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PERCEPTUAL-MOTOR INTEGRATION
AND MOTOR CONTROL
IN DOWN SYNDROME

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Anno Accademico 2011-2013

Le mamme sono dei purosangue,
i migliori cavalli da corsa del mondo.
Se punti su una mamma vinci sempre.
(La Leggenda del Pianista sull'Oceano)

Solo gli stolti non cambiano mai opinione.
(J. R. Lowell)

*A mia madre,
per avermi insegnato a mantenere salde le mie convinzioni,
e a cambiare opinione.*

Acknowledgements

Living with a disability forces the disabled person to an everyday fight. Persons with disability struggle for daily conquers that I, as a person without disability, can reach without effort. Sometimes, when overwhelmed by worries that might not be so important, one should take a moment to think about everything he has been allowed to achieve, just for the lucky coincidence of being born healthy. Thus, my first acknowledgement goes to the persons with disability whom I met during these years, and to their parents. They have shown me how brave and strong human nature can be, even when challenged continuously.

A second acknowledgement goes to my family, to my friends and to Ripa, the centre of my brand new family. I love every moment of our life together.

Working would not have been fun without the presence of my very nice colleagues and friends: Chiara, Firooz, Nicola and Veronica. A particular thanks to Chiara, who followed the development of my thesis and gave me precious advices about scientific research and life in general: we shared a lot more than an office. Thanks also to prof. Marcello Crivellini for being nice to me and for helping in the job research, which I appreciated much.

Last but not least, I would like to thank prof. Manuela Galli for giving me the opportunity to do this PhD and for following my research with enthusiasm and interest, and professors Paul Patti and Reinald Brunner for accepting to review this study and for providing their experienced opinion. I would also like to acknowledge prof. Giorgio Albertini and the staff of the IRCCS San Raffaele Pisana of Rome for their collaboration to this study.

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Abstract

Background and aims: The population prevalence of DS in developed countries is in order of 6-8 per 10000, accounting for 10-18% of people with intellectual disability.

Among other diseases (i.e. cardiological, polmonary, hearing, vision diseases etc) this syndrome leads to a different neurological development, which results in structural alterations and atypical patterns of brain activation. As a consequence, since the very early stages of their lives persons with DS experience difficulties in their motor and cognitive development, resulting in intellectual disability and in slowed and/or incomplete mastery of physical coordination. The widespread deficits caused by DS, together with the lack of clear-cut guidelines for rehabilitation, represent very limiting factors for these subjects, who experience reduced independency, reduced social participation, lower life quality.

While specific sensory, motor, cognitive and perceptual impairments have been widely reported in DS, the way these localized deficits impact on perceptual-motor processing and function remains unclear. Recent literature is focusing on the use of motion analysis tools for the assessment of hypothesis regarding how motor control acts and how motor plans are formed in DS. In this context, the studies since now indicate that the motor impairment documented in DS might be especially related to perception and extraction of sensory information, motor programming, and/or decision-making processes. The aim of the study was: (1) to define and apply an experimental set up for the quantitative evaluation of the different aspects of motor control and execution (perception and extraction of sensory information, motor programming, decision-making processes) during functional tasks in adult subjects with DS; (2) to define and apply an experimental set up for the quantitative evaluation of primitive motor control mechanisms (developed during infanthood) in adult subjects with DS; (3) to link the results about motor performance to the most recent literature about cognition and neurology in DS; (4) to provide some guidelines for a focused rehabilitation of persons with DS.

Materials and methods: a total of 37 adults with DS and 43 age-matched control group subjects took part to the study. The study was composed of two parts: the first part investigated the perceptual-motor integration in DS during the execution of two functional tasks (walking with an obstacle and arm tapping with an obstacle) by means of an optoelectronic system. The second part of the study investigated primitive reactions during resistance to an external perturbation of the

upper limb by means of EMG analysis (stretch reflex and pre-programmed reactions). Quantitative parameters were defined to describe which among perception and extraction of sensory information, motor programming and/or decision-making processes could represent the most significant impairment in DS, and to characterize primitive reactions in terms of time delay from the stimulus and in terms of muscular synergies.

Results: the main findings of the first set of experiments were that (1) whereas the persons with DS seemed to correctly extract the sensory information this information was not used in a pre-programmed fashion to plan the movement in advance and (2) the movement of persons with DS was highly dependent on feedback mechanisms, while control subjects depended more on feedforward mechanisms. However (3) the subjects with DS were able to successfully complete the tasks, although at the price of less movement efficiency.

The evaluation of primitive mechanisms of motor control revealed that (4) no basic abnormality was present in the early motor control mechanisms of subjects with DS; (5) these results provide evidence to the hypothesis that neuromotor patterns in DS are comparable to those of normally developing infants at the very beginning of their sensorial exploration of the external world, however (6) some changes occur, probably very soon after birth, which cause a different neuromotor development in DS, reflected by the differences highlighted in points (1), (2), (3) of the results.

Conclusions: The finding that subjects with DS have comparable primitive mechanisms for motor control, but employ different motor strategies in tasks that require higher control mechanisms suggests that at birth there could be ample room for intervention, highlighting the importance of early intervention programs in DS.

There is increasing body of evidence that early intervention can have a direct impact on brain development in several pathologies. Such brain plasticity is one of the best hopes for bringing about significant improvements in the prospects of individuals with DS. Given the high neural plasticity of the brain at birth and given the activity-dependent nature of neural modeling two most important suggestions can be given to therapists and neurologists in the field of DS:

- Early intervention is fundamental for the reorganization of the neural pathways, and should be given as soon as the child is born. Several possible treatments are present, although there is scarce evidence of which may be the best combination of treatments to harness the best results.

- Challenging the infant with an “enriched environment” may help balancing his lack of sensorial, cognitive and motor experiences, leading to earlier development of the motor milestones.

These considerations could be very useful for the definition of more focused rehabilitative approaches for persons with DS.

SUMMARY

This PhD Thesis is organized in six chapters, and it is summarized following.

1. INTRODUCTION

1.1 An overview on Down Syndrome

Down Syndrome (DS) implies a number of medical and health related complications, among which there are cognitive deficits and neuropathology. Various pathophysiological changes in the brain have been associated with the specific profile of intellectual disability that is observed in DS. These include changes in size of specific brain regions and their connectivity and alterations in the number and/or the morphology of subpopulations of neurons. While at birth it is often difficult to differentiate the brains of normally developing infants and of infants with DS rather clear differences between these two groups are present as early as 6 months of age. Investigations of neural function in early infancy suggest some abnormalities as well, such as in the auditory and visual systems.

The development of motor milestones in childhood is achieved with consistent delay in these children, and cognitive developmental deficits lead to both intellectual disability and to slowed and/or incomplete mastery of physical coordination. There are three factors which traditionally are believed to have an impact on the gross motor development of a child with DS: hypotonia, ligament laxity and decreased strength. Although these are well known and documented features of DS, some authors have recently questioned their major role in causing the delay or deficiency in motor skills acquisition in DS. However, rehabilitation in DS is still based on generic strengthening therapies for the correction of these aspects. The lack of incisive therapies and focused rehabilitative guidelines for persons with DS puts forward the need for a deeper understanding of how the nervous system of these persons counteracts its own limitations and of how to help maximize the residual motor capacities of these persons (for a review see chapter 1).

1.2 Trends in movement analysis

Several studies have shown that the movements of individuals with DS are slower, less smooth and more variable from trial to trial when compared with the movements of the overall population. All of these features have been referred to with the term “clumsiness”, widely used to described the

uncertain and shuffling movements of subjects with DS. Movement analysis has been “traditionally” used for these descriptive studies (an extensive review of the literature is provided in chapter 2). However, while specific sensory, motor, cognitive and perceptual impairments have been widely reported in DS, the way these localized deficits impact on perceptual-motor processing and function remains unclear. The researchers have recently started to use movement analysis for the assessment of hypothesis about how the motor control acts (see chapter 2). This new application of movement analysis aims at providing a deeper insight on the mechanisms underlying motor control and could help developing more focused rehabilitation treatments for persons with DS.

1.3 Background and aims

This research is located in the new field of movement analysis for the study of motor control and cognitive functions. In this study, in fact, quantitative motion analysis is used to gain deeper insight on the major movement deficits caused by DS and to provide some useful guidelines for a more focused rehabilitative treatment of subjects with DS.

The following points define the basis of the present research:

- Although there is some evidence of a normal development of the nervous system at birth, differences in the motor control of persons with DS respect to controls have been documented since their childhood, with a delayed acquisition of motor milestones in DS;
- Studies since now indicate that the motor impairment documented in DS might be especially related to perception and extraction of sensory information, motor programming, or decision-making processes;
- Despite the awareness about motor deficits in DS, however, there is a lack of studies on how to help persons with DS reach their full potentials in motor activities, and a lack of guidelines for clinical practitioners.

Starting from these points this PhD thesis was developed with the aim of defining and applying some experimental set up for the quantitative evaluation of the different aspects of motor control and execution in adult subjects with DS, and in particular:

- The first part of the experimental study (chapter 3) was dedicated to the analysis of perception and extraction of sensory information, motor programming and decision-making processes during complex functional tasks in adult subjects with DS. “Functional” movements are movements based on real-world situational biomechanics, that usually involve multi-planar, multi-joint movements which place demand on the body's core musculature and require greater cognitive effort to be carried out. Functional tasks where

chosen because they are more challenging than the simplified tasks usually used in laboratory settings, as they exert the interplay of high-level feedforward and feedback mechanisms;

- The second part of the experimental study (chapter 5) was dedicated to the analysis of simpler, more primitive mechanisms for motor control in adult subjects with DS, namely the monosynaptic reflex and the pre-programmed reactions (PPRs) (reviewed in chapter 4). In this case the paradigm was a simple reaction task movement, defined to elicit automatic responses and control mechanisms that intervene before voluntary movement occurs. These mechanisms provide resistance to an external perturbation, and are known to be present since the very early stages of life. They are very important for the acquisition of early motor skills, since maturation of human behavior passes from the primitive reflexes to the gradual appearance of automatic, postural and adaptive reactions which make higher activities possible. From these mechanisms all the more sophisticated feedback and feedforward mechanisms develop as a consequence of experience. It is important to clear out at which point of the neuromotor development differences between infants with and without DS begin to affect motor control. Understanding if differences in motor control are present since birth is very important for the definition of early and late intervention in rehabilitation.

These different experimental set ups were defined in order to have a general view of the motor difficulties in DS, from more primitive, automatic reactions to higher level mechanisms of motor control during voluntary movement. **The novelty and scientific importance of this study is to provide insight on the different aspects and mechanisms that regulate motor control in DS by means of quantitative motion analysis and to link these results to the most recent literature about cognition and neurology, in order to provide some guidelines for a focused rehabilitation of persons with DS.**

2. MATERIALS AND METHODS

37 subjects with Down Syndrome (DS) ageing from teen age to young adulthood and 43 control subjects were enrolled for the study. Subjects were recruited after neurological evaluation.

The materials and method section is divided for the three movements evaluated, the first two belonging to the evaluation of functional movements and the third belonging to the evaluation of primitive mechanisms for motor control.

2.1 Analysis of obstacle avoidance during walking (chapter 3)

The subjects walked along a walkway in three conditions: plain walking without obstacle, walking with obstacle at ground level, walking with obstacle at a higher level. Two different obstacle heights were used to allow studying the effect of the obstacle's presence on locomotion (extraction of the characteristics of the obstacle and visuo-motor integration). The tasks were acquired using quantitative movement analysis, composed of an optoelectronic system with eight infrared cameras. Markers were placed on the body according to a modified Davis' protocol which comprehended markers placement on the upper limbs, and two markers were put respectively at the two ends of the obstacle to define the obstacle position relative to the subject during the movement. Spatiotemporal and kinematic parameters were defined to A) describe relative distances between the feet and movement velocities and B) describe relative distances between the feet and the obstacle and C) to describe the kinematics of the upper and lower joints' movements. These parameters were used to analyze aspects of motor control such as: coordination of the limbs, stability, gait variability due to different walking conditions (without obstacle, with ground level obstacle, with high obstacle), extraction of visual information (related to the obstacle's characteristics) and of proprioceptive information (related to the body segments positions respect to the obstacle) and sensori-motor integration, clearing strategies and trajectories, planning of the movement (with particular attention to feedback and feedforward mechanisms).

2.2 Analysis of an arm tapping task with and without obstacle avoidance (chapter 3)

Participants sat comfortably on a chair, holding a cylindrical wooden dowel with the right hand. In front of them was a table with six target positions evenly spaced around a semicircle. In the first condition (plain tapping) subjects tapped consecutively between targets 1 and 2, 2 and 3, 3 and 4, 4 and 5, 5 and 6, a total of five tapping movements. In the second condition (tapping with obstacle), an obstacle (10 cm of height) was placed between targets 3 and 4; the subjects were asked to tap on the targets as described in the first condition, and to avoid the obstacle by crossing over it with the dowel. This task was selected because it required the execution of a sequence of movements, and thus allowed studying how and if pre-programming strategies were adopted in DS. In addition, the sequence was easy enough to be understood also by subjects with intellectual disability, and the protocol was administrable in clinical settings with minimum requests of space and short administration time.

The tasks were acquired using quantitative movement analysis, composed of an optoelectronic system with eight infrared cameras. Markers were placed on specific body landmarks using a marker set derived from previous studies (Rab's protocol). In addition, three markers were placed at

the top of the dowel to identify the dowel's position during the acquisition, and three markers were placed on the table to identify a reference system on the table. A marker was placed on the obstacle. Spatiotemporal and kinematic parameters were defined to A) describe the kinematics of the upper limb and trunk B) describe the trajectory of the hand and C) to describe the quality of the movement. These parameters were used to analyze aspects of motor control such as: coordination of the upper limb segments, trajectory variability due to different tapping conditions (with or without obstacle), extraction of visual information (related to the obstacle's characteristics) and of proprioceptive information (related to the body segments positions respect to the obstacle) and sensori-motor integration, clearing strategy, planning of the movement (with particular attention to feedback and feedforward mechanisms).

2.3 Analysis of monosynaptic reflexes and pre-programmed reactions (chapter 5)

The experimental protocol was designed with portable instrumentation, to allow easy transfer to every laboratory or clinical structure. The subject seated on a chair with his dominant arm flexed at approximately 90° and holding the handle of a bucket in his dominant hand. This preload was used to activate the motor units and elicit reflex activity. Two EMG sensors recorded the biceps brachii caput longum and triceps brachii lateral head activity of the dominant arm. At the bottom of the bucket a pressure switch was fixed; a small hole at the bottom allowed the wire to pass outside the bucket and to connect the sensor to the recording unit attached outside. Subjects were told that the examiner was going to throw a weight inside the bucket and that they had to resist the perturbation and come back to the start position as soon as possible. Vision was excluded to avoid preliminary adaptations as the weight approached the bucket.

Without giving notice to the subject, the experimenter let a 2kg weight fall inside the bucket. The initial position of weight-throwing was similar across trials, and it was close to the bucket border.

The task was repeated 20 times, with pauses every each 5 trials to allow arm rest.

The tasks were acquired using a portable wireless electromyograph integrated with a pressure switch. Each trial was band-pass filtered between 20 and 499Hz with a 150th order zero-phase forward and reverse digital FIR filter. A Kaiser window was used to design the filter. The Root Mean Square (RMS) of the filtered signal was calculated using a 10ms time constant to enhance the EMG peaks with no biasing of the temporal changes in the signal. EMG signals were aligned at the perturbation onset t_0 , defined as the instant in which the switch signal became "on", and averaged for each participant, then a moving average filter with a window of 8ms was used to smooth the data. The peaks of latency for the monosynaptic reflex (M1) and for the PPRs (M2, M3) were defined by visual selection on the smoothed data. After peaks detection the M1, M2 and M3

latencies from t_0 (ms) were computed. The cross-correlation functions (CCs) between the pairs of averaged EMG signals were calculated for each subject after filtering the EMGs with a 40Hz second-order Butterworth filter to analyze the presence of synergies between the biceps and triceps muscles.

3. RESULTS

The results from the first two experiments confirmed the picture of clumsiness and motor difficulties that is commonly described in DS. Moreover, the main findings of these experiments about motor control and sensori-motor integration during functional tasks revealed that whereas the persons with DS seemed to correctly extract the sensory information (i.e. the physical characteristics of the obstacles) this information was not used in a pre-programmed fashion to plan the movement in advance, and thus the movement of persons with DS was highly dependent on feedback mechanisms, whereas control subjects relied more on feedforward control mechanisms. The lack of anticipation in the planning of movement led to substantial modification of the movement parameters as the subjects approached the obstacle (with the lower limb in one case and with the upper limb in the second). The parameters evidenced the presence of different movement strategies and the major effect of a disturbing factor, such as an obstacle, on the motor performance and quality of movements in DS respect to controls. The subjects with DS were able to successfully complete the tasks, although at the price of less movement efficiency. Thus, as for a system that realizes its own limitations, the central nervous system of persons with DS seemed to choose different motor strategies and to trade movement efficiency for task accomplishment and safety. The results demonstrated the presence of differences in high-level motor control of subjects with DS.

After shedding light on motor control in complex, functional situations, the third experiment addressed the function of primitive mechanisms for motor control, namely the monosynaptic reflexes and pre-programmed reactions. This experiment was needed to clear out if the differences in motor control that are observed in adults are present since birth or are a consequence of neural development.

The results about latency of the reactions showed no differences between groups in terms of delay from the onset of the perturbation, suggesting that, in terms of latency, there was no evident difference between DS and controls in the monosynaptic reflex and PPRs. Since these mechanisms develop in the early phases of life, these results provide evidence to the hypothesis that neuromotor patterns in DS are comparable to those of normally developing infants at the very beginning of their

sensorial exploration of the external world. However, some changes occur very soon after birth, which cause a delayed or a different neuromotor development in DS.

A mix of alternating patterns and co-contraction strategies was found in the muscular activation patterns of antagonist muscles of both controls and subjects with DS, with a high percentage of co-contraction in both groups. Although the reciprocal pattern is more efficient, the desire to stabilize the trajectory of a joint during an unexpected, unpredictable external perturbation led to co-contraction of antagonist muscles in 75% of subjects with DS and in 66.5% of controls. The fact that co-contraction during the present task was present in most of subjects with DS, but not in all subjects, highlighted the fact that a part of the subjects was able to use synergistic patterns of activation. The fact that most of control subjects used co-contraction as well, suggests that this strategy provided better chances for task achievement in presence of unpredictability. Thus, the patterns of co-contraction, so frequently described in subjects with DS, may be seen as an adaptive mechanism in response to the inability of these subjects to make quick, accurate corrections, revealing a decision making problem more than a lack in the acquisition of other activation patterns.

4. CONCLUSIONS

The finding that subjects with DS have comparable primitive mechanisms for motor control, but employ different motor strategies in tasks that require higher control mechanisms seems to suggest that at birth there could be ample room for intervention.

The most important studies regarding neural organization in normally developing children and in children with lesions of the central nervous system underline the role of sensory-motor experience and of plasticity of the neural pathways in the shaping of the nervous system in the early phases of life. Studies about adults with DS support the hypothesis that a different shaping of the neural circuits occurs since the early phases of life in children with DS, due to factors such as delayed myelination, aberrant sensory information and sensory integrative dysfunction, higher sensory thresholds and a decreased ability to localize stimuli, that may cause this differentiation in the early stages of life.

Given the high neural plasticity of the brain at birth and given the activity-dependent nature of neural modeling two most important suggestion can be given to therapists and neurologists in the field of DS:

- Early intervention is fundamental for the reorganization of the neural pathways, and should be given as soon as the child is born. Several possible treatments are present, although there is scarce evidence of which may be the best combination of treatments to harness the best results.

- Challenging the infant with an “enriched environment” may help balancing his lack of sensorial, cognitive and motor experiences, leading to earlier development of the motor milestones.

5. FURTHER DEVELOPMENTS

The future developments of this study should be addressed at correlating the kinematics and motor performance of individuals with DS with the underlying brain dynamics to better characterize the nature of the “clumsy” motor behavior observed in this population. This may be of fundamental importance in the definition of focused therapies. Also, different early intervention programs should be tested in infants and children with DS to evaluate the impact of early intervention in the development of motor milestones and consequently in the development of functional afferent and efferent pathways that are fundamental for the learning of motor skills.

Chapter 1

Down Syndrome: from genomics to pathophysiology

For centuries, people with Down syndrome (DS) have been alluded to in art, literature and science. It was until the late 19th century, however, that John Langdon Down, an English physician, published an accurate description of a person with DS. It was this scholarly work, published in 1866, which earned Down the recognition as the “father” of the syndrome. Although others had previously recognized the characteristics of the syndrome, it was Down who described the condition as a distinct and separate entity.

Throughout the 20th century, advances in medicine and science enabled researchers to investigate the characteristics of people with DS. In 1959, the French physician Lejeune identified DS as a chromosomal anomaly when he observed 47 chromosomes present in each cell of individual with DS, instead of the usual 46. It was later determined that an extra partial or complete 21st chromosome results in the characteristics associated with DS.

In May of 2000 an international team of scientists successfully identified and catalogued each of the approximately 329 genes on chromosome 21. This accomplishment opened the door to great advances in DS research.

1.1 Genetics and recurrence risk

All cells in the human body contain a center, called a nucleus, in which genes are stored. Genes, which carry the codes responsible for all our inherited characteristics, are grouped along rod-like structures called chromosomes.

Normally, the nucleus of each cell contains 23 pairs of chromosomes, half of which are inherited from each parent. DS occurs when some or all of a person’s cells have an extra full or partial copy of chromosome 21 (figure 1.1.1). The most common form of DS is known as Trisomy 21. Two other less common forms occur: namely Translocation and Mosaicism.

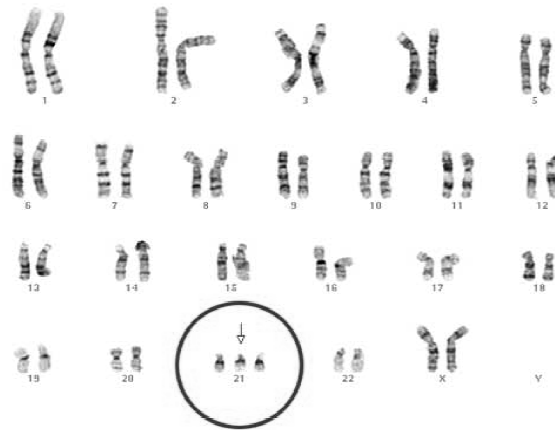


Figure 1.1.1: Karyotype showing three 21 chromosomes

Trisomy 21

Individuals with Trisomy 21 have 47 chromosomes instead of the usual 46 in each of their cells. The condition results from an error in cell division called non-disjunction (failure of separation of chromosome homologues). As the embryo develops, the extra chromosome is replicated in every cell of the body. This error in cell division is responsible for 95 percent of all cases of DS.

Translocation

Translocation, which accounts for 3 to 4 percent of cases of DS, occurs when part of chromosome 21 breaks off during cell division and attaches to another chromosome, usually chromosome 14. While the total number of chromosomes in the cells remains 46, the presence of an extra part of chromosome 21 causes the characteristics of DS.

Mosaicism

The least common form of DS, mosaicism, accounts for only 1 to 2 percent of all cases. Mosaicism occurs when non-disjunction of chromosome 21 takes place in one of the initial cell divisions after fertilization causing a person to have 46 chromosomes in some of their cells and 47 in others.

1.2 Incidence and maternal age

The population prevalence of DS in developed countries is in order of 6-8 per 10000 (Besser et al, 2007; Mantry et al, 2008), accounting for 10-18% of people with intellectual disability (Glasson et al, 2002; Mantry et al, 2008).

The cause of the extra full or partial chromosome is still unknown. What we do know is that it is not caused by environmental factors or anything the mother does before or during her pregnancy.

DS occurs in one out of every 650-1000 live births (Bittles et al, 2007). Reported live birth rates vary greatly between countries, from 0.23 per 1000 in Taiwan (Jou et al, 2005) to 2.98 in Ireland (O' Nuallain et al, 2007), reflecting differences in maternal age, access to antenatal diagnosis and social attitudes toward termination of pregnancy. The overall prevalence of people with DS is expected to increase for some time due to dramatic increases in median and average life expectancy, even where there is a drop in live birth rates (Torr et al, 2010).

Maternal age is the only factor that has been linked to an increased chance of having a baby with DS or other trisomies (figure 1.2.1) (Loane et al, 2012).

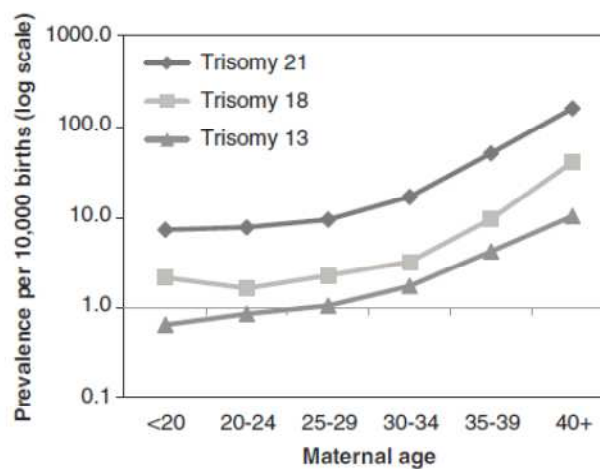


Figure 1.2.1 Total corrected prevalence per 10000 births (log scale) of trisomies 21 (DS), 18 and 13 by maternal age, 1990–2009, in 12 European countries

The rise in average maternal age in Europe over time has brought with it an increase in the number of pregnancies affected by trisomies 21, 18 and 13. However, the increasingly widespread practice of prenatal screening and termination of pregnancy has, on average, counteracted the effect of maternal age and resulted in a relatively stable live birth prevalence of the major trisomies since 1990 in the European population studied (Loane et al, 2012).

Once a woman has given birth to a baby with DS, the chance of having a second child with DS is about 1 in 100, although age may also be a factor. Maternal age, however, is not linked to the chance of having a baby with translocation. Most cases are sporadic, chance events, but in about one third of translocation cases, one parent is a carrier of a translocated chromosome. For this reason, the chance of translocation in a second pregnancy is higher than that seen in non-disjunction.

One of the most frequently occurring chromosomal abnormalities, DS affects people of all ages, races and economic levels. Today, individuals with DS are becoming active participants in the

educational, vocational, social and recreational aspects of our communities. In fact, there are more opportunities than ever before for individuals with DS to develop their abilities, discover their talents and realize their dreams.

1.3 Overview of the major clinical features

There are two types of phenotypes that are observed in trisomy 21: those seen in every patient and those that occur only in a fraction of affected individuals. For example, cognitive impairment is present in all patients with DS, whereas congenital heart defect occurs in 40% and atrioventricular canal defect in 16% of patients, duodenal stenosis/atresia occurs 250 times more frequently in patients with DS than in the general population. In addition, for any given phenotype there is considerably variability in expression. Following, a brief description of main diseases that often occur in DS subjects.

1.3.1 Heart diseases

The most common defects are Atrioventricular Septal Defect (formally called Endocardial Cushion Defect), Ventricular Septal Defect, Persistent Ductus Arteriosus and Tetralogy of Fallot. Some children with DS and major heart defects will present with heart failure, difficulty breathing and failure to thrive in the newborn period; however, because in some children the defect may not be at first apparent, it is important that all children born with DS, even those who have no symptoms of heart disease, should have an echocardiogram in the first two or three months of life. Congenital heart disease remains, nowadays, a leading cause of death among persons with DS (Tag et al, 2002; Torr et al, 2010). However, due to access to and advances in pediatric cardiac surgery the congenital heart diseases have lost some impact among the death causes in DS (Torr et al, 2010).

Atrioventricular Septal Defect: an Atrioventricular Septal Defect is caused by a failure of tissue to come together in the heart during embryonic life. This results in a large opening in the center of the heart, with usually a hole between the two pumping chambers (a Ventricular Septal Defect) and between the two collecting chambers (an Atrial Septal Defect) as well as abnormalities of the two atrioventricular valves, the mitral and tricuspid valves. This defect occurs in nearly 60% of the children with DS who are born with congenital heart disease. In less severe cases, Ventricular Septal Defects and Atrial Septal Defects can also occur separately. These defects result in increased blood flow going to the lungs as the blood goes through the septal defects from the high pressure

left heart into the low pressure right heart. This flooding of the lungs results in a buildup of pressure in the pulmonary circulation and this higher pressure and high flow leads to damage to the pulmonary circulation and pulmonary hypertension. In the first few months of life, signs of heart failure may be prominent with rapid breathing and failure to grow and gain weight. Later, progressive damage to the blood vessels and the lungs may result in reversal of the shunt and blueness of the skin (cyanosis).

Persistent Ductus Arteriosus: the ductus arteriosus is a channel between the pulmonary artery and the aorta and during fetal life diverts blood away from the lungs. After birth this channel usually closes on the first day of life. If it does not close, it is termed "persistent" and results in an increased flow of blood into the lungs.

Tetralogy of Fallot: this is a term given to a heart condition in which there is both a Ventricular Septal Defect and a narrowing of the passage from the right ventricle to the lungs causing Pulmonary Stenosis. The Pulmonary Stenosis causes the blue blood in the right ventricle to cross the Ventricular Septal Defect into the aorta and produces what is commonly called a "blue baby." Heart surgery to correct the defects is recommended and it must be done before age five or six months in order to prevent lung damage. Although the complexity of the defects raises the risk of surgery slightly above that of surgery on children without DS, successful surgery will allow many of the affected children to thrive as well as any child with DS who is born with a normal heart. There may be residual defects (such as imperfect valves, in cases of Atrioventricular Septal Defect), but their effect on health is often minimal.

1.3.2 Pulmonary diseases

The other major cause of death in the first year of life is respiratory infections. Respiratory disease in DS is 62 times greater than in non-DS population. Infections in general were 12 times greater in DS. Symptoms of snoring, mouth breathing, nasal drainage, and sleep apnea alert the clinician to upper respiratory problems. Upper airway obstruction may be one factor predisposing the child with DS to respiratory disease.

Gastroesophageal reflux is a problem in DS, which is an additional complication to the often already compromised upper respiratory system. In children with DS, the esophageal plexus ganglia have fewer neurons, which helps explain this dysfunction.

Pneumonia and tracheitis often can be bacterial infection in infants with DS. In fact, these infection can be life threatening especially during the ages of 2-12 months if they are not promptly and

vigorously treated. It is undisputed that the treatment of respiratory infections, once they start, needs to be aggressive in infants with DS. If appropriate, prevention techniques directed to the individualized problem, such as canal dilatation, can give good results.

1.3.3 Other diseases

Intestinal defects. About 12 percent of babies with DS are born with intestinal malformations that require surgery.

Vision problems. More than 60 percent of children with DS have vision problems, including crossed eyes (esotropia), near- or far-sightedness and cataracts. Glasses, surgery or other treatments usually can improve vision.

Hearing loss. About 75 percent of children with DS have some hearing loss. Hearing loss may be due to fluid in the middle ear (which may be temporary), a nerve or both. Babies with DS should be screened for hearing loss at birth or by 3 months of age. They also should have regular hearing exams so any problems can be treated before they hinder development of language and other skills.

Infections. Children with DS tend to have many colds and ear infections, as well as bronchitis and pneumonia.

Improvements in accommodations and deinstitutionalization, antibiotic treatments and vaccinations have contributed to the reduction of death from pneumonia and other infections. In 1950s death from respiratory infections was six times greater than for the general population (Ugazio et al, 1990), while recent studies have showed that the standardized mortality ratio for respiratory infection in DS has dropped consistently (Yang et al, 2002). However, respiratory infection is still one of the leading causes of death in adults with DS (Torr et al, 2010).

Thyroid problems and leukemia. Thyroid problem can be present at birth (congenital) or may occur at any age (acquired). The symptoms of low thyroid hormone are difficult to pick up, especially in infants. They include decreased growth, decreased development, an enlarged tongue and decreased muscle tone, all of which might be expected in an infant with DS.

Most children with DS nowadays live into adolescence and adulthood. Leukaemia is from 10 to 30 times more common in these children than in the general population. All of the different types of DS show a similar increased risk of leukaemia. This still only represents about 1 in 150 of children with DS. About 2% of all cases of childhood leukaemia occur in children who have DS.

Some individuals with DS may have a number of these problems, while others may have none. The severity of these conditions varies greatly. The outlook for individuals with DS is far brighter than it once was. Most of the health problems associated with DS can be treated, and life expectancy is now about 55 years.

1.4 Neurodevelopment

Neurology, the study of the human nervous system and its disorders, is important in the clinical care of persons with DS. Various pathophysiological changes in the brain have been associated with the specific profile of intellectual disability that is observed in DS. These include changes in size of specific brain regions and their connectivity and alterations in the number and/or the morphology of subpopulations of neurons (for a review, see Dierssen, 2012).

At birth it is often difficult to differentiate the brains of normal and of individuals with DS. Yet, both postmortem studies and various, more recent, non invasive neuroimaging studies have demonstrated rather clear differences between these two groups as early as 6 months of age. An immediately obvious difference is that the brains of individuals with DS are typically smaller than those of age-matched controls, at least after 6 months of age. Anyway, one possibility is that the difference in brain size could be a matter of allometry, since persons with DS have smaller bodies; also, there is no clear relation between brain size and “intelligence”, suggesting that the intellectual disability observed in DS results from something other than gross differences in brain size. Although the brains of DS individuals are indeed smaller overall, some brain areas are disproportionately affected. This differential impact is not predicted by allometry, and presumably offers important clues about how trisomy 21 brings about the intellectual disability so characteristic of DS. Before evaluating these clues another caveat is important: the probability that brain development is influenced by experience. There is increasing body of evidence, in fact, that early intervention can have a direct impact on brain development. Such brain plasticity is one of the best hopes for bringing about significant improvements in the prospects of individuals with DS. At this time it is not known, from a theoretical or empirical prospective, the extent to which experience can cause changes in normal brain development (Nadel, 2003). With these caveats registered, what can we say about nervous system development and function in DS? following DS neural development from birth, to childhood, to adulthood is briefly described.

1.4.1 Early development

A number of early studies point out to the already noted conclusion that the brain with DS at or shortly before birth is in main respects indistinguishable from the brain of a normal individual (Bar-Peled et al. 1991). The idea of a relative normalcy at birth is potentially of the greatest significance, since it seems to create the opportunity to do something about the not-yet-created differences that quite clearly do emerge during the period right after birth.

There is evidence, however, that some changes begin to emerge as early as 22 weeks gestational age (eg., Engidawork and Lubec, 2003; Schmidt-Sidor et al. 1990) and it is clear that by 6 months a number of important differences are already obvious. Some of these differences are expressed in terms of the proportion of individuals with DS who show abnormal values, rather than in terms of a uniform abnormality in all instances. This is of importance, as it highlights the variability in this population sharing the genotypic feature of trisomy 21. One quite noticeable difference concerns a postnatal delay in myelination (Wisniewski, 2005), global at first but then manifested primarily in nerve tracts that are myelinated especially late in development, such as the fibers linking the frontal and temporal lobes. This delay is observed in about 25% of infants with DS who come to post-mortem analysis between the ages of 2 months and 6 years. Delayed myelination has also been observed in a study employing magnetic resonance imaging on a single infant (18 months of age) with DS (Koo et al., 1992). While not underestimating the impact of this myelination delay, it is certainly worth noting that in all cases myelination is within normal range at birth, while in 75% of the cases it is within normal range throughout early development. However, the basic point remains that by early childhood there is an impoverishment in neocortex.

Neuropathological differences after 3-5 months of age include a shortening of the fronto-occipital length of the brain that appears to result from a reduction in growth of the frontal lobes, a narrowing of the superior temporal gyrus (observed in about 35% of cases), a diminished size of the brain stem and cerebellum (observed in most cases) and a significant reduction (20-50%) in the number of cortical granular neurons (Blackwood and Corsellis, 1976). Notwithstanding these differences, however, the overall picture at birth or shortly thereafter is one of only modest abnormalities, although individuals with DS tend to fall towards the bottom of the normal range (or outside it) on most measures. Investigations of neural function, as opposed to structure, in early infancy suggest some abnormalities: there is evidence of either delayed or aberrant auditory system development (Jiang et al. 1990) that might contribute to the widespread hearing disorders observed in DS. Obviously, such a disorder, if organic, could be related to many of the subsequent difficulties seen in the learning of language. Karrer et al. (1998) have reported delayed development of cerebral inhibition using visual event related potentials (ERP) in a visual recognition memory paradigm.

There is also evidence of a more widespread abnormality in EEG coherence (McAlaster, 1992) that seems to reflect the generally impoverished dendritic environment. This difference, like many of the others, emerges only sometime after birth. It appears that this effect is predominant in posterior, rather than anterior, brain regions, and in the left, more than the right, hemisphere.

1.4.2 Later development and adulthood

The evidence of neuropathological sequellae in DS is more extensive for the middle stage of life. Data from both post-mortem studies and from studies of brain function in this population indicate that the changes that begin to emerge early in life become more prominent and prevalent by early adolescence.

There have been relatively few studies of brain function in adolescents and young adults with DS, and the existing data are somewhat equivocal. Devinsky et al. (1990) reported relatively normal EEG alpha activity in young adults (< 40 years of age), while Schapiro et al. (1992) reported relatively normal brain metabolism in a similar group, using positron emission tomography (PET) measures of glucose uptake and regional blood flow. They did report some disruption of normal neuronal interactions between the frontal and parietal lobes, possibly including the language area of Broca. Overall, they concluded that in younger subjects with DS cerebral atrophy does not generally extend beyond what would be predicted by the smaller cranial vault and stature of these subjects.

Two recent studies (Kates et al., 2002; Pinter et al., 2001a) provide more specific information. Pinter et al. used high-resolution MRI methods to analyze brain structure in 16 youngsters (mean age 11.3 years) with DS. After correcting for overall brain volume, hippocampal, but not amygdala volume reductions were seen in this group. Kates et al. studied a group of 12 children (all males, mean age 5.94 years) with DS, and compared them to children with Fragile-X, developmental language delay, or typical development. The children with DS had smaller brain volumes than any of the others, with previously unreported reductions in parietal cortex as well as the often-reported reductions in the temporal lobe. Pinter et al. (2001b), on the other hand, noted the relative preservation of parietal cortex.

Five recent papers provide an up-to-date view on the neuropathology observed in adults with DS (Aylward et al., 1999; Raz et al., 1995; Kesslak et al., 1994; Lögberg & Brun, 1993; Weis, 1991). Weis (1991) applied stereological techniques in combination with magnetic resonance imaging scans to estimate the size of various brain regions in a group of 7 adults (30-45 years of age) with DS. The volume of the whole brain was smaller in subjects with DS. When the data were normalized and then considered as a ratio of the volume of the cranial cavity, specific differences were observed in cortex and white matter overall, with a not-quite-significant difference in

cerebellum ($p < .06$). The second study (Kesslak et al., 1994) studied 13 adults with DS, using MRI to assess the size of various brain regions. The main findings in the group without dementia were a decrease in the size of the hippocampus and neocortex, and a paradoxical increase in the size of the parahippocampal gyrus. No significant differences were observed in the superior temporal lobe, the middle and inferior temporal lobes, the lateral ventricles, or cortical or subcortical areas. In these DS subjects there were only two significant age-related changes: with aging, ventricle size increased and hippocampal size decreased. The third study (Raz et al., 1995) looked at 25 adults, 13 with DS, also using MRI. Most critically, their results were adjusted for body size, so they took into account differences resulting simply from allometry. The authors found that a number of brain regions were smaller in the subjects with DS, including the hippocampal formation, the mammillary bodies, and parts of the cerebellum and cerebral hemispheres. They also replicated the increase in size of the parahippocampal gyrus observed by Kesslak et al. (1994). There was some shrinkage of other brain regions, including the dorsolateral prefrontal cortex, the anterior cingulate cortex, the pericalcarine cortex, the inferior temporal and parietal cortex, and the parietal white matter. No differences at all were observed in orbito-frontal cortex, pre- and post-central gyri, and the basal ganglia. The fourth study (Lögberg & Brun, 1993) applied morphometric analyses to the brains of 7 subjects with DS (mean age of 25.3 years), and demonstrated a significant decrease in gyri in the frontal lobe. Finally, Aylward et al. (1999) used high-resolution MRI to show a selective hippocampal volume reduction in adults. These observed changes confirm earlier reports of decreased volume of cerebellum (Jernigan & Bellugi, 1990), and of decreased dendritic spines and volume in hippocampus (Ferrer & Gullotta, 1990). There have also been reports of neuropathology in the amygdala, in particular in those subregions most closely associated with the hippocampus (Murphy & Ellis, 1991), but the more recent findings that controlled for overall brain volume (Pinter et al. 2001a) cast some doubt on these data.

The earliest neuropathological changes with aging in DS seem to appear in parts of the hippocampal formation, especially the entorhinal cortex, but also involving the dentate gyrus, CA1 and the subiculum (Hyman, 1992). There is extensive cell loss in the locus coeruleus (Mann et al. 1990), a brainstem nucleus that projects to the hippocampal formation; this was most noticeable in cases of severe dementia.

In sum, there are widespread signs of neuropathology in older subjects with DS, but there is selectivity nonetheless, in terms of where signs are seen first, and where they are most prominent. In this regard, changes in hippocampal formation (Ball et al. 1986; Wisniewski et al, 1986), temporal lobe in general (Spargo et al. 1992), prefrontal cortex (Kesslak et al., 1994) and cerebellum (Cole et al. 1993) stand out.

In recent studies the motor alterations that are observed in individuals with DS have been related to defects in the cerebellum (Virji-babul et al, 2011, Rigoldi et al, 2009), although the actual pattern of phenotypic motor disturbances suggests that such alterations may result from structural defects across various brain regions. In addition, neuropsychological and functional neurimaging data show that the basal ganglia and the cerebellum have crucial roles in implicit learning and memory. Implicit memory is relatively conserved in people with DS (Vicari et al, 2000), which is a characteristic that has been related to the fact that these individuals exhibit normal morphology of the basal ganglia despite also showing severe cerebellar hypoplasia. Indeed, cognitive motor impairment presents as a specific deficit that can be related to impairment in the function of a cerebellar-frontal-striatal network (Brunamonti et al, 2011).

Along with these structural alterations, atypical patterns of brain activation have been demonstrated in DS (Jacola et al, 2011), allowing predictions about structural-functional maps in this disorder (Colom et al, 2010). For example, the poor performances in linguistic tasks can be partially explained in terms of impairment of the connectivity in frontocerebellar structures that are involved in articulation and verbal working memory and also in other structures such as the corpus callosum (Fabbro et al, 2002), whereas the reduced long-term memory capabilities may be related to abnormalities in the frontotemporal lobes and, specifically, to hippocampal dysfunction (Pennington et al, 2003).

Overall, the evidence from the study of subjects in mid-life is not yet conclusive. While there are clear problems in some cases, with some evidence for localized neuropathology, the general picture is quite diffuse. This, however, is not the case when one looks at studies focused on somewhat older subjects.

1.4.3 Ageing

Improvements in accommodations and deinstitutionalization, together with improvements in diagnostic tools, surgery techniques and rehabilitative treatments, has caused an exponential rise in early survival over the last 40-50 years, that has resulted in a rapid rise in the number of older people with DS (Torr et al, 2010). In their review about aging in DS, Torr et al (2010) detail the rise in the mean age of persons with DS in several developed countries, their life expectancy and the main problems and disorders associated with ageing in this population. As they state, dementia of Alzheimer's type is a most important age-related disorder in middle-aged adults with DS, and is associated with substantial comorbidity and mortality.

A neuropathology resembling that seen in Alzheimer's disease (AD) is in fact prevalent in individuals with DS after the age of about 35 years. Estimates vary, but a reasonable conclusion is

that 25 percent or more of individuals with DS over age 35 show clinical signs and symptoms of Alzheimer's-type dementia. The percentage increases with age. In the general population, Alzheimer's disease does not usually develop before age 50, and the highest incidence (in people over age 65) is between 5 and 10 percent. The incidence of Alzheimer's disease in the population with DS is estimated to be three to five times greater than in the general population. On this basis, DS has been proposed as a model to study the prodementia stages of AD (Mann, 1988). A large number of studies have concentrated on this issue, documenting the ways in which the neuropathology seen in DS is similar to, or different from, that seen in Alzheimer's disease. A very important fact emerging from the past 10 years of careful study, is that while virtually 100% of individuals with DS show neuropathology similar to that associated with Alzheimer's disease, less than 50% show the dementia invariably seen with AD. This uncoupling of the neuropathology from the dementia has of course occasioned considerable interest, with an initial emphasis on attempts to determine if there might be subtle differences between the cases of DS and AD that could explain the dissociation observed in DS but not in AD. It has not proven possible to point to any difference that could be said, with confidence, to account for this fact. Recently, however, it has been shown that there is a critical difference between DS and AD with regard to the nature of the amyloid deposits found in the plaques characteristic of the neuropathology common in these two syndromes. Dementia is only observed when insoluble amyloid, which causes the formation of fibrous tangles, is present. This type of amyloid is rarely seen in DS until after 50 years of age, regardless of the extent of gross neuropathology. Pyramidal neuron abnormalities with reduced dendritic arborization, decreased numbers of spines, spine atrophy and anomalies of spine orientation are already present in infancy and fetal stages of DS (Becker et al., 1991). Additionally, there are cytoskeletal abnormalities in DS (Mann et al., 1989). These developmental abnormalities make the brain of DS subjects vulnerable for any type of lesions and might contribute to the early onset of dementia in DS subjects. Therefore, the use of DS as a prodementia model of AD has to take into account that developmental abnormalities and DS-specific degenerative processes contribute to the neuropathological substrate of dementia in DS (Teipel and Hampel, 2006).

A few studies have addressed the modifications that occur in the DS brain that develops dementia. In their study with MRI, including two adult subjects with DS and dementia, Kessler et al (1994) found considerable brain atrophy and an enlargement of the ventricles in the DS subjects with dementia; in general a picture similar to that observed in Alzheimer's disease, but absent in the subjects with DS who were not clinically demented, even those as old as 51 years of age. Alyward et al (1999) sought to determine whether volumes of the hippocampus and amygdala were disproportionately smaller in subjects with DS and with dementia compared to non demented

subjects with DS. In agreement with Pearlson et al (1998) they found that volumes of both the hippocampus and the amygdala were smaller in the demented subjects with DS than in their comparison subjects, even when total brain volume was controlled for.

Apart from dementia, middle-aged adults with DS also face considerable levels of other age related morbidity and disability, especially sensory impairments and musculoskeletal disorders, which are earlier in onset and of greater prevalence than among other people with intellectual disability and the general population. There is in fact a strong association between increasing age and prevalence of vision and hearing impairments in people with DS (Torr et al, 2010).

A number of studies, reviewed by Torr et al (2010) have found significantly lower mineral density in adults with DS compared with age peer controls with other intellectual disabilities (Baptista et al, 2005; Guijarro et al, 2008) and controls without intellectual disability (Center et al, 1998). Higher rates of osteoporosis are reported for older adults with DS, from the age of 40 years, compared with the general population (milberger et al, 2002, van Allen et al, 1999), with higher rates of bone fractures.

