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(DINOGMI)

Developing new sensors and computer systems for the tele-rehabilitation and remote evaluation of the rehabilitation process of patients with neurological diseases

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1. SUMMARY

Rehabilitation is a significant part of overall disease management. Neurological diseases and related disorders are responsible for a large fraction of temporary and permanent disabilities in Italy and Europe. The benefits of therapeutic exercise and daily physical activity are known and play a fundamental role in the recovery of patients with neurological diseases. To date, clinical scales are relatively unspecific and are not sensitive enough to monitor and to detect the subtle and small changes or progress of the disease.

The progression of neuromuscular diseases affects the musculoskeletal system (structure, mechanical and contractile properties). In hereditary neuropathies like Charcot-Marie-tooth (CMT) disease enduring changes in the muscle and tendon structure may occur. Similarly, patients in the post-stroke phase, although affected by selective damage of the Central Nerve System (CNS), may undergo comparable muscular and tendon changes, which then need special attention and rehabilitative protocols to prevent irreversible deformities.

In the last years, many systems are available to help the patients in exercising. Therefore, in this project we have evaluated the sensors and robotic rehabilitation approach to address novel evaluation and rehabilitation systems, by the application of ICT and specific, innovative sensors.

The aims of the project are

1. Evaluation and effectiveness testing of different tools (sensors and devices either available on the market or developed by our research team)
2. Support of the patients in their care process and assistance of the health professionals to control the rehabilitation process and disease progression.

Through the system developed in these two pints, we aim to:

I. Monitor the rehabilitation and the evolution of recovery;

II. Develop new technologies and applications for specific activities in clinical evaluation, therapy and rehabilitation (following acute neurological disease and during a post-acute phase). After this phase, in future, we will transfer these activities from the hospital to the patient's home, to promote recovery within

the patient's environment, making these activities more relevant to their everyday lives.

We mainly focus on post-acute stroke survivors and persons with hereditary peripheral neuropathies and muscle disorders, e.g., Charcot-Marie-tooth disease. There is a strong need for close monitoring and long-lasting rehabilitative treatment of these patients.

2. INTRODUCTION

2.1 Hereditary neuropathies

Hereditary neuropathies constitute a complex and heterogeneous group of diseases of the Peripheral Nervous System (PNS) [(1)], generally characterized by insidious onset and chronic course. They are classified on the basis of the clinical/neurophysiological phenotype, the mode of transmission and the group of neurons prevalently involved, in hereditary motor, sensory-motor and sensory-autonomic neuropathies [(2)]. In this program, we only include the patients affected by Hereditary Motor and Sensory Neuropathy (HMSN), which represent about 90% of all hereditary neuropathies (Lovelace and Rowland, 1995).

2.1.1 Charcot-Marie-Tooth

Hereditary neuropathies include a variety of progressively disabling diseases, amongst them Charcot-Marie-Tooth (CMT) represents a genetically heterogeneous group of symmetrical peripheral neuropathies [(3)]. The clinical presentation of CMT is often characterized by motor deficits with a loss of proprioceptive reflexes [(1)]. It is the most common rare inherited neurological disorder with a prevalence of 1 in 2500 individuals [(4)].There are two main categories: CMT1 is the most common form (45–50% of all CMT cases), characterized by a primary demyelinating process. It shows slowing of motor nerve conduction velocity (NCV) and abnormality of myelin; CMT2 is primarily an axonal disorder and is less frequent (17-25% of all CMT) [(5)]. It shows relatively preserved motor NCV but a decrease in compound muscle action potential and axonal degeneration in the nerve [(6)]. Another form of CMT has a mixed model, characterized by both myelin and axonal abnormalities (CMTX1) accounting for about 8–10% of all CMT [(7)]. The treatment procedures of patients include physical therapy, orthotics, orthopaedic surgery and pain management [(8)].

2.1.2 Diagnostic method

Patients have variable symptomatology. For the diagnosis of the disease, Clinical observation, performed by the neurologist is fundamental. The typical symptoms and motor-sensory signs of the disease are hyposthenia and hypotrophy, disturbances in the walk, paresthesia, superficial and deep hypoesthesia, hyporeflexia. Therefore, determining a unitary evaluation able to describe the limbs function is fundamental to understand the progression of the pathology and how the different forms of the disease behave. Therefore, it is essential to develop the systems, using an objective evaluation report and as far as possible not operator-dependent to have a common language understandable by the different professionals involved in the care of the patient (neurologists, geneticists, physiotherapists, nurses, occupational therapists). Electrophysiological study, in particular nerve conduction velocity assessment (NCV), is fundamental to diagnosis [(9) (10) (11) (12)]. For example, the recording of NCV at the level of the median and ulnar nerves represents a diagnostic criterion for CMT patients. Generally, in the lower limbs, the speed of the motor and sensory conduction is severely altered and therefore not recordable. In the last years, magnetic resonance imaging (MRI) has become fundamental for diagnosis and monitoring the neuromuscular disorders, given its ability to show the severity and distribution of pathology, to identify specific patterns of damage distribution and to properly interpret some genetic variants. If collected data confirm the hypothesis of CMT, genetic diagnosis is performed.

2.1.3 Treatment and rehabilitation of Charcot Marie Tooth

The course of the pathology is defined as slowly progressive [(3)], from insignificant functional motor problems to complete limb atrophy. There is not much information in literature, in the matter of evaluation and progressive course of the disease, neither the effectiveness of rehabilitative treatment. To date, scientific literature focuses on the clinical aspects of CMT [(13)]. Nevertheless, there are still no effective pharmacologic treatments for these patients. As for physiotherapy treatment, studies show that individual training programs (resistance and aerobic exercise) improve muscular strength in both upper and lower limbs [(14) (15) (16) (17)]. Another treatment to improve balance and gait in CMT are externally applied devices for foot drop, like Ankle-foot orthoses (AFOs) [(18)]. AFOs, supporting the patients in ankle dorsiflexion, get better the need for compensatory hip action to control the foot drop [(19) (20)].

There is still a lack of consensus on the best way to rehabilitate patients affected by CMT [8]. Therefore, we need to conduct new clinical trials, including more case studies, and defining the gold standards in the rehabilitation. At present, Clinical scales are relatively unspecific and are not sensitive enough to monitor and to detect the subtle and small changes or progress of the disease.

Hand function in Charcot Marie Tooth

The normal function of the hand is a critical factor in a person ability to independently engage in everyday life. CMT is causing muscle weakening in the extremities [21]. Overwork weakness (OW) occurs in muscles that used more frequently; therefore, in the upper limb found the asymmetrical weakness because muscles are used more in the dominant hand. OW has been demonstrated in other neuromuscular diseases [22] [23] [24]. In the upper extremity, CMT may cause two types of deformities: i) "claw hand" characterized by marked curvature of the fingers which cause a first phalanx hyperextension and flexion of the other two phalanges; ii) "simian hand" which is a limited opposition ability and wasting of the thenar and hypothenar muscles, it can lead to limit participation in daily activities [9]. The role of OW in Charcot-Marie-tooth (CMT) neuropathy is still controversial. Explain whether it is present or not, could change the perspective of the physical or occupational therapy done to slow the progression of the disease before signs become evident. In literature, strength is evaluated by a dynamometer [25] [26] showed controversial results, some authors reporting that the non-dominant hand (NDH) is stronger than the dominant hand (DH) [27] [28] [29] and other authors stating that DH and NDH have similar strength [30] [29] [31]. Those who affirm that OW is not present because of both hands are similar. Therefore, there is no stronger evidence for the presence of OW in literature yet.

2.2 Stroke

Stroke is the third leading cause of mortality and the first cause of long term disability in Italy [32]. Clinical syndrome is characterized by the acute episode of a focal (sometimes global) neurological deficit with clinical aspects that allow the clinical diagnosis, like: change in the level of consciousness, hemiplegia, hemiparesis, numbness, or sensory loss affecting on side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke that reach the maximum level within a few seconds or minutes and persist for more than 24 hours [33] [34].

2.2.1 Epidemiology

According to the data of the SIIA- Italian Society of Hypertension, in Italy about 200,000 cases of stroke occur every year, 80% of which are new episodes and 20% recurrences. There are about 913,000 survivors of a stroke, with more or less disabling outcomes depending on the case. Approximately one third of them, one year after the event, have a high degree of disability [34].

2.2.2 Stroke classification

Strokes can be classified into two main types, which can then be divided into further subcategories.

- Ischemic: an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of the central nervous system tissue with symptoms persisting for more than 24 hours. If the symptoms last from minutes to hours- less than 24- it is transient ischemic attack [35].

- Hemorrhagic: an acute episode of focal or global cerebral or spinal dysfunction caused by intra parenchymal, intraventricular, or subarachnoid hemorrhage. Two different types are subarachnoid and intracerebral hemorrhage. The first one is result of a hemorrhage from a cerebral blood vessel, aneurysm or vascular malformation into the subarachnoid space. The second one is spontaneous extravasation of blood into the brain parenchyma [36].

The clinical consequences of a stroke depend on the affected anatomical region of the brain, as well as the volume of damaged tissue [37]. After a stroke, the occurrence of alteration of motor control, spasticity, fatigue and incoordination lead to the development of gait disorders [38] [39].

2.2.3 Stroke rehabilitation

Stroke rehabilitation includes: (a) assessment to identify and quantify the patient's needs (b) definition of realistic and achievable goals for improvement; (c) rehabilitative treatment, to achieve goals; and (d) revaluation, to assess progress against the objectives that have been set [40]. For this purpose, physiotherapists need simple tools that can accurately measure the improvement of patients, daily, weekly or monthly.

The brain, including the motor system, learns by training and repetition [38]. Neuroplasticity and the practice of specific functional tasks, underlie the improvement, which are seen in functional outcome after stroke. The clinical consequences of a stroke depend on the affected anatomical region of the brain, as well as the volume of damaged tissue [37]. Therefore, Standards of care are determined based on all clinical data available for an individual case.

Functional rehabilitation of upper limb

Functional deficit in the hand has a serious impact on quality of life; although most patients achieve reasonable recovery of the proximal extremities of the upper limb, recovery of the distal parts has proven to be ineffective [41]. Recent studies have shown how intensive, highly repetitive and task-specific exercise programs can assist the functional recovery [42] [43]. Technology-assisted rehabilitation allows increased therapy intensity and the patient’s physical-cognitive engagement through the use of challenging and motivating exercises promise to promote neural plasticity and a better functional outcome [44] [45] [46].

Functional rehabilitation of lower limb

Ambulation post-stroke is often the less efficient for diminution of functional capacity, gait asymmetry and changes in muscle activation [47]. Loads distribution usually gets altered and they avoid loading the paretic limb; therefore, the ambulatory step is an asymmetric manner accompanying reduced velocity and endurance of their walking [48]. Slow walking speed after stroke is generally associated with a reduced plantarflexor power burst at push-off [48]. The rehabilitation rule to recovering this essential movement can be classified into three phases: (i) the disabled patient is mobilized as soon as possible, (ii) rehabilitation and restoration of gait, and (iii) recovery and correction of gait [48].

2.3 Technology and innovation

Develop and enter new technologies and computer system in the rehabilitation research track, is the motivation why physical therapists and engineers are working together. This collaboration is to adapt or modify existing technologies and develop new technologies to enhance outcome measures, monitor change, or maintain quality of life [49]. Progress has been made in the following fields: robotic rehabilitation, virtual reality (VR) therapy, wearable sensors and monitors, video game therapy and all forms of interactive multimedia rehabilitation applications. Many studies have been published such as the effectiveness of robotic treatment, virtual reality (VR), monitoring with wearable sensors. These processes are still being developed and studied. However, we know that many of these technological innovations offer new intervention strategies to improve the quality of life.

Another point of view is about the importance of Rehabilitative therapy in the management and recovery of the neurological patient at every stage of the disease [50]. During hospitalization, under the constant control of the physiotherapist, is relatively easy to carry on the rehabilitation therapy in a personalized and specific way. Nevertheless, this is more difficult away from the hospital structure, where daily support is impossible to obtain. High technology strategies may be of great help in verifying the quality and results of rehabilitative therapy in the hospital, and the patient own living environment [51]. High technology strategies may be of great help in verifying the quality and results of rehabilitative therapy. In the latest years, many solutions have been proposed, both in the literature and on the market, to perform real-time monitoring of people [52] [53]. None of these has been developed to assist the patients in performing exercises correctly and allowing, at the same time, the professionals to monitor the quality of rehabilitation and progression of recovery.

2.3.1 Rehabilitation Robotics

The histories of rehabilitation robotics date back to the early 1990s, when the first assistive technologies have been developed and became available for clinical use [54] [55]. They have built-in technology and sensors, therefore integrating both therapeutic and measuring functionalities, to provide an accurate assessment of motor function [54]. In the rehabilitation field, there is crescent interest in the potential of robotic devices [56]. One important characteristic of robots is that they evaluate patient performance and their progress during treatment. But, the fundamental problems are the difficulty of personalization and high cost [57]. As yet, various robotics-assisted have been developed to facilitate upper or lower limbs functions. Some of them, currently on the market, are the following:

- The *Amadeo* by Tyromotion: is an end-effector device designed for the hand. It simulates the movement of grasp and through the individual digit supports move along a track to flex- extend the digits. Furthermore, is possible to personalize the type of treatment in a passive, active-assisted or active way [58].
- The *Armeo* by Hocoma: uses custom software, which enables the device to be used in different ways with an exoskeleton enveloping the user's arm and provides arm weight support. The device offers a functional training in the form of simulated activities of daily living [58].
- The *Diego* by Tyromotion: is an end-effector device that allows three-dimensional, unimanual, and bimanual movements of the shoulder joint, both in sitting and in standing, with gravity compensation. Support can be reduced over time as patients progress from passive to active therapy modes [59] [58].
- The Erigo by Hocoma: To propose patients a locomotion therapy at a very early stage of rehabilitation was developed "Erigo".The construction of the "Erigo" bases on an automated stepping training, in a physiological manner with the possibility of simultaneous verticalization of the patients [60]. The device can be tilted from a supine position up to 80 degrees adapted to the status of the patient. During the treatment, the upper body of the patient is secured through a harness [61].
- The Geo-system by Reha technology, Switzerland: is an end-effector device. This device is the easy setup and assists the patient during gait training with a system for partial unloading of the body weight. The harness secured patient stay on two-foot plates [62] (Figure1). The movements originate from the most distal segment of the extremity and look similar to the physiological

situation [63]. The most important advantage of using robot technology in rehabilitation intervention is the ability to deliver high-dosage and high-intensity training [64] [65] . Recent studies have also shown that higher intensities of walking practice result in better outcomes for patients after stroke [66] [67] .

Figure1: A) G-EO system end-effector gait rehabilitation robot; B) Control panel; C) The motion mechanism of the gait robot

2.3.2 Virtual reality

Recent developments in the field of virtual reality have made it possible to formulate new application paradigms obtained by integrating current rehabilitation pathways with instrumental interventions. In fact, thanks to their ability to simulate situations analogous to reality, they can give patients an opportunity to practice activities that could not be practiced within the hospital environment [68]. It enables the therapist to provide patients with a method of repetitive task specific training and does have beneficial effects on rehabilitation of patients with neurological disorders [69].

In a chapter of the present thesis is placed in this field of intervention and provides for the use of a sensor that detects movement: the Leap Motion Controller [70] [71] [72].

Leap motion controller

The leap motion controller (Figure2) is a new low-cost markerless motion-capture device that tracks the fine movements of fingers and hands without using data gloves and markers. Some of the important advantages of this technology are: simplicity and portability, commercial availability, low cost and non-invasive nature. It is also capable of controlling a virtual environment [72] [73].

Figure2: The Leap Motion® System

It contains two monochromatic cameras and three infrared LEDs. The software driver of the device implements a 3D model reconstructing the skeleton geometry of the forearm and hand and can stream to a computer the position data of finger/thumb tips, a center of palm, wrist and recognize the gesture. The Leap Motion Controller connects to PC via USB; the LEDs generate a 3D pattern of infrared light dots. If hands are placed within an approximate area up the device, they reflect the infrared signal and afterward processed by a Leap Motion Software for the creation of a hand model.

There are a number of other commercially available devices for rehabilitation; such as the ReoGo (Motorika), Hand Mentor Pro (Motus Nova), the Kinarm (BKIN), the HandCARE, the Proficio (Barrett); Microsoft Kinect, Nintendo Wii, Lokomat, FES. Each has a specific design that may have specific advantages. However, an extensive description of these devices is beyond the scope of this tease.

2.3.3 Music therapy

Music therapy is a therapy based on the use of music as an educational, rehabilitative or therapeutic tool. Many studies document the possibility that the use of music and sound during training or specific rehabilitation interventions can stimulate plastic processes in our brain, not only in the developmental age but also in adult (74) (75). Suggest, the plastic changes induced by music in the nodal points of the brain networks and the fibre fascias connecting the various areas. It could lead to effects tending to extend beyond the actual duration of the rehabilitative intervention (75) , and this is undoubtedly one of the most expected impacts of this work.

2.3.4 wearable sensors and monitors

Wearable sensors have monitoring applications and one of their capabilities is motion-sensing (76) (77). Inertial sensors include accelerometers, gyroscopes and magnetometers used to register movement data. Today, movement sensors are inexpensive and small, making them highly attractive for patient monitoring applications (78). Remote monitoring systems have the potential to provide rehabilitation treatments and assess the degree of clinical impairment and improvement to disabled persons living at home (79). This is an area of emerging and rapidly growing research (80). Home-based motion-sensing is particularly suitable for remote control rehabilitation and have proven efficacy (79). Appropriate and verifiable at-home rehabilitation protocols facilitate the discharge of the patient from the hospital and reintegration at home. To this purpose, monitoring of vital functions to guarantee the safety of home therapy is essential. Many systems are available to help the patients in exercising at home, as the wearable accelerometer-based devices (53) or the use of virtual reality (52) . Nevertheless, only a few devices for the assessment of the at-home activity are present on the market (81) . None of these has been developed to assist the patients in performing exercises correctly and allowing, at the same time, the professionals to monitor the quality of rehabilitation and progression of recovery.

3. AIMS OF THE THESIS

Aim of the projects, as suggested by the title, is the development new sensors and computer systems for the tele-rehabilitation and remote evaluation of the rehabilitation process of patients with neurological diseases. We also performed the evaluation of sensors and devise at present available in market and verification of the effectiveness of their activity in the rehabilitation or evaluation protocol.

In particular, we carried out:

- Investigation of new technologies to evaluate the hand of CMT patients compared to healthy controls, using a Hand Test System (HTS). In this setting we especially studied the occurrence of OW. The demonstration of OW existence is of fundamental importance. Especially when the patient undergoes rehabilitation treatment or when it is necessary to advise the right use of the upper limbs in the activities of daily living (ADL).

- Study of the use of a specific rehabilitative protocol for the upper limbs in CMT (according to the first aim), based on sub-maximal exercises, mainly to avoid the effect of OW and at the same time, improve the dexterity and overall functionality of the hand effect. It is sufficiently simple to be used by a therapist in the physical treatment of the hand.

- Investigation of new training and assessment method for the rehabilitation of hand motor function through musical sonification using the LMC. Main objectives of the study were to verify, through a randomized controlled study and an appropriate motor assessment, the effectiveness of rehabilitative hand treatment in post-acute stroke patients who use the technique of "sonification" and to evaluate if this technique reduces the fatigue and pain perceived during rehabilitation and also improves the patient's quality of life.

- Feasibility and usefulness of standard of care treatments associated with robotic treatments in intensive recovery after stroke. The aim of this retrospective study was to elucidate the effectiveness of two different kinds of rehabilitation protocols within the first 3 months of post-stroke recovery. In fact, the only difference being the use of the GEO-system. We were mostly interested in assessing the effects of robotic assisted rehabilitation over standard of care treatment on lower limb motor function, gait performance and balance.

  Furtherly, a significant aim of the present thesis is the development of new low-cost tools with sensors and related software for the evaluation of the movement in the lower limb:

- Testing of these devices in the hospital environment.
- Definition of validated parameters measured by the novel technology, as compared to gold-standard clinical scales and in healthy controls.

4. MATERIALS AND METHODS

As a first step, we evaluated the tools, sensors and platforms currently available and then we have verified the effectiveness of the activity.

4.1 Testing overwork weakness in Charcot-Marie-tooth disease

In the first study we use of an innovative tool which can objectively evaluate different aspects of the hand functionality comparing the data obtained with healthy controls. The aim is to study the OW using precise methods. In this work, we evaluate strength with a dynamometer, articulation with the Thumb Opposition test and manual dexterity with an innovative instrument developed by the University of Genoa, the Hand Test System (HTS).

4.1.1 Recruitment of subjects

We recruited 120 subjects, 60 normal controls and 60 CMT patients attending the Multidisciplinary Outpatients Clinic for Diagnosis and Treatment of Inherited Peripheral Neuropathies at the Policlinic San Martino-IST and Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal, and Child Health (DINOGMI), University of Genoa, Italy. Inclusion criteria: patients with clinical and genetic diagnosis with CMT1 or CMT2 disease, age between 19 and 80 years old. excluded patients with comorbidities that could interfere with muscle strength or hand function, story of surgery at the upper limb.

4.1.2 Outcome measures

The evaluation has been performed by the following tests: strength evaluation with a dynamometer, Thumb Opposition Test (TOT), Hand Test System (HTS)

Thumb Opposition Test (TOT)

The TOT is a fast and straightforward performing test which consisting the touch of the four long fingers with the tip of the thumb [82], as a follow:

Score 0: no opposition

Score 1: the tip of the thumb touches the lateral side of the middle phalanx of the index finger

Score 2: the tip of the thumb touches the lateral side of the distal phalanx of the index finger

Score 3: the tip of the thumb touches the tip of the middle finger

Score 4: the tip of the thumb touches the tip of the middle finger

Score 5: the tip of the thumb touches the tip of the ring finger

Score 6: the tip of the thumb touches the tip of the little finger

Then, moving the thumb proximally along the palmar side of the little finger

Score 7: the tip of the thumb touches the distal interphalangeal crease

Score 8: the tip of the thumb touches the proximal interphalangeal crease

Score 9: the tip of the thumb touches the proximal crease of the little finger

Score 10: the tip of the thumb touches distal volar crease of the hand

This test is valid only if the first stages are possible: a crawling thumb in the palm is not an opposition motion (figure3).

