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MHEALTH-BASED METHODS FOR NEUROMOTOR ASSESSMENT AND REHABILITATION

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"Una persona con disabilità ha mille e più ragioni per essere arrabbiata con la vita e quando accade nessuno ha il diritto di biasimarla. Però, posso dire con certezza che io senza le gambe ho scoperto di poter fare più cose di quante ne servono a riempire il tempo a disposizione e sono certo che sia così per tutti."

Alex Zanardi

"La salita, come la vedo io, è il mio territorio: ho la consapevolezza che quando sono in salita posso dettare le mie regole. Se sto bene, sono pericoloso e difficilmente qualcuno riesce a staccarmi."

Marco Pantani

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ABSTRACT

Recent years observed massive growth in wearable technology. A wearable device is basically a tiny computer with sensing, processing, storage, and communications capabilities. It may also include interfaces and actuation capabilities that provide feedback to the user. These technologies are prevalent in various fields: from wellness/sports/fitness to the healthcare domain. In 2011, the spread of this phenomenon led the World Health Organization to define the term 'mHealth' as "medical and public health practice supported by mobile devices, such as mobile phones, patient monitoring devices, personal digital assistants, and other wireless devices". mHealth apps appeared later, and they address a broad array of mHealth applications and the use of mobile phones, e.g., to monitor biological signals or support healthy lifestyles. Thus, mHealth apps allow mobile devices as healthcare systems: for prevention, assessment, therapeutic support, and rehabilitation of motor and non-motor functions. The deployment of mHealth can be achieved using the various sensors available inside smartphones (as a stand-alone system) or in conjunction with external wearable sensors (as an integrated system).

Furthermore, mHealth solutions are suitable to perform real-time wearable Biofeedback (BF) systems: sensors in the body area network connected to a processing unit (smartphone) and a feedback device (e.g., loudspeaker) to measure human functions and return them to the user as (bio)feedback signal.

During the COVID-19 pandemic, this transformation of the healthcare system has been dramatically accelerated by new clinical demands, including the need to prevent hospital surges and to assure continuity of clinical care services, allowing pervasive healthcare. Never as of today we can say that the integration of mHealth technologies will be the basis of this new era of clinical practice.

In this scenario, this thesis's primary goal is to investigate new and innovative mHealth solutions for the Assessment and Rehabilitation of different neuromotor functions and diseases (respectively, *Section II* and *Section III* of this thesis).

For the clinical assessment, there is a significant need to overcome the limitations of subjective clinical scales. Creating new mHealth solutions, this PhD thesis investigates the possibility of employing innovative systems for objective clinical evaluation. In addition, mHealth solutions also allow pervasive and self-administered systems, feasible in daily life situations [1]. In this perspective, the usability of the solutions proposed might be critical: it is essential to follow a User-Centered-Design (UCD) approach [2]–[4], also considering that fine motor skills issues (such as tremor) in persons with PD or older people may hinder their interaction with these wearable systems [5], [6].

This PhD thesis aims to clarify mHealth systems' impact in rehabilitation by developing and validating innovative solutions with BF capability. The design of such mHealth systems is challenging. In particular, the following points should be considered:

- The choice of the feedback variable/s (one or more), in accordance with the task [7];
- The sensory modality used for BF restitution: visual, auditory and/or verbal, somatosensory, or a combination of them (multimodal BF) [8];
- The design of accurate algorithms able to correctly and efficiently represent the BF variable in a way easy to learn and understand for the subjects [9];
- How to promote the motor learning process, developing an intelligent virtual trainer that can automatically switch the BF to overcome stagnation [8], [10];
- How to design a tailored rehabilitation approach, based on individual patient evaluation, clinical history, cognitive aspects, primary symptoms, patient's expectation, and medical knowledge.

Table 1 categorized each mHealth solution examined in this thesis. This work will describe solutions that need the supervision of a therapist in a clinical context compared to others that can be self-administrable in a pervasive way and require only a smartphone as a stand-alone system.

		Assessment	Rehabilitation	Supervised	UnSupervised Self-Adminstrable	Stand-Alone	Biofeedback Modality
mHealth systems	SA 1	X		X		X	-
	SA 2	X			X	X	*Audio & Haptic*
	SA 3	X		X			-
	SA 4		X		X		*Audio*
	SA 5		X		X		*Audio*
	SA 6		X		X		*Audio, Visual & Haptic*
	SA 7		X	X			*Feedback to Exoskeleton*

Table 1. Overview of the specific aims (SA) of this thesis. mHealth systems are organized according to their scope and relevant features. In green, the mHealth applications used for clinical assessment; in red, the mHealth applications used for neuromotor rehabilitation.

These specific aims (SA) are addressed in the following chapters:

SA 1 - Chapter 5: the Touchscreen Assessment Tool (TATOO) is an Android application (app) developed to assess hand skills essential for the interaction with a modern touchscreen. Aware that fine motor skills issues (such as tremors) in persons with PD or older people may hinder this interaction, it is crucial to have such a tool. This pilot study examines the feasibility of using the TATOO app to evaluate touchscreen ability in elderly individuals, also comparing it with traditional hand assessment tools (e.g., prehension strength and dexterity).

SA 2 - Chapter 6: developed three smartphone apps for self-administering an instrumented version of the 'Timed Up and Go' test (Self-TUG), the 'Standing tandem' test (Self-Tandem), and the 'Five times sit-to-stand' test (Self-STS). The apps were designed with an emphasis on ease of use for the target group. The apps are based on the same structure, and using inertial sensors of the smartphone, they can provide real-time audio- and haptic-feedback to guide the user during the test. The usability test of the apps was performed with target elderly groups.

SA 3 - Chapter 7: developed an ecological, obstructed walking paradigm to quantify the subjects' behavior while walking, avoiding vertical obstacles. With this walking paradigm, the aims are: explore differences in movement between subjects with Homonymous hemianopia (HH) and healthy controls; quantify the effect of the Audio-Visual Scanning Training (AViST) used to train subjects with HH to a better eyes-exploratory ability through a pre-post analysis.

SA 4 - Chapter 8: wearable sensing technology with mHealth system is a new way to deliver corrective feedback. It is highly applicable to gait rehabilitation for persons with Parkinson's disease (PD) because BF potentially engages spared neural function. During prolonged indoor walking, participants' motor adaptation to BF signaling a deviation from their normal cadence is characterized. When their cadence varied, they heard either intelligent cueing (bouts of ten beats indicating normal cadence) or intelligent feedback (verbal instruction to increase or decrease cadence).

SA 5 - Chapter 9: builds on the findings from **Chapter 8**. This study aimed to retrospectively compare the effectiveness of different BF variables to enhance the real-life locomotor performance of persons with PD. To this aim, the effectiveness of the feedback variables most frequently during a 6-week protocol for home-based rehabilitation is compared: Stride Length (SL), Gait Speed (GS), and Cadence (CAD). An exploratory analysis is performed to visualize long-term effects by showing how SL and GS changed along with the protocol.

SA 6 - Chapter 10: builds further on the findings of **Chapters 8** and **9**, this work presents an innovative system able to deliver multimodal BF during gait rehabilitation in PD subjects. The innovative nature of the mHealth solution that we are proposing here is that it lies in a multisensory approach, where visual and proprioceptive stimuli complement the auditory feedback. To achieve such multisensory feedback, we integrated the CuPiD system (shown in **Chapter 9**) with commercial smart glasses. We reported and described a specific Human-Centered testing phase.

SA 7 - Chapter 11: in collaboration with the Rehab Technologies - INAIL-IIT Lab, this proof of concept presents innovative smart crutches with an active, powered, and wearable lower-limb exoskeleton aiding and rehabilitating paraplegic patients' gait. Thanks to an Android app, two sensorized crutches communicate with a smartphone, worn on the chest with a belt, to estimate the trunk's and crutches' orientation in real-time.

The validity of the real-time orientation estimation of the crutches is tested using stereophotogrammetry as the gold standard.

Before presenting the Chapters described above, in *Section I*, an introduction and the theoretical background of this thesis are described:

- **Chapter 1** introduces the architecture of mHealth systems in the healthcare field;
- **Chapter 2** shows the main issues related to mHealth app development, together with the most common algorithms for orientation estimation;
- **Chapter 3** describes the mHealth sensors employed in this thesis and the techniques underlying unimodal and multimodal augmented Biofeedback (BF);
- **Chapter 4** reports the state-of-the-art of mHealth systems for the clinical assessment and neuromotor rehabilitation of elderly people (EP) and persons with Parkinson's Disease (PD).

Finally, in *Section IV*, a general discussion on this research project is reported.

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Section I - Introduction and Theoretical Background

Chapter 1

"Wearable Computing for Healthcare"

The evolution of mobile phones and electronic technology leads to continuous miniaturization, making the mobile phone a really wearable device. The use of mobile and wireless technologies to support health objectives can transform the face of health service delivery across the globe [1]. In 2011, the spread of this phenomenon had led The Global Observatory for eHealth of the World Health Organization to define the term 'mHealth' as "medical and public health practice supported by mobile devices, such as mobile phones, patient monitoring devices, personal digital assistants, and other wireless devices" [2]. In 2021, the number of smartphone users worldwide will grow to 3.8 billion, and today 45% of people in the world have smartphones [3]. This figure is up considerably from 2016 when there were 2.5 billion users, 34% of that year's global population [4]. Nowadays, mHealth reality is considered the biggest technological breakthrough, and its potential is increasing together with the utility of mHealth apps [5]. In particular, mHealth technologies are applicable for all stages of treatment in healthcare: from prevention to clinical evaluation and disease detection, moving on immediate care and rehabilitation solutions [6]–[8]. In the context of the on-going COVID-19 pandemic, these technologies have become more relevant than ever, thanks to the advantages they provide [9]. In fact, mHealth platforms, with appropriate information technology (IT) and health literacy, can empower patients to manage their condition better themselves [9]. For example, patients with diabetes can monitor their blood glucose through mobile apps improving both the quality of medical services and their safety [10].

In the following section of this introductive Chapter, a generic system architecture is presented to better understand mHealth components and workflow.

1.1 mHealth System Architecture

As a result of the growing demand for mHealth system, important research and development efforts have been carried out during the last years both by academia and industry in this area, driving great breakthroughs on enabler technologies, such as wireless communications, micro- and even nano-electronics, or sensing techniques and materials [11], [12]. Advances in microelectronics and wireless communications have made Body Area Networks (BAN), which represent the key functional component in a mHealth systems [6], [13]. BAN are composed of tiny smart sensors deployed in, on, or around a human body. These sensors are distributed on the human body consequently with the different physiological parameters or/and body function to measure. Thus, their location is an important aspect: it is possible to detect brain activity (Electroencephalography - EEG) using a sensor near the scalp, but locating the same sensor in a different place it is not possible. Finally, the sensors are connected with a portable processing unit, like a smartphone, to exchange information with clinicians and/or send it as feedback to the patient. Based on literature review,

we designed a schematic mHealth architecture, where the BAN are composed of various sensors properly located in the human body, **Figure 1**.

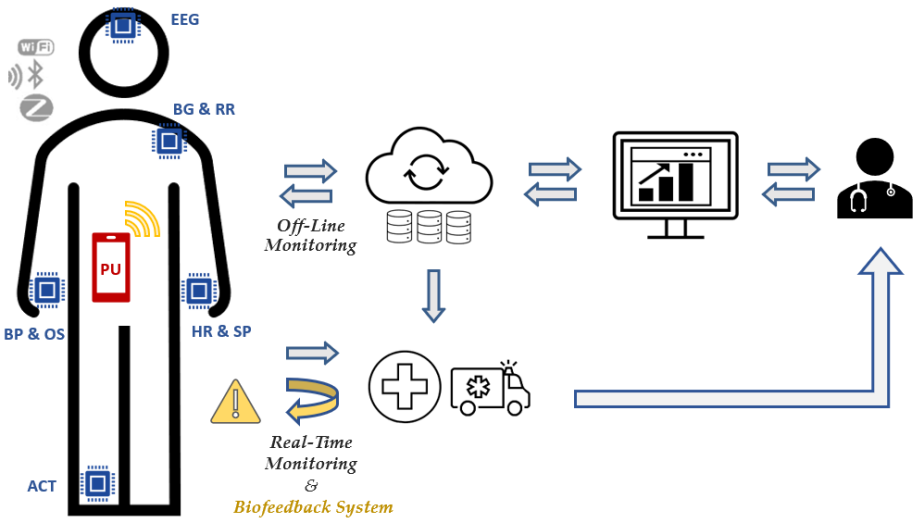

Figure 1. Schematic mHealth system architecture, adapted from [6], [13]–[15]. *PU (red)*, Portable Unit. List of sensors node *(blue)*: *EEG,* Electroencephalography; *BG*, Blood Glucose; *RR*, Respiration Rate; *HR*, Hearth Rate; *SP*, Skin Perspiration; *BP*, Blood Pressure; *OS*, Oxygen Saturation; *ACT*, Actigraphy.

Sensor Node

At first, we need to describe the sensor architecture or, better, the sensor node: a sensor network that is capable of performing some processing, gathering sensory information, and communicating with the data-logger present in the network [16], **Figure 2**.

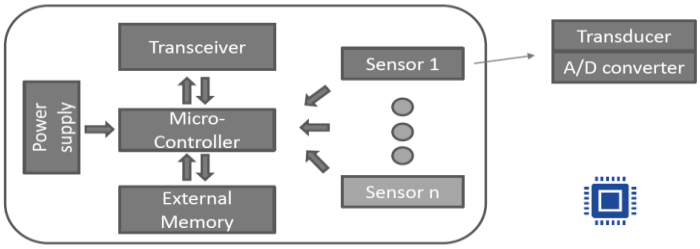

Figure 2. Schematic overview of a sensor node.

The main components of a sensor node are a microcontroller, transceiver, external memory, power source, one or more sensors, consisting of a transducer and A/D converter:

- *Transducer*: varies its electrical properties to varying environmental conditions. Usually MEMS technology (Micro Electro Mechanical Systems) ensures higher efficiency, lower production costs, and less power consumption than other types of sensors such as piezoelectric. However, depending on the application, a piezoelectric transducer can be more accurate: to analyze human movement in high dynamic tasks, it is common to prefer piezoelectric accelerometers [17], [18].

- *A/D Converter - Analog to Digital Converter*: converts the transducer's voltage value to a digital value. The A/D converter's resolution implies a quantization of the input: this necessarily introduces a small amount of error/noise. Furthermore, an ADC converts the input periodically, sampling the data: this limits the input signal's allowable bandwidth.
- *Micro-controller:* it manages and controls the hardware of the sensor node, can perform local online signal processing (filtering/amplify the signal, data fusion, feature extraction).
- *Transceiver:* it connects the sensor node to the network. It can be an optical or radio-frequency device.
- *External memory:* it is needed to store the program's binary code running on the sensor node.
- *Power supply*: source of power for communication (usually most affecting factor), sensing, and data processing.

Portable processing Unit (PU)

The portable processing unit (PU), also denominated as data-logger, is where all the information is gathered, containing the outputs and inputs of the mHealth system [6]. The communication between a node sensor and the data-logger is normally made through wireless protocols, avoiding loose wires around the body leading to a higher comfort and movement liberty. As **Figure 1** shows, PU can be a common smartphone with a custom application installed on it. PU can receive data from online monitoring devices and store it in a local memory. This two-way communication allows other devices to establish a wirelessly connection to a main device, which stores the data of several sensors. This system can also be helpful to label the timing of important events using external devices [13], [14], [19], [20]. The wireless protocols most popular in mHealth systems are Bluetooth, Wi-Fi, ZigBee and more recently LoRa (Long Range radio). Bluetooth is a short-range radio-frequency based connectivity between portables and fixed devices requiring low-power consumption and with a low-cost. It is widely implemented in commercial devices like smartphones and laptops. The new Bluetooth technology (version 4.0 and versions above) named Bluetooth Low-Energy (BLE) has even a lower power consumption with a smaller form factor. Wi-Fi protocol lower layers were adopted, allowing higher data throughput for low-power requirements applications, not as low as the Bluetooth technology but can also be a good connection protocol to use, mainly when a higher distance of communication is needed [6]. ZigBee is another technology used for low power and low data rate communication protected by the use of the Advanced Encryption Standard. This feature makes ZigBee ideal for medical applications because it can consume less energy than Bluetooth versions earlier than 4.0, but with a lower data transferring rate [6]. LoRa technology is a long distance coverage, low cost and low power consumption wireless protocol. According to Jeevan Kharel et al. [21] it is expected to overcome existing systems such as cellular technologies

in the near future. It has the disadvantage of low data rate, but a huge advantage of scalability and customization of several parameters such as frequency channel, transmission power and data rate.

Wireless Protocol	Max Range	Max Data Rate	Power Consumption
Bluetooth	100 m	1-3 Mbps	2.5 - 100 mW
Bluetooth Low-Energy - BLE	100 m	1 Mbps	10 mW
Wi-Fi	150-200 m	54 Mbps	1 W
ZigBee	100 m	250 Kbps	35 mW
LoRa	50 km	700 bps	LOW (customizable)

Table 1. Wireless Protocols main features. Source [6].

Table 1 summarizes some of the main features of these wireless protocols. Mobile telecommunications technologies can also be used to transmit real-time data. In the construction of a wearable device the communication protocol is very important in order to minimize the energy consumption [22].

Offline Monitoring

All data from vital signs can be stored in a portable unit (micro-SD memory card for example), for future use in medical analysis or just as a personal record. The data can be stored at the same time that a real-time monitoring is occurring. The main aim of such monitoring is to record vital data for clinic diagnosis and prediction by clinicians [6]. For example, sleep issues such as apnea, can be analyzed through saved data from the patient: a home sleep monitoring allows to monitor sleep in a familiar environment resulting in reliable data acquisition [20], [23]. Off-line monitoring allows a high level of data processing to give much more information that is valuable to the end-users and clinicians, for example, using data mining techniques to have more in-depth knowledge representation [23].

Real-Time Monitoring and Biofeedback System

With mHealth systems it is possible to perform clinical monitoring outside a medical environment, alert the patient in case of any physiological problem or monitor himself, and be updated on his vital signs during daily activities [14]. On the other hand, in a medical environment mHealth systems allows the patients monitoring inside the boundaries of a specific area, normally a Hospital, where the patients can move while their vital information is being wirelessly transmitted to a remote monitoring center and thus made available to clinicians [6]. These live systems can also be configured with a set of alarms for each patient helping in the detection of some required anomaly. The vital signs can also be recorded in Medical Information Systems to be later analyzed by clinicians [6], [13], [24]. However, the biggest advantage of mHealth systems in real-time

monitoring is the possibility of patient's monitoring at home and outdoors, using internet communications. This feature allows the patient to have a normal life while being monitored, with his vital signs continuously or intermittently transmitted to a remote monitoring center, with health support and, if needed, inform the patient of his medical status [6].

