (°)	**Shoulder Flexion-Extension (°)**	**0.556**†	**0.479**†	**-0.532**†	**-0.183**
	Shoulder Rotation (°)	0.278	0.073	-0.297	-0.062
	Elbow Flexion-Extension (°)	0.222	0.300	-0.301	-0.294
	Forearm Pronation-Supination (°)	0.156	0.115	-0.395	-0.124
	Wrist Flexion-Extension (°)	0.246	0.177	-0.339	-0.051

UPDRS-III: Unified Parkinson's Disease Rating Scale - Part III, H&Y: Hoehn & Yahr scale, HGS: Hand Grip Strength, APS: Arm Profile Score, AVS: Arm Variable Score. † $p<0.05$

5.5 Discussion

The analysis here presented was focused on UL kinematic assessment of pwDLB during the HTM task. The existence of relationships between kinematic parameters and clinical scores were also investigated.
Overall, the results of the UL kinematic analysis showed peculiar characteristics in motor disorder in DLB with respect to pwPD and HC, namely pwDLB experience more difficulties in effectively perform the HTM task, with slower and more hypermetric movements.

As regards spatio-temporal parameters, statistically significant differences were found between pwDLB, HC and pwPD. In particular, pwDLB spent more time compared to pwPD and HC to complete the task and precisely locate the mouth (AP). The velocity during the GP was found to be lower in pwDLB compared to HC and pwPD, consistently with previous findings (Fritz et al., 2016), while pwPD exhibited a hand speed comparable with HC (Bonfiglioli et al., 1998).

Moreover, pwDLB exhibited a significantly higher frequency of direction changes of the hand with respect to HC, a typical feature of Parkinsonism motor deficits (Heida et al., 2013). The absence of significant difference between pwPD and pwDLB denotes the presence of same level of tremor impairment in these groups.

Generally speaking, the movement of pwDLB appeared less accurate and stable with respect to pwPD and HC, as demonstrated by the significantly higher AS value. Coordination and adjustment are associated with basal ganglia (Leiguarda et al., 2000), and, thus, it could clarify this behaviour in DLB, which is a dementia characterized by basal ganglia damage (Walker et al., 2015). On the other hand, as it is known, basal ganglia are also involved in transformation of action plans to movement, thus deficits in basal ganglia could lead to praxic errors (Leiguarda et al., 2000; Zadikoff and Lang, 2005). And in fact, previous studies in AD have showed that the decline in UL movement coordination and automation is strongly related with a decline in cognitive functions (Scherder et al., 2008; Suzumura et al., 2016). Thus, the need to perform more adjustments and reduce the velocity to accomplish the task could be due to the cognitive impairments typical in pwDLB (Camarda et al., 2007).

As regards dynamic ROM, shoulder movements in pwDLB appeared reduced with respect to pwPD and HC. Looking the results about synthetic indexes, significant differences were found between pwDLB and HC. These results recall those of pwPD, who exhibited an APS_7

and AVS score of the forearm pronation-supination higher than unaffected people, thereby indicating significantly larger deviation from physiological UL motion. This suggests that these indexes are able to summarize the UL impairments associated with basal ganglia disorders, discriminating motor performance limitations of pwDLB and pwPD from those of HC.

These kinematic results could depend on the compromised fronto-parietal circuit for motor programming, which is reflected on movement of the proximal joint of the shoulder and distal movement of the forearm (Camarda et al., 2007).

No correlations were found between spatio-temporal and H&Y and UPDRS-III scores, while moderate correlations were found between MMSE and UL parameters. These findings suggest that the extrapyramidal deficits are not responsible of movement alteration, but are rather related to cognitive deficits (Ott et al., 1995; de Paula et al., 2016; Suzumura et al., 2016).