A range of major orthopedic problems are common in DS, such as ligament laxity and hypermobility of joints, that can result in instability, subluxation and dislocations of joints, which can increase with age (Hresko et al, 1993), as well as contribute to degenerative joint disease. Osteoarthritis of the spine and hips is common in older adults with DS (van Allen et al, 1999). Degenerative hip disease is an important cause of disability and pain in older adults with DS (Diamond et al, 1981). Finally, older people with DS have greater muscle weakness, slower walking speed, poorer balance and more impaired functional and sensorimotor performance.

1.5 Cognitive development

As pointed out in the previous paragraphs, the nervous system is always affected in DS. Developmental disabilities lead to both intellectual disability and to slowed and/or incomplete mastery of physical coordination.

There is a long-standing debate over whether development in children with DS can best be understood in terms of a slowed-down version of normal development, i.e. with only the rate and endpoint distinguishing development in children with DS from normally-developing children, or whether development in DS differs in fundamental ways from normal developmental processes. The data support the view that there are significant differences in how development unfolds in children with DS, and also suggest that some of these may stem as much from crucial differences in

the psychological environment in which children with DS grow and learn as from the biological disadvantages they carry from birth. This 'difference' account may not be the favored viewpoint, but it does have the considerable merit of being consistent with the growing body of data from the neurosciences showing significant differences in the structure of the DS brain and in how it works. We are still very far away from being able to make direct links between specific brain pathology and specific behaviors, least of all cognitive behaviors, but the characteristic reduction in size of the cerebellum, for instance, is likely to underlie the poor muscle tone and motor sequencing deficiencies commonly found with DS, and the immaturity found in frontal and temporal lobes is almost certainly implicated in the significant memory deficits and impairment in spatial representation and temporal sequencing skills seen in those with DS. Abnormal development in these areas might also be implicated in the accelerated aging process found in DS.

Limitations in the level of intellectual functioning are defined in clinical practice by the intellectual coefficient, or intelligence quotient (IQ). In people with DS, IQ is usually variable, ranging from 40 (moderate intellectual disability) to 70 (mild intellectual disability). This range reflects the high variability in cognitive disability that is observed across individuals with DS, as well as variation in additional (non-cognitive) symptoms. As occurs in children without intellectual disability, there is a linear trend of improved performance with age in subjects with DS, reflecting age-associated improvements in specific cognitive skills, namely verbal comprehension, perceptual organization, attention and behavioral inhibition (Edgin et al, 2010a). This observation is important because it suggests that functional brain maturation occurs in individuals with DS, albeit at a slower pace than that of typically developing children (Edgin et al, 2010b), and that functionally focused interventions may prove beneficial when commenced from the earliest possible age. However, the IQ of people with DS plateaus or even decreases in early adolescence (Nadel, 2003). This does not necessarily apply to a decline in functional skills however. Individuals continue to learn new skills, so the effect of this on the adult's actual ability to cope with the world and have an independent or supported lifestyle varies. This tailing off or dip in IQ has been related to the fact that DS is considered to be a neurodegenerative disorder in which some of the deficiencies are compensated for as the brain matures, whereas others remain stable or decline with age. The main problem of using only IQ to define the degree and quality of intellectual disability is that it is a composite measure of cognition, and may mask specific deficiencies because of its nonspecific nature.

A number of developmental disorders are characterized by intellectual disability, but interesting differences exist in their associated cognitive profiles despite a general similarity in IQ range (Vicari et al, 2005). For example, DS, Williams syndrome and fragile X syndrome are each associated with distinct memory profiles (Conners et al, 2011). In DS the ability to keep incoming

information online, the performance of mental computations on such information and the storage of this information for future use are disrupted (Lanfranchi et al, 2011; Baddeley and Jarrold, 2007). Typically, individuals with this disorder have an “uneven” working memory profile, in that they exhibit greater deficits in verbal short-term memory than in visuospatial short-term memory capabilities (Lanfranchi et al, 2011, Chapman and Hesketh, 2000). This functional dissociation stems from the representational content of memory (that is, verbal versus visual and spatial content) (Lanfranchi et al, 2011; Edgin et al, 2010a; Baddeley and Jarrold, 2007), although the level of impairment is also influenced by underlying alterations in sensory, motor and executive functions (Zimmer, 2008; Jarrold, 2005). In terms of spatial working memory, it should be noted that individuals with DS are poor at spatial-simultaneous memory tests, such as the Corsi-block (or tapping) test, but successfully perform spatial-sequential tasks (Lanfranchi et al, 2009). Accumulating evidence indicates that the storage and processing capabilities of the human working memory system influence individuals’ performances on a wide range of cognitive tasks (Nash and Heath, 2011; Colom et al, 2007). Thus, the deficits in short-term memory skills that are observed in people with DS impair their performance in a range of cognitive tasks, including language and vocabulary development and problem-solving tasks (Lanfranchi et al, 2010).

Individuals with DS exhibit various language weaknesses, including poor expressive and receptive language and an impaired reading ability (Nash and Heath, 2011). In addition, children with this disorder have a reduced ability to acquire new words and more-advanced language forms in their verbal repertoire (Jarrold et al, 2008). Rather than being mainly caused by auditory or speech production difficulties (Jarrold et al, 2002), which anyway are present, this phenotype has been attributed to the limited capacity of the verbal short-term memory system, which constrains the acquisition of vocabulary and syntax through its reduced ability to maintain and manipulate phonological representations online (Jarrold, 2005).

Evidence suggests that in DS long-term memory is affected in a similar manner to short-term memory, in that the modality of the information to be recalled is related to the degree of deficit. It has been suggested that a deficiency in memory consolidation, retrieval of stored information or learning strategies may be responsible for explicit memory impairment in DS (Vakil and Lifshitz-Zehavi, 2012). Of note, implicit memory (non-conscious memory) seems to be less affected than explicit long-term memory in this disorder (Vicari et al, 2000).

With ageing, if the subject develops Alzheimer’s Disease, progressive memory loss, personality deterioration and loss of functional motor capabilities happen. Early symptoms include loss of memory and logical thinking, personality change, decline in daily living skills, new onset of seizures, changes in coordination and gait and loss of continence in bladder and bowel habits.

However, not all individuals with DS will develop Alzheimer's disease, and even those showing Alzheimer's-type symptoms may not have Alzheimer's disease since other conditions can mimic the symptoms.

1.6 Motor development

Children with DS want to do what all children want to do: they want to sit, crawl, walk, explore their environment, and interact with the people around them. To do that, they need to develop their gross motor skills. There are three factors which traditionally are believed to have an impact on the gross motor development of a child with DS (Shumway-Cook and Woollacott, 2006), and which have been the focus of most of past, more "traditional" research on motor ability in DS, as reviewed in the next chapter:

Hypotonia: Tone refers to the tension in a muscle in its resting state. The amount of tone is controlled by the brain. Hypotonia means that that tone is decreased. It is most easily observed in children with DS when they are infants. Hypotonia affects each child with DS to a different degree: in some the effect is mild, and in others it is more pronounced. Although hypotonia diminishes somewhat over time, it still persists throughout life. Hypotonia will make it more difficult to learn certain gross motor skills; for instance, hypotonia of the stomach muscles will make it more difficult to learn to balance in standing.

Ligamentous laxity: Children with DS also have increased flexibility in their joints. This is because the ligaments that hold the bones together have more slack than is usual. Ligamentous laxity is particularly noticeable in the hips of infants with DS. When lying on his back, the legs of an infant with DS tend to be positioned with his hips and knees bent and his knees wide apart. When standing, his feet are flat. This increased flexibility tends to make the joints less stable, and it is, therefore, more difficult to learn to balance on them.

Decreased strength: Children with DS have decreased muscle strength. Strength can be greatly improved, however, through repetition and practice. Increasing muscle strength is important because otherwise children with DS tend to compensate for their weakness by using movements that are easier in the short run, but detrimental in the long run. For example, if the child wants to stand, because of weakness in his trunk and legs, he can only do so by stiffening his knees. He

therefore needs to develop the strength he needs so that he can stand properly without locking his knees.

Another factor to be considered is allometry (Shumway-Cook and Wollacott, 2006): the arms and legs of children with DS are short relative to the length of their trunks. The shortness of their arms makes it more difficult to learn sitting because they cannot prop on their arms unless they lean forward. When they fall to the side, they have to fall farther before they are able to catch themselves with their arms. The shortness of their legs makes it harder to learn to climb since the height of the sofa or stairs presents more of an obstacle.

Because of certain physical characteristics, which include hypotonia, ligamentous laxity, and decreased strength, children with DS don't develop motor skills in the same way that the typically-developing child does (Shumway-Cook and Wollacott, 2006). They attempt to compensate for their hypotonia, ligamentous laxity and decreased strength and these compensation often results in abnormal movement patterns, which make the child prone to developing orthopedic and functional problems. For example, ligamentous laxity and hypotonia in the leg lead to the abnormal patterns of hip abduction and external rotation, hyperextension of the knees and pronation and eversion of the feet. These abnormal patterns lead to walking with a wide base and on the medial borders of the feet. This is functionally inefficient, often painful and results in poor walking endurance.

These important aspects of walking in children and adults with DS will be reviewed in detail in the next chapter. Although these are well known and documented features of DS, some authors have recently questioned their major role in causing the delay or deficiency in motor skills acquisition in DS (Latash et al, 2008; Sacks and Buckley, 2003; Latash and Zatsiorsky, 1993; Shumway-Cook and Woollacott, 1985), as well be explained in the next chapters.

1.7 Health care guidelines for persons with Down Syndrome

As we have seen DS comprises a wide spectrum of diseases, among those are motor and cognitive problems. Recently the European Down Syndrome Association (EDSA) has published some health care guidelines for people with DS, undersigned by an international team of doctors and experts in DS. The guidelines are meant to provide a medical program for the treatment of this syndrome that includes both rehabilitation and social inclusion. The lack of clear-cut guidelines to practitioners (Cissik, 2012; Andriolo et al, 2005), in fact, is a very limiting factor for the treatment of subjects with DS, and in this sense the EDSA document is an attempt to provide some recommendations

about the treatment of the most important medical aspects for all paediatricians and general practitioners caring for people with DS of any age.

The document, that is divided in life periods (prenatal period, birth to one month, first year of life, from first to sixth year of life, from seventh to twelfth year of life, early adulthood, adulthood and old age), stresses the importance of many clinical examinations throughout the lifespan of persons with DS. If we focus on motor rehabilitation and physical therapy, the document suggests the participation to early rehabilitation programs from the age of one year to the age of six. Early intervention is therefore considered very important for the development of motor skills in DS. However, after this age, there is no further recommendation about motor rehabilitation, which is instead substituted by a general point: “school insertion and recreational activities”. From adolescence to adulthood and old age the EDSA program stresses the importance of encouraging recreational activities, active employment, sport and independence, without giving any further information about the types of activities that could better emphasize the motor and cognitive residual capacities of persons with DS. The failure in highlighting rehabilitation and therapeutic programs for the development and maintenance of motor skills during the lifespan of persons with DS is evidenced by this official document and by the general lack of literature on the topic. In theory, exercise programs would be beneficial to individuals with DS. Unfortunately, research on exercise and DS is lacking, can be contradictory, and rarely provides clear-cut guidelines to practitioners (Andriolo et al, 2005). In fact, it is impossible to provide guidelines for effective therapy if the reasons of the delay in DS are unknown (Sacks and Buckley, 2003).

However, a few authors have addressed the problem of how physical activity impacts on the life quality of subjects with DS and of which rehabilitative treatments should be better applied.

Physical activity

In addition to the several factors (reviewed in the previous paragraphs) that impact on their development of gross motor skills, individuals with DS have a reduced resting metabolic rate and a higher frequency of obesity when compared with individuals without DS that puts them more at risk for cardiovascular disease and metabolic syndrome (Koritsas and Iacono, 2009; Baynard et al, 2008; Roizen and Patterson, 2003). In addition to decreased strength and power, individuals with DS have a drastically lower peak oxygen consumption, lower aerobic capacity, and lower peak heart rate than individuals without DS (Shields et al, 2009; Baynard et al, 2008; Shields et al, 2008). These physical fitness variables impact on activities of daily life (Cowley et al, 2010).

Several reasons may exist for the reduced physical fitness seen in individuals with DS. First, the sympathetic and parasympathetic nervous systems may function differently in people with DS

(Fernhall and Otterstetter, 2003). Second, the combination of hypotonia, hypothyroidism, hypogonadism, obesity, and motor development challenges will have an impact on the difficulty of exercise. This may make someone with DS less likely to choose to pursue an exercise program. Third, the combination of motor development challenges and the intellectual disability in individuals with DS lead to an avoidance strategy when it comes to cognitive challenges (Roizen and Patterson, 2003). This means that they are less likely to take up physical activities that they are not familiar with (Shields et al, 2009).

Early intervention programs

Physical activity and movement in children with and without DS is a critical facilitator of learning (Ulrich and Ulrich, 1995). As infants and children move they learn about the changing properties of their own systems (e.g. limb lengths, muscle strength, postural control) and their environment (Thelen et al, 1994). In addition to the benefits in terms of daily living and independence, motor progress is also important because these abilities also influence social and cognitive development: as an example, being able to reach and grasp allows a child to begin to explore the characteristics of objects, being able to sit increases the ability to use arms and hands for playing, being able to walk allows a child to carry toys and objects and to explore the world more effectively than crawling, being able to move independently increases opportunities for social interaction and language learning (Sacks and Buckley, 2003).

Very limited research has been conducted on physical activity as it relates to learning of functional skills in children with and without DS, however the common view based on parent and professional reports is that young children with DS are less active than their age peers without DS (Mc Kay and Angulo-Barroso, 2006; Sharav and Bowman, 1992; Henderson, 1986). Henderson (1986) hypothesized that children with DS have “a self-perpetuating form of sensory-motor deprivation sparked off by an inbuilt passivity and disinclination to move”, which explains why infants and young children with DS experience significant delays in acquiring early movement skills. Ulrich and Ulrich (1995) compared the spontaneous leg movements of infants with DS and two groups of typically developing infants, respectively matched for chronological age and motor age. Their results suggested that the frequency of leg movements was not different between the three groups. However, infants with DS produced significantly fewer complex patterned leg movements in the form of kicks. In the three infant groups, infants who produced more kicks also walked earlier. McKay and Angulo-Barroso (2006) studied the spontaneous leg activity of infants with and without DS from three to six months of age. Their findings suggest that infants with DS spend a greater

duration of time throughout the day in low intensity leg activity. The authors reported a significant negative relationship between low intensity leg movement and the age of onset of walking.

These data suggest that poor motor skill development, over time, is likely responsible for low levels of physical activity demonstrated later in life. Early interventions that promote the development of efficient functional motor skills may, therefore, have a positive impact on multiple domains during infancy and may also create a solid foundation for future success in movement settings (Latash et al, 2008), that is why physical therapy should have an important role from the earliest phases of growth of these children.

Some authors (Shumway-Cook and Woollacott, 2006; Winders, 2001) suggest that the main aim of physical therapy in this phase of the child's development is to help the child avoid developing abnormal compensatory movement patterns such as the following compensatory movement patterns:

- Standing and walking with their hips in external rotation, knees stiff, feet flat and turned out,
- Sitting with their trunk rounded and pelvis tilted back,
- Standing with a lordosis (stomach out and back arched).

These patterns are likely to result in orthopedic problems in adolescence and adulthood that will impair physical functioning, but these problems can be avoided by proactively teaching optimal movement patterns so that strength is developed in the appropriate muscles. Early intervention services, which begin shortly after birth, can help children with DS develop to their full potential. The physical, speech and occupational therapies that early intervention programs provide can enhance a child's development.

Despite the benefits of early intervention and exercise for persons with DS, this is a population that has been poorly studied, and clear recommendations for the practitioners are not existent (Cissik, 2012). This probably is partly due to the fact that children with DS have not a unique learning style: physical therapy services need to be designed with the child's long-term functional outcome in mind. They should focus on lower-extremity gait, posture, and exercise. Physical therapy needs to begin with an understanding of the abnormal movement patterns that children with DS are prone to develop, and then proactively build strength in the right muscles so that the child with DS develops optimal movement patterns. Functionally this translates into walking with a narrow base, feet pointing straight ahead, the trunk developed without a kyphosis or lordosis.

Exercise programs

A limited number of studies have examined the effects of strength training and aerobic exercise programs on individuals with DS, as reviewed by Cissik (2012). These studies found that exercise

programs are effective at improving aerobic fitness measures and strength. Improvements in body mass and psychological variables are less clear.

Aguiar et al (2008) studied the effects of judo on motor coordination. In their study, subjects with DS participated in 16 weeks of supervised judo instruction, 3 times per week, each session for 50 minutes. The authors used a gross motor function measure that covered 88 items organized into lying/rolling, sitting, crawling/kneeling, standing, and walking/running/jumping to evaluate motor coordination. At the end of the study, the authors found a significant improvement for performance on the gross motor function measure but do not provide a breakdown of this performance improvement. Carmeli et al (2004) studied the effect of a training program involving pain-free low-intensity walking on elderly individuals with DS. Their subjects were divided into 2 groups, one with intermittent claudication (i.e., pain in the muscles during walking) and the other without. Subjects exercised on the treadmill for 15 weeks, 3 times per week at a speed below pain and breathless thresholds. Initially, subjects walked for 5–15 minutes and progressed to 40 minutes on the treadmill. Both groups made significant increases in the distances walked, duration on the treadmill, and speed. Mendonca et al (2011) studied whether adults with DS responded differently to an exercise program than adults without DS. After 12 weeks of combined cardiovascular and strength training, both groups made similar improvements in muscular strength and peak oxygen consumption.

Based on the literature reviewed, aerobic exercise and strength training appear to yield positive benefits to aerobic fitness and muscular strength/endurance in individuals with DS. These benefits seem to be similar to those seen in populations without DS. However, it is unclear if exercise has a positive effect on the body mass index or psychological variables (Dodd and Shields, 2005) in individuals with DS.

There are limitations to the scientific research on subjects with DS. First, it is not known whether the gains in fitness from an exercise program can be retained over time because there are no long-term studies. Second, it is not known whether age, gender, or concurrent health problems may impact exercise program outcomes. Finally, implications for long-term program effectiveness have not been studied (Mendonca et al, 2010).

Based on the limitations mentioned above, and extrapolating from populations without DS, Cissik (2012) drew several recommendations regarding exercise programs and individuals with DS. These recommendations deal with supervision, the inclusion of cardiovascular exercises, and the inclusion of strength training exercises.

First, this population requires supervision to ensure a successful exercise program (Dodd and Shields, 2005). This is important to keep the individual focused, motivated, and exercising at the

appropriate intensity. Second, people with DS will benefit from a cardiovascular exercise program. A lack of balance and motor skill may have an impact on an individual's comfort with walking, jogging, or elliptical cross-trainers (Dodd and Shields, 2005) Third, strength training is appropriate for people with DS, although it may need to be modified. Keeping in mind challenges with learning new motor skills and balance, individuals with DS should begin a strength training program using selectorized strength training equipment 2–3 times per week emphasizing the entire body.

There is no research to address the topic of free weights exercise in subjects with DS, but the characteristics of the syndrome suggest some caution: hyperflexibility could theoretically increase the risks of injury and it would take this population longer to master the motor skills associated with free weights due to a combination of hypotonia, balance, and intellectual disabilities (Cissik, 2012). Because of the physiological differences, it is unclear if individuals with DS will respond to exercise in a manner similar to the population without DS, how exercise should be programmed over the long term for people with DS, and if free weights are appropriate and how exactly they should be incorporated into the exercise program. Individuals with DS may benefit from a structured exercise program. Despite the benefits, there is a need for more research with this population. This is important for health, the ability to function in daily life, the opportunity to socialize, and may help enhance self-esteem and prevent depression.

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Websites

EDSA Healthcare Guidelines for People with Down Syndrome:

<http://www.down-syndrome.eu/html/publications.html>

Chapter 2

Trends in movement analysis in Down Syndrome

In the previous chapter the main features of DS were briefly explained. We have seen that the syndrome involves a wide spectrum of diseases, among which motor deficits are very important factors. It is in fact widely accepted that individuals with DS experience difficulty performing motor skills. Several studies have shown that the movements of individuals with DS are slower, less smooth and more variable from trial to trial when compared with the movements of the overall population. All of these features have been referred to with the term “clumsiness”, widely used to describe the uncertain and shuffling movements of subjects with DS (Rigoldi et al, 2011a). Despite the awareness about motor deficits in DS, however, there is a lack of studies on how to help persons with DS reach their full potentials in motor activities, and a lack of guidelines for clinical practitioners.

As reviewed in the following paragraphs, the movement deficits in DS have been extensively described to study how the limitations impact on movement in DS. Movement analysis has been “traditionally” used for these descriptive studies; on the other hand and more recently, the researchers are starting to use such tools for the assessment of hypothesis about how the motor control acts. This new application of movement analysis aims at providing a deeper insight on the mechanisms underlying motor control and could help developing more focused rehabilitation treatments for persons with DS.

2.1 Traditional applications of movement analysis

Traditionally, movement analysis of DS people has prevalently focused on the biomechanical evaluation and description of a narrow set of movements. From this literature it is well-known that subjects with DS present mechanical and chemical alterations that result ligament laxity and hypotonia, and altered movement patterns, of which slowness, longer reaction times, instability, and patterns of muscular co-contractions are some of the most recurrent features (Rigoldi, et al, 2011 a,b; Galli et al, 2010; Aruin et al, 1996). The studies concerning motor control in DS subjects focus on *basic skills* (those which are necessary for everyday life activities) and in particular on *gross motor skills*, which are concerned with whole body movements, such as walking (Rigoldi et al,

2011 a; Galli et al, 2008 a) and posture (Rigoldi et al, 2011 b; Galli et al, 2008 b). *Fine motor skills*, which belong to the basic skills group and require fine manipulation of fingers and hands, such as picking up objects, writing and keyboarding, are very seldom considered in literature, and so are *recreational or specialistic skills* (i.e. optional skills based on interests and aptitudes). The major literature on these topics is reviewed in the following paragraphs.

2.1.1 Studies on motor development and gait

A number of studies have investigated age-related changes in the motor development of infants and young children with DS. In infancy, these studies are frequently related to motor milestones such as sitting and walking. Data have generally been collected using clinical measurements and observations and a range of standardized assessment tools, including the Griffith Scales, the Gesell Scales and the Bayley Scales of Infant Development, the latter being the most frequently used. It is widely thought that the attainment of motor milestones is delayed in infants with DS even following intervention (Ramsey and Piper, 1980; Eipper and Azen, 1978; Fishler et al, 1964). There is however considerable variability in the rate at which those with DS attain motor milestones, (LaVeck and Brehm, 1978), and Carr (1970) have suggested that the level of variability is greater than that observed in normally developing children. In addition, some studies highlighted that in some cases infants with DS have reached motor milestones within the expected normative period (Berry et al, 1984; Berry et al, 1980).

The developmental sequence of motor milestones has also been of interest to researchers: that is, is the pattern and/or sequence of motor development the same as that for typically developing infants? This question has generally been addressed using either the Bayley Scales of Infant Development or the Uzgiris-Hunt Scales. Several studies have reported that the motor development of infants with DS paralleled that of the assessment scales, with hypotonia being a factor that altered the normality of this pattern (Cicchetti and Sroufe, 1976). Dunst (1988) reported that infants with DS made transitional progresses through the Uzgiris-Hunt sequences of development, albeit at a much slower rate than normally developing infants. Dyer et al (1990) analyzed the age at which 707 infants with DS passed or failed the Bayley Scales of Infant Development (BSID) test items. The results indicated that the developmental path broadly reflected the BSID scale. It was reported, however, that motor items that required aspects of strength and balance (such as standing and walking) developed more slowly than other motor behaviors and that the infants with DS showed a far higher degree of variability.

Griffiths (1976) reported that 25% of children with DS are able to walk at 2 years of age, with the mean age being 30 months. They also exhibit considerable variability in the attainment of

individual walking. Comparing percentile graphs of children with DS to those of other children, the curve for individuals with DS shifts markedly to the right, with a lesser slope indicating a slower rate of skill attainment. However, the overall shape of the curve was similar to the control group. Ulrich et al. (1992) reported that alternate stepping patterns are observed at 11 months of age. This indicates that the neural networks appear to be established, and that other factors are inhibiting locomotion.

Just as the attainment of walking has shown considerable variability, so has the range of the walking skills of children with DS. Parker and Bronks (1980) studied 7-years-old children with DS and found that walking patterns were similar to newly independent walkers rather than to the mature patterns seen in adults. One of the characteristic of these walking patterns was a shuffling gait pattern. Parker reported that a lack of planta-flexion of the ankle accompanied by reduction of hip extension resulted in a lack of propulsion and thus a stepping or shuffling-type gait pattern.

Another characteristic often seen is a consistent toeing out (Parker and Bronks, 1980, Lydic and Steele, 1979). Mahan et al (1983) found the amount of toeing out to be 16° of abduction. They hypothesized that this may be to provide a wider base of support to reduce lateral motion and so facilitate postural stability. From the research of Dyer et al. (1990) it appears that motor ability in BSID items relating to walking is relatively retarded in development. This was attributed to a lack in postural control, to hypotonia and to hypermobile joints. Lydic and Steele (1979) indicated that 34.7% of the 104 children had a wide-legged walk and a Duchenne gait, with a relatively large amount of hip extra-rotation and an abnormal arm position: 29.8% were not yet walking. In their view adequate trunk rotation was particularly lacking. Akerstrom and Sanner (1993) observed overextension of the foot in two out of five walking children The cause stated by the authors was a combination of muscular hypotonia and laxity of ligaments.

Lautenslager et al (1998) indicated a hypotonic leg action, problems of balance and a wide-legged gait with extra-rotated and abducted hips without trunk rotation. The explanation of the authors was a lack of stabilizing co-contraction related to hypotonia, as a result of which inadequate postural control, insufficient trunk rotation and balance developed.

Rigoldi et al (2011a) studied the development of gait during lifespan by evaluating the same group of subjects with DS during childhood, teenagehood and adulthood. DS subjects showed a motion pattern with compensatory strategies addressed at increasing stability more than at decreasing energy costs. The analysis evidenced reduced ranges of motion in the sagittal plane of the distal joints, whereas movement in the frontal plane increased to guarantee gait progression. The feeling of instability in these subjects, caused by hypotonia and ligament laxity, led to stabilizing strategies such as ankle and knee agonist and antagonist co-contraction, which allow an “inverse pendulum

strategy” and decrease the number of degrees of freedom to be controlled during the movement. The support base was increased as well to reduce instability.

The study of gait evolution through lifespan revealed that variability in the parameters of DS decreased with ageing, meaning that a specific gait developmental trend was present. With age, stride length increased, however knee and ankle stiffness increased too. While changes in the controls’ gait patterns were more marked from childhood to adolescence, showing more adequate performances in terms of motion dispersion and energy costs during adolescence and adulthood, DS subjects maintained and increased the joint stiffening strategy, in an attempt to reduce the to-be-controlled segments of the body and simplify the movement, at the cost of a less efficient strategy.

2.1.2 Studies on balance

The perceptual-motor coupling involved in postural control implies the integration of different sensory information sources. In fact, information about the environment and the position of the body in space as well as the relative position of the body segments is needed in order to keep balance during standing and locomotion. This information is provided not only by vision, but also by the vestibular and proprioceptive systems. Nevertheless, the study of perceptual control of posture, especially in children, is dominated by research investigating postural compensations to optic flow.

The optic flow field affords a wealth of information about the layout of the environment and the subjects’ movement. Many studies have shown a functional relation between optic flow and posture. One of the first experiments that examined the effect of visual information on posture made use of what has become known as the “moving room” paradigm, that is, a room that can be moved above a stable floor (Lee and Lishman, 1975; Lishman and Lee, 1973). When the room is moved subjects experience self-motion while they stand or sit. This results in falls and oscillations of the body with the motion of the room. The participants were children with and without DS in different groups matched according to their experience in independent sitting or in standing without support. The postural reaction to the moving-room were scored according to the rating scale developed by Lee and Aronson (1974), who categorized the visible reactions as sways, staggers or falls. The standing results indicated that although infants with DS responded as often as the control children, the amplitude of their response was different: in fact falls were more frequent in infants with DS than in children without DS. Thus, when standing, infants with DS who have just learned to stand compensate more than normal infants do. The results also revealed a decline in response occurrence with postural experience. The number of falls declined after more than 3 months of standing experience in normal children and after 7 to 12 months of experience in infants with DS. Infants

who had recently learned to stand without support were more destabilized by the experimentally induced discrepancy between visual and vestibular information than were the infants with more experience in standing. Usually this developmental trend is taken to indicate that the importance of vision in the control of balance decreases as infants gain experience in motor control. With increasing age or experience with a specific posture, postural control becomes more strongly linked to optic flow information in a way that ensures an increase in postural stability.

The classic interpretation would be that, after onset of independent standing, infants with DS remain dependent on visual information for a longer period of time than normal children. An alternative interpretation, however, might be that the delayed decline of falls seen in infants with DS is a consequence of the lack of general postural control (insufficient muscle strength, coordination). Nevertheless, another study that analyzed the dynamics of postural control in children with DS provided interesting results concerning their ability to cope with discrepant sensory information in postural control (Salversbergh et al, 2000). The experimental paradigm used in this work was different from the moving-room: the standing position was not perturbed by movement of the visual surroundings but was directly challenged by movement of the support base (movable platform). In this paradigm, one of the experimental conditions consisted of rotations of the platform that were in direct proportion to the magnitude of anteroposterior sway motion of the subject. The device ensured a fixed ankle joint angle and therefore reduced the orientational information from the ankle, resulting in an intersensory conflict between the ankle proprioception (indicating stability) and the visual and vestibular information (indicating body sway). In this study the muscular coordination of the legs was analyzed using surface electromyograms in children with and without DS aged from 15 months to 6 years. The results showed an interesting paradox in the response of children with DS: myotatic reflexes at normal latency were present, with delays in long latency postural responses that often led to increased body sway and loss of balance. According to the authors, this supports the suggestion of Davis and Kelso (1982) that muscle stiffness and motoneuron pool excitability are comparable to those of normal children. Hence, they concluded that the responses of children with DS could not be attributed to the pathology of the stretch reflex mechanism but rather were likely due to problems in the organizational processes underlying the resolution of multimodal sensory conflicts.

Hypotonia may have a strong effect on the development and use of equilibrium reactions (Haley, 1986). Low tone in the trunk of most infants with DS, in fact, is likely to be associated with the relatively earlier appearance of protective reactions (Haley, 1986). Infants with DS learn to use protective responses either as a more effective method of counteracting postural disturbance or as a substitute for the lack of equilibrium responses. Bobath (Bobath, 1971 a,b) contends that normal

tone must be present before mature postural reactions can develop. He described the importance of an adequate regulation of tone and of enough co-contractions for the development of posture and movement patterns. Cowie (1970) demonstrated that young DS children had reduced muscle tone, with a disadvantageous effect on the development of the posture and movement patterns of DS children. Cowie reported also that there is a clear connection between hypotonia and the lack of postural control, Davis and Kelso (1982) provided information about the quality of myogenous stabilization of joints on the basis of comparison between control and DS children. The group of DS was less able to stabilize a position of the joints and they had significantly more difficulty in maintaining the position if the joints with reducing resistance because of hypotonia. In their extensive research, Dyer et al. (1990) claimed that hypotonia has a disruptive effect on the proprioceptive feedback from sensory structures in the muscles and joints. Hypotonia in children with DS can influence the intrinsic information about posture and movement and can have a negative effect on the appropriateness of co-contraction and postural reactions. On the basis of a study comparing children with and without DS, Parker and James (2008) showed that the group with DS on average had more joints mobility and that both groups showed a decrease in mobility with increasing age. Livingston and Hirst (1986) reported that children with DS frequently had one or more hypermobile joints, but that there was no question of a generalized laxity of joints.

Increased joint mobility may contribute in a negative sense to postural control. Together with insufficiency of co-contraction this influences the stability of the joint. It is also possible that proprioceptive information from joint sensors is influenced and affects the registration of posture and movement. Rast and Harris (1985) emphasized the importance of early postural reactions for the development of balance reactions to ensure automatic stability of head, trunk and extremities, whereby normal movement and transfer of weight become possible. Authors, on the basis of their comparison between normal and DS children, concluded that postural reactions in the group of children with DS developed later and that children with DS demonstrated less variation in postural reactions: they developed only those reactions necessary to achieve a particular motor phase. Based on these studies it is possible to conclude that the postural instability of DS causes precarious equilibrium and risks of falls, which can partially explain the balance problems that are common in these subjects. The ligament laxity and hypotonia oblige DS subjects to limit sagittal movements to maintain stability and dynamic equilibrium. The reduction of joints ranges of motion observed in all planes suggests an increase of agonist-antagonist co-contraction. This is aimed at increasing stability and dynamic equilibrium by limiting the relative motion between body segments and increasing general stiffness to contrast hypotonia and ligament laxity (Rigoldi et al, 2011 b).

Quantitative analysis of the centre of pressure (COP) data in quiet standing was applied in several experiments. Several studies indicated differences in the amount of sway in both anteroposterior (AP) and mediolateral (ML) directions by measuring COP displacements, with more sway in AP direction than in ML direction in healthy subjects (Van Emmerik et al, 1993). Galli et al (2008 b) analyzed COP oscillations in adults with DS during standing with eyes open and with eyes closed. They reported that in AP direction the oscillation of subjects with DS were within the normal range, whereas in ML direction the oscillations were absolutely bigger for DS. No difference was instead found between eyes open and eyes closed conditions. In addition to the higher oscillations in the ML direction for DS compared to controls, the parameters in the frequency domain highlighted the presence of an increased instability also in the AP direction.

2.1.3 Studies on upper limb movements

Upper limb movements in subjects with DS have received less attention than walking and posture. Anyway, literature provides some pictures for the characterization of reaching and grasping in these subjects. Generally speaking, slowness and retarded reaction time (Anson, 1989), lower muscle tone and correlated lower voluntary muscle contraction force (Morris et al, 1982) are among the most described characteristics of subjects with DS in upper limb movements as well as in other movements. Another peculiarity of DS is the presence of reversed patterns of muscular activation (Anson, 1989): during the execution of fast reaching movements, in fact, a different pattern of muscular activation can be found in DS compared to controls. Normally, the initiation of fast, accurate movements of the upper limb is facilitated by either a proximal-to-distal or synchronous activation of the principal agonist muscles (Anson and Mawston, 2000; Karst and Hasan 1991). One reason and a potential advantage of a proximal-to-distal activation is that it may provide opportunity for on-line corrections or the chance to “fine-tune” the terminal phase of the response. This pattern is frequently absent in individuals with DS, and replaced by either a reversed distal-to-proximal pattern of muscle activation or a co-activation pattern (Karst and Hasan 1991). These co-contraction or reversed patterns of muscle activation increase joint resistance to external perturbations, independently of the direction of the perturbation. Thus, they can assure some acceptable level of stability even if there is some degree of uncertainty about the direction of the perturbation, although being unable to fully compensate for the effects of the perturbation (Aruin et al. 1996; Almeida et al. 1994) and can be a valid compensatory mechanism to contrast muscle weakness and ligament laxity. In line with these observations, the difficulty of subjects with DS to modify their movement parameters under changing conditions has been reported also as the presence of excessive forces in tests such as finger tapping or gripping (Cole et al, 1988), increased variability in motor

performance (Henderson, 1986) and a lack of adaptation to changes in sensory information (Cole et al, 1988).

2.2 New applications of movement analysis

As demonstrated by the literature review of the previous paragraph, through the years movement analysis in DS has focused prevalently on the biomechanical evaluation of a narrow set of movements, primarily walking and posture. These movements have been tested in laboratory, controlled conditions, with little influence of external and internal factors such as the environment and the subject's intention, providing the clinician a quantitative and detailed picture of the biomechanical status of the subject, which is very important for therapeutic and rehabilitative considerations but gives only a limited insight on the causes of the motor deficit. Many of the authors have assumed that the profile for motor development in DS is largely the result of physical differences, and in fact these works well-documented the characteristics of the biomechanical constraints of DS phenotype, such as hypotonia, ligament laxity, muscular co-contraction, precarious equilibrium, increased joint stiffness, all resulting in a functional limitation in everyday life. These clinical studies allowed the definition of some guidelines for the rehabilitative treatments of DS subjects (such as muscular strengthening to correct hypotonia). However, there is no evidence that physical and biomechanical characteristics are the major factors to explain motor deficits in DS (Sacks and Buckley, 2003). In fact, in the case of neurological and cognitive impairments such as DS, the description of the motor outputs is clearly not enough, because the deficit is localized at the upper levels of the nervous system, and thus a cognitive interpretation behind the biomechanical output is mandatory. Thus, most of these studies are of theoretical more than practical relevance, since they do not explain how to modify the sequence of actions of muscles when moving, or how to act at the central level to correct the motor patterns (Sacks and Buckley, 2003).

Recent studies (Virji-Babul and Brown, 2004; Sacks and Buckley, 2003) are stressing the fact that the motor alterations in DS are only partially due to biomechanical impairments, whereas they occur mainly as a consequence of a deficient central nervous system (CNS), whose inputs to the biomechanical system generate outputs "different" from normality. Differences in the quality of movement, such as slower or less coordinated movement, can be seen to have their origin in the brain. Thus, biomechanical aspects are recently beginning to be linked together with the specific sensory, motor, cognitive and perceptual impairments of DS, but it remains unclear how these localized deficits impact on perceptual-motor processing and function. An interpretation of

movement patterns that could take into consideration how the nervous system works could clearly advance the understanding and the rehabilitative techniques in DS.

2.2.1 From a biomechanical interpretation to a cognitive interpretation

In recent years the research on motor control has been expanding to the field of neuroscience, extending the evaluation of movement from the pure biomechanical aspects to the evaluation of cognitive and motor aspects that, together with external aspects, contribute to the definition of movement. The new trends in movement analysis are addressed towards the description of movement not only as a consequence of biomechanical impairments, but also as a consequence of the deficits at the cognitive level, that result in a particular biomechanical output. As an example, the muscle co-contraction that was observed in most of the clinical studies about DS and that was addressed to compensatory strategies due to hypotonia, changes its meaning from a pure biomechanical interpretation to a more profound cognitive interpretation if we hypothesize, as Latash et al (1996) did, that subjects with DS are affected by poor decision making, and thus are not able to adapt their movements to sudden changes in the environmental conditions, then co-contraction becomes an adaptation strategy more than the consequence of a primary motor deficit. In this light, although movement patterns and muscle activation patterns may differ from those observed in neurologically normal individuals, they can be viewed as optimal adaptations given a primary impairment of the decision-making process. This kind of interpretation shifts from the pure biomechanical definition of an action-reaction principle of stiffening joints in response to hypotonia to a wider interpretation embracing all motor control spheres.

Latash et al (1996) and Anson (1992) have questioned the role of hypotonia as a central problem in DS and, as Anson said, “*the role of hypotonia in accounting for movement disorders in individuals with DS can no longer be considered a default explanation when all alternatives fail*”.

Another example regards the well-documented “clumsiness” of subjects with DS, which has been largely related to the biomechanical features of DS’s movements. Recent literature (Elliott et al., 2010; Latash, 2007) points out that clumsiness may be a product of the limitations at the CNS level, more than a product of biomechanical constraints alone. In fact, a key-point in the study of motor control is the analysis of feedback and feedforward mechanisms; feedforward movements are made without the online use of sensory feedback, and require an internal model of accuracy. Such actions can occur rapidly, as there is no need to account for the delay of feedback loops. Feedback control, in contrast, involves modification of the ongoing movement using information from sensory receptors: this type of control allows for a high degree of accuracy, error detection and correction, but it is necessarily slow. Optimal movement control likely reflects a combination of both feedback

and feedforward processes, but literature has demonstrated that a higher reliance on feedback control is present in subjects with DS. These findings could partly explain the well-documented clumsiness observed in DS movements: if DS performers can mainly rely on feedback control, without the chance to deploy a forward model of the movement they have to perform, the execution of the required task will be subjected to the continuous modulation of feedback control, resulting in longer durations of movements with a high number of corrections. A diminished representation of the expected movement outcome will result in their aiming behavior being slow, inefficient, and “fragmented” in sub-movements, causing a biomechanical output of clumsiness and slowness.

Thus, the first important aspect of the newest researches in the field of movement analysis is the evaluation of motor outputs as an instrument to investigate cognitive inputs.

2.2.2 The task-oriented approach: evaluation of “functional” movements

Simplified conditions that have been traditionally employed in movement analysis, such as straight walking on a plain surface at constant velocity, do not recreate full realistic environmental conditions of walking and do not allow an exhaustive interpretation at the cognitive level. In fact, more cognitively demanding situations are required for this scope. We refer to these movements as “functional” movements, i.e. movements based on real-world situational biomechanics, that usually involve multi-planar, multi-joint movements which place demand on the body's core musculature and require greater cognitive effort to be carried out.

Functional movements emerge from the interaction of three factors: the individual, the task and the environment. Movement is organized around both task and environmental demands, and the individual generates movement to meet the demands of the task being performed within a specific environment. In this way, it can be said that the organization of the movement is constrained by factors within the individual, the task and the environment. The individual's capacity to meet interacting task and environmental demands determines that person's functional capability. Within the individual, movement emerges through the cooperative effort of many brain structures and processes, since it arises from the interaction of multiple processes, including those that are related to perception, cognition and action (Shumway- Cook and Wollacott, 2006). These many systems interact in the production of functional movement. While each of these components of motor control – perception, action, and cognition – can be studied in isolation, a true picture of the nature of motor control cannot be achieved without a synthesis of information from all three. The so-called “task-oriented approach” (Shumway- Cook and Wollacott, 2006) is one of the newest theories in motor control and it assumes that movement emerges as an interaction among many different systems, each contributing to different aspects of control. In addition, movement is organized

around a behavioral goal and is constrained by the environment. Assumptions regarding abnormal motor control suggest that movement problems result from impairments with one or more of the systems controlling movement. This concept is shown in figure 2.2.1 (Shumway- Cook and Wollacott, 2006).

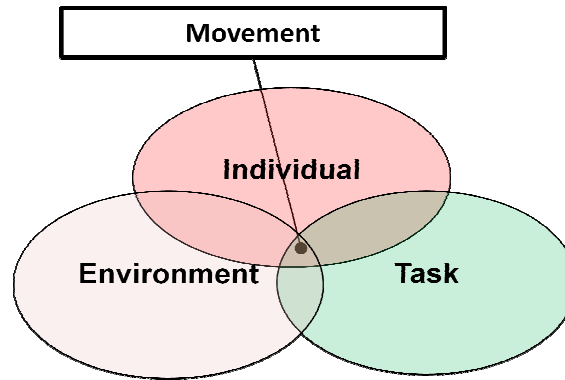


Figure 2.2.1: movement emerges from the interactions between the individual, the task and the environment

Movements observed in a subjects with cognitive impairment represent behavior that emerges from the best mix of the systems remaining to participate. This means that what is observed is not just the result of the impairment itself, but of the efforts to compensate for the deficit and still be functional (Shumway- Cook and Wollacott, 2006).

Movement and action

Movement is often described within the context of accomplishing a particular action. As a result, motor control is usually studied in relation to specific actions or activities. Understanding the control of action implies understanding the motor output from the nervous system to the body's effector systems, or muscles. The body is characterized by a high number of muscles and joints, all of which must be controlled during the execution of coordinated, functional movement. This problem of coordinating many muscles and joints has been referred to as the degrees of freedom problem (Bernstein, 1967).

Movement and perception

Perception is essential to action, just as action is essential to perception. Perception is the integration of sensory impressions into psychologically meaningful information. It includes both peripheral sensory mechanisms and higher level processing that adds interpretation and meaning to incoming afferent information. Sensory/perceptual systems provide information about the state of

the body (for example, the position of the body in space) and features within the environment critical to the regulation of movement. Sensory/perceptual information is clearly integral to the ability to act effectively within an environment (Rosenbaum, 2009). Thus, understanding movement requires the study of systems controlling perception and the role of perception in determining our actions.

Movement and cognition

Since movement is not usually performed in the absence of intent, cognitive processes are essential to motor control. These processes broadly include attention, motivation, and emotional aspects of motor control that underlie the establishment of intents or goals. Motor control includes perception and action systems that are organized to achieve specific goals or intents. Thus, the study of motor control must include the study of cognitive processes as they relate to perception and action.

2.2.3 Perceptual-motor behavior in Down Syndrome

Perception, action, and cognition are key-factors in the production of movement, and must be considered together in the study of movement. As previously discussed, it is important to recognize that the motor system does not function in isolation (Shumway- Cook and Wollacott, 2006). Instead, perceptual processes interact with motor processes during action production, action correction, and action comprehension (e.g., Wilson and Knoblich, 2005; Shiffrar and Pinto, 2002). It is not yet known how the pathophysiology of DS is related to the development of perceptual-motor behavior. Nadel (2003) reported that differences in brain structure begin to emerge in the first few months of life in infants with DS. These differences include reduced volume in the frontal cortex, superior temporal gyrus, brainstem, cerebellum and hippocampus. While the motor consequences of volumetric differences have not been well established, it is reasonable to hypothesize that these differences may impact on the mechanisms involved in processing perceptual motor information (Virji-Babul et al, 2006). Children with DS show both motor and perceptual impairments that may influence the development and learning of various fundamental and complex actions. These influences have been widely reported over the years, but unfortunately not many findings have addressed the functional coupling of information and movement (Savelsbergh et al, 2000). However, from literature it emerges that the main problems in DS have been associated with three factors: perception and extraction of sensory information, execution of appropriate strategies (motor planning), and decision-making processes (Virji-Babul and Brown, 2004).

Perception and extraction of sensory information

Subjects with DS often exhibit significant perceptual problems. Auditory problems, often in association with ophthalmologic disorders such as cataracts, strabismus and nystagmus, and visual (Courage et al, 1994) and tactual impairments have been reported (Savelsbergh et al., 2000).

Evidence of impairment in the perceptual-motor coupling in DS comes from the studies of the tasks requiring anticipatory actions, such as obstacle avoidance during walking and object catching and/or manipulation.

Walking in the natural environment often involves anticipatory adaptations to either avoid or negotiate obstacles. While walking is an automatised task, walking with an obstacle involves more contributions from voluntary control and resembles more daily-life situations.

In a recent study (Virjii-Babul et al., 2004) the authors examined the movement strategies used by young children with DS in crossing obstacles: they found that children with DS were able to successfully extract information about obstacle height and appropriately match this information to their movement, but the visual information about the obstacle was not used consistently to modulate movements early in the gait cycle. Thus, visual information required to appropriately modulate their crossing action was correctly extracted, but while control children used this information in a pre-programmed fashion, children with DS used it in an online fashion.

