Empowering patients in self-management of Parkinson's disease through cooperative ICT systems

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Abstract
The objective of this chapter is to demonstrate the technical feasibility and medical effectiveness of personalised services and care programmes for Parkinson's disease, based on the combination of mHealth applications, cooperative ICTs, cloud technologies and wearable integrated devices, which empower patients to manage their health and disease in cooperation with their formal and informal caregivers, and with professional medical staff across different care settings, such as hospital and home. The presented service revolves around the use of two wearable inertial sensors, i.e. SensFoot and SensHand, for measuring foot and hand performance in the MDS-UPDRS III motor exercises. The devices were tested in medical settings with eight patients, eight hyposmic subjects and eight healthy controls, and the results demonstrated that this approach allows quantitative metrics for objective evaluation to be measured, in order to identify pre-motor/pre-clinical diagnosis and to provide a complete service of tele-health with remote control provided by cloud technologies.

Keywords: Neurodegenerative motor disorders; Wearable devices; Inertial sensors; Patient's empowerment; Sustainable healthcare; Personalised healthcare; Early diagnosis; Remote monitoring; Parkinson's co-morbidities.

INTRODUCTION

The rapidly aging population due to increased life expectancy and a decline in fertility contribute to an older world where the number of persons aged 60 or over is expected to grow from 841 million in 2012 to 2 billion in 2050 (United Nations Population Fund [UNFPA] and HelpAge International, 2012). This demographic context is inducing both international and local communities to promote novel actions for guaranteeing that people age well and to investigate new strategies which are both economically and socially sustainable (Aquilano et al., 2012).
In this scenario, the active engagement of the elderly in the co-management of their health and well-being as well as in the treatment of their diseases, and the close cooperation with both clinicians and formal/informal caregivers, are key points in the development of novel and well-structured care paradigms.
New personalised services and care programmes able to empower patients in the management and treatment of their diseases in each phase according to their progress and to the level of their co-morbidities are needed.
For this purpose, and considering the growing interest of high-tech companies such as Apple, Samsung and LG in the healthcare industry, Information and Communication Technologies (ICTs) systems are investigated. The technological solutions have to be feasible, scientifically/technically effective, acceptable and sustainable, considering that the current healthcare system has to be improved both in terms of services provided and cost-effectiveness.
User-centred design techniques are mandatory in order to develop innovative technological solutions able to satisfy users' requirements and to provide efficient support to every stakeholder involved in the management of the disease.

Integration of mobile health (mHealth) applications, cooperative ICTs, cloud technologies and wearable devices can represent an optimal solution to empower patients to pursue healthy lifestyles and to manage their health and disease, in cooperation with their caregivers and professional medical staff, across different care settings, developing a health system aimed toward the home environment through the implementation of a remote control system and telemedicine service.

The overall aim of this chapter is to propose an innovative system able to support the neurologist for an objective, non-invasive and sustainable Parkinson's disease diagnosis, compared to the current practices. For this purpose a novel wearable ICT-based solution, equipped with inertial sensors, able to finely and objectively measure the motor performances both of patients with Parkinson's disease and subjects that show risk factors and related co-morbidities, is proposed. The technological instrumentation adopted, through its physical and measurement properties, is able to support the medical staff in diagnosis, overcoming the subjectivity and variability that currently affect the identification and assessment of the pathology, on the basis of typical semi-quantitative clinical scales.
Using the proposed system, the neurologist will be able to:

- identify the early worsening in motion skills of subjects in a preclinical phase of the disease, anticipating the diagnosis and pharmacological therapy, so as to delay the onset of the pathology, to slow down its development and eventually to reduce the number of patients in advanced stages of Parkinson's;
- accurately quantify the disease stage in patients with Parkinson's disease and to evaluate the response to pharmacological therapies, allowing a personalised monitoring and care service.

THE SOCIO-CLINICAL HYPOTHESES

The great impact of Parkinson's disease in the community in terms of well-being and costs leads to the characterisation and design of a personalised and pervasive care system able to favour the empowerment of patients in the management of their own disease as well as the optimisation of the national healthcare services. The system goal is the satisfaction of the patients' needs, both from a clinical and social point of view, extending their independence, not only through pharmacology therapies and assistance but also encouraging secondary prevention and self-care at home. In order to provide an adequate and useful healthcare system for PD management, three clinical and social hypotheses, suggested by expert neurologists, have to be taken into account:

- *HP1 – Subclinical latent phase:* In PD, latency between the beginning of the neurodegenerative process and the appearance of the typical motor symptoms of the disease is about five years (Fearnley & Lees, 1991; Morrish, Rakshi, Bailey, Sawle & Brooks, 1998; Marek et al., 2001; Brockmann & Berg, 2014), so the diagnosis is expressed when the disease is already widely developed. It is reasonable to assume that patients with Parkinson's (PwP) show a progressive worsening of motor skills over time that could be identified early exploiting new technologies. The demonstration of a subclinical motor decline and its improvement induced by levodopa administration are positive, reliable and low-cost tests to subsequently justify the execution of more invasive imaging techniques such as SPECT DATSCAN for the definitive early diagnosis of PD. In this way PD diagnosis could be anticipated 5–7 years earlier than it is now.
- *HP2 – Idiopathic Hyposmia:* Hyposmia is a PD co-morbidity in more than 95% of PwP (Ponsen, Stoffers, Wolters, Booij, & Berendse, 2010). Furthermore, in healthy subjects idiopathic hyposmia is associated with an increased risk of developing PD of at least 10% (Maremmani et al., 1991; Ponsen et al., 2004; Maremmani et al., 2012). Combining this information, subjects with hyposmia are supposed to be a convenient reference group in a pre-frailty state to test instrumentations and procedures for early diagnosis of PD.
- *HP3 – Pharmacological benefits:* Pharmacological therapies are essential to slow down the disease and to reduce the effects of its typical symptoms, so they are periodically assigned and modulated by clinicians according to the status of patients. Neuroprotective therapies give the best benefits when administered in the early stages of the disease, thus an adequate ICT instrumentation able to measure in a timely way the decline of motor performance could also induce the optimisation of the pharmacological therapies and their relative benefits.

These medical assumptions confirm the need to provide the clinical staff with novel and advanced technologies able to objectively support them for effectively measuring the metrics of PD, allowing an accurate diagnosis, at an early stage, and facilitating the modulation of both pharmacological treatment and therapeutic procedures.
The required ICT system has to be designed through appropriate acceptance criteria to properly fit the needs of the stakeholders involved; part of the care activities has to be moved from traditional healthcare facilities to patients' houses, with related benefits in terms of service efficiency, cost reduction and improvement of the quality of life (QoL), endorsing the implementation of a care system able to enhance the current one in a sustainable way.
The development of wearable devices based on inertial sensors, supported by reasoning capabilities of a cloud platform for data mining, are a concrete possibility to provide the clinicians with a novel and powerful system of diagnosis allowing the introduction of an innovative telemedicine service.