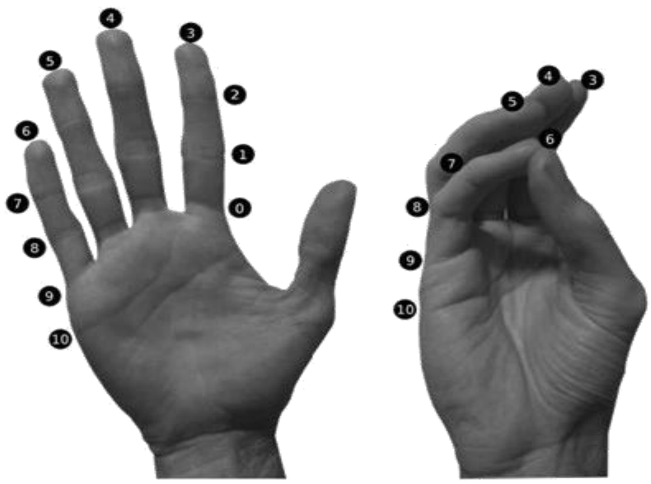

Figure3: Thumb opposition test (Leamy et al., 2014). Assesses the opposition of the thumb, scores from 0 = opposition is impossible to 10 = maximal opposition [83]

Dynamometer

A dynamometer is a device for measuring hand strength [84]. For ease of carrying, ease of test performance, reproducibility, and price, this device has been used for the hand-strength measurement [85]. The maximal isometric voluntary contraction was measured for both left and right hands with a hand-held dynamometer (Citec CT 3001; CIT Technics BV, Groningen, The Netherlands) measuring in order triple pinch and handgrip. Both were performed according to a standardized testing procedure [86] [87]. We made three attempts, alternating the DH and NDH, with a rest of 30 seconds between the tests.

Hand Test System (HTS)

Hand Test System (HTS) developed by the University of Genoa with the collaboration of ETT S.p.A (Sestri Ponente, Genoa, Italy), is a tool simple to wear and not exerting limitations during finger movements (figure 4). It is composed with a general connection scheme of laptop, acquisition board and an engineered glove system. Five small circuits of gold are present on the palmar surface of the distal phalanxes of the glove. They record the contact during opposition movements between the thumb and another finger [88]. Each spiral is connected to a specific connector. Five signals corresponding to the five fingers reach the USB-1208FS, Measurement Computing, USA. Engineered glove is able to record finger touches during sequences of finger opposition movements, to provide a quantitative description of finger motor performance without time constraints. Moreover, when no external events pace movements, subjects can be guided to perform a sequence of movements at their natural or maximal velocity form.

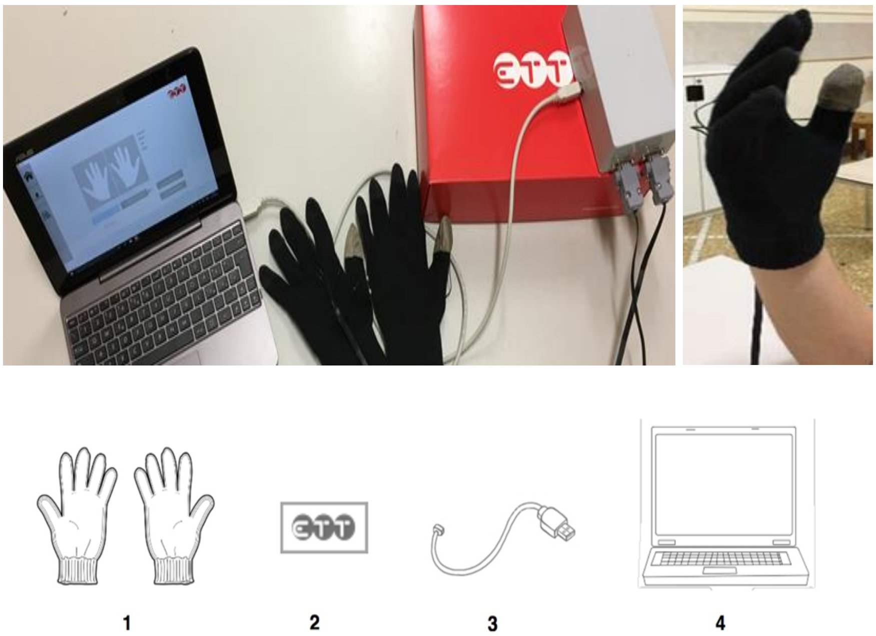

Figure4: The package of the device contains the four items: 1. sensor engineered gloves, 2. USB PC interface, 3. USB cable, 4. a convertible laptop 10.1- inch

An “eyes-closed paradigm” has been chosen to avoid possible confounding effects because of the integration of acoustic and visual information. The patients were instructed to execute finger opposition movements of different complexities: finger tapping (FT) sequence (opposition of thumb to index) and index-medium ring- little (IMRL) sequence (opposition of thumb to index, medium ring, and little fingers) at maximum velocity (MV). The tasks consisted of the execution of a repetition of each sequence lasting 30 seconds, alternating the hands. Data processed with customized software from Glove Analyzer System, which permits selection to acquisition and experimental protocol. The following parameters were measured:

- touch duration (TD) or contact time between thumb and another finger (in ms);
- inter-tapping interval (ITI) or time between the end of the contact of the thumb and another finger and the beginning of successive contact (in ms);
- movement rate (MR, 1/[TD + ITI]) or frequency of complete motor task (in Hz).

4.2 Hand Rehabilitation Treatment for Charcot-Marie-Tooth Disease

The second study is about a rehabilitation protocol based on sub-maximal exercises, mainly to avoid the effect of overwork weakness and at the same time, improve the ability and overall functionality of the hand. It is sufficiently simple to be used by a physiotherapist in the treatment of the hand.

We have observed that based on a precise and quantitative evaluation, using the instruments and sensors (part 4.1), we have the possibility of programming a more precise physiotherapeutic plane (Part 4.2). Accordingly, we decided to test other types of devices on the market (such as leap motion and robotic instruments), for the evaluation and/or the rehabilitation process of patients with post-acute neurological diseases such as stroke.

4.2.1 Recruitment of subjects

We recruited patients with a clinical and genetic diagnosis of different CMT types, excluded patients with uncontrolled pain, severe comorbidity and other pathology. Informed consent was obtained according to our institution policy and the declaration of Helsinki. Outcome measures were applied one day before the beginning of treatment (T0) and one week after the end of treatment (T1).

4.2.2 Outcome measures

In this study, the evaluation performed by the following tests: Hand-held dynamometer (Citec CT 3001, CIT Technics BV, Groningen, The Netherlands), Thumb Opposition Test (TOT) and Sollerman Hand Function Test (SHFT).

Hand-held dynamometer

To analysis the variation of the strength in an objective way we performed a maximal isometric voluntary contraction of both hands, measuring i) tripod pinch and ii) handgrip. Both were performed according to a standardized testing procedure [87] [86]. We made three attempts, alternating the dominant and non-dominant hand, with a rest of 30 seconds between the tests.

Thumb Opposition Test (TOT)

We described the test in the previous page part (4.1.2). The score range is 1-10 [82]. During the trial, the patient touches the four long fingers with the tip of the thumb.

Sollerman Hand Function Test (SHFT)

The Sollerman Test comprises 20 activities of daily living tasks:

1. Put the key into Yale lock turn 90°; 2. Pick coins up from the flat surface, put into purse mounted on board; 3. Open/close zip; 4. Pick up coins from purses; 5. Lift wooden cubes over edge 5 cm in height; 6. Lift iron over edge 5 cm in height; 7. Turn screw with a screwdriver; 8. Pick up nuts; 9. Unscrew the lid of jars; 10. Do up buttons; 11. Cut Play-Doh with knife and fork; 12. Put on Tubigrip stocking on the other hand; 13. Write with a pen; 14. Fold a paper, put into an envelope; 15. Put paper-clip on an envelope; 16. Lift telephone receiver, put to the ear; 17. Turn door-handle 30°; 18. Pour water from a bottle; 19. Pour water from a jug; 20. Pour water from a cup. Patients scored on a 5-point scale from 0 to 4. The test was performed according to the author instructions [89], asking the patients to use the preferred hand.

4.2.3 Rehabilitation protocol

Treatment duration lasted 4 weeks (two sessions of 45 minutes per week). Literature about this argument still lacks; therefore, the duration and the frequency has been determined inspiring to some papers about hand rehabilitation in chronic and acute diseases [90] [91]. Moreover, we choose a low frequency of session to avoid an overuse. Exercises had been listed in the table1 and three professional physiotherapists followed them scrupulously alternating each other in the sessions. Three parts composed the sessions: i) muscle recruitment phase, ii) stretching phase and iii) proprioceptive phase. While muscle recruitment and stretching exercises had been maintained the same over the 4 weeks, proprioceptive exercises had progressed. All exercises were performed alternating right and left hand and respecting a time of rest, avoiding the overwork weakness. Therapists made attention to the quality and the quantity of movements, searching for the best activation of the single muscles.

Strengthening (1-4 week)		
		Muscles involved
Abduction of the fingers with a submaximal effort	5 times per hand	Interosseous
Adduction of the fingers with a submaximal effort	5 times per hand	Interosseous
Thumb opposition with a submaximal effort	5 times per hand	Thenar eminence
Extension of the fingers with a submaximal effort	5 times per hand	Extensors
Opposition of all fingers with a submaximal effort	5 times per hand	Thenar and Hypothenar eminence
Stretching (1-4 week)		
Fingers flexors	5 times per finger	
Wrist flexors	5 times per wrist	
Pollicis adductor	5 times per hand	
Interosseous and lombrical (dorsal)	5 times per hand	
Interosseous and lombrical (palmar)	5 times per hand	
Proprioception (1-2 week)		
Turn 2 marbles in the palm per 60 sec	2 times per hand	
Theraputty manipulation: making stripes	4 times per hand	
Theraputty manipulation: little balls modeling (6 balls)	2 times per hand	
Proprioception (3-4 week)		
Turn 4 marbles in the palm per 60 sec	2 times per hand	
Theraputty manipulation: making stripes	4 times per hand	
Theraputty manipulation: little balls modeling (6 balls)	2 times per hand	
Extraction of 4 marbles from theraputty with pinch	2 times per hand	

Table1: Rehabilitation protocol followed by professionals

4.3 The sonification approach to the hand rehabilitation in post-acute stroke patients: a multicentric randomized controlled trial.

The third Project is a multicentric randomized controlled research, entitled SonicHand protocol. The study is composed by five operational units at the level of Italian territory that one of them is the Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, IRCCS AOU San Martino-IST, University of Genoa. The study, promoted by the musical therapy laboratory of the clinical scientific institutes of Pavia, is coordinated by Professor A. Raglio. As an operating unit collaborator to the study, provided with the appropriate equipment and software to carry out the data collection. The study proposes the use of an innovative training and assessment method for the rehabilitation of hand motor function through musical sonification using the LMC. Recent research has shown the feasibility of application and the validity of the assessment protocol for the rehabilitation of hand function [92].

In specific, this project aimed at assessing the effectiveness of a sonification training protocol for the improvement of hand motor function. Patients with the following conditions excluded: lesions older than 6 months from onset, multiple or bilateral lesions, presence of neglect, Mini-Mental State Examination < 24, previous or concomitant diseases affecting upper limb functions (e.g., Parkinson's disease, multiple sclerosis, Dupuytren disease, etc.), rehabilitation treatments with music in the last year.

4.3.1 Recruitment of subjects

The randomized controlled trial included 65 patients diagnosed with a stroke which allocated in two groups. The control group received a traditional motor treatment, for four weeks. The experimental group executed a traditional rehabilitation and "sonification" technique exercises for the same period. Inclusion criteria were: age between 40-85 years, the ischemic lesion in a single hemisphere (left or right hemiparesis), Mini-Mental State Examination > 24, acute onset no more than 180 days prior to enrolment in the study.

4.3.2 Outcome measures

Rehabilitation interventions evaluated at baseline (T0), at the mid-treatment period (T1), i.e. after two weeks, after the treatment period (T2), i.e. after four weeks by the following tests:

Motor evaluations

- *Fugl-Meyer Motor Assessment Scale* (proximal and distal upper limb motricity) [93] : This scale was first proposed by Axel Fugl-Meyer and his colleagues in 1975 as a standardized assessment test for post-stroke recovery [94]. It is now widely used for clinical assessment of motor function. The Fugl-Meyer (FM-UE) Assessment for upper extremity (maximum score of 66 points) is recommended as a clinical tool for evaluating changes in sensorimotor impairment in every stroke recovery and rehabilitation trial.

- *Box and Block Test* [95] : The idea for the Box and Block Test (BBT) originated with A. Jean Ayres and Patricia Holser Buehler. It is composed of a box divided by a partition in two compartments and one hundred and fifty, 2.5 cm, colored wooden blocks (figure 5.1). The patient is instructed to move, one by one, the maximum number of blocks as possible from one compartment to another a 60 seconds (figure 5.2-4). The test should begin with the unaffected upper limb and fingertips must cross the partition during a transfer of the blocks. In the beginning, 15 seconds trial period is permit [96].

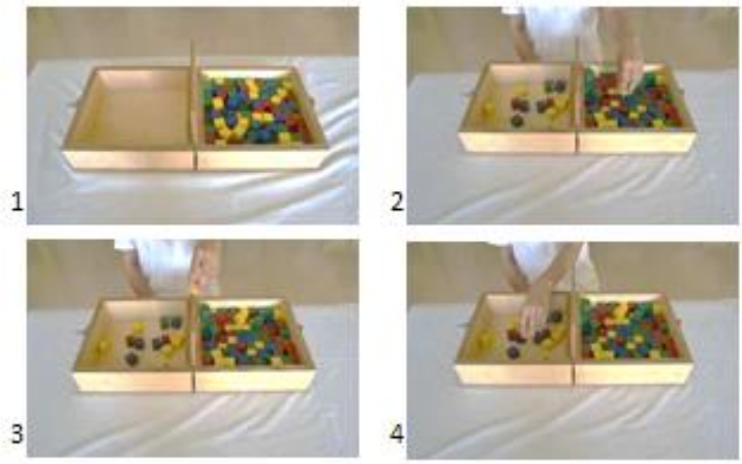

Figure 5: Box and Blocks Test. 1. Components; 2-4. User during test development

- Modified Ashworth Scale (spasticity rating) (97) The Modified Ashworth Scale (MAS) is generally applied in patients with Stroke to classify the level of spasticity and increased muscle tone. On a one-hand, the MAS is useful for qualifying response to treatment over time; on the other hand, it is a somewhat subjective tool. To appliance, the test, place the patient in a supine position. To test a muscle primarily flexes a joint, move the joint from maximally flexed to maximal extension position over one second.

4.3.2.1 Evaluation of the quantitative parameters obtained with the Leap Motion controller device

At 2019 Colombo R et al. in Maugeri Scientific Clinical Institutes IRCCS, Pavia, Italy, has published a protocol for the rehabilitation of hand motor function through musical sonification using the Leap Motion Controller (LMC®; Leap Motion, Inc., San Francisco, CA, USA). It is a low-cost device, based on infrared and stereo-vision motion capture technology. The LMC is capable to capture the movement of hands and fingers thanks to two monochromatic cameras and three infrared LEDs and it is able to do a vector representation of the hand, the fingers, the wrist and the forearm up to the elbow. In this trial we used a sampling rate of 25Hz. The protocol has demonstrated to be feasible, and the assessment protocol showed good to excellent between-group discrimination ability, reliability, and concurrent validity. Therefore, it is enabling the development of new personalized training programs for the rehabilitation of hand function. It was part of the present multicenter study which one of the centers is the University of Genoa, Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics and Maternal/Child Sciences.

The patient was sitting in a wheelchair with a transparent table. The LMC was positioned about 25 cm under the table level by a multi-articulated supporting arm attached to the wheelchair structure using a clamp (figure 6).

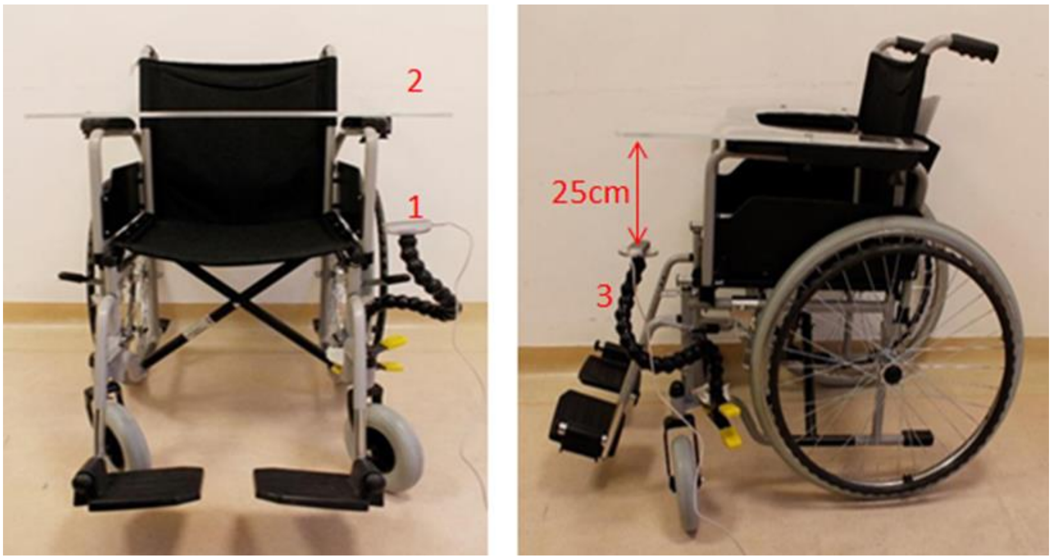

Figure 6: 1. Leap Motion Controller; 2. Transparent table; 3. Multi-articulated supporting arm

Evaluation of the quantitative parameters obtained with the LMC consisted of 3 exercises without sonification of movement: horizontal flex-extension of the wrist, pronation-supination of the wrist and grasp. These activities has been repeated for five times and during the repetitions the x,y,z positions of the fingertip, of the palm and of the wrist has been recorded (figure 7). Patients have to achieve the movements as naturally as possible, and then the average speed and fluidity during actions were calculated.

Figure 7: SonicHand Software Interface – Evaluation

1. Hand pronation/supination:

   Starting position: the patient opens the hand in the horizontal plane with the hand pronated. The recorded position of the "thumb tip" was computed at a Mean Velocity. The ratio between the peak tangential speed of the "thumb tip" and the mean velocity of the tip was used to calculate Movement fluidity. Pronation/Supination Angle was estimated by computing the angle between the vector from the palm center to thumb tip and the horizontal plane passing from the center of the palm. A 0° angle corresponded to the hand position completely supine and 180° considered the hand completely pronated.

2. Horizontal flex-extension of the wrist:

   Starting position: the hand open neutral position, the wrist was flexed and extended in the horizontal plane. In this movement, was calculated Mean Velocity by the recorded position of the "index fingertip". The ratio between the peak tangential speed of the "thumb tip" and the mean velocity of the tip was used to calculate Movement fluidity. The LMC software driver provides the signal of Wrist flexion/extension angle. Three parameters, corresponding to the maximum wrist flexion (negative values) and extension (positive values) angles and their difference were computed.

3. Hand grasp:

   Starting position: the hand horizontally pronated open, then closing it leaving the thumb outside the other fingers. In this movement, was calculated Mean Velocity by the recorded position of the "middle fingertip". The middle fingertip velocity profile, considered to compute Movement fluidity. Distance between the thumb tip and the little-fingertip calculated for grasp parameter. The minimum closing and the maximum opening distances and their difference calculated as a corresponding parameter.

4.3.3 Rehabilitation interventions

The control group received a traditional motor treatment, 35 minutes daily individual therapy for four weeks. The experimental group submitted for the same period a traditional rehabilitation (15 minutes passive muscle stretching) and achieved exercises supported by the "sonification" technique (for the remaining 20 minutes).

Standard Rehabilitation

The rehabilitative intervention for the upper limb in Occupational Therapy focused on the recovery of residual motor skills to facilitate the functional gesture. The first 15 minutes of the treatment focused on passive muscle stretching was aimed at relaxing muscle tone. The exercises were chosen based on the needs, abilities and residual motor skills of the patient; from among the following:

- opening and closing exercises of the fingers
- pronation-supination of the forearm
- mobilization of the wrist in the various planes.

In the second phase of the treatment (20 minutes) the patient resaved at least 6 exercises. Each exercise lasted 1 minute and 30 seconds and was followed by a break of 30-60 seconds. The exercises were chosen from the following

In the second phase of the treatment (20 minutes) included a set of different types of exercises and the patient resaved at least 6 exercises (each of them lasting about 1 minute and 30 seconds with a break of 30-60 seconds) chosen from the following:

Wrist: ulnarization/ radialization, horizontal extension- flexion, vertical extension-flexion

Hand and Fingers: pronation-supination, grasp, pinch, finger extensors, finger interosseous

Shoulder – Elbow: Forward thrust

First, movements were carried out in a passive way and then through an active-assisted mobilization. The exploration of the space was carried out using tools such as a table that facilitates sliding on the work surface. In case the patient's performance was adequate, it was possible to combine grip-release exercises of medium-volume objects and their displacement in space.

Rehabilitation with "sonification"

The use of the "sonification" technique has involved the use of the LMC to generate a harmonic sequence. Based on the movements (In-line with exercises in the standard treatment) selected for rehabilitation, some sound parameters identified that could be qualitatively added to the gesture: height (pitch), intensity (volume), spectrum (tonal quality).

Exercises classification:

1. Ulnarization/ Radialization: Starting with hand in a horizontal plane and pronated (palm turning downwards), the patient was asked to perform adduction and abduction movements of the wrist alternately repeatedly (figure 8).