Charlton et al. (2000) reported that children with DS had difficulty in properly adjusting both the spatial and temporal aspects of their grasp as a function of object size or task goal. They suggested that difficulties in the use of the perceived object properties in action planning may point to a dysfunction in relating information about limb position with respect to the environment and to task demands.

Motor planning processes

While Charlton et al (2000) evidenced differences in both the spatial and temporal aspects of planning in DS when performing motor tasks requiring anticipatory actions, some authors (Savelsbergh et al., 2000; Henderson et al., 1981) found differences mainly in the temporal aspects of planning. According to Henderson et al (1981) difficulties are present in two distinct temporal tasks: those in which a time criterion is applied and those in which a movement sequence has to be planned to coincide with an external event. The authors examined the two components of prediction, the spatial component and the timing component, in non retarded children and in retarded children with and without DS. They found that although the normal children were only 5 to 6 years old, their performance on a tracking task was very much superior to that of the much older retarded children. The performance of the normal children was coordinated in every respect,

extremely accurate and rhythmical, whereas that of the retarded children was inconsistent, inaccurate and rarely, if ever, rhythmical. DS children were impaired in using predictability in timing in order to control their movements by preprogrammed sequences. However, they were no less impaired than other retarded children in using spatial predictability. On the basis of these results, the authors concluded that a very subtle deficit in only one aspect of motor control, timing, can have far-reaching effects and may be responsible for the slowness typical of so many retarded children and especially of those with DS.

A study by Obhi et al. (2007) addressed the awareness of action in subjects with and without DS. In this work the authors asked the participants to look at a LED bar sequentially lighting, and to push a button they had in their hand triggered by the free will. They asked the participants to point at the position of the lit up LED at which the press had occurred. The results evidenced a judgment earlier in time than the button press response for the controls, attributed by the authors to the time at which the movement planning had occurred: previous study have linked this kind of bias to the neural processes associated with either movement planning per se or the establishment of an internal motor representation against which sensory feedback can be evaluated (Haggard and Eimer, 1999). DS subjects, instead, revealed a judgment later than the time in which the button press occurred: the authors concluded that DS performers were judging the temporal onset of their movements based on proprioceptive and visual feedback that resulted from the execution of the movement rather than on the planning process. Considering that young adults with DS judge the temporal occurrence of self-generated movements on response-associated feedback (late judgement) as opposed to pre-movement planning process (early judgement) (Obhi et al., 2007), their inability to form or maintain an internal model of goal-directed behaviour against which evaluating feedback seems to appear. Thus, it seems that people with DS cannot compare what they perceive with what they are expecting to perceive. These findings are consistent with the results obtained by Bunn et al (Bunn et al., 2007), who reported a greater difficulty to pantomime a movement rather than to concurrently imitate it for DS children. Indeed, these subjects encounter troubles in forming a stable representation of the to-be-performed action and demonstrate a higher dependence on direct visual information (Elliott et al., 2010).

During a reaching task, by looking at the differences in the relative proportions of time spent in the ballistic, preprogrammed phase and in the deceleration phase, it was found (Charlton et al, 1996) that children with DS spent a greater time in the deceleration than controls. Reaches from the control group were smooth during the deceleration time. That is, additional accelerations and decelerations or movement units following peak speed were rarely observed. In contrast, trajectories of the reaching movements of children with DS were extremely jerky and highly variable from trial

to trial. Some authors reported similar findings for adults with DS who exhibited very variable kinematic trajectories on consecutive trials on a simple, single-joint motor task (Latash and Corcos, 1991) and on a precision goal-directed aiming task (Elliott et al., 2010). The data for subjects with DS showed slowness, extended time in deceleration, and jerkiness of limb transport, consistent with the interpretation that subjects with DS are unable to generate an appropriate schema for reaching. Their reaching movements were spatially variable and inaccurate, and therefore were likely to require greater reliance on feedback guidance to correct spatial inaccuracies. The major reliance on feedback control may result in a fragmentation of movement into sub-movements, aimed at reducing the discrepancy between the position of the limb and the target by continuous corrections of the trajectory. Since control subjects relied mainly on feed-forward mechanism whereas subjects with DS used corrections in online-feedback mode, the assumption of the authors was that the performers with DS had problems with movement planning and feed-forward control (Elliott et al., 2010). As discussed in paragraph 2.2.1, these findings could partly explain the well documented clumsiness observed by all the authors studying DS movements: if DS performers can mainly rely on feedback control without a forward model of the movement they have to perform, the execution of the required task will be subjected to a continuous modulation by the longer and “more fragmented” feedback control. A diminished representation of the expected movement outcome would result in their aiming behaviour being very slow and inefficient.

Decision-making

On the other hand, it has also been argued that there are either no specific motor deficits associated with DS or that they are not really significant in comparison with the other deficits observed (Latash et al, 1996) whereas these problems are a reflection of an impaired decision-making process.

The information processing and the decision making requirements of a motor task, in fact, may influence an individual's ability to perform the task or the speed at which the task is performed. Some individuals may take more time to process information in the CNS and some may have more difficulty understanding the task requirements or following instructions (Sacks and Buckley, 2003). In this view, atypical patterns in persons with DS have been interpreted as adaptive and, in a sense, optimal for those individuals (Latash, 2007; Latash et al, 1996). As an example, the co-contraction or reversed patterns of muscular activation found by several studies (Aruin et al, 1996; Almeida et al, 1994; Karst and hasan, 1991) may be seen, in light of Latash's interpretation (Latash 1992), as a deliberate behavior resulting from a central nervous system that “realizes” its own limitations: in this view, subjects with DS optimize the probability of task achievement under changing conditions instead of optimizing accuracy and speed as controls do. Following this point of view, the

documented large kinematic and kinetic variability in actions by persons with DS (Kubo and Ulrich, 2006; Latash et al, 2002) may result as well from changes at the level of synergies that stabilize time profiles of potentially important action variables. Consider a simple motor task, e. g. reaching for or pointing at an object. The joints of the human arm are organized during such actions into synergies stabilizing the trajectory of the end point (e.g. Domkin et al, 2002). If a synergy is strong, it can compensate for any perturbations, both coming from intrinsic noise and from changes in the external conditions, by changing the individual joint involvement into the task. However, stability of an action comes at a price. For example, if a person suddenly sees an obstacle and tries to change the end point trajectory, the same synergy would act against such an avoidance maneuver. Indeed, when a steady-state performance turns into a quick action, multi-element synergies stabilizing important action variables are attenuated in anticipation of the action to make sure that the central nervous system does not have to fight its own synergies (Shim et al, 2005). So, on one hand, having strong synergies is beneficial for stability of performance. On the other hand, such synergies are undesirable if one wants to change performance quickly. Every-day actions consist of components, steady-state and quickly changing. If a person's ability to form and destroy synergies is impaired, like in DS, the central nervous system may opt for another strategy that does not involve strong synergies or quick changes in synergies. One predictable consequence of this strategy is high movement variability documented for persons with DS (reviewed in Latash, 2000). If components of the apparent "clumsiness" in persons with DS are indeed reflections of an adaptive strategy, they may be expected to be modifiable with proper practice.

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Chapter 3

Perceptual-motor integration and motor control in Down Syndrome

Literature review of the previous chapters as shown that, while specific sensory, motor, cognitive and perceptual impairments have been widely reported in DS, the way these localized deficits impact on perceptual-motor processing and function remains unclear. Traditional movement analysis as focused mainly on biomechanical aspects such as muscular hypotonia and ligament laxity. Notwithstanding the importance of these aspects in the development of subjects with DS, more recent literature is focusing on the use of motion analysis tools for the assessment of hypothesis regarding how motor control acts and how motor plans are formed in DS. To make this possible, “functional” tasks, that involve multi-joints movements and conscious cognitive resources, need to be introduced in the assessment of persons with DS. Studies since now indicate that the motor impairment documented in DS might be especially related to perception and extraction of sensory information, motor programming, or decision-making processes.

The present PhD Thesis is divided in two parts. In the first part of the study, reported in this chapter, we investigated perceptual-motor integration in a group of adults with DS and in age-matched group of controls, during the execution of two functional tasks. The aims of the study in this first part were:

- to define and apply an experimental set up for the quantitative evaluation of the different aspects of motor control and execution during a functional task in adult subjects with DS;
- starting from the motor outputs obtained by means of quantitative motion analysis, to point out some hypothesis about the cognitive functions underlying these motor outputs;

In this chapter two studies will be presented: the first one refers to the study of obstacle avoidance during walking in DS. The study’s purpose is to shed light on the mechanisms underlying integration of perceptual information, mainly visual information, into motor programs in DS and on anticipatory strategies that are employed by these subjects when challenged with a highly cognitive-demanding task such as obstacle avoidance. The second study is more focused on the motor control strategies employed by subjects with DS when performing an upper limb movement with and without obstacle avoidance, with particular attention to the feed-forward and feed-back mechanisms

that are at the basis of motor control. The results of this first part of the study have been the starting point for a more in-depth analysis on certain aspects and hypothesis drawn by the first set of experiments, which will be presented in the second part of the study (chapters 4-6).

3.1 Perceptual-motor integration during walking with obstacle avoidance in adults with Down Syndrome

When performing daily activities it often happens that our limbs have to either avoid or negotiate obstacles that are placed somewhere on the trajectory of our movements. This occurs both for the lower limbs (i.e. avoiding an obstacle during walking) and for the upper limbs (i.e. avoiding an obstacle during a reaching movement). The ability to avoid obstacles automatically obviously involves mechanisms in the brain that represent the properties of the obstacle (size, orientation, movement, etc.) and its location relative to the body and update these representations as the body moves (Pearson and Gramlich, 2010), together with the ability to make adaptive changes to the movement's trajectory (Virji-Babul et al, 2006). In order to study these aspects, in literature a growing body of research analyzes walking with obstacle avoidance in healthy subjects. Very few studies, instead, analyze walking with obstacle avoidance in subjects with DS. The next paragraph will address the study of this particular task with particular attention to perceptual-motor integration and clearing strategies in DS.

3.1.1 Introduction

Walking is a motor task characterized by highly flexible adaptation to different situations. As we walk we often must avoid obstacles either by navigating around them or stepping over them. The study of the anticipatory adaptations adopted to either avoid or negotiate obstacles is important for the assessment of the perceptual-motor integration ability of subjects (Virji-Babul et al, 2006). Knowledge of the mechanics of the locomotor system and of the control strategies adopted during this activity is helpful for a better understanding and identification of the risk factors for tripping, which is important in the prevention of falls (Chen and Lu, 2006).

Subjects with DS often exhibit both motor and perceptual difficulties that impact on motor development and on everyday life. Reduced step length and velocity are well-known features of DS walking patterns, which are related to the sense of instability perceived by DS (Rigoldi et al, 2010). A tendency towards flexion of the lower limb joints during plain walking is also well documented in DS, together with a predominance of movement in the frontal and horizontal planes (Rigoldi et al, 2010). Deficits in the perceptual-motor processing and function are also documented, but remain unclear (Virji-Babul and Brown, 2004). Anecdotal evidence suggests that individuals with DS often

have trouble avoiding obstacles, leading to increased frequency of trips and falling. Falls because of obstacles perturbing individual gait patterns are a leading cause of morbidity (Galli et al, 2013). It is thus important to understand if the deficits in avoidance strategies are related to difficulties in the visual perception of the object, in the execution of appropriate strategies, or are associated with attention-related processes (Virji-Babul and Bown, 2004).

Several studies have described the kinematics and kinetics of obstacle crossing in healthy adults (Weerdensteyn et al, 2005; Begg et al, 1998; Chen et al, 1991) and the role of vision during obstacle avoidance tasks (Patla, 1997).

It is known from the literature (Patla and Prentice, 1995) that in healthy subjects limb elevation for obstacle avoidance is achieved primarily by flexing the three joints of the swing limb, although the proximal joints, hip and knee, are more flexed than the ankle joint. Thus, in healthy subjects, obstacle avoidance, as well as plane walking, is prevalently directed in an antero-posterior direction, with a flex-extension joint movement.

Studies (Begg et al, 1998, Sparrow et al, 1996) have shown that the kinematic and kinetic characteristics of the leading limb (i.e. the limb that crosses the obstacle first) are different from those of the trailing limb (i.e. the support limb during the leading limb clearance) in a number of respects, highlighting different crossing strategies between them. Indeed, whereas the trailing limb moves upward as it crosses the obstacle, the leading limb begins its descent while going over the obstacle. Thus, the center of mass moves toward the supporting limb in the case of the trailing limb, while it is moving away from the supporting limb in the case of the leading limb. This puts the leading limb in a more threatening situation compared to the trailing limb (Patla et al, 1996). Also, the trailing limb is lifted higher than the leading limb, and the trailing foot pattern is approximately symmetrical and narrow, whereas the leading foot rises steeply before a gradual descent, making the profile skewed (Begg et al, 1998).

Different obstacle heights have been also taken into account, from “subtle” ground-level obstacles to higher obstacles (Begg et al, 1998; Chen et al, 1991). Chou et al (1997) found that toe clearance (i.e. the distance between the foot and the obstacle in the vertical direction) increased in presence of an obstacle compared to plane walking, but remained quite constant over a wide range of obstacle’s heights. Another parameter to be strictly controlled by the central nervous system during an obstacle avoidance task is the position of the feet respect to the obstacle in antero-posterior direction. Chou and Draganich (1998), in fact, found that this is a highly unvaried parameter with varying conditions (i.e. increasing obstacle height), because a closer than necessary proximity to the obstacle leads to limitations in the shank’s kinematics.

Chou et al (1997) noted that obstacle crossing was a more energy-consuming strategy than plane walking; in fact, additional energy was generated to increase foot-obstacle clearance and ensure safe progression of the foot over the obstacle.

Finally, Chen et al (1991) and Weerdensteyn et al (2005) described the different clearing strategies adopted by healthy younger and older adults. They found a “step-shortening” strategy in older adults when challenged by the presence of an obstacle, contrary to the “conservatism” strategy observed in younger adults (who maintained most of their walking parameters unvaried), and interpreted the elderly’ behavior as a safety strategy or as a difficulty in interpreting the sensory input given by the obstacle.

Although there are numerous studies dealing with obstacle avoidance in healthy subjects, only a few studies have addressed obstacle avoidance in pathological conditions. Of these, to the best of our knowledge, only three have focused on obstacle avoidance in subjects with DS (Smith and Ulrich, 2008; Wu et al, 2008; Virji-Babul et al, 2004). Another study (Galli et al, 2013) has addressed a similar topic: the step ascent and descent, to reproduce the conditions of climbing stairs in DS and to understand how to target suitable exercises to improve this important daily ability.

Virji-Babul and Brown (2004) examined the movement strategies and the role of vision in five children with DS (range: 5-6 years) and of six typically developing children (age range: 4-7 years) as they crossed obstacles of two different heights: a ”subtle” obstacle that was placed at a minimal height from the floor and an “obvious” obstacle that was placed at a much higher height off the floor. They focused on the step length and toe clearance parameters. Children with DS showed a robust scaling of toe elevation to obstacle height, implying that they were able to successfully extract information about obstacle height and appropriately match this information to their movements. However, visual information about the obstacle was not used consistently to modulate movements early in the gait cycle and, as a result, the children with DS maintained their “typical” gait pattern and waited until they reached the obstacle to extract the visual information needed to appropriately modulate their actions, and thus produced less smooth trajectories. Smith and Ulrich (2008) evaluated the adoption of stabilizing strategies in older adults with DS (35 to 62 years old) during obstacle avoidance, to determine whether the gait patterns of adults with DS showed early changes related to age, obesity and a sedentary lifestyle. They focused on walking speed, stride length, cadence and step width parameters and concluded that the combined effects of ligament laxity, low tone, obesity, inactivity and physiological decrements associated with ageing led to stability-enhancing adaptations at a younger chronological age than normally developed adults. Finally, Wu et al (2008) analyzed the same parameters as Smith and Ulrich (2008) to evaluate different treadmill interventions to improve obstacle avoidance ability in subjects with DS.

It thus emerges that obstacle avoidance in healthy subjects has received considerable attention in the literature, while little work has been done on the characterization of this task in DS. Furthermore, not only are DS subjects the focus of fewer studies on this topic, they have also been evaluated using only a limited number of spatiotemporal parameters, whereas lower limb evaluation in healthy subjects has involved a larger number of spatiotemporal, kinematic and kinetic parameters. Finally, there is a lack of studies on obstacle avoidance strategies in young adults with DS, although this kind of task can evidence important information about the perceptual-motor abilities of these subjects.

Starting from these observations, this study was developed to deeper analyze obstacle avoidance strategies in normally developed young adults (N) and in young adults with DS, with attention to both the lower and upper limbs, at different levels of obstacle heights, by implementing the parameters that were found to be more significant and characterizing in literature in the application on healthy subjects, and with particular attention to the following topics: 1) are there different strategies for clearing the obstacle between N and DS, that lead to an increased falling risk in DS? 2) How is the walking pattern modified by obstacle perception?

3.1.2 Methods

Subjects

31 subjects with DS (mean age \pm standard deviation: 22.6 \pm 6.8 years; 58.8% males, 45.2% females) and 22 age-matched normally developed subjects (N) (mean age \pm standard deviation: 24.9 \pm 2.4 years; 36.4 % males, 63.6% females) were evaluated. Inclusion criteria and more details can be found in appendix I.I and I.II.

Acquisition

The obstacle was a thin wooden stick of approximately two meters length, that was supported by two cones placed laterally to the walkway.

To allow studying the effect of the obstacle's presence on locomotion and on the visuo-motor integration, two different obstacle heights were used in the study:

- Ground level obstacle: the wooden stick laid on the ground, between two cones. The cones' function was to increase the perception of the obstacle's presence, although the obstacle was just a "visual obstacle" with no height;
- High level obstacle: the wooden stick was lifted at an height of approximately 10% of the subject's height.

The subjects walked along a walkway in three conditions: plain walking without obstacle (WLK, figure 3.1.1 on the left), walking with obstacle at ground level (OBST_LOW, figure 3.1.1 in the centre), walking with obstacle at a higher level (10% of the subject's height, OBST_HIGH, figure 3.1.1 on the right).

The subjects performed walking in each condition at least three times.

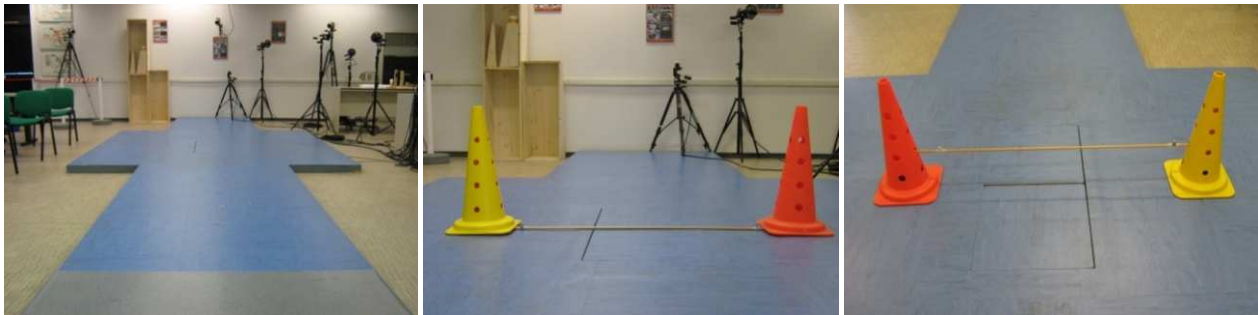


Fig. 3.1.1: Conditions: (on the left) plain walking without obstacle; (in the centre) walking with ground level obstacle; (on the right) walking with high level obstacle

Instrumentation

The tasks were acquired using quantitative movement analysis, composed of an optoelectronic system (Elite2002, BTS) with eight infrared cameras. More details about the laboratories and the instrumentation can be found in appendix II.

Markers were placed on the body according to a modified Davis' protocol (Davis et al, 1991, see Appendix III) which comprehended markers placement on the upper limbs, and two markers were put respectively at the two ends of the obstacle to define the obstacle position relative to the subject during the movement (figure 3.1.2). This protocol allows the reconstruction of the centers of instantaneous rotation (CIR) of the joints, from which it is possible to compute parameters related to joint movements in the three planes (i.e. ab-adduction, intra-extrarotation and flex-extension movements).

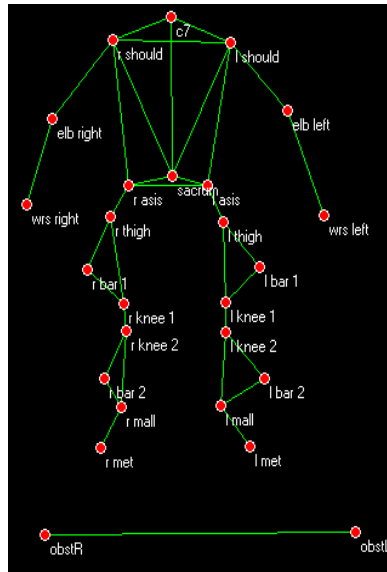


Figure 3.1.2: protocol for markers positioning

Data elaboration

The data acquired with the optoelectronic system, related to the kinematics of movement, consist in the three-dimensional coordinates of the centroids of the markers applied on the subject. The spatio-temporal evolution of these markers' coordinates were first of all labeled using Tracklab Software (BTS, Italy), so that each centroid was assigned the correct label from the protocol of figure 3.2 (see Appendix IV for more details).

The trials were then processed using the following software:

- ELITE-Clinic (BTS, IT, see Appendix IV): the standard parameters of gait analysis, generally used in literature (Davis et al, 1991), were calculated with this software, to evaluate the kinematics at the pelvis, hip, knee and ankle joints. More details about Davis' procedure can be found in Appendix III.
- SMART-Analyzer (BTS, IT, see Appendix IV): a dedicated protocol was developed to compute specific parameters that are important for the evaluation of the obstacle avoidance task. The acquired trajectories were interpolated and low-pass filtered with a cut-off frequency of 10Hz before starting with the calculation of the parameters.

Parameters

The limb that cleared the obstacle first was referred to as *leading limb (L)*, while the support limb during the leading limb clearance was referred to as *trailing limb (T)*. In figure 3.1.3 an example is reported, in which the left foot is the trailing limb and the right foot is the leading limb.

The movement was divided in two phases: the *approaching phase* (before the first foot contact of the T limb) and the *crossing phase* (after the first foot contact of the T limb, during obstacle avoidance).

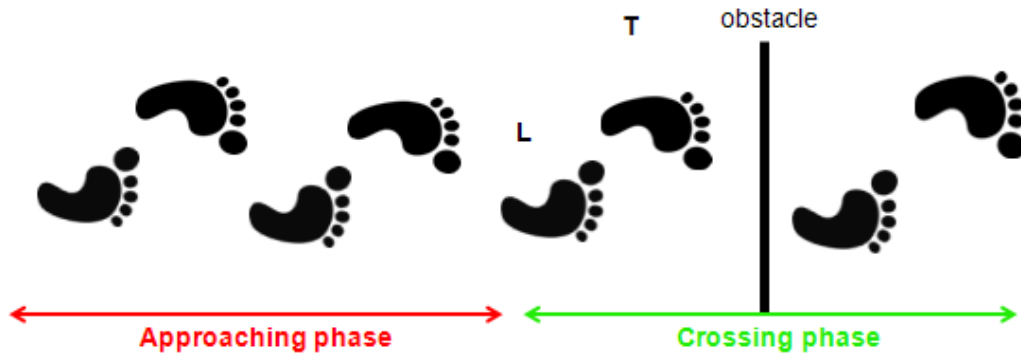


Figure 3.1.3: subdivision in the approaching and crossing phases for an hypothetical subject who steps over the obstacle with his right limb first (leading limb) and then with his left limb (trailing limb)

The *swing phase* was defined as the phase during which the foot was clearing the obstacle (from toe-off to second ground contact).

From the markers' coordinates some spatiotemporal parameters were computed to describe the movement strategy of the subjects. The parameters were used to A) describe relative distances between the feet and movement velocities and B) describe relative distances between the feet and the obstacle and C) to describe the kinematics of the joints' movements.

Parameters A:

- Step length [m]: distance (in antero-posterior direction, AP) between two consecutive heels contacts (both feet before the obstacle: SL_1 , astride the obstacle: SL_2 , both feet after the obstacle: SL_3 , for WLK: mean of three consecutive step lengths). Computed as the AP distance between the markers on the 5th metatarsi at initial contact. It measures the presence of step adaptations (i.e. step shortening/lengthening strategy in presence of an obstacle) (Weerdenstein et al, 2005; Chen et al, 1991), see figure 3.1.4.
- Mean velocity of approach: mean velocity of the marker on the sacrum during the approaching phase (before the first initial contact of the trailing limb) in AP direction ($V_{mean\ app.X}$). It is a measure of “conservatism” of the movement (Chen et al, 1991)

- Mean velocity during obstacle clearance: mean velocity of the marker on the sacrum during the avoidance phase (between the first and second trailing limb initial contact) in AP direction ($V_{mean\ obst.X}$).

Parameters B:

- Foot-obstacle distance [mm]: distance, in antero-posterior direction, between the foot (marker on the 5th metatarsus) and the obstacle, before obstacle clearance (for the trailing limb: T_{FO} , for the leading limb: L_{FO}), see figure 3. 1.4.
- Obstacle-foot distance [mm]: distance, in antero-posterior direction, between the obstacle and the foot (marker on the 5th metatarsus), after obstacle clearance (for the trailing limb: T_{OF} , for the leading limb: L_{OF}), see figure 3. 1.4.
- Max height [m]: maximum elevation of the foot from the obstacle during the swing phase of obstacle avoidance (for the trailing limb: $T_{Max\ height}$, for the leading limb: $L_{Max\ height}$, for WLK : mean of three consecutive maximum elevations). Computed as the difference between the maximum vertical height reached by the markers on the 5th metatarsi and the obstacle's height see figure 3. 1.4. It measures the ability of the subjects to estimate obstacle height and the "safety" margin adopted by the subjects during crossing (Chou et al, 1997).
- Crossing height [m]: elevation of the foot (marker on the 5th metatarsus) from the obstacle at the crossing instant (for the trailing limb: $T_{height\ cross}$, for the leading limb: $L_{height\ cross}$). Combined with the "Max height" parameter gives insight on the lifting strategy of the foot during obstacle clearance (i.e. the foot either crosses the obstacle at its maximum elevation, or is lifted to its maximum height and then crosses the obstacle or crosses the obstacle before its maximum elevation), see figure 3. 1.4 in the next page.

Parameters C:

Starting from the coordinates of the markers placed according to Davis' protocol the maximum (Max), the minimum (Min) and the range of motion (ROM) angular values in the three planes of movement for the pelvis (P), hip (H), knee (K) and ankle (A) joints during the swing phase were calculated for the L and T limb. For a detailed description of the angles definition and calculation see Davis et al (1991).

Max, Min and ROM values during the swing phase were computed for the trunk flexion angle, defined as the angle between the vector connecting the sacrum and c7 markers and the vector in the antero-posterior direction of the laboratory's reference system (figure 3. 1.5, next page).

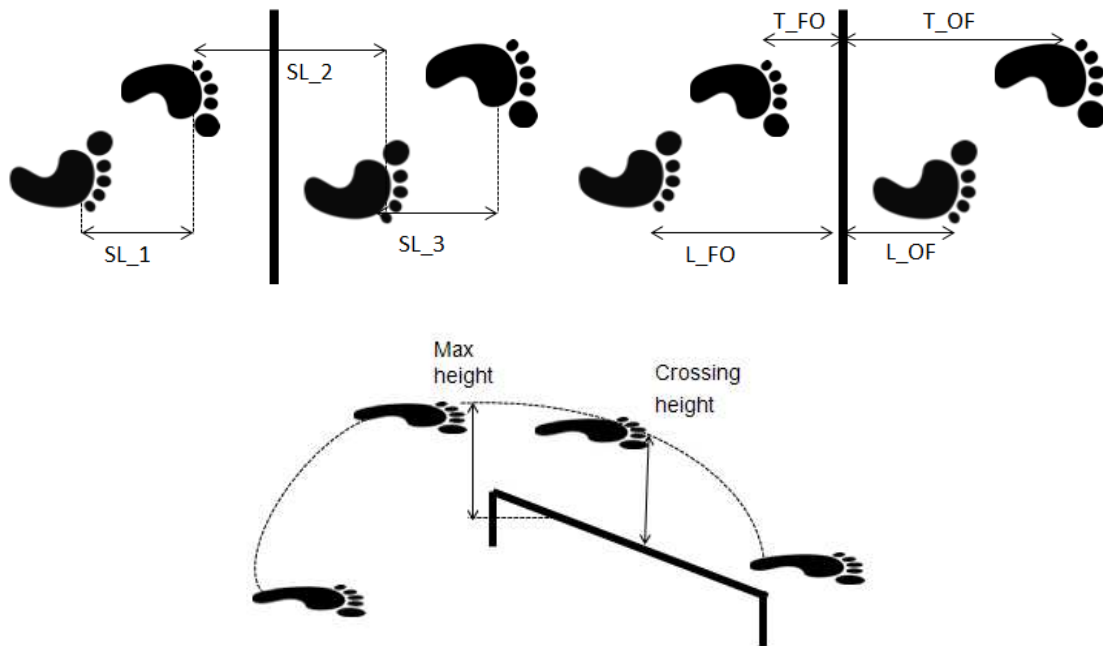


Figure 3. 1.4: illustration of some of the parameters for the trailing and leading limb. Up on the left: step length parameters; up on the right: foot-obstacle distance parameters in the AP direction. Down: foot-obstacle distance parameters in the vertical direction.

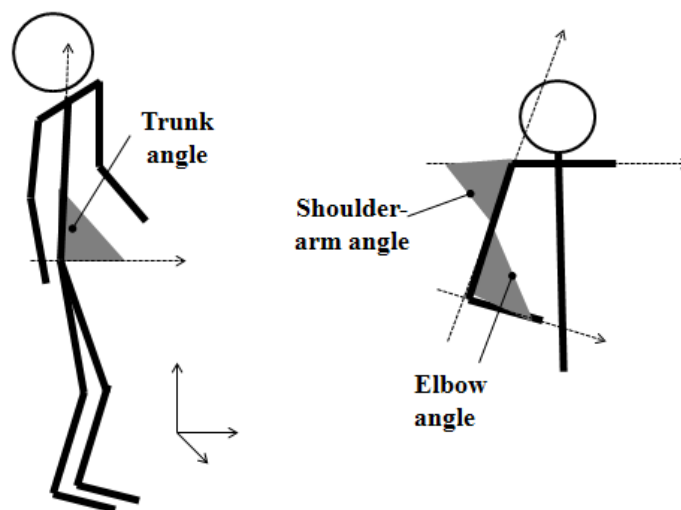


Figure 3. 1.5: on the left: trunk angle, on the right: shoulder-arm angle and elbow angle

Parameters D:

To evaluate upper limb kinematics the maximum (Max), the minimum (Min) and the range of motion (ROM) angular values of the shoulder-arm angle (S-A) and of the elbow angle (E) (figure 3.1.5) during the swing phase were calculated for the limb ipsi-lateral to the L limb (leading arm) and for the contro-lateral limb (trailing arm).

For each side, the S-A angle was defined as the angle between the vector connecting the markers on the shoulders and the vector connecting the elbow and shoulder markers. The E angle was defined as the angle between the vector connecting the elbow and shoulder markers and the vector connecting the elbow and wrist markers. We hypothesized that, if the presence of the obstacle challenged the subjects' stability, the subjects would react by lifting their arms (decreasing S-A angles at both sides) to stabilize their centre of mass and by flexing their elbows (decreasing E angles at both sides) to prepare for possible falls, as described by Marigold et al (2002) in a study describing gait perturbations in healthy adults.

Statistical analysis

Significance level was set at p-value=0.05. The distribution of the data was verified using the Kolmogorov-Smirnov test of normality. We used a 3 (conditions) x 2 (groups) x 2 (limbs) mixed ANOVA to analyze the presence of statistically significant differences (p-value < 0.05). Post hoc analysis, with Bonferroni's correction for multiple comparisons, was then used for further investigation.

3.1.3 Results

All the subjects were able to successfully complete the tasks. For the sake of brevity, only the statistically significant results most meaningful for the present analysis are presented.

In table 3.1.1 the results of the parameters A and B (median, 25th and 75th percentiles values) are presented for the WLK, OBST_LOW and OBST_HIGH conditions.

	DS			N			DS vs N
	WLK	OBST_LOW	OBST_HIGH	WLK	OBST_LOW	OBST_HIGH	
<i>Parameters A</i>							
SL_1 [m]	0.43 (0.40,0.50)	0.40 (0.35,0.50)	0.25 (0.10,0.40) [#]	0.69 (0.63,0.71)	0.70 (0.60,0.70)	0.60 (0.60,0.70)	1,2,3
SL_2 [m]	0.43 (0.40,0.50)	0.50 (0.40,0.60)	0.50 (0.40,0.73)	0.69 (0.63,0.71)	0.70 (0.60,0.70)	0.70 (0.60,0.70)	1,2,3
SL_3 [m]	0.43 (0.40,0.50)	0.40 (0.38,0.50)	0.30 (0.20,0.30) [#]	0.69 (0.63,0.71)	0.70 (0.60,0.70)	0.70 (0.60,0.70)	1,2,3
Vmean app.X [m/s]	0.70 (0.60,0.80)	0.70 (0.60,0.80)	0.50 (0.20,0.60) [#]	1.20 (1.10,1.30)	1.20 (1.10,1.30)	1.10 (1.00,1.20)	1,2,3
Vmean obst.X [m/s]	0.70 (0.60,0.80)	0.70 (0.50,0.90)	0.40 (0.23,0.50) [#]	1.20 (1.10,1.30)	1.30 (1.10,1.30)	1.00 (0.90,1.10) [#]	1,2,3

<i>Parameters B</i>							
L_FO [m]	--	0.70 (0.50,0.80)	0.50 (0.30,0.70) [#]	--	0.90 (0.88,1.00)	0.90 (0.90,1.10)	2,3
L_OF [m]	--	0.30 (0.20,0.33)	0.20 (0.23,0.30)	--	0.40 (0.30,0.40)	0.40 (0.30,0.40)	2,3
T_FO [m]	--	0.20 (0.20,0.30)	0.30 (0.20,0.40)	--	0.30 (0.30,0.30)	0.30 (0.20,0.30)	
T_OF [m]	--	0.70 (0.60,0.75)	0.50 (0.40,0.60)	--	1.00 (1.00,1.10)	1.00 (0.90,1.10)	2, 3
T_Max height [m]	--	0.20 (0.20,0.20)	0.34 (0.24,0.34) [#]	--	0.30 (0.20,0.30)	0.39 (0.29,0.39) [#]	
L_Max height [m]	--	0.20 (0.19,0.20)	0.24 (0.24,0.29) [#]	--	0.20 (0.20,0.20)	0.20 (0.19,0.29) [#]	
T_height cross [m]	--	0.20 (0.18,0.20)	0.30 (0.20,0.40) [#]	--	0.20 (0.20,0.20)	0.30 (0.30,0.40) [#]	
L_height cross [m]	--	0.10 (0.10,0.11)	0.20 (0.20,0.30) [#]	--	0.10 (0.10,0.11)	0.10 (0.10,0.20) [#]	2

Table 3.1.1: median (25th percentile, 75th percentile) values of the parameters. *=p<0.05 WLK vs OBST_LOW; #=p<0.05 OBST_LOW vs OBST_HIGH; 1= p<0.05 DS_WLK vs N_WLK; 2= p<0.05 DS_LOW vs N_LOW; 3= p<0.05 DS_HIGH vs N_HIGH

Reduced and more variable SL_1, SL_2 and SL_3 were found in all conditions for DS compared to N. In particular, SL_1 and SL_3 showed that DS had shorter and more variable step lengths particularly in the OBST_HIGH condition, when variability increased for DS (wider range between the 25th and 75th percentile), with a median value of approximately 50% the value of N. Thus, positioning of the feet to prepare to obstacle avoidance varied among DS, with a tendency to shorten step length (and thus to put their feet almost parallel in medio-lateral direction). After obstacle crossing, the same tendency was maintained. SL_2 was also reduced for DS compared to N, but the presence of the physical barrier of the obstacle in OBST_HIGH condition constrained the subjects with DS to maintain a longer step length than for SL_1 and SL_2 (even though shorter than N). No variation was instead found for N, who maintained the step length of unobstructed gait in all conditions.

Mean forward approach velocity was lower for DS than for N in all conditions. The velocity further decreased in OBST_HIGH (reaching values of approximately 50% than those of N subjects) for DS. N subjects, on contrary, maintained an unvaried velocity across all the conditions.

Mean forward velocity during obstacle avoidance decreased for both groups in OBST_HIGH but, as seen for the approach phase, the values were consistently lower for DS than for N. Variability (expressed by the percentiles range) was higher across all conditions for DS compared to N.

In the OBST_LOW condition L_FO was lower (i.e. foot closer to the obstacle) for DS compared to N. DS further decreased L_FO distance in the OBST_HIGH condition. No change was found across conditions for N subjects. After clearing the obstacle with the L foot, DS landed at a closer distance from the obstacle (L_OF) compared to N in OBST_LOW and OBST_HIGH conditions.

T_FO distance was similar between N and DS, so both groups selected a similar distance from the obstacle in their first initial contact with the T limb. However, while N landed further with their T limb after the obstacle (T_OF), DS landed closer to the obstacle in both OBST_LOW and OBST_HIGH conditions.

Analysis of the max height parameter showed that DS had similar excursions of the limbs compared to N in the OBST_LOW condition, bilaterally. In the OBST_HIGH condition the maximum foot elevation from the obstacle increased in both groups for the T and L limbs, with similar values across groups. In both groups, during both OBST_LOW and OBST_HIGH conditions, the L limb was lifted lower than the T limb.

Crossing height for the L limb (L_Height_cross parameter) was similar across groups for the OBST_LOW condition. The values increased in the OBST_HIGH condition for both groups, with a higher value for DS respect to N. In all conditions the values at crossing were lower than the maximum height values, so the L foot crossed the obstacle before or after the peak of maximum height.

Crossing height for the T limb (T_Height_cross parameter) was similar to the maximum height (T_Max_cross parameter) for DS and N, with an increase in the OBST_HIGH condition in both groups. Thus, the instant of obstacle crossing for the T limb occurred nearby the instant of maximum foot elevation.

To clarify the movement of the feet in the sagittal plane, figure 3. 1.6 shows an example of the patterns described for the T and L feet in the sagittal plane for a N subject (code 1584) and for a subject with DS (code: 5647) in the OBST_HIGH condition; the instant of obstacle crossing is defined by the square, while the instant of maximum vertical height is defined by the circle.

From figure 3.1.6 it is clearly shown that the clearing strategies were similar across groups, and that L and T limb had different patterns. The L limb had a peak of excursion anticipated respect to the crossing event: the subjects prepared to the crossing by lifting their limb higher, and then passed over the obstacle while decreasing foot height. L foot, instead, raised steeply before a gradual descent, making the profile skewed. The maximum height and crossing instants were almost

superimposed. The T limb was always lifted higher than the L limb. T limb passed over the obstacle approximately at its highest excursion and the T foot pattern was approximately symmetrical and narrow for both groups. This behavior was common to all of the subjects.

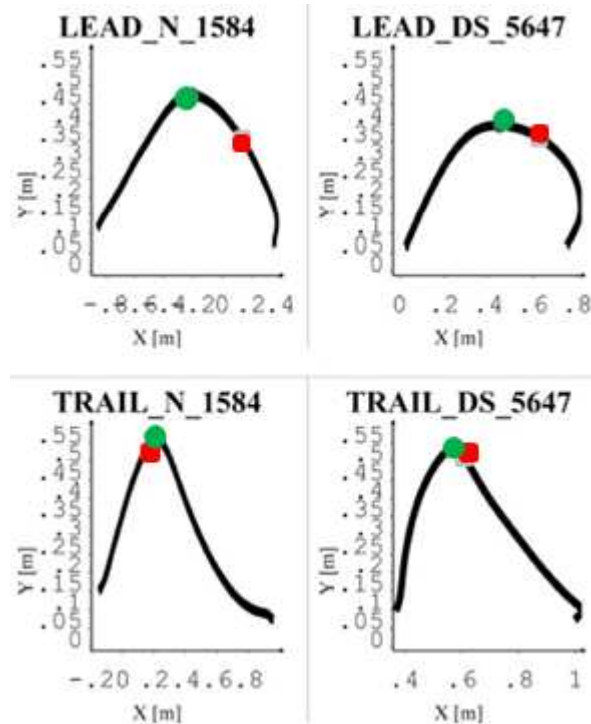


Figure 3.1.6: example of the patterns described by the T and L feet of a N subject (code: 1584) and of a subject with DS (code: 5647) in the sagittal plane during OBST_HIGH condition. Red square= crossing instant. Green circle= instant of maxim height

In table 3.1.2 the results of the kinematic parameters (parameters C) for the L limb (median, 25th and 75th percentiles values) are presented for the WLK and OBST_HIGH conditions. Kinematic parameters for the OBST_LOW condition are not presented since no substantial difference was found between this condition and plain walking.

	DS		N		DS vs N
Kinematic parameters					
	WLK	OBST_HIGH	WLK	OBST_HIGH	
<i>Trunk flexion [°]</i>					
Max	84.23 (80.46,84.59)	84.86 (84.01,87.63)	87.51 (85.43,89.21)	87.74 (84.93,89.50)	1,2
Min	80.53 (77.19,82.05)	76.06 (73.15,77.91) #	83.7 (82.66,85.83)	80.53 (77.90,83.31) #	1,2
<i>Pelvic tilt [°]</i>					

Max	16.08 (13.57,19.82)	14.35 (12.62,17.52)	7.77 (6.68,10.76)	10.42 (7.26,11.65)	1, 2
Min	13.57 (9.93,15.60)	3.96 (-1.02,7.09) [#]	5.72 (4.74,8.44)	1.81 (0.37, 5.80)	1
<i>Pelvic obliquity [°]</i>					
Max	1.92 (0.94,3.21)	12.79 (9.94,15.14) [#]	2.30 (1.53,2.96)	8.41 (5.44,9.66) [#]	1,2
Min	-2.73 (-4.49,-1.60)	1.25 (-0.03, 4.26) [#]	-4.26 (-5.44,-3.84)	-1.76 (-3.50,-0.61) [#]	2
<i>Pelvic rotation [°]</i>					
Max	8.51 (6.02,9.27)	15.84 (12.32,30.50) [#]	7.22 (5.08,8.68)	13.92 (10.59,20.16) [#]	
Min	-7.61 (-8.59,-5.98)	-3.97 (-10.03,-1.82)	-5.80 (-7.05,-4.92)	-8.77 (-10.58,-3.53)	
<i>Hip flex extension [°]</i>					
Max	36.41 (26.85,43.33)	79.33 (74.96,86.60) [#]	27.58 (23.95,30.01)	66.82 (64.52,71.40) [#]	1, 2
Min	1.65 (-0.79,10.38)	5.60 (-0.46,9.36)	-4.73 (-6.89,-0.86)	-3.25 (-4.96, -0.17)	1, 2
<i>Hip ab-adduction [°]</i>					
Max	-2.73 (-3.74,-0.19)	-5.65 (-7.720,-2.11)	-1.67 (-3.78,1.04)	-0.84 (-3.95,2.89)	
Min	-10.60 (-11.64,-8.09)	-14.87 (-18.78,-11.82) [#]	-9.29 (-9.89,-8.49)	-9.91 (-13.44,-8.37)	2
<i>Hip rotation [°]</i>					
Max	15.57 (6.71,23.33)	20.79 (14.93,25.47)	3.30 (0.84,9.10)	9.08 (3.41,15.64)	1,2
Min	4.57 (-3.93,11.73)	-2.60 (-4.93,11.73)	-4.96 (-9.95,-1.48)	-6.62 (-12.92,0.10)	1, 2
<i>Knee flex-extension [°]</i>					
Max	47.17 (39.41,52.36)	88.54 (85.47,88.97) [#]	53.66 (50.96,57.58)	88.73 (88.42,89.06) [#]	1
Min	5.87 (0.68,10.97)	13.72 (7.50,18.91) [#]	-0.34 (-2.47,4.49)	6.88 (4.41,9.97) [#]	1, 2
<i>Ankle dorsi-plantaflexion [°]</i>					

Max	4.32 (1.04,8.74)	9.27 (8.30,12.81) #	3.69 (-2.78,5.30)	9.23 (6.28,14.59) #	
Min	-6.45 (-10.39,-2.45)	-27.03 (-31.09,-22.08) #	-13.31 (-15.75,-7.34)	-21.95 (-25.30,-8.86) #	2

Table 3.1.2: median (25th percentile, 75th percentile) values of the leading limb parameters. #= $p < 0.05$ WLK vs OBST_HIGH; 1= $p < 0.05$ DS_WLK vs N_WLK; 2= $p < 0.05$ DS_OBST_HIGH vs N_OBST_HIGH

At the trunk, DS were more flexed than N in both conditions. DS had a more anterior pelvic tilt than N. The decrease in the pelvic tilt minimum value in DS_OBST_HIGH determined an increased ROM of the pelvis in the sagittal plane compared to the WLK condition. Pelvic obliquity and pelvic rotation increased in both groups in the OBST_HIGH condition, with similar values of rotation but with higher values of obliquity for DS than for N.

The hip joint was more flexed in OBST_HIGH for both groups, due to the need to avoid the obstacle by lifting the limb up; anyway, DS were more flexed than N in both WLK and OBST_HIGH conditions, with patterns shifted towards flexion throughout the crossing.

The minimum of hip abduction was lower in OBST_HIGH respect to WLK for DS, with DS being more abducted than N. Hip intra-rotation was higher for DS in both conditions respect to N.

At the knee joint, DS were more flexed than N in WLK, but both groups increased their flexion values in OBST_HIGH, approaching similar values of the maximum flexion. However, during OBST_HIGH the minimum values were higher for DS, resulting in reduced ROMs compared to N.

At the ankle joint, the maximum dorsiflexion increased for both groups in the OBST_HIGH condition, with similar values. The minimum plantarflexion values, instead, were lower for DS in OBST_HIGH.

In table 3.1.3 the results of the kinematic parameters (parameters C) *for the T limb* (median, 25th and 75th percentiles values) are presented for the WLK and OBST_HIGH conditions. Kinematic parameters for the OBST_LOW condition are not presented since no substantial difference was found between this condition and plain walking.