Summarizing, the differences found between pwPD and pwDLB suggest that the alteration in movement could be due to apraxia and it is not imputable to basal ganglia disorders. In fact, the results confirm that the absence of differences between PD and HC groups might be explained by the tendency of pwPD to compensate for a series of motor symptoms (i.e. rigidity, resting tremor, bradykinesia) in order to complete the movement (Tresilian et al., 1997; Bonfiglioli et al., 1998), while in pwDLB the motor planning ability seems to be disrupted (Zadikoff and Lang, 2005), as evidenced in other dementia subtypes (Camarda et al., 2007; de Paula et al., 2016; Suzumura et al., 2016). Moreover, the execution of a goal-oriented movement depends not only on the efficacy of movement planning but also on the efficient evaluation of the position of targets and consequently on the proper allocation of spatial attention (Zadikoff and Lang, 2005; Camarda et al., 2007).

5.6 Conclusion

The main goal of this analysis was to characterize the UL motor abilities in pwDLB during the HTM task. In particular, the feasibility of the application of synthetic measures to quantify the degree of UL motor deviations form physiological movement in pwDLB was assessed. Lastly, in order to clarify the usefulness of such approach for discriminating the UL impairments in people with different extrapyramidal disorders, we compared the UL movement features of pwDLB with those of pwPD during the HTM task.

In summary, pwDLB showed poorer performance compared to HC and pwPD, in terms of spatio-temporal parameters and joint kinematics. These features reflect both the basal ganglia and cognitive role in the HTM performance in pwDLB. In fact, basal ganglia dysfunction could lead to apraxia disorders (Zadikoff and Lang, 2005), while severity of cognitive deficits strongly influence the execution of UL movements (Ott et al., 1995; de Paula et al., 2016; Suzumura et al., 2016).

The results confirm that the use of quantitative kinematic measures may be useful in concurrently assessing altered UL movements and in understanding the impact of UL deficits on functional tasks in people with dementia. Moreover, 3D motion analysis can help physicians to distinguish the motor features of pwDLB from those of pwPD during ADL task.

However, some limitations of the study should be acknowledged: firstly the sample was quite reduced in size. Hence, additional test on a larger convenient sample of individuals would be performed. In addition, it could be interesting evaluate other dementia subtypes, such as FTD or AD, in order to clarify the role of the basal ganglia and the cognitive impairments in the movement performance. In fact, a comparative and extensive analysis of the UL motor profiles of these neurodegenerative disorders with 3D motion analysis system has not yet been performed. The results could aid physicians in early diagnosis of dementia subtypes (Scherder et al., 2008) and can be useful in distinguishing pwDLB from AD or FTD people (Fritz et al., 2016).

Conclusions and Future Work

The research activity described in this thesis has been focused on the application of 3D motion analysis techniques to assess upper limb (UL) kinematics in people with neurological diseases. The selected motor task (i.e. hand to mouth, HTM) while representative of important activities of daily living, is feasible to be performed by people with motor deficits but, at the same time, complex enough to reveal possible alterations in motor strategies associated with the presence of UL functional impairments.

Using a biomechanical model composed by eight segments (i.e. head, trunk, arms, forearms and hands), both 3D joint kinematics and spatio-temporal parameters were provided for the HTM task's analysis. Then, it was proposed a simplifying approach to summarize the whole kinematic pattern by means of synthetic measures: the Arm Profile Score (APS). The APS quantifies the kinematic deviation of the arm from physiological movement pattern during the HTM task and it is calculated on the basis of seven kinematic variables (Arm Variable Score, AVS) which take into account seven relevant movements, namely trunk flexion-extension, shoulder abduction-adduction, shoulder flexion-extension, shoulder internal-external rotation, elbow flexion- extension, forearm pronation-supination and wrist flexion-extension.

In order to understand how the HTM protocol and the synthetic measures' approach could be employed regardless etiology of the neurological disease, the 3D analysis was performed both in healthy and pathological individuals.