Figure 8: Ulnarization/ Radialization

2. Pronation-supination: Starting with hand in a horizontal plane, with palm turning downwards, the patient was asked to perform pronation and supination movement alternately repeatedly (figure 9).

Figure 9: Pronation-supination

3. Horizontal extension- flexion: Starting with hand open neutral position, the patient was asked to perform flexion and extension movement of the wrist alternately repeatedly (figure 10).

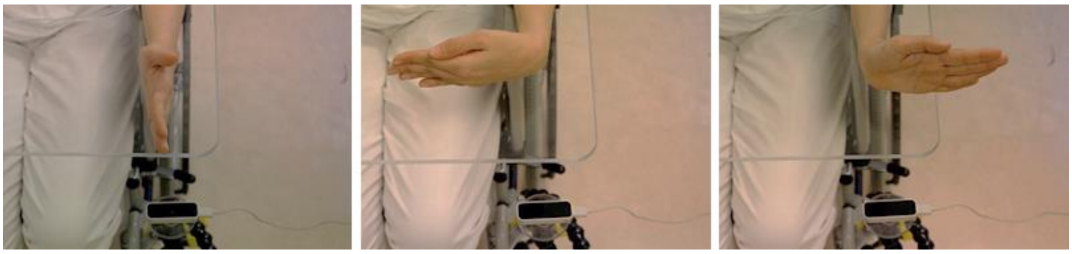

Figure 10: Horizontal extension- flexion

4. Vertical extension- flexion: Starting with hand in a horizontal plane (palm turning downwards), the patient was asked to perform flexion and extension movement repeatedly (figure 11).

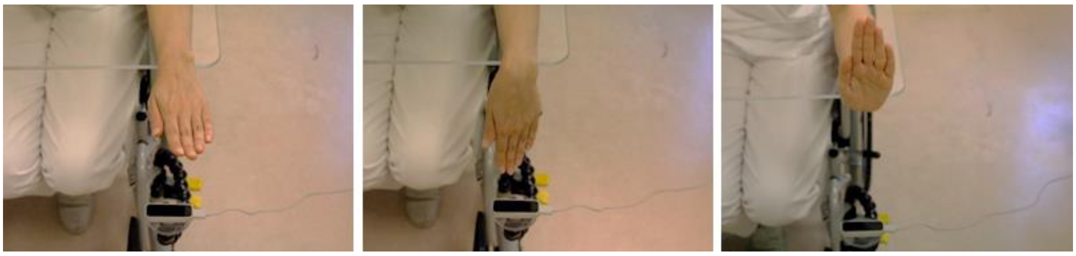

Figure 11: Vertical extension- flexion

5. Grasping: Starting with hand in a horizontal plane (palm turning downwards) open, then is closing it (figure 12).

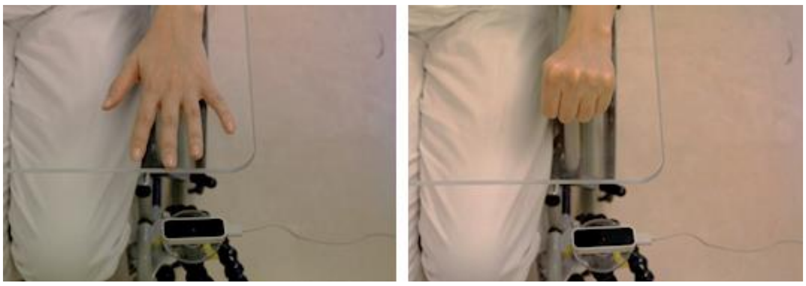

Figure 12: Grasping

6. Pinch: Starting with the hand in a horizontal plane (palm turning downwards), the patient was asked to repeatedly perform a pinch movement between the thumb and the rest of the fingers in sequence starting from the index finger (figure 13).

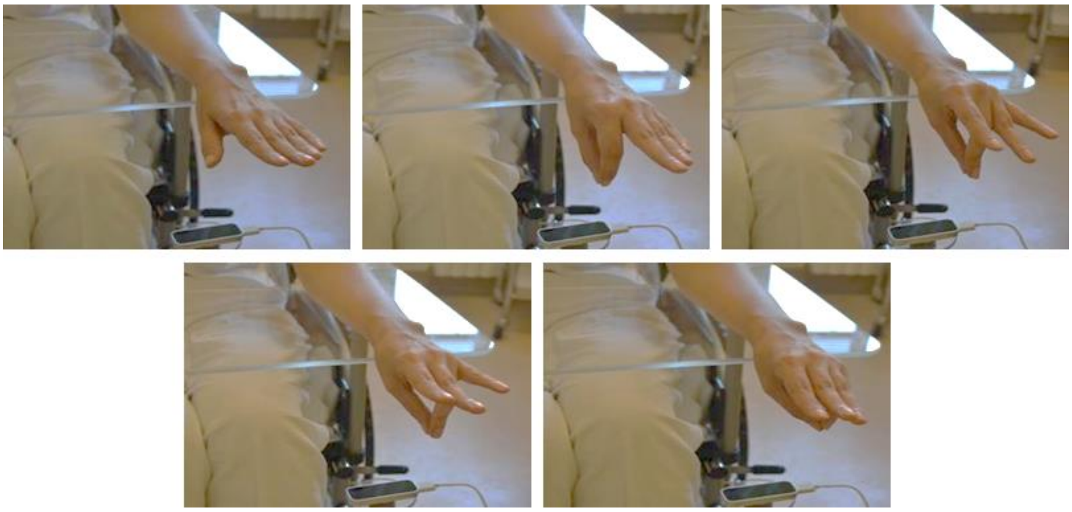

Figure 13: Pinch

7. Finger extension: Starting with hand in a horizontal plane (palm turning downwards), the patient was asked to repeatedly perform a single-finger extension movement in sequence, beginning with the thumb (figure 14).

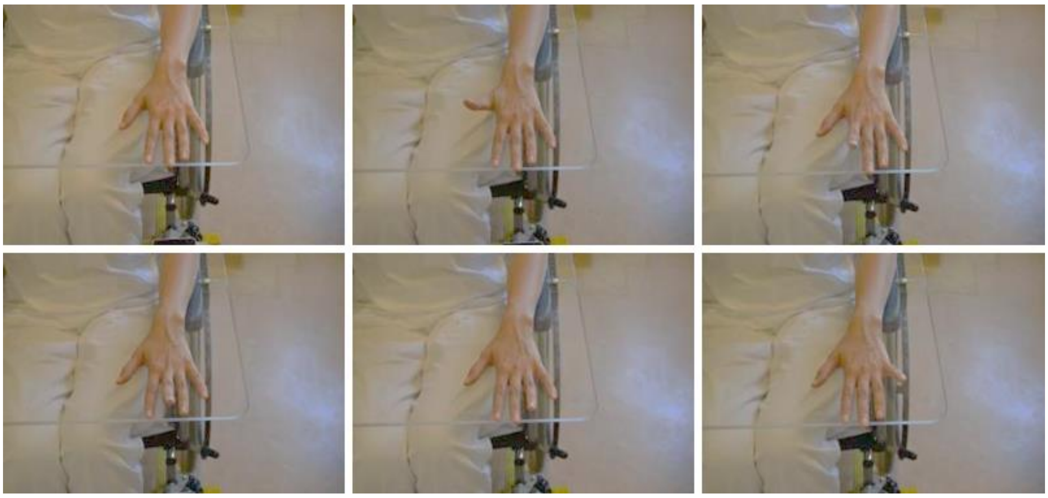

Figure 14: Finger extension

8. Finger interosseous: Starting with hand in a horizontal plane (palm turning downwards), the patient was asked to perform closing and opening of spread fingers repeatedly, which means adduction and abduction in the metacarpophalangeal joints (figure 15).

Figure 15: Finger interosseous

9. Shoulder - Elbow thrust forward: Starting with elbow 90°, close to the body and the palm turning downwards. The patient was requested to move the arm with the elbow 90° forwards and backwards (figure 16).

Figure 16: Shoulder - Elbow thrust forward

The treatment protocol provided for a total of nine exercises, but each session carried out six activities. When the patient was not in the condition to complete the sequence of daily practices, it was possible to adopt a simplified scheme consisting of four movements. The above strategies observe in Table 2.

Complete Scheme	Simplified Scheme
1 Day: 1,2,3,4,5,6	1 Day : 1,2,3,4
2 Day : 7,8,9,1,2,3	2 Day : 5,6,7,8
3 Day : 4,5,6,7,8,9	3 Day : 9,1,2,3

Table 2: The Complete and simplified Scheme of daily exercises

Movement sonification realized by a custom application developed with the Max 7 software programming environment (figure 17). The software program generated music sequences according to movements detected by the LMC (92). With the movements modulate a harmonic progression of the music or modulate the volume of a tone. It is a variety of tone modulation from low to bright of a pad sound, based on a harmonic progression created on the consecutive grades of the major range.

Before the experimental rehabilitation, the patients performed a short simulation with the non-plegic limb to experience the exercise (movement and motor audio feedback).

Figure 17: SonicHand Software Interface – Exercises

4.4 Efficacy of Lower limb robot-assisted and traditional rehabilitation therapy in treatment of post-acute stroke patients

In This study we focused on the feasibility and usefulness of standard of care treatments associated to robotic treatments in intensive recovery after stroke.

4.4.1 Recruitment of subjects

This retrospective study includes data of 158 individuals admitted between 2014 and 2016 at the Sestri Levante Hospital – S.C. Physical and Rehabilitation Medicine, ASL4, Liguria, Italy. We excluded 78 patients on the basis of extension of brain damage (bilateral injury or recurrence of stroke) and 40 patients because they did not meet all the inclusion criteria. Flowchart of the selection of the patients is reported in Figure 18.

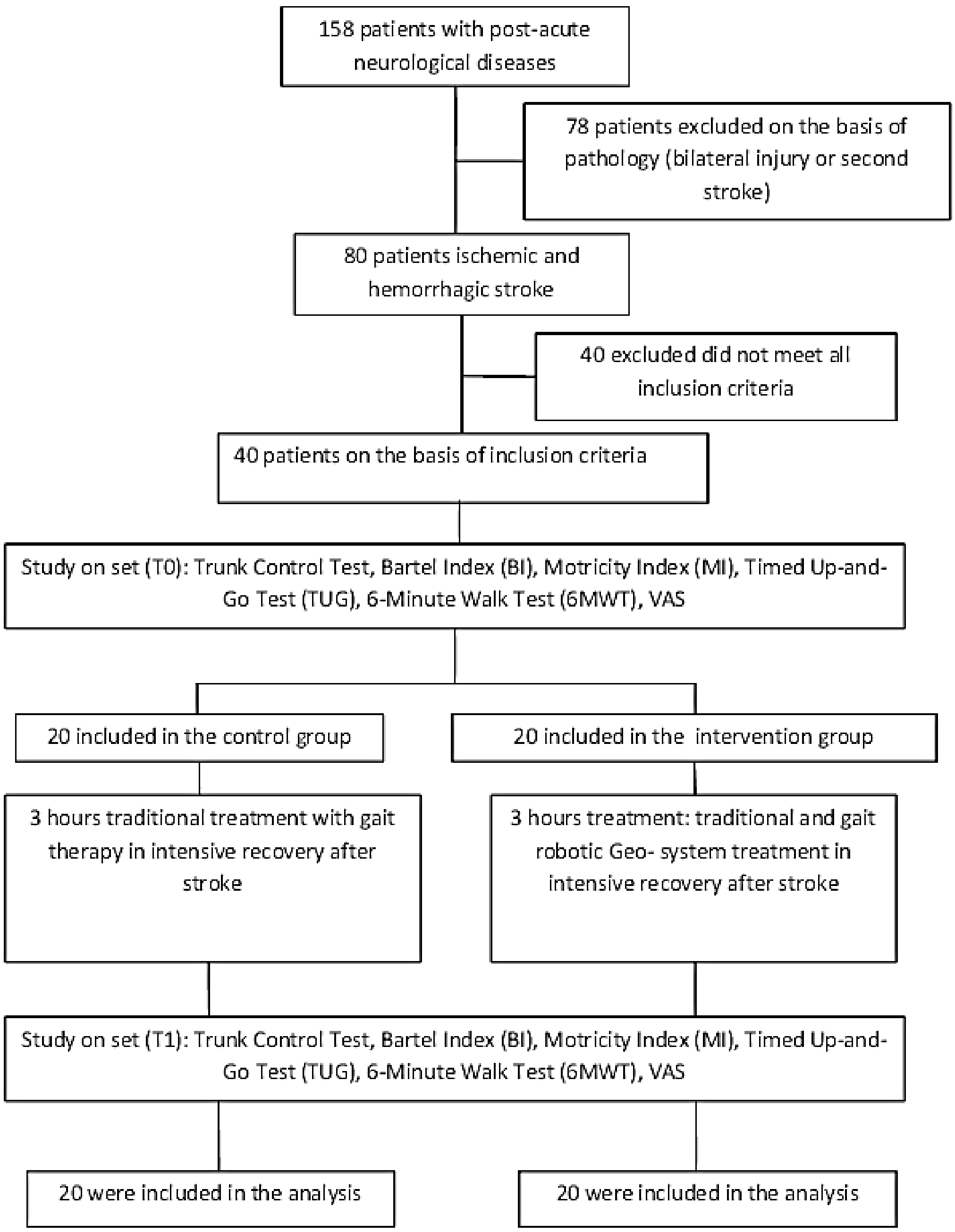

Figure 18: The Flow Chart of the study 4.4

Inclusion criteria were: ischemic or hemorrhagic stroke, age over 40 years, cognitive state not seriously affected, first 3 months post stroke, absence of bone fracture or ligaments instability. Patients with the following conditions were excluded: uncontrolled pain by medical or physical therapy; severe cardiovascular impairment; uncontrolled hypertension; pulmonary diseases with need of O2 therapy; severe fixed contractures affecting the lower limbs (hips, knees, ankle joints); bone instability (non-consolidated fractures, unstable spinal column, severe osteoporosis); skin lesions or open wounds in the area of treatment. Patients were divided depending on the anatomical site of the injury: Capsular Nucleus (CN), No Capsular Nucleus (NCN), and Pontine-Cerebellar (PC).

We further clustered patients in two groups of 20 patients each: an intervention group (IG) and a control group (CG) according to treatment.

4.4.2 Outcome measures

The outcome measures considered in the study were the Trunk Control Test (98) (99) (TCT), Barthel Index (100)(BI), Motricity Index (98) (MI), Timed Up-and-Go Test (101) (102)(TUG), 6-Minute Walk Test (103) (6MWT), Visual Analogue Scale (104) (VAS).

Patients underwent a clinical assessment at the beginning (T0) and at the end of treatments (T1).

4.4.3 Rehabilitation interventions

Participants received 3 hours of rehabilitative treatment per day, over 6 days a week, during the intensive rehabilitation hospitalization with a mean duration of 2 months. At first, both the IG and CG received standard of care treatment (individual therapy on the base of goals especially for the patient by a multidisciplinary team of healthcare, including occupational therapy (OR), physiotherapy (PT) and language therapy (LT)). Until clinical stabilization was attained (i.e. blood pressure normalized and stable, normal level of consciousness, O2 saturation), pre-deambulation exercises were performed. The IG then followed the robotic treatment protocol (G-EO System Gait) consisting of maximum 30 minutes treatment depending on the patient tolerance (including the setting of the machine). Each session consisted of a simulated floor walking, self-walking. Speed was adapted according to patient tolerance, beginning with a mean speed of 0.5 m/s and arriving to a maximum speed of 0.8 m/s throughout treatment.

4.5 Developing new sensors and computer systems for the tele-rehabilitation and remote evaluation of the rehabilitation process of patients with neurological diseases

The final project based on the application of Information Communication Technology (ICT) and specific, innovative sensors to monitor rehabilitation. We are, therefore, developing a device called SmartPants (SP), which will be used to monitor the evolution of the recovery activity of people who suffered from stroke; providing the measure of amplitude, direction and angle of movement and the distribution of the weight, with electronic interfacing for collecting and conditioning signals from sensors. It is the result of the collaboration between the different areas of research (S.C. physical medicine and rehabilitation Hospital Sestri Levante, University of Genoa (DINOGMI, DITEN), VAR Connect).

- University of Genoa (DITEN) and VAR Connect have intervened:
  In the definition of the software of a standard communication interface for technological devices that can be used for functional evaluation in neuromotor rehabilitation in a hospital environment.
- S.C. Physical and Rehabilitative Medicine Hospital Sestri Levante and University of Genoa (DINOGMI) have intervened:
  1. In identifying the selection of patients to be treated
  2. In defining the outcome measures to be used and related to the sensor system used

The device has been authorized for clinical validation by the Liguria Ethical Committee (N. Registration CER Liguria: 206REG2017) and has been certified as a medical device by the Italian Health Ministry (DGDMF/P/I.5.i.m.2/2018/1265).

SP includes a set of sensors belonging to two categories: IMU and pressure. IMU sensors are enclosed within a plastic container along with other electronic components and positioned on the patient’s lower limb through elastic bands. The device has four IMU nodes posted: on femurs (left and right) and on tibias (left and right). IMU sensors considered as a combination of gyroscopes and accelerometers to create an inertial measurement unit which provides up to nine degrees of freedom (figure 19 A). The IMU nodes acquire data from its embedded accelerometer and the gyroscope and make such data available to be wirelessly sent to a Mobile Device (MD), such as a tablet or a smartphone, through the data constructor and the WiFi modules. Moreover, they have a power supply module which consists of a commercial LIPO battery that provides energy to the accelerometer and the gyroscope. These modules compose the IMU sensor and are in charge of providing the accelerations and the orientation of the whole node on the three-axis X, Y and Z, respectively. Furthermore, the IMU nodes placed on the tibias are associated via wired cables to the two pressure sensors that are embedded within insoles composed (figure 19 B). Pressure sensors are resistors that change their resistive value depending on how much they are pressed. Combining the data extracted from both the sensor typologies, our platform can infer high-level information related to the patient's movements. The detail of the position of the IMU and pressure sensors is reported in figures 20- 21.

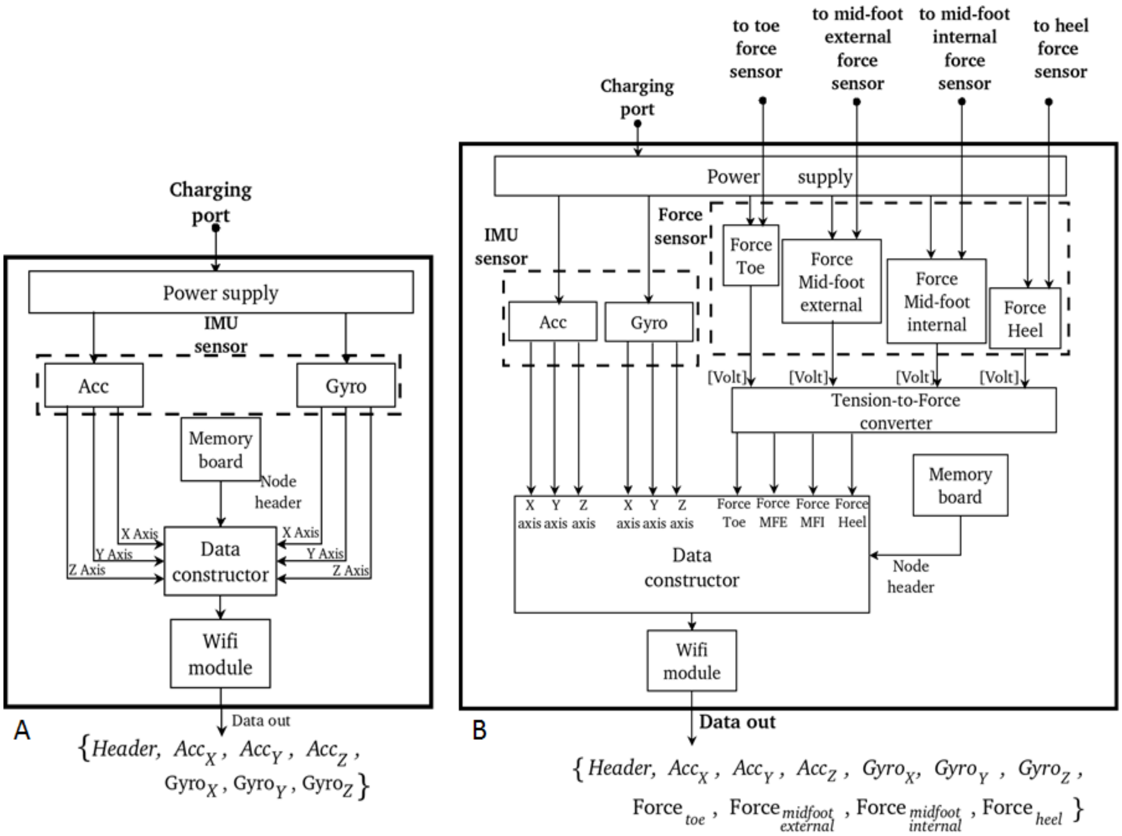

Figure 19: A) The Schemes of the femur IMU node; B) The Schemes of the tibia IMU node

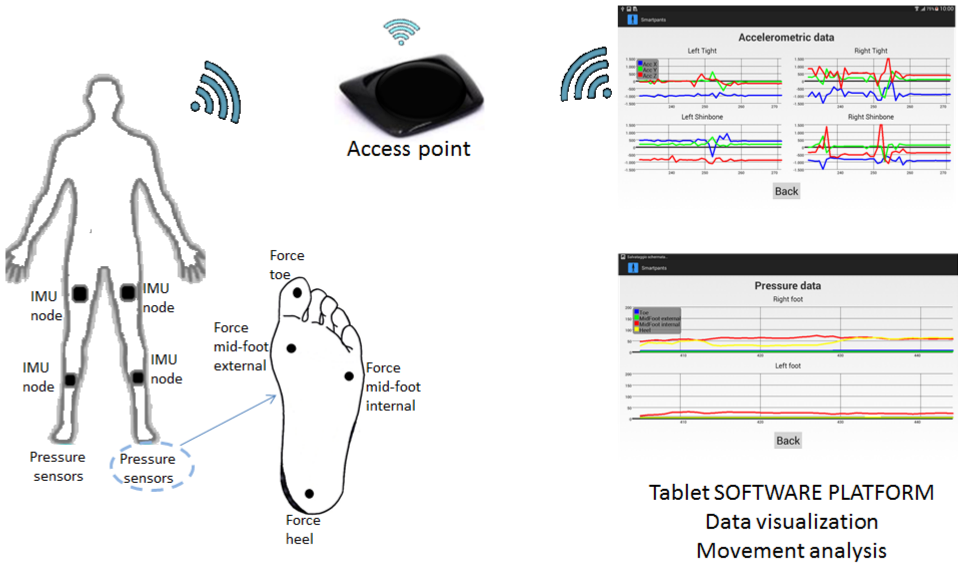

Figure 20: A detail of the SmartPants device and the communication scheme of the system

The device can capture motion parameters and also the distribution of the weight and transmit them via Wi-Fi to the network through a tablet and then to a server for data processing (figure 20). Data produced by each exercise execution are processed to extract valuable clinical information that is stored on the server available for download and visualization.