	DS		N		DS vs N
Kinematic parameters					
	WLK	OBST_HIGH	WLK	OBST_HIGH	
<i>Trunk flexion [°]</i>					

Max	99.85 (95.78,103.78)	85.20 (78.30,85.90) [#]	95.30 (92.70,103.90)	86.80 (84.35,89.30) [#]	2
Min	94.25 (90.78,98.90)	66.50 (61.20,73.80) [#]	88.60 (84.30,91.00)	78.40 (75.85,81.90) [#]	1,2
<i>Pelvic tilt [°]</i>					
Max	16.08 (13.57,19.08)	16.93 (16.01,21.3)	8.74 (7.21,10.72)	9.77 (7.88,14.29)	1, 2
Min	13.48 (11.22,14.98)	3.33 (-3.82,5.84) [#]	6.35 (3.93,7.35)	2.60 (-0.63,4.19) [#]	1
<i>Pelvic obliquity [°]</i>					
Max	4.64 (2.77,4.85)	13.05 (9.79,14.60) [#]	4.81 (3.49,5.77)	8.48 (5.64,9.74) [#]	2
Min	-3.36 (-5.21,-2.69)	-1.28 (-2.07, 0.25)	-4.64 (-5.61,-3.90)	-2.76 (-4.00,-1.45)	
<i>Pelvic rotation [°]</i>					
Max	8.51 (6.02,9.27)	15.84 (12.32,30.50) [#]	7.22 (5.08,8.68)	13.92 (10.59,20.16) [#]	
Min	-7.61 (-8.59,-5.98)	-3.97 (-10.03,-1.82)	-5.80 (-7.05,-4.92)	-8.77 (-10.58,-3.53)	
<i>Hip flex extension [°]</i>					
Max	38.79 (27.93,41.26)	81.82 (76.41,83.35) [#]	27.58 (23.95,30.01)	68.35 (64.79,73.15) [#]	1, 2
Min	1.85 (-14.49,7.66)	7.38 (-0.54,13.93) [#]	-15.05 (-17.28,-13.38)	-13.87 (-16.88, -9.47)	1, 2
<i>Hip ab-adduction [°]</i>					
Max	-1.78 (-3.10,1.17)	-3.64 (-7.20,-0.99)	-0.74 (-2.46,1.61)	-2.86 (-4.67,2.86)	
Min	-9.93 (-12.05,-8.05)	-14.73 (-18.70,-11.11) [#]	-9.94 (-10.57,-8.69)	-9.65 (-13.50,-8.18)	2
<i>Hip rotation [°]</i>					
Max	19.11 (6.90,23.63)	16.20 (11.22,25.02)	6.22 (0.04,11.75)	10.40 (-1.33,15.42)	1,2
Min	6.51 (-6.12,10.61)	1.50 (-8.98,11.75)	-3.67 (-10.54,-1.25)	-3.40 (-12.73,1.34)	1, 2
<i>Knee flex-extension [°]</i>					

Max	48.55 (39.50,54.57)	88.73 (87.93,89.52) #	55.31 (51.36,58.43)	89.18 (88.84,89.51) #	1
Min	5.96 (0.30,10.71)	10.40 (-3.31,11.13)	-4.50 (-6.23,-0.64)	-2.33 (-5.93,-0.10)	1, 2
<i>Ankle dorsi-plantarflexion [°]</i>					
Max	1.47 (-0.61,4.66)	8.30 (6.86,13.41) #	-0.03 (-2.40,1.94)	9.73 (4.83,12.42) #	
Min	-12.27 (-15.16,-8.24)	-23.45 (-28.54,-17.00) #	-17.33 (-21.05,-12.49)	-22.55 (-24.04,-10.86) #	

Table 3.1.3: median (25th percentile, 75th percentile) values of the trailing limb parameters. #= $p < 0.05$ WLK vs OBST_HIGH; 1= $p < 0.05$ DS_WLK vs N_WLK; 2= $p < 0.05$ DS_OBST_HIGH vs N_OBST_HIGH

At the trunk, flexion increased from the WLK to the OBST_HIGH condition, where DS were more flexed than N. DS had a more anterior pelvic tilt than N. The pelvic tilt minimum value decreased in both groups in the OBST_HIGH condition, increasing the ROM of the pelvis in the sagittal plane compared to the WLK condition with comparable values across groups in OBST_HIGH. Pelvic obliquity and pelvic rotation increased in both groups in the OBST_HIGH condition, with similar values of rotation but with higher values of obliquity for DS than for N.

The hip joint was more flexed in OBST_HIGH for both groups, due to the need to avoid the obstacle by lifting the limb up; anyway, DS were more flexed than N in both WLK and OBST_HIGH conditions, with patterns shifted towards flexion throughout the crossing. The minimum of hip abduction was lower in OBST_HIGH respect to WLK for DS, with DS being more abducted than N. Hip intra-rotation was markedly higher for DS in both conditions respect to N.

At the knee joint, DS were more flexed than N in WLK, but both groups increased their flexion values in OBST_HIGH, approaching similar values of the maximum flexion. However, during OBST_HIGH the minimum values were higher for DS, resulting in reduced ROMs compared to N.

At the ankle joint, the maximum dorsiflexion increased for both groups in the OBST_HIGH condition, with similar values. The minimum plantarflexion values, instead, became more negative in OBST_HIGH, with comparable values across groups.

Figure 3.1.7 shows the kinematic patterns at the lower limb joints for the trailing limb of a subject with DS and for a N subject, to give an example of the differences between these two groups. A normality band for normal walking is shown as well (grey band) to allow a qualitative analysis of the modifications in the gait patterns during OBST_HIGH respect to normal walking.

TRAILING LIMB

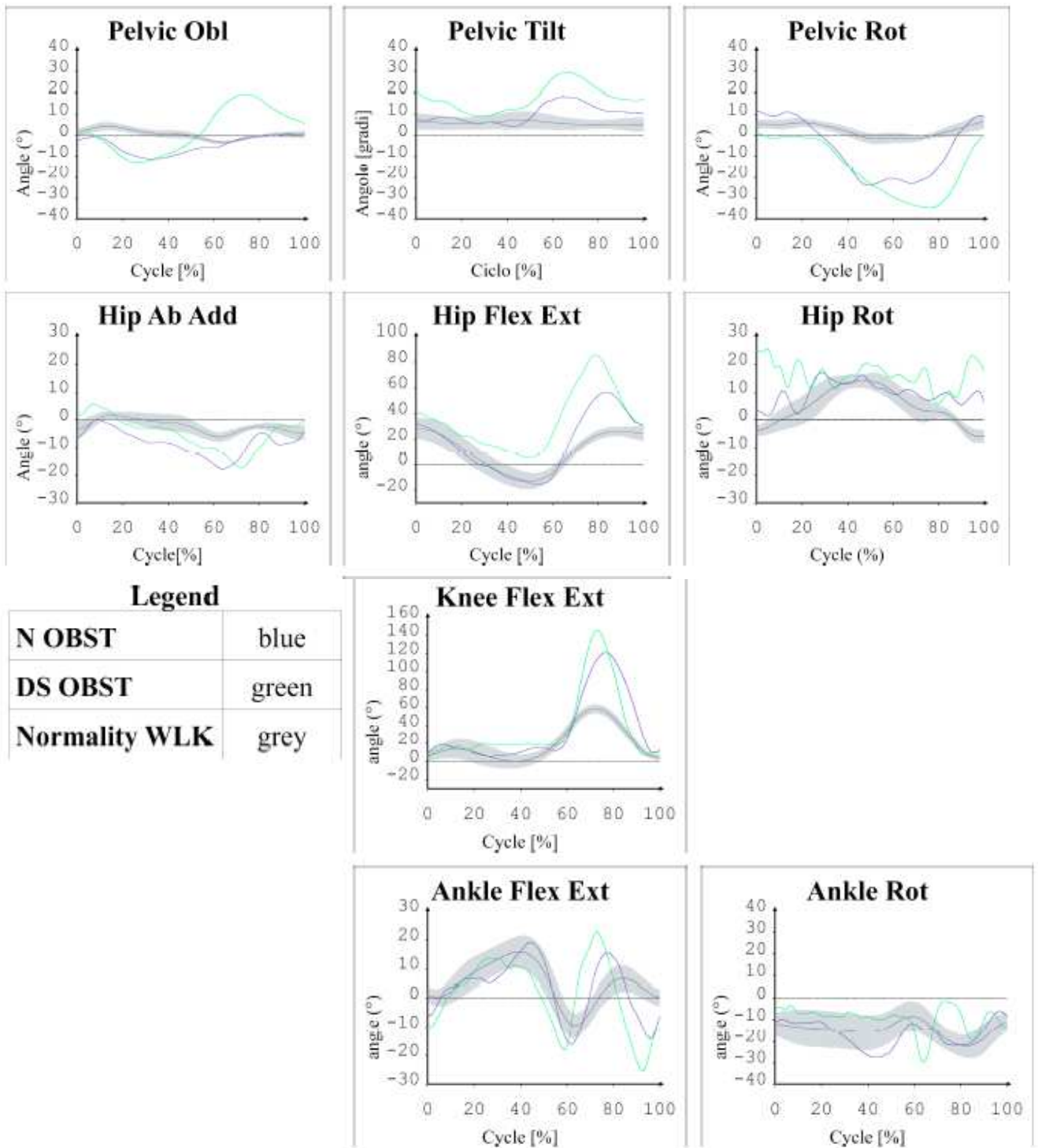


Figure 3.1.7: kinematic patterns at the lower limb joints for the trailing limb of a subject with DS (green line) and for a N subject (blue line). Note the difference between normal walking and walking with obstacle. Note also the tendency towards flexion at the pelvic and hip joints and the increased movements in the horizontal and frontal plane in DS.

In table 3.1.4 the results of the parameters D, for the L and T arms (median, 25th and 75th percentiles values) are presented for the WLK and OBST_HIGH conditions.

	DS		N		DS vs N
	WLK	OBST_HIGH	WLK	OBST_HIGH	
<i>Elbow angle [°]</i>					
L_Min	138.90 (137.03,141.75)	119.80 (105.30,125.30) [#]	136.80 (128.85,140.30)	133.30 (120.60,139.90)	2
T_Min	145.25 (141.65,148.55)	123.70 (114.80,130.30) [#]	132.40 (128.65,137.40)	129.20 (114.73,134,73)	2
<i>Shoulder-arm angle [°]</i>					
L_Min	66.05 (63.03,69.75)	58.30 (56.40,65.70) [#]	68.00 (66.30,71.45)	68.80 (67.20,72.83)	1,2
T_Min	65.60 (57.60,69.53)	53.20 (50.80,58.20) [#]	75.20 (65.65,76.20)	69.90 (63.25,74.03)	1,2

Table 3.1.4: median (25th percentile, 75th percentile) values of the upper limbs parameters. #= $p < 0.05$ WLK vs OBST_HIGH; 1= $p < 0.05$ DS_WLK vs N_WLK; 2= $p < 0.05$ DS_OBST_HIGH vs N_OBST_HIGH

The E angle minimum values for both arms were higher for DS in WLK compared to OBST_HIGH. Compared to N, DS flexed their elbows more in the OBST_HIGH condition. No difference was found across conditions for N.

The S-A angle minimum values for both arms decreased for DS in the OBST_HIGH condition compared to the WLK condition. DS displayed lower values than N in all conditions.

3.1.4 Conclusions

The study of obstacle avoidance during walking involves aspects of perceptual-motor integration (i.e. visual estimation of the obstacle height, information about limb position respect to the obstacle etc), and therefore is of major interest for the evaluation of motor control abilities in DS subjects. From the comparison between conditions and groups we aimed at characterizing the task and at verifying the presence of deficits in obstacle avoidance strategies related to difficulties in the visual perception of the object and in the execution of appropriate strategies, and in particular: 1) are there different strategies for clearing the obstacle between N and DS, that lead to an increased falling risk in DS? 2) How is the walking pattern modified by obstacle perception?

Strategies for obstacle clearance

Reduced step length and velocity are well-known features of DS walking patterns, which are related to the subjects' perceived instability (Rigoldi et al, 2010). In all conditions, but especially in OBST_HIGH, the DS subjects, compared with the N group, displayed higher variability and lower values of step length before, during and after obstacle clearance, and reduced velocity in the approach and obstacle phases. The “step shortening” strategy was described by Chen et al (1991) and Weerdestein et al (2005) in the case of elderly healthy subjects, and may be interpreted as a safety strategy due to the perceived increased instability caused by the presence of the obstacle, or as a difficulty in interpreting the sensory input (visual and proprioceptive) adequately. Thus, in presence of the obstacle, a less conservative strategy was being used by DS.

On contrary, N maintained similar parameters of step length and approach velocity in all conditions, while only mean velocity in the obstacle phase decreased in OBST_HIGH (but with values that remained higher than for DS). These findings underline the presence of a “conservatism strategy”, as stated by Chen et al (1991), in N subjects, who are able to adjust their walking patterns to maintain their walking parameters (velocity, step length) unvaried across conditions.

Concerning feet elevation, the T limb was lifted higher than the L limb for both groups and conditions, and different strategies were adopted for clearance by the T limb and L limb, as found by several authors (Begg et al, 1998; Patla et al, 1996) who studied obstacle crossing in healthy adults. As described in figure 3.1.6 for the OBST_HIGH condition, and accordingly to Begg et al (1998), T foot pattern in the sagittal plane was approximately symmetrical and narrow, whereas L foot raised steeply before a gradual descent, making the profile skewed. T foot crossed the obstacle close to the peak of vertical displacement, whereas L foot crossed as it raised to a peak. Thus, similar foot patterns were present for DS and N in the sagittal plane.

In figure 3.1.8 a representation of the feet placement relative to the obstacle during maximum elevation (max height parameter) is shown for DS and N, to provide a global view of the subjects' behavior in vertical direction. During OBST_LOW condition, maximum foot elevation was similar in DS compared to N. In the OBST_HIGH condition, the presence of a “real” obstacle elicited a higher safety margin in both N and DS, with comparable values between groups. The safety margin was increased for both limbs. In a study by Chou et al (1997) it was found that while plane walking emphasizes the reduction of mechanical energy consumption at the swing limb, walking when stepping over an obstacle is not energy efficient, since additional energy is generated to increase the clearance between the foot and the obstacle. This, in line with our results, suggests that safety may

become a more dominant criterion than energy cost when stepping over an obstacle, both for DS and N.

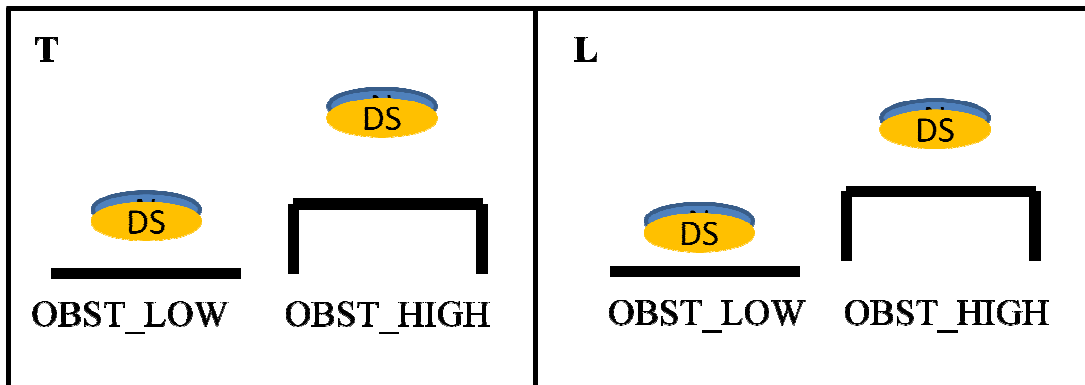


Figure 3.1.8: sagittal view of maximum feet height for the OBST_LOW and OBST_HIGH conditions. On the left: trailing limb (T); on the right: leading limb (L). Superimposed circles mean that there is no significant difference between N and DS

In figure 3.1.9 a representation of the feet placement for DS and N subjects is shown to provide a global view of the subjects' behavior in the antero-posterior direction.

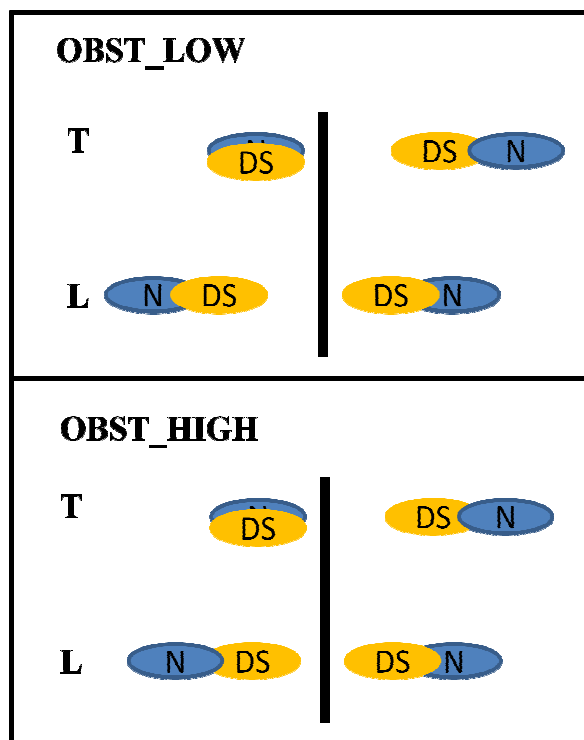


Figure 3.1.9: horizontal view of the distance of the feet from the obstacle in antero-posterior direction. On top: OBST_LOW condition; on bottom: OBST_HIGH condition

Chou and Draganich (1998) described the effect of decreasing toe-obstacle distance in antero-posterior direction on joint moments of the limbs in healthy adults and found that, when stepping

over an obstacle of various height, the location of foot placement relative to the obstacle was not varied, instead it was precisely controlled by the central nervous system to ensure a safe crossing. This was the case of the N subjects in our study, who did not display any change in feet positioning with increasing obstacle height. DS had a quite constant feet positioning in the two conditions as well, although L_FO decreased in OBST_HIGH condition, with increased variability in the parameter's values.

Compared to N, DS subjects tended to lay their leading (L) foot closer to the obstacle before (L_FO) and after the crossing (L_OF), and to lay their trailing (T) foot closer to the obstacle after the crossing (T_OF) in both obstacle conditions. N, instead, had higher distance values of L_FO, L_OF and T_OF, and lower variability. According to Chou and Draganich (1998), the control of feet position relative to the obstacle is of central importance, because a correct distance allows the shank to move anteriorly and the ankle to dorsiflex as the body moves forward. When toe-obstacle distance is reduced, anterior motion of the shank and thus dorsiflexion of the ankle is limited by the closer proximity of the obstacle to the shank. Thus, while N subjects had excellent foot positioning control, DS were only partially able to control foot position across different trials (L_FO varied), and they chose a distance of their L foot from the obstacle that was presumably too close to allow a correct kinematics of the limb. Also, they landed closer to the obstacle with both limbs, increasing again the risk of contact with the obstacle, and did not exploit their limb elevation to move forward (lower step lengths). Provided that obstacle avoidance is more expensive, in terms of energy consumption, than plane walking (Chou et al, 1997), the “unexploited” limb elevation in DS leads presumably to additional energy expenditure respect to N.

For what concerns kinematics, in the OBST_HIGH condition N subjects adjusted their movement to the presence of the obstacle by increasing hip and knee flexion, and by increasing ankle dorsiflexion bilaterally to avoid hitting the obstacle with the foot. As the limb was being lifted and moved forward, pelvic obliquity and intra-rotation increased. An increased plantar-flexion of the ankle at final stance allowed N subjects to land with the foot in an “tiptoe” position.

In OBST_HIGH condition DS increased their knee flexion, and increased dorsi-flexion of the ankle to avoid the obstacle with values similar to N, whereas the trunk, pelvis and particularly hip joint flexion remained higher than for N bilaterally, characterizing DS's movement in the sagittal plane. Thus, on the sagittal plane, a strategy similar to N subjects was found, even though the values of flexion were higher for DS. In the other planes, pelvic obliquity and hip abduction in DS showed values higher than N bilaterally. Hip intra-rotation remained higher than for N bilaterally. It is known that the increase in pelvic obliquity and hip abduction represents a strategy to guarantee gait progression in DS (Rigoldi et al, 2010). Thus, while N subjects modified their movement mainly in

the main plane of movement (i.e. sagittal plane, consistently with the study by Patla and Prentice, 1995), DS displayed increased values for the sagittal, frontal and horizontal planes.

The upper limbs parameters revealed that the presence of the obstacle was perceived as a source of instability by subjects with DS, who in fact lifted their arms (decreasing S-A angles at both sides) to stabilize their centre of mass and flexed their elbows (decreasing E angles at both sides) to prepare for possible falls. Thus, in DS the presence of the obstacle enhanced stabilization and safety strategies at the upper limbs, which were elevated forward and outward in an attempt to stabilize the center of mass and to prevent for possible falls, in line with the upper limbs movement strategies described by Marigold et al (2002) in healthy subjects challenged with perturbations during gait.

These results provide evidence for a different avoidance strategy in DS, and for a difficulty in regulating gait parameters when challenged with a more complex situation as the presence of an obstacle. Thus, walking with obstacle avoidance seems to be more destabilizing for subjects with DS, and their adaptation to the presence of the obstacle seems to be more energy consuming than for N. These results may be linked to an increased risk of fall, as reported by anecdotal evidence (Virji-Babul and Brown, 2004). A rehabilitative therapy based on obstacle avoidance tasks could be helpful in subjects with DS to improve stability and motor strategies, and to decrease the risk of falling.

Influence of the obstacle on perceptual-motor processing

Approaching and stepping over an obstacle requires visuo-motor coordination, which involves the integration or process of visual information defining the height and location of the obstacle with precise control of a limb's motion (Law and Webb, 2005). The integration prompts the subject to proactively adjust the distance between the supporting limb and the obstacle (T_FO, L_OF), which allows sufficient space for the crossing limb to clear the obstacle with adequate foot clearance.

In the present study the OBST_LOW condition did not elicit significant changes in step length, foot elevation nor velocity parameters in N subjects compared to the WLK condition, suggesting that visual information about the obstacle was extracted at the initiation of gait (Patla, 1997). In N subjects, modifications of the mean obstacle velocity and T foot elevation in the OBST_HIGH condition were found, while the other parameters remained consistent across conditions, suggesting that the nervous system maintained a steady state gait pattern and modulated the gait in response to the environment by varying these parameters.

In DS subjects the values of maximum T and L foot elevation in WLK and OBST_LOW conditions were similar to those of N in both OBST_LOW and OBST_HIGH conditions. The presence of the

“real” obstacle in the OBST_HIGH condition elicited a higher foot elevation in both groups compared to the “subtle” ground-level obstacle in OBST_LOW condition. Thus, DS showed an appropriate scaling of foot elevation to obstacle height, with values similar to N. This is in agreement with the study by Virji-Babul and Brown (2004) about obstacle avoidance in children around 5 years old with and without DS, where it was found that children with DS had values of foot elevation in presence of the obstacle comparable to those of children without DS.

The correct scaling of foot elevation suggests that DS, as well as N, were able to extract information about obstacle height and match it to their movements. However, it should be investigated whether this information was used in a feed-forward or on-line mode of control. The results by Virji-Babul and Brown (2004) seem to indicate that visual information about the obstacle was not used consistently to modulate movements early in the gait cycle: the authors reported that, while typically developing children showed a smooth progression from walking to stepping over the obstacle, most of the children with DS stopped in front of the obstacle before stepping over. In our study subjects with DS in most cases did not stop before the obstacle, but a significant reduction in the mean approach phase velocity was recorded. Also, an incorrect (too close) foot placement was found relative to the obstacle.

These results seem to suggest that there is a lack in the anticipatory movement adjustments in DS when challenged with a more complex situation such as the presence of an obstacle on the walk-path and provide further evidence of the presence of difficulties in perceptual-motor coupling in DS. While the obstacle’s features seems to be correctly extracted by N as well as by DS, the way in which this information is used to program the movements seems to be different among N and DS. The next study (paragraph 3.2) will analyze more in depth the role of motor programming in the motor control deficits of DS.

3.2 Motor strategies and motor programs during an arm tapping task with and without obstacle avoidance in adults with Down Syndrome

As we have previously discussed, recent studies suggest that the motor alterations are not just a consequence of biomechanical impairments, but rather a consequence of a deficient central nervous system (CNS), whose inputs to the biomechanical system generate outputs “different” from normality.

An important aspect of performing functional movements is related to the kind of motor strategies that guide the movement, namely a feed-forward (pre-programmed) strategy or a feedback (on-line) strategy. These two strategies cooperate in complex movements to a different degree, depending on accuracy constraints, availability of perceptual information, degree of automatization of the task.

The next paragraph will address the study of motor strategies and planning in DS during the execution of an arm tapping task with and without obstacle avoidance.

3.2.1 Introduction

Motor behaviors can occur along a continuum of control, ranging from feedback to feedforward. Feedforward movements are made without the online use of sensory feedback evolving during the action, and require an internal model of accuracy. Such actions can occur rapidly, as there is no need to account for the delay of feedback loops. Figure 3.2.1 shows a simple scheme of feedforward control: a command signal comes from a hypothetical central controller and, after some processing, produces a certain output. Variables the controller uses to formulate command signals are called control variables. It is assumed that the controller may supply these variables while ignoring possible changes in the output or in any other external factor. Certainly, this does not mean that the controller cannot change a control variable based on peripheral information. The important thing is that it has a choice of reacting or not to this information.

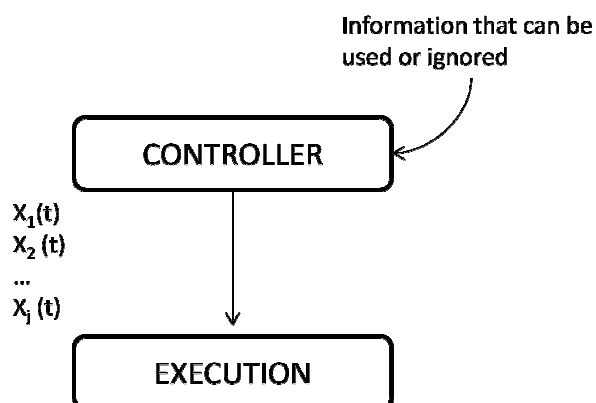


Figure 3.2.1: in this scheme of feedforward control, the controller uses control variables $(x_1(t), \dots, x_j(t))$ to formulate command signals sent to lower (executive) structures

If the controller supplies the signal independently of the output, it provides feedforward control (or open-loop control).

Feedback control, in contrast, involves modification of the ongoing movement using information from sensory receptors. This type of control allows for a high degree of accuracy, as well as for error detection and correction, but it is necessarily slow (figure 3.2.2). An important component of a feedback control system is a comparator, a unit that compares a system's current output with a desired output and changes command signals based on the discrepancy between the actual and the desired effects.

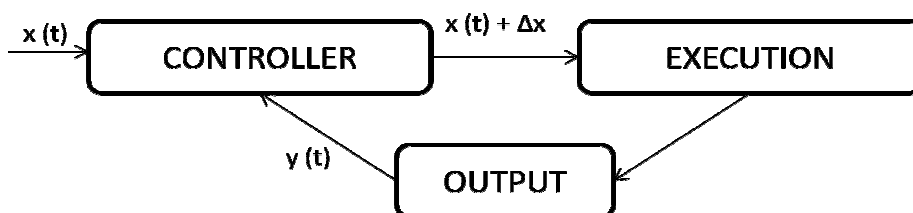


Figure 3.2.2: feedback control changes command signals based on their outcome.

Two important parameters characterizing feedback loops are gain and delay. Gain can be defined as the ratio of a change in a control variable to a change in a peripheral variable ($\Delta x / \Delta y$). Delay can be measured in units of time. Feedback control achieves its functional purpose of decreasing error only if its gain is high enough and its delay is within certain limits. Large delays can lead to unexpected circumstances. Therefore, if speed is vital, feedforward control may be preferred; if accuracy is more important than speed, feedback control is advantageous. Optimal movement control likely reflects a combination of both feedback and feedforward processes (Seidler et al, 2004).

Reaching movements in healthy adults are characterized by a bell-shaped velocity profile that consists of one acceleration and one deceleration (Van der Heide et al, 2005; Jannerod 1984). When reaching movements come into adult configuration, trajectories become straighter, faster and smoother (Kuhtz-Buschbeck et al 1998; Von Hofsten, 1991). The increase in smoothness of reaching movements is due to the decreased number of corrections in the movement path, which is caused by several aspects. Among these are improved control of inertia and interaction torques and increasing ability to process sensory information. The development of feedforward mechanisms, which become prevailing respect to feedback based movements, plays a central role as well, leading to less reliance on sensory information and consequently to a decreased number of corrections in the trajectory.

It is known (Elliott et al, 2010) that persons with DS have difficulty in performing precision goal-directed movements with any degree of speed or efficiency. The movements in fact appear slower in this population, with lower peak velocities and with multiple discontinuities in the acceleration profile in comparison with controls. The presence of these discontinuities in the trajectory is thought to reflect feedback-based corrections designed to reduce the degree of discrepancy between the position of the limb and the target. Because these corrections are necessary, the assumption is that performers with DS have problems with movement planning and feed-forward control (Elliott et al, 2010). According to the authors, in fact, the preprogramming part of the movement is spatially inaccurate for subjects with DS, causing the need for successive corrective movements and for greater reliance on feedback, rather than feed-forward, guidance.

A study by Charlton et al. (1996) analyzed the kinematic characteristics of reaching to grasp in a group of seven children with DS (mean age: nine years) compared with two control groups, a chronological age-matched and a mental age matched group. Movement time, peak velocity of the wrist and number of movement units (NMU) were among the analyzed parameters. In particular, NMU was derived from velocity profiles (von Hofsten and Ronnqvist 1993; von Hofsten 1991), and each movement unit comprised a period of acceleration and deceleration. The results showed that children with DS moved slower and with reduced peak velocity, as found in previous studies (Aruin et al. 1996; Latash and Corcos 1991). More interestingly, trajectories of DS children exhibited greater irregularities and a greater NMU. According to the authors, the preprogramming part of the movement is spatially inaccurate for subjects with DS, causing the need for successive corrective movements and for greater reliance on feedback, rather than feed-forward, guidance than the control children. Feedback-based corrections take time and thus larger NMU was associated with longer durations of the deceleration phase. As an alternative interpretation, the irregularities in the deceleration phase were interpreted as difficulties with the grasping part of the action. Both the studies by Elliott et al (2010) and Charlton et al (1996) suggest that persons with DS have trouble performing a stable representation of the to-be-performed action, and are dependent on direct visual information for performance. It is still unproved whether the major reliance on feedback control in subjects with DS comes from a specific impairment in pre-programming (Elliott et al, 2010; Charlton et al, 1996) or as a strategy (Latash et al. 1993; Latash 1992) to account for the perceived instability and for their difficulty in finely-tune the movement in response to perturbations. According to this second view, it has been hypothesized (Latash et al. 1993; Latash 1992) that the central nervous system of persons with DS could use motor strategies that are typically seen in unimpaired subjects, but “prefers” to use different patterns, to compensate for a primary deficit in decision-making. For example, a prevalence of synchronized bursts of activity in the agonist and

antagonist muscles was found in subjects with DS for single-joint and multiple-joint upper limbs movements (Aruin et al. 1996; Almeida et al. 1994) and for the lower limbs joints during standing and walking (Galli et al, 2008) instead of the physiological alternating patterns. These co-contraction patterns of muscle activation increase joint resistance to external perturbations, independently of the direction of the perturbation. Thus, they can assure some acceptable level of stability even if there is some degree of uncertainty about the direction of the perturbation, although being unable to fully compensate for the effects of the perturbation (Aruin et al. 1996; Almeida et al. 1994) and can be a valid compensatory mechanism to contrast muscle weakness and ligament laxity (Galli et al, 2008).

Another difference in patterns activation is the so called “distal-to-proximal” activation pattern, contrary to the “proximal-to-distal” activation pattern recorded in typical population (Karst and Hasan 1991). Neurologically normal individuals, in fact, tend to activate proximal muscles prior to distal muscles (Anson and Mawston 2000; Karst and Hasan 1991). One reason and a potential advantage of a proximal-to-distal activation is that it may provide opportunity for on-line (feedback based) corrections or the chance to “fine-tune” the terminal phase of the response. Although it is not clear why subjects with DS adopt an inverse activation pattern, the distal-to-proximal behavior of individuals with DS may be seen, in light of Latash’s interpretation (Latash 1992), as a deliberate behavior resulting from a central nervous system that “realizes” its own limitations. For individuals with DS performing fast and accurately may be defined by quite different benchmarks, in which generating a response in itself might be regarded as successful, independent of the “finer” issues of accuracy and speed. According to this view the apparently abnormal patterns of muscle activation in persons with DS should be considered adaptive rather than pathological. On the other hand, by using abnormal patterns of activation, subjects with DS are trading efficiency for safety, and this choice may be at the cost of experiencing the full richness of motor opportunities (Anson and Mawston 2000). The “adaptive reaction” perspective suggests that there is ample room for improving motor performance of these individuals by defining clinical therapeutic interventions (Aruin et al. 1996; Almeida et al. 1994; Latash and Corcos 1991;).

The studies reviewed above mostly deal with patterns of muscle activation. Whereas a detailed characterization of these patterns is given, little is told about the kinematic output generated by these activations, apart from considerations about general slowness and reduced velocity peaks in subjects with DS compared to typical population (Aruin et al. 1996; Latash and Corcos 1991).

In the present study, we evaluated the movement strategies of adult subjects with DS and of age-matched controls during an arm tapping task with and without obstacle avoidance. We used quantitative motion analysis not only to describe movement differences in DS respect to typical

population, but also to provide a means of interpreting such differences in terms of the underlying different control processes. In addition, our study aims at adding body of evidence to the work by Charlton et al. (1996) on children with DS, by extending the evaluation to adults with DS. These authors gave two alternative interpretations of the increased NMU in children with DS, one due to feedback programming and one related to problems with grasping. We hypothesize that, if the former hypothesis is correct, than a higher NMU will be present in our reaching task as well, where no final grasping is required.

Finally, by introducing a perturbing factor (i.e. an obstacle) during the arm tapping task, we aim at expanding the evidence about motor control in DS by evaluating the influence of the obstacle on motor control strategies. Obstacle avoidance in DS has received very little attention in literature; the only studies that are present (Smith and Ulrich, 2008; Wu et al, 2008; Virji-Babul et al, 2004) regarded lower limbs obstacle avoidance during walking. However, it is evident from literature that the presence of an obstacle on the pathway can elicit modifications in the gait patterns and can give insight on the motor strategies that are regulating the movement. Literature, however, completely lacks of studies about upper limb obstacle avoidance in DS. This is surprising if we consider that most of everyday tasks involve reaching movements of the upper limbs towards objects for the aim of manipulation. In these conditions, an obstacle can frequently be on the path, and needs to be avoided for the safe and efficient accomplishment of the task. Also, the object itself can become an obstacle if not adequately approached (for instance, hitting a cup of hot tea could cause a burn). Thus, daily life is full of obstacle avoidance tasks performed with the upper limbs. The evidence for obstacle avoidance difficulties during lower limbs movements in DS suggests questions about how obstacle avoidance is managed by these subjects in the upper limb movements. Starting from this evidence, we analyzed if the presence of obstacle-introduced modifications in the motor control strategies elicited a higher reliance on feedback control in the two groups respect to the plain tapping (without obstacle) condition.

3.2.2 Methods

Subjects

13 right-handed subjects with DS (mean age \pm standard deviation: 24.2 ± 7.1 years; 84.6% males, 15.4% females) and 22 right-handed, age-matched N subjects (mean age \pm standard deviation: 22.6 ± 6.8 years; 58.8% males, 45.2% females) were evaluated. Inclusion criteria and more details can be found in appendix I.I and I.II.

Acquisition

Participants sat comfortably on a chair, holding a cylindrical wooden dowel with the right hand. In front of them was a table with six target positions evenly spaced around a semicircle. The experimental set up was adapted from a previous study (Van der Wel et al. 2007), although the aim of our study was different from the one of that study. The targets were black dots that had been printed on adhesive paper pasted on the table (figure 3.2.1). In the first condition (plain tapping, figure 3.2.1, on the left) subjects tapped consecutively between targets 1 and 2, 2 and 3, 3 and 4, 4 and 5, 5 and 6, a total of five tapping movements. In the second condition (tapping with obstacle, figure 3.2.3, on the right), an obstacle (10 cm of height) was placed between targets 3 and 4; the subjects were asked to tap on the targets as described in the first condition, and to avoid the obstacle by crossing over it with the dowel.

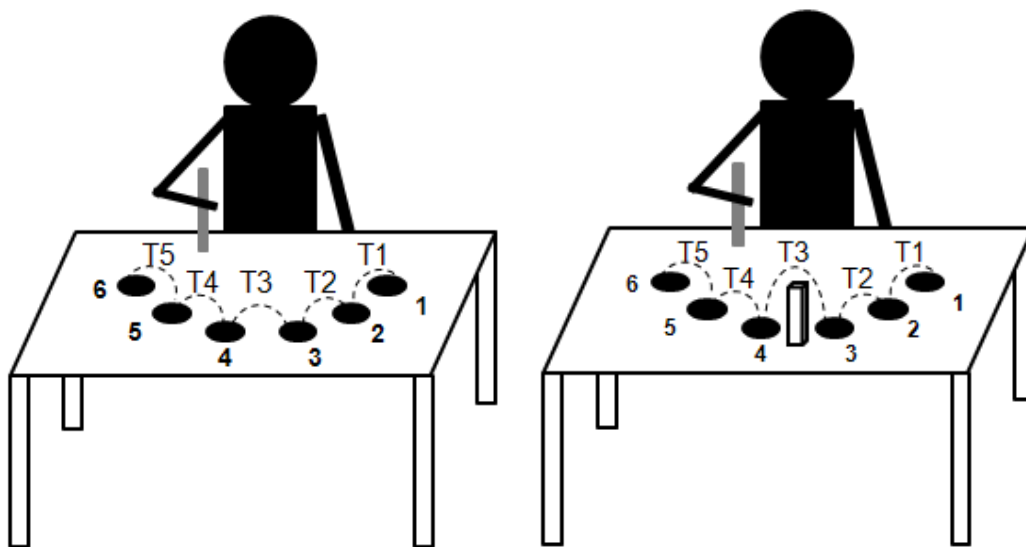


Figure 3.2.3: experimental set up for plain tapping condition (on the left) and tapping with obstacle condition (on the right). The numbers indicate the order in which the targets were tapped, but were not present on the table. the subject tapped from target 1 to target 6 (black dots) with the dowel (grey rectangle). Labels T1 to T5 indicate the name given to each tapping movement (e.g. T1= tapping 1) . In the “obstacle” condition an obstacle was placed between targets 3 and 4

This task was selected because it required the execution of a sequence of movements, and thus allowed studying how and if pre-programming strategies were adopted in DS. In addition, the sequence was easy enough to be understood also by subjects with intellectual disability, and the protocol was administrable in clinical settings with minimum requests of space and short administration time.

Instrumentation

The tasks were acquired using quantitative movement analysis, composed of an optoelectronic system (Elite2002, BTS) with eight infrared cameras. More details about the laboratories and the instrumentation can be found in appendix II.

Markers were placed on specific body landmarks using a marker set derived from previous studies (Petuskey et al. 2007; Menegoni et al, 2009). In addition, three markers were placed at the top of the dowel to identify the dowel's position during the acquisition, and three markers were placed on the table to identify a reference system on the table (figure 3.2.4). a marker was placed on the obstacle.

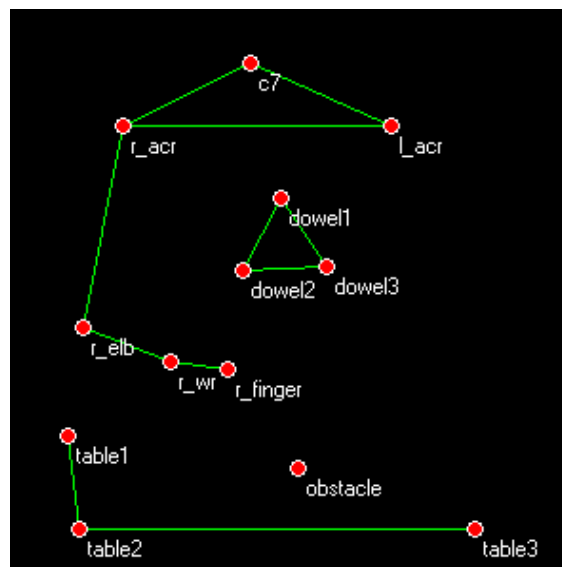


Figure 3.2.4: protocol for markers placement; r= right, l=left

Parameters

Data was analyzed with Smart Analyzer software (BTS, Italy) to define a dedicated protocol for the extraction of quantitative parameters (see Appendix IV).

To characterize the movement strategy of DS and N subjects we considered the elbow and wrist angles, defined according to the vectors between markers on the shoulder, elbow, wrist and finger, and the rotations of the trunk in the three planes of movement respect to the reference system on the table, as illustrated in figure 3.2.5, and we computed the following parameters for upper limb kinematics:

- Trunk ROMs ($^{\circ}$): range of motion of the rotations of the trunk respect to the reference system in the three planes of movement. *Trunk ROM_x*: ROM of rotation in the frontal plane; *Trunk ROM_y*: ROM of rotation in the horizontal plane; *Trunk ROM_z*: ROM of rotation in the sagittal plane.
- Elbow ROM ($^{\circ}$): range of motion of the elbow angle
- Wrist ROM ($^{\circ}$): range of motion of the wrist angle.

These ROMs were calculated by subtracting the minimum angular value from the maximum angular value during the total movement.

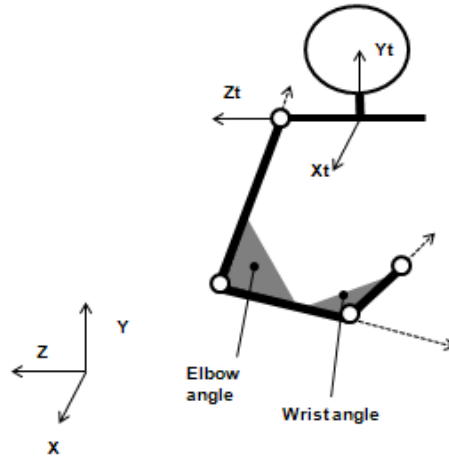


Figure 3.2.5: definition of the elbow and wrist angles, trunk reference system (x_t,y_t,z_t) and table reference system (x, y, z)

We named the tapping movements consecutively from 1 to 5, so that tapping between target 1 and 2 was named “tapping 1”, between target 2 and 3 was named “tapping 2” and so on, as illustrated in figure 3.2.3. We then calculated, for each tapping movement, the following parameters:

- Number of Motor Units, *NMU*: a MU consists of one acceleration and one deceleration in the velocity profile of the marker on the wrist. NMU is the number of velocity peaks over a threshold represented by the 10% of the mean PV (Rigoldi et al. 2012; Menegoni et al, 2009; Van der Heide et al. 2005). In healthy adults’ feed-forward movements, NMU approaches the value of 1 (Von Hofsten and Ronnqvist 1993; Von Hofsten 1991).
- Exceeding NMU, *eNMU*: proportion of trials during which the tapping movement consisted of more than one MU (Van der Heide et al. 2005). This parameter is important to understand the motor program being used by the subject.
- Skeweness, *SK_n* %: for each tapping movement it describes the time to peak height (figure 3.2.6) of the trajectory of the vertical coordinate of the marker on the wrist and it is calculated as:

$$SK_n = \frac{Tp_n}{TD_n} \times 100$$

Where *Tp_n* (s) is the time from the start of the movement to the maximum height of the vertical coordinate of the marker on the wrist and *TD_n* (s) is the tapping duration at the *n* tapping movement, with *n*=1-5 (figure 3.2.6). The mean skeweness (*SK_m*) was then

calculated by averaging SK_n . It gives information about the shape of the trajectory (Menegoni et al, 2009).

- Peak velocity, PV_n (m/s) of the marker on the wrist during the n tapping movement, with $n=1-5$; The mean peak velocity (PV_m) was then calculated by averaging PV_n .
- Index of curvature, IC_n : ratio of the actual length of the reaching path of the n tapping and the length of the straight line between targets n and $n+1$. The mean index of curvature (IC_m) was then calculated by averaging IC_n . This is a measure of movement effectiveness: the lower the IC is, the closer the subject is to a straight, optimized path towards the target (Menegoni et al, 2009).
- Tapping duration, TD_n (s), calculated as the time needed to complete the n tapping movement, with $n=1-5$;

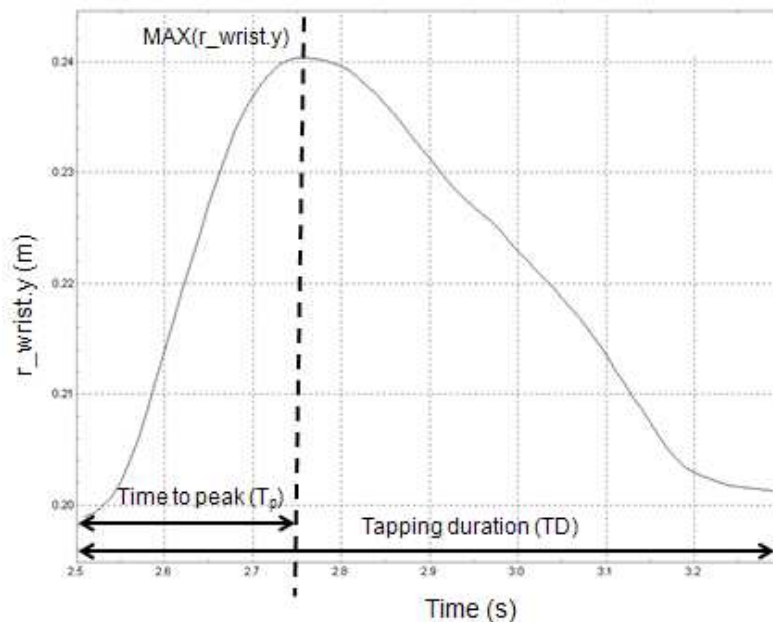


Figure 3.2.6: definition of the time to peak and tapping duration parameters

Statistical analysis

Significance level was set at p -value=0.05. Normality distribution of the data was tested with the Kolmogorov-Smirnov Normality Test. The median, 25^o and 75^o percentiles were computed for each parameter for the two groups. A 2 (condition) x 5 (target location) x 2 (groups) mixed ANOVA was used to analyze the presence of statistically significant differences (p -value < 0.05). Post hoc analysis, with Bonferroni's correction for multiple comparisons, was then used for further investigation.

3.2.3 Results

For the plain tapping task no difference was found among the parameters due to target position in DS. As well, no difference was found for N group either. Thus, target position did not influence the parameters in the plain tapping condition. For this reason, the median, 25° and 75° percentiles values of the parameters over the five tapping movements are shown in the results. Table 3.2.1 displays the median, 25° and 75° percentiles and the results of the statistical analysis for the considered parameters in the two groups of subjects.