Furthermore, vital signs can also be transmitted to portable devices, such as smartphones and smartwatches, to visualize and analyze persons' health status, allowing the so-called Biofeedback (BF) process. BF is defined as *a process in which a system or agent accurately measures and feeds back, to persons and their therapists, information with educational and reinforcing properties about their physiological processes in the form of analog or binary, auditory, and/or visual feedback signals. The objectives are to help persons develop greater awareness of, confidence in, and an increase in voluntary control over their physiological processes that are otherwise outside awareness and/or under less voluntary control* [25]. With BF the information fed back to the patients adds or reinforces their physiological sensory channels: thus, BF was also defined as augmented feedback [26]. With such self-monitoring systems [6], clinicians must carefully teach patients how to use them at home, in particular, how to understand and react to BF alerts [25]. For example, this is what already happens in the treatment of type 1 diabetics' subjects. Several artificial pancreases have been developed to help manage type 1 diabetes [27], [28]. To obtain satisfactory results, the clinician's contribution to patient education is crucial [10], [29]. In the last decades, self-monitoring and BF systems were used in many areas such as instrumental conditioning of autonomic nervous system responses, psychophysiology, behavior therapy, and medicine, stress research and stress management strategies, electromyography, consciousness, electroencephalography, cybernetics, and sports [25]. Nowadays, thanks to mHealth and technological progress, BF systems will become more achievable.

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Section I - Introduction and Theoretical Background

Chapter 2

"mHealth Apps and Orientation estimation"

In this Chapter, we describe the principal issues related to mHealth apps' development and real-time algorithms for the orientation estimation.

2.1 mHealth Apps - Guideline

Healthcare systems have recognized the advantages of using Information and Communication Technologies (ICT), including mHealth systems, to improve the quality of care, and they are now working, although at a different pace worldwide, to turn traditional into smart healthcare [1]. To meet the increasing demands of an aging population with chronic diseases and comorbidities, technology appears to be to shift from clinic-centric to patient-centric healthcare [2]. Nevertheless, to accelerate the shift toward the brave new world of mHealth, technology must be appropriately designed with the aid of end-users. Many mHealth technologies have failed to innovate the current clinical practice because they ignored the interaction between technology, human characteristics, and socio-economic environment [3].

As an alternative to the technical industrial mindset, User-Centered Design has proven to be an effective tool to realize products and services for the Healthcare sector. User-Centered approach has to be included in the design process since the starting phases to develop a product or system that is effective due to the close relationship with the users' requirements and the high capacity of satisfaction of their needs [4]–[6].

In general, many important factors should be considered when developing a mHealth app [7], [8]. In terms of validity and reliability, the algorithms used must be robust and well-written. Moreover, as already mentioned, the usability and user-friendliness of the apps are a fundamental determinant for technology adoption, in particular, among older adults [4]–[6], [9], [10]. In particular, usability is defined in the official International Organization for Standardization (ISO) guidelines as “the extent to which a product can be used by specified users to achieve specified goals with effectiveness, efficiency, and satisfaction in a specified context of use” [11]. In addition, perceived usefulness and ease of use causes people to accept or reject information technology [9]. The first is defined as the “degree to which a person believes that using a particular system would enhance his or her functions". The latter, in contrast, refers to "the degree to which a person believes that using a particular system would be free of effort” [9].

Furthermore, when measuring aspects of one's health, the accuracy of the results relies on the correct administration of the test. Thus, any usability problem associated with using a mobile app should be identified and addressed before it is made available to end-users. This is usually done through several iterations of testing with target user groups, ideally until no major usability problems exist with regards to using the apps and administering the test. Usability studies are most often carried out in a lab setting, convenient and offers a high degree of control, as opposed to field-based usability testing. However, field-

based testing, which, in this context, would be a home setting, provides insight into how the system is used under more realistic situations. Depending on the system being tested and the development phase, usability should ideally be tested in both lab and home settings [12].

In sight of this, the success of any innovative product depends on:

- Its effectiveness in successfully understanding the user's needs and meeting them, preferably using a User-Centered approach;
- Its compatibility with or similarity to existing products or solutions to facilitate its use;
- The extent of behavioral change needed to use the new product;
- Its costs should be low in order to support a massive deployment;
- The improvement in the quality of life (or performance);
- The enhancement of the user's convenience.

mHealth apps intrinsically satisfy many of these points. In fact, smartphone apps provide a solution in a fully wearable and stand-alone system; they have the great advantages of pervasiveness, ubiquity and exploitation of common apps usage experience. Moreover, the choice of off-the-shelf smartphones would also keep the mHealth system costs low, also increasing its compatibility with external commercial devices. On the other hand, there are several challenges associated with the development of mHealth apps:

- Design for all model and system available with the same performance (different smartphones have different capabilities);
- Built-in sensors do not have priority in the mobile OS (smartphones were born to handle calls and/or messages);
- Safety measures in order to ensure the patients' safety and privacy, developing strategies to ensure data are only accessible to those authorized to access [8];

To date, there is a lack of standardized regulation methods to evaluate the content and quality of mHealth apps [13]–[15]. The quality assessment of mHealth apps is challenging as it is difficult to identify the core components of quality and appropriate measures to assess them [16]. Besides, the different smartphone models available in the market make this assessment more complicated. For example, smartphone built-in inertial sensors do not have a fixed sample frequency: frequency changes dynamically around a fixed value depending on the operating systems (OS) requests, and it varies across the different smartphone models. Moreover, some features are only available in certain smartphones and not in others (or in other cases the feature could be limited): BLE connection could be absent in some smartphones or limited to only few megabytes in others, not allowing data exchange with external sensors.

On a more general ground and from a healthcare system perspective, introducing guidelines for app development and use may be highly effective to improve the quality standards. In the US, the FDA regulates mHealth within the existing framework for medical devices [17]. Only a limited number of apps meet the definition of medical device and are, as such, subject to the US FDA regulation [17]. In Europe, the new regulations on medical devices (MDR [EU] 2017/745) describe whether mHealth products must be medical devices [18]. As a result, apps that support a medical diagnosis and have medical use must be CE marked as medical devices [19]. While the implementation of the new, more stringent MDR might lead to the development of more high-quality apps and improved patient safety, it might also limit the development and release of new apps and software on the market. Classifying a device as class IIa or higher requires evaluation by a notified body, which can be very costly and, therefore, a barrier to entry for app developers [19].

2.2 Orientation estimation

Depending on the use and the application, there are different solutions to estimate the angle information from inertial and magnetic sensors (M-IMU). In the next paragraphs, we report the more common methods, including those used in our research projects, for real-time and offline orientation estimation. Following, we describe an application of these methods that allow real-time estimation of spatio-temporal gait parameters. Before that, it is important to highlight that M-IMU raw data are not ready to use, and they need to be calibrated. To calibrate these data, scale factors (the difference between the sensor raw data and the real data), nonorthogonality (3-axis misalignment), and bias (out of zero) must be taken into account. Besides, to calibrate the raw magnetometer data, magnetic deviations (soft and hard iron) should be considered on the host platform. Hard iron distortions are created by objects that produce a magnetic field. They can easily be compensated, in contrast to soft iron distortions, which are considered deflections or alterations in the existing magnetic field and more difficult to manage [20], [21].

2.2.1 Representation of Orientation [22]

For motion on or near the earth surface, at speeds far below orbital velocity, it is convenient to describe a rigid body's orientation using two coordinate systems: the earth fixed coordinate system and the body-fixed one. The first is an inertial coordinate system specified by the right-handed orthonormal basis E = {e1 e2 e3}, whose axes are defined conventionally and fixedly. A possible solution is to consider the 3-axis directed to the local north, east and down directions (NED), as reported in Figure 1. The body-fixed coordinate system is a non-inertial coordinate system specified by the right-handed orthonormal basis B = {e1' e2' e3'}. In the

aeronautics jargon, its coordinate axes are named 'Roll (φ) - Out the nose', 'Pitch (θ) - Out the right side' and 'Yaw (ψ) - Out the belly' (Figure 1).

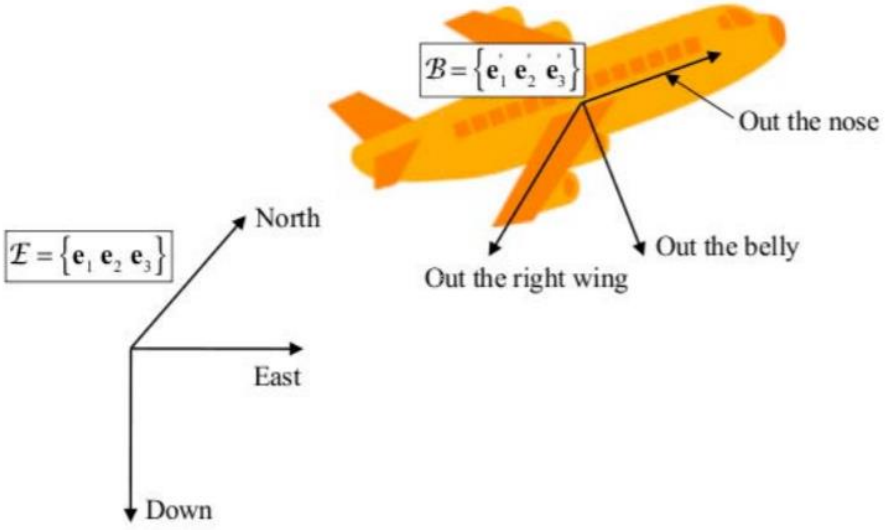

Figure 1. Earth-fixed frame and body-fixed frame on a toy aircraft. Source [22].

Thus, an arbitrary vector *x* in the 3D space can be written in the equivalent forms:

$$\boldsymbol{x} = \boldsymbol{e_1} + \boldsymbol{x_2 e_2} + \boldsymbol{x_3 e_3} \qquad (1)$$

$$\boldsymbol{x} = \boldsymbol{x'_1 e'_1} + \boldsymbol{x'_2 e'_2} + \boldsymbol{x'_3 e'_3}$$

It is also possible to represent the vector *x* considering either basis, with the relation:

$$\boldsymbol{x_B} = {}^{\boldsymbol{B}}_{\boldsymbol{E}}\boldsymbol{C}\ \boldsymbol{x_E} \qquad (2)$$

The subscripts *E*, *B* indicate which basis is used for representing the vector *x*, and ${}^{\boldsymbol{B}}_{\boldsymbol{E}}\boldsymbol{C}$ identifies the direction cosine matrix (DCM), also called attitude (orientation) matrix. DCM columns represent the $\boldsymbol{e_i}$ with respect to *B*, while the rows represent the $\boldsymbol{e'_i}$ with respect to *E* (in 3D space, i = 1, 2, 3). Thus, the attitude matrix is a 3x3 orthogonal matrix with unit determinant, which belongs to the three-dimensional special orthogonal group SO (3) of rotation matrices. Although the orientation matrix is the fundamental representation of the orientation, the orthogonality requirement forces six constraints on its nine elements, namely the column (row) vectors have unit norm and are mutually orthogonal, yielding that the special orthogonal group SO(3) of rotation matrices has dimension three. Therefore, the rotation matrix through an angle *α* can be written, according to Euler's formula, in the following two equivalent expressions:

$$\begin{cases} \boldsymbol{R}(\boldsymbol{n},\boldsymbol{\alpha}) = \mathrm{c}\alpha\ \boldsymbol{I_3} + (\mathbf{1} - \mathrm{c}\alpha)\boldsymbol{n}\boldsymbol{n}^{\boldsymbol{T}} - \ \mathrm{s}\alpha\ [\boldsymbol{n}\ \mathrm{x}] \\ \boldsymbol{R}(\boldsymbol{n},\boldsymbol{\alpha}) = \ \boldsymbol{I_3} - \ \mathrm{s}\alpha\ [\boldsymbol{n}\ \mathrm{x}] + (\mathbf{1}\ -\ \mathrm{c}\alpha)[\boldsymbol{n}\ \mathrm{x}]^{\mathbf{2}} \end{cases} \qquad (3)$$

Where $\boldsymbol{I_3}$ denotes the 3x3 identity matrix, ***n*** any unit column vector, **cα** and **sα** respectively a compact notation for **cos(α)** and **sen(α)**, [***n*** x] the skew-symmetric matrix of ***n***.

Euler's theorem states that the most general motion of a rigid body with one point fixed is a rotation by an angle *α* (rotation angle) about some axis *n* (rotation axis), yielding another representation of the orientation in terms of the rotation vector:

$$\alpha = \alpha_n \tag{4}$$

It is important to underline that the rotation vector space does not contain singularity points. The orientation of the body-fixed frame relative to the earth-fixed frame can also be described using the Euler angle formulation, namely in terms of three consecutive rotations through three body-referenced Euler angles. Although, in principle, twelve possible ways exist to define three independent body-referenced Euler angles; we discuss here the 3-2-1 rotation sequence, which is the one commonly adopted in the aeronautics community. The orientation of the body-fixed frame (nose-wing-belly) relative to the earth-fixed frame (NED) is described by performing the three rotations as follows. Start with a body-fixed frame in the reference orientation, i.e., one in which all of its body-fixed axes are aligned with the corresponding earth axes; first, the body is rotated about the belly axis through an angle ψ usually called heading angle, or Yaw (ψ ∈]−π, π]); second, the object is rotated about the wing axis through an angle θ (elevation angle, or Pitch attitude) (θ ∈]−π/2, π/2]); third, the object is rotated about the nose axis through an angle φ (bank angle, or Roll attitude), to match the body-fixed frame (φ ∈]−π, π]). The rotation matrix as a function of the three Euler angles is given by:

$$R(\psi, \theta, \varphi) = \begin{bmatrix} c\theta c\psi & c\theta s\psi & -s\theta \\ s\varphi s\theta c\psi - c\varphi s\psi & s\varphi s\theta s\psi + c\varphi c\psi & s\varphi c\theta \\ c\varphi s\theta c\psi + s\varphi s\psi & c\varphi s\theta s\psi - s\varphi c\psi & c\varphi c\theta \end{bmatrix} \tag{5}$$

Thus, the gravity vector *g* is represented in the body-fixed coordinate system:

$$g_B = R(\psi, \theta, \varphi) \begin{bmatrix} 0 \\ 0 \\ g \end{bmatrix} = g \begin{bmatrix} -s\theta \\ s\varphi c\theta \\ c\varphi c\theta \end{bmatrix} \tag{6}$$

Equation (6) shows that a body-fixed tri-axial accelerometer does not convey heading information but only Roll and Pitch angles. The time rates of change of the Euler angles are related to the components of the angular velocity $\omega_B = [p\ q\ r]^T$ resolved in the body-fixed frame by the following system of first-order nonlinear differential equations:

$$\begin{bmatrix} \frac{d\varphi}{dt} \\ \frac{d\theta}{dt} \\ \frac{d\psi}{dt} \end{bmatrix} = \begin{bmatrix} 1 & \frac{s\varphi s\theta}{c\theta} & \frac{s\varphi s\theta}{c\theta} \\ 0 & c\varphi & -s\varphi \\ 0 & \frac{s\varphi}{c\theta} & \frac{c\varphi}{c\theta} \end{bmatrix} \begin{bmatrix} p \\ q \\ r \end{bmatrix} \quad (7)$$

Equation (7) can be used to update the rigid body's orientation in the time given the angular velocity. As for all unconstrained representations of orientation, Euler angles suffer from singularities, commonly referred to as gimbal-lock: for instance, in the case of the 3-2-1 rotation sequence, if the Pitch angle is ± π/2, the last two terms of the first and last rows in (7) go to infinite, and the Euler angle integration becomes indeterminate. In particular, the gimbal lock corresponds to losing a degree of freedom in the rotation matrix (5).

Finally, starting from Euler's formula, it is possible to derive another mathematical representation of the orientation matrix based on the Euler-Rodrigues symmetric parameters or quaternion representation. The main advantages of using the quaternion parameterizations over the rotation matrix are errors associated with numerical integration of the kinematic equations and the computational speed. Quaternion representation is characterized by fewer numerical integration errors and does not require the computation of trigonometric functions. Notably, the quaternion representation avoids the gimbal lock singularity. A deeper analysis and explanation of quaternions can be found in [22].

2.2.2 Orientation Estimation Algorithms

Data provided by body-fixed inertial/magnetic sensors are affected by noise and time-varying biases. The use of algorithms is necessary to process the data and obtain a smooth and bias-free estimation of the orientation. The paragraphs below reported different common solutions used to solve this problem.

Inclinometer

As described above, in certain specific tasks, the Accelerometer and/or the Gyroscope output can be used to obtain the orientation. Pitch (θ) and roll (φ) angles were calculated from the accelerometer output (a_x, a_y, a_z) following a trigonometry approach as follows [23]:

$$\theta = \tan^{-1}(-a_x/\sqrt{(a_y^2 + a_z^2)}) \quad (1)$$

$$\varphi = \tan^{-1}(a_y/a_z) \quad (2)$$

Usually, the raw accelerometer data stream was low-pass filtered to reduce noise (2-5 Hz corner frequency) before the angle calculations [23]. From **Figure 1**, it is clear that Yaw angle cannot be derived with the trigonometry approach: no change appears in the accelerometer by rotating around the axis of gravity. These pitch and roll estimations are fast to calculate and are ideal for real-time applications, but they cannot be applied in dynamic activities such as running. Besides, the range of use is limited by the singularity of the trigonometric function.

Gyroscope integration and Inclinometer

Gyroscope signals in each axes are integrated to produce angle estimates. However, the integration accumulates noise and offsets over time and turns them into the drift, the main problem with this approach [24]. It is common to start the task in a stationary position for a few seconds to reduce angular velocity noise, then subtract this noisy term (auto-nulling). In addition, when the inertial sensor is quite still, accelerometers are used to compensate for the linear drift in the gyroscope integral (auto-resetting). The combination of error-correcting (auto-resetting) and offset correction (auto-nulling) techniques have been proposed [25], [26] and they are indicated for real-time estimation of pitch and roll angles.

Sensor Fusion approach

Sensors-fusion algorithms are necessary to process the data and obtain a smooth and bias-free estimation of the 3D space orientation, particularly for the Yaw angle. There are mainly two different types of algorithms, proposed to solve the so-called Wahba's problem (originally introduced in 1965) [27], that provide an estimate of the orientation: deterministic and stochastic. The first one is a least-squares approach that tries to minimize a least-square loss function. It consists in a constrained least-squared optimization problem whose goal is to find the rotation matrix from vector measurements taken at a single time. This single-frame method relates to the operation of gyro-free aiding sensor systems and it can solve Wahba's problem without the need of an a priori estimate. The deterministic approach is based on the vector matching concept and, to work properly in human motion tracking, requires the measurements of constant reference vector that are gravity and earth magnetic field. The stochastic approach (or Kalman filtering, first proposed in 1961 [28]) is based on the minimum-variance sequential estimates of orientation and of other parameters, such as sensor biases, using information obtained from motion dynamics. In other words, in order to produce the most accurate estimate of the system state, these algorithms use a model for predicting some aspects of a dynamic system and a model of the sensor measurements. It is important to notice that both the presented sensor-fusion algorithms operate in the temporal domain; however, there are other approaches that operate in the frequency domain: complementary filters, such as Madgwick [29] and Mahony [30] filters. These

solutions put together gyroscope data with acceleration and magnetic field measurements from sensors, in order to obtain an orientation estimation in quaternion form. A complementary filter performs high-pass filtering on the orientation estimated from gyroscope data affected by low-frequency noise. On the other hand, it performs a low-pass filter on accelerometer data affected by high-frequency noise: the fusion between the two estimations can ideally return an all-pass and noise-free orientation estimation. However, without going into the conceptual and implementation details of the different sensor-fusion algorithms, the only thing that can be said is that in literature there is not yet an algorithm that is able to optimally estimate the orientation starting from inertial and magnetic sensors. Each of the algorithms presented in the literature has its strengths and weaknesses. More detailed information related to sensor-fusion algorithms can be found in [22]. The main issues related to this approach are: i) the trade-off between the time needed to elaborate the estimation of the angle starting from the raw M-IMU data and its accuracy; ii) time-drift and magnetic deviations. For this reason, their use in real-time applications is not always immediate. Nevertheless, many filters embedded into the M-IMU sensors (proprietary) have been implemented to estimate real-time orientation with acceptable accuracy [31]–[33]. Also inside our smartphone, there are M-IMU's embedded filters created by the smartphone's companies to obtain the quaternion rotation vector of our device [34], from which it is possible to extract yaw, pitch, and roll angles in real-time.