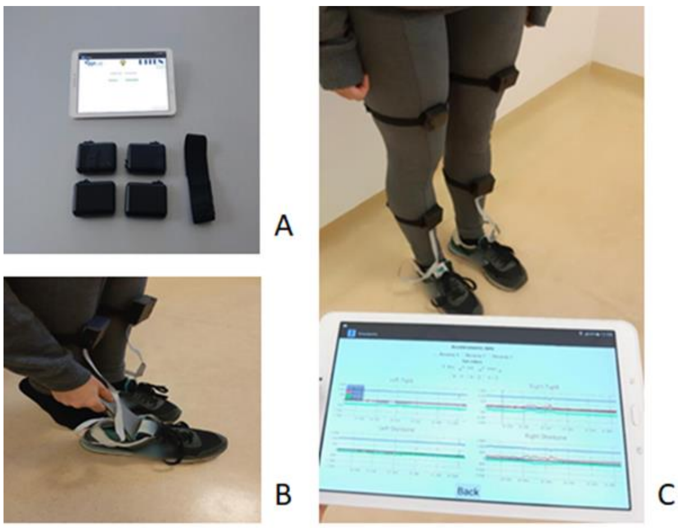

Figure 21: A,B) SmartPants device includes: 4 Motion sensors, Elastic bands for stabilization of the sensors on the limbs, 1 Tablet PC, 2 Sensorized insoles; C) Four motion sensors: positioned on femurs (left and right); on tibia (left and right).

Report on Risk/ Benefit: The SP device is the class I of medical devices according to the rule I. It is designed for the acquisition of the data on patients, aimed at determining the processing necessary to extract high-level information relating to the movement which can be monitored in real-time by the medical staff. The risk analysis for the SP medical device was carried out according to the 14971: 2012 standards. According to publications on the various types of sensors for the analysis of movement available on the market, there were no consequences due to tolerability or adverse events caused by use. The devices must be worn on the patient's limbs, respecting the positioning guidelines provided by medical personnel.

Different exercises as follow have been considered for testing the performance of the proposed monitoring system. They are simple physical movements that are commonly used during a rehabilitation session in different positions.

Through three exercises we can evaluate the muscle groups of the lower limb (such as gluteal muscles, quadriceps, hamstring, tibialis anterior, triceps, and peroneus) which are fundamental to the standing position.

1. The bipodal bridge: It gives information on several articulations (hip, knee and ankle) if appropriately activated, it allows the patient also to reach the standing position correctly. To create the bridge are needed hip extensions, the knee flexes, control of the hip and distribution of weight on the heel and front of the foot.
2. Moving from a sitting to a standing position: In the sitting position, we can see the patient how she/he is holding the pathological lower limb. For example, if she/he cannot keep the knee flexed, she/he won’t be able to hold the weight (or with the knee flexed) so she/he cannot stand up. Actually, for standing up, we need the knee to remain extended for a prolonged time. It also gives information about the angle of the knee (if it remains flexed, extended or hyperextended).
3. Load distribution of the weight while standing up: Stroke patients with more asymmetrical body-weight distribution while rising or sitting down have a higher incidence of falls. In this position, we evaluate the percentage of weight on the right /left limb, also the load distribution on the front/back of the foot.

Other movements that can be monitored: extension, abduction and walking.

4.5.1 Recruitment of subjects

To select which parameters better represent the patient's condition and the quality of movement or exercises, we have chosen 7 patients affected by stroke based on the criteria of inclusion/exclusion. The evaluation of quantitative parameters obtained with the SP device carried out in the first week of their rehabilitation (T0) and during the last week of hospitalization to perform the last evaluation before discharge (T1). Moreover, patients wore SP in the hospital twice a week for ten sessions during specific exercises (e.g. lower limb muscle recruitment exercises, flexion/extension and abduction).

4.5.2 Outcome measures

Outcomes were assessed through rehabilitation evaluation scores. It means the effectiveness of therapy intervention monitored and reviewed by the routine use of standardized outcome measures and the SP device monitored the evaluation of the quantitative parameters obtained. SP usability assessed through medical doctors and physiotherapists. Inclusion criteria were: the age > = 18 years; sufficient motor ability and the movement of the lower limb; the cognitive state not severely affected (ability to do two simple orders); Trunk Control; Cooperation of family or caregiver. Exclusion criteria were: pain not controlled by the medical or physical therapy: severe comorbidity; the presence of pacemakers (possible interference to electronic signals in "wireless"); oncological pathology; lack of family or caregiver. Standardized outcome measures for motor assessments: Motricity index [98]; Modified Barthel Index [100]; Time up and go [101] [102]; 6minute walking test [103]; Trunk control test [98] [99]. The patient's data was processed under current legislation in compliance with the European GDPR regulation.

Signals (accelerometer, gyroscope and pressure) acquired by the device must be processed to extract high-level information, to recognize the rehabilitation exercises the patient is performing. The elaboration is made by performing the following steps:

1) Pre-processing: This step consents to obtain a more correct and a smoother signal that will assist in reducing the errors during the classification step. Therefore, values that saturate the number representation are removed from the raw signals.

2) Windowing: Signals are divided in time windows that last 2 seconds to reduce the amplitude of the discontinuities at the boundaries of each finite sequence. It is employed to provide a short-time analysis of the signals.
3) Feature extraction: We use as features the mean and the variance of each signal (accelerometer, gyroscope and pressure sensor) for each axis (X, Y and Z) for each employed nodes. We compute 12 features (six means and six variances) for each IMU node on the femurs and 20 elements (six means and six variances for accelerometer and gyroscope and four means and four variances for each pressure sensor) for each IMU node placed on the tibias. Accordingly, the total number of 64 features has been considered in this part of the description.
4) Classification: To provide a comprehensive analysis, state-of-the-art machine learning algorithms have been tested: tree-based algorithms (J48, Random Forest (RF) and C4.5 Random Tree (RT)), hyper-plane decision algorithms (Sequential Minimal Optimization (SMO) and LibSVM), probabilistic algorithms (Naive Bayes (NB) and Logistic Regression (LOGREG)) and neural network-based algorithms (MultiLayer Perceptron (MLP)). The employed testing procedure is 10-fold cross-validation.

4.6 Statistical analyses

Statistical analysis was performed using SPSS for Windows version 22. Mean and standard deviations were defined to describe variables. Qualitative variables were summarized as frequencies and percentages. Repeated measures analysis of variance with one factor was used to assess potential differences between baseline and end of treatment for the endpoints. Different pre-specified imputation techniques were applied, generalized linear mixed models to handle missingness at single timepoints within the outcomes measured repeatedly over time. Kolmogorov-Smirnov tests were performed to test normal distribution of data. If data were not normally distributed, Mann-Whitney and Wilcoxon non-parametric analysis were performed, either wise; if data were normally distributed, T-test parametric analysis was adopted. We considered a P-value < 0.05 statistically significant. Correlation analysis was used to evaluate interaction between variables.

All the performed experiments with SP have been realized by acquiring actual data on real patients by using the provided SP platform and by post-processing all the data offline by using Weka, an open-source machine-learning algorithm.

5. RESULTS

5.1 Testing overwork weakness in Charcot-Marie-tooth disease

Thumb opposition test: In the TOT performance healthy controls show the same ability of opposition in both hands and with parameters in the normality range (Figure 22A; dominant hand [DH]: 9.6 ±0.56; non-dominant hand [NDH]: 9.63±0.51; P = 0.71). CMT patients, instead, have a statistically significant impairment of the DH and both hands have a slightly low rate if compared with normal controls (Figure 22B; dominant hand [DH]: 7.78±1.95; non-dominant hand [NDH]: 8.23±1.72; P = 0.01).

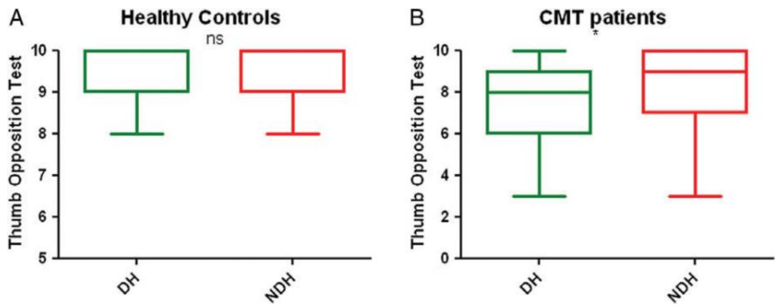

Figure22: Thumb opposition test (TOT) in healthy controls compared to Charcot-Marie-tooth (CMT) patients.

Dynamometry: Tripod pinch and hand grip measurements are comparable. Normal subjects are stronger in the DH (Figure 23A, tripod pinch: DH: 92.22±34.29 N; NDH: 84.26±32.55 N; $P < 0.0001$; Figure 23C, hand grip: DH: 203.70±79.79 N; NDH: 185.40±72.16 N; P = .0003). CMT patients are not different in strength, between DH and NDH (Figure 23B, tripod pinch: DH: 54.50 ±29.23 N; NDH: 53.10±28.97 N; P = 0.43; Figure 23D, hand grip: DH: 117.80±65.61 N; NDH: 122.80±65.18 N; P = 0.19).

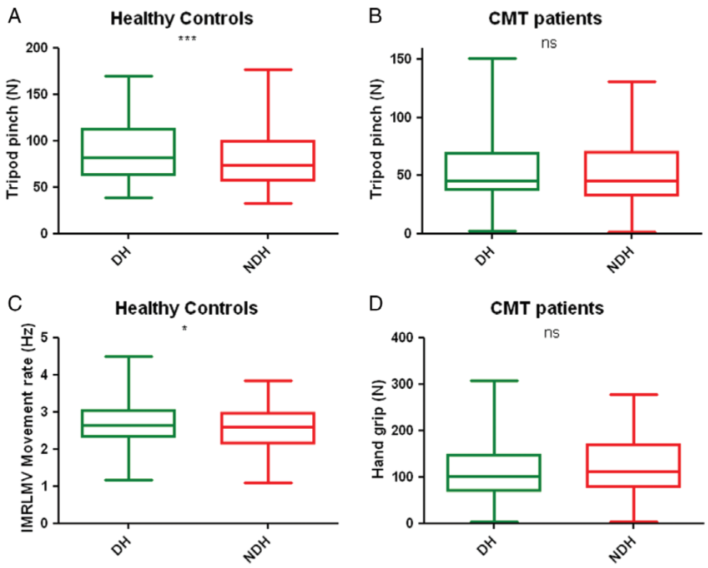

Figure 23: Dynamometry test in healthy controls compared to Charcot-Marie-tooth (CMT) patients. Triple-pinch and hand grip measurements are comparable in both healthy controls and CMT patients.

Hand test system: In healthy controls, FT performance, evaluated with MR value, is significantly better in the DH (Figure 24 A, DH: 4.50 ±0.85 Hz; NDH: 4.01 ±0.88 Hz; P < 0.0001) and IMRL exercise behaves similarly (Figure 24 C, DH: 2.57 ±0.59 Hz; NDH: 2.44 ±0.57 Hz; P = 0.02). In CMT patients, FT and IMRL performance are virtually identical in the DH and NDH (Figure 24B, FT: DH: 3.45 ± 1.30; NDH: 3.38 ±1.04; P = 0.37, Figure 24 D, IMRL: DH: 2.30 ± 0.67 Hz; NDH: 2.30 ±0.64 Hz; P = 0.93).

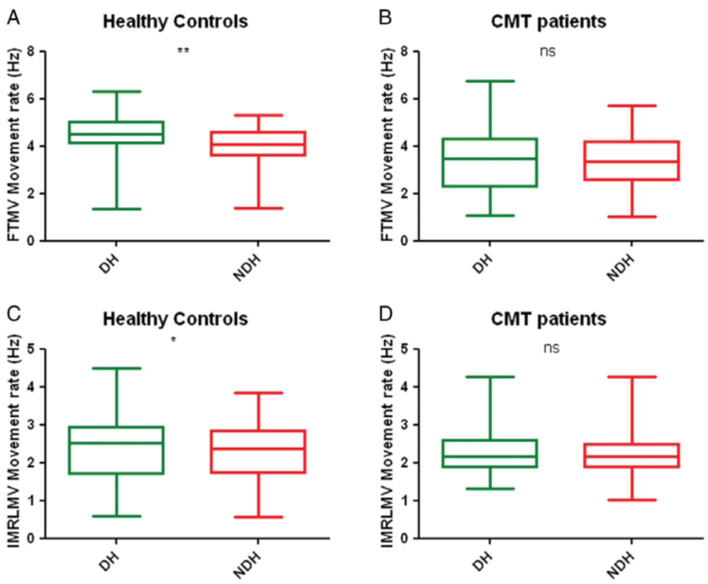

Figure 24: Hand Test System (HTS) performances in normal controls compared to Charcot-Marie-tooth (CMT) patients.

5.2 Hand Rehabilitation Treatment for Charcot-Marie-Tooth Disease

We recruited 9 patients (2 males and 7 females) with a clinical and genetic diagnosis of different CMT types. The mean age was 54.3 ± 11.4 (range 32 to 69). (Table 3)

Patients (N=9)	
Mean age (SD)	54.3 (11.0)
Range of age	32-69
Males/Females	2/7
CMT1A	4 (2 Males/2 Females)
CMT1B	3 (3 Females)
CMT4C	1 (1 Female)
CMTX1	1 (1 Female)

Table 3: information of recruited patients Age, sex and CMT type

All the patients followed the entire treatment and we did not have any drop out. We evaluated the results of the right and left hand. The right hand shows a significant improvement at T1 of the strength in the tripod pinch (T0: 41.67 ± 17.48 N; T1: 52.26 ± 24.10 N; p=0.04) and in the hand grip (T0: 99.19 ± 32.02 N; T1: 112.4 ± 41.18 N; p=0.02. Figure 25A and Figure 25C). The left hand also shows an improvement of the strength in the tripod pinch (T0: 42.26 ± 15.74 N; T1: 50.52 ± 23.02 N; p=0.20) and in the hand grip (T0: 118.6 ± 40.66 N; T1: 119.3 ± 42.74 N; p=0.88), although not statistically significant (Figures 25B and 25D).

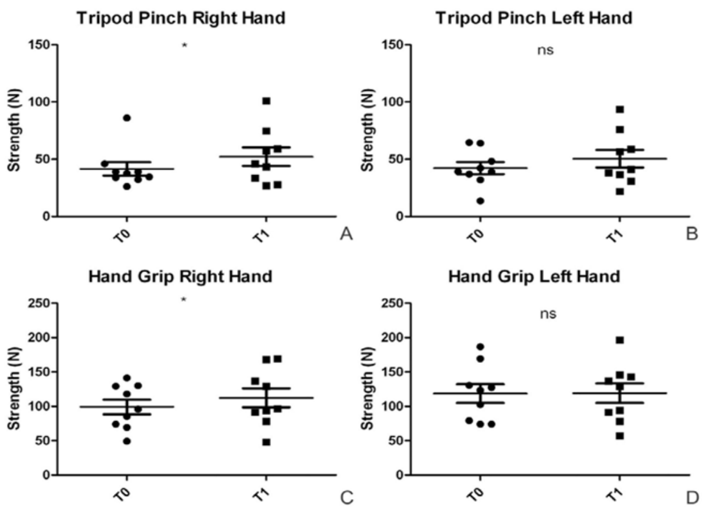

Figure 25: Evaluation of tripod pinch and hand grip strength before and after the treatment

Interestingly, the TOT improves significantly, on average, in both hands (Right: T0: 7.3 ± 2.0; T1: 8.0 ± 1.7; p=0.02. Left: T0=7.8 ± 1.76; T1=8.3 ± 1.5; p=0.03; Figures 26A and 26B). More importantly, the SHFT, which reflects the functional impairment of the hand, showed a significant improvement after the rehabilitation intervention (T0: 73 ± 4.1; T1: 76.3 ± 5.3; p=0.02) (Figure 26C).

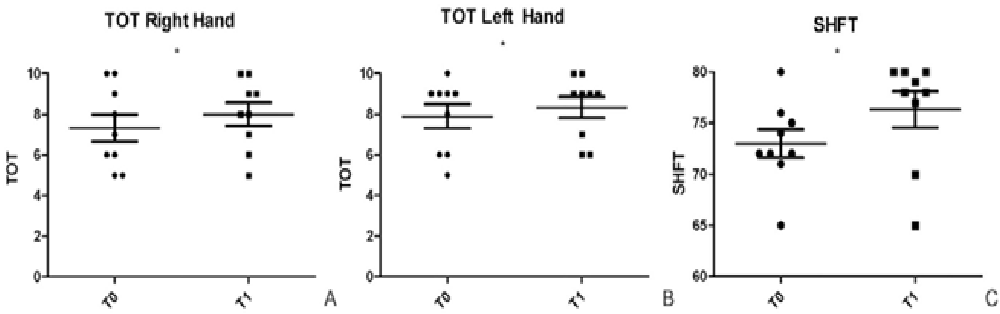

Figure 26: TOT and SHFT evaluation at T0 and T1

5.3 The sonification approach to the hand rehabilitation in post-acute stroke patients: a multicentric randomized controlled trial

As the paper is a multicentral study coordinated by Professor A. Raglio, imminent and not yet published, so, we can present some preliminary data on a small sample as follows. The clinical characteristics of the subjects are reported in Table 4. Experimental Group (Ex-G) was slightly younger than the Control Group (Ct-G), but the difference was not statistically significant. In the Ex-G, 5 out of 16 patients (31%) had a right upper limb impaired, and 11 of them (69%) had a deficit on a left side. In the Ct-G, 8 out of 16 patients had a right upper limb deficit (50%) and the same number a left upper limb impaired (50%).

	Experimental (n=16)	**Control (n=16)**
Age	59.8 ± 8.4	64.7 ± 16.0
Sex (M/F)	7 (44%) / 9 (56%)	7 (44%) / 9 (56%)
Acute event distance	42 (median) 47 interquartile range min: 14 – max : 194	23 (median) 18.5 interquartile range min: 15 – max : 148
Treated limb	5 R (31%) / 11 L (69%)	8 R (50%) / 8 L (50%)

Table4: Sample characteristic (36/65)

The study showed an improvement of the Ex-G compared to the Ct-G in the upper limb motricity between T0-T2. FM-UE global scores (Time*Group interaction: p=0.038) significantly improved in the Ex-G compared to those of Ct-G. In the final version, there is the significance in global, distal, wrist and hand scores in favour of the Ex-G. Details regarding the FM-UE assessment are reported in Table 5.

	Global Scores				Prox.				Dist.			
	Mean	SD	p (time)	p (Group*Time)	Mean	SD	p (time)	p (Group*Time)	Mean	SD	p (time)	p (Group*Time)
Ex_G T0	35,00	11,10	<0.001	0.038	19,69	6,79	<0.001	0.15	12,93	5,15	<0.001	0.12
Ex_G T2	51,79	15,35			29,54	8,50			19,07	5,37		
Ct_G T0	33,38	15,24			18,31	8,80			11,50	7,32		
Ct_G T2	43,00	20,66			24,69	11,76			15,44	9,55		

Table 5: Proximal and distal motricity: Fugl Meyer Assessment Scale (T0 vs T2)

Report scores of BBT was not significant (Time*Group interaction: p=0.33) (Table 6).

	Paretic limb				Healthy limb				Paretic limb/Healthy limb report			
	Mean	SD	p (time)	p (Group*Time)	Mean	SD	p (time)	p (Group*Time)	Mean	SD	p (time)	p (Group*Time)
Ex_G T0	12,40	11,69	0.025	0.63	30,73	12,84	0.17	0.71	0,36	0,28	0.003	0.33
Ex_G T2	17,13	13,97			34,40	17,39			0,48	0,27		
Ct_G T0	12,56	10,77			29,06	10,93			0,42	0,34		
Ct_G T2	15,69	12,97			31,19	10,98			0,48	0,35		

Table 6: Box and Block Test (T0 vs T2)

In addition, Ex-G showed a significant reduction in NPRS scores compared to the Ct-G (Time*Group interaction: p=0.035). (Table 7)

	mean	SD	p (Time)	p (Time*Group)
Ex_G T0	3,60	3,01	0.023	0.035
Ex_G T2	1,60	2,10		
Ct_G T0	1,70	2,05		
Ct_G T2	1,54	2,23		

Table 7: NPRS scores (T0 vs T2)

Other significant results were not found in the study.