	DS		N		DS vs N
	Plain tapping	With obstacle	Plain tapping	With obstacle	
Trunk ROMx (°)	33.46 (23.52,39.27)	27.71 (21.88,31.47)	12.02 (8.41,16.83)	11.16 (9.64,16.64)	1,2
Trunk ROMy (°)	46.19 (41.00,51.83)	38.80 (34.52,45.60)	30.21 (26.39,38.09)	27.14 (22.39,34.19)	1,2
Trunk ROMz (°)	18.22 (14.34,25.17)	19.87 (15.40,22.69)	13.41 (12.01,17.41)	15.98 (10.66,19.96)	1,2
Elbow ROM (°)	22.97 (20.57,25.93)	26.53 (23.62,33.50) ^Δ	33.41 (29.02,40.05)	34.35 (30.35,39.03)	1,2
Wrist ROM (°)	8.49 (5.93,10.04)	13.71 (11.02,23.72) ^Δ	7.91 (4.72,8.44)	11.46 (10.03,15.40) [°]	2
eNMU₁	1.00 (0.00,1.00)	0.50 (0.00,1.00)	0.00 (0.00, 0.20)	0.00 (0.00,0.10)	1,2
eNMU₂		1.00 (0.00,1.00)		0.00 (0.00,0.10)	1,2
eNMU₃		1.00 (1.00,1.00) ^Δ		1.00 (0.00,1.00) [°]	1,2
eNMU₄		1.00 (0.00,1.00)		0.00 (0.00,0.10)	1,2
eNMU₅		0.50 (0.00,1.00)		0.00 (0.00,0.10)	1,2
SK₁	54.63 (52.59,59.64)	59.07 (54.85,62.98)	46.42 (42.49,48.63)	46.90 (45.11,48.39)	1,2
SK₂		58.72 (54.10,62.19)		44.28 (42.53,47.33)	1,2
SK₃		50.30 (47.34,55.24) ^Δ		45.08 (42.72,46.93)	1,2
SK₄		54.54 (48.77,61.67)		45.27 (41.97,49.62)	1,2
SK₅		55.35 (51.32,60.27)		45.42 (42.98,48.15)	1,2

PV₁ (m/s)	0.42 (0.40,0.48)	0.61 (0.47,0.70) ^Δ	0.53 (0.48,0.57)	0.53 (0.48,0.59)	1
PV₂ (m/s)		0.52 (0.46,0.57) ^Δ		0.48 (0.44,0.56)	1
PV₃ (m/s)		0.90 (0.70,1.07) ^Δ		0.86 (0.81,1.02) [°]	1
PV₄ (m/s)		0.57 (0.51,0.66) ^Δ		0.53 (0.46,0.63)	1
PV₅ (m/s)		0.49 (0.40,0.60) ^Δ		0.53 (0.47,0.61)	1
TD₁ (s)	0.89 (0.71,1.00)	0.73 (0.54,0.83) ^Δ	0.64 (0.58,0.72)	0.56 (0.49,0.62)	1,2
TD₂ (s)		0.61 (0.48,0.83) ^Δ		0.55 (0.49,0.62)	1,2
TD₃ (s)		0.93 (0.76,1.37) ^Δ		0.83 (0.78,0.88) [°]	1,2
TD₄ (s)		0.67 (0.60,0.81)		0.58 (0.53,0.66)	1,2
TD₅ (s)		0.72 (0.57,0.87)		0.58 (0.53,0.64)	1,2
IC₁	1.33 (1.23,1.45)	1.54 (1.24,1.62) ^Δ	1.16 (1.08,1.26)	1.13 (1.05,1.17)	1,2
IC₂		1.52 (1.29,1.82) ^Δ		1.13 (1.10,1.23)	1,2
IC₃		2.37 (2.16,3.02) ^Δ		2.19 (2.03,2.34) [°]	1,2
IC₄		1.50 (1.41,1.63) ^Δ		1.19 (1.15,1.33)	1,2
IC₅		1.39 (1.23,1.60) ^Δ		1.16 (1.10,1.20)	1,2

Table 3.2.1: results. Median (25°,75° percentiles). 1=p-value<0.05 DS vs N in plain tapping condition; 2=p-value<0.05 DS vs N in tapping with obstacle condition; °=p-value<0.05 plain tapping vs tapping with obstacle in N; ^Δ=p-value<0.05 plain tapping vs tapping with obstacle in DS

The ROMs at the trunk were higher in DS than in N in the three planes of movement, with similar values across conditions. Elbow ROM was lower for DS than for N in the plain tapping condition, but the values increased in DS in the tapping with obstacle condition, where DS approached but did not reach N values. Wrist ROM was comparable among groups in the plain tapping condition, where for both groups the angular motion was limited with respect to the total wrist ROM

(approximately 140° in flex-extension) (Boone and Azen, 1979), because the task did not require a major involvement of wrist motion. The value increased for both groups in the tapping with obstacle condition, where the presence of the obstacle required a higher motion of the wrist during the crossing, with higher values for DS.

The exceeding number of motor units was very close to zero for N subjects, both in the plain and obstacle conditions, with the exception of eNMU₃ during tapping with obstacle avoidance, where the value increased in N. In DS NMU_n values were always higher than for N in both tapping conditions. In NMU₃ the value further increased in DS.

For what concerns the skeweness of the trajectory, the analysis of plain tapping and of tapping with obstacle avoidance revealed that DS's trajectories during tapping were more skewed than N's, with a delayed peak of maximum vertical height. A decrease of the value was found for DS in SK₃ of the tapping with obstacle condition compared to the plain tapping condition, although the values remained higher than for N.

Peak velocity was lower for DS than for N in the plain tapping condition but not in the tapping with obstacle condition, where it reached N values. For N subjects values remained comparable across conditions, with the exception of PV₃ of the tapping with obstacle condition, where the value increased compared to the plain tapping condition.

Trial duration was higher for DS than for N in both conditions. In tapping with obstacle avoidance, an increase in TD₃ was found for both groups, but DS maintained higher values than N. TD₁ and TD₂ decreased in DS in the tapping with obstacle condition compared to plain tapping, but values did not reach N values.

The index of curvature was higher for DS than for N in both conditions, leading to less efficient trajectories. In tapping with obstacle avoidance, N increased IC values compared to plain tapping only in the IC₃, whereas DS maintained higher values than N and increased IC during tapping with obstacle during tappings 1 to 4.

3.2.4 Conclusions

Conclusions will follow the two main topics of feedback reliance during an arm tapping in absence and in presence of a perturbing factor such as the obstacle.

Feedback reliance during an arm tapping task

The results of the plain tapping condition highlighted a major involvement of the trunk in DS compared to N, while the elbow had narrower ROMs for DS than N. Thus, the two groups of subjects followed distinct motor strategies to accomplish the tapping task: N subjects privileged the

motion of the elbow to pass from one target to the next and reduced trunk rotations, while DS maintained a stiffer elbow, with low ranges of motion, and used the trunk to progress from one target to the other. The behavior of the two groups was similar only at the wrist, which was kept rigid to hold the dowel, with very low excursions (mostly below 10°). Thus, at the wrist both groups were using a co-contraction strategy to enhance stability in response to external perturbations, but while N subjects exploited the movement of the elbow to create fluid trajectories between targets, DS reduced the degrees of freedom at the distal joints and compensated with higher movements of the trunk.

These findings may be in agreement with the presence of a reverse pattern of co-contraction (Aruin et al. 1996; Almeida et al. 1994) and muscle activation (from distal to proximal) in DS (Anson and Mawston 2000; Karst and Hasan 1991), with the movement being mostly executed by the trunk and only to a reduced proportion by the elbow.

As revealed by the exceeding number of motor units, which was around zero in the control group, the tapping trajectories of N subjects were consisting of one acceleration and one deceleration, in agreement with Van der Heide (2005) and Rigoldi et al. (2012). Instead, for subjects with DS, the exceeding number of motor units displayed higher values. Thus, DS corrected their wrist trajectory more than N subjects, giving shape to a multi-peaked velocity profile. Lower peak velocity and the multiple discontinuities in acceleration led to longer trial durations. These results are in agreement with the findings by Charlton et al. (1996) on children with DS, and support the hypothesis of a great reliance on feedback programming in subjects with DS. The skewed vertical trajectory of the wrist further supports this hypothesis, since it suggests that the motor program was not defined before starting the movement (feedforward), whereas a first trajectory was implemented at the start, which was then corrected by successive feedback programming when the hand got close to the target (Rigoldi et al. 2012; Van der Heide 2005). Thus, feedback-based corrections are designed to reduce the degree of discrepancy between the position of the limb and the target in DS. The presence of these corrections suggests that subjects with DS rely more on feedback control, and particularly on sensory feedback, because they have problems with movement planning and feed-forward control (Elliott et al. 2010). The clinical implication of these findings is that, while defining a rehabilitative strategy for subjects with DS, part of the rehabilitation should be directed to retraining feed-forward control mechanisms or, in subjects where the reliance on feedback is too prevailing, to empowering and improving feedback control mechanisms.

Longer duration of the trials and a higher index of curvature suggest that the different strategy operated by subjects with DS led to a different task performance, that was somewhat less efficient. On the other side, this different strategy was “efficient enough” to accomplish the task, given that

no speed and accuracy constraint had been given. In this sense, an analysis of the accuracy of tapping (position of the dowel respect to the black dots) would have been useful to quantify the trade-off between task achievement and efficacy of the performance in DS. However, to facilitate the task, in this experimental set up black dots had a higher diameter than the dowel's, so an accuracy analysis could not be performed without biasing the results. Further analysis may stress the aspects of accuracy and velocity during arm tapping in DS, extending the interpretation of motor planning and parameters optimization in subjects with DS.

Effect of a perturbing factor (obstacle) on motor control strategies

In the study by Virji-Babul and Brown (2004) about walking with obstacle avoidance in children with DS it was found that the presence of an obstacle on the pathway elicited online corrections in the walking trajectory, whereas there was a lack in anticipatory movement adjustments in DS. The results from paragraph 3.1 provided similar evidence in adults with DS. Here we combined an obstacle avoidance task to an arm tapping task to analyze the presence of obstacle-introduced modifications in the motor control strategies and to clarify if the presence of an obstacle elicited a higher reliance on feedback control in N and DS.

As for plain tapping condition, the results of the tapping with obstacle avoidance condition confirmed a major involvement of the trunk in DS for both tapping conditions. During tapping with obstacle avoidance, however, the ROM at the elbow and wrist increased in DS. The presence of the obstacle, in fact, required higher ROMs at the distal joints to allow a successful avoidance. Subjects with DS were partially able to cope with this necessity by modifying their patterns of muscle activation and thus increasing the ROMs at elbow and wrist. Thus, they were able to switch from a muscle co-contraction pattern to a more physiological pattern of activation of the distal joints.

The exceeding number of motor unit, in agreement with the previous work, was higher for DS than for N across both conditions. Interestingly, however, the value increased in both groups during tapping 3, when the subjects were clearing the obstacle.

Figure 3.2.7 shows an example of the velocity traces and the MUs of a N subject and of a subject with DS during plain tapping and tapping with obstacle. The figure depicts the increased variability in the velocity profiles of DS and the effect of the obstacle on the performance of both N and DS subjects (increased NMU).

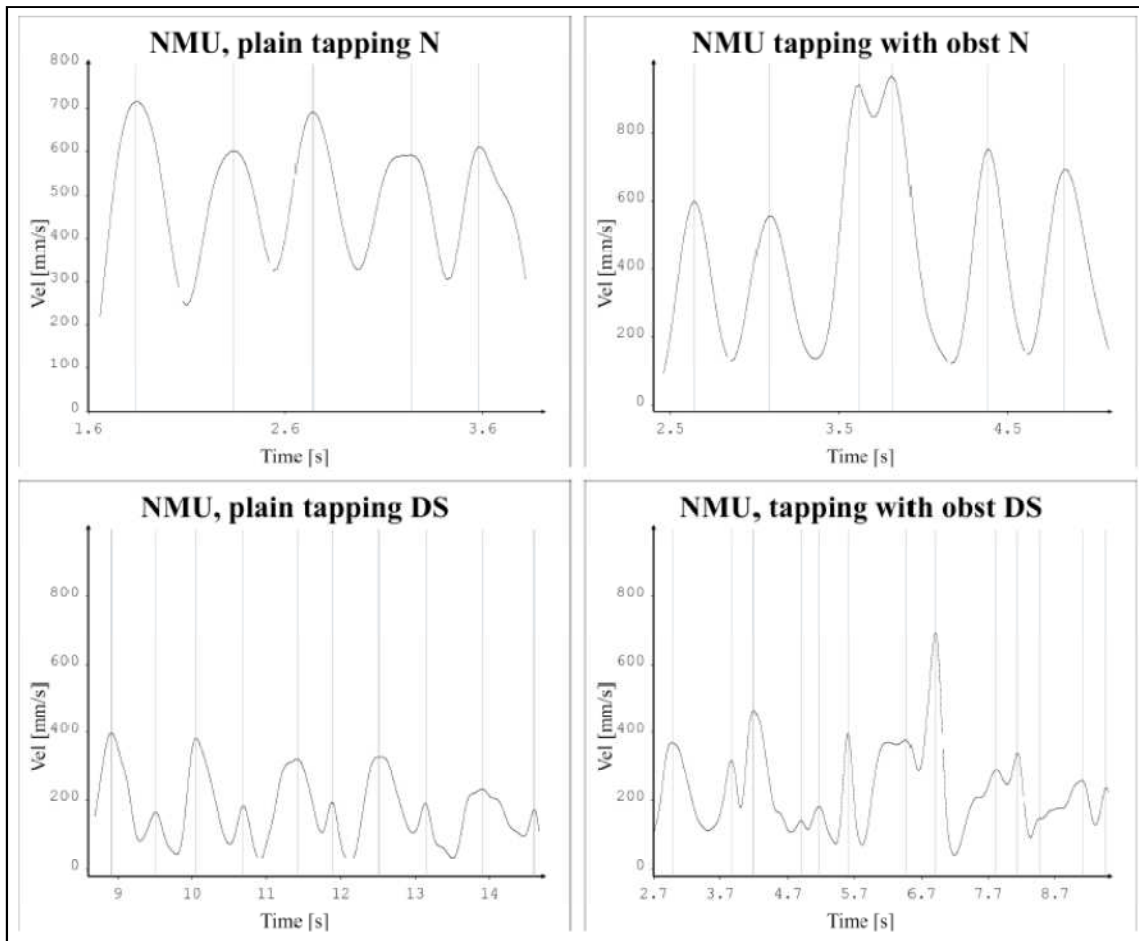


Figure 3.2.7: example of the velocity traces and the MUs of a N subject (upper panel) and of a subject with DS (lower panel) during plain tapping (on the left) and tapping with obstacle (on the right). Note that NMU is higher for the subject with DS, and it increases for both subjects from plain tapping to tapping with obstacle

Although an increase in trajectory corrections was found for both groups, $eNMU_3$ was higher for DS than for N. Thus, the presence of the obstacle elicited a higher reliance on feedback control in both groups. Probably in presence of an obstacle the subjects preferred to privilege a safe execution of the task (avoiding collisions, that can be dangerous in real situations), and thus switched to the more controlled feedback modality. The effect of obstacle presence on trajectory modifications was higher for DS, who already relied on feedback control for plain tapping. Probably, the increase in ROMs at the distal joints, with consequent increase in the degrees of freedom to be controlled, led this subjects to rely even more on feedback guidance.

The delayed peak of vertical trajectory of the wrist (skewness) in DS remained unchanged across conditions, although a little reduction of the values in DS was found for SK_3 . This parameter, together with $eNMU$, provides evidence for online corrections in DS, since it suggests that the motor program was not defined before starting the movement (feedforward), whereas a first

trajectory was implemented at the start, which was then corrected by successive feedback programming when the hand got close to the target (Rigoldi et al. 2012).

In N subjects, during tapping with obstacle avoidance an increase in peak velocity was recorded only for tapping 3, when obstacle avoidance took place, while peak velocity increased in all tapping movements in DS compared to plain tapping, approaching but not reaching N values. As seen for the elbow and wrist values, DS were able to modulate peak velocity in presence of an obstacle. The use of higher peak velocities can be seen as an attempt to optimize the movement: in fact, the presence of the obstacle increased the time necessary to complete the task (because of a longer trajectory to be drawn over the obstacle). By increasing peak velocity, however, the subjects compensated for the longer trajectory and thus partially optimized the movement in relation to the presence of the obstacle. However, for DS an increase in IC_1 to IC_5 was found, with values higher than for N, whereas in N the index of curvature increased only during tapping 3, because obviously the trajectory required to clear the obstacle was longer. Probably DS subjects introduced a safety margin over the obstacle, which was kept for all the tappings, thus rising their arm higher from tapping 1 to tapping 5. This increased the chances to successfully avoid the obstacle, at the price of a less efficient movement.

In the plain tapping condition the longer duration of the trials and the higher index of curvature in DS suggested that the different strategy operated by subjects with DS led to a different task performance, which was somewhat less efficient. In the tapping with obstacle avoidance condition we found that the presence of an obstacle in the pathway elicited some corrective strategies in DS: some were in the direction of increasing efficiency (higher peak velocities and shorter durations, increasing ROMs at the distal joints) but some other were in the direction of increasing safety and stability of the performance (higher index of curvature, higher reliance on feedback control). For most of the parameters, DS modified their values in the tapping with obstacle condition in the same direction of N (for instance they increased elbow ROM, wrist ROM and peak velocity) but they usually were not able to reach N values. The capability to increase ROMs at the distal joints, in particular, suggests that subjects with DS are able to switch between one motor strategy and the other when needed, although they “preferred” the safer co-contraction strategy, in agreement with some authors (Latash et al. 1993; Latash 1992) who postulate that the motor strategies selected by DS are those that allow them to account for the perceived instability and for their difficulty in finely-tune the movement in response to perturbations.

In presence of an obstacle, DS subjects were actually able to modify their motor strategy, but they tried to balance the uncertainty caused by these modifications by increasing online corrections on the trajectory. However, DS were not the only group of subjects that increased feedback reliance

during tapping with obstacle avoidance: N subjects, who moved in a pre-programmed fashion during plain tapping, switched as well to a higher reliance on feedback control during tapping with obstacle avoidance, thus partially adopting DS's strategy. Therefore, we can conclude that the presence of an obstacle elicited changes in the motor strategies of both DS and N, with a destabilizing effect that led subjects to rely more on feedback control.

DS showed some aspects of movement efficiency that were in accordance with N strategies, but the prevailing factor of optimization in these subjects remained safety. A focused rehabilitation could help DS subjects to develop more efficient motor strategies in the presence of motor uncertainty and perturbations by developing a more conscious approach. In particular, rehabilitation could be focused on two different aspects: on one side, if we suppose (in agreement with Latash et al. 1993; Latash, 1992) that DS subjects have the capability to exploit feedforward programs but prefer to rely on feedback control because it's safer, they could be trained to switch from a feedback-based modality to a more feedforward-based modality through appropriate exercises and practice. On the other side, improving feedback control could also lead to better performance in daily activities. In both cases, we believe that these data evidence that rehabilitation techniques for subjects with DS (reviewed in chapter 1.7) should go beyond the simple and most used muscular strengthening therapies to a higher level therapy that takes into account both the motor and neural level. In particular, subjects with DS could benefit from this kind of therapies from the very early stages of their lives, when most of motor programs are formed. This would allow developing their motor milestones sooner.

An important development of the study would be the introduction of neural measurements (such as electroencephalography and electromyography) integrated with kinematic measurements, which could possibly provide a deeper insight of the cortical and peripheral correlates of feedback in DS. As a further development, the study of activation at the arm and forearm muscles could add important information about the co-contraction and distal-to-proximal activation strategies.

3.3 General conclusions drawn from these studies

We have seen how the evaluation of movement in DS is recently beginning to be studied not only in relation to the biomechanical outputs of movement but also in relation to the neural mechanisms that guide motor control. The lack of incisive therapies and focused rehabilitative guidelines for persons with DS, in fact, puts forward the need for a deeper understanding of how the nervous

system of these persons counteracts its own limitations and of how to help maximize the residual motor capacities of these persons.

From the literature review it appears that three factors mainly affect motor control in DS: perception and extraction of sensory information, motor planning and decision making processes (Virji-Babul and Brown, 2004). Based on this, in this chapter we tried to investigate how these processes worked during the execution of “functional movements”, or real-world situation based movements. These movements are more complex from the point of view of the definition of the experimental set ups, because they require controlled conditions on many variables, but they are more cognitively challenging for the subjects, because they imply richer environmental conditions. For this reason, these movements can give a deeper insight on the motor deficit of persons with DS. In particular, we focused on obstacle avoidance tasks that required lower limb or upper limb clearance. The main findings of our experiments in this chapter were that (1) whereas the persons with DS seemed to correctly extract the sensory information (i.e. the physical characteristics of the obstacles) this information was not used in a pre-programmed fashion to plan the movement in advance and (2) the movement of persons with DS was highly dependent on feedback mechanisms. However (3) the subjects with DS were able to successfully complete the tasks, although at the price of less movement efficiency. Thus, as for a system that realizes its own limitations, the central nervous system of persons with DS seemed to choose different motor strategies and to trade movement efficiency for task accomplishment and safety.

We have demonstrated the presence of differences in the motor control of subjects with DS but this is not enough to draw some rehabilitative guidelines for subjects with DS. Some important clinical questions still need to be answered:

- What are the neural bases of these differences?
- Are these differences present since birth or do they result from the interplay of neural development and sensory, cognitive and motor experiences as the child grows up?
- What are the rehabilitative strategies that could possibly lead to a maximization of the residual abilities of DS?

A number of early studies points out to the conclusion that the brain with DS at or shortly before birth is in main respects indistinguishable from the brain of a normal individual (Bar-Peled et al. 1991). The idea of a relative normalcy at birth is potentially of the greatest significance, since it seems to create the opportunity to do something about the not-yet-created differences that quite clearly do emerge during the period right after birth. Understanding if differences in motor control are present since birth is thus very important for the definition of rehabilitation strategies: if primitive control mechanisms are preserved in DS then we can hypothesize that the nervous system

of children with DS is potentially normal at birth, and that differences develop with growth. Instead, if primitive reactions are found to be different respect to controls, we can hypothesize that the differences in DS are present since birth, and probably before. Choosing between these hypotheses may provide information about the validity of early and late intervention programs in DS.

In order to provide a partial answer to these questions, in the following chapters we will study the first movement control mechanisms, the ones that develop since the very early stages of life: monosynaptic reflexes and pre-programmed reactions.

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Chapter 4

Mechanisms for fast movement correction

In chapter 3 we studied perceptual-motor abilities and motor control during complex, functional movements in subjects with DS and in controls. In this chapter, we will introduce the most primitive forms of motor control: monosynaptic reflexes and pre-programmed reactions, which will be the focus of the experimental study of the next chapter.

Most human voluntary movements are performed not in laboratory controlled conditions but in the real world life, with unexpected changes in sensory information, force fields, targets etc. During multi-joint movements, corrections to unexpected perturbations can occur at different levels within the system for movement production, at different characteristic time delays, and with different degrees of controllability. Some of these mechanisms are muscle and tendon elasticity and muscle reflexes, that generate changes in muscle force against the perturbing force. Other mechanisms, that come at a short delay (although the delay is longer than that of monosynaptic reflexes), are called pre-programmed reactions (PPRs) and provide context-specific corrections of movement or posture in cases of unexpected external perturbations (Latash, 2008). Finally, voluntary (conscious) corrections intervene.

Monosynaptic reflexes and PPRs are known to be present since the early stages of life. Evidence for the presence of immature monosynaptic reflex pathways was found by 14 weeks post conception (Clowry, 2007). Bawa (1981) evaluated changes in the short latency and postmyotatic reflexes of children between 2 and 10 years of age. He found that by 8 years of age the reflex reactions resembled those of adults. Bawa (1981), Forssberg and Nashner (1982) and Myklebust (1990) stressed the importance of these reflexes for the acquisition of early motor skills. Maturation of human behavior, in fact, passes from the primitive reflexes to the gradual appearance of automatic, postural and adaptive reactions which make higher activities possible (Fiorentino, 1972).

4.1 Monosynaptic reflexes

Among the several definitions about “reflexes” let us consider this: a reflex is a muscle contraction induced by an external stimulus that cannot be changed by pure thinking, that is, by a volitional act that is not accompanied by another muscle contraction (Latash, 2008).

Many reflexes have been studied in animal preparations. Such procedures may involve surgically separating the spinal cord from the brain (spinal preparation). If we assume that every volitional act comes from the brain, then in a spinalized animal all muscle reactions to external stimuli are apparently reflexes, because signals from the brain cannot reach the spinal cord.

In the beginning of the 20th century, muscle reflexes were considered building blocks for voluntary movements, based on the experiments by Sir Charles Sherrington and colleagues performed on spinalized animals (Stuart et al, 2001) and on the studies by Pavlov (reviewed in Bernstein 2003). Later, the growing awareness of the complexity and variability of voluntary movements led Bernstein (1967, see also Bongaardt, 2001) to conclude that movements cannot be viewed as combinations of reflexes. Recently, muscle reflexes were once again brought to the center of attention by hypotheses of motor control which consider voluntary movements as consequences of central modulation of parameters of certain reflexes (i.e. equilibrium point hypothesis).

A central notion common to all muscle reflexes is the reflex arc (figure 4.1.1).

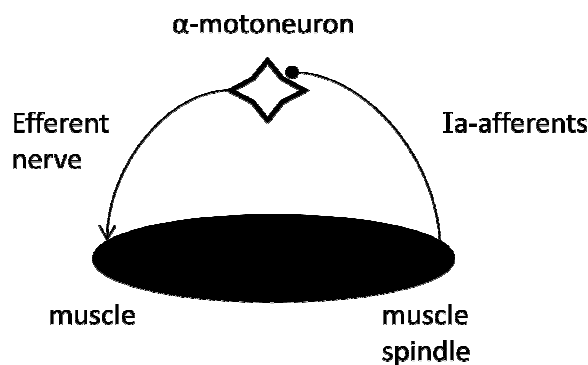


Figure 4.1.1: a monosynaptic reflex has only one synapse in its reflex arc. This synapse is between an afferent fiber and a α -motoneuron

The reflex arc consists of an afferent neuron that senses an external stimulus, a central processing unit and an efferent neuron that induces a muscle contraction. The central processing unit may be very simple, involving just one synapse (monosynaptic reflex), or very complex, comprising numerous synapses and integrating information from different sources (polysynaptic reflex). Each reflex involves a time delay between the stimulus and the reaction, called reflex latency (figure 4.1.2) (Latash, 2008). It consists of three components: time of afferent conduction, central delay, and time of efferent conduction. Conduction time apparently depends on the speed of the action potential propagation along the involved neural fibers and on the length of the fibers. Central delay depends mostly on the numbers of synapses involved in processing the afferent volley and in generating an efferent command.

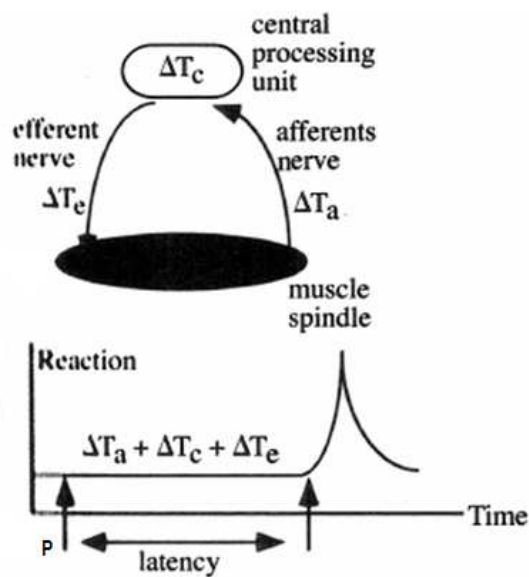


Figure 4.1.2: the delay between a stimulus and a reflex reaction is called reflex latency. It consists of an afferent conduction time (ΔT_a), a central delay (ΔT_c) and an efferent conduction time (ΔT_e)

One type of monosynaptic reflex is the stretch reflex (or myotatic reflex) which exerts a muscle contraction in response to stretching within the muscle, providing automatic regulation of skeletal muscle length in response to perturbations. According to the original description by Liddell and Sherrington (1924) the stretch reflex represents the reflex contraction of a functionally isolated muscle which is passively extended. When a muscle lengthens, the muscle spindle is stretched and its nerve activity increases. This increases alpha motoneurons activity, causing the muscle fibers to contract and thus resist the stretching. A secondary set of neurons also causes the opposing muscle to relax. The reflex functions to maintain the muscle at a constant length.

4.2 Pre-programmed reactions

Strong perturbations commonly induce muscle responses at an intermediate latency (50–90 ms) that have been addressed as long-latency reflexes, pre-programmed reactions, functional stretch reflexes, M2-M3 and triggered reactions (Tatton et al, 1978; Cordo, 1981; Bawa, 1991; Forssberg and Nashner, 1982; Chan and Kearney, 1982 Myklebust, 1990). The variety of terms reflects the different understandings of the nature and functional significance of these reactions. For convenience, we will refer to these reactions as pre-programmed reactions (PPRs).

PPRs have been described for both single-joint and multi-joint tasks (Nashner, 1976, Marsden et al., 1978, Cordo, 1981, Lacquaniti and Soechting, 1986 and Koshland et al., 1991). Their salient

features involve, in particular, dependence on the instruction or context in a wide sense. PPRs are triggered by a sensory stimulus and induce fast, crude corrections based on an earlier assessment of the mechanical effects of the perturbation (Marsden et al., 1981, Rothwell et al., 1982 and Rothwell et al., 1986).

In multi-joint tasks, PPRs have been shown to possess a number of features that suggest their rather complex central organization. These features involve non-local character of PPRs (their emergence in muscles whose state is not directly affected by the stimulus), their relative independence of the local joint kinematics, and the fact that their electromyographic (EMG) patterns look like those during voluntary movements performed by the same muscle groups (Lacquaniti and Soechting, 1986, Gielen et al., 1988 and Koshland et al., 1991). Hence, it has been hypothesized that PPRs represent peripheral effects of control patterns corresponding to fast corrective movements in involved joints (Gielen et al., 1988).

Pre-programmed reactions have been hypothesized to represent a transcortical reflex (a reflex whose loop involves neurons in the brain cortex), and this idea is still very much alive (Chan et al, 1979; Cheney and Fetz, 1984; Day et al, 1991). However, these reactions were observed in decerebrate animals and even in spinalized animals (animals without neural pathways connecting the cortex with the spinal cord) (Ghez and Shinoda, 1978; Miller and Brooks, 1981).

Latash (2008) describes one of the most common procedures for eliciting a PPR as follows. A subject maintains a constant position in a joint with a steady muscle contraction against an external load. For example, a load provided by a motor. The subject is instructed to return to the starting position as fast as possible in cases of external perturbations. The motor produces unexpected, rapid changes in load that give rise to a sequence of EMG events in the muscle (figure 4.2.1).

The first event M1 corresponds (according to its latency) to monosynaptic transmission and probably represents the phasic stretch reflex, a reflex similar to the one observed during a tendon tap T-reflex. After that, two (sometimes poorly differentiated) peaks appear at an intermediate latency. The first peak is addressed as M2, while the second one is called M3. These peaks are followed by a voluntary reaction. The latency of the intermediate reactions typically ranges from 50 to 100 ms, depending on the position of the muscle. The bottom panel of figure 4.2.1 shows an actual EMG activity of a human biceps brachii in response to loading (stretch), in which the M2-M3 peaks are clearly visible.

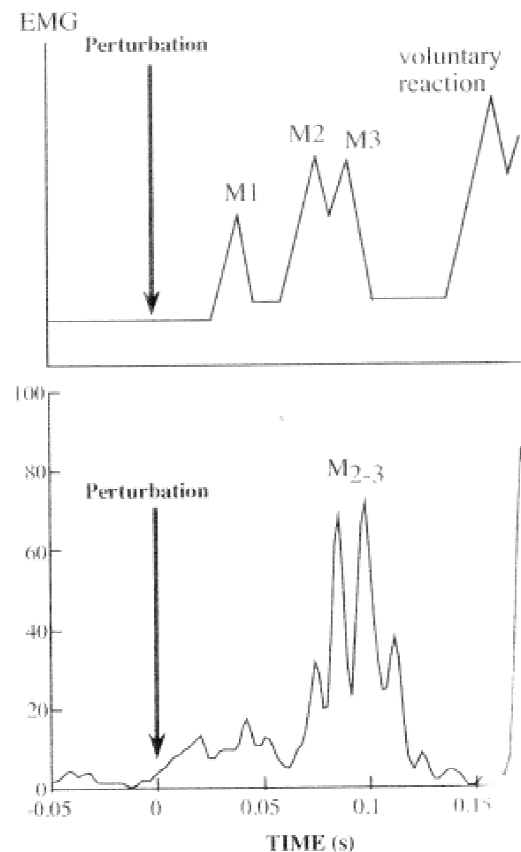


Figure 4.2.1: an unexpected perturbation of a joint creates a sequence of EMG events in the stretched muscle. The first comes at a short latency (under 40ms, M1); next are two peaks (M2, M3) that come at a latency between 50 and 100ms. These are PPRs. Later, voluntary reaction comes. The bottom panel shows an actual recording of the reaction of a human biceps muscle to an unexpected loading (perturbation)

PPR differ significantly from other reflexes in that they strongly depend on the instruction to the subject. For example, if we repeat the experiment described earlier but this time we instruct the subject not to resist to the perturbation, the amplitude of the pre-programmed reaction decreases significantly, and the reaction may even disappear.

4.2.1 Pre-programmed reactions versus stretch reflexes

Several experimental findings prevent us from considering PPRs as a stretch reflex because in PPRs the magnitude of the response does not depend unambiguously on the change in muscle length. Depending on the instruction to the subject, PPRs can be observed in stretched muscles, in muscles shortened by the perturbation and even in muscles whose length is not changed by the perturbation (Cordo, 1981). In addition, the amplitude of the PPR does not correlate with the amplitude of the applied perturbation if the latter cannot be predicted by the subject. Thus, in different trials the

compensation of the perturbation by PPRs can vary from 0% to 100% to overcompensation (Houk, 1976).

The fact that these responses are independent of the magnitude of perturbation suggests that the perturbation represents a non-graded signal for the response generation – a trigger- and that the response magnitude is define before the stimulus arrives. The, certainly, these reactions can be called *triggered* or *pre-programmed*. Consider figure 4.2.2: the instruction to maintain a joint position against a load requires the subject to generate a voluntary command to the muscles controlling this joint.

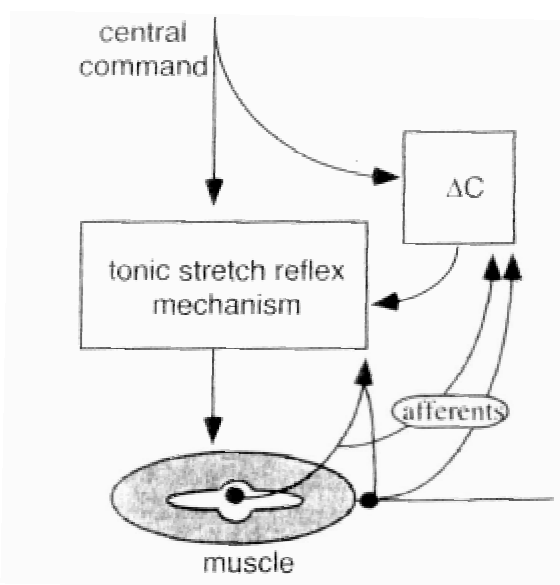


Figure 4.2.2: a subject sends a central command to a muscle to hold a position in a joint against a load. If the subject knows that a perturbation can occur he can prepare the central command to compensate for the predicted perturbation. The PPR (ΔC) is triggered by peripheral signals generated by the perturbation and attenuates the mechanical effects of the perturbation

If the subject knows that a perturbation can occur, a corrective command can be prepared in advance and be ready to be triggered by an appropriate peripheral signal. Note that this scheme implies that a “higher” center such as the cortex prepares the PPR, while the loop of the reaction may not involve the “higher” centers (Latash, 2008).

4.2.2 Afferent source of the pre-programmed reactions

Considering PPRs as triggered by a signal provided by a perturbation suggests that the search for a unique afferent source of these responses will provide unreliable results. In fact, the actual source of the triggering signal is not important as long as the signal carries sufficient information about the occurrence of the perturbation. In this context, signals for the PPRs can be provided by virtually any

peripheral receptors that deliver information on changes in load, position, pressure on the skin, etc. that is why experiments that selectively blocked the transmission along certain afferent systems have not provided conclusive information about the role of these afferents in generating PPRs (Latash, 2008). The PPRs disappear after total deafferentation of the limb, when the CNS does not receive any signals about the perturbation (Bawa and Mc Kenzie, 1981).

4.2.3 Main features of pre-programmed reactions

Three features of PPRs are worthy emphasize (Latash, 2008; Latash et al, 1993):

- PPRs depend significantly on the instruction given to the subject. Namely, the responses take place when the instruction is to compensate for the effects of perturbations as quickly as possible, whereas they are small or absent when the instruction is to ignore the perturbation. Thus, the subject can decide whether to pre-program or not.
- The emergence of PPRs in a muscle shortened by a perturbation is quite understandable since the subject can program any combination of command functions to any muscle or muscle group independently of a future perturbation on the muscle length.
- Since the amplitude of the PPR is defined before the perturbation occurs, random changes in the perturbation amplitude do not determine the amplitude of the PPR – there is no correlation. This reflects the preprogrammed nature of these responses
- PPRs are assumed to be triggered by multimodal sensory inputs, with important contributions from proprioceptive, visual and vestibular receptors.

4.3 Voluntary activation of muscles

Presently, two views exist on voluntary muscle activation. According to the first view, central commands directly specify the activity levels of α -motoneuronal pools and therefore specify the levels of muscle activation (Gottlieb, 1996; Gottlieb et al, 1989a,b). Reflex mechanisms are assumed to play a minor role, contributing mostly in cases of unexpected changes in the external forces (perturbations).

This view, however, is incompatible with some observations. For example, imagine that a person strongly activates a muscle against a large load and is instructed not to change the level of muscle activation (figure 4.3.1) (Latash, 2008).

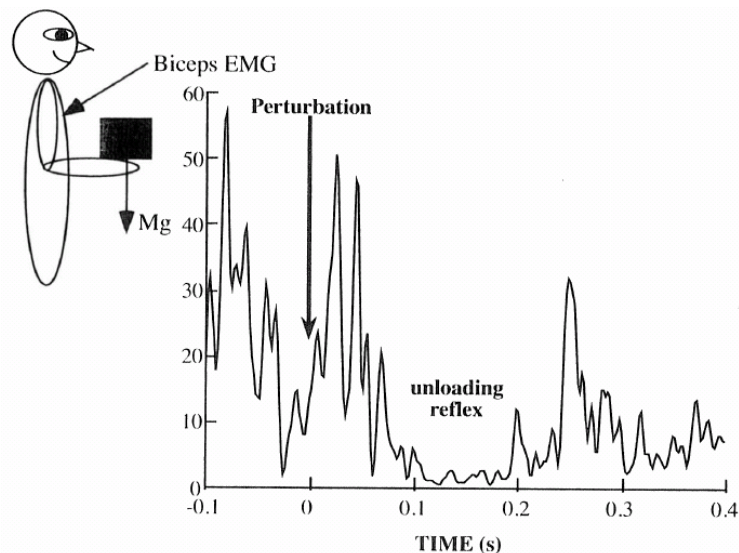


Figure 4.3.1: the subject holds a position at the elbow by activating the biceps against a load. The load is suddenly removed. The EMG of the biceps shows a period of complete silence (the unloading reflex) even if the subject tries to keep the biceps activity constant. This means that muscle activity is not an independently controlled variable

Now if the load is unexpectedly and quickly removed a fast movement will occur. An EMG of the muscle will show that, immediately after the unloading, there is a period of virtually total silence in the muscle activity. This effect is called the unloading reflex. Unloading leads to a quick shortening of the muscle (a decrease in its length at a high negative velocity), and so the sensory endings in the muscle spindles become silent and their reflex effects on the homonymous α -motoneuron disappear. The unloading reflex may be considered an inverse of the stretch reflex. The disappearance of muscle activity during the unloading reflex shows that the reflex effects may be strong enough to eliminate 100% of voluntary muscle activation. Thus the alternative view, the equilibrium point hypothesis, looks much more attractive.

According to the second view on voluntary muscle activation, central commands use muscle reflexes to change the levels of muscle activity and specify parameters of these reflexes. This view emerged as a formal language for describing a body of experimental data on single-muscle force-length characteristic curves in animals and single-joint torque-angle characteristic curves in humans (reviewed in Latash, 1993). Most animal experiments were performed on cats with a lesion of the CNS leading to a lack of the ability to make voluntary movements. An electrical stimulator was placed on the stump of the residual part of the brain to stimulate different descending commands. At a fixed level of stimulation and a constant external load, the muscle-load system will be in equilibrium at a certain length.

The combination of muscle length and force at equilibrium is called equilibrium point (figure 4.3.2).

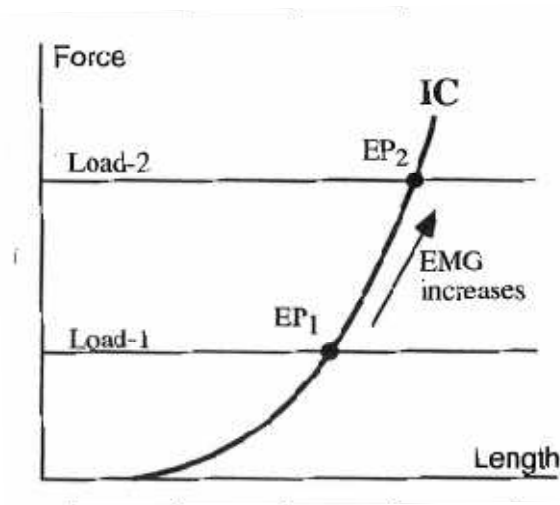


Figure 4.3.2: according to the equilibrium point hypothesis, muscle reflexes specify a relationship between muscle force and muscle length. This relation is called the invariant characteristic (IC).the muscle-load system is in equilibrium when the muscle force equals the external force (load). This point is termed the equilibrium point (EP). If the external load changes both muscle force and length will change and reach a new EP (EP₂). Muscle activity (EMG) changes along the IC

This is a central notion within the equilibrium-point hypothesis (Feldman 1966, 1986; reviewed in Latash, 1993; Feldman and Levin, 1995). A change in the external loads leads to a change in muscle length that alters the level of muscle activation via the tonic stretch reflex arc. Thus, a constant descending command does not mean a constant level of muscle activation. Altered muscle activation can be accompanied by changes in both muscle length and muscle force until a new equilibrium point is achieved. For a fixed descending command, all the equilibrium points form a curve on the force-length plane. This curve is called the invariant characteristic (IC).

In an animal experiment, if a different level of electrical stimulation is used to change the descending signals, a new IC emerges that is shifted with respect to the first one (figure 4.3.3). We can introduce a variable that encodes the location of an invariant characteristic, such as the point at which activation of α -motoneurons occurs (the threshold of the tonic stretch reflex). This variable may be viewed as a control variable because changes in the external load can only move the equilibrium point along the IC (Latash, 2008). Within this scheme, movements may result from changes in the external load, as in figure 4.3.2, or from central shifts of the IC, as in figure 4.3.3. A shift of the IC may have different peripheral effects, depending on the external load. In figure 4.3.3, a standard shift of the IC may change muscle length (compare EP₀ and EP₁, isotonic conditions),

muscle force (compare EP0 and EP2, isometric conditions), or both (compare EP0 and EP3, if the load is elastic).

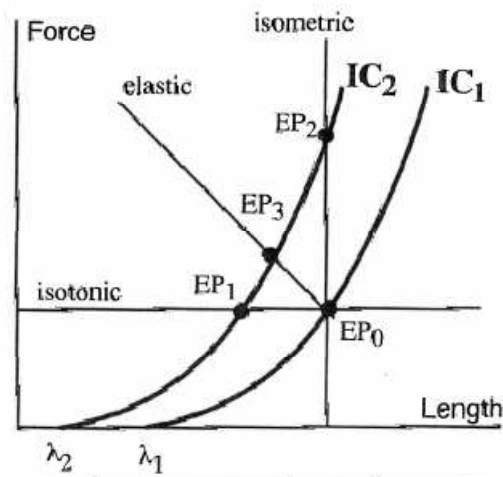


Figure 4.3.3: a central command specifies the location of an IC for a muscle. This can be described as a shift in the threshold of the tonic reflex (λ). Depending on the external load, a shift in λ can change muscle length (isotonic conditions, EP₁), muscle force (isometric conditions, EP₂), or both (elastic load, EP₃). EMG changes will depend on both the central λ changes and the external load

As far as neurophysiological mechanisms are concerned, the equilibrium-point hypothesis assumes that the tonic stretch reflex, providing for the muscle ICs, incorporates all the reflex loops that can be influenced by the activity or excitability of γ -motoneurons, α -motoneurons and inter-neurons. It does not single out one anatomical structure as being the most relevant. Moreover, the feedback loops from receptors other than muscle receptors (for example skin and subcutaneous receptors) can also help define the shape of the ICs. Thus it is assumed that central commands for voluntary movements involve a balanced combination of signals to all types of spinal neurons (figure 4.3.4) (Latash, 2008).

Control of voluntary movement consists in the central modulation of the threshold of the tonic stretch reflex for the participating muscles. Tonic stretch reflex and the peripheral muscle and tendon elasticity provide for the spring-like muscle behavior. Reflex effects play an important role in defining the levels of muscle activation.

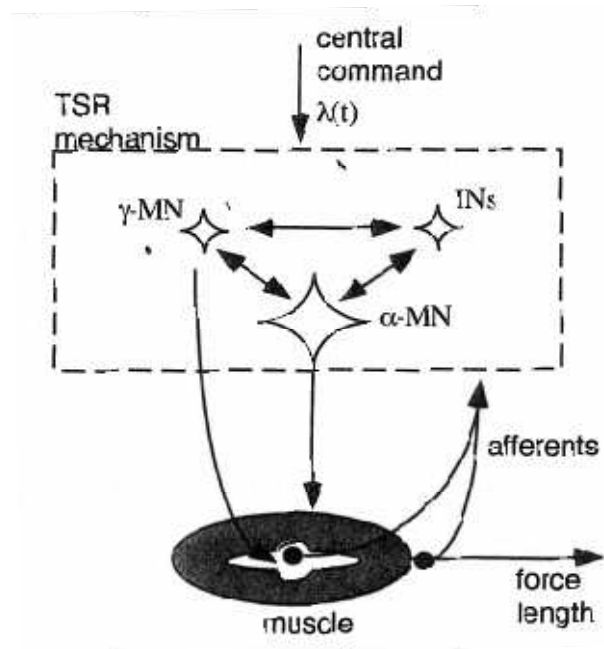


Figure 4.3.4: according to the equilibrium point hypothesis a central command represents a balanced combination of descending signals to all groups of spinal neurons, including α -motoneurons, γ -motoneurons and interneurons (INs). The tonic stretch reflex is assumed to incorporate all the reflex effects from all the peripheral receptors. Changes in muscle length (movement), muscle force and muscle activation emerge with equally important contributions from central commands and signals from peripheral receptors.