The aforementioned considerations point out the need to identify and to develop a care system that specifically examines personalised services and care programmes for Parkinson's disease, with a strong emphasis on the users' needs and their empowerment in the management of the pathology, also reducing the number of severe episodes and complications, supporting different levels of prevention.
The main objectives of the health system for PD care can be synthesised as follows:

- improvement of quality of life (QoL) for patients with Parkinson's (PwP), maintaining for longer the possibility of being independent, active and involved in the community and guaranteeing, at the same time, their safety and health and also reducing the burden of formal and informal caregivers that take care of them;
- engagement of the PwP in the co-management of the disease, encouraging secondary prevention and well-being outcomes, encouraging self-care and domiciliary services;
- support for clinical staff in objective diagnosis and monitoring of a large number of patients, minimising both intra-rater and inter-rater variability due to neurologist subjectivity in patients' assessment;
- implementation of a sustainable system able to reduce the economic impact of the disease on National Healthcare Systems (NHS).

In this chapter, an overview of Parkinson's disease, its incidence, motor and non-motor symptoms and its co-morbidities are presented. Then the ICT-based solution proposed for the development of a healthcare system for Parkinson's disease management, taking into account the technological background in order to contextualise the suggested system, is shown and detailed. A preliminary experimental test is described, defining requirements for recruitment, involved participants, experimental protocol and interesting features to extract for data analysis. Results of the experimentations are reported and discussed, concluding with considerations about the feasibility, expected impact and clinical-scientific and technological implications in the use of the proposed solution for PD care.

THE CLINICAL BACKGROUND: PARKINSON'S DISEASE AND ITS CO-MORBIDITIES

Parkinson's Disease (PD) is a common progressive neurodegenerative pathology which afflicts approximately one million US citizens (Parkinson's Disease Foundation [PDF], 2014) and more than 1.2 million Europeans (European Parkinson's Disease Association [EPDA], 2012). The estimated annual cost in the EU only is 13.9 billion euros and the number of patients is forecast to double by 2030 (Dorsey et al., 2007). The incidence of the disease increases with age, but an estimated 4% of people with PD are diagnosed before 50 years old and men are one and a half times more likely to have Parkinson's than women. Idiopathic PD is a complex disorder of unknown cause, a consequence of both genetic and environmental factors, characterised by a typical asymmetric onset. Pathology shows deficiency of pigmentated cells in the pars compacta of the substantia nigra; when the drop of cells containing neuro-melanin and producing neurotrasmitter of dopamine exceeds 60% there is a critical lack of dopamine in the forebrain, resulting in motor symptoms. The cardinal clinical features (Figure 1) are:

- **Tremor**: appearing in 70% of PD patients (Factor & Wiener, 2007), it is the most common symptom and at the beginning it usually involves one side only. The prevalent type is resting tremor that generally appears when limbs are not intentionally moved, when patient is sitting (typically a pill-rolling tremor of the hands, sometimes affecting lower limbs or jaw) or walking with arms dangling.

- **Postural Instability**: the loss of balance can often lead to falls. Significant impairments of postural reflexes usually occur about 6–10 years after the onset of the disease, while in early PD the posture may show a slight flexion of the neck or trunk with a slight lean to one side.
- **Bradykinesia and Hypokinesia**: slowness and decreased bodily movement are very disabling for patients with Parkinson's because they lead to delay in movements, frequent stops, fatigue and inability to perform dual tasks.
- **Muscular Rigidity**: the increase in muscle tone causes resistance to passive movement nearly equal in both agonist and antagonist muscles and generally uniform throughout the whole range of movement.

A combination of previous motor symptoms leads to walking with difficulty or complications as festination (rapid small steps taken to balance the forward shift of the centre of gravity) and freezing of gait (motor blocks in gait especially at the start, changing direction or moving in narrow places) which undermine subjects' autonomy and independence.

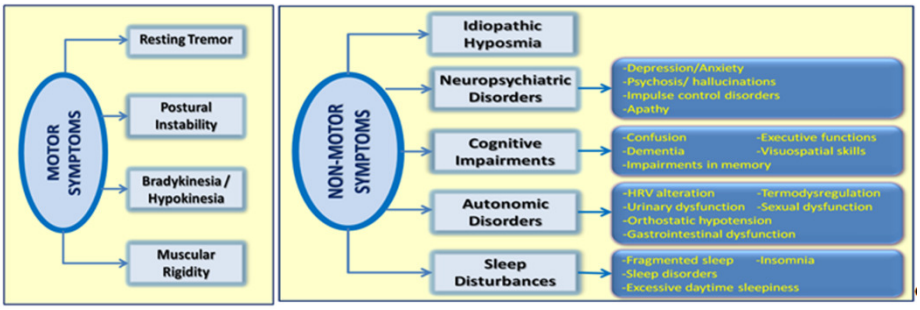

Figure 1: Motor (left) and non-motor (right) symptoms of Parkinson's disease

Although PD is typically diagnosed by means of motor symptoms, it is increasingly recognised that non-motor symptoms are also very frequent (Pahwa & Lyons, 2010; Hickey & Stacy, 1992; Chen, 2010) and can diminish patients' QoL (Soh, Morris, & McGinley, 2011), with a great prevalence in PwP of depression, anxiety, apathy, impulse control disorders, psychosis and cognitive impairments (Figure 1). These symptoms, often untreated (Lyons & Pahwa, 2011), can be very disabling and they have a very negative impact on patients' health-related quality of life (HRQOL) (Soh, Morris, & McGinley, 2011; Leentjens et al., 2008). In Italy, about 80% of PwP are cared for at home by family and this can lead to difficulties in the caregiver/patient relationship, due to the cognitive, psychological and behavioural disorders caused by the pathology and the burden and stress due to the assistance requirements of PwP.
The main non-motor symptoms are:

- **Depression**: occurring in about 50% of PwP, it can appear as loss of appetite, lack of motivation, slowed movement, slowed thinking or confusion and sleep disturbances. It has generally both psychological and organic origin, often requiring treatment with medication (Olanow, Stern, & Sethi, 2009), although counselling or other forms of psychotherapy can be helpful.
- **Anxiety**: nearly 40% of PwP fulfil criteria for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (e.g. generalised anxiety disorder, panic disorder and social phobia). Anxiety is often present 3–8 years prior to the development of the overt movement disorders (Gonera, Hof, Berger, van Weel, & Horstink, 1997) and usually co-occurs with depression. It appears generally through excessive worry, fatigue, concentration problems, sleep disturbance, restlessness, increased tremor and worsening motor function. Anxiety is related to the neurochemical changes in the brain and gets worse also with increasing disability.
- **Impulse control disorders**: they can occur in about 5–10% of PwP appearing in various ways such as pathological gambling, compulsive shopping, binge eating and hypersexuality. Impulse control disorders may lead to significant impairments in psychosocial functioning, interpersonal relationships, physical health and QoL.
- **Apathy**: this is a common condition in 40% of PwP, generally defined as a lack of motivation and manifested by reduced goal direction, with decreased social and emotional engagement. It is associated with more severe cognitive dysfunction and decreased performance in activities of daily living (ADL) (Starkstein et al., 2009).