5.4 Efficacy of Lower limb robot-assisted and traditional rehabilitation therapy in treatment of post-acute stroke patients

Forty patients were included in the study (24 males; 16 females) of whom 25 (62.5%) suffered from an ischemic stroke whereas 15 (37.5%) from a hemorrhagic stroke. The IG comprised a group of 8 CN, 8 NCN and 4 PC; the CG of 20 stroke subjects matched by lesion location with the IG (9 CN, 8 NCN and 3 PC). (Table 8)

Variable	Intervention-group	Control-group	All
Patients (M/F)	20 (12/8)	20 (12/8)	40 (24/16)
Age	64.15±11.58	71.50±11.07	67.83±11.78
Ischemic/Hemorrhagic	13/7	12/8	25/15
(%)	65% , 35%	60% , 40%	62.5% , 37.5%
Hemiparesis (R/L)	20 (12/8)	20 (10/10)	40(22/18)
(%)	54.5%, 45.5%	50%, 50%	55%, 45%
Recovery duration(Day)	59.60±24.82	60.85±29.6	60.23± 26.69
Lesion Location	20	20	40
C N/NCN /PC	8/8/4	9/8/3	17/16/7

Table8: Data and generalities of patients at T0. Capsular Nucleus(CN), No Capsular Nucleus (NCN), Pontine- Cerebellar(PC)

TCT, VAS, MI, 6MWT, BI resulted in being homogeneous amongst the IG and the CG at baseline (See table 9). Hospitalization length with an average of 60 days was also similar.

T0			
Group	CG(n:20)	IG(n:20)	p-value (n.s)
TCT	56.25±37.79	60.65±31.25	0.429
VAS	3.08±3.22	2.24±2.79	0.546
MI RL	69.10±37.32	66.55±33.60	0.822
MI LL	77.90±30.56	80.05±32.68	0.831
6MWT	62.2±58,21	71.18±55.03	0.583
BI	26±22.86	29.75±22.09	0.529
hospitalization time	59.60±24.82	60.85±29.6	0.862

Table 9: Outcome measure at T0: two groups were not significantly different. Trunk Control Test (TCT), Visual Analogue Scale (VAS), Motricity Index Right Limb (MI RL), Motricity Index Left Limb (MI LL), 6-Minute Walk Test (6MWT) and the Barthel Index (BI)

At T1 results are summarized in table 10. TCT, MI, 6MWTand BI significantly improved in both groups. Only the VAS was not changed, again in IG ad CG.

At T1, all the outcome measures showed not statistically significant difference between the two groups after the treatments (Table 10). Interestingly, the BI in CN lesion showed remarkable divergence, between the IG and the CG ($p<0.02$).

	CG (n:20)			**IG (n:20)**			**P-value**
	T0	**T1**	**P-value**	**T0**	**T1**	**P-value**	**CG - IG**
TCT	56.25±37.79	75.75±30.59	0.002	60.65±31.25	85.35±21.15	0.001	0.414
VAS	3.08±3.22	1.61±2.5	0.114	2.24±2.79	1.47±2.06	0.27	0.83
MI RL	69.10±37.32	79.05±30.526	0.012	66.55±33.60	75,45±27.66	0.008	0.478
MI LL	77.90±30.56	82.15±27.32	0.043	80.05±32.68	88.65±22.60	0.018	0.461
6 MWT	62.2±58.21	118.8±112,2	0.001	71.18±55	131.48±109.84	0.003	0.678
BI	26±22.86	56.25±28.42	0.0024	29.75±22.09	69.50±22.41	0.00001	0.11

Table 10: Summary table of the outcome measures evaluated. Trunk Control Test (TCT), Visual Analogue Scale (VAS), Motricity Index Right Limb (MI RL), Motricity Index Left Limb (MI LL), 6-Minute Walk Test (6MWT) and the Barthel Index (BI)

TUG improved significantly in both groups after the treatment. (Table 11)

TUG0									
TUG0 _ CG					TUG0_IG				
≤ 14 s	≤ 20 s	≤30 s	>30s	Tot	≤ 14 s	≤ 20 s	≤30 s	>30s	Tot
0	0	0	3	3	1	0	0	1	2

TUG1									
TUG1_ CG					TUG1_ IG				
≤ 14 s	≤ 20 s	≤30 s	>30s	Tot	≤ 14 s	≤ 20 s	≤30 s	>30s	Tot
3	1	3	9	16	3	5	4	5	17

Table11: TUG0_CG: Timed Up and Go test _ Control Group at T0; TUG0_IG: Timed Up and Go test _ Intervention Group at T0; TUG1_CG: Timed Up and Go test _ Control Group at T1; TUG1_IG: Timed Up and Go test _ Intervention Group At T1

At T0 only 5 patients were able to perform the TUG test in 30 seconds or longer [CGT0: 3 patients (15%) which two of them were CN lesion and one of them was NCN; IGT0:2 patients (10%) one out of two with the CN lesion and another one NCN]; at T1 most of the patients were able to perform TUG [CGT1: 16 (6 CN mean: 44.97±18.75s; 7 NCN, mean: 44±41.08s; 3 PC, 29.08±11.66s) patients (80%), 41,58±29,14s; IGT1: 17 (8CN, mean:23.11±15.85s; 5 NCN, mean: 48.91±55s; 4 PC, mean:33.09±22.06s) patients (85%), 33,05±32,97s]. Moreover, at T1, in IG TUG had better performances (Figure 27). Eight patients (5 CN, 2 NCN, 1 PC) in the IG were able to complete TUG in 20 seconds or less, whereas only 4 (3 NCN, 1 PC) could do it in the CG.

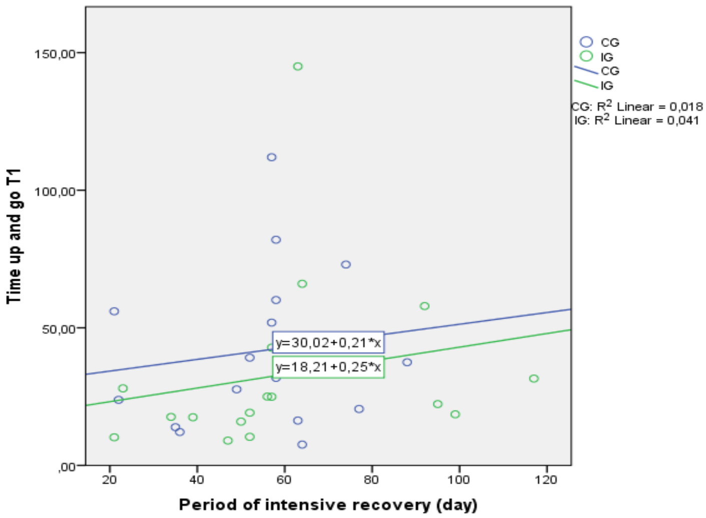

Figure 27: Performances in TUG1

Significant correlation between the improvement in TUG1 and BI was found (CG: r = - 0.710, p< 0.002; IG: r = - 0.849, p<0.0002), with slightly better performances in the IG. (Figure 28)

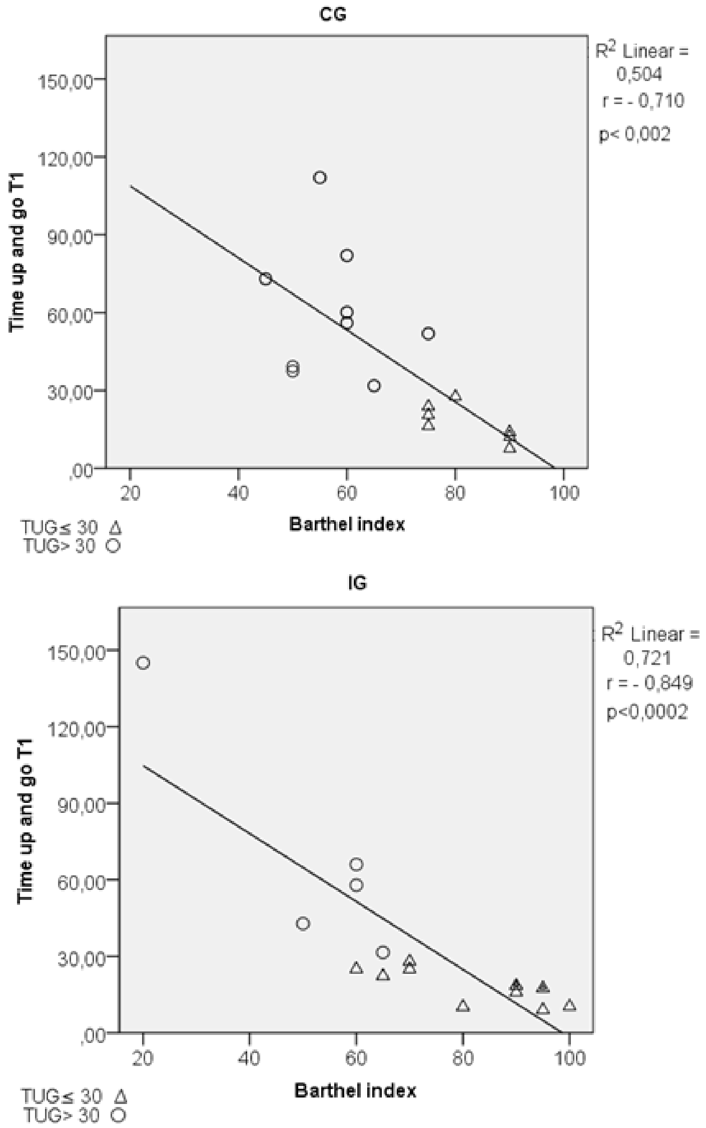

Figure 28: Correlation coefficient between the BI score and the TUG1 scores in the CG and IG

At T1 no significant correlation was found neither between age and TUG1 (CG: r = 0.382, p = 0.144; IG: r = 0.092, p = 0.725) (figure 29 A, 29B), nor between age and 6MWT1 (CG: r = - 0.328, p = 0.158; IG: r = - 0.092, p = 0.701) (figure 29 C, 29 D).

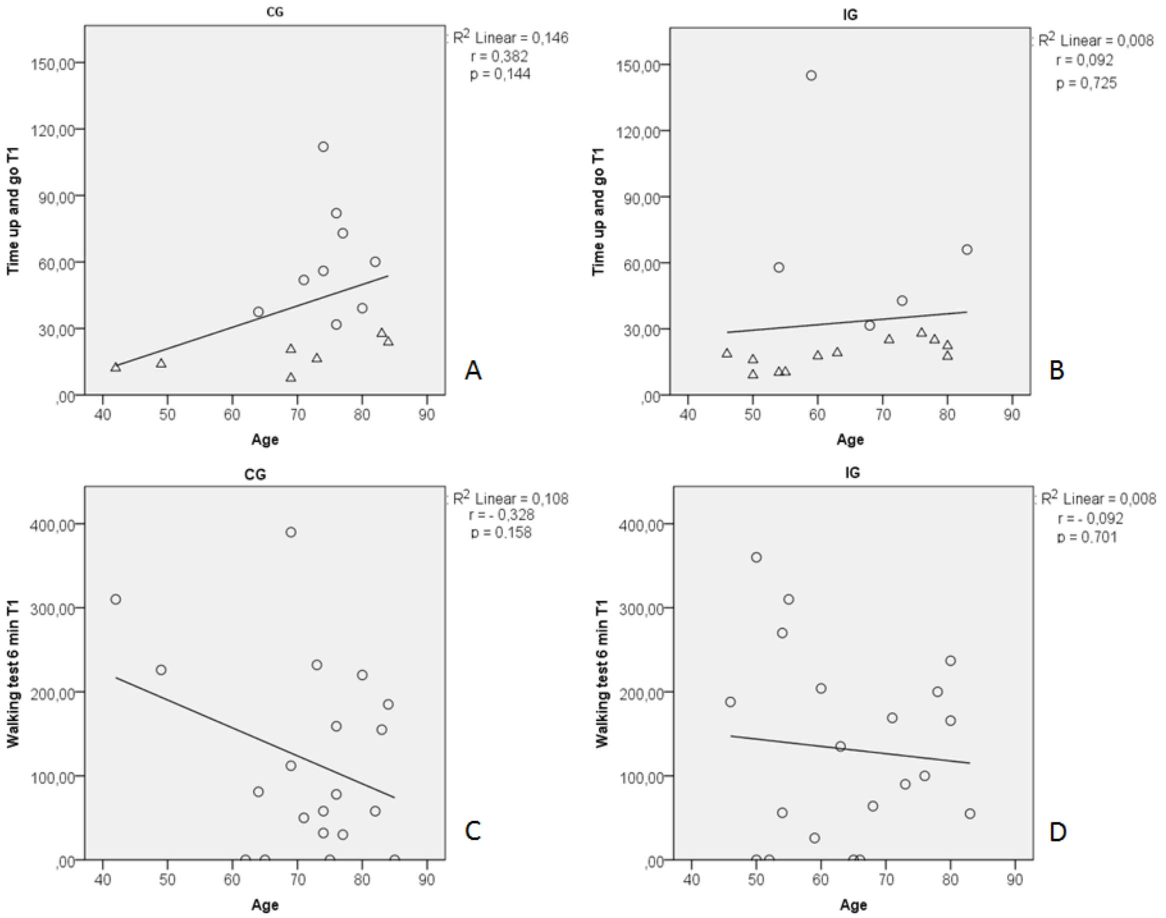

Figure 29: Correlation coefficient between the age and the TUG_1 scores, $6MWT_1$ score in the CG and IG.

5.5 Developing new sensors and computer systems for the tele-rehabilitation and remote evaluation of the rehabilitation process of patients with neurological diseases

The Table shows the average performance of the system when considering different machine learning classifiers. The average True Positive Rate (TPR), False Positive Rate (FPR), Precision, Recall and F-Measure (F1-Score) was considered as performance parameters.

Results show that the movement recognition algorithm produces excellent results in terms of classification performance (average TPR = 91%, with an FPR of 3.2%). (Table 12)

Classifier	True Positive Rate	False Positive Rate	Precision	Recall	F-Measure
J48	0.876	0.041	0.875	0.876	0.875
Random Forest	0.993	0.003	0.993	0.993	0.993
Random Tree	0.943	0.018	0.943	0.943	0.943
SMO	0.876	0.048	0.884	0.876	0.873
LibSVM	0.887	0.044	0.896	0.887	0.885
Naive Bayes	0.824	0.065	0.834	0.824	0.826
Logistic Regression	0.910	0.031	0.910	0.910	0.910
Multilayer Perceptron	0.979	0.008	0.979	0.979	0.979
Average [%]	91.1	3.2	91.4	91.1	91.1

Table12: Performance of exercise recognition with different classifiers. tree-based algorithms (J48, Random Forest (RF) and C4.5 Random Tree (RT)), hyper-plane decision algorithms (Sequential Minimal Optimization (SMO) and LibSVM), probabilistic algorithms (Naive Bayes (NB) and Logistic Regression (LOGREG)) and neural network-based algorithms (MultiLayer Perceptron (MLP)).

We tested the effectiveness of the system features when considering the accuracy of each single movement, with different machine learning classifiers. Some movements exhibit slightly lower accuracy values concerning the other exercises, such as the Bipodal Bridge (figure 30). This lower accuracy value is perhaps because of the Bipodal Bridge, a complicated activity, consisting of different movements, and not easy to perform. This fact could lead to a higher probability of mis-classifying the movement. It is possible to note that the most remarkable results pertain to the Sit-2-Stand exercise, which can achieve about 100% accuracy in almost all cases.

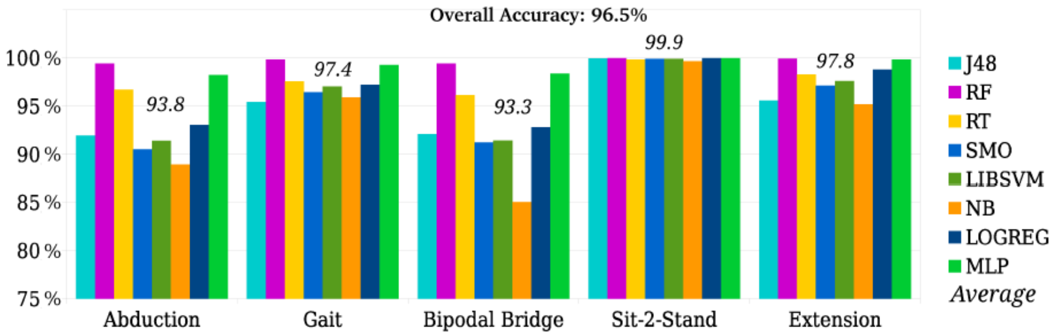

Figure 30: Comparison of recognition accuracy for each exercise with different classifiers. The overall accuracy, averaged over the classifiers and the exercises, is around 96.5%.

The overall accuracy averaged over the classifiers and the exercises, is around 96.5% which further demonstrates the validity of the proposed approach (figure 30).

Table 13 reports the results related to the estimation of the execution time of each exercise. The column labeled as Actual, refers to the actual execution time of the movement, measured while the person is performing the exercise. The columns Place and Axis refer to the position of the node (Tibias (T) or femurs (F)) and to the accelerometric axis employed for the Execution Time estimation. Exercises such as Abduction and Extension are performed with left and right lower limb separately. Therefore, results are displayed in two different columns, one for each limb.

		Times [s]			
		Right lower limb	Left lower limb	Place	Axis
		Actual	Actual		
ABDUCTION	μ	2,328	2,336	Tibia	x
	σ^2	0,041	0,020		
EXTENSION	μ	2,004	1,828	Tibia	y
	σ^2	0,018	0,009		

		Actual	Place	Axis
GAIT	μ	0,705	Tibia	y
	σ^2	0,004		
SIT TO STAND	μ	4,312	Femur	y
	σ^2	0,136		
BIPODAL BRIDGE	μ	7,106	Femur	z
	σ^2	0,417		

Table 13: SmartPants performance in the estimation of exercise

Results of clinical study

We monitored 7 patients who underwent a rehabilitation process at the intensive rehabilitation department. The group of patients followed a standard rehabilitation protocol (Table 14).

Patient Group (n:7)	
Gender (F/M)	5/2
Age (years)	71.57 ± 12.23
Affected side (R/L)	3/5
Stay in intensive rehabilitation (days)	63.87±20
Ischemic/ Hemorrhagic	6/1

Table 14: Patients characterization

Clinical evaluation was performed at admission (T0) and the end of the intensive rehabilitation period (T1). In this interval of time, all patients improved compared to the beginning values of all the scales (Table 15).

Clinical Scales	T0	T1
TCT	67.42±33.1	84.71±24
NRS	2.57±3	2.14±2.8
MI RL	66.33±3.21	75.55±5.50
MI LL	64.50±20.5	77.6±16.7
BI	58.28±21.46	76.75±19.2
TUG	N.V	18.55±6.5
6 MWT	N.v	197.40±103.1

Table 15: Outcome measure at T0 and T1; Trunk Control Test (TCT), Numerical Rating Scale(NRS), Motricity Index Right Limb (MI RL), Motricity Index Left Limb (MI LL), Barthel Index (BI), Time up and go (TUG) and 6-Minute Walk Test (6MWT)

Variation between T0 and T1 was also monitored with SP in order to visualize improvements from baseline.

The device has been used to measure and record the distribution of foot plantar pressure (big toe, midfoot internal, outer midfoot external and heel). The use of the pressure sensor is easily applicable in a static and dynamic position. Table 16 shows the distribution of weight during walking for each case, from T0 to T1.

Standing balance with postural symmetry is essential for ambulation and the performance of daily activities. Loads distribution over the different part of foot plantar usually gets altered in the stroke patients (figure 31-32).

The mean percentage of the load distribution during the walking was varied from one patient to another one. Also, SP showed an improvement of the patient between T0 with T1.

	Feet Pressure															
	T_0								T_1							
	Left Foot				Right Foot				Left Foot				Right Foot			
	Toe	MidExt	MidInt	Heel	Toe	MidExt	MidInt	Heel	Toe	MidExt	MidInt	Heel	Toe	MidExt	MidInt	Heel
P1	20%				80%				38%				62%			
(L)	5%	30%	38%	27%	16%	23%	32%	29%	0%	20%	38%	42%	10%	17%	32%	41%
P2	64%				36%				57%				43%			
(R)	10%	%30	31%	29%	28%	25%	12%	35%	18%	20%	25%	37%	25%	18%	23%	34%
P3 (L)	Patient was not able to walk								Patient was not able to walk							
P4	50%				50%				57%				43%			
(R)	18%	30%	24%	28%	25%	14%	39%	22%	20%	33%	30%	17%	20%	20%	42%	18%
P5 (L)	Patient was not able to walk								Patient was not able to walk							
P6	49%				51%				51%				49%			
(L)	5%	21%	26%	48%	6%	19%	22%	53%	3%	38%	22%	37%	10%	30%	16%	44%
P7	55%				45%				55%				45%			
(R)	13%	30%	30%	27%	19%	17%	25%	39%	22%	24%	17%	37%	17%	23%	21%	39%

Table 16: The distribution of weight during walking for each case, from T0 to T1; Toe: big toe, MidExt: Midfoot External, MidInt: Midfoot internal, and Heel.

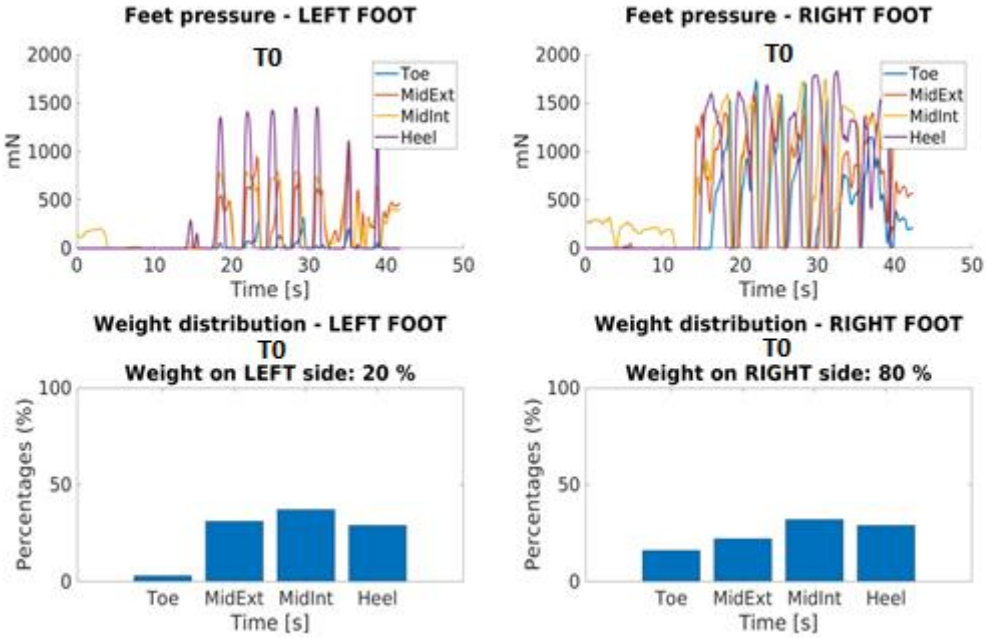

Figure 31: Example of SmartPants registration obtained for one representative patient initiating gait and distribution of the weight at the beginning of the treatment period. The figure is the representation of the different phases of gait in a patient. Graph comparing paretic and non-paretic lower limb.