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Chapter 5

Monosynaptic reflexes and pre-programmed reactions in Down Syndrome

In daily life movements result from the balance between feedforward and feedback control (Seidler et al, 2004). However, in the previous chapter we have seen that motor planning is impaired in persons with DS and that they rely more on feedback than feedforward control. This results in slower movements. In addition, feedback control seems to be less efficient than in subjects without DS, leading to clumsier movements in DS.

We have demonstrated the presence of differences in the motor control of subjects with DS but before drawing some conclusions about rehabilitative guidelines for DS we need to clear out what the neural basis of these differences are and at which point of the neuromotor development differences between infants with and without DS begin to affect motor control. Understanding if differences in motor control are present since birth is very important for the definition of early and late intervention in rehabilitation.

A number of studies points out to the conclusion that the brain with DS at or shortly before birth is in main respects indistinguishable from the brain of a normal individual (Bar-Peled et al. 1991), whereas changes are present within 6 months of life (Dierssen, 2012). If this is confirmed, then subjects with DS should be able to exploit early control mechanisms, which are automatic responses to external perturbations, in the same way of controls. If not, they should always reveal different motor control strategies and different EMG activation patterns, as found in chapter 3 for more complicated functional movements. For these reasons we decided to focus on the most “primitive” motor control mechanisms, the monosynaptic reflexes and the pre-programmed reactions (PPRs), reviewed in chapter 4. These reactions allow to investigate how the first control mechanisms, the ones developed since the earliest phases of life, work in DS, drawing important information on the early neuromotor development in DS.

Bawa (1981), Forssberg and Nashner (1982) and Myklebust (1990) stressed the importance of the stretch reflex and PPRs for the acquisition of early motor skills. Maturation of human behavior, in fact, passes from the primitive reflexes to the gradual appearance of automatic, postural and adaptive reactions which make higher activities possible (Fiorentino, 1972). Monosynaptic reflexes and PPRs are the first to occur and the principal mechanisms for fast movement correction. From

these mechanisms all the more sophisticated feedback and feedforward mechanisms develop as consequence of experience.

Monosynaptic reflexes have been studied in literature regarding DS because they are strongly linked to hypotonia. The physiological basis for hypotonia, in fact, have been defined as decreased segmental motoneuron pool excitability and pathology of the stretch reflex mechanism (Gilman et al, 1981). Hypotonia has been largely addressed as the main problem in the motor deficits of persons with DS (Cicchetti et al, 1976; Dyer et al, 1990; Akerstrom and Sanner, 1993; Lauteslager et al, 1998), as reviewed in chapter 2. Recent work, however, casted doubts on this hypothesis (Davis and Kelso, 1982; Shumway-Cook and Woollacott, 1985; Latash and Corcos, 1991; Anson, 1992).

In this chapter we will review the principal literature about PPRs and the stretch reflex in DS and we will further analyze these phenomena.

5.1 Introduction

Stretch reflex and PPRs have been studied in relation to postural control of the standing position and in relation to responses to external perturbations in the upper limb, as reviewed following.

Stretch reflex and pre-programmed reactions during postural control

Stretch reflexes and PPRs are important components of everyday activities, particularly of postural control and locomotion. Unexpected perturbations of vertical posture, in fact, elicit compensatory reactions at low and intermediate latencies before voluntary reactions intervene at longer latencies (Nashner, 1976; Nashner et al, 1979).

Studies on postural reactions usually employ a rotating or translating platform on which the subject is standing and have shown that normal children (14 months to 10 years) and healthy adults compensate for externally induced body sway in the sagittal plane through the activation of automatic postural responses. These responses are characterized by stereotyped patterns of muscle activations in the leg and trunk (Nashner, 1976; Shumway-Cook and Woollacott, 1985). Some of these reactions seem rather general, such as coactivating agonist-antagonist muscle pairs stabilizing a postural joint regardless of the direction of the perturbation. Other reactions are specific to the direction and type of perturbation (Latash, 2008). These long latency postural responses have been shown to be more effective than the monosynaptic stretch reflex in returning the centre of mass within the base of support (Gurfinkel et al, 1971).

Shumway-Cook and Woollacott (1985) studied the dynamics of postural control in children with DS and developmentally normal children in two age groups (1-3 years and 4-6 years) by using a

displacement platform and measuring EMGs from the lower limbs muscles. They pointed out some interesting observations about the nature of functional balance deficits in DS. Their results questioned the common view that attributes developmental delays and balance problems in DS to decreased segmental motoneuron excitability and pathology of stretch reflex mechanism leading to hypotonia (Gilman et al, 1981). In fact, the presence of the monosynaptic reflex during platform perturbations at normal latencies suggested that the balance problems in children with DS did not result from hypotonia, but rather resulted from defects within higher level postural mechanisms. This is in agreement with a previous study (Davis and Kelso, 1982) which demonstrated a comparable ability in subjects with DS and with normal development to set or modulate voluntarily muscle stiffness. However, Shumway-Cook and Woollacott (1985) found that onset latencies of long latency responses (PPRs) in children with DS were significantly slower than in normal children, and resulted in increased body sway and, in some instances, in loss of balance. The presence of myotatic reflexes at normal latencies in conjunction with significant delays in long latency postural responses is consistent with the results from studies that examined the effect of cerebellar lesions on long latency postural responses. Those studies found normal short latency (myotatic) responses but delayed PPRs in patients with cerebellar lesions and in animals with reversible cooling of the cerebellar nuclei (Nashner et al, 1983; Marsden et al, 1977; Vilis and Hore, 1980).

Stretch reflex and pre-programmed reactions during upper limb movement perturbation

Stretch reflex and PPRs during upper limb movements have been studied in literature with several modalities (Gielen et al, 1988; Latash et al, 1993; Koshland et al, 1991; Yamamoto et al, 2000; Latash and Corcos, 1991). Usually, they have been observed in response to load perturbations applied at the wrist joint during isometric elbow flexion-extension and/or supination-pronation by measuring EMG activity to the flexors and extensor muscles. A pre-load was usually applied to the arm and perturbation magnitude and direction could be either known or unknown to the subject in advance.

Latash and Corcos (1991) studied the kinematic and EMG characteristics of single-joint movements in ten teenage and young adults with DS and in six age-matched controls. The subjects were required to occupy the initial position (90° flexion in the elbow joint) against an extensor bias torque and wait for the perturbation. Changes in the bias torque were delivered randomly about every 8 seconds, with loadings and unloadings. Subjects were asked either to “let the arm do what it wants” (let go) or “to return to the initial position as fast as possible” (react). Superficial EMG

activity from the biceps brachii, brachioradialis and lateral and long heads of the triceps was measured.

All the subjects with DS demonstrated all the typical EMG components seen for the control subjects. These included a short-latency reflex (under 50ms), presumably monosynaptic, and a longer-latency PPR about 70 to 80 ms. These reactions started as an increase in the agonist activity in cases of loading and a decrease in case of unloading. When the instruction to the subjects was changed from “react” to “let go” the PPRs EMG components did not demonstrate any visible modulation for 9 out of 10 subjects with DS. Thus, these subjects failed to demonstrate appropriate changes in the PPRs when the instruction was changed, corroborating the idea that individuals with DS are deficient in their ability to adapt their motor commands to unexpected changes in sensory information (Cole et al, 1988; Shumway-Cool and Wollacott, 1985). For the 10th subject, however, the biceps EMG burst at a latency of about 80 to 90 ms was considerably higher under the “react” instruction (figure 5.1.1).

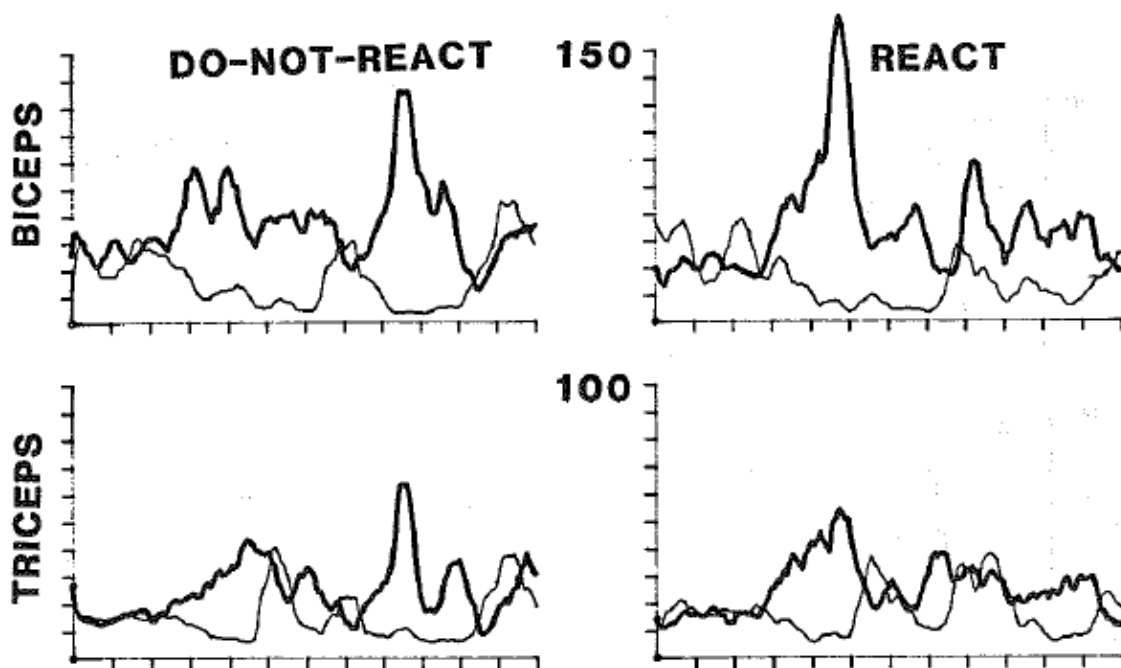


Figure 5.1.1: averaged data for the only subject with DS who demonstrated modulation of the PPRs to perturbation (torque). Note three components of the reaction to the biceps loadings in the EMGs of biceps (thick traces): the first one, monosynaptic, with a latency of about 30ms, the second one, re-programmed, with a latency of about 70ms and the third one, voluntary, with a latency of about 250ms. when the instruction was changed from “do-not-react” to “react” the amplitude of the second component increased. EMG scales are in μV , time scale in ms

This is an encouraging finding because it suggests that the ability to modulate these reactions might not be totally absent in all individuals with DS but, rather, that these reactions may be profoundly impaired.

To further analyze PPRs in DS, Latash et al (1993) applied predictable and unpredictable perturbations to a group of eight persons with DS (aged between 15 and 35 years), with the same apparatus of the previous study. Subjects underwent three sessions: in the first session they were instructed not to react to an unpredictable load, in the second session they were instructed to react to the unpredictable load and in the third session they had to react to a predictable perturbation (they were told the direction of the perturbation). They found PPRs occurring at about 60 to 70 ms (figure 5.1.2).

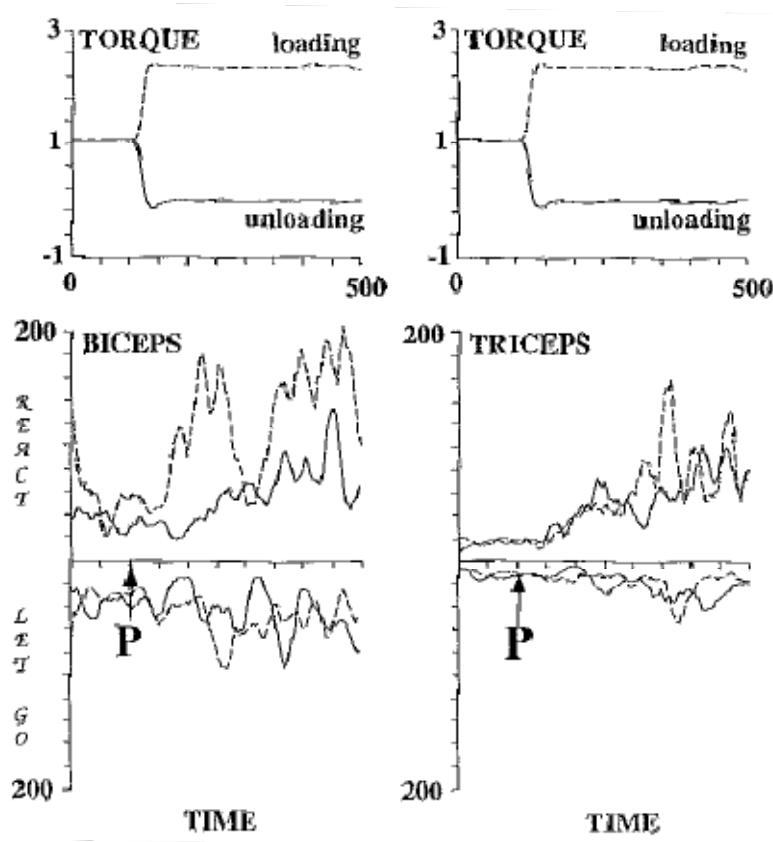


Figure 5.1.2: examples of the averaged EMG reactions in the biceps and lateral head of the triceps of a subject to the maximal loading (increase in the extending torque, broken traces) and maximal unloading (decrease in the extending torque, solid traces). The upper pairs of EMG traces correspond to the instruction “react”, and the lower traces correspond to the instruction “let go”. The EMG for the “let go” are inverted to provide better visual comparison. P=instant of perturbation onset. EMG scales are in μV , time scale in ms.

Unlike their previous study (Latash and Corcos, 1991) and other reports on deficits in pre-programming in DS (Sumway-Cook and Wollacott, 1985) all of the subjects with DS were able to modulate their PPRs in at least one muscle group in response to a change in the instruction, although with quite different patterns of modulation. Patterns of muscle activation in DS represented a mix of reciprocal strategy for the biceps and of a co-activation strategy for the other muscles acting around the elbow joint. The authors explain these findings in light of a decision-making problem that may have caused an incomplete understanding of the instructions in previous work. Also psychological variables, such as nervousness, may have played a role in masking the capacity of PPRs modulation in previous work.

Subjects with DS demonstrated the ability to modulate the PPRs depending on the direction of the perturbation (loading or unloading). In particular, a consistent increase was found in the corrected EMG integrals for the biceps in response to the loadings and a consistent decrease was found in response to the unloading. Unexpectedly, however, no predictability effect was found, and predictable perturbations did not lead to more reproducible and pronounced PPRs, probably due to a residual doubt about the task conditions.

The authors stress that no abnormality was found in the motor control mechanisms of subjects with DS. In their opinion this happened because the reproducible and “friendly” conditions of the laboratory lead to virtually normal performance in the motor tests, whereas in daily-life conditions persons who feel unconfident in their abilities to make quick judgments concerning current motor tasks, current conditions of execution and their possible future changes will tend to suppress those control mechanisms that may be potentially harmful, such as fast movements and modulation of PPRs. If this hypothesis stands, the authors conclude, most of the differences between DS and controls may be subjected to correction by extensive explanation and practice. This is in agreement with what has been demonstrated by Corcos et al (1993) and Almeida et al (1994) for single joint voluntary movements in individuals with DS: these authors showed that subjects with DS can use patterns of muscle activation that are quantitatively indistinguishable from those used by neurologically normal individuals and, with appropriate training, they can achieve similar levels of motor performance.

Methodological problems in the analysis of stretch reflex and pre-programmed reactions

When analyzing the EMG signal, especially in relation to PPRs, some methodological difficulties are stressed in literature. These problems are related to the analysis of the signal and to physical features of DS.

Analysis of EMG signal

A core problem when analyzing stretch reflex and PPRs is signal processing. Most of the studies record EMG signals from surface electrode to avoid the invasive and painful needle technique, at a price of a more noisy measure. Once the signal has been recorded (at a frequency $\geq 1000\text{Hz}$) it must be processed. As stated by Latash (2008), it is hard to offer rules for EMG processing, particularly when dealing with a very noisy signals, such as the PPRs components in persons with DS, whose peaks are quite commonly merged and poorly differentiated. However, some guidelines are present in literature (Yamamoto et al, 2000; Latash et al, 1993). The EMG is amplified (1.600x) and high-pass filtered with a cut-off frequency of 40-60 Hz to reduce instrumentation noise as well as possible electrode reactions to purely mechanical factors. A low-pass filter with cut off frequency of 500 Hz is then used. Trials are full-wave rectified and smoothed by a 10 ms or 25ms moving window. The instant of the perturbation onset (t_0) is defined by visual inspection and all the EMG signals were aligned at time t_0 for averaging. About 10-12 trials are collected for averaging. The latencies of the M1 (monosynaptic reflex), M2 and M3 (PPRs) peaks are then calculated. Starting from the time of perturbation (t_0), different latency ranges have been proposed for the monosynaptic and PPRs reflexes of the upper limb, depending on the distance between the muscle and the spinal cord and on the type of perturbation. Table 5.1 in the next page shows different activation ranges for the upper limb muscles, as described in literature, during external perturbations with a preload and the request to “resist the perturbation”.

It can be noted that the ranges of latency are variable across authors and that the latencies for subjects with DS and for control subjects resulted in the same ranges. Authors agree that reasonable latencies for the monosynaptic reflex of the flexor and extensor muscles of the upper limb are around 25ms whereas PPRs should occur between 50 and 80ms. Yamamoto et al (2000) found higher values for the peak M3, whereas Gielen et al (1988), who performed needle EMG, noted that over 75ms voluntary reactions already start to play a role.

Extraction of PPRs peaks is complicated by the fact that the amplitudes of the reflexes are not defined in the papers and peak M2 is not always present (Latash, 2008). Thus, the identification of a peak relies mostly on the kind of pre-processing used, on the latency range defined for that reaction and on visual evaluation of the signal.

Authors	Group (number)	Kind of analysis	Muscles, perturbation direction	Monosynaptic lat. mean (sd) (ms)	PPR lat. mean (sd) (ms)
Gielen et al, 1988	Healthy adults (5)	needle EMG	Triceps b., flexion	31 (2) ms	56 (4)
			Triceps b., pronation	none	61 (4)
			Brachialis m., extension	28 (1)	52 (2)
			Biceps b., extension pronation	25 (2)	50 (4)
			Biceps b., flexion supination	31 (3)	N/A
Yamamoto et al, 2000	Healthy adults (10)	Surface EMG	Biceps b., extension	15-30	M3: 75-90
Latash and Corcos, 1991	Teenagers and adults <u>with DS</u> (10); Healthy adults (6)	Surface EMG	Biceps b., extension	<50	70-80
Latash et al, 1993	Teenagers and adults <u>with DS</u> (8)	Surface EMG	Biceps b., extension	<50	60-70

Table 5.1: activation ranges for the upper limb muscles during external perturbations with a preload and the request to “resist the perturbation”

Velocity of signal conduction and allometric features in DS

When analyzing EMG signals one should take into account at least two possible features of subjects with DS that may play a role in nerve conduction and result in differences in the EMG signals of controls and subjects with DS.

The first difference deals with velocity of signal conduction. Some evidence (Chen and Fang, 2005; Epstein, 2001; Ferri et al, 1996; Shah, 1979; Stimson et al, 1969) is present of a slowed velocity of conduction in children and adults with DS, which has been linked to DS-specific neuropathologic and neurochemical abnormalities, such as abnormal dendritic spine morphologic features and numbers and different myelin composition. Other authors (van Trotsenburg et al, 2006) suggest that thyroid hormone deficiency may also be related to nerve conduction abnormalities in DS.

The second feature to be considered is allometry: people with DS, in fact, have lower heights than the general population, with shorter arms and legs, which obviously affects conduction time. In general, the studies reviewed about EMG analysis in DS (Gielen et al, 1988; Koshland et al, 1991; Yamamoto et al, 2000; Latash and Corcos, 1991; Shumway-Cook and Wollacott, 1985) do not take into account these problems, except for Latash et al (1993), in which the authors did not provide a control group of reference because of allometric differences between controls and DS. However, the authors discussed their findings in light of qualitative comparisons with the control population of other studies present in literature.

Thus, it seems that velocity of signal conduction and allometry do not prevent EMG analysis and comparisons with controls. Another consideration in support to this hypothesis is the notable amount of experiments regarding reaction time tasks in DS (for example Brunamonti et al, 2011; Obhi et al, 2007; Davis et al, 1991; Nettlebeck and Brewer, 1981). Clearly, velocity of conduction and allometry play an important role in this kind of studies, which are among the most used to analyze rapid processing and decision-making in DS in comparison with controls.

Literature stresses the importance of the stretch reflex and, moreover, of PPRs mechanisms for movement correction and proper motor control. These mechanisms develop since early ages and can thus help investigate the early stages of motor control development. Since subjects with DS show impairments in higher motor control mechanisms it could be interesting to evaluate the efficacy of the primitive control reactions in this population, to understand whether the difficulties in motor control are present since birth or if they develop later as a consequence of the different child's sensorial, cognitive and motor experiences.

To partially shed light on this important topic, we analyzed the pre-programmed reactions (PPRs). These reactions were chosen because they had some interesting features:

- they are among the first mechanisms to develop in early stages of the child development and, given the fact that children with DS experience delays in the motor milestones compared to their peers without DS, they can be linked to early phases of motor development in DS;

- since they are crude responses modulated by prior instruction, once the instruction has been fully understood by the subject they are less affected by decision making deficits: while the preparation of the PPR implies the work of a “higher” center such as the cortex, the loop of the reaction does not involve the “higher” centers and it allows studying control mechanisms with a less masking effect from voluntary will;
- they can be studied with a simple experimental set up (in terms of instrumentation, duration, instructions to the performer), avoiding fatigue and loss of attention by the subjects.

In combination to this, the study of stretch reflex may add evidence to the hypothesis of the presence/absence of a deficit in the regulation of the stretch reflex in DS, providing important information on the role of hypotonia in DS, and consequently on the therapeutic strategies that may be applied. For these reasons, and given the little literature regarding DS, we analyzed fast movement correction mechanisms during resistance to an external perturbation of the upper limb in subjects with DS and in controls.

5.2 Methods

Subjects

8 subjects with DS (mean age \pm standard deviation: 22.6 ± 9.2 years; 58.8% males, 45.2% females) and 21 age-matched normally developed subjects (N) (mean age \pm standard deviation: 29.0 ± 4.0 years; 50.0% males, 50.0% females) were evaluated. Inclusion criteria and more details can be found in appendix I.I and I.II.

Acquisition

The experimental protocol was designed with portable instrumentation, to allow easy transfer to every laboratory or clinical structure. Most of the methods in literature require controlled movements. However, we decided not to constrain the joint movement, to allow more natural conditions of testing (Latash et al, 1999; Lacquaniti and Soechting, 1986).

As shown in figure 5.2.1 the subject seated on a chair with his dominant arm flexed at approximately 90° and holding the handle of a bucket in his dominant hand. This preload was used to activate the motor units and elicit reflex activity (Gielen et al, 1988).

Two EMG sensors recorded the biceps brachii caput longum and triceps brachii lateral head activity of the dominant arm.



Figure 5.2.1: experimental set up

At the bottom of the bucket a pressure switch was fixed; a small hole at the bottom allowed the wire to pass outside the bucket and to connect the sensor to the recording unit attached outside (figure 5.2.2). Subjects were told that the examiner was going to throw a weight inside the bucket and that they had to resist the perturbation and come back to the start position as soon as possible. Vision was excluded to avoid preliminary adaptations as the weight approached the bucket. Extensive explanation and demonstration was provided to make sure that they had understood the instructions.



Figure 5.2.2: the pressure switch (on the left) was fixed at the bottom of the bucket, whereas the record unit (on the right) was attached outside the bucket

Without giving notice to the subject, the experimenter let a 2kg weight fall inside the bucket. The initial position of weight-throwing was similar across trials, and it was close to the bucket border. The task was repeated 20 times, with pauses every each 5 trials to allow arm rest.

Instrumentation

The tasks were acquired using a portable wireless electromyograph integrated with a pressure switch (BTS, Italy). More details about the laboratories and the instrumentation can be found in appendix II.

Data elaboration

The EMG and switch data were exported in .txt files using SmartAnalyzer (BTS, Italy), see Appendix IV. The files were then uploaded and processed in MatLab (MathWorks, USA). Each trial was band-pass filtered between 20 and 499Hz with a 150th order zero-phase forward and reverse digital FIR filter. A Kaiser window was used to design the filter. The Root Mean Square (RMS) of the filtered signal was calculated using a 10ms time constant to enhance the EMG peaks with no biasing of the temporal changes in the signal (Weeks et al, 2000; Merletti and Di Torino, 1999).

Figure 5.2.3 shows the steps of elaboration (raw signal, filtering, RMS) for a single signal.

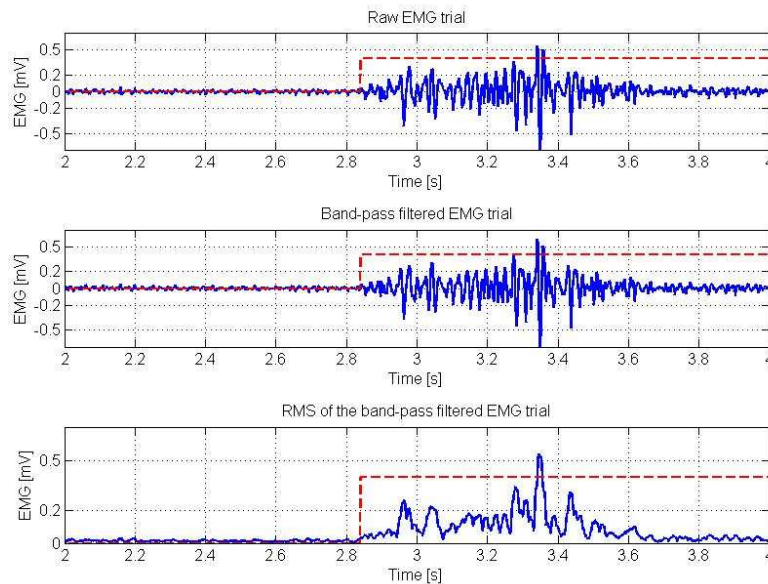


Figure 5.2.3: EMG signal (in blue) for a subject with DS and pressure switch signal (in red) that shows the instant of perturbation onset. Upper panel: raw signal; central panel: band-passed filtering; lower panel: root mean square (RMS)

EMG signals were aligned at the perturbation onset t_0 , defined as the instant in which the switch signal became “on”, and averaged for each participant, then a moving average filter with a window of 8ms was used to smooth the data (figure 5.2.4)

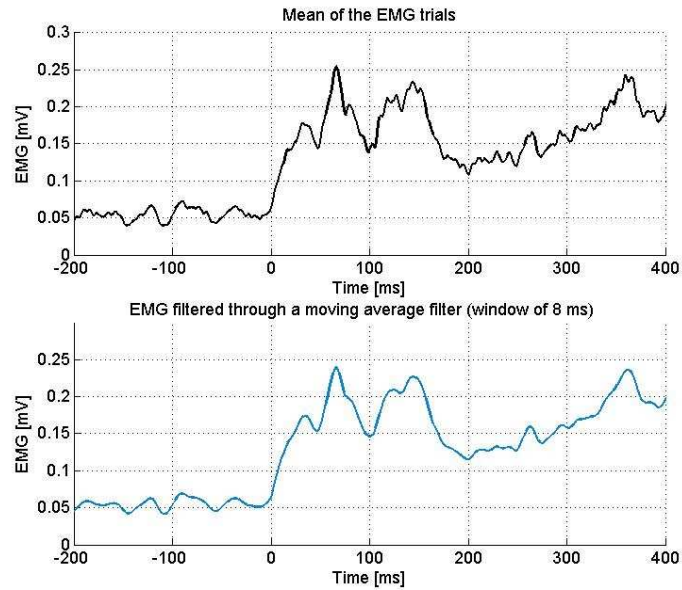


Figure 5.2.4: average of 20 trials from the same subject with DS (upper panel) and smoothing with a moving average filter (lower panel)

The peaks of latency for the monosynaptic reflex (M1) and for the PPRs (M2, M3) were defined by visual selection on the smoothed data. In particular, the M1 latency range was set between 20 and 49 ms, M2 and M3 latency ranges were set between 50 and 80ms (figure 5.2.5) (Latash and Corcos, 1991; Latash et al, 1993). After peaks detection the M1, M2 and M3 latencies from t_0 (ms) were computed.

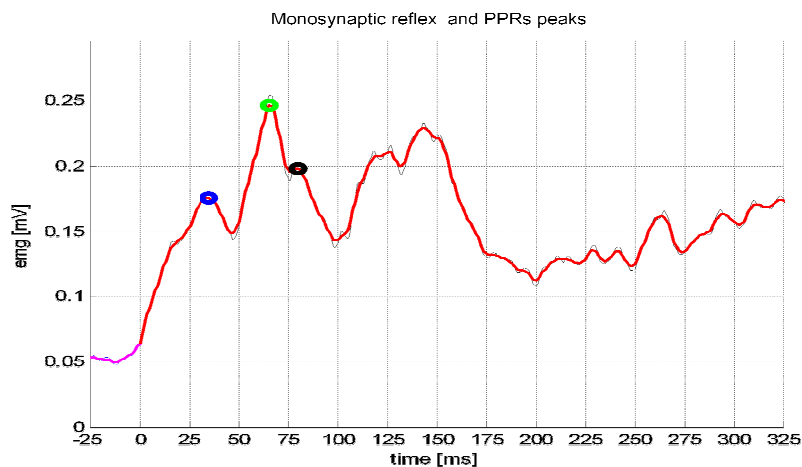


Figure 5.2.5: definition of the peaks M1 (in blue), M2 (in green) and M3 (in black) for the biceps of a subject with DS

The cross-correlation functions (CCs) between the pairs of averaged EMG signals were calculated for each subject after filtering the EMGs with a 40Hz second-order Butterworth filter (figure 5.2.6)

to analyze the presence of synergies between the biceps and triceps muscles (Latash et al, 1995; Aruin et al, 1996).

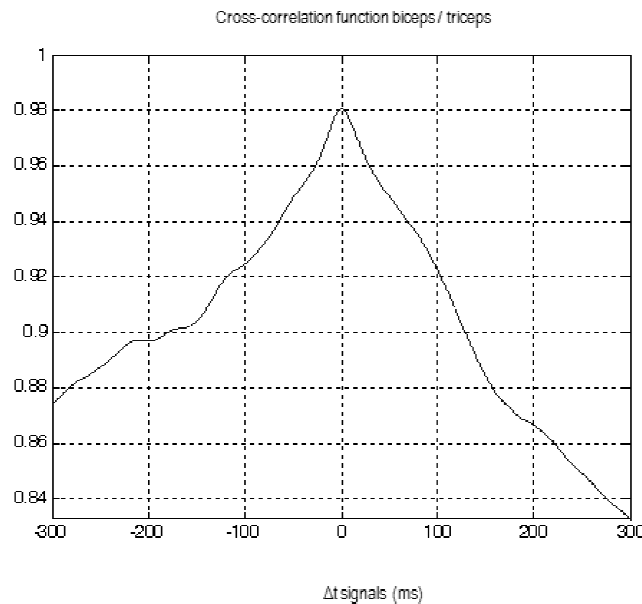


Figure 5.2.6: normalized cross-correlation function for biceps and triceps EMG signals in a subject with DS

Such additional filtering was done to obtain the relative timing of EMG envelopes. The CCs describe the probability as a function of time that there is activity in one muscle given the activation of another muscle. Such an analysis provides a ready visualization of the temporal relationships between the patterns of activation of different muscles. The CCs was normalized between 0 and 1. Peak values of the normalized CCs and time shifts (ms) of the peaks were measured (for convention we defined the shift of the biceps respect to triceps).

Co-contraction was defined as a zero time shift in the CC peak (CC shift=0 ms) and the percentage of occurrence of co-contraction was calculated for the two groups.

We preferred the CCs analysis rather than the measurement of time delays between the onsets of EMG bursts because the second method works reliably only in cases of well-defined EMG bursts on the background of a relatively quiescent muscle. Previous experience suggested that persons with DS could demonstrate a substantial level of background muscle co-contraction that would make this method unreliable. In addition, holding the forearm and the hand in the initial position required a degree of muscle co-contraction even in control subjects (Latash et al, 1995; Aruin et al, 1996).

Statistical analysis

Significance level was set at $p\text{-value}=0.05$. The distribution of the data was verified using the Kolmogorov-Smirnov test of normality. A Mann-Whitney U- Test was used to compare results from the Ds and N groups ($p\text{-value} < 0.05$). The median, 25° and 75° percentile values were used to describe the data.

5.3 Results

All the subjects were able to complete the evaluation. None of the subjects reported fatigue or demonstrated loss of attention during the execution.

Data analysis revealed that peak M2, corresponding to the first PPR, was not always present in the subjects, because sometimes the two peaks M2 and M3 merged into one, in agreement with what was found in literature (Latash, 2008; Yamamoto et al, 2000).

Figure 5.3.1 shows an example of a subject that presented only the monosynaptic and M3 responses (panel A) and of a subject that presented the complete set of peaks (panel B).

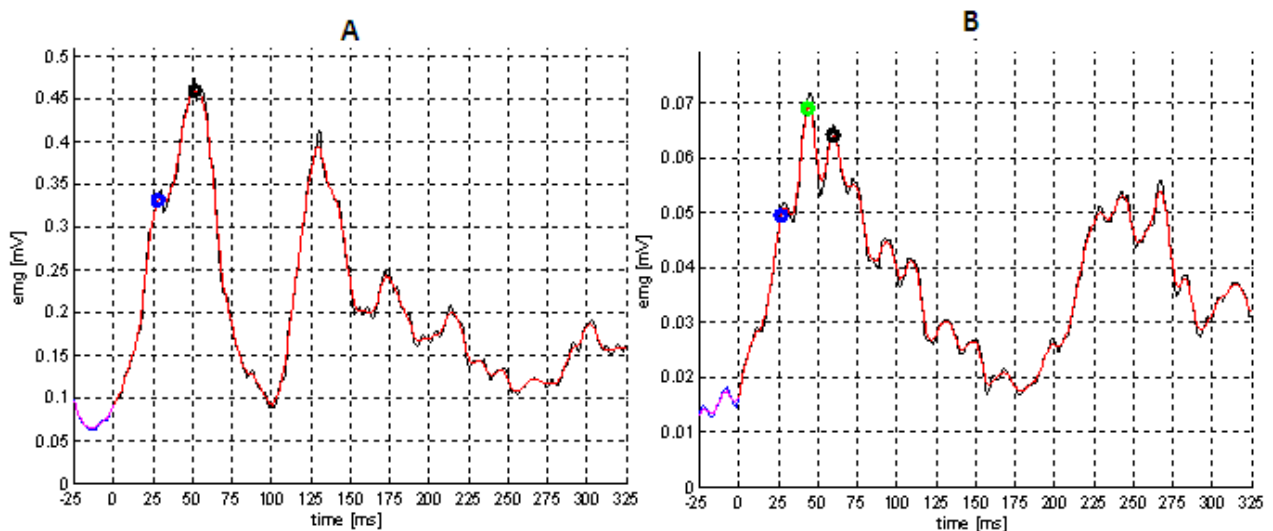


Figure 5.3.1: RMS of the EMG signals from a subject that showed only the monosynaptic and M3 response (panel A) and of a subject who showed the complete set of peaks

Table 5.2 displays the latency values for the peaks M1, M2 and M3 and the CC shift for N and DS. Note that peak M1 was not considered for the triceps, since the perturbation caused an extension movement of the elbow, stretching the biceps and shortening the triceps.

	DS	N
Latency (ms)		
<i>Biceps</i>		
M1	34.00 (27.25, 38.75)	35.50 (28.25, 38.75)
M2	59.00 (52.50, 62.50)	56.00 (51.50, 59.00)
M3	60.00 (58.50, 62.50)	60.00 (59.00, 72.00)
<i>Triceps</i>		
M1	--	--
M2	53.00 (52.00, 55.00)	58.00 (50.50, 59.25)
M3	64.50 (60.25, 66.75)	67.50 (64.50, 76.25)
Cross-correlation		
Presence of co-contraction (%)	75.00	66.50
CC shift (ms)	-0.50 (-1.25, 0.25)	-2.00 (-6.00, 0.00)
CC peak	0.96 (0.94,0.98)	0.97 (0.96,0.98)

Table 5.2: median (25°, 75° percentile) values for the latencies of the peaks M1, M2, M3 of the biceps and triceps muscles and for the CC shift in DS and N.

The results evidenced no significant difference between the peaks latencies of N and DS. Also the time delay between biceps and triceps, as represented by the CC shift, was comparable in DS and N. However, a tendency towards a more predominant use of co-contraction was suggested in DS by the percentage of co-contraction and by the values of the CC shift (closer to 0.00), even though with no statistical significance. More subjects may be needed in the DS group to give this trend a statistical significance.

5.4 Discussion

In previous chapters we documented the perceptual-motor difficulties of subjects with DS when executing a functional task and the decreased use of feedforward control in these subjects, with consequent slowed down and less efficient performances. The previous chapters gave proof of the prevailing effect of motor planning deficits in DS, but left us with some unanswered questions about how to design a focused rehabilitative therapy:

- What are the neural basis of the motor control differences between subjects with DS and controls?
- Are these differences present since birth or do they result from the interplay of neural development and sensory, cognitive and motor experiences as the child grows up?
- What are the rehabilitative strategies that could possibly lead to a maximization of the residual abilities of DS?

It is essential to understand whether motor control difficulties are present since birth or if the neuromotor patterns of subjects with DS are potentially normal at birth, to provide evidence for the necessity of early intervention programs in this population. In addition, it is important to provide evidence on the debate about the role of hypotonia in DS. Hypotonia, which is associated to the pathology of the stretch reflex mechanism (Gilman et al, 1981), has been largely addressed as the main problem in the motor deficits of persons with DS (Cicchetti et al, 1976; Dyer et al, 1990; Akerstrom and Sanner, 1993; Lauteslager et al, 1998), but this view has been recently questioned (Davis and Kelso, 1982; Shumway-Cook and Woollacott, 1985; Latash and Corcos, 1991; Anson, 1992).

To study the functioning of these elements in the motor control of DS we defined a very easy-to-apply set up. We chose portable and user-friendly instrumentation to allow the acquisitions to take place virtually everywhere.

We calculated the latencies from perturbation onset for the monosynaptic reflex and for the PPRs, and in addition we computed the cross-correlation function between pairs of antagonist muscles of the upper limb to investigate the presence of synergies.

Mechanisms for fast movement correction in Down Syndrome

This study evaluated the stretch reflex and PPRs mechanisms for movement correction. The results about latency showed no differences between groups for the peaks in the biceps and triceps in terms of peak delay from onset of the perturbation, suggesting that, in terms of latency, there is no evident difference between DS and controls in the monosynaptic reflex and PPRs. This is partially in agreement with Sumway-Cook and Wollacott (1985), who found normal stretch reflexes but

delayed long latency responses during perturbation of the standing position in children with DS, and is in total agreement with Latash and Corcos (1991), who evaluated perturbations in the upper limb in teenage to young adults with DS, an age range comparable to the one of our study.

These results provide evidence that, since the stretch reflex seems normal, motor deficits in persons with DS do not result from hypotonia, or at least this is not the primary cause, but instead they result from deficits in higher afferent pathways and/or efferent pathways in response to the stimuli. Thus, we can agree with Latash et al (1996) and Anson (1992) who questioned the role of hypotonia as a central problem in DS, and stated that the role of hypotonia in accounting for movement disorders in individuals with DS can no longer be considered a default explanation. This may explain why traditional treatments that focus on improving muscle tonus in children with DS show little functional gains in the acquisition of developmental skills.

In the course of this study we did not find any basic abnormality in the early motor control mechanisms of subjects with DS. The presence of normal stretch reflexes and PPRs suggests that under friendly and encouraging laboratory conditions and extensive explanation of the task subjects with DS can reveal normal patterns of activation for fast movement corrections. Since these mechanisms develop in the early phases of life, these results provide evidence to the hypothesis that neuromotor patterns in DS are comparable to those of normally developing infants at the very beginning of their sensorial exploration of the external world. However, some changes occur very soon after birth, which cause a delayed or a different neuromotor development in DS (we will try to shed light on the possible causes of these changes in the next chapter). This is clear if we take into account previous results from chapter 3, where we tested complex functional movements, finding not only slowed down performances, but also different motor strategies in DS. Whether development in children with DS can best be understood in terms of a slowed-down version of normal development, i.e. with only the rate and endpoint distinguishing development in children with DS from normally-developing children, or whether development in DS differs in fundamental ways from normal developmental processes is a long-standing debate in physiotherapy, because it leads to different conclusions about the best rehabilitative strategy to be adopted. Some data support the view that there are significant differences in how development unfolds in children with DS (Latash et al, 2008; Nadel, 2003), consistently with the growing body of data from the neurosciences showing significant differences in the structure of the DS brain and in how it works (Dierssen, 2012), whereas other propend for the delayed development hypothesis (Sacks and Buckley, 2003), noting that all the basic motor skills are achieved by infants and children with DS in the same order, but usually at significantly older ages when compared with typically developing infants and children (Sacks and Buckley, 2003 a,b; Berry et al, 1980, Winders, 1997).

Patterns of muscle activation in Down Syndrome

Co-contraction is a well known feature of DS in voluntary movements (Almeida et al. 1994; Aruin et al. 1996). An indirect proof of the presence of co-contraction strategies in voluntary movement in DS was found in chapter 3 for the tapping task. Several groups of researchers noticed that EMG patterns during PPRs induced by external mechanical perturbations looked like those during voluntary movements performed by the same muscle groups (Gielen et al, 1988; Koshland et al, 1991; Lacquaniti and Soechting, 1986). Therefore, PPRs can tentatively be viewed as consequences of central commands corresponding to a quick voluntary movement in an appropriate direction. According to the views of Gelfand and Tsetlin (1996) voluntary movements of a limb are controlled not with individual commands to muscles and joints but by uniting joints into a structural unit which is controlled as a whole. One may hypothesize that such an organization is flexible and based on the lifetime experience of a person. As such, it can show differences among persons while being reproducible within each particular subject across tasks (Latash, 2000). This would explain the different motor strategies found for the subjects of our study as well: in fact, a mix of muscular patterns was found in both groups, with subjects showing reciprocal patterns of muscular activation and others showing co-contraction patterns.

The mixed strategies in the groups of subjects resulted in no significant difference between groups in the patterns of muscular activation. A high percentage of control subjects and subjects with DS used co-contraction, with median values of the CC shift close to zero. Figure 5.4.1 in the next page shows the RMS traces of the EMG of a subject who showed an alternated pattern of activation (panel A) and of a subject who showed a co-contraction strategy (panel B).

Two factors may play a major role in the organization of muscular patterns: the desire to preserve control over the trajectory of the most important point, typically the endpoint (Latash, 1996) and the desire to stabilize the trajectory of a joint whose deviations exert significant effects on the endpoint trajectory (the elbow joint in our study). The latter factor may lead to co-contraction of antagonist muscles when a movement occurs, as we found in 75% of subjects with DS and in 66.5% of controls. Latash (2000) compared the efficacy of the co-contraction and of the reciprocal pattern strategies by measuring deviations from initial position at 200ms after movement perturbation. He found that the reciprocal pattern of PPRs seemed more efficient than the co-activation one. However, both strategies allowed task achievement, and co-contraction was more used in presence of uncertainty in the external conditions, as in the case of our experiment, where a sudden, unpredictable perturbation required a fast response.

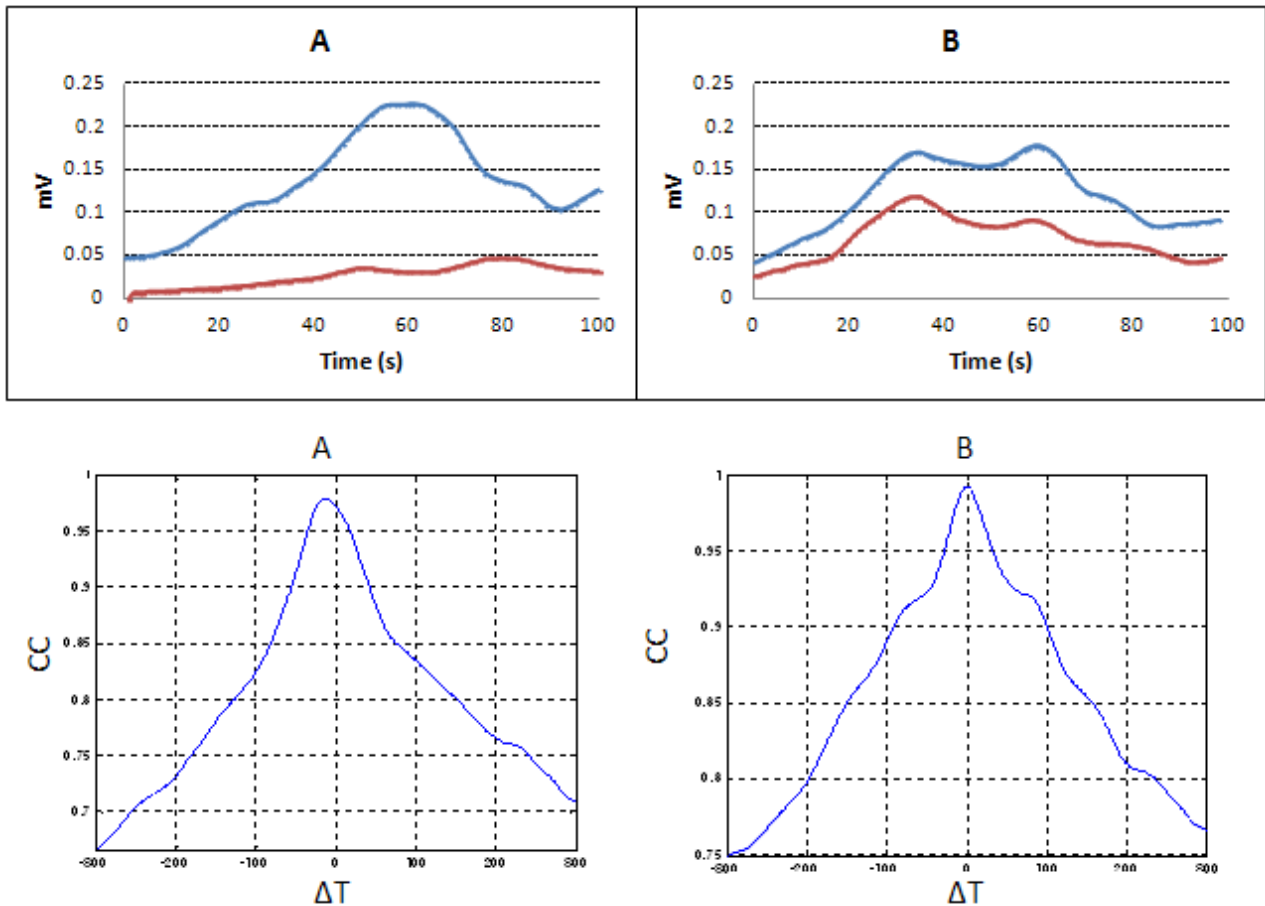


Figure 5.4.1: RMS of the biceps (in blue) and triceps (in red) signals and cross correlation function (in black). Panel A: subject who showed a synergistic behavior with an activation delay between biceps and triceps (CC peak in $\Delta t < 0$); panel B: subject who showed a co-contraction strategy with a simultaneous activation of the biceps and triceps (CC peak in $\Delta t = 0$)

The fact that co-contraction during the present task was present in most of subjects with DS, but not in all subjects, also highlights the fact that a part of the subjects was able to use synergistic patterns of activation. The presence of friendly, predictable laboratory circumstances and the extensive demonstrations and explanations provided before experimental execution may have lifted some of the self-imposed restrictions in the subjects' movements, leading to a change of motor strategy in at least some of the subjects with DS.