- **Psychosis**: this is associated with older age and is typically a late feature of PD with a prevalence of 22% in PwP population. Common psychotic symptoms are hallucinations, illusions and paranoid delusions (Lee & Weintraub, 2012). Psychosis in PwP likely results from a complex interaction of medication exposure, PD pathology, aberrant REM-related phenomena and co-morbidity vulnerabilities.
- **Cognitive Impairments**: a mild cognitive impairment occurs in 19% to 38% of the PwP who do not have dementia (Litvan et al., 2011) and these defects are associated with poor QoL (Soh, Morris & McGinley, 2011). Cognitive deficits emerge especially in executive functions (e.g. information processing speed, impaired planning, working memory), visual-spatial deficits and divided attention. PD medications may actually worsen cognitive function, so it is important to tailor therapy in order to achieve motor control while minimising cognitive decline (Varanese, Birnbaum, Rossi, & Di Rocco, 2011).
- **Hyposmia**: this is a reduced olfactory sensitivity accompanied by poor perception of flavours which affects over 95% of patients with PD (Ponsen et al., 2010); it is observed independently from disease gravity and duration and it does not worsen with PD development. Idiopathic Hyposmia (IH) dysfunction in healthy adult subjects is associated with an increased risk of developing PD of at least 10% (Ponsen et al., 2010; Maremmani et al., 2012).
- **Autonomic dysfunctions**: **Orthostatic hypotension** is the most common cardiovascular feature in advanced PD (Lyons & Pahwa, 2011), involving 30–58% of PwP (Goldestein, 2006). It appears as a drop in systolic and diastolic blood pressure when rising from a lying down or sitting position to a standing position. It presents with dizziness, light-headedness, cloudy thinking, generalised weakness, or syncope and it can be related to poor intake of fluids, side effects of general medications (e.g. anti-hypertensives), or other medical conditions (e.g. cardiac dysfunction and/or autonomic nervous system). **Thermodysregulation** has been reported in up to 64% of PwP and involves intolerance to cold and heat, as well as excessive sweating (Swinn et al., 2003). **Heart Rate Variability alteration**: HRV is the oscillation of the heart rate in a series of successive heartbeats for a variable period of observation. HRV reveals differences between untreated PwP and healthy controls (Kallio et al., 2002) with an attenuation in PD of autonomic activities and circadian rhythm of the sympathetic nervous system (Devos et al., 2003, Niwa, Kuriyama, Nakagawa, & Imanishi, 2011).
- **Sleep Disturbances**: these are seen in up to 98% of PwP (Lyons & Pahwa, 2011), and may manifest as sleep fragmentation, insomnia, excessive daytime sleepiness, altered sleep-wake cycle or rapid eye movement (REM), sleep behaviour disorder (RBD), and other sleep disorders (Varanese, Birnbaum, Rossi, & Di Rocco, 2011; Stacy, 2002).

THE TECHNOLOGICAL BACKGROUND

The state of the art concerning ICT systems to provide a complete service of care, including diagnosis and monitoring using integrated wearable devices, cloud computing platform and end-users' web and mobile applications has been analysed. A conspicuous ensemble of academic articles and patents dealing with the development of wearable technologies used for different purposes has been taken into account. In particular, devices in the prototype stage or already commercial products are utilised to faithfully reproduce and measure the movements of the human body.

In some cases attention is focalised on the detection of the hand movement and posture as well as on methods of gesture recognition exploiting wearable technologies, mainly in the shape of gloves such as the commercial examples represented by Cyber Glove (Vinjamuri, Crammond, Kondziolka, Lee, & Mao, 2009) or 5DT Data Glove (Huber et al., 2010). The devices are mainly featured by flex (Choi, 2011) and inertial sensors (Amma, Georgi, & Schultz, 2012; Niazmand et al., 2011; Vutinuntakasame, Jaijongrak, & Thiemjarus, 2011; Kim et al., 2011; Mera, Heldman, Espay, Payne, & Giuffrida, 2012) or a combination of these (Ali, Ambar, Jamil, Wahi, & Salim, 2012) and they are also employed to assist patients with movement disorders (Dai, Otten, Mehrkens, D'Angelo, & Lueth, 2013).

In particular, commercial solutions to be worn on the upper limbs are used in the study of Parkinson's disease such as the Parkinson's Kinetigraph (Griffiths et al., 2012), engineered to evaluate the distal bradykinesia; the Kinesia inertial ring (Mera et al., 2012), developed to analyse the tremor frequency; and the G-Link integrated accelerometer node, used to evaluate the symmetry of arm swing (Huang et al., 2012).

Several wearable solutions are used to carry out a postural analysis or for the evaluation of asymmetries, freezing and other typical impairments of the gait in patients with PD.

These devices generally exploit the features of the inertial systems, differing in the level of technological integration, making available the data of 3-axial accelerometers (Stamatakis, Cremers, Maquet, Macq, & Garraux, 2011) or a combination of accelerometers and gyroscopes (Sabatini, Martelloni, Scapellato, & Cavallo, 2005; Barth et al., 2011; Liu, Inoue, & Shibata, 2009; Mariani et al., 2010). The aforementioned studies applied the sensor systems to the extraction of parameters to assess the motor capabilities of patients with Parkinson's disease according to the analysis of exercises extracted from section III of the UPDRS (Fahn & Elton, 1987).
Commercial devices to be worn on the lower back or lower limbs are used and adapted within research studies such as the Xsens Motion Trackers (Moore, MacDougall & Ondo, 2008), the Physilog biomechanical analyser (Zampieri et al., 2010; Salarian et al., 2010), the Stride Sensor Bluetooth Smart gait analyser (Moore, MacDougall & Ondo, 2008), the postural analysers SwayStar (Visser et al., 2007) and DynaPort MiniMod (Mellone, Palmerini, Cappello, & Chiari, 2011).
In addition to the development of wearable devices applied in healthcare, industry and the scientific community have shown interest in computing systems for processing the sensor data so that they can be used by remote control through web-based telemedicine services. The most common approach is leveraging sensing technology to automatically evaluate the performance of specific motor tasks and collect data locally or on a remote server (Patel, Park, Bonato, Chan, & Rodgers, 2012). Usually these systems have to be used in a controlled environment, typically at home, especially with the emergence and spread of cloud platforms.
Presently there are European projects in progress or just finished focused on Parkinson's disease, which aim to develop a system of monitoring remotely, especially during daily activities.
DiPAR (DiPAR, 2010) project proposes a system to support clinical processes to diagnose PD and consists of a unique hand-held sensor (a sensor writing device on a recording table) and a relative software with an intelligent decision and support unit. PERFORM (PERFORM, 2008) project aims to develop a reliable tool that can remotely and wirelessly monitor the status of neurodegenerative disease patients. REM-PARK (REM-PARK, 2011) proposes the development of a Personal Health System (PHS) with closed loop detection, response and treatment capabilities for the management of PD patients. REM-PARK and TEMPUS-G (TEMPUS-G, 2008) aim to provide support through gait guidance systems able to help the patient in real time during their daily activities. SENSE-PARK (SENSE-PARK, 2011) aims to develop and validate a sensor information and data capture system of disease-relevant parameters in PwP daily life, including routine and leisure activities. CuPiD (CuPiD, 2011) project provides a home-based personalised rehabilitation tool for PwP, using biofeedback devices for the training of daily activities, Virtual Reality (VR) has external cues to avert freezing of gait (FOG) and training of its prevention. A further two projects about PD are actually in progress: NEUROTREMOR (NEUROTREMOR, 2012) and NEUWALK (NEUWALK, 2012), which use implantable neuroprothesis for neurostimulation and neuroprosthetic systems.
The easy access to information made available by the web/cloud platform as well as the diffusion of smart and mobile devices led to the growth of Mobile health (mHealth) applications, a term used for the practice of medicine and public health supported by mobile devices. In fact, more than 97,000 mobile apps are available for health and fitness, with 52% of smartphone users gathering health information (COMMCREATIVE, 2014). To date the top 10 mobile health apps generate up to four million free and 300,000 paid downloads per day (Verasoni Worldwide, 2012) and by 2017 it is expected that 50% of smartphone users will have downloaded mHealth applications (Mobile Marketer, 2013).
The rising popularity of mHealth apps leads to a large number of downloads: 50 million for weight loss, 26.5 million for exercise, 10.5 million for women's health, 8 million for sleep and meditation, 7.5 million for pregnancy, 6 million for tools and instruments and 18 million for other topics (Verasoni Worldwide, 2012).
Also doctors recommend the use of mHealth applications: 40% of physicians believe mHealth technologies can reduce the number of visits to clinicians' offices; more than 25% of physicians are using mobile technology to provide patients' care; 80% of physicians use smartphone and medical apps; 93% of physicians believe that mobile health apps can improve patients' health; 93% of physicians find value in having a mobile health app connected to Emergency Health (Points Group, 2014).