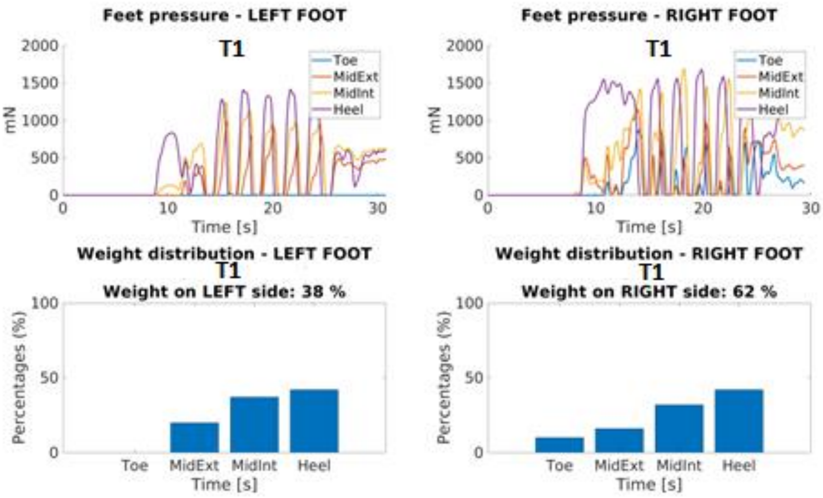

Figure 32: Example of SmartPants registration obtained for one representative patient initiating gait and distribution of the weight at the end of the treatment period. The figure is the representation of the different phases of gait in a patient. Graph comparing paretic and non-paretic lower limb

The stroke patient, usually, cannot perform the Bipodal bridge exercise correctly. In the bridge, she/he tries to put pressure on the front of the foot (for schematic extension of pathology) or the unaffected lower limb. Sometimes, she/he cannot keep knee flexed; therefore, she/he does not put pressure on the pathological lower limb (figure 33-34). Table 17 shows the distribution of weight during bipodal bridge for each case, from T0 to T1.

Feet Pressure																
	T_0								T_1							
	Left Foot				Right Foot				Left Foot				Right Foot			
	Toe	MidExt	MidInt	Heel	Toe	MidExt	MidInt	Heel	Toe	MidExt	MidInt	Heel	Toe	MidExt	MidInt	Heel
P1 (L)	2%				98%				34%				66%			
	0%	100%	0%	0%	4%	0%	0%	96%	0%	0%	15%	85%	15%	0%	10%	75%
P2 (R)	85%				15%				76%				24%			
	2%	2%	17%	79%	0%	4%	23%	73%	0%	0%	12%	88%	0%	0%	0%	100%
P3 (L)	2%				98%				0%				100%			
	48%	13%	39%	0%	0%	29%	2%	69%	0%	0%	0%	0%	0%	31%	21%	48%
P4 (R)	55%				45%				49%				51%			
	15%	8%	25%	52%	17%	0%	49%	34%	19%	24%	11%	46%	8%	0%	67%	25%
P5 (L)	0%				0%				17%				83%			
	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	100%	0%	4%	0%	96%
P6 (L)	50%				50%				60%				40%			
	0%	1%	15%	84%	0%	0%	0%	100%	0%	3%	23%	74%	0%	3%	1%	96%
P7 (R)	100%				0%				49%				51%			
	6%	0%	0%	94%	0%	0%	0%	0%	0%	0%	0%	100%	0%	0%	0%	100%

Table 17: The distribution of weight during Bipodal bridge for each case, from T0 to T1; Toe:big toe, MidExt: Midfoot External, MidInt: Midfoot internal, and Heel.

Figures 33 and 34 show the outcome of the rehabilitative bipodal bridge exercise monitored with SP. Foot pressure is asymmetrical in this exersice because the patient does not produce force on the pathological lower limb (left side). The different plots show foot pressure (first and second rows), acceleration (third row) for the left and right limbs. The measurements start with the patient lying on his back with knees bent and feet flat on the floor. In this phase, the acceleration plots show for the Z-axis (yellow line) and X-axis (blue line) the gravity acceleration, while for the Y-axis (red line) value close to 0.

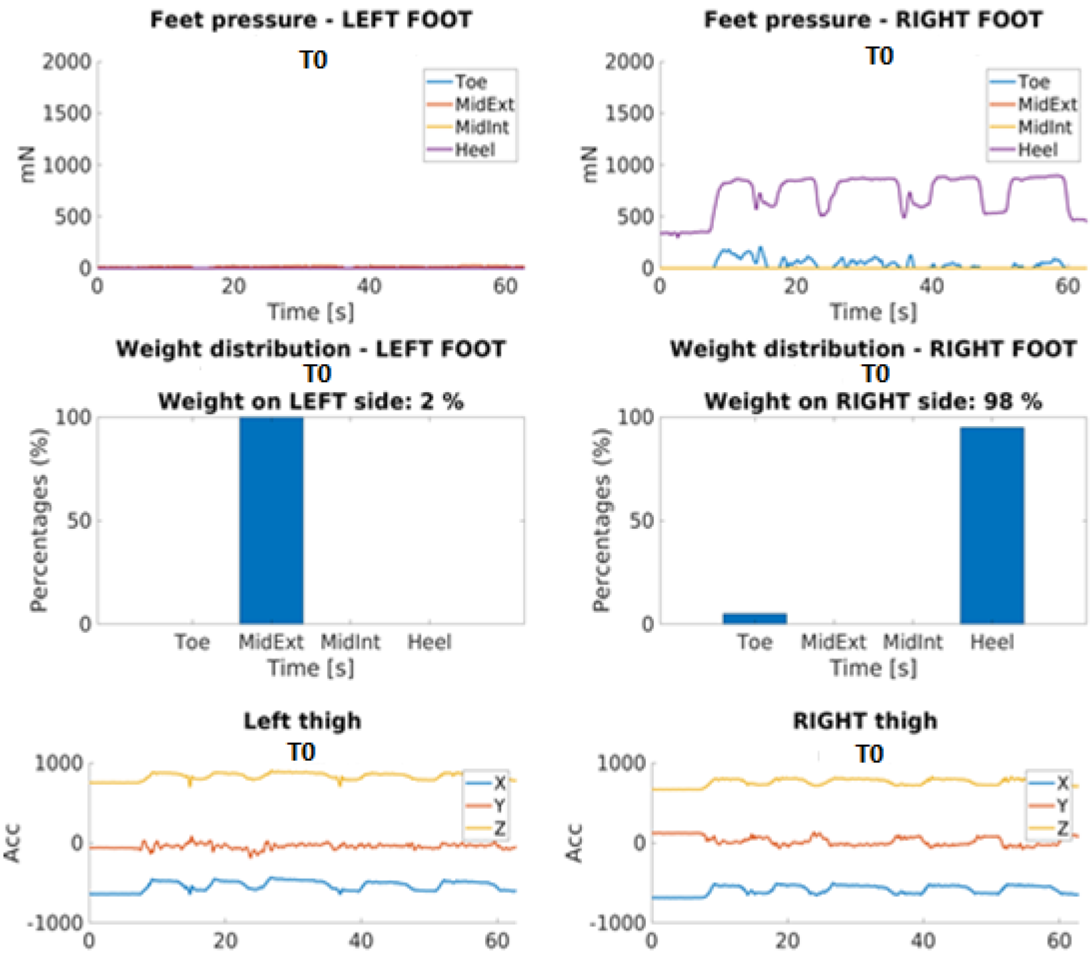

Figure 33: Example of SmartPants registration obtained for one representative patient initiating Bipodal bridge and distribution of the weight at T0. Graph comparing paretic and non-paretic lower limb

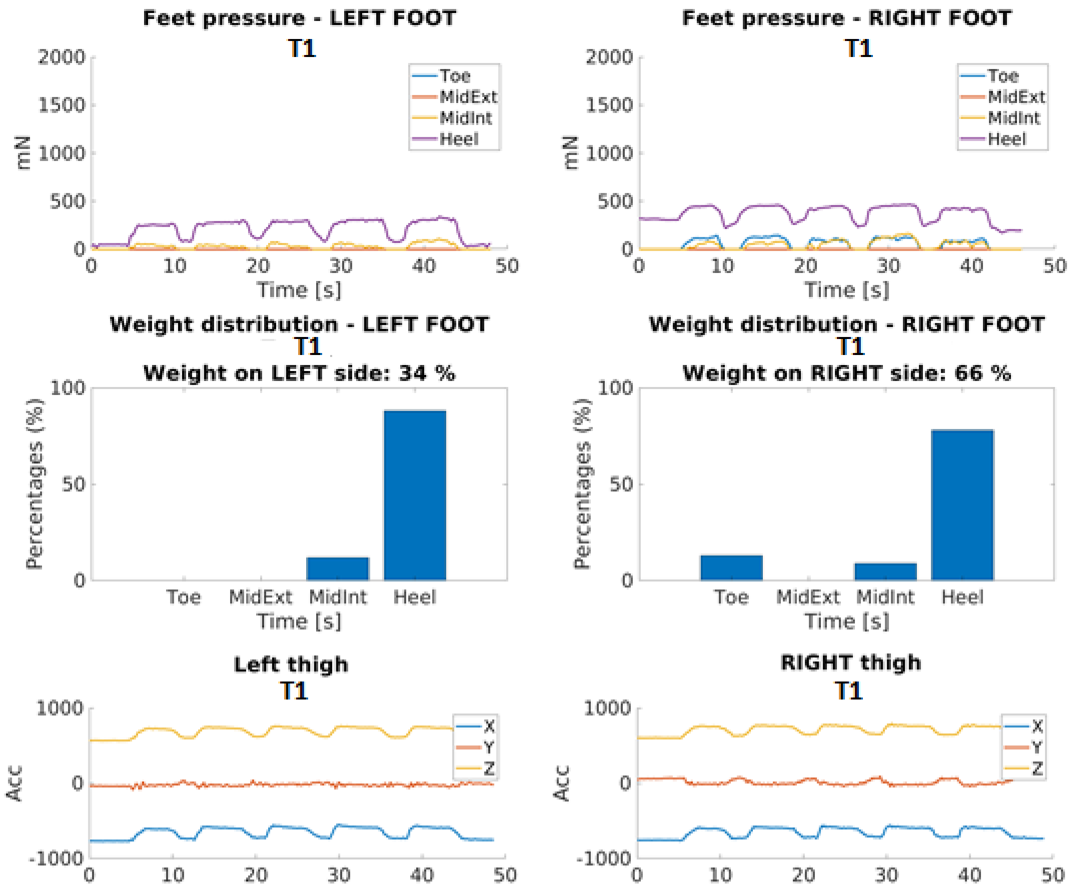

Figure 34: Example of SmartPants registration obtained for one representative patient initiating Bipodal bridge and distribution of the weight at T1. Graph comparing paretic and non-paretic lower limb

6. DISCUSSION

The application of innovative technologies, like robotic or the use of sensors, to the rehabilitation process is extremely important both in the evaluation and treatment phases. This is especially important in the rehabilitative therapy of the neurological patients at every stage of the disease (105), since a long-term physical therapy is often necessary. Furthermore, high technology strategies may be of great help in verifying the quality and results of the rehabilitative therapy in the patient own living environment (51). To this purpose, the so-called Information and Communication Technologies (ICT), widely used for home monitoring of patients with different pathologies (106), can be applied. ICT is changing the way we think, act and communicate in the world and in the field of health care (107). ICT are particularly suitable to remotely control the at home rehabilitation and have proven efficacy, at least in allowing health professionals to plan home exercises and verify the patients adherence to the rehabilitation program (79). Home based tele-rehabilitation, which can be defined as a method by which physiatrists and physiotherapists use ICT to provide therapeutic treatments and assess the degree of clinical impairment and improvement to disabled persons living at home (79), is an area of emerging and rapidly growing research (80). Monitoring of vital functions to guarantee the safety of the home therapy is, therefore, important. Many systems are available to help the patients in exercising at home, as the wearable accelerometer based devices (53) or the use of virtual reality (52), whereas only few devices for the assessment of the at home activity are present on the market (81). None of these has been developed to assist the patients in performing exercises correctly and allowing, at the same time, the professionals to monitor the quality of rehabilitation and progression of recovery.

Therefore, aims of this PhD project are the application of existing robotic and sensor-based technologies and the development of new sensors and computer systems for the evaluation of the rehabilitation process of patients with neurological diseases. Ultimately, we aim, through the combination of ICT and sensor-based technologies, at the definition of an effective and low cost system for the remote control of the rehabilitative therapy (tele-rehabilitation).

First, we studied by clinical and instrumental testing [Hand Test System (HTS)], the impairment of the distal upper limbs in Charcot-Marie-tooth peripheral neuropathy, with the special objective of evaluating the occurrence of OW at the hands level. OW is manifested in various neuromuscular diseases at the level of the upper and lower limbs (108) (22) (109). However, in CMT, it has not yet been conclusively demonstrated. In the first research, was tested the dexterity of the subjects with an innovative quantitative operator-independent method, the HTS (110). We identify the OW in the hand's function of CMT patients, studying the strength and the functional aspects. Also, we used healthy controls to investigate the normal behavior of both hands. We used only quantitative methods, while other studies used as strength evaluation the Medical Resource Council (MRC) scale, which is a subjective type of the assessment (111) (112). Although the effect of the hand dominance in the dexterity in healthy subjects is unknown, we expect that DH performs better than NDH. In CMT patients, few works affirm to evaluate the dexterity with the 9 hole peg test, and even if the results reported seem to be accurate and responsive, they refer to a small population (112) (113). Healthy controls of our study are homogeneous to CMT patients. Also, the population distributed homogeneously between axonal and demyelinating CMT. We compared the TOT, which is one of the significant determinants of the manual dexterity in CMT (86) so we hypothesized that this parameter could be affected by OW. Indeed, TOT evaluates the ability of opposition of the thumb and could be considered an indirect measure of the range of movement of the hand and, considering that in CMT hand deformities develop along the time, they may depend to overuse. Healthy controls have no differences between DH and NDH, and the average value is in the normal limits. As expected, in CMT patients, the TOT is significantly impaired compared to healthy controls. However, according to our hypothesis of OW, the DH shows significant better scores than NDH. We can speculate that hand deformities occur first in the DH, because of muscular weakness. Then, we evaluated the behavior of the strength of the intrinsic and extrinsic muscles, using the tripod pinch and the handgrip at dynamometry (114). In healthy controls, the DH is stronger than NDH, and we can confirm the 10% rule (115) (116) in a population of prevalent right-handed subjects. Likely, in a population of left-handed subjects, there are not stronger hands, as already demonstrated. On the contrary, in CMT patients, the strength of the tripod pinch and the handgrip is similar in DH and

NDH, not respecting the 10% rule. We then speculate that DH in CMT patients loses strength more than the NDH during the time following a normal overuse. As expected, in handgrip and tripod pinch, CMT patients show less strength than healthy controls. Dexterity, a compromised ability in CMT patients, has been evaluated with an innovative quantitative tool, which is reliable and sensitive as previously demonstrated [110] the HTS. This glove is a very interesting instrument because it is easy to use, and the evaluation takes little time. Based on previous observations, we considered the FT and IMRL exercises at the maximum velocity with eyes closed paradigm [110]. In both exercises, normal subjects have a statistically significant better performance in the DH, proving the superiority of the DH [116] even in the dexterity. CMT patients show the worst performance than normal controls at the HTS and the performances of the DH and the NDH are virtually identical.

Applied innovative instrumental testing of hand function in CMT patient, using the HTS, demonstrated it is sensitiveness to measure the severity of hands dysfunction. The results of the first study support the importance of avoiding supramaximal exercises and educating patients to prevent incorrect movements. Therefore, based on the results of Part I, we presented the rehabilitation protocol to patients with a clinical and genetic diagnosis of CMT of different types. The protocol was well tolerated and has shown high compliance. All the subjects performed the entire program, and none of them dropped out. In the final interview, all patients stated to feel better after the treatment and to be satisfied. This result is exciting because, in our personal experience, home self-administered exercises are difficult to follow and show deficient compliance by the patients. Accordingly, different cases of domiciliary treatment have been reported with poor or unclear results [117] [118]. At the baseline, all the measured parameters show an impairment of the strength, of the articularity and the functionality of the hand compared to previously published data normal controls (Part I). The rehabilitative protocol resulted in an improvement of the performance of both hands, but the dominant hand shows better significant results. All the outcome measures (TOT, SHTF and dynamometer) in the right hand significantly improved after the treatment. A slight improvement is present also in the left hand, which is the non-dominant hand for all. We can speculate that since the non-dominant hand is generally less affected (part I), it will take more time to recover strength and so that more prolonged treatment may be needed. It is also possible that the dominant hand, being more affected due to the presence of the overwork weakness (part I), is easier to treat using a rehabilitation protocol. We have strictly dosed, and we paid more attention to recruit the hand muscles in a submaximal way to avoid overwork. The results of this open-label pilot study highlight the importance of using a three components approach for the hand rehabilitation of patients affected by CMT based on recruitment, stretching and proprioception. Another fundamental aspect is the sensitiveness of the therapist who must estimate with precision the ability of the patients and dose the applied resistance.

Along with the study of sensors (HTS) and verification of the effectiveness of the activity in the evaluation protocols in the CMT neuropathy, we have evaluated the sensors and robotic rehabilitation approach to the patients in the post-stroke phase (Upper and lower limbs).

The data provided by the LMC protocol device showed the execution of the training protocol was feasible. All patients could properly execute without difficulties the exercises selected by their residual ability. The results demonstrated the device with sonorous-music support was provided intrinsically by the patient's movements. This characteristic permits the patient to focus on the exercise and, at the same time, to receive direct feedback on its quality. A correct movement produces a fluent musical progression, and it can help the patient to improve movements during the rehabilitative therapy. Data showed the perceived pain reduce significantly through the presence of musical patterns. Also, the patients underwent sonification intervention were more motivated to the rehabilitative program. Perhaps, the harmonic and melodic changes can have provided to creating attractive and facilitate the execution of the movements. Based on the preliminary data, a great realization and practicality associated with easy and simple learning were observed in the experimental group. One of the main limitations of the study is the lack of stronger evaluation methods, i.e. neuroimaging techniques as the fMRI, to evaluate possible changes in the brain connectivity and their possible correlation with post-treatment performance indexes.

As walking is another one of the common abilities affected by stroke, we evaluated the efficacy of a robotic system vs conventional rehabilitation, to improve the ambulation capacity of either ischemic or hemorrhagic post-stroke patients. Overall, the results of our study show how both kind of treatments are beneficial for recovery of patients although a further improvement is seen in TUG and BI for the robotic assisted group. As a matter of fact, recent studies have shown how robot assisted training prove to be effective in improving walking patterns and functional abilities in stroke patients (119) (120) (121) (122). Nonetheless, we support the idea that before starting working on walking abilities, post-acute stroke patients should first undergo pre-ambulation exercises with a physiotherapist (122). Although these exercises might be time consuming and delay beginning of sessions with robotic assisted rehabilitation, we believe they play a fundamental role in the potential of motor function recovery. Furthermore, guidelines recommend that rehabilitation should start as soon as safely possible (123), repetition always represents a mainstay of rehabilitation as favors neural plasticity, as a mechanism favoring functional improvement in stroke (124). In fact, previous studies have shown that higher intensities of walking practice result in better outcomes for these patients (125). Our findings suggest that both the IG and the CG globally improve, as demonstrated by the similar amelioration of TCT, TUG, 6MWT, BI and MI scores. To support that G-eo System is more confident with movement and walking. We observed a significant correlation between the TUG and BI at T1 in both groups, with a slightly better performance for the IG. Many previous papers show that the time taken to complete the TUG test strongly correlates to the level of functional mobility. More precisely patients, who are able to complete the task in less than 20 seconds, show less dependency in activities of daily living (ADL) (126) (127). In contrast, patients requiring 30 seconds or more to complete the task tend to be more dependent in ADL, require assistive devices for ambulation and score lower on the ADL assessment scale (126) (127). Our results strongly support this conclusion, in fact 8 patients in IG were able to perform TUG in 20 seconds or less, and 5 of them had a CN lesion. Four patients in CG were able to complete TUG in 20 seconds or less, and none of them had a CN lesion. Patients in the IG increased performances in gait and balance. BI was used to assess functional mobility as this measure is mostly used in rehabilitation studies to explore and describe the activities defined by the International Classification of Functioning (128) (129). Nonetheless, the cut-off level to consider patients evolving from a full dependency to an assisted independence is highly variable (128) (130) (131) , with some Authors considering 60 as cut-off score (130), and others choosing a BI score of 75 or higher in order to achieve an adequate ADL outcome (128). The correlation found in our study for which patients reaching a BI of 70 or higher had TUG results <20 seconds, with better results in the IG, supports the latter conclusion. Age represents one of the major risk factors involved in stroke and a critical point in functional outcome when it comes to post-stroke recovery (132). In this study, the age range of the patients was between 42 to 85 years (mean 67.83±11.78 years). However, performance and risk of falls are considered is not the only factor (133). In fact, various intrinsic factors such as balance impairment, neurological disorders, sensory deterioration, musculoskeletal disorders, and postural hypotension- may cause falls (133). We did not observe any correlation between TUG1 and the age. We also did not find any significant relationship between 6MWT1 and the age. We then speculate that, at least in our study, functional outcome depends more on stroke severity than age of the patients in both treatment protocols A study pointed out different mechanisms of post stroke recovery: Donghyeon et al. (134) found that pathophysiology of cell death and repair in capsular infarct resulting from the occlusion of the end arteries in subcortical stroke is likely to be different from large artery gray-matter cortical stroke. Based on our results at T1, adding GEO-system to the physiotherapy treatment possibly increases the recovery of CN lesion. Although this training improves clinical recovery, studies have shown that the important factors of recovery are: Position and volume of the lesion, structural changes in the perilesional tissue and in bi-hemispheric networks (135). In this study, self-walking speed was adjusted according to patient's abilities before each training session, with a mean speed of 0.5 m/s at the beginning of treatment, reaching a maximum of 0.8 m/s at the end of treatment in IG. Finally, although not all subjects demonstrated a statistically significant improvement in gait, all subjects showed a tendency to improve in respect to baseline.