Thus, it seems reasonable to hypothesize, in line with Aruin et al (1996) and Latash et al (2003), that the presence of co-contraction may be an adaptive mechanism in response to the inability of subjects with DS to make quick, accurate corrections, and that it may be seen more like a voluntary choice than like an inability in exploiting other activation patterns. The fact that co-contraction during the present task was present in most of subjects with DS, but not in all subjects, highlighted the fact that a part of the subjects was able to use synergistic patterns of activation. The fact that

most of control subjects used co-contraction as well, suggests that this strategy provided better chances for task achievement in presence of unpredictability. Thus, the patterns of co-contraction, so frequently described in subjects with DS, may be seen as an adaptive mechanism in response to the inability of these subjects to make quick, accurate corrections, revealing a decision making problem more than a lack in the acquisition of other activation patterns.

These findings highlight the importance of early intervention programs in DS: the idea of a relative normalcy at birth is potentially of the greatest significance, since it seems to create the opportunity to do something about the not-yet-created differences that quite clearly do emerge during the period right after birth. There is increasing body of evidence that early intervention can have a direct impact on brain development in several pathologies. Such brain plasticity is one of the best hopes for bringing about significant improvements in the prospects of individuals with DS. At this time it is not known, from a theoretical or empirical perspective, the extent to which experience can cause changes in normal brain development (Nadel, 2003). However, some of the differences found within 6 months of age in infants with DS are expressed in terms of the proportion of individuals with DS who show abnormal values, rather than in terms of a uniform abnormality in all instances. Thus, the variability in the population with DS, even in the first stages of life, seems to support the idea that early varied experiences may be fundamental for the neuromotor development of these subjects, leading to different degrees of neuromotor disability based on the amount of experience practiced.

The use of imaging techniques in infants with DS may help investigate the delicate early stages of their development, providing major information for the definition of rehabilitative treatments. Two questions seem to be most relevant:

- What kinds of changes occur in the very first stages of infants' development, which are responsible for the neuromotor development in DS?
- Should we refer to the motor development in DS as a "delayed" version of normal development or as a "different" development?

In the next chapter we will review the literature about motor development in DS with a focus on the neural patterns that develop at early stages. We will also draw some conclusions about rehabilitation in DS, based on this literature and on the results of this study.

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Chapter 6

General conclusions drawn from these studies and from recent literature on neural development: implications for rehabilitation

We have seen from the previous chapter that the most primitive reactions, the ones that are present since the very beginning of life, seem to be comparable with controls in DS. However, important differences in motor control arise if we evaluate functional movements, such as the ones analyzed in chapter 3, where more complex reactions are needed and the interplay between feedforward and feedback mechanisms defines the successful accomplishment of the task. In this last case, in fact, subjects with DS seem to employ different motor strategies and to choose movement safety over movement efficiency as the main parameter of optimization. For this reason, subjects with DS seem to rely more on feedback control, whereas control subjects rely more on feedforward control. Clearly, something occurs in the very first phases of development, that leads from the potentially normal mechanisms of control of the early stages of life to the different motor control strategies of older infants and adults with DS. This may be viewed in light of a retardation or in light of a different development. A wide debate in literature is present in fact about whether motor development in DS should be considered as a slowed down version of “normal” development or as a standalone development that follows alternative paths. If the first hypothesis applies then rehabilitation could be focused at bringing back the patterns of movement into normality ranges. However, if the second hypothesis applies, rehabilitation should be focused at improving the already formed strategies in the adult, whereas an ample room of improvement could be present in the early stages of life. The purpose of this chapter is to review recent literature on the role of neural pathways development in the acquisition of motor skills in infants with DS, to provide evidence either for the “different” or the “delayed” motor control hypothesis and to match the neuroimaging findings to our results from previous chapters. In particular, the following literature review will focus on the development of the corticospinal tract in normally developing children and following brain damage. The study of brain damage can give important insights also for pathologies, like DS, where there is no focalized “damage” but generalized differences in several sites at different neural levels, because it helps understanding how certain changes in the contour conditions affect development of the neural circuits.

Finally, based on all the considered factors, we will outline some important therapeutic advices for a focused treatment of children and adults with DS.

6.1 Corticospinal development and plasticity in normal development and following damage

In the 1950s, animal research first showed development in the sensory regions after birth. During sensitive periods, the environment plays a major role in normal development. This research indicated that from early postnatal time through the next several months or years, the brain went through synaptogenesis followed by synaptic pruning, which represents the creation and elimination of synapses during growth.

The corticospinal system (CS), critical for controlling skilled movements, develops during the late prenatal and early postnatal periods (Martin et al, 2007; Porter and Lemon, 1993). Eyre (2003) reviewed the studies about CS development and brain plasticity in animals and humans. Studies on embryonic human brain development between 6 and 7 weeks postconceptional age (PCA) revealed that the cortical plate is barely formed at that time. Surprisingly, the most widely quoted studies of human CS tract development (Humphrey, 1960; O'Rahilly and Muller, 1994) claim that CS tract axons reach the medulla by 8 weeks PCA. Decussation is thought to occur before 15 weeks PCA, and CS axons to reach as far as the lumbar enlargement by 18 weeks PCA. Remarkably little neuroanatomical work on the developing human CS tract has been done since the original observations. Eyre et al (2000a, 2002) recently confirmed that human CS axons reach the lower cervical spinal cord by 24 weeks PCA at the latest. Following a waiting period of up to a few weeks, they progressively innervate the grey matter such that there is extensive innervation of spinal neurons, including motoneurons before birth. By 40 weeks PCA CS axons have begun to express neurofilaments and to undergo myelination. The anatomical findings of early CS innervation are confirmed by neurophysiological studies demonstrating that functional synaptic CS projections to motoneurons and to spinal interneurons are established prenatally during the final trimester of pregnancy (Eyre et al.,2000b). The combined morphological observations provide strong evidence for prenatal establishment of functional CS innervation in man, even though it is not associated with a significant developmental milestone of motor behavior (Eyre, 2003). Rather than furthering motor control per se, this early innervation most likely occurs to allow activity in the CS system as a whole to shape the development of the motor cortex and the spinal motor centers (Eyre et al., 2000b; 2001).

In the newborn, Eyre et al (2001) demonstrated significant bilateral innervation of spinal motoneuronal pools from each motor cortex. In longitudinal and cross-sectional studies of normal

babies and children, neurophysiological findings that are consistent with withdrawal in significant numbers of CS axons over the first 24 postnatal months have been observed (Eyre et al., 2001). Furthermore, rapid differential development of the ipsilateral and contralateral projections occurs over this time, so that responses at 2 years postnatal age in ipsi-lateral muscles are less frequent, significantly smaller, and have longer onset latencies and higher thresholds than responses in contralateral muscles, giving start to the neural differentiation and shaping. This differential development of the ipsilateral responses is consistent with a greater withdrawal of ipsilateral corticomotoneuronal projections than contralateral, as has been observed during the development of the CS tract in animals (Joosten et al., 1992). In addition, it is consistent with faster growth of axonal diameters in the contralateral CS projection than in the ipsilateral projection. The small and late ipsilateral responses observed in older children and adults are consistent with the persistence of a small ipsilateral corticomotoneuronal projection, with slower conducting axons than contralateral projections. This conclusion is supported by the results of anatomical studies in man and monkeys demonstrating that, in maturity, the CS tract has approximately 8 to 15 percent of uncrossed axons (Nathan et al., 1996). These ipsilaterally growing projecting axons have been shown in man and in non-human primates to arise from similar areas of the cortex and to have a similar pattern of spinal innervation to the contralateral projection (Liu & Chambers, 1964; Nathan et al., 1996; Galea & Darian-Smith, 1994).

It is now increasingly appreciated that the CS system is capable of substantial reorganization after lesions and such reorganization is likely to underlie the partial recovery of function (Eyre et al., 2001; Eyre et al., 2002). Clearly the developing nervous system has a much greater potential for plasticity, which can involve plasticity not only of the motor areas of the ipsi-lesional cerebral cortex but also of the contralesional cortex, the CS tract, and the spinal cord network (Benecke et al., 1991; Carr et al., 1993; Cao et al., 1994; Lewine et al., 1994; Maegaki et al., 1995; O'Sullivan et al., 1998; Balbi et al., 2000; Eyre et al., 2000a; Eyre et al., 2001). Since the young human brain is highly plastic, brain lesions occurring during development interfere with the innate development of the architecture, connectivity, and mapping of functions and trigger modifications in structure, wiring, and representations (for review see Payne & Lomber, 2001).

Repeated observations in man have demonstrated substantial plastic reorganization of the motor cortex and CS projections following prenatal or perinatal lesions to the CS system (Benecke et al., 1991; Carr et al., 1993; Cao et al., 1993; Lewine et al., 1993; Maegaki et al., 1993; Graveline et al., 1998; Balbi et al., 2000; Eyre et al., 2000a; 2001; Thickbroom et al., 2001), as reviewed by Eyre (2003). The findings of these studies are remarkably consistent with those made in animals

following perinatal lesions to the CS system. In children and adults who have suffered extensive damage to one motor cortex early in development, significant bilateral CS innervation of spinal motoneuronal pools persists from the undamaged hemisphere. These observations have been made following perinatal unilateral brain damage arising from a variety of pathologies, including infarction, dysplasia, and arteriovenous malformations (Benecke et al., 1991; Carr et al., 1993; Maegaki et al., 1993; Balbi et al., 2000; Eyre et al., 2000a; 2001; Thickbroom et al., 2001). Short latency ipsilateral responses do not occur in normal subjects outside the perinatal period. Nor do they occur in subjects who acquired unilateral cortical lesions in adulthood, establishing that fast ipsilateral responses are not simply unmasked by unilateral lesions (Netz et al., 1997; Eyre et al., 2000). Furthermore, the responses in contralateral muscles evoked by stimulation of the intact motor cortex, although within the normal range for age are abnormally clustered toward short onset latencies and low thresholds (Eyre et al., 2001). Together these findings imply not only bilateral innervations of motoneuronal pools but also an increase in the number of both fast conducting ipsilateral and contralateral CS axons from the intact hemisphere following perinatal unilateral lesions of the CS system. This conclusion is supported by the direct measurement of CS axonal number in the bulbar pyramidal obtained at post mortem. These measurements demonstrated significant increases in the number of CS axons, particularly the larger diameter axons projecting from the intact hemisphere in adult subjects with spastic hemiplegic cerebral palsy in comparison with normal subjects and those with lesions acquired in childhood (Verhaart, 1950; Scales & Collins, 1972). Similarly, magnetic resonance studies of subjects with early unilateral brain damage demonstrate an increased size of the CS projection from and shift of cortical sensorimotor functions to the intact hemisphere (Cao et al., 1994; Lewine et al., 1994; Maegaki et al., 1995; Graveline et al., 1998; Muller et al., 1998; Holloway et al., 1999; Wieser et al., 1999; Chu et al., 2000). Taken together, these observations support the persistence of ipsilateral and contralateral CS projections from the intact hemisphere following unilateral brain damage early in development, which would normally have been withdrawn during subsequent development. While the results of some studies indicate that the increased ipsilateral CS projections arise from the primary motor cortex of the intact hemisphere (Sabatini et al., 1994) a more common finding is that of the projection arising from non primary motor and multimodal association areas of the non affected hemisphere (Pascual-Leone et al., 1992; Cao et al., 1994; Lewine et al., 1994; Graveline et al., 1998; Chu et al., 2000). These observations imply the maintenance of CS projections in the damaged nervous system from areas of the cortex where axons projecting to the spinal cord would normally have been withdrawn during development. Thus, any lesion at the central nervous system level leads to a reshaping of the neural pathways according to a “use it or lose it” principle. Although these studies regard damage at

the central nervous system level, a similar reasoning may be applied if differences (not necessarily related to lesions) occur in the peripheral nervous system. Differences at any level of the neural pathways, from afferent sensory pathways to efferent pathways, in fact, may be related to a different development of the central neural system as the loop of the neural system shaping evolves. In this process, the role of afferent sensory circuits, that provide information to the nervous system and through which the shaping of the neural system evolves, seems to be very important and will be further discussed in the next paragraph.

6.1.1 Plasticity and the role of sensory-motor experiences

A key question is the extent to which motor development reflects a sequence of events that is largely independent of an individual's particular experiences. Early-developing brain stem motor tracts (Martin et al, 1980) and spinal circuits could mediate the simple postural responses and rhythmic behaviors that comprise most of a neonate's motor repertoire. The late-developing CS tracts (Martin et al. 1980; Martin, 2005) could mediate the more complex and integrated movements that are expressed in older infants. Genetically-timed sequences of motor pathway and circuit development could set the stage for an experience independent elaboration of controlled movements that humans, and animals alike, show during early postnatal life. Alternatively, early motor development may depend on motor experience and other activity-dependent processes (Martin et al, 2007). It is known that the molecular guidance governs the formation of topographic sensory maps in the brain function in cooperation with the activity of sensory neurons. Moreover, learning of new skills is a life-long function of the motor systems. Early motor system development may rely on active learning and experience to help direct the myriad of structural changes taking place, especially after motor pathway axons grow to their targets. Surprisingly, little is known of the importance of motor experience and activity-dependent processes in shaping development of the motor system and the behaviors they control. Martin et al (2007) focused on the CS system and on the development of some of the movements it controls. This system largely develops postnatally as human infants and many animal species begin to express adaptive and visually-guided movements. As the last motor system to develop, and the one that develops in parallel with a neonate's expanding motor repertoire, the CS system is an excellent candidate for examining the influence of activity-dependent processes. As an animal matures, some CS axon branches are pruned, which leads to more focused activation of spinal circuits. Other axon branches grow denser terminals and develop more presynaptic sites, which leads to stronger connections with spinal motor circuits and, together with stronger facilitation, a greater capacity of the CS system to regulate spinal motor circuit functions. This is development of connectional specificity, the process determining the

particular circuits a CS neuron engages, and thus the neuron's motor control functions. To understand what drives this refinement process Martin et al (2007) conducted experiments in which the level of CS activity was either decreased or increased during early postnatal development in the cat. They decreased CS system activity between weeks 5 and 7, the period when the distribution of CS axons in the gray matter normally is refined. The inactivation was reversible in 2-3 days after cessation of the treatment. They examined the effect of this inactivation on development of the distribution of CS axon terminations in the spinal cord (Martin et al. 1999). Unilateral inactivation changes in the distribution of CS axon terminals were found from both the silenced as well the contralateral active side. After inactivation, ipsilateral terminations from the active side may have additional functions because they terminate in lateral zones for controlling limb muscles. Thus, the reduction in terminations of the silenced side was balanced on that side by maintenance of ipsilateral terminations of the active system, according to the "use it or lose it" principle (Martin et al. 1999). The anatomical changes seen after inactivation paralleled the changes in CS system organization in cerebral palsy patients with spastic hemiplegia (Carr et al, 1993). Importantly, left untreated, these topographic changes persisted into maturity. These findings show the importance of the level of neural activity in shaping the early postnatal refinement of CS terminations.

While aberrant CS connectivity in the spinal gray matter correlates with the motor control impairments, this does not preclude a contribution by other components of the motor systems. It is plausible that the impairments also reflected aberrant development of cerebellar circuitry, as a consequence of aberrant CS system development. Many features of motor map development in the cat can be modified by early motor experiences during the period of map formation (between weeks 7 and 14). By promoting early experiences with prehension training, the electrical threshold for evoking responses decreased, while the percentages of effective sites and multi-joint sites both increased (Martin et al. 2005). In contrast, preventing limb experience during development of the motor map increased the threshold for evoking responses and decreased the percentages of effective sites and multi-joint sites. These changes in map organization reverted to control values several months after normal experience returns (Martin et al. 2005). This return back to control levels reflected plasticity that persists throughout life, as suggested by studies in the rat (Kleim et al. 2003). Activity independent processes, such as combinatorial transcriptional codes for CS neuronal specification (Lee and Pfaff, 2001; Arlotta et al. 2005) and guidance cues for axon pathfinding (Tessier-Lavigne and Goodman, 1996), play key roles in the initial development of the CS system. The role of activity-independent processes in the development of the CS projection to the spinal cord is only beginning to be understood (Dottori et al. 1998; Joosten and Bar, 1999; Liu et al.

2005). After CS axon terminals contact their spinal (and brain stem) targets, activity-dependent processes are key to refining connections and establishing the mature pattern of topographic and connectional specificity. Activity- and experience-dependent mechanisms assure that neural events at the time of motor circuit formation play a critical role in the long-term function of the system and in the definition of motor programs for learning motor schemes.

6.1.2 Relationship between the cat CS developmental model and human CS system impairments

The pattern of bilateral CS projections from the active side after unilateral M1 inactivation in the cat (Martin et al, 2007) is remarkably similar to changes in the laterality of transcranial magnetic stimulation (TMS)-evoked motor responses in cerebral palsy patients with spastic hemiplegia after perinatal brain trauma (Carr et al, 1993). TMS of the less impaired side in patients evokes bilateral responses (Farmer et al. 1991; Carr et al. 1993; Eyre et al. 2001). By contrast, strokes in adults that produce hemiparesis do not augment the ipsilateral response, showing that the effect in cerebral palsy is linked to damage during early development, possibly at a time when the CS system has bilateral connections with the cord (Eyre et al. 2001). These findings are consistent with the hypothesis that the impaired side is rendered much less competitive in securing and maintaining spinal synaptic space than the normal or less impaired side. Cerebral palsy is a condition in which the child “grows into” the impairment because spastic hemiplegia is not expressed immediately after the perinatal traumatic event (Bouza et al. 1994). Eyre and colleagues propose that the damaged side progressively loses capacity to control motor circuits during development (Eyre, 2003).

Thus, cerebral palsy may be progressive during early development as CS terminations are competing for synaptic targets and the hemiplegic signs are becoming expressed. Later in development, when the competitive balance between the two sides stabilizes in favor of the undamaged side, the motor signs stabilize. In the adult with stroke, instead, the learning has occurred through the regular neural pathways and motor schemes. The arise of the stroke causes a loss of the possibility to use the schemes learnt during development, leading to the necessity of learning new motor schemes compatible with the new neural condition after the stroke.

6.1.3 Prospects for harnessing activity to restore CS connections and function in the damaged nervous system

In their experiments with cats Martin et al (2007) examined whether after an early period of reduced activity or limb disuse there could be room to improve connections by activity- and use-dependent

neural competition. To examine this question they focused on the anatomical and behavioral defects that are produced by inactivation of M1 between weeks 5 and 7 from birth, with the goal of augmenting functions and connections of the previously silenced CS system. This may be done in two ways: first, stimulation of the previously silenced CS system can increase the activity of its spinal terminations, and this in turn may enhance their competitive advantage in securing and maintaining synaptic contacts. Second, inactivation of the contralateral CS system, the one that was active between 5 and 7 weeks from birth, would silence both its aberrant ipsilateral connections as well as the contralateral terminals. The authors chose the second approach and they showed that alternate M1 inactivation significantly augmented the density of ventral CS terminations on the affected side of the cord (i.e., inactivated during the critical refinement period) and significantly restored more accurate visually-guided locomotion in the cat. Bilateral CS synaptic interactions onto common neural circuits, combined with a protracted period of development of local connectivity, established conditions conducive to connectional plasticity and rehabilitation.

They proposed that the spinal intermediate zone is a key site of convergence of contralateral projections from the affected side and aberrant ipsilateral terminations from the unaffected side. However, other sites where ipsilateral CS projections develop after inactivation, such as the red nucleus and reticular formation (Martin et al. 1999), could be affected by the alternate inactivation treatment.

An important issue that is not yet resolved is the extent to which the alternate inactivation, in addition to promoting contralateral projections, also reduces the efficacy of the aberrant ipsilateral terminations from the unaffected side. From a clinical perspective, is it sufficient to promote a normal topography of CS terminations or must the aberrant ipsilateral cortical terminations additionally be diminished? These ipsilateral fibers terminate both laterally and medially in the gray matter, where they could contact premotor circuits for limb and axial control, respectively. The aberrant ipsilateral projection—especially the lateral one—is likely to be limited in control and flexibility. In the cat, the ipsilateral projection after inactivation is predominantly comprised of branches of CS axons projecting contralaterally (Martin et al. 1999); and this may be the case in hemiplegic cerebral palsy (Farmer et al. 1991; Carr et al. 1993; Eyre et al. 2001). Thus, the control signals carried by these branches are likely to be adaptive for contralateral control and maladaptive for ipsilateral control. Indeed, motor unit activity in cerebral palsy patients can be strongly correlated between the two sides and mirror movements are common (Farmer et al. 1991; Carr et al. 1993). Whether maladaptive or not, the aberrant ipsilateral projection may be the dominant CS input to the affected side of the cord. And this may be better than not having any projections. Martin

et al (2000) showed that the aberrant ipsilateral terminations help to mediate more effective control. Nevertheless, a reasonable working hypothesis is that it is first essential to restore the normal topographic pattern in the hopes of restoring appropriate connectivity. The cat model shows that one way this can be done is to block activity on the other side (Martin et al, 2007). Preventing use of the limb on the unimpaired side may be similar to M1 activity reduction. Preliminary experiments suggest that electrical stimulation of the affected side can also lead to a re-distribution of connections from dorsal to more ventral laminae (Salimi et al. 2006). Importantly, these studies show that an intervention is needed to restore function; one that is specifically targeted to enhance the ability of the affected CS projections to compete with other terminations to secure synaptic space on spinal neurons. Without such an intervention, the disadvantaged CS system is unable to catch up and regain lost connections and function. The results from Martin et al (2007) in the cat lead to two considerations for devising rehabilitation strategies in patients with cerebral palsy or other conditions that affect development of CS system connectivity. First, it is essential to synchronize an activity-based therapy with CS developmental periods. The refinement period for CS axon topography in humans may be within the first year of life when the ipsilateral motor potentials evoked by TMS diminish to their smallest values (Eyre et al. 2001). Intervention during this period could have the most robust effects. However, it is important to recognize that immature CS neurons are very plastic and preventing activity on the unimpaired side may impede motor development on that side, similar to what was found in kittens that were prevented from using one forelimb. Here, lessons have been learned from the treatment of children with strabismus, where controlled daily monocular deprivation leads to improved performance of the impaired eye without deterioration of the well-sighted eye (Mitchell et al. 2003). Constraint induce movement therapy (CIMT) may be necessary to permit sufficient plasticity on the affected side. In CIMT, the less-affected arm is restrained to encourage the patient to use the affected arm in tasks. Many CIMT protocols combine constraint with training of the affected side (Gordon et al. 2005). Manipulations of CS neural activity can be achieved non-invasively in humans. Repetitive TMS, at lower frequencies than the electrical stimulation used in the cat, could augment activity levels. Moreover, particular TMS parameters have been shown to suppress the contralateral M1 (Ferber et al. 1992; Kujirai et al. 1993). Thus, repetitive TMS to one side of M1 would balance activity between the two sides by concurrently activating the stimulated side and inhibiting the controlateral side.

6.2 Patterns of neural organization in Down Syndrome

As reviewed in chapter 1, various pathophysiological changes in the brain have been associated with the specific profile of intellectual disability that is observed in DS. These include changes in size of specific brain regions and their connectivity and alterations in the number and/or the morphology of subpopulations of neurons (for a review, see Dierssen, 2012).

At birth it is often difficult to differentiate the brains of normal and of individuals with DS (Bar-Peled et al. 1991). The idea of a relative normalcy at birth is potentially of the greatest significance, since it seems to create the opportunity to do something about the not-yet-created differences that quite clearly do emerge during the period right after birth.

Yet, both postmortem studies and various, more recent, non invasive neuroimaging studies have demonstrated rather clear differences between these two groups as early as 6 months of age (eg., Schmidt-Sidor et al. 1990; Engidawork and Lubec, 2003). In particular the brains of individuals with DS are typically smaller than those of age-matched controls. Another quite noticeable difference concerns the postnatal delay in myelination (Wisniewski, 1990). Myelination is within normal range at birth, while in 75% of the cases it is within normal range throughout early development. By early childhood there is an impoverishment in neocortex of subjects with DS.

Investigations of neural function, as opposed to structure, in early infancy suggest some abnormalities as well, such as the delayed or aberrant auditory system development (Jiang et al. 1990) and vision (Courage et al, 1997), that might contribute to the widespread hearing and sight disorders observed in DS and a more widespread abnormality in EEG coherence (McAlaster, 1992) that seems to reflect the generally impoverished dendritic environment. This difference, like many of the others, emerges only sometime after birth.

These and other studies have shown that there are significant differences in the structure of the brain in DS. However, there are considerable gaps in our understanding of the functional significance of these structural differences (Virji-Babul et al, 2011). A key issue in neuroscience is how different brain regions are connected functionally and how the interactions between brain regions support cognition, perception and motor control. Virji-Babul et al (2011) studied the spatial localization and functional connectivity during voluntary movements of the right index finger in controls and in subjects with DS, while recording cortical responses with magnetoencephalography (MEG). They found for the control group most significant activations approximately in the left primary motor and sensorimotor regions (figure 6.2.1 a), whereas two distinct patterns of brain activation were found in the DS group: a contralateral pattern and an ipsilateral pattern, as shown in figure 6.2.1 (b, c). For the contralateral group the strongest peaks were observed in the left sensorimotor regions, similar to the control group. The locations of the activations, however, were more anterior. The ipsilateral

group showed largest activations in the ipsilateral temporal region at low frequencies. At high frequencies the distribution was bilateral, involving both motor and temporal regions.

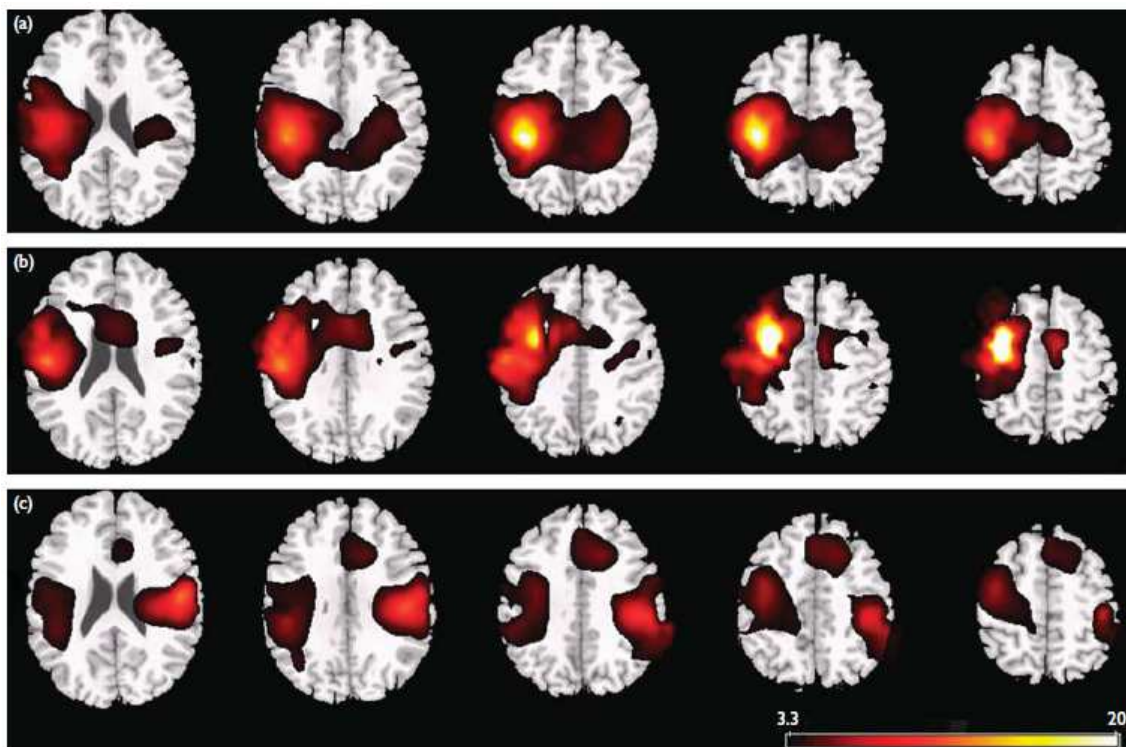


Figure 6.2.1: groups averages of peak activity in the 0.2-12 Hz range in three groups: (a) control group; (b) DS controlateral group; (c) DS ipsilateral group

This study represents the first evidence of altered synchronization during a simple motor task in individuals with DS, showing the presence of two distinct subgroups associated with the performance of the same motor task, and both different from the patterns of activation of the control group, suggesting that altered functional connectivity may be the basis of some of the motor control impairments in DS. The ipsilateral DS group showed further alterations in synchronization and in the locations of peak activations in comparison with both the control and the controlateral DS groups. The pattern in this group was in fact characterized by a more fragmented and less coherent pattern of activation with phase locking occurring within virtually all frequency bands in widely different brain regions. Phase locking between neural networks has been proposed as a mechanism for integration and exchange of information (Varela et al, 2001). Virji-Babul et al (2011) observed two general differences between the control group and the two groups with DS in relation to the pattern of phase locking. First there was a lack of, or no evidence (depending on the group) of low-frequency phase locking during the pre-movement phase. Low-frequency coherence before the onset of movement has been observed in a number of studies (Ohara et al, 2001). It has been proposed that one possible role for low-frequency activity may be in functional coupling between

pre-motor sources and sensori-motor regions to provide task-related information in terms of movement planning or feedback (Darvas et al, 2009). Alternatively, the synchronization between the frontal and parietal regions may be related to cognitive and memory performance related to the task (Ohara et al, 2001). The functional significance of this low-frequency synchronization remains unclear, however the alterations or lack of low-frequency synchronization coupled with γ activation in both groups with DS suggest that the coupling and integration for movement planning and coordination may be impaired.

The second major difference between the groups was related to γ activation. Gamma band oscillations are considered to be important for cortico-cortical functional coupling, serving as a binding function between different neural populations (Fries et al, 2007). Gamma rhythms within the 40-60Hz band, in particular, are thought to link different neuronal regions involved in sensory feedback and controlling the ongoing movement. In their study, Virji-Babul et al (2011) observed phase coupling in 40-60Hz activity primarily within sources in the left hemisphere, particularly between the parietal and temporal regions, suggesting a role for sensori-motor integration. The lack of γ -coupling within these regions in both DS groups during the movement phase is further evidence of impaired sensori-motor integration.

The atypical right hemisphere activation pattern combined with the altered brain dynamics may be a possible explanation for the impaired motor control and motor coordination that has been observed in recent studies of DS (Virji-Babul et al, 2010; Virji-Babul et al, 2008) and in our studies presented in the previous chapters.

6.3 Implications for intervention

Literature demonstrates that the high plasticity of the young brain can lead to different shaping of the neural connections depending on the sensorial, cognitive and motor experiences of the child, and that following a lesion different shaping occurs, leading to different neural pathways and to redistribution of the neural activation. Literature on new-borns with DS demonstrates that at birth the neural structures of children with and without DS are quite comparable, however adults with DS demonstrate differences in the neural patterns of activation respect to controls. Thus, it seems reasonable to hypothesize that during infancy and development the different experiences done by infants with DS leads them to develop different neural pathways and consequently different activation patterns, causing the different motor strategies observed in adulthood. Delayed myelination (Wisniewski, 1990), aberrant sensory information and sensory integrative dysfunction (Uyanik et al, 2003; Courage et al, 1997; Jiang et al. 1990; Roizen et al, 1994; Chen and Fang,

2005), higher sensory thresholds and a decreased ability to localize stimuli (Hennequin and Feine, 2000) are among the factors that may cause this differentiation in the early stages of life.

Since the deficit begins to develop as soon as the first months of life, the findings suggest that much emphasis should be put on early intervention in DS. There is increasing body of evidence, in fact, that early intervention can have a direct impact on brain development, as underlined by Martin et al (2007) in the case of cerebral palsy. At this time it is not known, from a theoretical or empirical prospective, the extent to which early experience can cause changes in normal brain development but such brain plasticity is one of the best hopes for bringing about significant improvements in the prospects of individuals with DS as well (Nadel, 2003).

6.3.1 Early intervention programs

Studies in literature have shown that different therapeutic approaches have been used to facilitate mental and motor development in infants with motor and/or cognitive developmental problems. Among those, sensory integrative therapy, perceptual-motor training, neurodevelopmental therapy (NDT), vestibular stimulation and play therapy have been used either as sole treatment programs or as combined programs according to the necessity of the children (Woollacott and Shumway-Cook, 1986; Harris, 1981; Stratford, 1980; Kantner et al, 1976; Kelly, 1989; Anderson et al, 1987; Bobath, 1980).

Some of these studies (Kantner et al, 1976; Kelly, 1989) have shown that effectiveness of the vestibular stimulation training had a positive effect on motor skills in children with DS, increasing reflex integration, balance, intellectual functions, perception-motor skills, hearing-language and socioemotional development. On contrary, neurodevelopmental NDT did not show significant improvements, as noted by Harris (1981). Anderson et al (1987) stated that play therapy in addition to NDT developed cognitive and perceptual skills and was useful for increasing subjects' motivation for participating in the therapy.

Blauw-Hospers et al (2005) reviewed and analyzed the effect of early intervention programs (between birth and 18 months of life) in children at high risk for developmental motor disorders. They considered both specific intervention programs, such those aimed at improving walking skills, and more general intervention programs, aimed at improving all developmental domains. The review indicated that intervention which might be beneficial for infants at preterm age was different from the type which was effective in infants who had reached at least term age. At preterm age, infants seemed to benefit most from intervention aimed at mimicking the intrauterine environment, whereas after term age intervention by means of specific or general developmental programs, which consisted in stimulation of motor development by means of the promotion of self-produced motor

behavior, had a positive effect on motor development. No evidence was found for a beneficial effect of traditional forms of paediatric physiotherapy such as NDT and treatments according to Vojta (Bauer et al, 1992). Blauw-Hospers et al (2007) analyzed whether early intervention programs focusing primarily on motor development had an effect also on cognitive outcome. The hypothesis underlying this assumption was that improvement of early motor development allows the infant more opportunities to interact with the environment, which in turn may facilitate cognitive development. The review provided some evidence that intervention during the neonatal intensive care unit period in infants at high risk of developmental motor disorders had a beneficial effect on cognitive development. The studies in which intervention had started after term age indicated that intervention by means of a general developmental program might be beneficial for cognitive development. NDT and treatments according to Vojta, instead, did not produce benefits in the cognitive domain, a finding supported also by earlier studies (Butler and Darrah, 2001; Harris 1981). Blauw-Hospers et al (2007) also studied the effect of a new intervention program, the COPCA (Coping with and Caring for infants with neurological dysfunction), based on the principles of the Neuronal Group Selection Theory (NGST, Edelman, 1993) and on new insights in the field of education and family care. According to NGST, typical development is characterized by two phases of variability, i.e. primary and secondary variability. During primary variability, the nervous system explores all motor possibilities available. In typically developing infants, this phase is characterized by abundant variation. At function-specific ages, the infant reaches the phase of secondary variability. The child gradually learns to select the most efficient solution for a given task out of his motor repertoire. This selection is based on trial and error. This means that during the phase of secondary variability, the child learns to adapt his/her motor behavior to specific situations (Hadders-Algra, 2000a). Infants with a brain lesion resulting in a developmental motor disorder have a reduced repertoire of motor strategies available for exploration. In addition, these infants have problems with the selection of the most appropriate solution for a certain task out of the repertoire (Hadders-Algra, 2000a). Therefore, COPCA aimed at promoting variation in motor behavior and trial-and-error experiences, with the ultimate goal that the child will be able to find an appropriate solution for any motor task. Equally important bases of COPCA are new insights in the field of education and family care (Dale, 1996; Law et al., 1998; Rosenbaum et al., 1998). Family-centered care implies a partnership between the family and the professional, in which the family defines the priorities for intervention, while the therapist assists the family through-out the intervention period (Law et al., 1998). Even though further research is needed to explore clinical effectiveness of the COPCA programme, preliminary results on a group of 9 children assigned to the COPCA intervention and 11 children assigned to the control group (who received

physiotherapeutic guidance indicated by the paediatrician) indicate that COPCA had a significant effect on the development of sitting abilities and that COPCA might be able to counteract the cognitive deterioration.

Uyanik et al (2003) compared different therapeutic approaches aimed at improving postural reactions in children with DS, and in particular neurodevelopmental approaches sensory integrative therapy and vestibular stimulation (Kokubun et al, 1991; Kantner et al, 1976; Sullivan et al, 1972). The results showed that sensory integration, vestibular stimulation and neurodevelopmental therapy were effective in children with DS. The authors suggested that when designing rehabilitation programs for children with DS all treatment methods should be applied in combination, and should support each other according to the individual needs of the child.

Programs for learning of functional early movements

Physical activity and movement in children with and without DS is a critical facilitator of learning (Ulrich and Ulrich, 1995). As infants and children move they learn about the changing properties of their own systems (e.g., limb lengths, muscle strength, postural control) and their environment (Thelen et al, 1994). Neural solutions to movement problems encountered must be discovered as the young child moves within his/her changing environment. Very limited research has been conducted on physical activity as it relates to learning of functional skills in children with and without DS. The common view based on parent and professional reports is that young children with DS are less active than their age peers without DS (Henderson, 1986; Mc Kay and Angulo-Barroso, 2006; Sharav and Bowman, 1992). Based in part on these anecdotal reports, Henderson (1986) hypothesised that children with DS have "a self-perpetuating form of sensory-motor deprivation sparked off by an inbuilt passivity and disinclination to move". If this hypothesis is true, it would help to explain why infants and young children with DS experience significant delays in acquiring early movement skills. Limited research has been published to test this hypothesis. Ulrich and Ulrich compared the spontaneous leg movements of infants with DS and two groups of typically developing infants matched for chronological age and motor age (Ulrich and Ulrich, 1995). Their results suggest that the frequency of leg movements were not different between the three groups. These data suggest that poor motor skill development, over time, is more likely responsible for low levels of physical activity demonstrated later in life than is an inherent disposition toward inactivity. Early interventions that promote the development of efficient functional motor skills may, therefore, have a positive impact on multiple domains during infancy and may also create a solid foundation for future success in movement settings. In the Ulrich and Ulrich study (1995), where they evaluated the spontaneous kicking movement in infants with DS, they did report that the infants

with DS produced significantly fewer complex patterned leg movements in the form of kicks. In the three infant groups, infants who produced more kicks also walked earlier. The explanation provided for the relationship between kicking and age of walking relates to Edelman's model (Edelman, 1987; Sporns and Edelman, 1993) which suggests that infants' self generated kicks belong to the same category of behaviors as the leg movements used to walk (hip, knee, and ankle flexions and extensions). The flexion and extensions used in walking are similar to what is seen in kicking. Given that the overall frequency of leg activity was not different between the three groups, it casts doubt on the inherent inactivity hypothesis. It is hypothesized that inactivity may be a learned or adaptive pattern of behavior that emerges with age (Latash et al, 2008).

McKay and Angulo-Barroso (2006) conducted a longitudinal study of the spontaneous leg activity of infants with and without DS from three to six months of age. They placed an activity monitor on the right ankle of each infant for a period of 48 hours. Their findings suggest that infants with DS spend a greater duration of time throughout the day in low intensity leg activity. They also reported a significant relationship between low intensity leg movement and the age of onset of walking. The lower intensity activity might be attributable to the muscle properties and slowness of movement discussed in the first section of this paper.

A small longitudinal intervention study was conducted to test if it was possible to increase kicking in 4-6 month old infants with DS and, if so, what the effects would be on age of walking onset (Loyd and Ulrich, 2006). In this randomized study, infants with DS were given a Kick Start Gym (figure 6.3.1) or a Tummy Time Gym and the protocol required parents to place their infant under the device that employed a conjugate reinforcement system (Rovee and Rovee, 1969) for 20 minutes five days each week for 12 weeks.



Figure 6.3.1: Inexpensive Kick Start Gym

In brief, the Kick Start Gym is designed to reinforce kicking in a supine posture and the Tummy Time Gym is designed to reinforce reaching in a prone posture. Each time the infant produced a

kick that resulted in the foot touching the kick pad, a short burst of music and spinning toy resulted in reinforcing the kick. The frequency of kicks in both groups prior to the intervention was similar. Results following 12 weeks of the intervention demonstrated that the infants in the kicking group significantly increased their kicking compared to the reaching group. The kicking group also acquired the locomotor milestones earlier but did not reach statistical significance primarily due to inadequate statistical power. Future research is needed applying Edelman's model (Edelman, 1987) to early motor intervention and functional skill development.

Programs for the development of functional locomotor behaviors

Acquiring the ability to locomote is important to infants because of the impact on cognitive and social/emotional skills, as well as for the more obvious relevance to subsequent motor skill development. At the cognitive level, researchers have demonstrated that, for typically developing infants, experience with locomotion accounts for the onset of a broad array of psychological skills, which include: the onset of wariness of heights, the concept of object permanence (that objects hidden from sight may still exist), a shift from self-centered to landmark-based spatial coding strategies, the ability to follow the pointing gestures and gaze of another person, aspects of social referencing, and detour reaching (Bertenthal and Campos, 1990; Campos et al, 2000; Kermoian and Campos, 1988). These data suggest that infants learn more about spatial cognition and the world around them as they become able to locomote independently and can actively explore their environment than through passive observation, i.e., being held or carried through space. Rosenbloom further suggested that not only is locomotion important but the quality of movement also effects subsequent development (Rosenbloom, 1971). He proposed that inefficient locomotion may inhibit development by limiting the attention and energy infants can focus on exploring stimuli in their environment. Thus, acquiring stable motor skills may be especially important for the cognitive development of infants with DS (Latash et al, 2008).

The onset of the ability to walk alone represents an important milestone for both infants and their parents, for social and emotional reasons. Parents of infants with DS report that walking is one of the goals they value most for their young children. Family and friends repeatedly ask them if their child has yet begun to walk and talk, a disconcerting question, as the delays become longer. These are behaviors that are apparently universally accepted as important. When infants finally walk their own parents are relieved and reassured by this quite tangible evidence that progress is indeed being made. Jones et al (1991) documented that, following walking onset, typically developing infants demonstrated greater independence (moved away from mother more frequently than when they

could only crawl) and showed an increase in positive affect during play. Treatments are therefore recommended to start early so that the child may achieve optimal development (Latash et al, 2008). In the motor domain, stable and efficient locomotor skills form the foundation for developing more complex motor skills. Children use these skills to interact with other children in games and activities. In school and neighborhood settings, children with poor motor skills are often excluded from, or, choose to avoid physical activity.

The unwillingness of persons with DS to explore alternative strategies during walking, as documented by the study by Virji-babul (2004) and by our study on walking with obstacle avoidance, is in line with their primary goal of remaining safe, other than optimizing efficiency of the movement, as they move in their environment (Latash, 2000) and their inability to use advance visual information as they move. Based on the accumulation of research on the acquisition of early motor behaviours in DS, one has to conclude that researchers and clinicians have not been successful in meaningfully reducing the delay in onset of critical locomotor behaviours and improving performance (Latash et al, 2008).

One intervention approach, treadmill training, has consistently demonstrated positive outcomes in reducing the age of onset of many locomotor milestones (Ulrich et al, 2001; Ulrich et al, 2008). Treadmill training of infants with DS is founded on the theory of neuronal group selection (NGS) (Edelman, 1987; Hadders-Algra, 2000) and principles of dynamic systems theory (DST) applied to motor and cognitive development (Ulrich and Ulrich, 1993; Thelen et al, 1994). Being supported on a small infant sized treadmill by the parent (see figure 6.3.2), long before independent walking emerges, affords the infant with skill specific practice using the alternating stepping pattern employed later in independent walking.



Figure 6.3.2: Mother implementing treadmill training

It was hypothesised that the experience resulting from stepping practice over a longitudinal period strengthens and stabilises the synaptic connections among motor neurons (neuronal groups) that drive the stepping pattern. By providing the infant with frequent opportunities implemented in the home to explore multiple leg coordination patterns in an upright posture, promotes earlier selection of alternation as the preferred leg coordination pattern. The treadmill stepping practice also advances critical subsystems needed to walk: leg extensor strength and postural control.

Treadmill training increases leg strength needed to support the child's body weight during walking, and promotes specific postural control mechanisms that are needed to maintain upright balance as the infant transfers his weight from one leg to the other. The treadmill intervention initiated by 10-11 months of age takes advantage of a period of maximum neural plasticity and meets Latash's recommendation of encouraging the infant with DS to engage in early exploratory activity to facilitate the discovery of general rules of motor coordination (Latash, 2000).

The results of two randomized intervention studies employing the treadmill intervention as a supplement to physical therapy with infants who have DS have clearly demonstrated that the intervention significantly increases alternating stepping and reduces the age of onset of independent walking and other pre-walking locomotor behaviors. The intervention did not produce obvious harmful effects and may have had additional positive outcomes related to gait and physical activity (Ulrich et al, 2001; Ulrich et al, 2008).

More interventions, based on principles on principles such as NGS and DST, are needed to improve important functional movement behaviors for children with DS and other disabilities (Latash et al, 2008).

6.4 General conclusions

We have seen that the motor development of subjects with DS may be seen either as a different development, following its particular pathways, or as a delayed version of "normal" development. Data coming from neurological and neuroimaging studies, concerning both DS and pathologies caused by brain damage at birth, however, seem to strongly support the first hypothesis. Part of the literature confirms that at birth the neural structures of individuals with and without DS are not distinguishable (Dierssen, 2012; Nadel, 2003), in agreement with our finding that the most primitive mechanisms of motor control are comparable to control subjects. However, some anatomical differences begin to emerge as soon as at six months of life (Dierssen, 2012; Nadel, 2003), right in the period in which children with normal development experiment a large reorganization of neural circuits (Galea and Darian-Smith, 1994; Eyre, 2001). Thus, it may be

hypothesized that something occurs during this period that may cause a different organization at a neural level. Literature on early neural damage in infants with cerebral palsy seem to support this hypothesis, since lesions occurring in the perinatal period lead as well to a different modeling of the neural structures as the infant grows. Infants with DS do not experience a structural damage of the neural structures, however they do have structural and functional differences compared to their peers. These differences may include delayed myelination, delayed sensory and sensory-integration development, biomechanical deficits and attentional deficits and may dramatically affect the infant's interaction with the environment and the infant's early experiences. Since the reorganization of neural connectivity is activity-dependent (Eyre, 2001) and during the development of the nervous system there is much more potential for plasticity of the cortex and spinal networks than in the adult (Balbi et al, 2000; Eyre, 2000-2001; Thickbroom et al, 2001) it seems reasonable that different contour conditions and different experiences caused by these difficulties and/or deficits may lead to a differentiation in the patterns of activation of the neural circuits, which in turn may lead, with time, to the prevalence of different neural synapses and to the definition of unique neural patterns in the adults subjects with DS, as evidenced by the neuroimaging study by Virji-Babul et al (2011). This results in learning of different motor strategies, as evidenced by the studies presented in chapter 3.