DESCRIPTION OF THE SYSTEM

The ICT system necessary for the provision of an exhaustive and satisfactory care service for PwP in terms of screening, (early) diagnosis and monitoring, is based on the development of modular and wearable technologies and a cloud infrastructure for data management. The wearable devices able to finely and

objectively measure the PwP biomechanical performance consists of smart inertial units mainly composed of a microcontroller and an inertial measurement unit (IMU), individually used or in properly coordinated synchronous networks. In particular, the combined use of these units gives origin to modular and wearable sensorised devices adaptable to different parts of the body.
The aim of the adopted technological solution is to measure parameters related to the movement of hands and feet (e.g. tapping motor tests), to extract gait indexes, to quantify the tremor linked to the pathology and to carry out a postural analysis. The inertial units are worn on the last phalanx of the fingers (finger unit) and on the wrist (control units) which coordinate the sensorised network through a wired communication based on the CAN-BUS protocol (Figure 2):

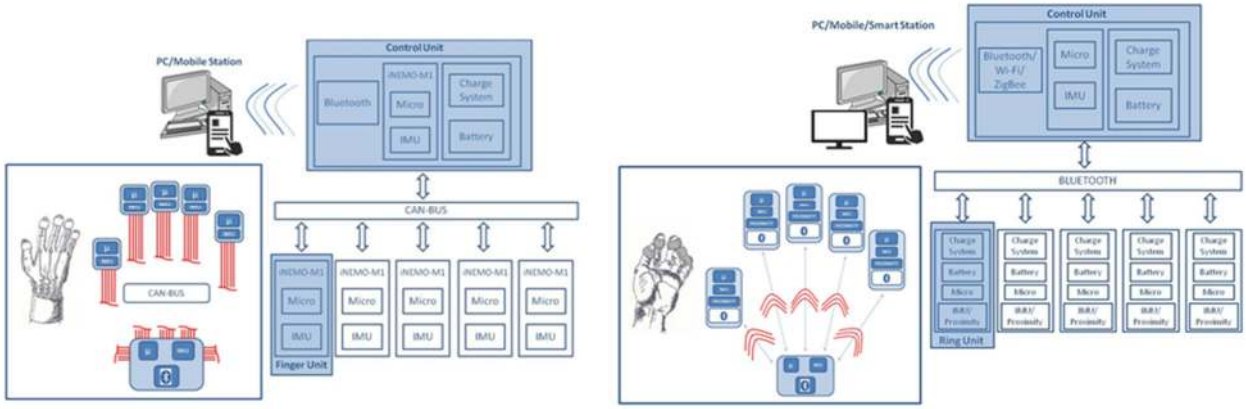

Figure 2: Block diagram of the hand-wired device (left) and of the wireless wearable version (right)

The core of the device is represented by the iNEMO-M1 system on board (STMicroelectronics, Italy) placed on each one of the finger units and on the coordinator; this Micro Electro-Mechanical Systems (MEMS) incorporates a Cortex-M3 family microcontroller and complete 9-axis inertial system composed of a 3-axis accelerometer, a 3-axis gyroscope and a 3-axis magnetometer necessary to characterise all the hand's degrees of freedom (DoF). Sensor data are acquired at high sampling frequencies of working and sent through a Bluetooth standard towards a PC or mobile station for post analysis; the system is powered through an embedded rechargeable battery and relative charge module.
An advanced ICT solution is represented by a device composed of smart inertial and wireless rings (Figure 2) which substitute the finger units and the cable connections, increasing the wearability and modularity of the technology.
The sensorised rings are complete and autonomous inertial systems with a small dedicated rechargeable battery, a power management module, a microcontroller, a IMU (i.e. MPU-9250 Nine-Axis MEMS MotionTracking Device, Invensense, United States) and a RF module such as a Bluetooth technology class-2 module (i.e. SPBT2632C2A, STMicroelectronics, Italy); Furthermore, other sensors are present (temperature, proximity/gesture recognition, force sensors) able to provide aggregated data, improving the characterisation of the patients' motor performances. The Bluetooth wireless network is established through the constitution of a piconet computer network which allows one master device to interconnect with up to seven active slave devices. The coordinator placed on the wrist can assume the role of master and it is also featured with a ZigBee and Wi-Fi module to establish a connection and data exchange with different control stations such as a PC unit, mobile phones, or smart devices increasingly spread in the global market.
To analyse the subjects' lower limb motor parameters a wireless network, similar to that of the hand, is established appropriately placing the inertial units on the instep (Figure 3) through small bands, or directly in the shoes; this sensor network is composed of two nodes, one for each foot, capable of measuring the PwP gait and foot-tapping performance and equipped with the same technological features of the sensorised rings: an embedded battery and a rechargeable system, a microcontroller and relative IMU, a Bluetooth module, proximity and force sensors. The coordinator of the network and master of the piconet, whose task is to make available the collected sensor data, can be an external dongle or one in the foot unit.

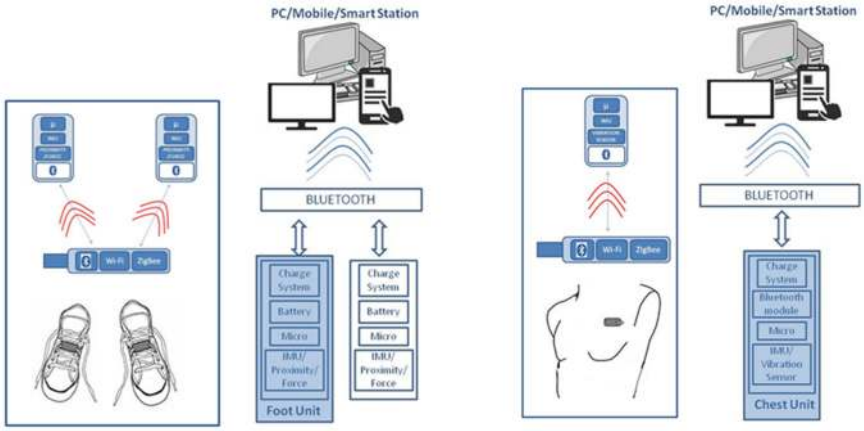

Figure 3: Block diagram of the foot-wearable device (left) and of the analyser posture device (right)

An inertial unit can be adapted also for a postural analysis (Figure 3), incorporating the electronic components within a chest strap or brooch exploiting the 9-DoF system onboard for 3D space orientation. This simple device is very useful considering the PwP inability to identify an incorrect posture that can be avoided through the inertial backhoe and a vibrational feedback-type.
The sensor data collected are analysed to objectively measure the motion parameters related to tasks extracted from section III of MDS-UPDRS (Goetz et al., 2008), typically evaluated in a semi-quantitative and subjective way by the neurologist, conducting an accurate post analysis both in the spatiotemporal and frequency domains.
The reasoning algorithms capable of aggregating data, extracting information and quantitative index meaningful for PwP are available through the use of web applications. In order to provide a wide range of access to the service the potentiality of a cloud computing platform is exploited considering its three fundamental layers:

- Data-Layer, for the storage of information collected from different devices.
- Core-Layer, for data processing.
- Presentation-Layer, for data visualisation.