Real-time estimation of Spatio-Temporal Gait Parameters

The first prerequisite for monitoring locomotor performance is the availability of wearable sensing and computing systems that acquire and real-time process gait signals. Firstly, there is the need to identify gait cycles, i.e., the estimation of distinctive events such as initial contacts (ICs) and foot off (FOs) [35], [36]. From the knowledge of ICs and FOs it is possible to obtain temporal gait parameters, e.g., stride duration or cadence. Many approaches to locate ICs and FOs have been proposed in the literature, which differ in terms of accuracy and setup complexity [37]. Differently, two main approaches have been proposed to estimate in real-time spatial gait parameters: the classical use of a biomechanical model, which has excellent accuracy at the expense of practical usability [38], and strap-down integration methods [39]. In accordance with the strap-down integration methods, with two IMUs located on the feet it is possible to determine IMU's orientation from angular rate integration, and subsequently, the position from the double integration of acceleration produced by the movement. However, as we have already seen, inertial sensors suffer from measurement errors and corresponding integration drifts that severely limit pose estimation during long-term measurements. By placing the IMUs on the feet, drift can be effectively corrected on a step-by-step basis by exploiting the constraint that feet keep zero velocity (ZV) during the second rocker (i.e., the period of the stance phase in which the shank rolls over the ankle joint [40]) [41]. This correction is known as “zero velocity update” (ZUPT) and was first proposed in the field of gait analysis by Sabatini et al. [39] and then

further developed by others [42], [43]. These implementations can be ascribed to the broader discipline named as pedestrian dead-reckoning (PDR). The most common method for applying ZUPT to gait data is the Kalman filter [37]. In **Figure 2** the flow chart of a PDR system developed by Ferrari et al. [37]:

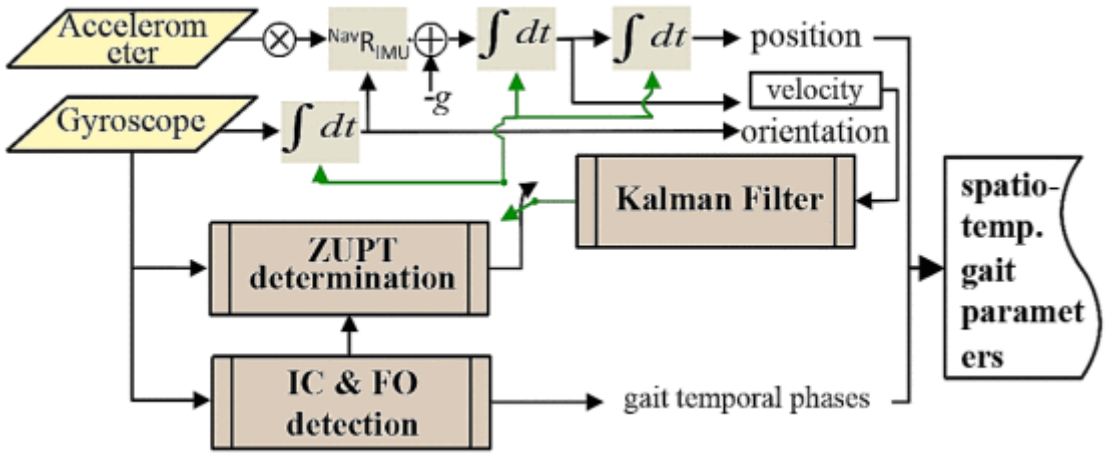

Figure 2. Flow chart of a PDR system with its three main modules: the algorithms for IC and FO detection, ZUPT determination, and the KF. $^{Nav}R_{IMU}$ 3×3 rotation matrix to transform the accelerations from sensor frame to navigation frame. Source [37].

Innovatively, this PDR system is used to monitor locomotor performance and design tutoring systems that are able to generate timely and appropriate feedback about users' gait in daily-life [44], [45].

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Section I - Introduction and Theoretical Background

Chapter 3

"Theoretical Background"

In this Chapter, we present the main sensors that were embedded into the mHealth solutions used in this thesis (accelerometer, magnetometer, gyroscope, touchscreen technology, and load cell). Then, we address the potential of unimodal and multimodal augmented biofeedback (BF) in the framework of motor learning theories.

3.1 Fundamentals on mHealth Sensors

Accelerometer

A monoaxial accelerometer is a device that measures the applied acceleration along an axis. It consists of an inertia element whose movement may be transformed into an electric signal [1], using the property of bodies to maintain constant translational and rotational velocity, unless disturbed by forces and torques, respectively. For this reason, it is called an inertial sensor (as for the gyroscope). Typically, a monoaxial accelerometer can be specified as a single-degree-of-freedom device, which has some type of seismic mass (sometimes called proof mass), a spring-like supporting system, and a frame structure with damping properties (**Figure 1**). Mass *(m)* is supported by a spring having stiffness *(k)* and the mass movement is damped by a damping element with a coefficient *(d)*. The mass may be displaced with respect to the accelerometer housing only in the horizontal direction.

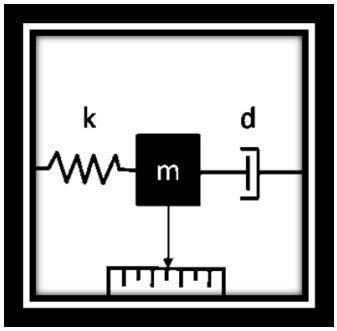

Figure 1. A schematic representation of the mechanical model of an accelerometer is reported.

A detailed mathematical model of a monoaxial accelerometer can be found in [1], together with the resolution of the related differential equation. The differential equation that links acceleration and displacement of mass *m* [1] suggests that it is enough to measure displacement to directly derive the body acceleration. Due to this fact, any displacement transducer (capable of measuring microscopic movements under strong vibrations or linear acceleration) can be employed to generate an electrical signal as a function of the acceleration. Examples are capacitive, piezoresistive, and piezoelectric transducers. A capacitive displacement conversion is one of the proven and reliable methods. A capacitive acceleration sensor essentially contains at least two components, where the first is a “stationary” plate (i.e., connected to the

housing) and the other is a plate attached to the inertial mass, which is free to move inside the housing. These plates form a capacitor whose value is a function of a distance between the plates. Overall, the correct type of accelerometer must be selected for each specific application [2]. Everything illustrated for the monoaxial accelerometer can be easily generalized to the triaxial accelerometer, which consists of three orthogonal monoaxial accelerometers, providing measurements on each axis. Using accelerometers provides a practical and low-cost method for:

- measuring motion ('slow' changes in velocity and position), including human motion, such as gait, postural sways, and falls;
- measuring inclination, tilt, or orientation as referenced from the gravity acceleration;
- measuring vibration, through the oscillating motion about a position of equilibrium. Examples: an electric motor, turbine, or bearing monitoring;
- measuring a shock/impact, through a sudden high change in acceleration (automotive crash testing, drop testing).

Gyroscope

Angular velocity can be measured with a gyroscope, which consists of a spinning wheel mounted on a movable frame. When the wheel is spinning, it tends to retain its initial orientation in space, regardless of the central forces applied to it. When the direction of the axis is externally altered, a torque proportional to the rotation rate of the axis of inclination arises, which can be used to detect angular velocity [2]. An example of this type of transducer is the dynamically tuned gyroscope. Typically, micromachined gyroscopes are specialized vibrating accelerometers that measure Coriolis forces. A basic vibratory gyroscope consists of a proof mass mounted on a suspension that allows the proof mass to move in two orthogonal directions. To generate a Coriolis force, the proof mass must be in motion [2]. To this end, the proof mass is electronically forced to oscillate in a direction parallel to the chip surface. If the gyroscope chip is rotated about the axis perpendicular to the chip surface, then a Coriolis force causes the proof mass to be deflected in the second direction. The amplitude of this oscillatory deflection is proportional to the rate of rotation, so that capacitive sensing, as in the case of the accelerometer discussed above, can be used to produce a voltage proportional to the angular rotation rate. A tuning fork directly detects the angular velocity in a vibratory gyroscopic sensor. The tines of the tuning fork are piezoelectrically excited perpendicular to the wafer surface. **Figure 2** presents an example of a tuning fork gyroscopic sensor.

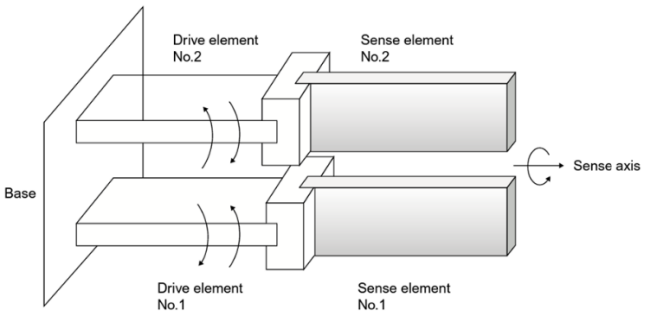

Figure 2. Configuration of a tuning fork. Source [2].

The angular rate input axis is parallel to the wafer surface, and the tines are excited with piezoelectric actuators. Due to the Coriolis effect, an angular velocity parallel to the axis of the stem generates a periodic torque, which results in a torsional oscillation of the stem. The torsional oscillation is detected with an implanted piezoresistor located in the middle of the stem. Gyroscopes are used in stabilization devices, weapons, robotics, tunnel mining, and in many other systems where a stable directional reference is required.

Magnetometer

A magnetometer is a device that measures the strength and direction of the magnetic field in its system of reference. Common magnetic sensors are based on the Hall effect, **Figure 3**, which generates magnetic impedance and magnetic resistance as a result of the interaction between moving electronic carriers and an external magnetic field. In metals, these carriers are electrons.

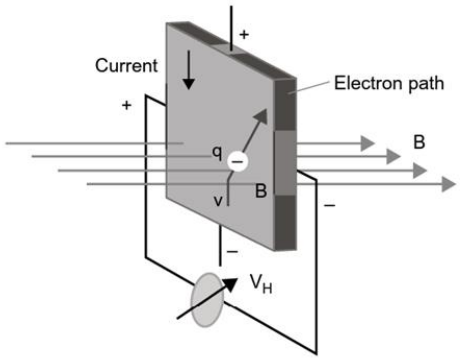

Figure 3. The Hall effect principle. Source [2].

The most recent arrival on the low-cost-magnetometer scene is Lorentz force magnetometers — MEMS devices that detect the motion of a miniature bar magnet. The fact that these magnetometers can be manufactured on the same wafer holding MEMS and CMOS circuitry could mean that devices based on this method can be made at low cost, but this remains to be seen. The Lorentz force sensor's magnetic field resolution is limited by electronic noise from the detection electronics, and its structure's relatively high

natural frequencies make it less sensitive to acceleration [1]. One of many advantages of using the magnetic field for sensing position, orientation, or distance is that any nonmagnetic material can be penetrated by the field with no loss of accuracy. Stainless steel, aluminum, brass, copper, plastics, masonry, and woods can be penetrated, without loss of accuracy. The big disadvantage is due to the presence of external magnetic distortion. In general, magnetometers are widely used for measuring the Earth's magnetic field, and in geophysical surveys, to detect magnetic anomalies of various types. In an aircraft's attitude and heading reference system, they are commonly used as a heading reference.

Touchscreen technology

Embedded in phones, office equipment, speakers, digital photo frames, TV control buttons, remote controls, GPS systems, automotive keyless entry, and medical monitoring equipment, touchscreens are everywhere. As a component, they have reached into every industry, every product type, every size, and every application at every price point. In fact, if a product has an LCD or buttons, a designer somewhere is probably evaluating how they too can implement touchscreen technology. As with any technology, there are many different ways to implementation approaches, many promises of performance, and many different technical considerations when designing a touchscreen [3]:

- *Resistive Touchscreens* are the most common touchscreen technology. They are used in high-traffic applications and are immune to water or other debris on the screen. Resistive touchscreens are usually the lowest-cost touchscreen implementation. Because they react to pressure, they can be activated by a finger, gloved hand, stylus, or other objects.
- *Surface Capacitive Touchscreens* provide a much clearer display than the plastic cover typically used in a resistive touchscreen. In a surface capacitive display, sensors in the four corners of the display detect capacitance changes due to the touch. These touchscreens can only be activated by a finger or other conductive object.
- *Projected Capacitive Touchscreens* are the latest entry into the market. This technology also offers superior optical clarity, but it has significant advantages over surface capacitive screens. Projected capacitive sensors require no positional calibration and provide much higher positional accuracy. Projected capacitive touchscreens are also very exciting because they can detect multiple touches simultaneously.

The projected capacitance sensing hardware consists of a glass top layer, followed by an array of X sensors, an insulating layer, then an array of Y sensors on a glass substrate. The panel will have a wire for each X and Y sensor, so a 5 x 6 panel will have 11 connections (**Figure 4**), while a 10 x 14 panel will have 24 sensor connections [4].

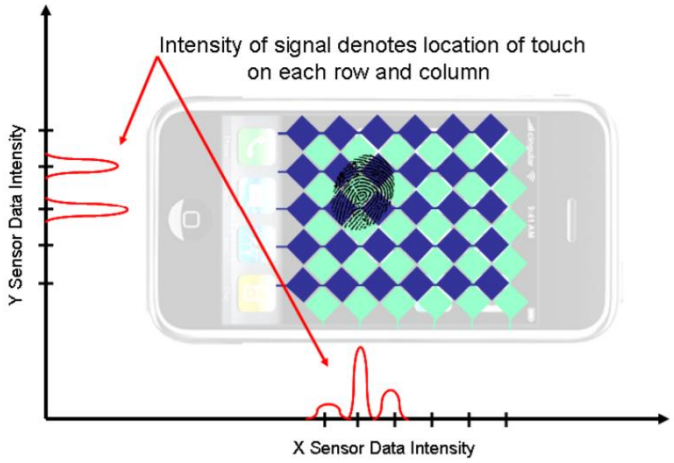

Figure 4. Signal Intensity at Rows and Columns Denote Location of Touch. Source [4].

As a finger or other conductive object approaches the screen, it creates a capacitor between the sensors and the finger. This capacitor is small relative to the others in the system (about .5pF out of 20pF), but it is readily measured [4]. A projected capacitive sensor array is designed so that a finger will interact with more than one X sensor and more than one Y sensor at a time (**Figure 4**). This enables software to accurately determine finger position to a very fine degree through interpolation. Since projected capacitive panels have multiple sensors, they can detect multiple fingers simultaneously, which is impossible with other technologies. In fact, projective capacitance has been shown to detect up to ten fingers at the same time [4].

Load Cell

A load cell is a physical element (transducer) that can translate pressure (force) into an electrical signal. There are three main ways a load cell can translate an applied force into a measurable reading [5]:

- *Hydraulic load cell* use a conventional piston and cylinder arrangement to convey a change in pressure by the movement of the piston and a diaphragm arrangement which produces a change in the pressure on a Bourdon tube connected with the load cells;
- *Pneumatic load cell* use air pressure applied to one end of a diaphragm, and it escapes through the nozzle placed at the bottom of the load cell, which has a pressure gauge inside of the cell;
- *Strain gauge load cell*, which is a mechanical element of which the force is being sensed by the deformation of a (or several) strain gauge(s) on the element.

Strain gauge load cells are the most popular due to their high accuracy, low price point, and general ease of use. They have a high-frequency response for dynamic loads and are not sensitive to temperature variations. Because they can fit into a wide variety of load-mounting configurations, they lend themselves to almost any industrial application [6]. In **Figure 5** a representation of a strain gauge load cell is reported:

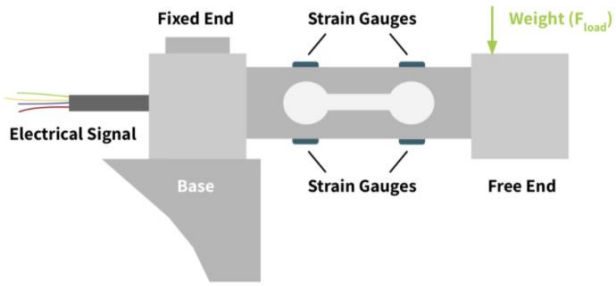

Figure 5. Strain Gauge Load Cell Diagram. Source [6].

Load cells are precision force measuring instruments. They offer a relatively low-cost, durable, and easy-to-install solution to almost any load measurement need. Load cells have been providing quality measurements in aerospace, agriculture, medicine, industrial weighing, and many other applications for decades. Ongoing advancements in load cell technology have broadened their use further.

3.2 Fundamentals of Biofeedback (BF)

Chapter 1.1 introduced a generic mHealth system architecture to understand better its components and the typical workflow within the real-time biofeedback (BF) process. It is generally accepted that BF, provided by a human expert or a technical display, effectively enhances motor learning. However, the discussion of the way to most effectively provide BF has been controversial [7]. In neuromotor rehabilitation, therapists want their patients to recover lost motor functions as quickly and permanently as possible. Depending on the motor feature to be learned, trainers and therapists switch modalities to instruct the motor task. The strength of BF is that it can help recover the internal map of the movement, augmenting internal sensory afferents, **Fig. 6**:

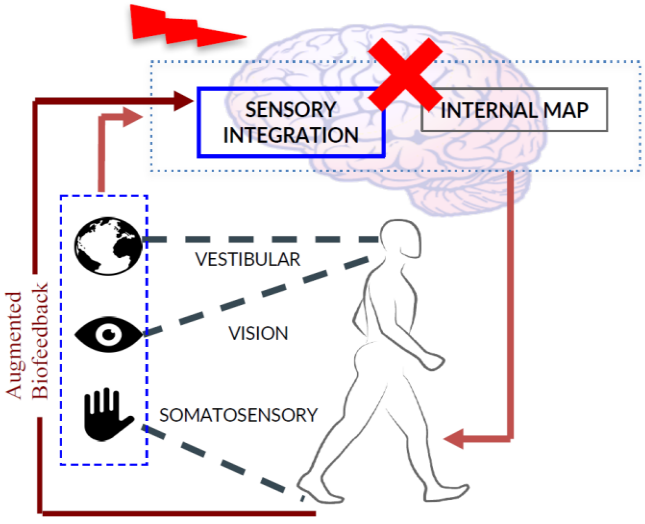

Figure 6. Schematic representation of augmented BF.