Given the high neural plasticity of the brain at birth and given the activity-dependent nature of neural modeling two most important suggestions can be given to therapists and neurologists in the field of DS:

- Early intervention is fundamental for the reorganization of the neural pathways, and should be given as soon as the child is born. Several possible treatments are present, although there is scarce evidence of which may be the best combination of treatments to harness the best results.
- Challenging the infant with an "enriched environment" (such as the kick-start gym of Loyd and Ulrich, 2006) may help balancing his lack of sensorial, cognitive and motor experiences, leading to earlier development of the motor milestones. In particular, development of walking is fundamental because it allows the child to start exploring the environment in an independent way, providing new sources for sensory, cognitive and motor experiences and resulting in a further enrichment of his environment, with major fallouts on the motor skills development of the child.

6.4.1 Limitations

In this study we analyzed both automatic correction movements and functional voluntary movements. The aim of the study was to switch from a traditional use of motion analysis for the evaluation of biomechanics to a newer approach incorporating not only biomechanical analysis but also considerations about upper level functions and mechanisms that cooperate in the control and execution of movement. Thus, this was a preliminary study aimed at highlighting some important matters that could be of importance in the treatment of DS but, since it was a start up study, it did not mean to be completely exhaustive. In fact, several limitations were present due to these preliminary features.

First of all, the group of subjects with DS was limited to 13 subjects for the tapping task and 8 subjects for the EMG evaluation. A higher number (31 subjects) was gathered for the obstacle task. Although these numbers of subjects are comparable with studies in literature that apply similar set ups, it is evident that a limited number of subjects can only give an indication of the trend of the examined parameters, but of course it cannot be representative of the whole population, thus it is necessary to extend the protocols to a higher number of subjects. Subjects with DS were included after a neurological evaluation from an expert neurologist to ensure a sample of subjects with similar cognitive and physical characteristics, and thus to lower the standard deviations in the parameters by collecting data on a group as homogeneous as possible. Inclusion criteria for the DS group were teenage to adult age, no severe obesity, low to medium intelligence quotient, no clinical sign of dementia and no orthopedic problems that could restrain the subjects from maintaining a correct posture during the tasks. The variety of the syndrome, however, makes it difficult to provide such a homogeneous group, and this again leads to the necessity to extend the protocols to a higher number of subjects with DS.

Finally, clinical scales about specific neurocognitive, psychological and motor aspects, in addition to IQ measures, may have helped to select the group of subjects with DS with more detail. IQ, in fact, is a general score, which takes into account several aspects of cognitive ability. This score comprises an important part on verbal abilities together with the evaluation of non verbal cognitive performance. Thus, for instance, poor verbal ability can influence the score. Since the test is not focused on the cognitive abilities related to movement programming and generation, but on a wide range of aspects, it may be useful to integrate this score with other evaluations for a detailed characterization of the cognitive state of the subjects before including them in the study. An example of a possible employable clinical scales is the neurocognitive Arizona Cognitive Test Battery for DS (Edgin et al, 2010) which includes general cognitive ability and prefrontal, hippocampal and cerebellar function and was developed to assess a range of skills, be non-verbal

(so as not to confound the neuropsychological assessment with language demands), have specific correlates with brain function and be applicable to a wide range of ages and across contexts.

6.4.2 Further developments

The future developments of this study should be addressed at correlating the kinematics and motor performance of individuals with DS with the underlying brain dynamics to better characterize the nature of the “clumsy” motor behavior observed in this population. This may be of fundamental importance in the definition of focused therapies.

The study should evaluate a higher number of subjects, divided by narrower age ranges and by different neuromotor disability (as evaluated by neurological and clinical examinations) to define a more detailed and precise picture of the performance of persons with DS in these tasks and to confirm the results of this preliminary study.

Other intellectual disabilities may be tested, to define the points in common with DS in managing automatic and functional movements and to understand to what extent the operating approach seen in persons with DS is characteristic of the syndrome itself and to what extent it is a result of a general condition of intellectual disability.

Finally, to provide strong evidence about the correctness or incorrectness of the hypotheses drawn by the results of this study (the hypotheses about motor development and the importance of early intervention in DS), different early intervention programs should be tested in infants and children with DS to evaluate the impact of early intervention in the development of motor milestones and consequently in the development of functional afferent and efferent pathways that are fundamental for the learning of motor skills.

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Appendix I

Participants to the study

Subjects with Down Syndrome

37 subjects with Down Syndrome (DS) ageing from teen age to young adulthood were enrolled for the study. The subjects with DS were assigned to the different experimental sessions as described in table I.I. The acquisitions took place at the Movement Analysis Laboratory of IRCSS San Raffaele Pisana, Tosinvest Sanità, Rome, Italy.

The subjects and their legal guardians gave their informed consent to the study. The study was approved by the ethical committee of IRCSS San Raffaele Pisana, Tosinvest Sanità, Rome, Italy.

Inclusion criteria for the DS group were:

- teenage to adult age ($13 < \text{age} < 43$);
- no severe obesity (normal to overweight Body Mass Index, $18.5 < \text{BMI} < 34$);
- low to medium intelligence quotient ($34 < \text{IQ} < 80$);
- no clinical sign of dementia;
- no orthopedic problems that could restrain the subjects from maintaining a correct posture during the task.

Table I.I displays the list of subjects included in the DS group and details to which experiments each subject took part.

Code	Group	Sex (M/F)	Age (years)	Exp. sessions	Code	Group	Sex (M/F)	Age (years)	Exp. sessions
5644	DS	M	18	OBST EMG	6461	DS	M	19	OBST TAPP
5645	DS	F	23	OBST TAPP EMG	6487	DS	F	21	OBST
5647	DS	F	18	OBST	6490	DS	M	17	OBST
5686	DS	M	14	OBST TAPP	6496	DS	M	18	OBST TAPP

5754	DS	M	24	OBST TAPP	6502	DS	F	14	OBST EMG
5807	DS	M	28	OBST TAPP	6652	DS	F	20	OBST
5907	DS	M	17	OBST TAPP	6672	DS	F	24	OBST
5911	DS	M	20	OBST	6673	DS	F	23	OBST
5914	DS	M	36	OBST TAPP	6773	DS	F	18	OBST
5935	DS	M	19	OBST TAPP	6797	DS	F	22	OBST
5995	DS	M	29	OBST TAPP	6802	DS	F	35	OBST
6018	DS	F	13	OBST	6804	DS	F	37	OBST
6081	DS	M	19	OBST	6400	DS	M	25	EMG
6086	DS	F	27	OBST TAPP	1515	DS	M	42	EMG
6223	DS	M	23	OBST TAPP	6402	DS	F	15	EMG
6310	DS	M	37	OBST TAPP	6163	DS	M	15	EMG
6335	DS	M	23	OBST	7334	DS	M	20	EMG
6391	DS	F	30	OBST	X001	DS	F	31	EMG
6460	DS	M	16	OBST					
Mean age (standard deviation)					23.0 ± 7.4				
Median (25°, 75° percentile)					21.0 (18.0, 27.0)				
% Males					56.8%				
% Females					43.2%				

Table I.I: subjects of the DS group. Experimental sessions: OBST = paragraph 3.1 “Perceptual-motor integration during walking with obstacle avoidance in adults with Down Syndrome”; TAPP= paragraph 3.2 “Motor strategies and motor programs during an arm tapping task with and without

obstacle avoidance in adults with Down Syndrome”; EMG= chapter 5 “Pre-programmed reactions in Down Syndrome”

Subjects without Down Syndrome

43 normally developed subjects (N) ageing from teen age to young adulthood were enrolled for the study. The subjects were assigned to the different experimental sessions as described in table I.II. The acquisitions took place at the Movement Analysis Laboratory “Luigi Divieti” of the Electronics, Information and Bioengineering Department of the Polytechnic University of Milan, Milan, Italy. The subjects gave their informed consent to the study. The study was approved by the ethical committee of IRCSS San Raffaele Pisana, Tosinvest Sanità, Rome, Italy.

Inclusion criteria for the N group were:

- teenage to adult age (13<age<43);
- no severe obesity (normal to overweight Body Mass Index, 18.5<BMI<34);
- no clinical sign of neuro-motor problems and/or dementia;
- no orthopedic problems that could restrain the subjects from maintaining a correct posture during the task.

Table I.II displays list of subjects included in the N group and details to which experiments each subject took part.

Code	Group	Sex (M/F)	Age (years)	Exp. sessions	Code	Group	Sex (M/F)	Age (years)	Exp. sessions
1580	N	F	24	OBST TAPP	1609	N	M	24	EMG
1584	N	F	25	OBST TAPP	1610	N	M	29	EMG
1585	N	F	24	OBST TAPP	1611	N	F	28	EMG
1586	N	M	25	OBST TAPP	1612	N	M	26	EMG
1587	N	F	25	OBST TAPP	1613	N	F	33	EMG
1588	N	M	27	OBST TAPP	1614	N	F	25	EMG
1589	N	F	25	OBST	1615	N	F	27	EMG

				TAPP					
1590	N	M	21	OBST TAPP	1616	N	F	25	EMG
1591	N	F	26	OBST TAPP	1617	N	F	35	EMG
1592	N	F	26	OBST TAPP	1618	N	M	35	EMG
1593	N	M	20	OBST TAPP	1619	N	F	34	EMG
1594	N	F	27	OBST TAPP	1620	N	F	29	EMG
1595	N	M	27	OBST TAPP	1621	N	F	36	EMG
1596	N	F	29	OBST TAPP	1622	N	M	35	EMG
1598	N	F	21	OBST TAPP	1623	N	M	30	EMG
1599	N	M	22	OBST TAPP	1624	N	F	24	EMG
1600	N	F	26	OBST TAPP	1625	N	F	28	EMG
1602	N	M	22	OBST TAPP	1626	N	M	28	EMG
1603	N	M	25	OBST TAPP	1627	N	F	26	EMG
1606	N	F	26	OBST TAPP	1628	N	F	25	EMG
1607	N	F	26	OBST TAPP	1629	N	F	27	EMG
1608	N	F	28	OBST TAPP					
Mean age (standard deviation)					26.9 (3.9)				

Median (25°, 75° percentile)	26.0 (25.0, 28.0)
% Males	34.9%
% Females	65.1%

Table I.II: subjects of the N group. Experimental sessions: OBST = paragraph 3.1 “Perceptual-motor integration during walking with obstacle avoidance in adults with Down Syndrome”; TAPP= paragraph 3.2 “Motor strategies and motor programs during an arm tapping task with and without obstacle avoidance in adults with Down Syndrome”; EMG= chapter 5 “Monosynaptic reflexes and pre-programmed reactions in Down Syndrome”

Appendix II

Laboratories and instrumentation

The study of functional movements in subjects affected by cognitive and motor abnormalities can yield crucial information in establishing the level of functional limitation attributable to the underlying pathology and in following its evolution over time. Furthermore, these studies can provide important elements for the evaluation of the effectiveness of rehabilitative interventions aimed at reducing the functional limitation due to a pathology.

Most commonly, observational movement analysis is used to evidence gross abnormalities in movements such as walking; however, as functional limitation and movement complexity increase, objective and more precise analysis becomes necessary. The specific clinical need is to reach multi-factorial and quantitative information of functional limitation related to the pathology - i.e. 3D quantitative kinematics (abdo-adduction, flex-extension, intra-extra rotation angles of the main joints, velocity and accelerations profiles), 3D quantitative kinetics (forces, joint moments and joint powers), quantitative evaluation of muscle activity (electromyography) and energy expenditure. The availability of innovative techniques and avant-garde instruments for the description, quantification and evaluation of motion achieves precisely this objective. Quantitative evaluation of motion emerges as a fundamental instrument in the analysis of human movement, thanks to several important features: it is non-invasive, it allows the examination to be repeated a number of times within a short period of time and it supplies quantitative and three-dimensional data.

II.I The laboratories

The present study was possible thanks to the collaborations between two Motion Analysis Labs (MAL): the “Luigi Divieti” MAL at the Electronics, Information and Bioengineering Department of Polytechnic of Milan (Milan, Italy) (Figure II.I.I) and the MAL of the IRCCS San Raffaele Pisana, Tosinvest Sanità, Rome (figure II.I.II).

Acquisitions of the control group took place at the “Luigi Divieti” MAL, were also data analysis and interpretation was carried out, whereas acquisitions of subjects with DS took place in San Raffaele Pisana’s MAL.

Both labs are equipped with equivalent instrumentation for quantitative motion analysis.



Figure II.I.I: “Luigi Divieti” MAL at Polytechnic of Milan



Figure II.I.II: IRCCS San Raffaele Pisana’ s MAL, Tosinvest Sanità, Rome

II.II The equipment

The instruments present in the MALs that took part to the study are the following:

Optoelectronic system

The optoelectronic system measures the three-dimensional coordinates of reflective markers (figure 3a) positioned at specific points of reference on the patient’s body. The markers are illuminated at regular intervals by an infrared light on each of the cameras (figure II.II.Ia) and the reflection is captured by the camera positioned coaxially in relation to the light source (figure II.II.Ib). Acquisition frequency is 100Hz.

Since these cameras use infrared rays the system is totally non-invasive. The system measures the three-dimensional coordinates (XYZ) of the markers positioned on the patient's body. Once the three-dimensional coordinates of the markers are known, it is possible to calculate angles of flex-extension, ab-adduction and intra-extrarotation of the main joints, speed, accelerations, and thus to know, in detail, the kinematics of the body segments on which the markers have been positioned.

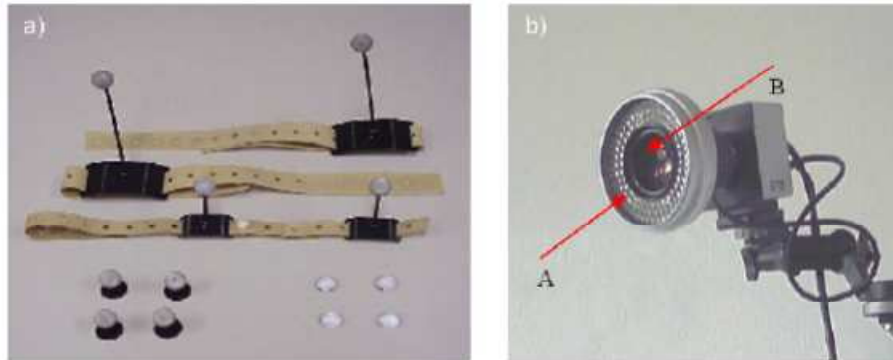


Figure II.II.I: a): markers used in gait analysis. b) optoelectronic camera

Since these cameras use infrared rays the system is totally non-invasive. The system measures the three-dimensional coordinates (XYZ) of the markers positioned on the patient's body. Once the three-dimensional coordinates of the markers are known, it is possible to calculate angles of flex-extension, ab-adduction and intra-extrarotation of the main joints, speed, accelerations, and thus to know, in detail, the kinematics of the body segments on which the markers have been positioned. The markers are usually fixed to the patient's body simply using bi-adhesive tape and they are not a source of hindrance or irritation to him.

Two optoelectronic systems were used in this study: an *Elite2002* (BTS, Italy) and a *SmartD* (BTS, Italy). The first one was used for the walking with obstacle study (paragraph 3.1), because the cameras of this system cover a higher calibration volume that is necessary to analyze several steps of walking, whereas the second one was used for the arm tapping study (paragraph 3.2), where the person was sitting at a table, and a reduced calibration volume was needed.

Force Platforms

Force platforms measure the system of ground reaction forces (figure II.II.II) with an acquisition frequency of 200Hz. Once the system of ground reaction forces is known and the kinematic parameters have been acquired using the optoelectronic systems, the moments and powers of the different joints can be calculated.

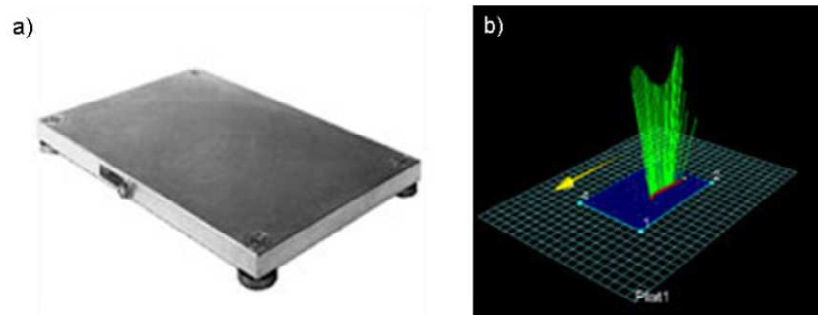


Figure II.II.II: a) force platform. b) an example of GRF during gait

Electromyography

Electromyography is a system that, via surface electrodes, records the responses of muscles to electrical stimulation - i.e., electrical signals generated by muscle contraction (figure II.II.III), with an acquisition frequency of 1000Hz. The system is wireless, is portable and is able to collect and store data.



Figure II.II.III: Electromyograph (FreeEMG, BTS, Italy)

Pressure switches

Pressure switches (BTS, Italy), integrated with the portable electromyograph, record on/off pressure signals with an acquisition frequency of 1000 Hz (figure II.II. IV).

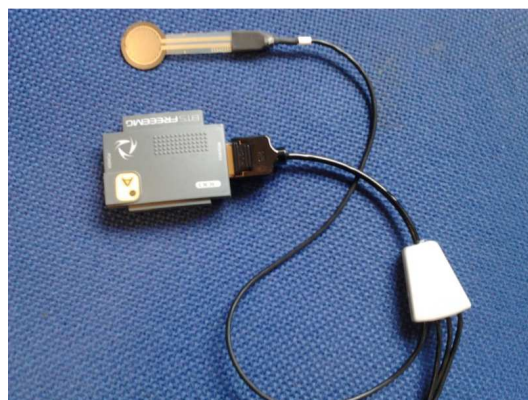


Figure II.II.IV: switch unit and sensor of pressure

Video recording systems

Video recordings allow the clinician to observe a child's motor action from a qualitative point of view (figure II.II.V). Analysis of video recordings is very important from a didactic point of view, because a graph representing the joint kinematics can be easily understandable if there is the opportunity to observe the patient's actual movement, too.



Figure II.II.V: Camera system for the video recording (Video Controller, BTS, Italy)

This instrumentation allows extremely precise quantitative information by means of multifactorial integrated analyses, that is the acquisition of kinematic (e.g., motion trajectories) and kinetic data (e.g., ground reaction forces), and data related to muscle activation (electromyographic, or EMG, data) at the same time.

Appendix III

Davis' protocol for gait analysis

III.I Markers' placement and acquisition of walking

In the walking with obstacle experiment (paragraph 3.1) we used the most widely used international protocol for the evaluation of walking, known as the Davis' protocol. The protocol starts with measurement of the subject's anthropometric parameters (height, weight, tibial length, distance between the femoral condyles or diameter of the knee, distance between the malleoli or diameter of the ankle, distance between the anterior iliac spines and thickness of the pelvis). Most of MALs generally use the Davis protocol for gait analysis because of the international nature of this protocol and the need to generate data that conforms to the international literature. Once these measurements have been taken, reflective markers are placed at special points of reference on the subject's skin (figure III.I.I, on the left). The optoelectronic system measures the coordinates of the markers placed on the subject's body (figure III.I.I, in the centre) and through an algorithm estimates, starting from these trajectories and from the anthropometric measures, the centres of rotation of the joints (Figure III.I.I, on the right).

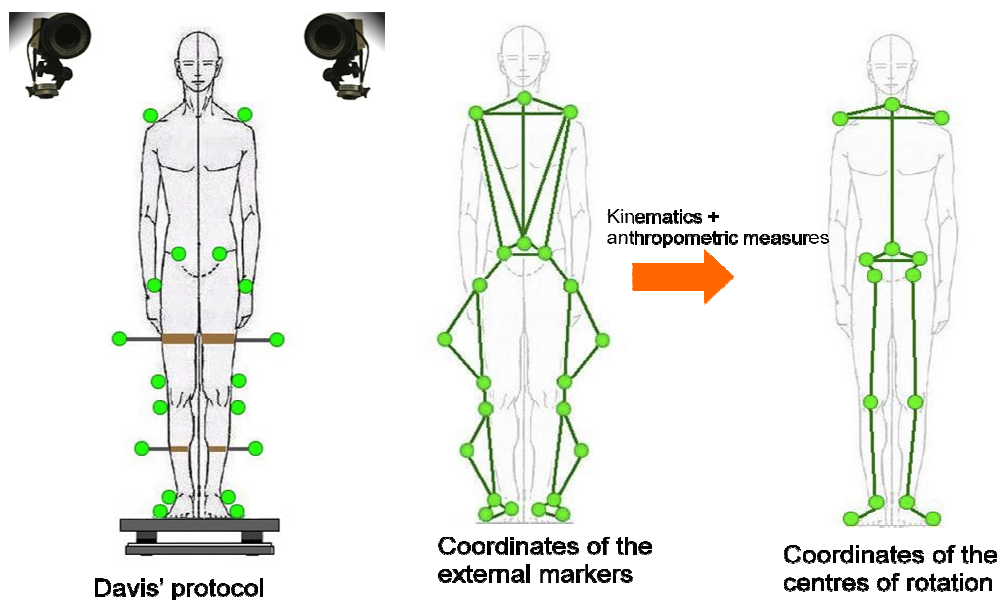


Figure III.I.I: on the left: marker positioning according to Davis. In the centre: acquisition of the coordinates of the external markers. On the right: estimation of the coordinates of the centers of rotation of the joints

Starting from these calculations the angles of flexion-extension, abduction-adduction and extra-intra rotation of the hip, knee and ankle joints are defined; the ground reaction forces measured using the force plates and the kinematic data are then used to calculate the moment and power at the different joints.

The patient is required to maintain a normal upright position for around 5 seconds to allow measurement of the orthostatic parameters. After this, he is asked to walk at his normal speed, each time starting from a pre-defined point so that he places just one foot on each of the force plates. Once this procedure has been repeated enough times to establish the consistency of the measurement (usually 5/6 acquisitions), then this session is over. Generally, it is also deemed opportune to carry out additional tests positioning not only reflective markers, but also electrodes, in order to record muscles EMG activity.

III.II Data Processing and Results

Once the acquired data have been analyzed using appropriate data processing techniques, a stick (or segmental) representation of the patient's body can be created. From this representation the following information can be derived from gait analysis:

- spatial-temporal parameters, such as duration of the stance and swing phases, and stride length, walking velocity, step width, etc;
- kinematic data, especially the angles of flexion-extension, abduction-adduction and extra-intra rotation of the main joints (hip, knee, ankle and pelvis);
- kinetic data, in particular moments and powers of the hip, knee and ankle joints (data relating to the sagittal plane are particularly significant);
- EMG data, in particular the electrical signals associated with muscle activation and deactivation.

III.III Clinical report

Figure III.III.I shows the results of a GA trial, in particular a GA report, which is organized as follows:

- Page 1: anamnesis data of the patient and spatio-temporal parameters (figure 2a);
- Page 2: kinematic graphs relating to motion on the frontal plane (figure 2b, first column), on the sagittal plane (figure 2b, second column) and on the horizontal plane (figure 2b, third column) of the pelvis (figure 2b, first line), the hip (figure 2b, second line), the knee (fig

figure 2b, third line) and the ankle joints (figure 2b, fourth line) of the right leg (blue line) and left leg (red line) of the patient;

- Page 3: kinetic graphs relating to moment (figure 2c, second line) and power (figure 2c, third line) on the sagittal plane of the hip (first column), the knee (second column) and the ankle joint (third column);
- Page 4: Graphs of forces and centre of pressure (figure 2d);
- Page 5: EMG signals (figure 2e).

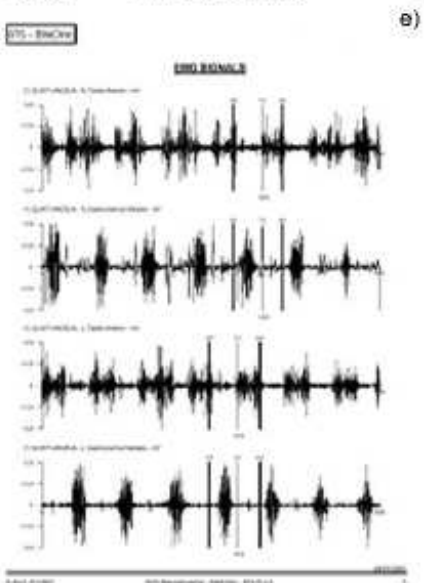
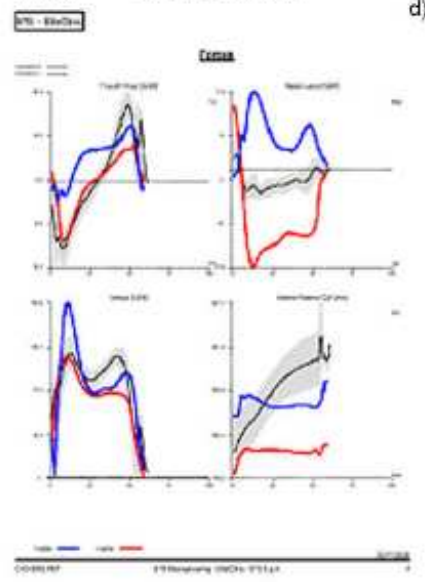
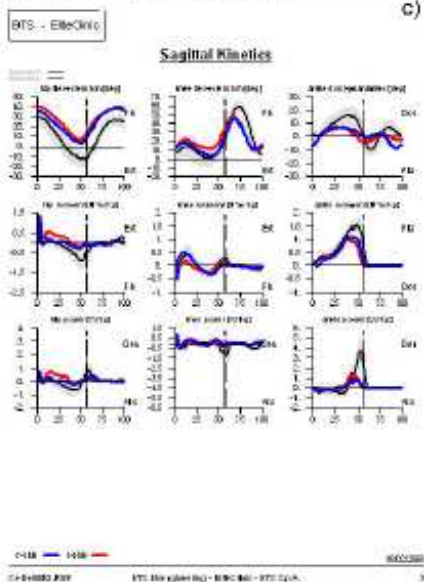
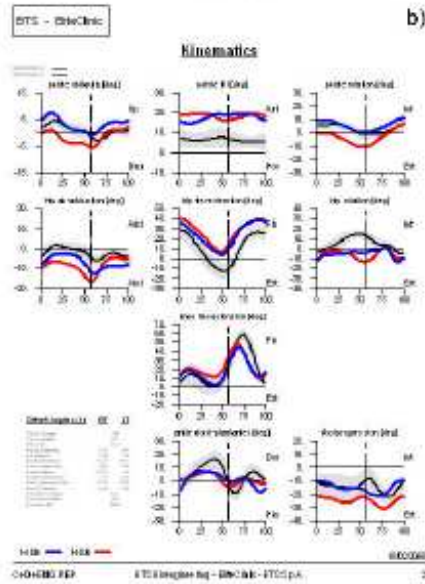


Figure III.III.I: The five pages of a standard clinical report

Appendix IV

Software

The data acquired from the laboratories of motion analysis was collected and analyzed at the “Luigi Divieti” Laboratory at Polytechnic of Milan using dedicated software, as briefly described following.

IV.I Tracklab and SmartTracker

The first step in data elaboration is the labeling of the centroids of the markers that have been acquired during the trial. This can be done using Tracklab Software (BTS, Italy), if the trajectories were acquired with Elite2002, or with SmartTracker Software, if they were acquired with SmartD. By labeling the markers, each centroid is assigned the correct label from the protocol. In figure IV.I.Ia and IV.I.Ib the main steps of the labelling process are illustrated in the case of the Davis protocol.

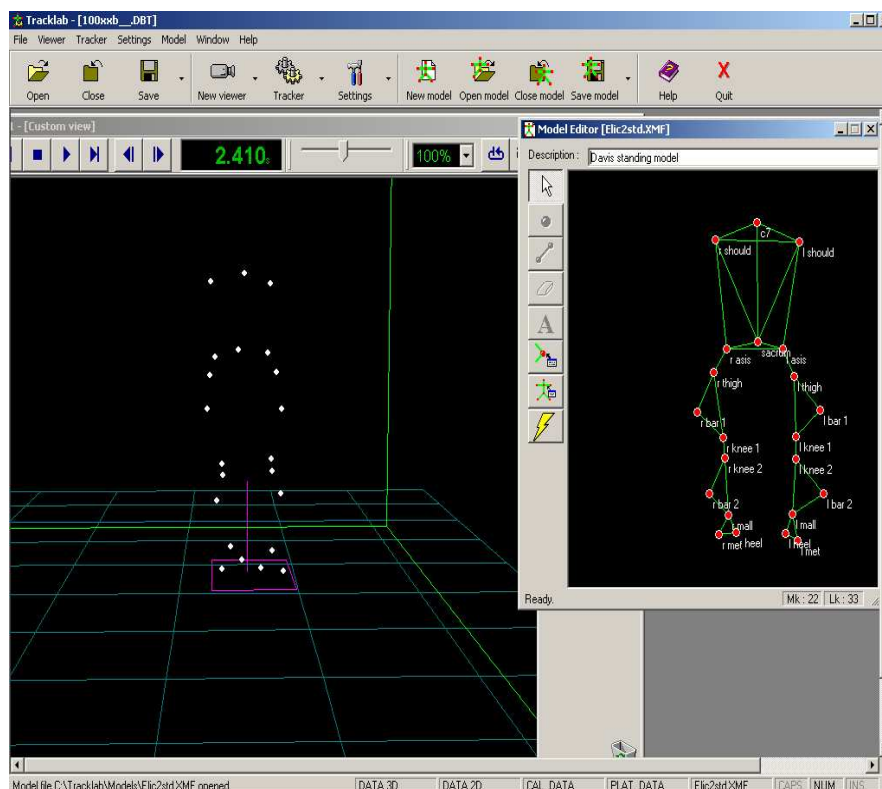


Figure IV.I.Ia: on the right: centroids of the markers acquired during a standing trial. On the left: Davis protocol with the labels of the markers that need to be assigned to the centroids on the left

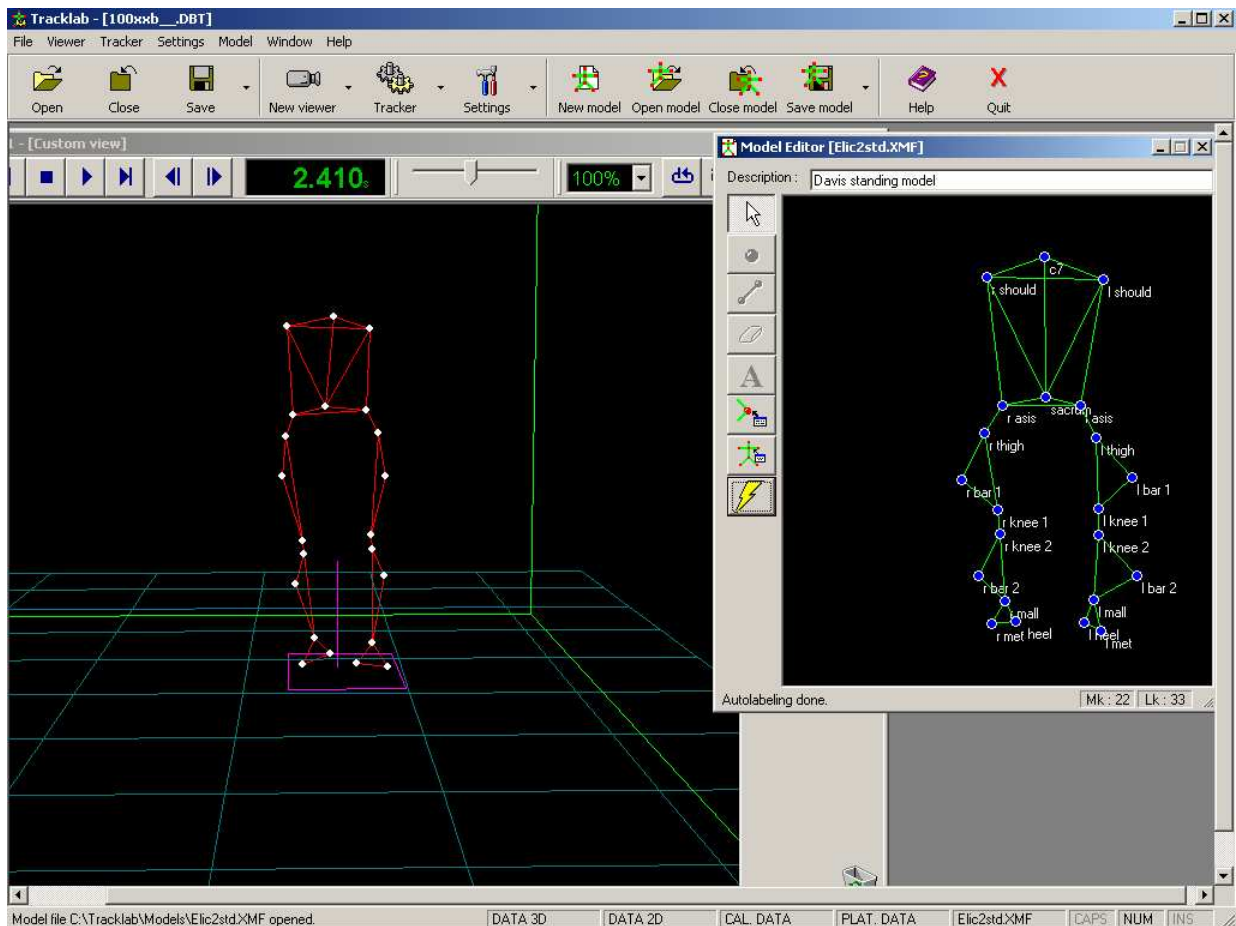


Figure IV.I.Ib: the labels of Davis protocol (on the right) are assigned to the centroids of the markers acquired (on the left)

In this way it is possible to proceed with the calculation of the parameters using two software: EliteClinic, which allows computing the standard parameters for gait analysis according to Davis, and SmartAnalyzer, which is a more powerful tool that allows defining “ad hoc” protocols for the study of movements other than walking.

IV.II EliteClinic interface

The EliteClinic interface (figure IV.II.I) allows the computation of the spatiotemporal and kinematic parameters commonly used in gait analysis and referred to the definition of the Davis’ protocol (see Appendix III). Starting from the trajectories of the labeled centroids, and from the anthropometric measures of the subject, it estimates the centres of joint rotation at the pelvis, hip, knee and ankle joints. Then, it allows the calculation of spatiotemporal and angular parameters for the lower limb joints over a gait cycle. Starting from the force platform data and from the

kinematics, the software allows computing the kinetic patterns of the lower limb joints. Muscular activation patterns can also be viewed over the selected gait cycle.

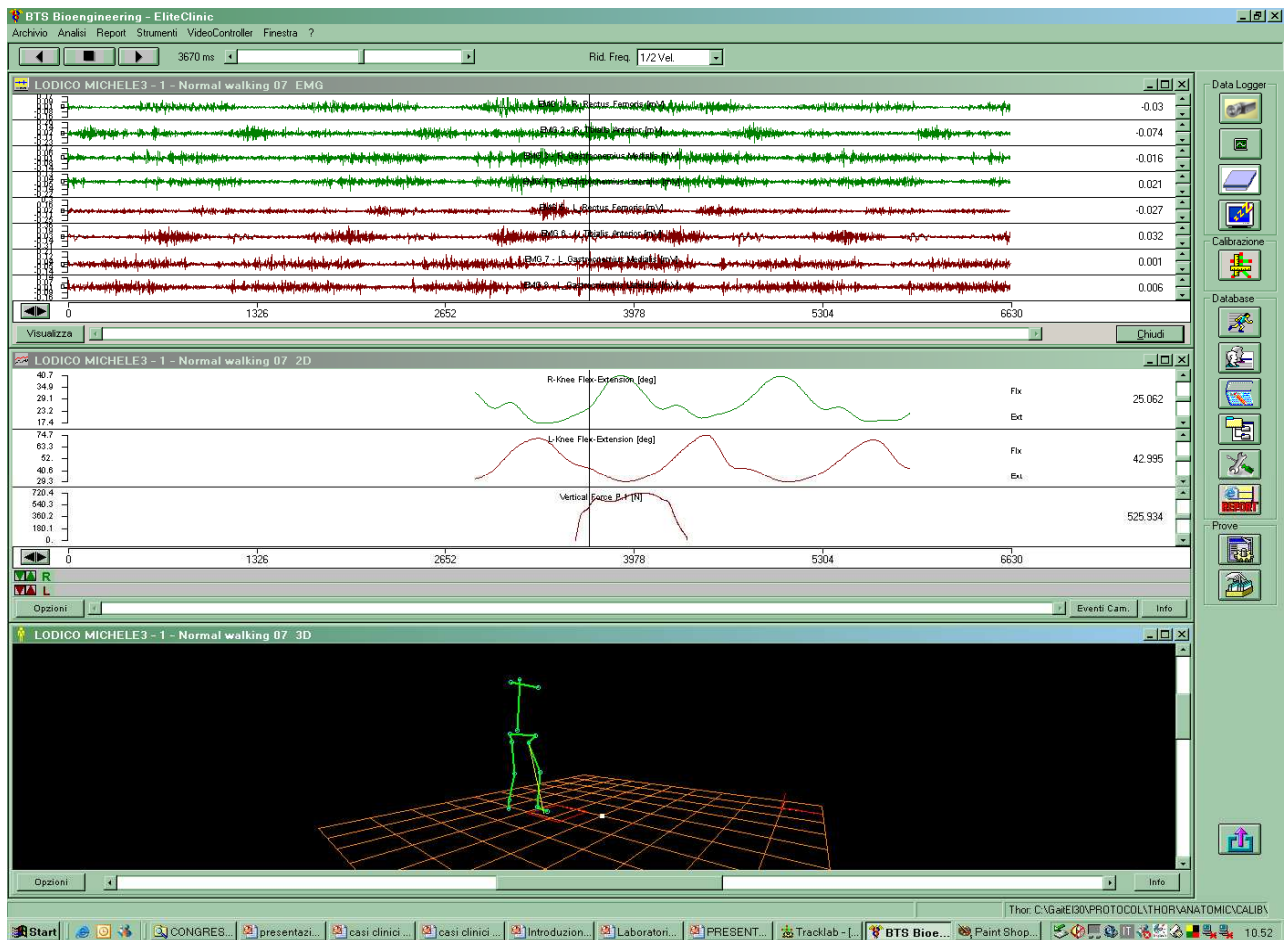


Figure IV.II.I: EliteClinic interface: definition of the gait cycle during a walking trial

The output of these elaboration is a standard gait analysis report comprehensive of spatiotemporal, kinematic, kinetic and EMG parameters (see Appendix III).

IV.III Smart Analyzer interface

Smart Analyzer allows the calculation of the same parameters implemented in EliteClinic, but in addition it is possible to define “ad hoc” semi-automatic protocols for the evaluation of parameters that are not commonly used in standard gait analysis, such as the parameters analyzed in this study. In figure IV.III.I an example of a Smart Analyzer interface is shown. The parameters are calculated in a block diagram fashion, and can be plotted as graphs. The software allows the calculation of both trajectories and punctual parameters.

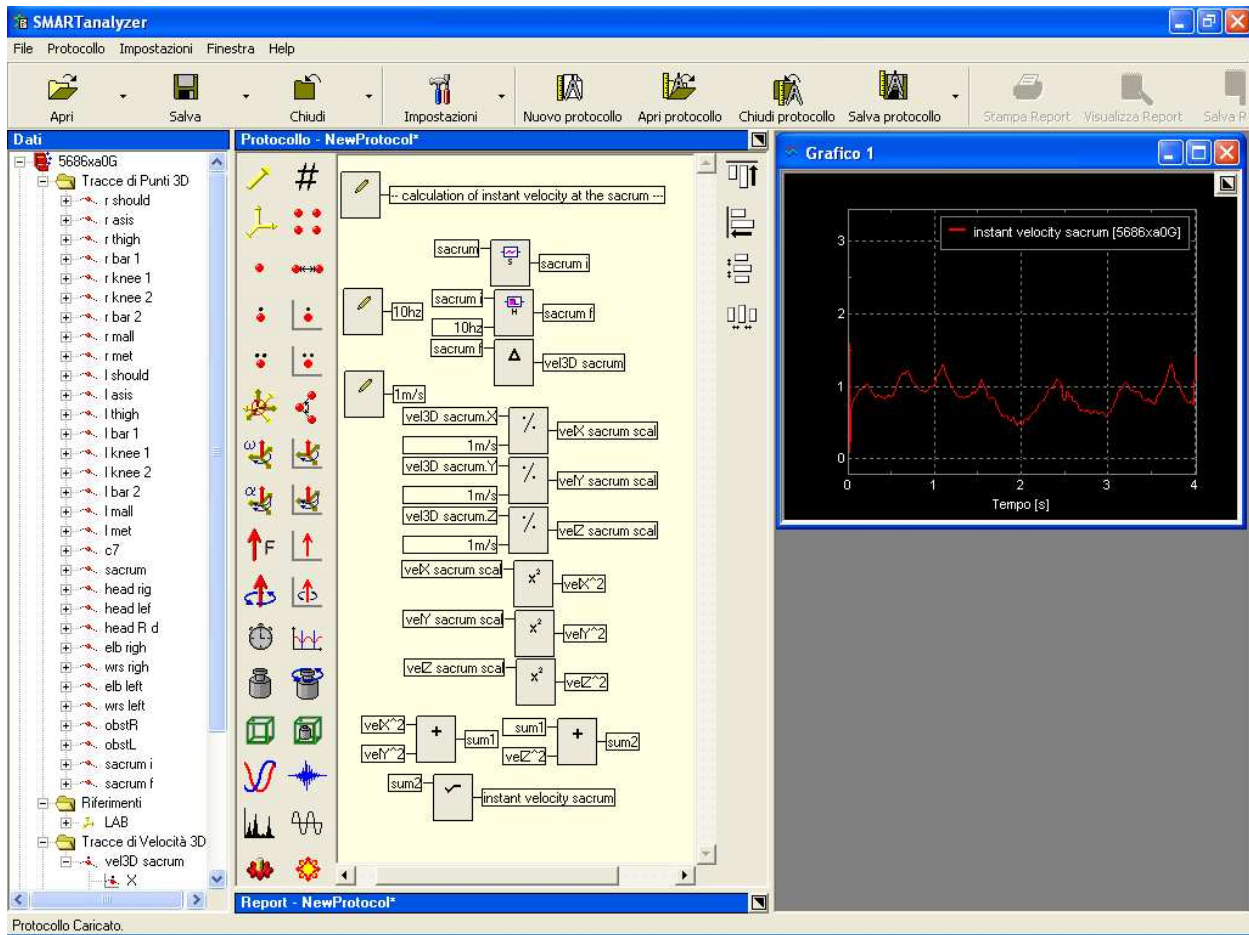


Figure IV.III.I: Smart Analyzer interface. Left side shows the part of the interface where data contained in the acquisition can be observed, together with the new variables defined during the definition of the protocol; in the centre the calculation blocks that compose the protocol are shown; on the right the trajectory of the parameters of interest can be plotted as graphs

A report can be then realized starting from the computed parameters (figure IV.III.II).

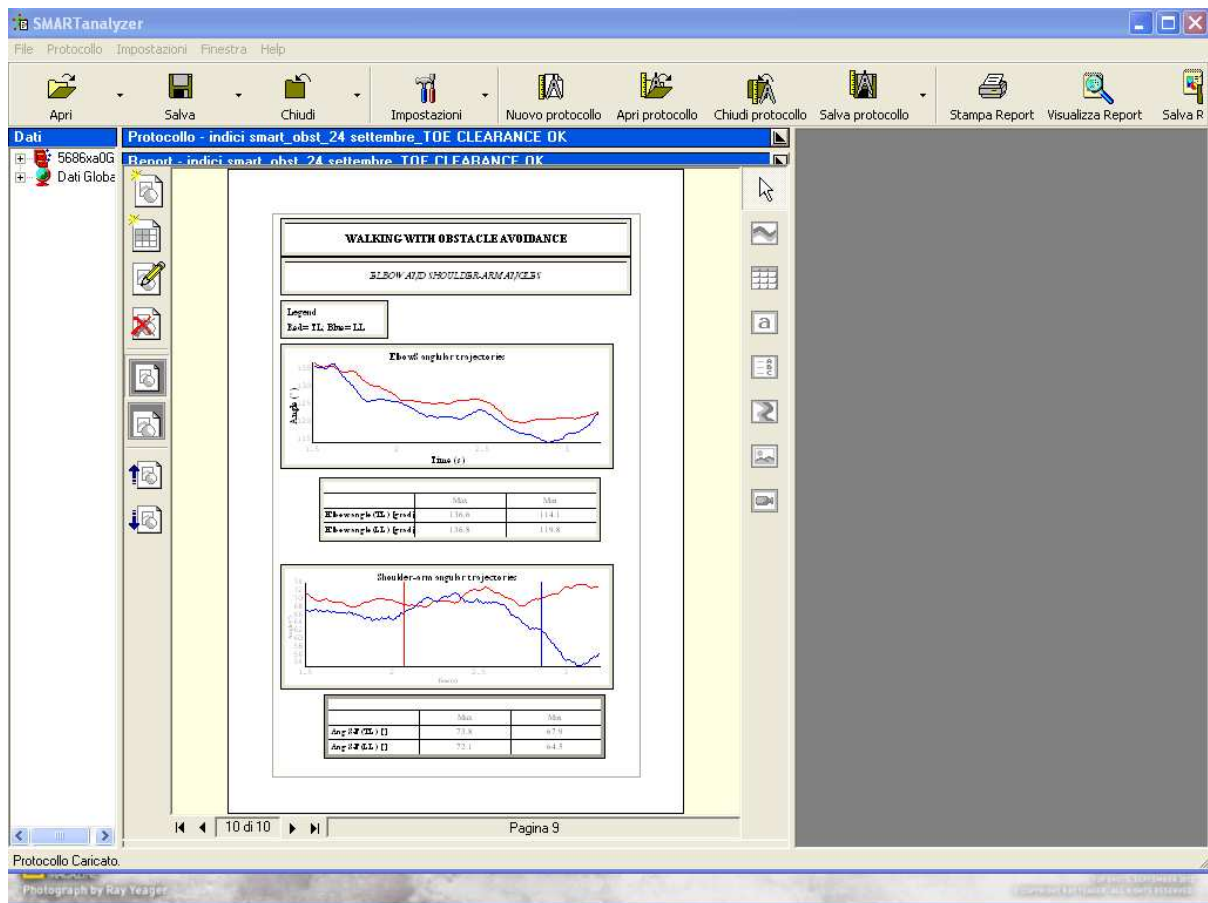


Figure IV.III.II: one page from the report realized with Smart Analyzer software