Filtering (Butterworth, high-pass, low-pass, attitude and heading reference system – AHRS), extraction of relevant information, data mining and inference of metadata are necessary actions to drive the cloud database (DB) represented by the Data-Layer.
The web-based service ensures the possibility of spreading the care service across different settings, transferring part of the assets from the healthcare facility to the patient's home through efficient remote monitoring.
The outcomes of the reasoning algorithms made available by the cloud infrastructure are remotely accessible for all the stakeholders involved (PwP, medical staff, formal and informal caregivers) through the design and implementation of dedicated web interfaces. The improvement of the quality and effectiveness of the healthcare service as well as the empowerment of the PwP in the self-management of the disease is also favoured by the development of mHealth application for mobile devices, without increasing the cost for the care service.
The ICT system (Figure 4) is completed by the use of smart devices (e.g. smartphones and smart-TV) which allow immediate and direct data access also on the move, the timely diffusion of useful information (i.e. pharmacological prescriptions and changes in the therapy) and healthy guidelines, the counsel of a personal psychological and cognitive diary and the enjoyment of personalised video-assisted rehabilitative training in a customised care service.

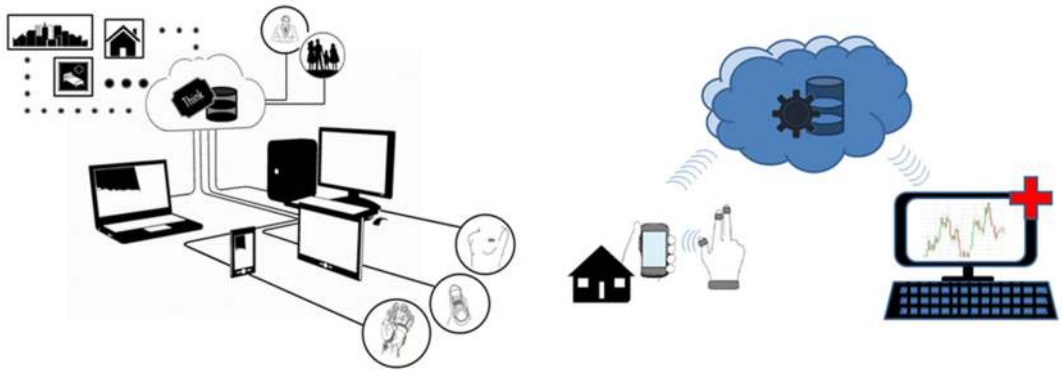

Figure 4: The ICT system: wearable and smart devices, cloud platform and mHealth applications

CLINICAL EXPERIMENTATION

An accurate experimentation based on the clinical hypothesis described in section 2.2 has been carried out in the healthcare facilities of ASL1 Massa and Carrara (Tuscany region, Italy) in order to validate the utility of the wearable instrumentation as a novel means of objective support for PD diagnosis. Inertial units were worn to analyse the biomechanical performances of three different groups of subjects:

- patients already suffering from Parkinson's disease with different degrees of severity;
- people suffering from idiopathic hyposmia as pre-clinical test to validate the method of early diagnosis;
- healthy subjects of control as a term of reference for the extraction of significant indices or thresholds.

Recruitment of Patients

In the following sections, the results of the biomechanical analysis of a sample of 24 subjects, extracted from the study conducted at the ASL1, are presented. This sample is able to show the differences between PD patients, IH subjects and healthy controls.
The sample is composed of eight patients suffering from PD (five male and three female, mean age ± SD, 70.4 ± 5.7 years), eight subjects with idiopathic hyposmia (six male and two female, mean age ± SD, 65.5 ± 4.3 years) and eight healthy volunteers as a control (six male and two female, mean age ± SD, 65.9 ± 2.8 years). All PwP were in the on-medication state before and during the experiments. Exclusion criteria were impairments or diseases other than PD that could affect the performance of daily activities (i.e. neurological or orthopaedic problems). The studies' procedures received the approval of ASL1 Massa and Carrara Ethics Committee (n°1148/ 12.10.10).

Clinical Assessment

Patients attending the study were firstly evaluated by a neurologist by means of clinical semi-quantitative scales typically used for PD assessment such as MDS-UPDRS, for a general evaluation of the disease, Hoehn–Yahr scale (HY) for identifying disease stage, progress and disabilities (Hoehn & Yahr, 1967) and Schwab & England scale (S&E) for assessing a person's ability to perform daily activities (Schwab & England, 1957) as reported in Table 1:

Clinical Characteristics of PD Patients	**Mean±SD**	**N°**
-Disease stage (HY):	2.4±1.1	8
Very Early (HY 1)		2
Early (HY 2)		2
Moderate (HY 3)		3
Advanced (HY 4)		1
-Activity limitation (S&E%)	82.5±18.3	8
-Disease Severity:UPDRS (total)	31.3±18.0	8
-MDS-UPDRS III (motor section)	15.0±10.2	8

Table 1: Scores assigned to PD patients in relation to clinical evaluation scales

The eight PD patients present in this study were almost equally distributed in the four stages of the HY scale, with a very good level of autonomy in performing daily activities represented by the value of S&E scale (82.5% on 100.0%). The moderate values assigned in total UPDRS scale and in the motor section (section III) of the MDS-UPDRS scale showed an average good condition of the examined people.

Experimental Protocol

According to the neurologist and to MDS-UPDRS scale, an experimental protocol composed of thirteen exercises (six for lower limbs and seven for upper limbs motion analysis) was proposed to analyse the motor skills of the subjects who attended the study. A short preliminary training to try all required movements was granted to every subject.