Furthermore, one of the major aims of our project was the development of innovative and low-cost sensor/ICT-based technologies to monitor the rehabilitation process at the hospital and home levels. A first phase (4 above study) was necessary to implement and develop an electronic device. It was essential to gradually improve our system, starting from medical aspects related to rehabilitation. We have defined adequate parameters to allow the evaluation of the quality of the exercise in terms of performance. This phase was led to technological development, consisting of the analysis of signals and sensor positions. We believe, today, to achieve a real evolution in treatments is necessary to define therapeutic paths and protocols of effective clinical-health application. Successively, on the base of the results is fundamental to guarantee the development of innovative technologies with a very high scientific content, to reach the realization of prototypes that can be rapidly industrialized and proposed to the market.

SP system is specifically designed for the rehabilitation and acquisition of the data as a smart rehabilitation platform. It can be used in the neurological field; the context of use is a hospital, ambulatory and, in future, domestic. To monitor the patient's activity, we used multiple wearable nodes, and software SP made up of platform providing real-time feedback on the patient's movements. The system through a machine learning tool can automatically recognize the type of exercise the patient is performing during the rehabilitation session and providing real-time feedback during activity. We carried out an extensive performance analysis to evaluate the capacity of the system to identify the current movement correctly. Results show that the average recognition accuracy is about 96.5%.

Stroke patients constitute a heterogeneous population with variable recovery times and different functional capacity between subjects. Better knowledge of the altered functional control mechanisms in these patients is essential to allow clinicians to target specific rehabilitation programs. For example, gait may be a challenging task in stroke patients because of their sensory and motor impairments [(136) (137)]. Decreased plantar flexor, hip flexor and hip extensor power, on the paretic side [(138) (139)] could be the motivation of reduction in the duration of the swing phase, step length, walking velocity. Additionally, the paretic leg muscles give less to the load of the paretic side, create less power. Thus, bodyweight distribution between both legs can influence stability during gait [(140).] For this kind of patients, personalized rehabilitation with continuous monitoring is fundamental elements for the best rehabilitation outcome. Another critical factor is the evaluation of objectification of improvements. SP was demonstrated adequate dispositive in this process. The device allowed performing the personalized quantitative evaluation in 8 different patients.

Moreover, exercises for the evaluation with SP were set based on the patient's ability. Choose of the difficult test, such as walking, was depending on the capacity of the patients. SP has proved to be a useful support for our rehabilitation process that begins with the adequate functional evaluation scales and successively a personalized rehabilitation treatment. The preliminary results presented in this thesis showed the validity of monitoring with SP in the intensive rehabilitation process in the post-stroke petitions. The SP has demonstrated very positive capacity to monitor the patients using IMU and presser sensors, in terms of the distribution of the weight in static and dynamic position and functional ability.

Furthermore, were evaluated new simple rehabilitation exercises to support care interventions, aimed at future home rehabilitation. The device was programmed to monitor specific parameters related to movement. During the hospitalization phase the feasibility of monitoring the sensors evaluated by the physiotherapist. So, the simulation in the clinical environment can become a tool to modulate the needs of rehabilitation in the external domestic context in a personalized and specific way.

7. CONCLUSION

This PhD project demonstrates that existing and newly developed robotic and sensor-assisted technologies may be fruitfully applied to the rehabilitative evaluation and treatment. In particular, the upper-limb valuation with the Hand Test System (HTS) disclosed that CMT patients show the reduced ability of opposition, strength and dexterity in both hands compared with normal subjects. Their DH is worse than NDH at least in some measurements. These observations have practical implications for scheduling preventive occupational therapy sessions and for planning a correct rehabilitative program. It is essential to avoid the overload of the DH and to teach the patients to stop the activities when the fatigue sensation begins. These essential precautions are proposed to slow the disease progression at the UL level. Moreover, this study could be the basis for future randomized, single-blind projects.

VR technology (sonification training protocol), has demonstrated to be an effective tool in neurorehabilitation. The interesting and different virtual sound improves more motivation of patients comparing with the traditional rehabilitation. Sonic Hand protocol can complement the information provided by the clinical tools. These characteristics, in combination with the sonification model, enable the improvement of personalized treatment programs for the post-stroke rehabilitation of hand function.

System design of lower-limb rehabilitation robot, although not in contrast with the hypothesis that adding a robot technology to standard rehabilitation has a significant positive impact on disability, supports that traditional treatment alone may be as well performed. However, we observed a positive trend of the outcomes in the walking ability of post-acute stroke in the robotic treatment group associated with a standard rehabilitation. The impact of robotic treatment in different regions of the brain, including CN, is poorly understood in stroke rehabilitation. To confirm the results and evaluate the multiform aspect of brain reorganization during stroke recovery, functional imaging studies (MRI), with higher numbers of patients are required. We propose that further prospective studies are needed for this important point.

In the main study, we proposed a sensor system called SP, specifically created for the monitoring of the lower limb rehabilitation in post-stroke patients. The system is produced by heterogeneous wireless sensors that provide real-time assistance to post-stroke patients during physiotherapy training. The proposed platform can recognize the current exercise, and to send useful information collected by sensors to a remote server that evaluates by healthcare professionals. Experimental results, evaluated through appropriate metrics, demonstrate that the proposed movement recognition algorithm provides excellent results in terms of classification performance, with an overall accuracy of around 96.5%.

In our opinion, future researches on the innovation of rehabilitation technologies should focus on the following aspects: i) high technology strategies. That may be of great help in verifying the quality and results of rehabilitative therapy. ii) Transfer of physiotherapy activities from the hospital to the home of the patient. Many neurological diseases have a strong need for continuous and long-lasting rehabilitative treatment. sensorized device, telemonitoring and tele-rehabilitation could be the ideal basis for future projects.

Bibliography

1. *Hereditary Neuropathies.* **Eggermann K, Gess B, Häusler M, Weis J, Hahn A, Kurth I.** s.l. : KurDeutsches Arzteblatt international, 2018, Vols. 115(6), 91–97.

2. **Loeb, al e.** *Neurologia di fazio loeb.* Roma : Società editrice Universo, 2003.

3. *The Role of Rehabilitation in the Management of Patients with Charcot-Marie-Tooth Disease: Report of Two Cases.* **Dimitrova EN, Božinovikj I, Ristovska S, Pejcikj AH, Kolevska A, Hasani M.** s.l. : Maced J Med Sc, 2016, Vols. 4(3):443–448.

4. *The influence of somatosensory and muscular deficits on postural stabilization: Insights from an instrumented analysis of subjects affected by different types of Charcot–Marie–Tooth disease.* **Lencioni T, Piscosquito G, Rabuffetti M, Bovi G, Calabrese D, Aiello A, et al.** s.l. : Neuromuscular Disorders, 2015, Vols. 25:640-645.

5. *Natural history, and management of charcot-marie-tooth disease.* **Pareyson D, Marchesi C. Diagnosis.** s.l. : Lancet Neurol, 2009, Vols. 8:654-667.

6. **Kazunori Sango, Junji Yamauchi, Toru Ogata, Keiichiro Susuki.** *Myelin Basic and Clinical Advances.* s.l. : Springer, 2019. 978-981-32-9636-7/2214-8019.

7. *Cmt subtypes and disease burden in patients enrolled in the inherited neuropathies consortium natural history study: A cross-sectional analysis.* **Fridman V, Bundy B, Reilly MM, Pareyson D, Bacon C, Burns J, et al.** s.l. : J Neurol Neurosurg Psychiatry, 2015, Vol. 86:873.

8. *Inherited neuropathies .* **Schenone A, Nobbio L, Monti Bragadin M, Ursino G, Grandis M.** s.l. : Curr Treat Options Neurol, 2011 , Vols. 13(2):160-79.

9. *Clinical and electrophysiological aspects of charcot-marie-tooth disease.* **Pareyson D, Scaioli V, Laura M.** s.l. : Neuromolecular Med, 2006, Vols. 8:3-22.

10. *Correlates of functional ankle instability in children and adolescents with charcot-marie-tooth disease.* **Rose KJ, Hiller CE, Mandarakas M, Raymond J, Refshauge K, Burns J.** s.l. : J Foot Ankle Res, 2015, Vol. 8:61.

11. *Rehabilitation medicine approach to charcot-marie-tooth disease.* **Njegovan ME, Leonard EI, Joseph FB.** s.l. : Clin Podiatr Med Surg, 1997, Vols. 14:99-116.

12. *Charcot-marie-tooth disease: Electrophysiology, molecular genetics and clinical management.* **Carter GT, England JD, Chance PF.** s.l. : IDrugs, 2004, Vols. 7:151-159.

13. *Rehabilitation Management of the Charcot–Marie–Tooth Syndrome A Systematic Review of the Literatur.* **Bruno Corrado, Gianluca Ciardi, and Chiara Bargigli.** s.l. : Medicine (Baltimore), 2016, Vol. 95(17): e3278.

14. *Strength training in patients with myotonic dystrophy and hereditary motor and sensory neuropathy: a randomized clinical trial .* **Lindeman E, Leffers P, Spaans F, et al.** s.l. : Arch Phys Med Rehab, 1995, Vols. 76:612–620.

15. *Progressive resistance training in neuromuscular patients. Effects on force and surface EMG.* **Lindeman E, Spaans F, Reulen J, et al.** s.l. : J Electromyogr Kinesiol , 1999, Vols. 9:379–384.

16. *Aerobic anti-gravity exercise in patients with charcot-marie-tooth disease types 1a and x: A pilot study.* **Knak K.L., Andersen L.K., Vissing J.** s.l. : Brain Behav, 2017, Vol. 7:e00794.

17. *Safety and efficacy of progressive resistance exercise for Charcot-Marie-Tooth disease in children: a randomised, double-blind, sham-controlled trial.* **Burns J., Sman A.D., Cornett K.M.D., Wojciechowski E., Walker T., Menezes M.P., Mandarakas M.R., Rose K.J., Bray P., Sampaio H., et al.** s.l. : The Lancet Child & Adolescent Health, 2017, Vols. 1(2):106-113.

18. *Assessment of appropriate ankle-foot orthoses models for patients with charcot-marie-tooth diseas.* **Guillebastre B., Calmels P., Rougier P.R.** s.l. : Am. J. Phys. Med. Rehabil, 2011, Vols. 90:619–627.

19. *Foot drop splints improve proximal as well as distal leg control during gait in charcot-marie-tooth disease.* **Ramdharry G.M., Day B.L., Reilly M.M., Marsden J.F.** s.l. : Muscle Nerve, 2012, Vols. 46:512–519.

20. *Charcot-Marie-Tooth: From Molecules to Therapy .* **Jonathan Morena, Anirudh Gupta, and J. Chad Hoyle.** s.l. : Int J Mol Sci, 2019 , Vol. 20(14): 3419.

21. *Handgrip impairment in Charcot-Marie-Tooth disease.* **Vinci P, Villa L. M, Castagnoli L, Marconi C, Lattanzi A, Manini M. P, Calicchio M. L, Vitangeli L, Di Gianvito P, Perelli S. L, Martini D.** s.l. : Europa Medicophysica , 2005, Vols. 41(2):131-4.

22. *Amyotrophic lateral sclerosis:a comprehensive rehabilitation approach.* **Janiszewski DW, Caroscio JT, Wisham LH.** s.l. : Arch Phys Med Rehabil, 1983, Vols. 64:304-307.

23. *Pseudohypertrophic muscular dystrophy. Distribution of degenerative features as revealed by an anatomical study.* **CA, Bonsett.** s.l. : Neurology, 1963, Vols. 13:728-738.

24. *Over-work weakness in facioscapulohuumeralmuscular dystrophy.* **Johnson EW, Braddom R.** s.l. : Arch Phys Med Rehabil, 1971, Vols. 52:333-336.

25. *Comparison of three methods to assess muscular strength in individuals with spinal cord injury.* **Noreau L, Vachon J.** s.l. : Spinal Cord, 1998, Vols. 36:716-723.

26. *Hand dynamometer: effects of trials and sessions.* **Reddon JR, Stefanyk WO, Gill DM, Renney C.** s.l. : Percept Mot Skills, 1985, Vols. 61:1195-1198.

27. *Hand weakness in Charcot-Marie-tooth disease 1X.* **Arthur-Farraj PJ, Murphy SM, Laura M, et al.** s.l. : Neuromuscul Disord, 2012, Vols. 22:622-626.

28. *Evaluation of muscle strengthand manual dexterity in patients with Charcot-Marie-tooth disease.* **Kobesova A, Nyvltova M, Kraus J, et al.** s.l. : j.Hand Ther, 2016, Vols. 29:66-72.

29. *The hypothesis of overwork weakness in Charcot-Marie-tooth: a critical evaluation.* **van Pomeren M, Selles RW, van Ginneken BT, Schreuders TA,Janssen WG, Stam HJ.** s.l. : J Rehabil Med, 2009, Vols. 41:32-34.

30. *Is overwork weakness relevant in Charcot-Marie-tooth disease? .* **Piscosquito G, Reilly MM, Schenone A, et al.** s.l. : J Neurol Neurosurg Psychiatry, 2014, Vols. 85:1354-1358.

31. *Examining hand dominance using dynamometric grip strength testing as evidence for overwork weakness in Charcot-Marie-tooth disease: a systematic review and meta-analysis.* **Roberts-Clarke D, Fornusek C, Fiatarone Singh MA, Burns J,Hackett DA.** s.l. : Int J Rehabil Res, 2016, Vols. 39:189-196.

32. *Secondary prevention of stroke in italy: A cross-sectional survey in family practice .* **Filippi A, Bignamini AA, Sessa E, Samani F, Mazzaglia G.** s.l. : Stroke, 2003, Vols. 34:1010-1014.

33. *Managing Stroke During Transcatheter Aortic Valve Replacement.* **Hecker F, Arsalan M, Walther T.** s.l. : Interv Cardiol, 2017, Vols. 12(1):25–30.

34. *SPREAD – Stroke Prevention and Educational Awareness Diffusion. Ictus cerebrale: Linee guida italiane di prevenzione e trattamento.* 2016. Vol. VIII Edizione. VIII Edizione.

35. *Stroke: classification and diagnosis .* **Parmar, Paresh.** s.l. : Clinical Pharmacist, 2018, Vol. 10 .

36. *Treatment of intracerebral haemorrhage.* **Stephan AMayer, Fred Rincon.** s.l. : The lancet Neurology, 2005, Vols. 4:662-672.

37. *Strength training in individuals with stroke .* **JJ, Eng.** s.l. : Physiother Can, 2004, Vols. 56:189-201.

38. *Alterations of muscle activation pattern in stroke survivors during obstacle crossing.* **Ma C, Chen N, Mao Y, Huang D, Song R, Li L.** s.l. : Front Neurol, 2017, Vol. 8:70.

39. *Distribution of muscle strength impairments following stroke.* **Andrews AW, Bohannon RW.** s.l. : Clin Rehabil, 2000, Vols. 14:79-87.

40. *Stroke rehabilitation.* **Langhorne P, Bernhardt J, Kwakkel G.** s.l. : Lancet, 2011, Vols. 377:1693-1702.

41. *Hand rehabilitation robotics on post-stroke motor recovery.* **Yue, Z., Zhang, X., & Wang, J.** s.l. : Behavioural neurology, 2017, Vol. 2017:20.

42. *What do motor 'recovery' and 'compensation' mean in patients following stroke?* **M. F. Levin, J. A. Kleim, and S. L. Wolf.** s.l. : Neurorehabil Neural Repair, 2009, Vols. 23, no. 4: 313–319 .

43. *What is the evidence for physical therapy poststroke? A systematic review and meta-analysis.* **al., J. M. Veerbeek et.** s.l. : PLoS ONE, 2014, Vol. 9: e87987.

44. *Shaping plasticity to enhance recovery after injury.* **Nudo, N. Dancause and R. J.** s.l. : Prog. Brain Res, 2011, Vols. 192:273–295.

45. *Effects of augmented exercise therapy time after stroke: a meta-analysis.* **al., G. Kwakkel et.** s.l. : Stroke, 2004, Vols. 35:2529–2539.

46. *Design strategies to improve patient motivation during robot-aided rehabilitation.* **R. Colombo, F. Pisano, A. Mazzone et al.** s.l. : Journal of NeuroEngineering and Rehabilitation , 2007, Vol. 4: 3 .

47. *EMG biofeedback for the recovery of motor function after stroke .* **Woodford H, Price C.** s.l. : Cochrane Database Syst Rev, 2007, Vols. 2007,2.

48. *Changes in muscle group work associated with changes in gait speed of persons with stroke.* **Parvatanemi K, Olney SJ, Brouwer B.** s.l. : Clin Biomech (Bristol, Avon), 2007, Vols. 22:813-820.

49. *Innovative Technologies for Rehabilitation and Health Promotion: What Is the Evidence?* **Carolee Winstein, Philip Requejo.** s.l. : Physical Therapy, 2015, Vols. 95:294–298.

50. *Rehabilitation service models for people with physical and/or mental disability living in low-and middleincome countries:A systematic review.* **A D. Furlan, E Irvin, C Munhall , M Giraldo-prieto et al.** s.l. : Medical Journals Limited, 2018, Vols. 6: 487-498.

51. *The home stroke rehabilitation and monitoring system trial: a randomized controlled trial.* **Linder SM, Rosenfeldt AB, Reiss A, et al.** s.l. : International journal of stroke, 2013, Vols. 8: 46-53.

52. *Rehabilitation that incorporates virtual reality is more effective than standard rehabilitation for improving walking speed, balance and mobility after stroke: a systematic review.* **Corbetta D, Imerib F, Gattic R.** s.l. : Journal of Physiotherapy, 2015, Vols. 61:117-124.

53. *Facilitating Stroke Management using Modern Information Technology.* **Nam HS, Park E, Heo JH.** s.l. : J Stroke, 2013, Vols. 15:135–143 .

54. **Roberto Colombo, Vittorio Sanguineti.** *Rehabilitation robotics : technology and application.* s.l. : London : Academic Press, 2018.

55. *Rehabilitation Robotics.* **Riener, Robert.** s.l. : Foundations and Trends® in Robotics, 2013, Vols. 3:1-137.

56. *Robotic-assisted gait training and restoration .* **A. Esquenazi, A. Packel.** s.l. : American journal of physical medicine & rehabilitation, 2012, Vols. 91:228-231.

57. *Recent Development of Rehabilitation Robots.* **Z, Qian Z and Bi.** s.l. : Advances in Mechanical Engineering, 2017, Vols. 2017: 563062-563062.

58. *The use of robots in stroke rehabilitation: A narrative review.* **Weber L. M., & Stein J.** s.l. : NeuroRehabilitation, 2018, Vols. 43: 99-110 .

59. *Improving the Efficiency of Robot-Mediated Rehabilitation by Using a New Organizational Model: An Observational Feasibility Study in an Italian Rehabilitation Center.* **Aprile I, Pecchioli C, Loreti S, Cruciani A, Padua L, Germanotta M.** s.l. : Applied sciences, 2019, Vol. 9:5357.

60. *Reha-Stepperlocomotion therapy in early rehabilitation of paraplegic patients.* **Rupp R, Eberhard S, Schreier R, Colombo G.** s.l. : Biomedizinische Technik (Berl), 2002, Vols. 47:708-711.

61. *Novel Tilt Table with integrated robotic stepping mechanism: Design Principles and Clinical Application.* **Colombo G, Schreier R, Mayr A, Plewa H, and Rupp R.** s.l. : IEEE 9th International Conference on Rehabilitation Robotics, 2005, Vols. 2005: 227 - 230.

62. *Innovative gait robot for the repetitive practice of floor walking and stair climbing up and down in stroke patients .* **Hesse S, Waldner A ,& Tomelleri C.** s.l. : J NeuroEngineering Rehabil , 2010, Vols. 7, n.30.

63. **Wirz M, Rupp R.** *Application Issues for Robotics.* s.l. : Springer, 2016. Vols. 141-160. 978-3-319-28601-3.

64. *Robot-assisted therapy in stroke rehabilitation.* **Chang WH, Kim YH.** s.l. : J Stroke, 2013, Vols. 15:174-181.

65. *Systematic review of outcome measures used in the evaluation of robot-assisted upper limb exercise in stroke.* **Sivan M, O'Connor RJ, Makower S, Levesley M, Bhakta B.** s.l. : J Rehabil Med, 2011, Vols. 43:181-189.

66. *The impact of physical therapy on functional outcomes after stroke: What's the evidence? .* **Van Peppen RP, Kwakkel G, Wood-Dauphinee S, Hendriks HJ, Van der Wees PJ, Dekker J.** s.l. : Clin Rehabil., 2004, Vols. 18:833-862.

67. *Electromechanical-assisted training for walking after stroke.* **Mehrholz J, Werner C, Kugler J, Pohl M.** s.l. : Cochrane Database Syst Rev, 2007.

68. *Cochrane review: virtual reality for stroke rehabilitation .* **Laver K, George S, Thomas S, Deutsch JE, & Crotty M.** s.l. : European journal of physical and rehabilitation medicine, 2012, Vols. 48:523-30.

69. *Virtual Reality Clinical Research: Promises and Challenges.* **Garrett B, Taverner T, Gromala D, Tao G, Cordingley E, Sun C.** s.l. : JMIR Serious Games, 2018 , Vol. 6(4):e10839.