Accordingly, BF can be provided with different modalities: visual (screens, head-mounted displays), hearing/audio (speakers, headphones), proprioceptive/haptics (robots, vibrotactile actuators), or a combination of them [7], [8]. Feedback strategies may also be classified according to the point in time at which BF is provided: either during motor task execution (real-time/concurrent) or after it (terminal) [7]. Over the last decade, a significant number of studies investigating the effect of different BF modalities on motor learning have been published [7]. In the next paragraphs, we describe the main findings organized by BF sensory modalities. In conclusion, a focus on BF to ameliorate FOG and improve gait in PD is reported.

Visual BF

Vision is often regarded as the most important perceptive modality during interaction with the environment in daily life. At least for perceiving spatial information, vision dominates other senses [7]. Many possibilities exist for visualizing errors in kinematic or kinetic variables, ranging from abstract visualizations, such as simple plots, gauges, bars, lines, or numbers, to less abstract (natural) visualizations, such as virtual mirrors [7]. Abstract visualizations seem to be efficient since they can represent a key feature of a movement in an unambiguous way. Moreover, common metaphors should be respected, such as red color standing for "wrong" and green for "correct." However, there are two main disadvantages of abstract feedback designs. First, in the long run, they might become boring and, thus, hinder the learning process by demotivation. Second, feedback about complex multidimensional movements can hardly be abstracted [7]. In general, real-time visual BF enhances performance in the acquisition phase of motor learning, but the performance gains are lost in retention tests, especially in simple motor tasks [7]. This finding is explained by the guidance hypothesis, which states that permanent feedback during acquisition leads to a dependency on the feedback [9]–[11]. The guidance forces learners to ignore their intrinsic feedback (proprioception).

Audio BF

Visual concurrent BF may overload capacities of visual perception and cognitive processing. To minimize perceptual overload, real-time BF could also be triggered acoustically (or haptically) [7]. Auditory BF may not only reallocate perceptual and cognitive workload but also reduce distraction [12], [13]. However, the impact of auditory feedback depends considerably on the intuitive and correct interpretation of the applied mapping functions and metaphors. Applied functions and metaphors have to be carefully selected, since listening to auditory displays is less common than viewing visual displays [7]. For example, an audio alarm is simple to interpret: the subjects can immediately recognize in which direction they have to correct their movement and when the intended performance is gained. However, on the basis of such a discrete BF, the users cannot recognize to what extent they have to correct their movement [7]. Recognition of the extent requires a continuous representation of movement data values or more complex verbal instruction [7]. In comparison

with visual BF, real-time auditory BF is effective for perceiving temporal information: periodicity, regularity, and speed of motion [14]–[16].

Haptic BF

In our early days, the haptic sense lays the foundation for sensory integration [17]. This is because the haptic sense is the only one that enables us to interact with the world around us and, at the same time, to perceive these interactions [18]. This unique characteristic is called the bidirectional property of the haptic sense, which provides the basis to further enhance motor learning through haptic interactions [19]. Thus, it seems natural to investigate the effectiveness of haptic interactions in motor learning. In general, vibrotactile BF has mainly been developed to improve navigation and orientation in order to reduce the workload of the visual and auditory system [7]. Appropriate sites on the body for the vibrators must be found; for example, the vibration must be easy to perceive, and at the same time, the vibrators should not hinder movement [7]. Interestingly, some sites might have an initial advantage in representing specific information, due to its naturalness; however, the advantage dissolves when users are given enough time to become familiar with less intuitive sites [20]. Moreover, appropriate signal ranges and modulations (e.g., pulse or amplitude modulation) of the vibration must be evaluated [21]. In general, the perception of haptics can fulfill relatively high demands on processing both temporal and spatial information [7] and is believed to be the most direct form of motor information [22].

Multimodal BF

However, in daily life, multimodal, rather than unimodal, stimuli are present. Not only are humans used to processing stimuli in different modalities at the same time, but also multimodal information even facilitates acting in the world. Hence, it can be hypothesized that in motor learning, augmented multimodal BF is more efficient than unimodal BF [7]. Many researchers believe that the positive effect of multimodal learning originates from a reduction of the cognitive load due to a distribution of information processing [23]. This theory refers to the multiple-resource theory of Wickens [24], which states that distribution of information to different modalities is superior to providing the same amount of information in one modality. The multiple-resource theory is in line with Baddeley's [25] theory of working memory; visual-spatial information is maintained in one area, and auditory-verbal information in another area of the working memory. All these findings on memory and cognitive load imply that if the workload is high in one modality, augmented BF should be given in another modality or in a multimodal way. This might prevent cognitive overload and, therefore, might enhance motor learning. In particular, these positive effects are believed to be beneficial during complex motor task learning [7]. Another benefit of multimodal feedback may lie in its support in understanding several aspects of a movement simultaneously. For example, augmented visual feedback could facilitate the learning of spatial aspects of the movement effectively, and at the same time, auditory

feedback could support the understanding of temporal elements. A deeper analysis and explanation of the different biofeedback modalities can be found in [7].

Designing BF solutions: key points

The optimal BF modality/modalities should be chosen to gain the most precise perception, but, thereby, the challenge is to prevent a dependency on the augmented BF. Multimodal BF can be applied to exploit the specific advantages of each modality, such as the aptitude of visualizations to display spatial aspects and of sound or haptic BF to reveal temporal aspects as well as a more direct response. Moreover, a possible trade-off between performance and comfort should be considered [7], and it is also crucial to the extent that each subject is visually-, auditory-, or somatosensory-dependent. The central nervous system uses augmented sensory information differently, depending primarily on individual proclivities to rely on a sensory channel over another to control motor behavior [26].

Innovatively, thanks to wearable technologies, it is possible to provide feedback only when one or more specific features (for example, gait speed or body sway) deviates from its normal state, allowing the so-called closed-loop system. In contrast to open-loop systems, in closed-loop systems the external information does not necessarily become part of the participants' movement representation (as explained by the “guidance hypothesis”), thus possibly decreasing the development of dependency [9].

BF to ameliorate FOG and improve gait in PD subjects

In **Figure 7**, Sweeney et al. [8] synthesized the effect of different external BF modalities (cue) to ameliorate freezing of gait (FOG) and improve gait in PD subjects.

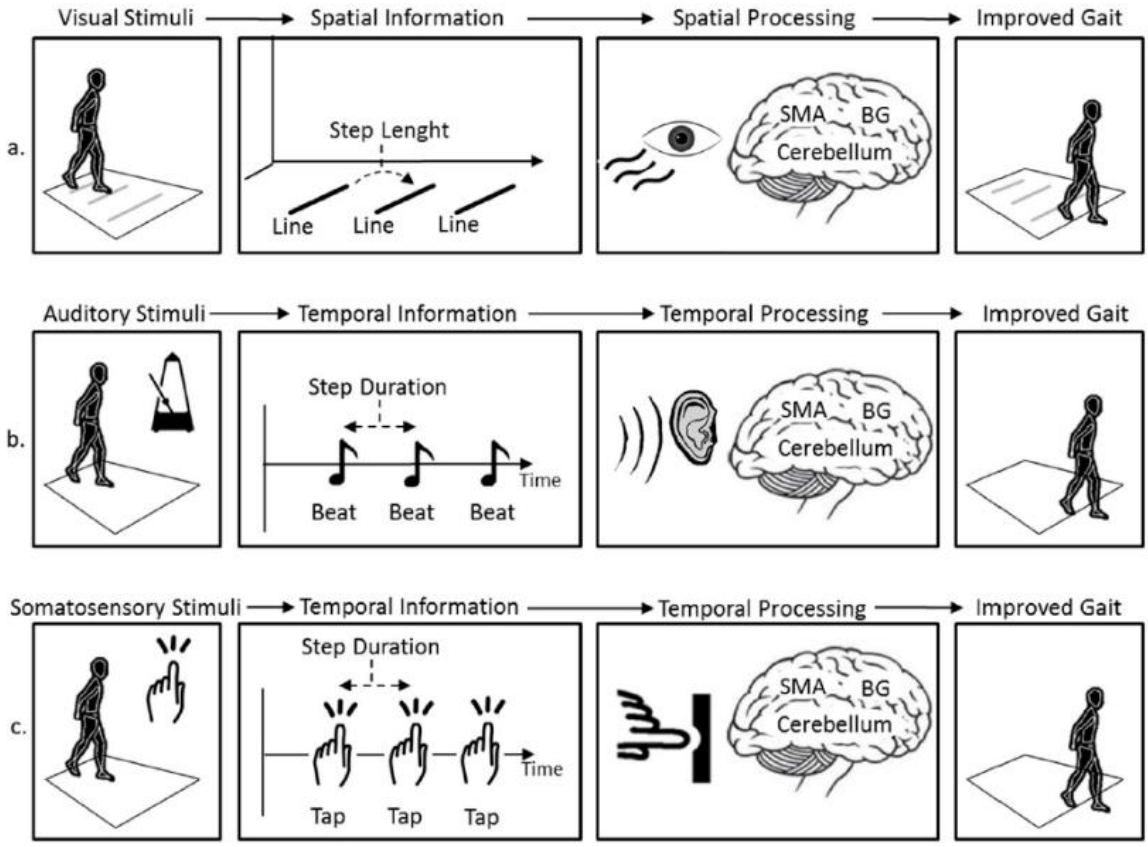

Figure 7. BF modalities to ameliorate FOG and improve gait in PD subjects. (a) Visual: parallel lines marked on the ground at a fixed distance apart, convey *spatial information*, such as step length; (b) Auditory: a metronome producing auditory stimuli at a set beat, conveys *temporal information*, such as step duration; (c) Somatosensory: Tapping of a person with PD shoulder at a set rhythm, also conveys *temporal information*, such as step duration. Both spatial and temporal information may be perceived by persons with PD and processed through multiple brain regions (BG—basal ganglia, SMA—supplementary motor area, and cerebellum). Source [8].

The precise mechanisms underlying the effectiveness of BF to ameliorate FOG in PD is unclear; however, in line with the above results, Sweeney et al [8] suggested that:

- BF may compensate for the defective internal rhythm generator of the basal ganglia, consequently affecting the coordination and execution of movement [27], [28]. In this way, PD subjects may use auditory or somatosensory BF to provide temporal information [29];
- PD subjects may use visual BF to provide spatial information to scale and guide movements, which may allow them to bypass their defective basal ganglia area during gait [30];
- Previous studies also suggested that cognitive/attentional mechanisms might explain the positive effects of BF and cueing on FOG. Namely, auditory, visual or somatosensory solutions may shift the attention of subjects with PD to the task of walking, helping them to consciously think of what to do next [31].

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Section I - Introduction and Theoretical Background

Chapter 4

"Relevant needs associated with the Management and Prevention of functional decline due to Ageing and Neurodegeneration"

In this chapter, a general introduction will be given regarding the degenerative processes underlying ageing and Parkinson's Disease (PD). They constitute the main categories addressed in this doctoral thesis. Thus, the principal neuromotor dysfunctions experienced by elderly people (EP) and persons with PD will be presented, followed by an overview of options for their clinical assessment and rehabilitation.

4.1 Degenerative processes underlying Ageing and Parkinson's Disease

Elderly People, EP

Ageing is emerging as a key policy issue because both the proportion and the number of older people in populations around the world are increasing dramatically. Figure 1 shows a projection of the proportion of people aged 60 years or older by country for 2050 [1]. There will be many countries where this proportion will exceed 30%: from Europe to North America, but also China and the Russian Federation. There were 703 million persons aged 65 years or over in the world in 2019. The number of older persons is projected to double to 1.5 billion in 2050 [2].

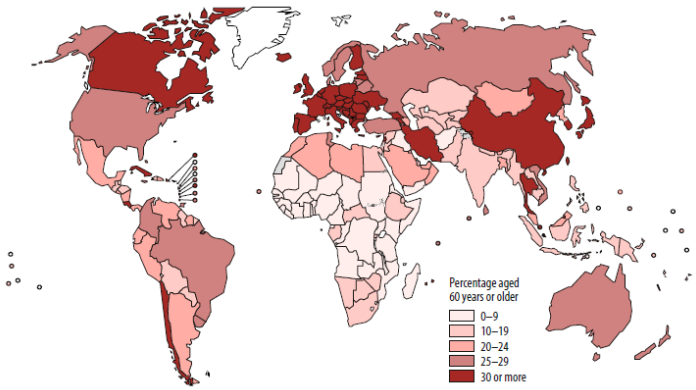

Figure 1. Proportion of population aged 60 years or older, by country, 2050 projections. Source [1].

At the biological level, ageing results from the impact of the accumulation of a wide variety of molecular and cellular damage over time. This leads to a gradual decrease in physical and mental capacity, a growing risk of disease, and ultimately, death. But these changes are neither linear nor consistent, and they are only loosely associated with a person's age in years [1]. While some 70 year-olds enjoy extremely good health and functioning, other 70 year-olds are frail and require significant help from others [1]. The normal physiological changes occur with ageing in all organ systems [3]. Common conditions in older age include the proprioceptive and visual deficit, hearing loss, cataracts and refractive errors, back and neck pain and osteoarthritis, chronic obstructive pulmonary disease, diabetes, depression, and dementia [1]. Furthermore, as people age, they are more likely to experience several conditions at the same time. Older age is also characterized by the emergence of several complex health states that tend to occur only later in life and do not fall into discrete disease categories [1]. These are commonly called geriatric syndromes. They are often

the consequence of multiple underlying factors and include frailty, urinary incontinence, falls, delirium, and pressure ulcers [1]. In particular, the next paragraph highlights the decline in motor functions in EP.

Motor functions

After a peak in early adulthood, muscle mass tends to decline with increasing age, and this can be associated with declines in strength and musculoskeletal function [4]. One way of measuring muscle function is to measure handgrip strength, a strong predictor of mortality, independent of any disease-related influences [5]. Women tend to have weaker grip strength than men, and strength declines with increasing age for both sexes. Ageing is also associated with significant changes in bones and joints. With age, bone mass, or density, tends to fall, particularly among postmenopausal women. This can progress to a point where fracture risk is significantly increased (a condition known as osteoporosis), which has serious implications for disability, reduced quality of life, and mortality. Hip fractures are a particularly devastating type of osteoporotic fracture, and as a result of population ageing they will become more common, reaching an estimated annual global incidence of 4.5 million in 2050 [6]. These and other age-related declines ultimately impact broader musculoskeletal function and movement. This is reflected in a decrease in gait speed. Gait speed is influenced by muscle strength, joint limitations, and other factors, such as coordination and proprioception, and has been demonstrated to be one of the most powerful predictors of future outcomes in older age [7].

Parkinson's Disease, PD

PD is an age-related condition that affects 1–3% of the global population older than 65 years, though it can be present from young adulthood [8], [9]. Because of the aging population, the worldwide prevalence of the disease is expected to increase significantly, from 6.9 million people in 2015 to an estimated 14 million by 2040 [10]. PD is characterized by the progressive degeneration of crucial brain areas; the nigrostriatal pathway is the most prototypical. This system connects the substantia nigra pars compacta (SNpc) dopaminergic neurons with the striatum [11]. This nigrostriatal connection is crucial for motor control. The classic parkinsonian motor manifestations of bradykinesia, rigidity, and rest tremor [12], [13] appear when the loss of dopaminergic cells in the nigrostriatal system exceeds a certain threshold, approximately 50–60%, which typically causes the patient to seek consultation, leading to a diagnosis. Current therapies for these manifestations are based mainly on dopamine replacement, which enables significant control of the symptoms until the disease reaches advanced stages. When PD symptoms are very severe, and medications become less effective, surgery and deep brain stimulation can be considered as the final options of treatment: Deep brain stimulation (DBS) overrides the abnormal neuronal activity within the basal ganglia bringing the system to a more normal state [14], [15]. DBS gives that good response from levodopa for a more extended period with fewer side effects than medication, even if these benefits have to be weighed against potential surgery-related adverse events, device-related complications, and stimulus-induced side

effects [15]. The diagnosis of PD is still a clinical one. Various clinical criteria have been developed to standardize the diagnosis (*Paragraph 3.1*). All these criteria still rely on the cardinal motor manifestations of bradykinesia, tremor, and rigidity related to nigrostriatal impairment:

- *Bradykinesia* is characterized by a progressive decrease in speed and amplitude of movement in one part of the body [16]. This is the primary sign related to dopamine deficiency, and it is what specialists try to quantify to diagnose parkinsonism and to optimize therapy.
- *Parkinsonian tremor* is an intermittent oscillatory movement, present mainly in the limbs. Typically, parkinsonian rest tremor has a low frequency (4–6 Hz), is inhibited by movement, and may reoccur after a few seconds following a change in posture [17]. Additionally, patients with PD can have a postural/kinetic tremor at a higher frequency than the resting tremor. Contrary to general belief, not all patients exhibit tremor (PD tremoric phenotype), as they may manifest mainly bradykinesia (akinetic phenotype) or stability and gait problems (postural and gait disorder phenotype) [18].
- *Rigidity* is described as the resistance to the passive mobilization of any body part due to increased tone. Rigidity can be present in the head and trunk and in both upper and lower limbs. Similar to bradykinesia or tremor, rigidity is a cardinal motor manifestation that shows a relevant clinical response to levodopa therapy [12], [13].

In addition to nigrostriatal impairment and the above-described motor cardinal manifestations, other systems are affected, leading to nonmotor symptoms. These include olfactory dysfunction, gastrointestinal disorders, dysautonomia, sensory disturbances, sleep disorders, and cognitive and neuropsychiatric symptoms, **Figure 2** [19].

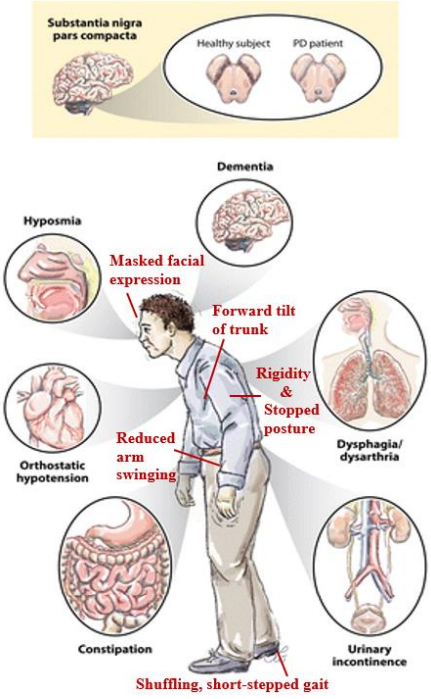

Figure 2. Illustration of the main motor (in red) and nonmotor clinical manifestations of Parkinson's disease (PD). Motor manifestations are the main cardinal features and are related to cell depletion in the substantia nigra (top). Adapted from [20].