Exercises Description

During the trial session, subjects assumed a comfortable and standardised sitting posture holding right angles between trunk and thigh (at the hip) and between thigh and shin (at the knee). For each exercise a beginning specific fixed position was established to permit a static acquisition to calibrate every trial. The exercises had to be performed for 10 seconds (except for gait and rotation) as quickly and as widely as possible. The exercises are described as follows:

- *Heel Tapping, Toe Pin (HTTP)*: the subject taps their heel on the floor always keeping the forefoot in contact with the ground.
- *Toe Tapping, Heel Pin (TTHP)*: the subject taps their toe on the floor always keeping the heel in contact with the ground.
- *Heel-Toe Tapping (HETO)*: the subject taps alternately their heel and their forefoot on the floor.
- *Heel Tapping (HEEL)*: the subject taps their heel on the floor always keeping the forefoot raised from the ground.
- *Rotation (ROTA)*: the subject has to stand still with arms alongside them both at the beginning and at the end of the cycle. The subject turns in clockwise/anticlockwise direction for 360°. The rotation is performed in clockwise direction, with right foot sensorised and in anticlockwise direction with left foot sensorised.
- *Gait (GAIT)*: the subject begins the gait with non-sensorised foot and they walk 15 metres in a linear way until they reache a finish line. The subject has to walk in the most natural way they can at their preferred velocity.
- *Thumb-Forefinger Tapping (THFF):* the subject is directed to keep the hand fixed on the desk, so that the plane between thumb and forefinger is parallel to the table. In the starting position, the thumb and the forefinger are in contact, then the subject taps the forefinger against the thumb.
- *Thumb-Middle Finger Tapping (THMF)*: the subject is directed to keep the hand fixed on the desk, so that the plane where the thumb and middle finger join is parallel to the table. In the starting position, the thumb and the middle finger are in contact, then the subject taps the middle finger against the thumb.
- *Forearm Pronation-Supination (PSUP)*: the subject is asked to put the sensorised arm outstretched in front of him, with the wrist stable, the hand in prone position. The prono-supination movements have to be performed in parallel to the floor.
- *Hand Opening-Closing (OPCL)*: the subject is directed to flex the arm at the elbow that is fixed on the table keeping the palm of the hand in front of them. Subject has to alternately open and close the sensorised hand, holding the forearm and the wrist fixed.
- *Rest Tremor (REST)*: the subject is directed to put the sensorised hand on the table in prone position, with the elbow on the table. They remain in rest position for the whole duration of the exercise keeping the hand fully relaxed (they must not contrast the eventual tremor).
- *Postural Tremor (POST)*: the subject is directed to put the sensorised arm outstretched in front of them with wrist stable, the hand in prone position and the fingers outstretched approximately 1 cm apart from each other. They remain in rest position for the whole duration of the exercise.

- *Swing Arms (ARMS)*: the subject walks in the most natural way they can at their preferred velocity for 15 metres in a linear way.

Extracted Features

For every motor exercise that subjects performed, some biomechanical parameters, such as frequency, amplitude and velocity of the movements are measured (Table 2). The tasks proposed by MDS-UPDRS scale could be thus evaluated in an objective way by means of the assessment of these features, avoiding the subjectivity of medical judgment.

Ex.	**Biomechanical Features**
HTTP	-Heel frequency (taps/s) and Number of taps; -Heel angle (deg): angle between the ground and the sole corresponding at the moment in which only the toe contacts ground and the heel reaches its highest position; -Variability in amplitude and in frequency; -Energy expenditure; -Number of hesitations.
TTHP	-Toe frequency (taps/s) and Number of taps; -Toe angle (deg): angle between the ground and the sole corresponding at the moment in which only the heel contacts ground and the toe reaches its highest position; -Variability in amplitude and in frequency; -Energy expenditure; -Number of hesitations.
HETO	-Toe frequency (taps/s); – Heel frequency (taps/s); – Heel-Toe frequency (taps/s); -Number of taps; -Heel angle (deg): angle between the ground and the sole corresponding at the moment in which only the toe contacts ground and the heel has reached its highest position; -Toe angle (deg): angle between the ground and the sole corresponding at the moment in which only the heel contacts ground and the toe has reached its highest position. -Variability in amplitude and in frequency; -Energy expenditure; -Number of hesitations.
HEEL	-Average power of Power Spectral Density; -Fundamental frequency; -Maximum peak in signal power; -Energy expenditure.
ROTA	-Rotation time (s): time spent to cover 360°; -Number of strides in a rotation of 360°; -Rotation frequency (strides/s); -Stance time (s): time during rotation in which the sensorised foot contacts the ground; -Relative stance (%): ratio between stance time and rotation time.
GAIT	-Gait time (s): time spent to cover 15 metres; -Number of strides in 15 metres gait; -Gait frequency (strides/s); -Stride time (s): time from initial contact of one foot with the ground to the next initial contact of the same foot with the floor; -Swing time (s): period of stride time when the foot is not in contact with the ground; -Stance time(s): period of stride time when the foot is in contact with the ground; -Relative stance (%): ratio between stance time and stride time. -Angular excursion (deg): angular range covered by the ankle in the sagittal plane during a stride.
THFF	-Number of taps and frequency (taps/s); -Amplitude (deg) of index finger movement; -Opening and closing velocity (deg/s) of the forefinger; -Variability in amplitude and in frequency; -Number of hesitations;

	-Energy expenditure.
THMF	-Number of taps and frequency (taps/s); -Amplitude (deg) of middle finger movement; -Opening and closing velocity (deg/s) of the middle finger; -Variability in amplitude and in frequency; -Number of hesitations; -Energy expenditure.
PSUP	-Number of rotations and frequency (rotations/s); -Amplitude (deg) of the movement; -Velocity (deg/s) in supination and pronation movements; -Variability in amplitude and in frequency; -Number of hesitations; -Energy expenditure.
OPCL	-Number of movements and frequency (movements/s); -Amplitude (deg) of the movement; -Opening and closing hand velocity (deg/s); -Variability in amplitude and in frequency; -Number of hesitations; -Energy expenditure.
REST	-Signal Power; -Fundamental Frequency (Hz); -Power in tremor frequency band.
POST	-Signal Power; -Fundamental Frequency (Hz); -Power in postural frequency band.
ARMS	-Swing frequency (movements/s) and number of oscillations; -Amplitude (deg) of the movement; -Front and back arm velocity (deg/s); -Variability in amplitude and in frequency; -Energy expenditure.

Table 2: Extracted Biomechanical Features

RESULTS

The extraction of features from the motor exercises took place through the implementation of algorithms for event detection that allowed segmentation of the inertial signals acquired by the sensor devices and calculation of the biomechanical parameters of interest for the analysis of the motion. Digital filters to eliminate high-frequency noise, threshold algorithms and signal integration were applied to conduct the analysis in the spatiotemporal and in the frequency domains to obtain the parameters of interest.
The results of the performed experimentation demonstrate the technical feasibility of the system to measure clinical parameters according to neurologist evaluation and MDS-UPDRS assessment. In particular, the system was able to distinguish and classify the investigated subjects based on their group identity and, for the PD patients, based also on the level of their pathology.

Biomechanical Assessment

An appropriate statistical analysis (univariate ANOVA analysis between three groups, $p<0.01$) allows selection of the most significant parameters in distinguishing the groups with great sensitivity, specificity and overall accuracy. The parameters that best describe differences in groups can be combined in the Principal Component Analysis (PCA) which represents the distribution of the subjects in the space of the PCs. Single analysis has been conducted for each limb and each side, to emphasise the differences in every case (Figure 5), considering Parkinson's disease onset is typically asymmetric and it often involves one side or one limb only.
Patients with Parkinson's disease and healthy controls are reasonably placed in different regions of the space

and easily separable, while subjects affected by idiopathic hyposmia are irregularly distributed, matching in some cases with the 'healthy zone', according to clinical hypothesis HP2, whereby only about 10% of IH subjects will develop the pathology.