Significant differences in UL spatio-temporal parameters and joint kinematics between the pathological groups and healthy controls suggest that the HTM task's analysis is suitable to quantitatively evaluate the residual UL motor performance. Moreover, the results show that the use of quantitative synthetic measures effectively quantifies UL kinematics regardless the specific disease, as suggested by the significant correlations found between APS_7/AVS and the clinical scores (i.e. EDSS and NHPT score for MS, H&Y and UPDRS for basal ganglia disorders). Thus, the results of this dissertation suggest that the APS_7/AVS scores are able to effectively describe magnitude and features of the abnormalities exhibited by affected individuals due to the presence of the disease. In details, the quantitative assessment of HTM and the use of synthetic measures to detect the deviation from normal movement were able to discriminate in accurate and objective way motor performance limitation of people characterized by a broad spectrum of signs and symptoms (namely MS). The methods were successful employed also in people with basal ganglia disorder (PD and DLB), confirming the potential of the use of quantitative kinematic measures to detect and represent the UL alterations associated also with the basal ganglia disorder. Specifically, in MS distal and proximal arm alterations were found, while in basal ganglia disorders distal kinematics appeared significantly impaired.

This approach appears, thus, sensitive enough to the type of neurological disease and able to quantitatively assess subtle UL dysfunctions that are not possible to detect with standard clinical tests, including those associated with mild disability levels. The quantitative assessment seems crucial to support physicians in monitoring the individual's deficit progression and in planning suitable intervention for managing the UL movement disorders (i.e. spasticity, rigidity, muscle weakness, ataxia) even at early stages of the disease. For these reasons, the summary measures may represent a useful and objective quantitative measure of motor impairments potentially suitable for assessing and monitoring the rehabilitative treatments. Moreover, the analysis here proposed provides a framework for 3D motion analysis of UL motor functions in people with neurological disease during the HTM movement. The quantitative variables of UL kinematics, spatio-temporal parameters, and the APS_7/AVS scores provide valuable features regarding the quality of UL movements during a functional relevant task. A characterization of the movement disorders associated with the disease will improve the monitoring of the deficits progression as well as the assessment of the therapies effects.

Some limitations of the study should be acknowledged. First of all, it must be considered the intrinsic nature of the APS_7/AVS indexes that, being only based on kinematic variables (i.e. joint kinematics) neglect other set of variables such as spatio-temporal or kinetic variables. Furthermore, their values (expressed in degrees) do not provide any indication about the direction of the movement deviation (i.e. the same values of AVS of elbow may indicate either a hyper-flexed or extended elbow). For these reasons, APS_7 and AVS should be supported by the kinematic graphs as well as by the joints ROMs for a complete knowledge of the level of alteration in the UL motor pattern (Jasper et al., 2011; Butler et al., 2012; Pau et al., 2014).

As each of the studies reported for the three different conditions investigated are cross-sectional, further investigations are needed to confirm the capability of the approach for detecting UL impairments. Indeed, in order to have more meaningful results from a statistical point of view, additional tests on a larger convenient sample of individuals would be performed and longitudinal studies should be integrated in order to identify the disease-specific features and determine if synthetic indexes are sensitive enough for clinical applications, such as the monitoring of the disease progression also in terms of minimal detectable changes of UL motor features.

Moreover, in order to fully describe the motor strategies employed by people with UL impairments to perform goal-oriented daily tasks, it would be interesting to integrate kinematic analysis of movement with joint synergies assessment (Leiguarda et al., 2000; Michaelsen et al., 2001). In particular, interjoint coordination during the HTM task should be investigated to support kinematic analysis here presented and better clarify what mechanisms are involved to control arm joint interactions during a multi-joint movement.

In addition, surface electromyography (EMG) assessment (which gives physiological information of muscles while doing motions)may help to identify specific neuromuscular mechanism implicated in movement alterations, aimed to understand which muscles and which characteristics may be causing the change in motor strategy and how these are related to motor dysfunction. It appears noteworthy to integrate kinematic analysis with an assessment of the relationship between specific muscle activity patterns and motor dysfunctions. How muscle synergies determine the impairment and the residual abilities in people with neurological disease.

Lastly, in order to perform an extensive characterization of the body movement disability in presence of neurological disease, an integration of the lower and upper limbs analysis should be performed. Besides, quantitative assessment and the use of synthetic measures could be employed in other ADL tasks, such as drinking, grooming or reaching to a shelf or an object, allowing an extensive characterization of the UL motor abilities with neurological diseases in different tasks of daily living.

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