In what has been termed the preclinical phase of PD [21], certain nonmotor symptoms are frequently present before the onset of the classical motor features and when progressive dopaminergic cell loss occurs. Olfaction impairment, constipation, depression, and rapid eye movement sleep behavior disorder exemplify the clinical features that appear during this phase [22]. Subtle motor manifestations can also be part of preclinical PD, but not in the form of the cardinal signs [23], [24]. Thus, we can distinguish three different periods within the natural history of PD: (a) a preclinical phase; (b) a clinical stage, when the onset of the classical motor and nonmotor features occurs; and (c) a more advanced clinical period, characterized by the worsening of motor features, the appearance of various motor and nonmotor complications, and greater difficulty in optimizing therapies [25]. Compared with the preclinical and the early clinical phases of PD, advanced PD is characterized by the emergence of complications related to long-term levodopa treatment, including motor fluctuations, dyskinesias, and nonmotor fluctuations [26], [27]. Motor fluctuations have a variable expression, ranging from the wearing-off phenomenon (i.e., a good response to treatment followed by the return of symptoms before the next dose of medication is taken) to sudden off periods (i.e., when the effect of medication suddenly disappears without warning), among others [28]. Dyskinesias are characterized by excessive involuntary movement affecting the whole body [29]. Motor fluctuations are present in 60–90% of patients within ten years of disease onset and significantly affect the quality of life and daily living activities [30]. The signs and symptoms of PD evolve, and this evolution and the appearance of other clinical features have relevant diagnostic implications. For example, the progression of PD is characterized by worsening of motor features after several years, including falls and freezing of gait (FOG), brief episodes during which the patient is unable to generate active stepping movements, usually at the initiation of the step or while turning. Patients experience these problems as instability and concern about falling [20]. These considerations concerning the different manifestations and the natural history of PD must be kept in mind when using or developing new technology to diagnose or monitor the condition.

4.2 Clinical Assessment

The health state's measurement is essential in both clinical practice and research to assess the severity and progression of a patient's health status, the effect of treatment, and alterations in other relevant factors. The miniaturization of sensing, feedback, and computational devices has opened a new frontier for movement assessment and rehabilitation [31]. Wearable systems are portable and can enable individuals with various movement disorders to benefit from analysis and intervention techniques that have previously been confined to research laboratories and medical clinics [31].

Elderly People, EP

The clinical assessment of frail older people is challenging, as they often have multiple comorbidities and diminished functional and physiological reserves [3]. In addition, the physical illness or adverse effects of drugs are more pronounced resulting in atypical presentation, cognitive decline, delirium or inability to manage routine activities of daily living (ADLs) [32]. ADLs include the fundamental skills typically needed to manage basic physical needs, comprised the following areas: grooming/personal hygiene, dressing, toileting/continence, transferring/ambulating, and eating [33]. Successful ADLs' performance is a significant health indicator that can predict mild cognitive impairments, dementia, and mortality in older adults [34], [35]. Hence, it is crucial to measure ADLs in EP effectively. Several types of approaches have been used to quantify the level of independence in ADLs. ADLs may be measured by self-report, proxy/caregiver/informant report, and/or direct observation filling ad hoc scale/questionnaire [36]–[39]. These tools obtain a general sense of the level of assistance needed and the most appropriate setting for the patient [33]. Self-report measures are convenient to administer and are frequently used when direct observation is not possible or when individuals are relatively cognitively intact. However, they may be less valid when individuals have poor insight into their functional impairments [40], [41]. Informant-based ratings are commonly completed by caregivers who know the patient well, but how also may be biased by their own burden in caring for the individual or by over or underestimating the patient's true functioning [33]. The use of performance-based measures can provide objective data about ADL functioning and they may be able to detect change over time [42], but generally require more training to administer as compared with self or informant reports [33]. To objectively evaluate some items of ADLs, such as gait and balance functions, different instrumented tests can be performed, **Table 1**:

	Description	Normal Values
Turn 180° [43]	A measure of dynamic postural stability, asking a patient to take few steps and then turn around by 180° to face the opposite direction. Count the number of steps taken to complete a 180° turn	Five or less steps
3-m TUG test [44]	A measurement of mobility. A person is asked to stand up from a seated position, walk for 3 m, turn and walk back to a chair and sit down. Measure the time taken in seconds	12 or fewer seconds, can vary with age by 2–4 s
Near tandem stand [45]	A measure of balance and ankle strength. A person is asked to stand in a near tandem position with their bare feet separated laterally by 2.5 cm with the heel of the front foot 2.5 cm anterior to the great toe of the back with their eyes closed. A person can hold arms out or move the body to help keep the balance but do not move the feet	Able to stand >30 s with eyes closed
Alternate step test [46]	A measure of strength, balance, coordination, and stair climbing. It provides a measure of mediolateral stability. A person should be asked to place alternate whole left and right barefoot onto a 19-cm high stepper for a total of eight times	10 or fewer seconds, can vary with age by 2–4 s
Sit-to-stand test [47]	A measurement of functional mobility, balance, and lower limb strength. A person should be able to stand up and sit down five times with crossed arms from a 45-cm straight-backed chair	11.4 s (60–69 years); 12.6 s (70–79 years); 14.8 s (80–89 years).

Table 1. Gait and Balance Assessment Tools.

Innovatively, thanks to the great advances in wearable technologies this is now possible not only in clinical, but also continuously at home in a self-administrable way [48]. This is crucial for the prevention of movement

dysfunctions in EP. For example, a solution that permits objective evaluation of body posture and gait in EP subjects is the mTUG/mSWAY mHealth system. It uses a single inertial sensor worn on the wrist (mTUG) or on the lower back (mSWAY), and monitors activities by use of a wireless-connected smartphone app, which provides automatic objective measurements of body posture and gait, such as gait speed [49], [50]. In general, a combination of self-report and performance-based measures of ADL performance may be the best way to fully capture the picture of disability for a given EP [51].

Parkinson's Disease, PD

Parkinson's disease (PD) is a complex disorder expressed through many motor and nonmotor manifestations, which cause disabilities that can vary both gradually over time or come on suddenly. In addition, there is a wide interpatient variability making the appraisal of the many facets of this disease difficult [52]. Two kinds of measures are used for the evaluation of PD. The first is subjective, inferential, based on rater-based interview and examination or patient self-assessment, and consist of rating scales and questionnaires. These evaluations provide estimations of conceptual, non-observable factors (e.g., symptoms), usually scored on an ordinal scale [52]. The new second type of measure is objective, factual, based on technology-based devices capturing physical characteristics of the pathological phenomena (e.g., sensors to measure the frequency and amplitude of tremor) [52]. The following sections present a summary of the most widely used scales, questionnaires, and technological resources currently applied to the assessment and progression of PD.

Rating scales and questionnaires

Rating scales are extremely valuable instruments when developed explicitly to standardize clinical observations [20]. Their practical advantage over existing technologies is how they can integrate multiple manifestations of a disease in a single instrument in a straightforward way [53]. One of the first scales used for PD, the Schwab–England scale [54]. As with other scales, the absence of exact definitions within the scoring system made it difficult to guarantee interrater reliability [55]. Thereafter, Hoehn & Yahr [56] developed a scale based on their seminal study describing the natural progression of the disease, identifying five different stages. This scale is still one of the most widely used, although it only roughly characterizes the disease features [57]. The fact that many clinical investigators in the field of parkinsonism used different scoring scales (including the Schwab–England and Hoehn and Yahr scales, among others) made it difficult to compare results from different groups [58]. It became essential to create a unified scale that would guarantee clinometric assessment and that could be used in all studies to allow easy comparison of the results [53]. This idea led to the development of the Unified Parkinson's Disease Rating Scale (UPDRS). UPDRS is divided into four different sections covering the whole range of clinical manifestations [53]. UPDRS-III concretely assesses specific parkinsonian signs such as tremor, rigidity, bradykinesia, and postural instability/gait disturbance. It

provides an overall idea of the motor status of the patient and offers a global measure of functioning in PD. A new revision of UPDRS sponsored by the Movement Disorder Society (MDS), named MDS-UPDRS, offers improvements over the original version [59]. The MDS-UPDRS motor subscale includes 27 different items, which are scored from normal function to severe impairment [60]. Motor status is evaluated at a single point in time, either in an "on" (with medication) or an "off" (without medication) state [60]. Both clinical examination and MDS-UPDRS remain the standard for most PD assessments [60]. Also, as with other clinical rate scales, UPDRS is based on the opinion of experts and is hence prone to subjectivity and bias. Most clinical scales are ordinal and do not allow for continuous, quantitative assessment of each manifestation [20]. An additional drawback is that most clinical scales or examinations reflect the state of the patient at a precise moment, without reflecting the fluctuations in the motor state that may occur throughout the day [55]. This is a familiar source of error in clinical trials, as a measure taken at a single point in time cannot properly identify relevant changes in motor status over extended periods of time. Objective measurement instruments are needed and are now being developed to overcome the subjective, imprecise, and nonlinear measures resulting from clinical ratings, as current techniques do not have the replicability and greater accuracy that is needed (a) for the detection of subtle motor differences, (b) for the differential diagnosis of parkinsonism, (c) for the precise monitoring of response to therapies, and (d) because of lack of good interrater reliability [20].

Technology-based solutions

Recently, there has been a growing interest in developing an objective assessment of the symptoms in PD, and its health-related outcomes, using new technology-based tools, worn or operated by patients either in a healthcare or domestic environment [52]. The most important new technologies to aid in the treatment monitoring of PD patients are based on the use of inertial measurement units (IMU). Most commercially available IMUs have a triaxial accelerometer and a triaxial gyroscope, although a magnetometer is also commonly included. Over time, sensors have become more sophisticated, and they can be worn unobtrusively and can be attached to almost any body part to measure movement. These wearable devices can record not only the orientation, amplitude, and frequency of movements [20]. These data allow clinicians to assess, for example, the presence and severity of the cardinal features and complications of PD (i.e., tremor, bradykinesia, and dyskinesias) [61]. According to Monje et al. [20], **Figure 3** shows a schematic representation of an IMU worn over a finger, which detects tremor and bradykinesia in PD subjects.

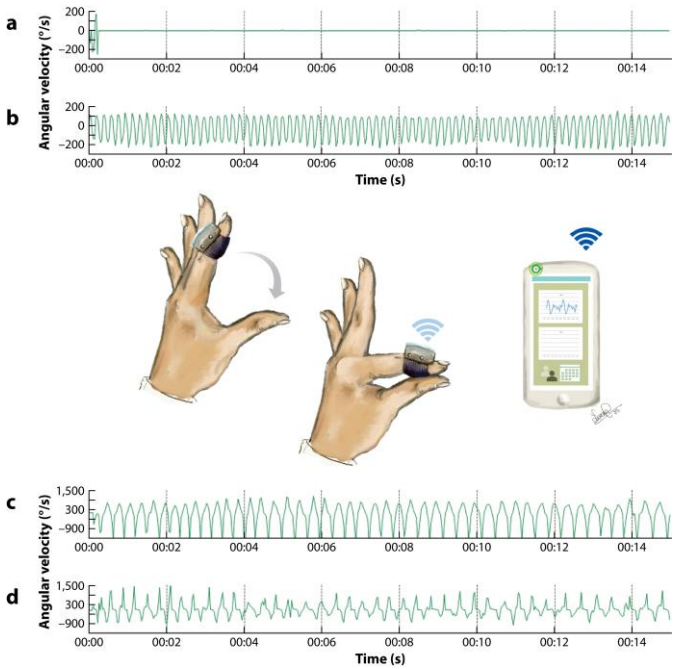

Figure 3. Schematic representation of an inertial measurement unit and graphic representation of a gyroscope signal. Graphic representation of the signal from a gyroscope obtained with the arms in the resting position in (a) a healthy subject and (b) a patient with Parkinson's disease (PD) with rest tremor. The signal shows no tremor in the healthy subject, and a rhythmic oscillatory movement at 5.5 Hz is observed in the patient with PD. Graphic representation of the gyroscope signal during finger tapping in (c) a healthy subject and (d) a patient with PD. Compared with the healthy subject, there is a progressive decrease in the rhythmicity and velocity of the finger taps in the PD patient, characteristic of bradykinesia. Source [20].

To this end, several technology-based solutions are available for clinical and home use [20], [52]. Kinesia, a wireless system for automated assessment of PD tremor [62], uses an IMU placed on the patient's index finger or the heel and can differentiate between a healthy subject and a patient with bradykinesia. Kinesia system can also record tremor with high reliability and agreement with MDS-UPDRS rest and postural tremor items [62], [63]. Objective gait and balance quantification are important for the overall evaluation of the motor status of the PD patient [20]. However, as these symptoms in PD can be both episodic (FOG, hesitation, difficult turning) and continuous (slow gait) associated with variability in performance, clinical examination at a point of time is often inadequate in elucidating the full spectrum of problems [52]. Optoelectronic systems are considered the gold standard in movement analysis because of their high reproducibility and accuracy [64]. At present, these systems have been extensively used in the assessment of PD in a research setting, mainly but not exclusively for the investigation of axial features, including balance, posture, and gait analysis [65]. However, their cost has precluded widespread use and adoption in clinical practice [20]. Thanks to the great advances in wearable technologies this is now possible not only in clinical, but also continuously at home, yielding an unexpected amount of objective information to complement what has traditionally been obtained in clinical settings [66]. Various sensor-based and wearable technologies are now being used for the assessment and monitoring of movement patterns during clinical visits and the daily lives of PD patients [20], [52]. In addition, wearable sensors, frequently worn in the lower body segment, have emerged as a

novel tool to quantitatively assess FOG during real life with more reliability than clinical measures alone [67], [68]. For example, a solution that permits objective evaluation of body posture and gait in PD subjects is the mTUG/mSWAY system [49], [50]. To date, numerous smartphone applications have been designed specifically for patients with PD. Existing applications include those devised for assessment of motor, cognitive, and psychological symptoms, as well as those intended to adjust and control treatment [69]. For example, Lopane et al. [70] implemented a system that allows optimizing the levodopa therapy in PD subjects according to disease progression to establish the minimum dose required over time. Thanks to its integrated technology-based platform, the protocol can be performed under a physician's supervision, but also self-administer at home [70]. Thus, smartphones seem to be a useful tool for the detection, assessment, and potential care of patients with PD [71], [72]. However, high-quality studies are lacking, although they are certainly feasible, due to smartphones' accessibility and ease of use [20]. In conclusion, clinical scales are the most widely employed standards for the evaluation of patients with PD [20]. Their limitations include subjectivity and the inability to monitor the disease continuously [20]. New sensors and wearable devices provide objective, accurate, and reproducible measurements that can overcome these barriers and complement the use of traditional methods. However, the use of these new technologies is still limited in practice because most of the studies performed to date were heterogeneous and non-standardized [20].

4.3 Neuromotor Rehabilitation

Neurorehabilitation aims to cement patients' existing skills, retrieve any lost skills, and promote the learning of new abilities, allowing people to function at their highest possible level despite their physical impairment. A variety of factors may have a significant effect on neurorehabilitation and influence motor learning processes. These factors include verbal instructions, characteristics, and variability of training sessions, the individual's active participation and motivation, positive and negative learning transfer, posture control, memory, and feedback. All of these factors are clinically applicable, and they provide the basis for emerging or established lines of research having to do with retraining sensorimotor function in neurological patients [73]. The miniaturization of sensing, feedback, and computational devices has opened a new frontier for movement assessment and rehabilitation [31], [74]. Wearable systems are portable and can enable individuals with a variety of movement disorders to benefit from analysis and intervention techniques that have previously been confined to research laboratories and medical clinics [31].

Elderly People, EP

Rehabilitation can play an essential strategic role to counteract impairments and disability which characterize the aging process. Correct rehabilitative programs have to be approached on the functional limitation and residual abilities of EP. Leading a more active lifestyle and regular physical activity including aerobic and

resistance exercises have been demonstrated to improve cardiovascular, respiratory, musculoskeletal, and cognitive wellbeing in EP [75]. Physical activity interventions for people with an intact cognition are well documented and shown to be effective in improving balance and reducing falls. People with dementia are two to three times more likely to fall and multimodal interventions that combine cognitive, as well as motor therapy, should be performed [76]. Physical activity is beneficial for reducing overall morbidity and mortality in EP [77]. Exercise recommendations for all individuals > 65 years of age are shown in a **Table 2**:

Recommendations [78]**:**
Aerobic:
• 30 to 60 min, may be accumulated in smaller increments of time • ≥ 5 days/week • Moderate intensity = 5 to 6 on a 10-point scale (where 0 = sitting, 5 to 6 = "can talk," and 10 = all-out effort)
Strength:
• 8 to 10 exercises (major muscle groups) • 1 to 3 sets of 8 to 12 repetitions each • ≥ 2 nonconsecutive days/week • Moderate to high intensity = 5 to 8 on a 10-point scale (where 5 to 6 = "can talk" and 7 to 8 = short of breath)
Balance:
• ≥ 2 days/week • Flexibility to maintain/improve range of motion (stretching of major muscle/tendon groups, yoga) • Balance exercises for those at risk for falls (tai chi, individualized balanced exercises)

Table 2. Physical activity counseling for older adults. Source [78].

The physical activity recommendations intended for all older adults may need to be modified for particular health conditions and disorders, using specific types of exercise to correct or ameliorate identified impairments and functional limitations [77]. Physical therapists, exercise physiologists, and physicians specializing in rehabilitation (physiatrists) can help to tailor the exercise prescription to meet patient needs. In addition, health care providers are perceived as respected sources of health information and should take an active role in promoting physical activity. Primary care clinicians should emphasize the importance of physical activity for health maintenance, ask patients if they are physically active, and advise patients to become physically active [77]. Innovatively, a recent European project (www.preventit.eu) developed and tested a personalized mHealth solution aimed at behavioral change in EP, in order to decrease the risk for age-related functional decline. The project consists of a mobile app to motivate older persons to exercise, and that shows how to integrate mobility exercises in daily living activities. This app, created by a multidisciplinary team, was already developed [79] and a feasibility study was performed [80]. Results indicated that the developed interventions were feasible and safe. Participants liked the concept of lifestyle-integrated activities, managed to change their daily routines towards increased activity, and were positive about the app [80].

Parkinson's Disease, PD

Despite optimal medical management, most patients with PD continue to experience a wide range of motor and nonmotor symptoms [81], [82]. All of these influence activities of daily living and affect the patient's quality of life [83], [84]. Examples of motor symptoms that respond insufficiently to medication or surgery

include impairments in speech, postural stability, and freezing of gait. Additional disability arises from the presence of nonmotor symptoms (e.g., cognitive impairment, depression, or psychosis), that are sub-optimally controlled with current medical management [81], [85]. This situation creates treatment challenges, not only in advanced disease stages, but even early on in the course of PD [86]. Moreover, although it is recommended to early start rehabilitation, it should be considered that PD is a chronic progressive disorder and the intervention must be adjusted to changing clinical conditions and tailored to the individual patients' needs [87], [88]. A widely held belief holds that nonpharmacological management might offer symptomatic relief of motor or nonmotor symptoms that are otherwise difficult to treat. Hence, a multidisciplinary approach involving non- and pharmacological treatment is the standard nowadays [89].