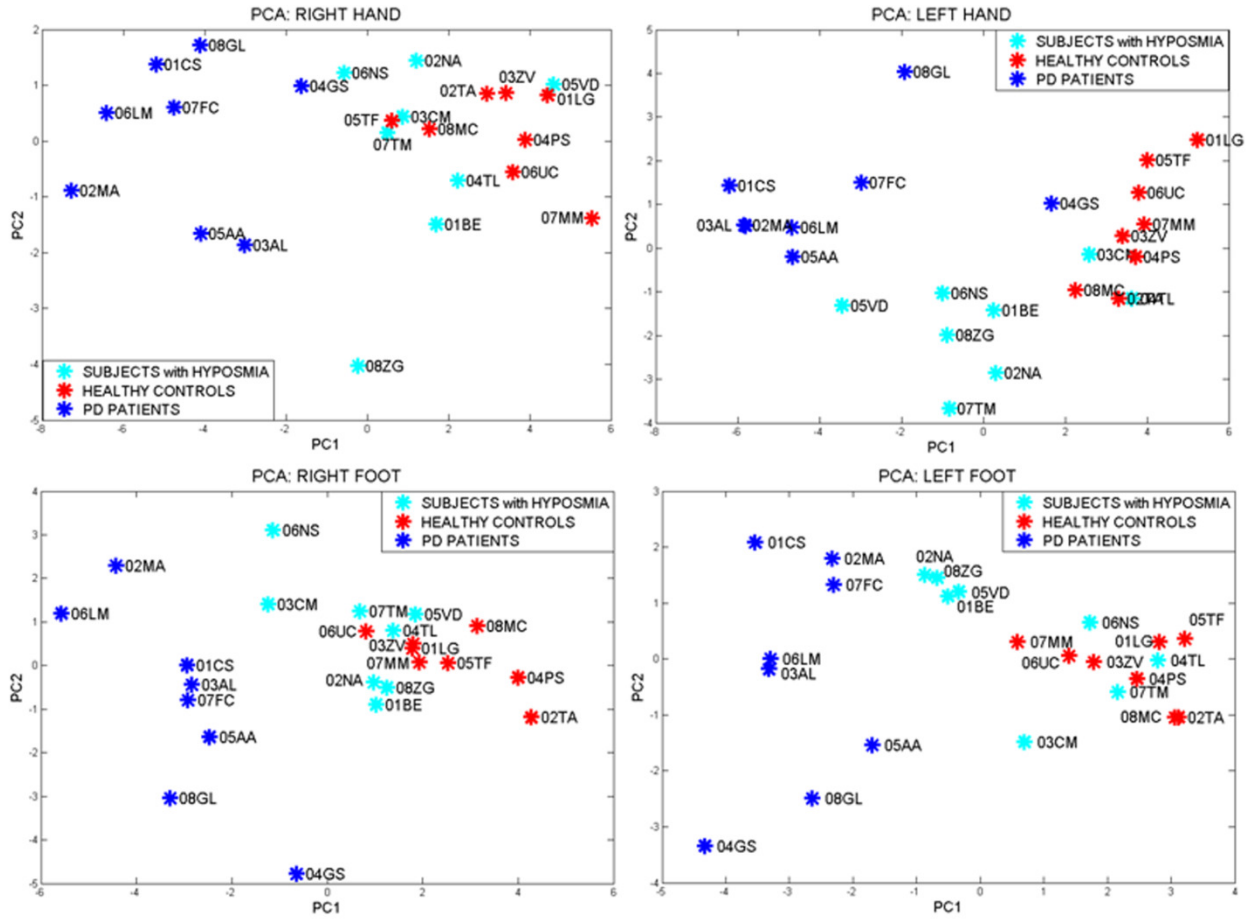

Figure 5: Results of motor performances of the three examined groups were summarised through PCA: healthy volunteers of control in red, PD patients in blue and subjects affected by idiopathic hyposmia in cyan blue

Correlation to Clinical Assessment

A statistical correlation between the clinical scores assigned subjectively to PD patients by the neurologist and the quantitative outcome measures of their motor performances obtained by the wearable devices can be performed through a multiple linear regression analysis. To demonstrate the effectiveness of the system to measure in a subtle way, and according to the clinical assessment, the level of impairment due to the pathology, single items of MDS-UPDRS III (motor section) are taken into account. The medical evaluations of those items are compared with the values of the related biomechanical features extracted. Parameters highly correlated one to each other (Pearson's correlation coefficient analysis) are excluded from the regression. The analysis results being in high correlation between sensor assessment and clinical evaluation (Table 3) show that the system is able to assess patients with Parkinson's disease in the various stages of development.

Single Items	Multiple R
Leg agility	0.95
Gait	0.95
Finger tapping	0.97
Hand opening/closing	0.99
Forearm pronation/supination	0.95
Postural tremor	0.92

Rest tremor amplitude	0.62
Rest tremor continuity	0.71

Table 3. Correlation to single items of MDS-UPDRS III

Clinical Scales	Multiple R
MDS-UPDRS III	0.99
MDS-UPDRS I–IV	0.99
Hoehn & Yahr	0.99
Schwab & England	0.99

Table 4. Correlation to clinical scales

For the items of MDS-UPDRS III which show a wide correspondence with the exercises proposed in the experimental protocol (e.g. finger tapping, hand opening/closing, leg agility) the multiple R is very high ($R>0.92$), specifying a very large correlation.

For other items of MDS-UPDRS III (e.g. postural instability, posture) the correlation is not so obvious due to methodological differences between the clinical evaluation of the neurologist and the outcomes of the instrumentation; however, also in this case the data from the wearable devices can be considered as an additional support to the medical diagnosis integrating or simplifying the medical protocol. Furthermore, other exercises not included in the typical neurological examinations have been proposed in the experimental protocol allowing the identification and quantifying of some relevant impairments in the motor skills of patients that nowadays are not evaluated in a specific way.

Finally, the overall comparison between statistical significant extracted parameters and assessment based on clinical scales such as MDS-UPDRS, Hoehn & Yahr and Schwab & England show a very high correlation (≥ 0.99), confirming the ability of the system to accurately evaluate clinical parameters (Table 4).

DISCUSSIONS

The opportunity to objectively and quantitatively measure the motion capabilities of upper and lower limbs in patients with PD and people at risk to develop the pathology with the solution promoted in the chapter, evidently represents an innovation from the clinical-scientific point of view. The accurate properties of measurement of the proposed devices allow detailed values to be provided representative of motion performances of the examined subjects in terms of amplitude, velocity, frequency, variability and other parameters, providing the neurologist with a reliable instrument of assessment, able to support them in diagnosis of the pathology and its level of progression. The proposed solution allows the identification of small variations in performance that are not visible to the clinician during typical neurological examinations. The PD diagnosis can be anticipated in a pre-motor phase, currently not identifiable, allowing early detection of the pathology and, consequently, a promptly therapeutic intervention, 5–7 years earlier than usual, with great benefits and efficacy in disease treatment. The timely neuroprotective therapy should delay the onset of the disabling symptoms of PD, slow down the progression of the pathology and reduce those factors for patients in advanced stages of the disease which are related to poor quality of life and continuous assistance. The possibility to objectify the measurement of motion exercises proposed in the MDS-UPDRS III scale, defining a novel method of assessment for the motor symptoms of PD, and the opportunity to store the acquired data from patients in a type of archive containing the information for each patient, can induce a consistent reduction in the variability which currently affects the classical neurological examinations for PD. At present, indeed, motion evaluations are subjected to intra-rater variability, caused by following observations of a clinician on the same patient, and inter-rater variability, due to examinations of different clinicians on the same patient.