70. *Analysis of the accuracy and robustness ofthe leap motion controller.* **Weichert F, Bachmann D, Rudak B, Fisseler D.** s.l. : Sensors, 2013, Vols. 13(5):6380-6393.

71. *Evaluation of a portable markerless finger position capture device: accuracy of the Leap Motion controller in healthy adults .* **Tung JY, Lulic T, Gonzalez DA, Tran J, Dickerson CR, Roy EA.** s.l. : Physiological Measurement, 2015, Vol. 36(5):1025.

72. *Validation of the Leap Motion Controller using markered motion capture technology.* **Smeragliuolo AH, Hill NJ, Disla L, Putrino D.** s.l. : Journal of Biomechanics, 2016, Vols. 49:1742-1750.

73. *Leap motion controlled video game-based therapy for upper limb rehabilitation in patients with Parkinson's disease: a feasibility study.* **Fernández-González P, Carratalá-Tejada M, Monge-Pereira E, et al.** s.l. : J Neuroeng Rehabil, 2019, Vol. 16(1):133.

74. *Neural reorganization underlies improvement in stroke-induced motor dysfunction by music-supported therapy.* **Altenmüller E, Marco-Pallares J, Münte TF, Schneider S.** s.l. : Annals of the New York Academy of Sciences, 2009, Vols. 1169:395-405 .

75. *Part VI introduction: listening to and making music facilitates brain recovery processes.* **G, Schlaug.** s.l. : Annals of the New York Academy of Sciences, 2009, Vols. 1169:372-3.

76. *Wearable medical systems for p-Health.* **Teng X-F, Zhang Y-T, Poon CCY, Bonato P.** s.l. : IEEE Reviews in Biomedical Engineering , 2008, Vols. 1: 62-74.

77. *Wearable sensors and systems. From enabling technology to clinical applications.* **P, Bonato.** s.l. : IEEE Eng Med Biol, 2010, Vols. 29: 25-36.

78. *A review of wearable sensors and systems with application in rehabilitation .* **Patel S, Park H, Bonato P, Chan L, and Rodgers M.** s.l. : Journal of NeuroEngineering and Rehabilitation, 2012, Vol. 9:21.

79. *Telerehabilitation Approaches for Stroke Patients: Systematic Review and Meta-analysis of Randomized.* **Chen J, Jin W, Zhang X, Xu W,Liu X, Ren C.** s.l. : Journal of Stroke and Cerebrovascular Diseases, 2015, Vols. 24: 2660-2668.

80. *Telerehabilitation: State-of-the-Art from an Informatics Perspective.* **Parmanto B, Saptono A.** s.l. : International journal of telerehabilitation, 2009, Vols. 1:73–84.

81. *Inertial Sensor Measurements of Upper-Limb Kinematics in Stroke Patients in Clinic and Home Environment.* **Held JPO, Klaassen B, Eenhoorn A, et al.** s.l. : Front Bioeng Biotechnol, 2018, Vol. 6:27.

82. *Clinical test of apposition and counter-apposition of the thumb.* **Kapanji, A.** s.l. : Ann Chir Main, 1986, Vols. 5:67-73.

83. *An exploration of EEG features during recovery following stroke – implications for BCI-mediated neurorehabilitation therapy.* **Leamy, D.J., Kocijan, J., Domijan, K. et al.** s.l. : J NeuroEngineering Rehabi, 2014, Vol. 11.

84. *Grip Strength Predicts Cause-Specific Mortality in Middle-Aged and Elderly Persons.* **Sasaki H, Kasagi F, Yamada M, Fujita S.** s.l. : The American Journal of Medicine , 2007, Vols. 120: 337-342.

85. *A quantitative assessment of the eating capability in the elderly individuals.* **Laguna L, Sarkar A, Artigas G, Chen J.** s.l. : Physiology & Behavior , 2015, Vols. 147:274-281.

86. *Tripod pinch strength and thumb opposition are the major determinants of manual dexterity inCharcot-Marie-tooth disease type 1A.* **Videler AJ, Beelen A, van Schaik IN, Verhamme C, van den Berg LH, de Visser M, Nollet F.** s.l. : J Neurol Neurosurg Psychiatry, 2010, Vols. 81:828-833.

87. *Reliability of clinical outcome measures in Charcot-Marie-tooth disease.* **Solari A, Laura M, Salsano E, Radice D, Pareyson D.** s.l. : Neuromuscul Disord, 2008, Vols. 18:19-26.

88. *An engineered glove for investigating the neural correlates of finger movements using functional magnetic resonance imaging.* **Bonzano L, Tacchino A, Roccatagliata L, Inglese M, Mancardi GL, Novellino A, Bove M.** s.l. : Front Hum Neurosci, 2015, Vol. 9:503.

89. *Sollerman hand function test: A standardised method and its use in tetraplegic patients.* **Sollerman C, Ejeskär A.** s.l. : Scand J Plast Reconstr Surg Hand Surg, 1995, Vols. 29:167–176.

90. *Physical and execises therapy for treatment of rheumatoid hand.* **Buljina A, Talijanovic M, Avdic D, Hunter T.** s.l. : Arthritis Care Res Offiicial J Am Coll Rheumatol, 2001, Vols. 45:392–397.

91. *Exercise therapy for multiple sclerosis (Review).* **Rietberg M, Brooks D, Uitdehaag B, Hwakkel G.** s.l. : Cochrane Database Syst Rev, 2004, Vol. 2004:3.

92. *The SonicHand Protocol for Rehabilitation of Hand Motor Function: A Validation and Feasibility Study.* **Colombo R, Raglio A, Panigazzi M, Mazzone A, Bazzini G, Imarisio C, Molteni D, Caltagirone C, Imbriani M.** s.l. : IEEE Trans Neural Syst Rehabil Eng, 2019, Vols. 27:664-672.

93. *Acupuncture treatment for ischaemic stroke in young adults: protocol for a randomised, sham-controlled clinical trial.* **Chen L, Fang J, Jin X, Keeler CL, Gao H, Fang Z, Chen Q.** s.l. : BMJ Open, 2016, Vol. 6:e010073.

94. *The post-stroke hemiplegic patient. 1. a method for evaluation of physical performance.* **Fugl-Meyer AR, Jääskö L, Leyman I, Olsson S, Steglind S.** s.l. : Scand J Rehabil Med, 1975, Vols. 7(1):13-31.

95. *Validation of the Box and Block Test as a Measure of Dexerity of Elderly People: Reliability, Validity, and Norms Studies .* **Desrosiers J, Bravo G, Hébert R, Dutil E, Mercier L.** s.l. : Arch Phys Med Rehabil , 1994, Vols. 75: 751-5.

96. *Adult norms for the Box and Block Test of manual dexterity.* **Mathiowetz V, Volland G, Kashman N, Weber K.** s.l. : American Journal of Occupational Therapy, 1985, Vols. 39: 386-391.

97. *Reliability of measurements of muscle tone and muscle power in stroke patients.* **Leathley MJ, Moore AP, Smith TL, Sharma AK, Watkins CL., Gregson JM.** s.l. : Age Ageing, 2000, Vols. 29:223-8.

98. *Assessing motor impairment after stroke: A pilot reliability study .* **Collin C, Wade D.** s.l. : J Neurol Neurosurg Psychiatry, 1990, Vols. 53:576-579.

99. *Clinical measurement tools to assess trunk performance after stroke: A systematic review.* **Sorrentino G, Sale P, Solaro C, Rabini A, Cerri CG, Ferriero G.** s.l. : Eur J Phys Rehabil Med, 2018, Vols. 54:772-784.

100. *Improving the sensitivity of the barthel index for stroke rehabilitation.* **Shah S, Vanclay F, Cooper B.** s.l. : J Clin Epidemiol, 1989, Vols. 42:703-709.

101. *Predicting levels of basic functional mobility, as assessed by the timed "Up and go" Test, for individuals with stroke: Discriminant analyses.* **Faria CD, Teixeira-Salmela LF, Nadeau S.** s.l. : Disabil Rehabil, 2013, Vols. 35:146-152.

102. *Issues in selecting outcome measures to assess functional recovery after stroke.* **Barak S, Duncan PW.** s.l. : NeuroRx, 2006, Vols. 3:505-524.

103. *The six-minute walk test.* **Enright, PL.** s.l. : Respir Care, 2003, Vols. 48:783-785.

104. *Assessment of pain.* **Breivik H, Borchgrevink PC, Allen SM, Rosseland LA, Romundstad L, Hals EK, et al.** s.l. : Br J Anaesth, 2008, Vols. 101:17-24.

105. *Rehabilitation service models for people with physical and/or mental disability living in low- and middle-income countries: A systematic review.* **Furlan AD, Irvin E, Munhall C, Giraldo-Prieto M, Fullerton L, McMaster R.** s.l. : J Rehabil Med, 2018, Vols. 50(6):487-498.

106. *What is telemedicine? A collection of 104 peer-reviewed perspectives and theoretical underpinnings.* **Sood S, Mbarika V, Jugoo S, Dookhy R, Doarn CR, Prakash N, Merrell RC.** s.l. : Telemed J E Health, 2007 , Vols. 13(5):573-90.

107. *Telerehabilitation clinical and vocational applications for assistive technology: research, opportunities, and challenges.* **Schmeler MR, Schein RM, McCue M, Betz K.** s.l. : Int J Telerehabil, 2009, Vols. 1(1):59–72.

108. *Randomized controlled trial of strength training in post-polio patients.* **Chan KM, Amirjani N, Sumrain M, Clarke A, Strohschein FJ.** s.l. : Muscle Nerve, 2003, Vols. 27:332-338.

109. *Pseudohypertrophic muscular dystrophy. Distribution of degenerative features as revealed by an anatomical study.* **CA, Bonsett.** s.l. : Neurology, 1963, Vols. 13:728-738.

110. *Innovative quantitative testing of hand function in Charcot-Marie-tooth neuropathy.* **Alberti MA, Mori L, Francini L, Poggi I, Monti Bragadin M, Bellone E, et al.** s.l. : J Peripher Nerv Syst, 2015, Vols. 20:410-414.

111. *Relationship between two measures of upper extremity strength: manual muscle test compared to hand-held myometry.* **Schwartz S, Cohen ME, Herbison GJ, Shah A.** s.l. : Arch Phys Med Rehabil, 1992, Vols. 73: 1063-1068.

112. *Is overwork weakness relevant in Charcot-Marie-tooth disease? .* **Piscosquito G, Reilly MM, Schenone A, Fabrizi GM, Cavallaro T, Santoro L, et al.** s.l. : J Neurol Neurosurg Psychiatry, 2014, Vols. 85:1354-1358.

113. *Hand function in Charcot Marie tooth: testretest reliability of some measurements.* **Svensson E, Hager-Ross C.** s.l. : Clinical Rehabilitation, 2006, Vols. 20:896-908.

114. *Intrinsic-extrinsic muscle control of the hand in power grip and precision handling. An electromyographic study .* **Long C 2nd, Conrad PW, Hall EA, Furler SL.** s.l. : Journal of Bone & Joint Surgery, 1970, Vols. 52:853-867.

115. *Grip test; the use of a dynamometer with adjustable handle spacings .* **CO, Bechtol.** s.l. : Journal of Bone & Joint Surgery, 1954, Vols. 36-A:820-824.

116. *Superiority of the dominant and nondominant hands in static strength and controlled force exertion .* **Noguchi T, Demura S, Aoki H.** s.l. : Percept Mot Skills, 2009, Vols. 109:339-346.

117. *Poor compliance with ankle-foot-orthoses in Charcot-Marie-Tooth disease.* **Vinci P, Gargiulo P.** s.l. : Eur J Phys Rehabil Med, 2008, Vols. 44:27–31.

118. *A pilot study of proximal strength training in Charcot-Marie-Tooth disease.* **Ramdharry GM, Pollard A, Anderson C, Laurá M, Murphy SM, et al.** s.l. : J Peripher Nerv Syst, 2014, Vols. 19(4):328–332.

119. *Does repetitive task training improve functional activity after stroke? A cochrane systematic review and meta-analysis.* **French B, Thomas L, Leathley M, Sutton C, McAdam J, Forster A, et al.** s.l. : J Rehabil Med, 2010, Vols. 42:9-14.

120. *Who may benefit from robotic-assisted gait training? A randomized clinical trial in patients with subacute stroke.* **Morone G, Bragoni M, Iosa M, De Angelis D, Venturiero V, Coiro P, et al.** s.l. : Neurorehabil Neural Repair, 2011, Vols. 25:636-644.

121. *Robot-assisted upper and lower limb rehabilitation after stroke: Walking and arm/hand function.* **Hesse S, Mehrholz J, Werner C.** s.l. : Dtsch Arztebl Int. , 2008, Vols. 105:330-336.

122. *Robot-assisted gait training for stroke patients: Current state of the art and perspectives of robotics.* **Morone G, Paolucci S, Cherubini A, De Angelis D, Venturiero V, Coiro P, et al.** s.l. : Neuropsychiatr Dis Treat, 2017, Vols. 13:1303-1311.

123. *Rehabilitation is initiated early after stroke, but most motor rehabilitation trials are not: A systematic review.* **Stinear C, Ackerley S, Byblow W.** s.l. : Stroke, 2013, Vols. 44:2039-2045.

124. *Modulation of neural plasticity as a basis for stroke rehabilitation.* **Pekna M, Pekny M, Nilsson M.** s.l. : Stroke, 2012, Vols. 43:2819-2828.

125. *Conflicting results of robot-assisted versus usual gait training during postacute rehabilitation of stroke patients: A randomized clinical trial.* **Taveggia G, Borboni A, Mule C, Villafane JH, Negrini S.** s.l. : Int J Rehabil Res, 2016, Vols. 39:29-35.

126. *The timed "Up & go": A test of basic functional mobility for frail elderly persons .* **Podsiadlo D, Richardson S.** s.l. : J American Geriatrics Society, 1991, Vols. 39:142-148.

127. *Predicting the probability for falls in community-dwelling older adults using the timed up & go test .* **Shumway-Cook A, Brauer S, Woollacott M.** s.l. : Geriatric Physical Therapy , 2000, Vols. 80:896-903.

128. *Acute phase predictors of 6-month functional outcome in italian stroke patients eligible for in-hospital rehabilitation.* **Franceschini M, Fugazzaro S, Agosti M, Sola C, Di Carlo A, Cecconi L, et al.** s.l. : Am J Phys Med Rehabil, 2018, Vols. 97:467-475.

129. *Utility of international classification of functioning, disability and health's participation dimension in assigning icf codes to items from extant rating instruments.* **Granlund M, Eriksson L, Ylven R.** s.l. : J Rehabil Med, 2004, Vols. 36:130-137.

130. *Stroke rehabilitation: Analysis of repeated barthel index measures.* **Granger CV, Dewis LS, Peters NC, Sherwood CC, Barrett JE.** s.l. : Arch Phys Med Rehabil, 1979, Vols. 60:14-17.

131. *Optimizing cutoff scores for the barthel index and the modified rankin scale for defining outcome in acute stroke trials.* **Uyttenboogaart M, Stewart RE, Vroomen PC, De Keyser J, Luijckx GJ.** s.l. : Stroke, 2005, Vols. 36:1984-1987.

132. *Effect of sex and age interactions on functional outcome after stroke.* **Kim TH, Vemuganti R.** s.l. : CNS Neurosci Ther, 2015, Vols. 21:327-336.

133. *Assessment of simple gait related dual and triple tests in predicting the risk of fall in adults above age of 50 years.* **Paranjape S, Chitalia D.** s.l. : Cureus, 2016, Vol. 8:e651.

134. *Longitudinal changes in resting-state brain activity in a capsular infarct model .* **Kim D, Kim RG, Kim HS, Kim JM, Jun SC, Lee B, et al.** s.l. : J Cereb Blood Flow Metab, 2015, Vols. 35:11-19.

135. *Recovery potential after acute stroke.* **Seitz RJ, Donnan GA.** s.l. : Front Neurol, 2015, Vol. 6:238.

136. *The Relation between limb loading and control parameters of gait initiation in persons with stroke .* **Brunt D, Vander Linden DW, Behrman AL.** s.l. : Arch Phys Med Rehabi, 1995, Vols. 76:627–34.

137. *Kinematic and kinetic asymmetries in hemiplegic patients' gait initiation patterns.* **Bensoussan L, Mesure S, Viton J-M, Delarque A.** s.l. : J Rehabi Med, 2006, Vols. 38:287–94.

138. *Relation between gait speed, knee muscle torque and motor scores in post-stroke patients.* **Lindmark B, Hamrin E.** s.l. : Scand J Caring Sci, 1995 , Vols. 9:195–202.

139. *Analysis of the clinical factors determining natural and maximal gait speeds in adults with a stroke.* **Nadeau S, Arsenault AB, Gravel D, Bourbonnais D.** s.l. : Am J Phys Med Rehab , 1999, Vols. 78:123–30.

140. *Anticipatory Postural Adjustments During Gait Initiation in Stroke Patients.* **Delafontaine A, Vialleron T, Hussein T, Yiou E, Honeine JL, Colnaghi S.** s.l. : Front Neurol, 2019, Vol. 10: 352.

141. *The effects of rate and sequence complexity on repetitive finger movements.* **Bove M, Tacchino A, Novellino A, Trompetto C, Abbruzzese G, Ghilardi MF.** s.l. : Brain Research, 2007, Vols. 1153:84-91.

List of publications

List of Papers

- Prada V, Schizzi S, Poggi I, Mori L, Gemelli C, Hamedani M, Accogli S, Maggi G, Grandis M, Mancardi GL, and Schenone A. Hand Rehabilitation Treatment for Charcot-Marie-Tooth Disease: An Open Label Pilot Study. Journal of Neurology & Neurophysiology. 2018, 9:3. doi: 10.4172/2155-9562.1000465.

- Prada V, Mori L, Accogli S, Rivarola M, Schizzi S, Hamedani M, Schenone A. Testing overwork weakness in Charcot-Marie-tooth disease: Is it true or false? J Peripher Nerv Syst. 2018 Jun;23(2):124-128. doi: 10.1111/jns.12270.

- Hamedani M, Prada V, Calamari ML, Flora GA, Salerno A, M, Grandis M, Tognetti P, Focacci A, Schenone A, Leonia V. Efficacy of Lower limb robot-assisted and traditional rehabilitation therapy in treatment of post-acute stroke patients. Manuscript submitted

- Raglio A, Panigazzi M, Colombo R, Tramontano M, Iosa M, Baiardi P, Molteni D, Baldissarro E, Imbriani C, Hamedani M, Pistarini C, Mancardi GL, Caltagirone C. The sonification approach to the hand rehabilitation in post-acute stroke patients: a multicentric randomized controlled trial. Manuscript submitted

Oral presentation for National and International Meeting

- Igor Bisio, Chiara Garibotto, Mehrnaz Hamedani, Fabio Lavagetto, Valeria Prada,Angelo Schenone and Andrea Sciarrone. Towards IoT-based eHealth Services: a Smart Prototype System for Home Rehabilitation. IEEE Global Communications Conference (GLOBECOM), Hawaii, USA, December 2019

- Mehrnaz Hamedani, Valeria Leoni, Paola Tognetti, Valeria Prada, Andrea Sciarrone, Igor Bisio, Fabio Lavagetto, Angelo Schenone. Innovazione tecnologica nel percorso neuroriabilitativo tramite sensori accelerometrici. Quale tecnologia per quale riabilitazione 2° edizione, Rom, Italy, Decembre 2019

- Mehrnaz Hamedani, Valeria Leoni, Valeria Prada, Susanna Accogli, Andrea Sciarrone, Igor Bisio, Fabio Lavagetto, Paola tognetti, Angelo Schenone. Developing of new sensors and computer systems for the tele-rehabilitation and remote evaluation of the rehabilitation process of patients with neurological diseases. WORKSHOP "INNOVATION IN REHABILITATION TECHNOLOGIES", Genova, Italy, May 2019

- Hamedani M, Brescia M, Chioggia S, Schenone A, Tognetti P, Leoni V. sclerosi multipla grave e trattamento robotizzato con erigo. National Meeting of Italian Society of Neurological Rehabilitation(SIRN), Trieste, Italy, April 2018

- Hamedani M, Calamari M, Flora G, Prada V, Schenone A, Leoni V. Efficacia del recupero dell'andatura nei pazienti con ictus post acuto tramite robot G-eo system e trattamento fisioterapico. National Meeting of Italian Society of Neurological Rehabilitation(SIRN), Trieste, Italy, April 2018

- Hamedani M, Abbruzzese G, Leoni V , Pelosin E , Schenone A , Bianchetti P. Screening e trattamento dell'incontinenza urinaria nei pazienti con malattia di Parkinson. National Meeting of Italian Society of Physical Medicine and Rehabilitation (SIMFER), Genoa, Italy, October 2017

- Hamedani M, Schenone Angelo, Vernazzano Dario, Leoni Valeria. La riabilitazione robotica con Erigo in pazienti affetti da sclerosi multipla grave, case report. National Meeting of Italian Association of Physical Medicine and Rehabilitation (SIMFER), Genoa, Italy, October 2017

Poster for National and International Meeting

- Valeria Prada, Mehrnaz Hamedani, Giulia Mennella, Alberto Polimone, Laura mori, Marina Grandis, Chiara Gemelli, Angelo Scenone. efficacy of a video game intervention in Charcot- Marie- tooth balance and gait training: a randomized single blind study. International Peripheral Nerve Society (PNS) Annual Meeting, Genoa, Italy, July 2019

- Hamedani M, Ceretto C, Germano M, Chioggia S, Prada V, Schenone A, Tognetti P, Leoni V.The effectiveness of Robot-Erigo to reduce the pain in patients with advanced MS(EDSS ≥7).PAIN SCIENCE IN MOTION III, International and Interdisciplinary Colloquium on Research Methodsin Pain Sciences.Savona, Italy, May 2019

- Hamedani M, Calamari M, Flora G, Prada V, Schenone A, Leoni V. Effectiveness of Lower limb robot-assisted and traditional rehabilitation therapy in treatment of sub-acute stroke patients. National Meeting of Italian Society of Physiotherapy (SIF), Milan, Italy, October 2018