Physiotherapy

The physiotherapy domain that has been studied most extensively is exercise. Exercise aims at improving both physical and cognitive disabilities [90], [91]. Recent studies show that physical activity and exercise also have a positive impact on the global burden of non-motor symptoms in PD [92], [93] and some evidence suggests its potential to reduce fatigue [94]. As the disease progresses, therapeutic targets have to be adapted to the changing needs of the individual. In the early stage, therapy aims to prevent inactivity and to maintain physical capacity in order to avoid secondary complications [95], [96]. In the later stages the therapeutic aim shifts to maintaining physical function and preventing falls [95]. Given the significant impact of gait quality on mobility [95], [97], [98] and quality of life [99], gait is considered a primary target for symptomatic treatment in PD [87], [100]. As the disease progress, teaching alternative and compensatory strategies, such as providing extra attention or external guidance for the movement via cueing or feedback, are recommended [101].

Cueing for gait

PD affects different neural networks and neurotransmitters, leading to impaired ability to learn and express automatic actions, such as walking [102]. The use of external sensory cues (e.g., auditory, visual) to reinforce attention toward the task [103] is an effective gait-rehabilitation strategy for persons with PD; the cues stimulate the executive voluntary component of action [104]–[106] by activating the attentional-executive motor control system and bypassing the dysfunctional, habitual, sensorimotor BG network [102], [104], [105], [107]–[109]. This strategy helps people with PD improve gait consistency and rhythmicity. In the past, auditory cueing during gait has typically been provided continuously in an open loop (regardless of gait performance). As early as 1996, Thaut et al. showed that providing an external auditory rhythm by means of a metronome improves gait in PD subjects [110]. Since then, these findings have been replicated frequently and have been summarized in several systematic reviews [111]–[113]. In the therapeutic context, people are instructed to match foot strike with each beat of the auditory rhythm: these so-called ‘cues’ [112] facilitates the initiation or continuation of the movement. In addition, visual and somatosensory cueing modalities have

been investigated. Visual cues are offered as horizontal lines taped directly onto the floor [114]. Somatosensory cues are offered as rhythmical pulsed vibrations applied to a bony structures, so that the stepping rhythm can be matched to the vibratory cues [115]. Interestingly, the different cueing modalities have a differential effect on gait rehabilitation: while visual cueing primarily improves spatial gait parameters (e.g. stride length), auditory and somatosensory cueing primarily improve temporal gait features (e.g. gait speed and cadence) [116]. Verbal instructions are an alternative to cueing, even if the effectiveness of different verbal instructions such as 'walk fast' or 'walk while swinging the arms' should be tested [117]. Verbal instructions seem to direct conscious attention towards gait, improving performance [118], [119]. Despite these positive effects, there are two strong limitations: a) all these solutions need the supervision of an expert, such as a therapist, in a clinical environment; b) for long-term application, continuous cueing may result in cue-dependency and habituation on external stimuli [120]–[123].

Technology-based solutions: Biofeedback for gait

One of the most innovative developments in the quantitative assessment and management of PD symptoms is the use of wearable technologies during gait [124], which are able to overcome traditional open-loop cue, providing customized cueing: stimuli are triggered when gait deviates from normal, thus providing patients with immediate feedback on their performance. These closed-loop stimuli (audio [125]–[127], visual [128], [129], audio-visual [130] or proprioceptive [131]) are known as intelligent inputs [126], [127]. Closed-loop systems are based on the Knowledge of Performance [132], which is indicated as one of the optimal techniques for motor rehabilitation in PD subjects [133]. In contrast to open-loop systems, in closed-loop systems the external information does not necessarily become part of the participants' movement representation (as explained by the "guidance hypothesis"), thus possibly decreasing the development of cue-dependency [120]. The possibility of real-time biofeedback represents an important step toward the maximum benefit and clinical impact of wearable sensors. Wearable systems also permit data collection in a more naturalistic environment [125], [130]. Many real-time biofeedback studies have been performed in laboratories with grounded equipment, demonstrating the clinical benefits of real-time gait retraining [20]. For example, Ginis et al. [126], [127] compared the effects of intelligent auditory cueing (IntCue) and intelligent verbal feedback (IntFB) on gait as alternatives to traditional open-loop continuous cueing (ConCue). Those studies showed that during prolonged indoor walking both IntCue and IntFB conditions were at least as effective as ConCue for optimizing gait in PD [126], [127]. Casamassima et al. [134] developed a unique system made of wearable sensors and a smartphone that provides the same IntFB described above in order to improve the dynamic balance and gait performance of people with PD [125], [135], [136], **Figure 4**.

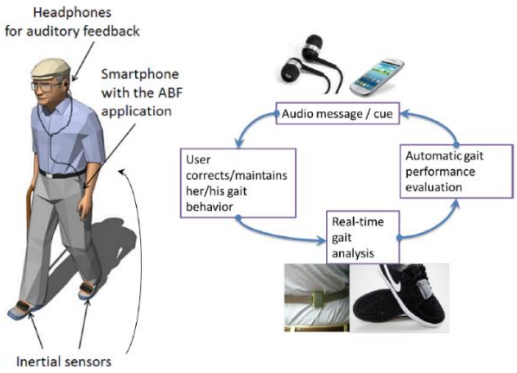

Figure 4. Scheme of the scenario for the use and the components of the system. Source [134].

Ginis et al. [125] tested the feasibility of this system in a real-life context: they discovered that the wearable system was well-accepted and seemed to be a practical approach to promote gait training in PD subjects. Although, the potential of real-time biofeedback in gait rehabilitation through wearable devices is underexploited [20], these new real-time systems seem to increase adherence to treatment, self-management, and quality of life [137], allowing also personalized and tailored rehabilitation on the individual patients' need [125].

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Section II - Clinical Assessment Solutions

Chapter 5

"Evaluation of Touch Technology for the Aging Population"

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Ph.D. candidate's main Contribution:
Developed the Touchscreen Assessment Tool (TATOO) android app.

Abstract

Optimal and effective hand function is essential for performing activities of daily living e.g., eating and dressing. Multiple advances in technology typical of our modern era overwhelmingly affect today's environment. Operating these technologies, which are necessary for performing a wide variety of basic and instrumental activities of daily living, often require perfecting new manual skills. A touchscreen is an excellent example of a modern technological application that has become prevalent in all aspects of modern life and its use requires fine motor skills to perform a range of activities such as tapping, swiping, and virtual pinching. However, traditional hand assessment tools are not able to capture the skills necessary to operate a touchscreen. The ability to assess these skills is essential for the development of appropriate treatment protocols as well as for determining technological adaptations necessary for making touchscreens accessible to all.

The Touchscreen Assessment Tool (TATOO) is a software application developed to comprehensively and objectively assess the hand performance abilities necessary for operating a touchscreen. The current pilot study examined the usability of the TATOO application by individuals in two age groups: elderly individuals (over 75 years) and middle-aged adults (over 45 years). The validity of the TATOO was examined by comparing the performance of the two age groups. Additionally, the correlations between the results of the TATOO and with traditional hand assessment tools (e.g., prehension strength and dexterity) were determined for the elderly group.

Usability, as assessed with the System Usability Scale, was very good in both age groups. Discriminative validity was demonstrated with elderly individuals demonstrating less accurate and significantly longer performance time. No correlation was found between the TATOO variables and prehension strength (grip and pinch strength) or dexterity skills.

The TATOO has the potential to become an important novel supplement to the toolbox available to clinical professionals treating the elderly in the modern world. Future studies with larger samples of elderly individuals are warranted in order to establish a normative database.

Introduction

The world's population is aging, with the global population aged 60 years or over in 2017 more than double the number in 1980 [1]. These numbers are expected to double again by 2050 reaching nearly 2.1 billion elderly individuals worldwide [1]. The fast-growing process of aging is expected to create a demographic shift, with a considerable impact on many aspects of the life of elderly individuals as well as on society at large [1]. Elderly adults are generally defined as individuals 65 years and above. Yet, being a very heterogeneous population in terms of chronological age, biological, psychological, and social factors, they cannot be considered as a single entity. Thus, some researchers classify older adults according to their chronological age, for example, considering adults ranging in age between 65-74 years as a younger-old group, and adults over the age of 75 years as the older-old group [2]. Others use a more functional approach, classifying the elderly population as: fit older people, frail older people, and disabled people [3].

Almost in parallel to the noted demographic changes, we are also witnessing rapid changes in technological advances which affect almost all aspects of modern society, including our work environments, communication avenues, healthcare facilities, and leisure activities. Due to these changes, elderly individuals are obliged to interact safely and successfully with an ever-growing number of technological devices, which can enable them to maintain independence in daily activities, render their participation in leisure activities more meaningful, and generally enhance their self-esteem and psychological wellbeing. Thus, the assessment of the elderly should not be limited to biological, physiological, and social changes, but should also consider existing environmental changes [4].

The ability to operate many of the technological devices present in our modern era is dependent on one's manual capabilities. The hand, consisting of the wrist and finger joints, is the organ at the end of the upper extremity and is responsible for manipulating technological devices present in our environment. The movement patterns of the hand are dependent on the specific task desired [5]. For example, goal-directed hand movements to visual targets and grasping tasks are two typical hand movements requiring different capabilities. Proper function of the hand depends on timely and accurate interpretation and integration of multimodal sensory input, such as visual input from the target and sensory input from the skin, joints, tendons, and muscles of the hand, leading to fine motor coordination of multiple muscle groups responsible for temporally and spatially accurate movements. Such movements are dependent on the proper interpretation of forward and backward feedback coordinated by the nervous system [6-8].

Normal aging is characterized by multi-system changes and deterioration, which have a direct effect on general physiological and functional capabilities, including those related to arm and hand function [9].

These detrimental changes are particularly significant after the seventh decade of life [6]. Thus, for example, aging is often accompanied by morphological changes in muscle tissues [10] resulting in reduced strength. It

is interesting to note that handgrip strength alone has been shown to be an accurate and universal marker of aging and an indicator of frailty in the elderly [3, 11]. Other age-related changes particularly significant to hand function involve the peripheral and central nervous systems, such as the slowing down of motor and sensory nerve conduction velocity, which results in reduced manual dexterity and sensory acuity [7, 8, 12, 13], strongly impacting the activities of daily living. [14]. In addition, Kalisch et al. [15] found healthy older adults tend to favor bilateral arm-hand usage.

Furthermore, the incidence of joint disorders, such as osteoarthritis (a noninflammatory disease resulting primarily from wear and tear processes) and rheumatoid arthritis (an inflammatory disease as a consequence of an autoimmune condition) increases with age [16]. These conditions which are accompanied by pain at rest and /or during motion, have a severe impact on hand function as they affect joint flexibility, muscle strength, and fine motor skills. Overall, the age-related changes in the musculoskeletal system and the nervous system, reducing strength, accuracy, and speed of performance, may have a crucial effect on many basic and instrumental activities of daily living, such as buttoning a shirt, selecting coins from a wallet, or unlocking doors [17], which are all directly linked to the individual's independence and participation.

As previously mentioned, given the increasing presence of technology in today's environment, it is necessary for the elderly to use multiple technological devices developed for the general (and often young) population in order to maintain their independence and quality of life. One such ambient technological device is the touchscreen, which is the focus of the present study. Indeed, touchscreens are rapidly becoming a key interface in multiple applications necessary for the performance of a variety of daily activities. Thus, for example, touchscreens are used for communication via smartphones, for activities such as ordering food at a restaurant or a ticket at a theatre, and in daily functional activities such as paying for goods in the supermarket or withdrawing money from an ATM. Differences in the ability to successfully operate a touchscreen between young and old adults are expected. These differences may be intensified in older adults and frail adults with age-related pathological conditions, such as arthritis. In order to devise training protocols that will assist elderly individuals to master the skills necessary to operate touchscreens, and furthermore, to help improve the design of such screens to match the capabilities/limitations of elderly individuals (i.e., change visual contrast or pressure needed to operate the device) it is vital to develop tools which are able to assess hand performance capabilities. Different reliable and valid assessment tools have been developed over the years to determine various aspects of hand function. Thus, for example, a dynamometer is used to provide quantitative data on handgrip strength [18], motor functional abilities can be assessed using the Jebsen Hand Function Test [19], and manual dexterity skills can be assessed using the Functional Dexterity Test [20]. However, to the best of our knowledge, none of the existing assessment tools provide valid and reliable data regarding hand performance ability to actually operate touchscreen devices.

The Touchscreen Assessment Tool (TATOO), developed by Daniel-Saad and Chiari [21] was designed to fill this void. This software application tool was developed by gaining a consensus regarding the user skills required to operate various touchscreen devices. A six-step procedure was used to collect and validate the required skills by a multidisciplinary team of 52 experts.

TATOO consists of six tasks providing information on the performance of different functional components required to effectively use a touchscreen (i.e., tapping, swiping, pinching, and dragging). Performance of each task is summarized by numeric and graphic reports of the following aspects:

1. Temporal aspects such as reaction time, time duration, etc.
2. Kinematic aspects such as movement range, drag path, and finger pressure.
3. Number of fingers used to operate each skill.
4. Movement accuracy assessed using indices such as the number of taps completed successfully, location of the first tap, and the number of drag attempts completed or not completed successfully.

The TATOO was developed primarily to assess the touchscreen performance of children. Currently, we are in the process of adjusting the system interface to assess the performance of the elderly population, particularly focusing on the detection of early stages of frailty. This chapter presents preliminary results obtained from middle-aged adults (age 45-65 years) and elderly individuals (above 75 years old). The objectives are to determine the usability of the TATOO system, compare performance between the two age groups, and determine the correlation between the TATOO variables and traditional hand function assessments. The presented analysis pertains to temporal and movement accuracy variables obtained in three of the six tasks performed with the TATOO system. This chapter presents preliminary results from a large ongoing study that will examine the psychometric properties of the TATOO and compare performance across a wide range of age groups.

Methods

A. Participants

The study was approved by the Ethical Review Board at the University of Haifa. Snowball sampling was used to recruit volunteers for the study. Inclusion criteria were as follows: 1. Age 45-65 years and >75 years; 2. Ability to understand and follow simple commands; 3. Living independently in the community or in independent living facilities; and 4. Ability to walk independently with or without a walking aid. Exclusion criteria were as follows: 1. Medical conditions (e.g., neurological, orthopedic, or cardiopulmonary pathologies) affecting the performance of daily activities; 2. Severe pain affecting functional performance; and 3. Serious uncorrected vision or hearing impairment. The participants were recruited from community

centers for the elderly. All the participants provided written consent for participation following a detailed explanation of the study.

B. Procedure

Each eligible and consenting volunteer underwent a series of assessments conducted in a fixed order during one 45-minute-long session. Data collected included the following:

1) Subject's characteristics:

a. Demographic Information – face-to-face interviews with a structured questionnaire were used to determine age, gender, experience with touchscreen devices, and level of education.
b. Health Status - interviews also determined known medical conditions, use of a walking device, and number of falls in the last year;
c. Cognitive Status - assessed with the Hebrew version of the Montreal Cognitive Assessment (MoCA) questionnaire, which has been shown to be a reliable tool for determining mild cognitive impairment (MCI) in older individuals. The cut-off for MCI proposed by the developer of the tool is 26 out of 30 [22, 23].

2) Traditional Hand Function Assessment

a. Strength – Bilateral handgrip strength and strength of two types of thumb-finger pinch grips (tip to tip, and three fingers pad to pad) were measured using a calibrated JAMAR hand dynamometer (Sammons Preston Rolyan, IL, USA) [18]. The measurements were repeated thrice for each hand and their means were used for analysis. The cut-off scores of handgrip strength for determining frailty are 29–32 kg for males and ≤17–21 kg for females (stratified by BMI classifications) [3, 24].
b. Manual dexterity – The Functional Dexterity Test (FDT) which is a validated and reliable tool was used to assess precision handling of objects necessary for many daily tasks. The test measures the time (in seconds) required to pick up 16 pegs in a predetermined order, turn them and replace them in peg holes [20]. Total time, in seconds, necessary to complete the task as well as scores combined with penalty points for mistakes are calculated for each hand. Normative data for the dominant and non-dominant hand are available. Mean scores of 21 are representative of functional hands, and scores above 50 and 55 seconds for the dominant and non-dominant hand, respectively, are representative of nonfunctional hands [20]. However, these scores may not be representative of older adults. Aaron and Jansen's original study [20] did not include participants older than 70 years [25].

3) Touchscreen Assessment Tool (TATOO)

The subjects performed six tasks comprising the TATOO in a fixed order while sitting comfortably in front of the touchscreen placed on a stable table. The duration of the test was approximately 10 minutes. Bilateral performance was recorded, starting with the dominant hand. Each task was repeated once following detailed verbal instructions. Subjects habitually using reading glasses were requested to use them while performing the tasks. The following three TATOO tasks presented in this study:

a. **Touch all corners** - The evaluation starts with a fishpond on the screen with the four covered corners. The clinician asks the individual to touch a covered corner of the screen until the cover disappears, and then to raise his/her finger and move it to another corner, this continues until all four corners are touched. Following the disappearance of the four rectangles, four new rectangles appear and the subject is asked to do the same action as before. Reaction time and test duration were measured in this task.
b. **Double-tapping** - A series of fish appear in the pool, one at a time. The clinician asks the individual to double tap each fish to make it disappear. When the fish disappears, the next fish appears at a new location (four appear in one of the corners and one in the middle of the screen). The interval between the appearance of the fish taps is fixed. Reaction time, test duration, and number of taps were measured in this task. A low number of taps represents a higher level of accuracy.
c. **Drag in all directions** - the individual is instructed to drag five items of clothing and to place them correctly (pressing while moving and releasing). (See **Figure 1** for the screen display). When the test starts, a rope with a shadow of clothes appears on the screen, then a t-shirt appears and the individual has to drag it to its place on the rope. The clinician asks the individual to correctly place each piece of clothing on the rope. When the item is dragged to its place, the next item appears. Reaction time, test duration, number of total drag attempts, number of drags completed successfully, and number of total touches outside the target were measured in this task.