Finally, from a clinical-scientific point of view, the value of the proposed care system is considerable, promoting the research for the definition of a novel methodology and new protocols for PD diagnosis, as well as in a pre-motor phase, considerably reducing the use of invasive and highly expensive tests, and also providing a monitoring and assistance system, in healthcare facilities and at home, in order to enhance the

management of the pathology, improving also the relationship between patients and health professionals, and empowering the patients in the care process.
From a technical point of view, the ICT system described, composed of inertial modules, shows clear advances beyond the state of the art related to technologies currently used in PD assessment. The technological advantages of the wearable solutions proposed have many benefits: physical properties (i.e. miniaturisation, lightness and wearability, independence of physical build, independence of artefacts caused by the movement), properties of measurement (complete inertial system, repeatability and duration of the sensors, few calibration procedures, sensor data aggregation) and additional properties such as low-cost components, low power consumption and longer life thanks to the reduced liability to deterioration.
The integration of the wearable-tech, the cloud platform and the end-user interfaces based on web/mobile applications is the key to the provision of an effective ensemble of services tailored to the severity of the disease and the needs of all the stakeholders involved across various care settings.
The implementation of a platform based on cloud computing and web API facilitates the deployment of personalised, flexible and ubiquitous services to patients, caregivers and neurologists as well as the easy adaptation of user interfaces to reduce the difficulties encountered by users in fully participating in society. The amount of data gathered in different situations and locations will be managed and processed to derive clinically-relevant information; sensor data will be accessible, by the use of different standards such as ETSI SR 002 564 (applicability of existing ETSI and ETSI/3GPP deliverables to eHealth) and ETSI TS 102 747 (Personalisation and User Profile Management), and through responsive web/mobile apps that automatically adapt the user interface according to different parameters using adaptive interfaces going beyond Universal Design principles by addressing specific needs of PD patients through adaptive personalised interfaces.

Finally, the improvements due to the introduction of the integrated PD care system promoted in this chapter can be synthesised considering four key aspects:

- early diagnosis with biomechanical parameters;
- support to the clinician in objective diagnosis, minimising both intra-rater and inter-rater variability due to neurologist subjectivity, defining a database in which the measured performances of each patient can be stored;
- development of advanced wearable devices;
- integration of technological solutions (wearable devices, cloud computing platform, mHealth applications) aimed at the provision of a complete service to manage Parkinson's disease.

Economic, Social and Ethical Impact

The deployment of a pervasive healthcare service tailored towards the home environment, at the same time based on the strong and more efficient involvement of caregivers and clinical staff, can ensure the empowerment of patients in the management of PD. The methodology introduced in the early phases allows high acceptability and very low invasive early diagnosis for PD, which means an improvement of secondary prevention, increasing the potentiality of pre-treatment and maintaining future PD-related problems under control through the slowdown of the disease. The system of remote monitoring, support and PD management can ensure a qualitative and quantitative improvement of the care service and timely detection of the actual patient conditions (reduction of the signal-response time) through the technologies provided, but also improving the effectiveness of the therapy by means of a more efficient treatment (better understanding of disease evolutions for forecasting future conditions and programming visits or changes in therapy).
The expected clinical impact has a socio-economic counterpart with a net benefit both from the healthcare system and the patients' perspectives. The costs sustained by the national healthcare system (NHS) can certainly be reduced through a decrease in hospitalisations and in additional care expenditure, due to more compliance and therapy adherence.
Regarding the patients' and relatives' perspectives, a tele-monitoring service can reduce direct non-health costs (e.g. travelling for visits) and the waiting time for exams, both of which strongly impact the PwP's quality of life (QoL).
Patients could improve their role in the definition, organisation and self-management of the disease with a reduction in the stress and depression of relatives caused by the high psychological and physical effort in assisting them (reducing also the related costs of psychological support), and also an increase in the informal caregivers' productivity.

The physician and formal caregiver perspectives show not only an increasing efficacy and efficiency of care (i.e. increasing number of patients that can be daily monitored) but also the opportunity to manage more information not only about the treatments (prescriptions or changes in therapy), but also about the PwP's personal habits, with the opportunity to offer psycho-cognitive assistance by periodically suggesting healthy guidelines and behaviour.
The current annual costs in Italy of Parkinson's disease (about 250,000 PwP in Italy) for the national healthcare system (NHS) and society (Parkinson Italia, 2013; Epicentro, 2013) are reported in Table 5:

Stakeholders	Average cost (€) in Italy
NHS	1.1–1.3 billion
Society	2.2–2.9 billion

Table 5: Italian average annual costs of Parkinson's disease for NHS and society

The diffusion of a pervasive, secure and reliable remote care service is expected to reduce the costs of the national healthcare system by about 15–20%, as well as greatly improving the quality of life of PwP, giving them independence for longer and social inclusion.
Economic and social aspects must take into account the ethical issues related to patients' privacy and to the dissemination, processing and protection of personal data. The telemedicine service not only ensures access for everyone to preventive healthcare and the right to benefit from medical treatment (under the conditions established by national laws and practices) but also reinforces these concepts through a more efficient, safe and easily accessible care service ensuring respect for sex, race, colour, ethnic or social origin, genetic features, language, religion or belief, political or any other opinion, membership of a national minority, property, birth, disability, age or sexual orientation.

CONCLUSIONS

This chapter proposes an innovative technological solution to develop and sustain a novel care paradigm for patients affected by Parkinson's disease. The preliminary experimentation showed the feasibility and the scientific and technical effectiveness of a modular wearable sensor system for fine motor skills analysis and its usefulness for the assessment of objective metrics in diagnostic procedures of PD, recognising patients from other non-pathological or pre-clinical groups. The objectivity guaranteed from the system result is very useful in giving support to neurologists in the clinical diagnosis of PD through quantitative measures able to drastically reduce both intra-rater and inter-rater variability due to doctors' subjectivity in patients' assessment. The fine accuracy of the measurements also greatly encourages an early diagnosis of the pathology, in a pre-clinical stage, when the motor symptoms are not clearly manifested.
Furthermore, the proposed ICT solution opens several possibilities in the application of feasible personalised healthcare services, not only in well-structured facilities, but also in domestic environments, to support the remote monitoring of patients with neurodegenerative motor disorders. Indeed, being easy to use, low-cost and easily connectable to the cloud platform, it is particularly suitable for empowering patients to manage their diseases and thus to design new customised services that also encourage secondary prevention and well-being outcomes. The implementation of such a system is also able to reduce the economic impact of the disease both for national healthcare systems (NHS) and for patients and caregivers, improving at the same time the quality of the provided service. The possibility of a sustainable service that improves the quality of life of patients with Parkinson’s, maintaining for as long as possible their independence and active involvement in the community, guaranteeing their safety and also reducing the burden of formal and informal caregivers that take care of them, can be both a great clinical and economic advance in the treatment of the pathology.

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