Start Time:	09:04
Reaction Time [sec]:	0.52
Test Duration [sec]:	19
Total Flight Time [sec]:	9
Total Touch Time [sec]:	5.9
Total Drag Attempts:	6
Drag Completed Successfully:	5
Drag Not Completed:	0
Total Touch Outside the Target:	5
Touch with Multi-Fingers:	0

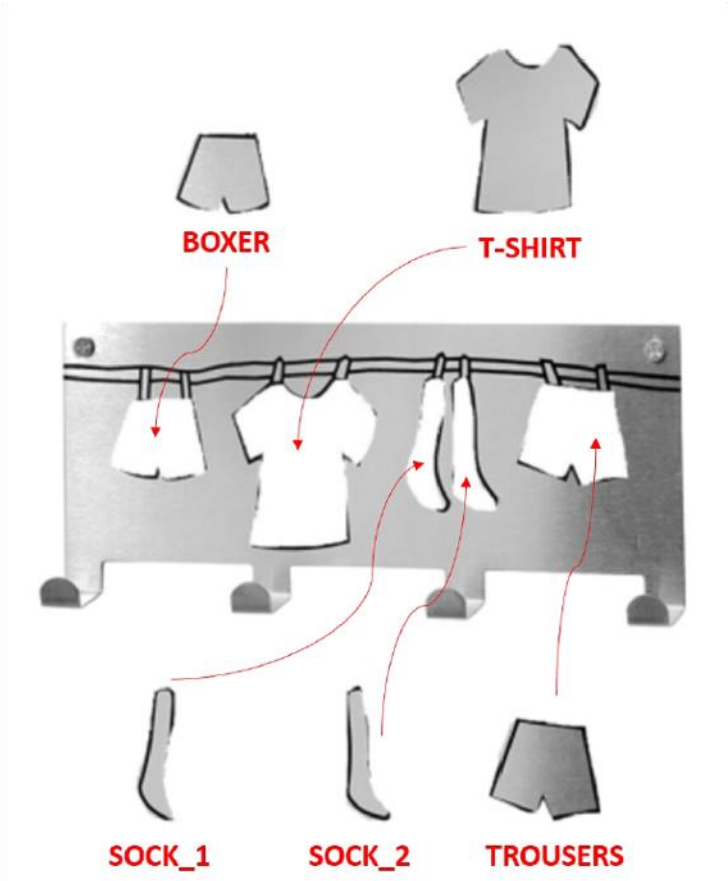

Fig. 1: Example of a screen display of the "drag in all directions" task.

4) Usability Assessment

Following completion of the TATOO test, the users' subjective assessment of its usability was determined with the System Usability Scale (SUS), which is used to assess the usability of hardware and software products [26]. The scale includes10 items, such as, "I thought the system was easy to use "covering three facets of usability: effectiveness (the ability of users to complete the relevant tasks and the quality of the tasks'

output), efficiency (the level of resources consumed to perform the tasks), and satisfaction (users' subjective reactions to using the system) [27]. The items are graded on a 5-point Likert scale, in which "1" indicates complete disagreement and "5" indicates complete agreement. Scores above 70 are considered to be ''very good'' and scores below 50 are considered to be ''very weak'' [28]. Internal consistency of the SUS was found to be high ($\alpha = 0.91$) and concurrent validity was found to be moderate ($r = 0.81$, $p < 0.001$) [29].

C. Statistical Analysis

Descriptive statistics were used to present the characteristics of the study sample and results of the traditional hand function assessment and the three tasks measuring the TATOO performance of each group. Construct validity of the TATOO was evaluated using Pearson correlations with traditional hand assessment tools. Independent groups (middle-aged adults vs. elderly individuals) were compared using the t-test. Probabilities at or below 0.05 were considered significant. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

Results

Sixteen community-dwelling elderly individuals (aged >75 years) and 12 middle-aged individuals (aged >45 years) participated in this study. All the subjects reported being independent in the basic and instrumental activities of daily living. The subjects' characteristics are presented in **Table 1**. Results of traditional hand function assessments in each group are presented in **Table 2**. No difference between the two groups was noted for the two types of pinch strength tests in either hand, except for the three-point pinch strength test of the non-dominant hand, in which the strength was significantly lower in the elderly group compared to the middle-aged group. The elderly group demonstrated significantly lower bilateral handgrip strength as well as poorer manual dexterity, as assessed by the FDT.

VARIABLES	Middle-aged Group (n=12)	Elderly Group (n=16)
Age, years mean ± SD; (range)	52.2±5.5; (46-60)	81. 6±4.7; (75-90)
Gender, n; (%) Male/Female	4 (33.3%) / 8 (66.7%)	5 (31.2%) / 11 (68.7%)
MoCA - Montreal Cognitive Assessment (out of 30)	21.3±4.4	29.3±0.9
Use of assistive device, n; %	0 (0%)	5 (31.3%)

Table 1. Characteristics of the study sample (n=28).

VARIABLES	Middle-aged Group (n=12)	Elderly Group (n=16)	*P-Value*
Strength [kg]:			
Handgrip strength*			
Dominant hand	33.8 ± 11.0	20.9±6.9	***0.001***
Nondominant hand	32.6 ± 12.7	19.5±5.8	***0.001***
Pinch tip to tip			
Dominant hand	4.07 ± 1.2	4.4±3.1	*NS*
Nondominant hand	3.9 ± 1.0	3.8±3.2	*NS*
Three-point pinch			
Dominant hand	6.3 ± 2.1	5.4±1.3	*NS*
Nondominant hand	5.8 ± 1.9	4.5±1.0	***0.020***
FDT - Manual dexterity [s]:			
Dominant hand	28.3 ± 9.7	43.8±14.8	***0.004***
Nondominant hand	32.4 ± 11.0	50.4±21.4	***0.013***

*The dominant hand of all the subjects in the study was right.
FDT- Functional Dexterity Test.
NS - not significant.

Table 2. Results of the traditional hand function assessment (n=28).

No correlation was found between the TATOO results and the prehension strength (grip and the prehension tests) or the dexterity test of the elderly individuals. The elderly group demonstrated lower performance ability in the TATOO application as was reflected by the temporal measures (e.g., reaction times and duration times) and reduced accuracy (**Table 3**). Usability of the TATOO application was reported as good by both the elderly and middle-aged groups, as determined by the SUS (76.2±20.7 and 80.0±15.4, respectively), with no significant difference between the two groups.

TASK	VARIABLES	Middle-aged group (n=12) Right / Left	Elderly group (n=16) Right / Left	*P-value* Right / Left
Touch all corners	Reaction time [s]	1.2 ± 0.6 / 0.9 ± 0.2	1.9 ± 1.1 / 1.5 ± 0.8	***0.04*** / ***0.01***
	Test duration [s]	10.7 ± 0.7 / 10.8 ± 0.6	11.7 ± 1.1 / 11.7 ± 1.2	***0.01*** / ***0.03***
Double tap	Reaction time [s]	1.3 ± 0.6 / 1.1 ± 0.5	2.0 ± 0.6 / 1.5 ± 0.5	***0.01*** / ***0.03***
	Test duration [s]	8.6 ± 1.9 / 8.1 ± 0.9	17.9 ± 10.0 / 18.7 ± 11.6	***0.00*** / ***0.01***
	Number of taps	11.3 ± 3.4 / 10.6 ± 1.4	19.4 ± 10.4 / 23.3 ± 14.9	***0.02*** / ***0.01***
Drag in all directions	Reaction time [s]	2.1 ± 1.0 / 1.5 ± 0.5	4.5 ± 3.1 / 3.6 ± 2.6	***0.02*** / ***0.01***
	Test duration [s]	29.8 ± 14.8 / 24.5 ± 9.7	65.4 ± 25.1 / 60.0 ± 25.3	***0.00*** / ***0.00***
	Number of drags completed	4.9 ± 0.3 / 4.9 ± 0.3	3.7 ± 1.6 / 3.8 ± 1.3	***0.02*** / ***0.01***
	Number of drag attempts	8.8 ± 3.9 / 6.3 ± 1.5	14.5 ± 5.6 / 8.00 ± 3.00	***0.01*** / *0.07*
	Number of touches outside the target	1.7 ± 1.5 / 1.7 ± 2.7	8.8 ± 6.7 / 14.2 ± 9.5	***0.00*** / ***0.00***

Table 3. Comparison of the TATOO performance between the two age groups.

Discussion

The results of this preliminary study indicate that the TATOO prototype can be used successfully by both middle-aged and elderly adults as a hand performance assessment tool, as it provides important information regarding an individual's ability to successfully perform the unique skills necessary for operating touchscreens. Furthermore, the TATOO can differentiate between the performance of elderly and middle-aged adults in touchscreen-related tasks such as tapping, swiping, pinching, and dragging. The ability to perform these tasks is essential for successful participation in today's modern environment, and consequently, for the physical and psychological well-being of aging individuals.

Furthermore, the lack of correlation between the TATOO variables and the measures obtained by traditional hand assessment tools used to determine strength and dexterity supports the claim that traditional tools cannot accurately predict an individual's ability to operate common technological applications relying on the manipulation of a touchscreen.

The present study results suggest that the TATOO has the potential to become an important novel supplement to the toolbox available to clinical professionals assessing and treating the elderly in the modern world. Future studies with larger samples of elderly individuals are warranted in order to establish a normative database for the entire gamut of skills necessary for the efficient operation of a variety of touchscreens.

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Section II - Clinical Assessment Solutions

Chapter 6

"App-based Self-administrable Clinical Tests of Physical Function: Development and Usability Study"

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Ph.D. candidate's main Contribution:
Developed the Self-STS android app, version 2 and version 3 of the Self-Tandem and Self-TUG apps.

Abstract

Background: Objective measures of physical function in older adults are widely used to predict health outcomes such as disability, institutionalization, and mortality. App-based clinical tests allow users to assess their own physical function and have objective tracking of changes over time by use of their smartphones. Such tests can potentially guide interventions remotely and provide more detailed prognostic information about the participant's physical performance for the users, therapists, and other health care personnel. We developed 3 smartphone apps with instrumented versions of the Timed Up and Go (Self-TUG), tandem stance (Self-Tandem), and Five Times Sit-to-Stand (Self-STS) tests.

Objective: This study aimed to test the usability of 3 smartphone app-based self-tests of physical function using an iterative design.

Methods: The apps were tested in 3 iterations: the first (n=189) and second (n=134) in a lab setting and the third (n=20) in a separate home-based study. Participants were healthy adults between 60 and 80 years of age. Assessors observed while participants self-administered the tests without any guidance. Errors were recorded, and usability problems were defined. Problems were addressed in each subsequent iteration. Perceived usability in the home-based setting was assessed by use of the System Usability Scale, the User Experience Questionnaire, and semi-structured interviews.

Results: In the first iteration, 7 usability problems were identified; 42 (42/189, 22.0%) and 127 (127/189, 67.2%) participants were able to correctly perform the Self-TUG and Self-Tandem, respectively. In the second iteration, errors caused by the problems identified in the first iteration were drastically reduced, and 108 (108/134, 83.1%) and 106 (106/134, 79.1%) of the participants correctly performed the Self-TUG and Self-Tandem, respectively. The first version of the Self-STS was also tested in this iteration, and 40 (40/134, 30.1%) of the participants performed it correctly. For the third usability test, the 7 usability problems initially identified were further improved. Testing the apps in a home setting gave rise to some new usability problems, and for Self-TUG and Self-STS, the rates of correctly performed trials were slightly reduced from the second version, while for Self-Tandem, the rate increased. The mean System Usability Scale score was 77.63 points (SD 16.1 points), and 80-95% of the participants reported the highest or second-highest positive rating on all items in the User Experience Questionnaire.

Conclusions: The study results suggest that the apps have the potential to be used to self-test physical function in seniors in a non-supervised home-based setting. The participants reported a high degree of ease of use. Evaluating the usability in a home setting allowed us to identify new usability problems that could affect the validity of the tests. These usability problems are not easily found in the lab setting, indicating that, if possible, app usability should be evaluated in both settings. Before being made available to end-users, the apps require further improvements and validation.

Introduction

At the time of retirement, at the age of 60-70 years, many people experience a significant decline in physical activity levels [1], and balance, gait, and mobility typically start to decline at a higher rate than before [2,3]. Thus, detection of changes in physical function at an early stage could be crucial to improve or prevent future declines in physical function and to sustain physical function over time. Objective assessment of physical function in health care settings is resource-demanding and therefore limited to people with a pressing need to have their function assessed, such as individuals who have experienced falls or who have been diagnosed with a condition known to affect physical functioning. Because functional decline typically occurs slowly, it might not pose an issue for the individual until their ability to perform activities of daily life is affected. Consequently, it might not be obvious why younger or well-functioning seniors should have their physical function assessed until it has come to this stage.

Innovations in mobile health (mHealth) technology have paved the way for new possibilities in assessing physical function. Most smartphones are equipped with sensors such as accelerometers, gyroscopes, and magnetometers and have high computational power; therefore, smartphones can be considered an inertial measurement unit enabling an objective and reliable assessment of physical function [4]. Considering that seniors are the fastest-growing group of smartphone users [5] and that, in 2017, 42% of adults aged 65 or older in the United States owned a smartphone [6], there is great potential for using smartphones as a tool for self-assessing physical function [7]. Furthermore, well-designed and evidence-based apps represent new opportunities in preventive strategies for the senior population as a valuable tool in helping to make changes in their lives that can prevent functional decline.

Three such smartphone apps for self-assessment of physical function were developed as part of the PreventIT (early risk detection and prevention in aging people by self-administered ICT-supported assessment and a behavioral change intervention, delivered by use of smartphones and smartwatches) project. PreventIT was a European Union Horizon 2020 Personalising Health and Care project. The apps allow users to self-administer instrumented versions of the Timed Up and Go (Self-TUG), tandem stance (Self-Tandem), and Five Times Sit-to-Stand (Self-STS) tests in order to measure mobility and dynamic balance, static balance, and leg strength, respectively. When developing a mHealth app for self-assessment of physical function, the usability of the app must be carefully considered, as it has been shown to be a fundamental determinant for technology adoption among older adults [8]. Usability is defined in the official International Organization for Standardization (ISO) guidelines as “the extent to which a product can be used by specified users to achieve specified goals with effectiveness, efficiency, and satisfaction in a specified context of use” [9]. Furthermore, when measuring aspects of one’s health, the accuracy of the results relies on the correct administration of the test. Thus, any usability problem associated with using an app-based test should be identified and addressed before it is made available to end users. This is usually done through several iterations of testing

with target user groups, ideally until no major usability problems exist with regards to using the apps and administering the test. Usability studies are most often carried out in a lab setting, which is convenient and offers a high degree of control, as opposed to field-based usability testing. However, field-based testing, which, in this context, would be a home setting, provides insight into how the system is used under more realistic situations. Depending on the system being tested and the phase of development, usability should ideally be tested in both lab and home settings.

The overall aim of this study was to evaluate whether people in our target group of seniors between the ages of 60 years and 80 years were able to reliably self-administer the tests on their own using the smartphone, apps, and instructions we provided without any interaction with the assessors. In this chapter, we describe the 3 iterations of usability testing with target user groups that were needed to identify all major usability problems. Each iteration consisted of a development phase and subsequent testing phase. In the first 2 iterations, we performed the usability tests in a controlled lab setting, where the assessors had prepared the test setup and necessary materials for the participants beforehand. For the third testing phase, participants were in their own homes, where they needed to prepare the test setup themselves by following instructions presented within the apps. This study does not address the topic of algorithms for signals and data processing nor how to present specific information and feedback to the users based on the test results.

Methods

Design Overview

We developed 3 app-based self-tests of physical function within the European Union Horizon 2020 project PreventIT [10]. Technology development in PreventIT followed the ISO standard 9241-210 [9] on user-centered development of products, and an iterative design approach was used to develop and test the usability of the apps. Because our target group is community dwellers and not clinical patients, we did not follow the ISO norm for medical devices. The target group of the apps was community-dwelling people aged 60 years and older, able to walk independently, and without any cognitive, functional hearing, or visual impairments. The overall aim of the mobile-based, self-administrable functional tests is early identification of risk for age-related functional decline by extracting relevant digital biomarkers from the smartphone-embedded inertial sensors. The intended context of use for the apps is to guide preventive intervention strategies for the general population. An initial version (version 1) of the Self-TUG and Self-Tandem apps was included for the first iteration. The apps were upgraded based on the results of this testing, and the Self-STS was added as a third self-test. All 3 apps were tested under similar conditions during the second iteration (apps version 2). After further upgrades, version 3 of the apps was tested in a summative usability evaluation with a new group of volunteers in a home setting.

Participants

We included participants from two studies. First, we included participants from a multicenter, 3-armed, feasibility randomized controlled trial conducted within the PreventIT project. For the first and second iterations, we included participants from the main study if they had performed the self-administration of the apps during baseline (iteration 1) and follow-up (iteration 2). The inclusion criteria for the participants are described in detail in the protocol paper for the PreventIT trial [10]. In short, for iterations 1 and 2, we included 189 and 134 community-dwelling adults, respectively, aged between 61 and 70 years from Trondheim, Norway; Stuttgart, Germany; and Amsterdam, the Netherlands. For iteration 3, we included 20 community-dwelling adults ranging in age from 60 years to 80 years (mean 68.7 years, SD 5.2 years) in Trondheim, Norway. Inclusion criteria were community-dwelling status, age between 60 years and 80 years, ability to walk 500 meters independently, Norwegian-speaking, ability to hear sound from a smartphone, and current user of a smartphone. Participants were excluded if they reported any severe cardiovascular, pulmonary, neurological, or mental diseases.

Description and Development of the Apps – From Version 1 to Version 3

We developed the apps using Android Studio 3.1.2 (Google, Mountain View, CA). Versions 1 and 2 of the apps were installed on a Samsung Galaxy S3 (Samsung, Seoul, Korea), while version 3 was installed on a Samsung Galaxy S8 (Samsung, Seoul, Korea).

Self-Timed Up and Go, Self-Sit to Stand, and Self-Tandem Apps

We created separate apps for each of the clinical tests (TUG, Five Times STS, and tandem stance). The apps were developed to be used as standalone tests, so one or more tests could be skipped if participants felt unsafe or did not want to perform a test. The TUG is a measure of mobility, in which the participant is timed while rising up from a chair, walking 3 meters, turning around, walking back, and sitting down again. In the Five Times STS, the participant is supposed to stand up from a chair and sit down again repeatedly 5 times as fast as possible, while being timed. In the tandem stance, the participant is supposed to place one foot in front of the other, heel-to-toe, in a straight line for 15 seconds, if possible. The Self-TUG uses an algorithm to detect the different phases of the TUG and the transitions between them (i.e., sit-to-stand, walking, turning, turn-to-sit) from the sensor signals. Further, it calculates features from these phases, such as duration, velocity, jerkiness, and signal range, as well as gait features including number of steps, step duration, and gait speed. For the Self-STS, the algorithms analyze the sensor signals and calculate several features from the whole task, transitions, and separate sit-to-stand and stand-to-sit phases of each repetition. Finally, for Self-Tandem, the algorithms analyze the sensor signals and calculate features such as signal frequency, ellipse area, velocity, sway path, jerkiness, signal range, and spectral entropy.

Version 1

A multidisciplinary team designed the apps with emphasis on ease of use for the target group, corresponding to the term “perceived satisfaction” in the ISO terminology [9]. This included displaying buttons and icons in relatively large sizes and using contrasting colors on a white background. In addition, to ease the demands on working memory, the app screens were designed with as few elements and text as possible. All apps are based on the same structure (**Figure 1**). For example, when opening the self-TUG app, a green “play” button appears. Pressing the button prompts a dialog box with a 5-second countdown and a red stop button. The countdown gives the user time to attach the smartphone to the lower back by means of a waist belt case (see Procedures). After the countdown and as soon as no movement is detected by the inertial sensors, an audio signal initiates the start of the test. At the end of the test, when the user is again sitting still, an audio signal indicates that the test is completed. The Self-STS has the same structure (i.e., audio signals for both the start and end of the test when the participant is sitting still). One important difference for the Self-Tandem is that the start and end signals are activated by time and not by movement. Thus, the audio start signal is initiated immediately after a 5-second countdown, followed by the end signal after 15 seconds.

Version 2

In version 2 of the Self-TUG and Self-STS, the smartphone was worn in the front trouser pocket instead of the waist belt case. We also integrated instruction videos into the apps. By pressing “play,” a dialog box appears with a question asking whether the participants want to see the instruction video (with a yes/no choice; **Figure 2**). Pressing “yes” starts the instruction video for how to perform the self-test. Pressing “no” results in the question “Do you want to start the test?” with the options “Yes” or “No, play the instruction video.” A reminder of what to do (insert phone in pocket for Self-TUG and Self-STS, hold against chest for Self-Tandem) was added to the countdown dialog box. The apps were otherwise similar in structure as in version 1.

Version 3

The upgrades made for the third version of the apps included new instructional videos, with updated voiceover and footage, and new graphical elements in the video to emphasize important details of how to perform the tests (Multimedia Appendix 1) as well as a new menu structure where the user could choose to view instructions or start the test. Instructions consisted of a submenu with two options: watch the instructions for how to prepare the test setup or how to perform the test. In particular, for the Self-TUG app, following these instructions, each user should measure the path on the floor autonomously or with a caregiver's help. In addition, new features (**Figure 3**) included a warning message that popped up if a user tried to perform a test without having watched both instructions; voiceover that instructed the user on what to do once the test sequence had been initiated (i.e., “Put the phone gently in your right pocket. Sit down

and wait for my instructions"); and real-time verbal feedback based on the inertial signals from the smartphone (e.g., "sit down," "get up from the chair," "proceed with the test," and count of repetitions for the Self-STS). The instruction videos were made for Norwegian study participants; thus, voiceover and text elements were in Norwegian. The text on the menu and dialog box was automatically adapted to the system language of the phone.

Procedures

Testing of Version 1

The testing of version 1 was carried out in a lab setting by trained assessors. Before testing, the assessors prepared the setup, which included a chair placed against the wall with a 3-meter walkway in front of it and a beanbag at the 3-meter mark. Following a standardized introduction of the general purpose and procedures of a usability test, the participants were asked to self-administer the tests using the app on the smartphone. The participants did not receive any guidance from the assessors during the tests, and the materials they needed to perform the test were placed on a chair in front of them. This included the smartphone, written instructions, and a belt case for wearing the phone during the Self-TUG. The assessors observed while the participants attempted to self-administer the tests, recording issues and errors on a sheet with predefined errors and issues that we expected in addition to a free-text box to record other errors and issues.

Testing of Version 2

For the second step, the Self-STS was added to the self-test battery. Testing happened under the same conditions as during testing of the first version, with one exception for the Self-TUG and Self-STS, namely that the smartphone placement was changed from the belt case to the front trousers pocket.

Testing of Version 3

An instructor visited the participants in their homes to get a realistic impression of how the system would be used in a real-world home setting. After a standardized introduction, the participants were asked to prepare and self-administer each of the 3 self-tests 3 times, without guidance from the instructor. One GoPro camera (GoPro, San Mateo, CA) was attached with a harness to the participant's chest and worn during the test sequence to record the participant's interaction with the smartphone. A second GoPro camera was placed in the room in a position where all movements could be recorded. The participants were encouraged to think aloud when using the system. After performing the self-tests, we asked participants to complete two questionnaires: User Experience Questionnaire (UEQ) and Systems Usability Scale (SUS) [11]. This was followed by an audiotaped semi-structured interview that was developed specifically for this study, where we aimed to collect end users' views on topics relevant to the apps, such as user experience, feedback/results, suggestions for improvements, and general usefulness of the apps.

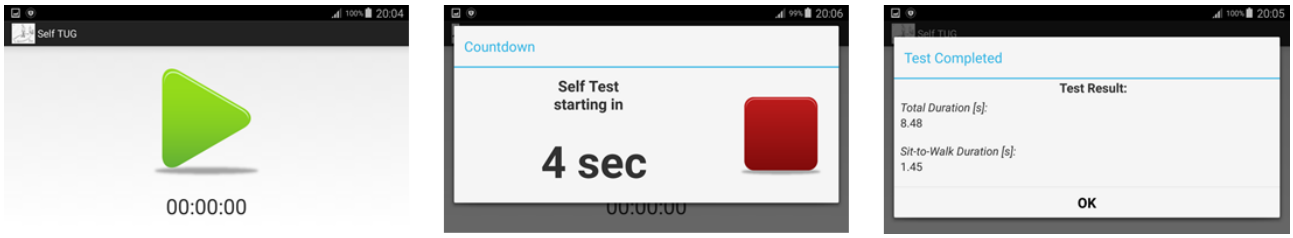

Figure 1. Screenshots of the first version of the Self-Timed Up and Go test.

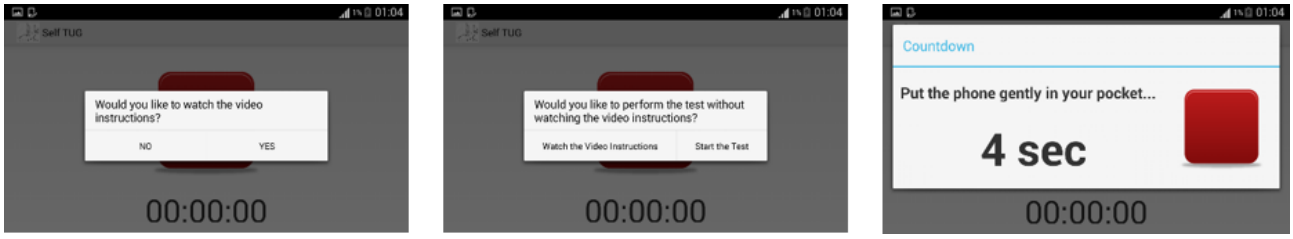

Figure 2. Screenshots of the second version of the Self-Timed Up and Go test.

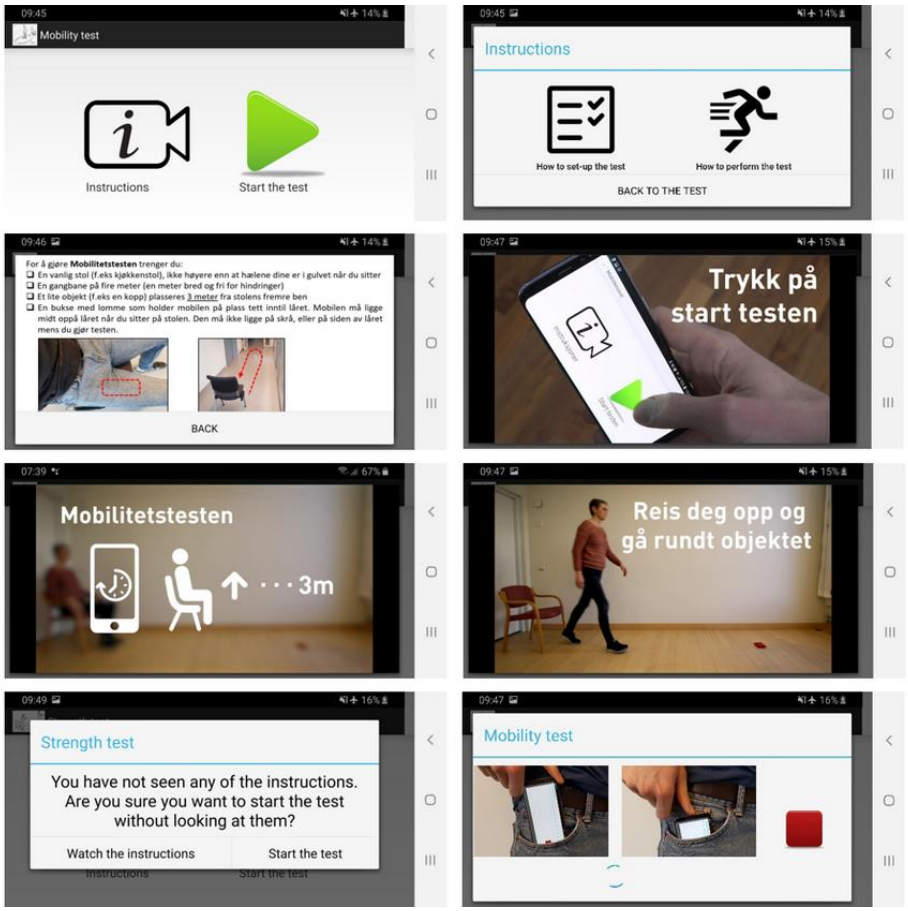

Figure 3. Screenshots of the third version of the Self-Timed Up and Go, including the start menu, instructions menu, test setup, instruction video screenshots, warning prompt when trying to start the test without having opened the instructions first, and instructions after starting the test.

Data Processing and Analyses

We defined errors as deviations from the test instructions and counted the number of errors from the clinical record forms in the first and second iterations and from video recordings in the third iteration (Multimedia Appendix 2). SUS scores, based on 5-point Likert-scale items, were averaged for each participant and converted into a usability score with a range from 0 to 100 (with a higher score indicating better usability). UEQ Likert-scale items were scored from 0 (highly agree) to 4 (highly disagree), and frequencies of responses within each category across all items were calculated. The interview transcripts were analyzed using thematic analysis [12] to identify relevant themes. Quotes were extracted for each subtheme and translated from Norwegian to English for analysis. The questions presented to the participants were "What did you think about using these apps to test your physical function?" and "Do you have any ideas for how the apps can be improved?"

Ethics

The data collection was performed in accordance with the Helsinki ethical guidelines. The first and second usability testing phases were approved by the ethical committees in Norway (REK midt, 2016/1891), Stuttgart (registration number 770/2016BO1), and Amsterdam (METc VUmc registration number 2016.539 [NL59977.029.16]). The Norwegian Center for Research Data approved that the data protection for the third usability testing was in accordance with current regulations (ref. no. 391684). All participants included in this study gave their informed consent.

Results

Participants' characteristics are presented in **Table 1**.

Cohort	App version	n	Age (years), mean (SD)	Male gender, n (%)	Has smartphone experience, n (%)	Years of education, mean (SD)
PreventIT study	1	189	66.3 (2.4)	90 (47.4)	157 (83.1)	15.6 (4.6)
PreventIT study	2	134	66.3 (2.5)	64 (47.8)	108 (80.0)	15.9 (4.8)
Summative usability evaluation	3	20	68.7 (5.2)	11 (55.0)	20 (100.0)	—[a]

[a]Data were not collected.

Table 1. Participant characteristics.

The usability problems identified, numbers of participants who experienced these problems, and what was done to eliminate or reduce these problems are presented in **Tables 2-4**.

Problem ID	Usability problem	Rate of errors/trials	Improvements made
1	Incorrect performance	120/378 (32%)	Added instruction video
2	Performed test without starting app	22/378 (6%)	Implemented instruction video that clearly demonstrates that the play button needs to be pressed before performing the test
3	Did not sit still and wait for start signal after test was started	23/189 (12%)	Added instruction video (demonstrating sitting still and waiting for the start signal before starting the test) and shortened the delay in the algorithm to limit any confusion
4	Incorrect placement of phone	32/378 (8%)	Changed placement to front pocket for Self-TUG[a] and Self-STS[b] and added a reminder in the countdown screen on what to do first (eg, "put the phone gently in your pocket")
5	Did not hear/perceive instructions	18/378 (5%)	Changed placement to front pocket for Self-TUG and Self-STS
6	Accidentally cancelled the test	15/378 (4%)	Not possible to override the home button function in the android OS, change of placement the preferred solution to reduce this problem

[a]TUG: Timed Up and Go.
[b]STS: Sit to Stand.

Table 2. Usability problems in version 1 of the Self-Timed Up and Go and Self-Tandem apps, rate of errors, and solutions (n=189).

Problem ID	Usability problem	Rate of errors/trials	Improvements made
1	Incorrect performance	66/402 (16%)	Added new, improved instructions to the videos (new voiceover and added graphical elements to draw attention to the details of the test procedures); added a warning message that appears if trying to start the test without watching instructions; and added real-time TTS[a] voice feedback on the number of repetitions in the Self-STS[b]
2	Started performing test (during instruction video) without starting the test in the app	28/402 (7%)	Changed structure of the app: main window now has two separate buttons, one for "start test" and one for "instructions"
3	Did not sit still and wait for start signal after test was started in the app	39/268 (15%)	Added real-time verbal step-by-step instructions that are initiated after the test is started in the app
4	Incorrect placement of phone	11/402 (3%)	Added real-time verbal instruction explaining where to place the phone and when to do this
5	Did not hear/perceive instructions	4/402 (1%)	Changed settings in the app so that the volume is always on maximum levels during testing, to prevent participants from accidentally pressing the "volume down" button
6	Accidentally cancelled the test	8/402 (2%)	Reduced the size of the "stop" button

[a]TTS: text-to-speech.
[b]STS: Sit to Stand.

Table 3. Usability problems in version 2 of all 3 self-tests, rate of errors, and solutions (n=134).

Problem ID	Usability problem	Rate of errors/trials
1	Incorrect performance	19/60 (32%)
2	Performed test (during instruction video) without starting the test in the app	5/60 (8%)
3	Did not sit still and wait for start signal after test was started in the app	0/40 (0%)
4	Incorrect placement of phone	0/60 (0%)
5	Did not hear/perceive instructions	2/60 (3%)
6	Accidentally cancelled the test	1/60 (2%)

Table 4. Usability problems identified in version 3 of all 3 self-tests and the rate of errors (n=20).

Iteration 1

In total, at least 1 error was made in 120 of 378 (32%) trials during the first usability testing with the Self-TUG and Self-Tandem. Forgetting or misunderstanding the written instructions were the leading causes of errors. In order to reduce the errors caused by this usability problem, we created video instructions to replace the written instructions.

Iteration 2

In the second usability test, errors due to usability problem 1 (incorrect performance of test) were made in 66 of 402 trials (16%). Percentage of errors due to usability problems 2 (performs test without starting app) and 3 (did not sit still and wait for start signal after test was started) increased from the first usability test, while the frequency of problems 4-6 (incorrect placement of phone, did not hear/perceive instructions, accidentally cancelled the test, respectively) decreased.

Iteration 3

In the third summative usability evaluation, errors due to usability problem 1 (incorrect performance of test) were made in 19 of 60 (32%) trials. Usability problems 3 (did not sit still and wait for start signal after test was started) and 4 (incorrect placement of phone) were eliminated, while the frequencies of usability problems 2 (performs test without starting app), 5 (did not hear/perceive instructions), and 6 (accidentally cancels the test) remained similar.

Table 5 presents an overview of the proportions of correctly performed (first) trials of self-tests for all tests in all iterations.

	Self-TUG[a], n (%)	Self-STS[b], n (%)	Self-Tandem, n (%)
Testing of version 1	42 (22.0)	N/A[c]	127 (67.2)
Testing of version 2	108 (83.1)	40 (30.1)	106 (79.1)
Testing of version 3	14 (70.0)	5 (25.0)	18 (90.0)

[a]TUG: Timed Up and Go.
[b]STS: Sit to Stand.
[c]Not yet developed.

Table 5. Number of correctly performed self-tests (first trial) with versions 1, 2, and 3.

Perceived Ease of Use

UEQ scores for iteration 3 are presented in **Table 6**, indicating a positive or very positive user experience on all 6 items. Seven sub-themes of perceived ease of use were identified in the analysis of interview transcripts and are presented in Multimedia Appendix 3 with accompanying sample quotes, mapped to proposed solutions.

Likert scale items	Strongly agree	Agree	Neither agree/disagree	Disagree	Strongly disagree
The set-up instructions were clear and easy to follow	14	4	1	0	0
The text in the app was easy to read	15	4	0	0	0
The buttons in the app were easy to discern from other elements	12	5	0	2	0
The signals were easy to hear	15	3	0	1	0
It was easy to navigate around in the apps	10	6	0	1	1
The instruction videos were clear and easy to follow	14	5	0	0	0

Table 6. Frequency of scores across the 6 items in the User Experience Questionnaire administered in the summative user evaluation (n=19).

The mean score on the SUS for version 3 was 77.63 points (SD 16.1 points, range 42.5-97.4 points). Of the 20 participants, 14 participants scored the SUS above 66.5 points, which is the average SUS score for cell phones [13].

Discussion

This chapter describes the development and usability testing of the Self-TUG, Self-STS, and Self-Tandem through 2 iterations in the lab and 1 in a home setting. Our aim was to develop app-based, self-administrable tests of physical function that participants could use with a high degree of effectiveness and perceived ease of use. The first phase of testing revealed usability problems that affected the validity of the test results, illustrating a clear need for improvements. We addressed all usability problems by making changes to the app design, test algorithms, and test setup, which led to a large decrease in the number of trial errors in the second usability testing. The work on the third version of the apps then started, which included updating and adding new instructions for a version fully adapted for use in a home-based setting.

The results from the SUS, UEQ, and thematic analysis from the usability testing in the home setting indicated that the participants experienced high levels of perceived ease of use when using the apps. Still, errors were made that may affect the validity of the tests, most of which were caused by misunderstanding the instructions. As an example, the most common error for Self-STS was not performing it as fast as possible, which was the main reason why only 25.0% (5/20) performed it correctly on their first attempt. This is lower than in the second version tested in the lab (40/134, 30.1%). This misunderstanding was caused by a delay in the real-time counting of repetitions that was implemented in the third version of Self-STS. The verbal announcement of repetitions, which is also done by the assessor when the original Five Times STS is administered in the clinic, was implemented to motivate the participant to perform it faster and as a way for the participant to keep track. However, as can be seen in the sample quotes from the participant interviews (Multimedia Appendix 3), there was a delay in the real-time feedback, making many of the participants stop and wait in a standing position for the TTS to announce the repetition before sitting down. This slowed down the performance and thus impaired instead of improving the validity of the test.

During the Self-TUG, a common error was to measure an incorrect distance for the walkway during the set-up. Although the instructions state that the walkway should be 3 meters, the participant responses indicate that they did not consider it crucial to measure exactly 3 meters. However, it has to be exactly 3 meters if the total test duration, walking duration, or gait speed is to be used as an outcome measure, as these features rely on a standardized distance walked. A clarification in the instruction, where it is specified that the walkway needs to follow a straight line of exactly 3 meters, could be one way to increase the reliability of the test. However, as the distance walked by the participant cannot be accurately measured by the app, another approach could be to only exploit the distance-independent signal features, such as those calculated from the sit-to-stand, turning, and turn-to-sit phases. This will improve the system reliability in assessing motor performance, but it will not ensure full compatibility with the standard clinical measure of the total test duration.

Another common error with the Self-TUG was to press “Start test” without watching the instructions first. Although we had implemented a pop-up warning if this happened, a bug prevented this from happening in 5 of the 7 times this occurred. For the 2 participants who received the pop-up warning, 1 ended up watching the instruction video and performing the test correctly, while the other ignored the warning and proceeded to perform the test without watching the instruction video, thus performing it incorrectly. Because of the bug, we do not have sufficient information to make a safe claim regarding the effectiveness of the warning message. However, we assume that this problem will be resolved by fixing the bug and specifying in the warning message that a correct trial depends on having watched the instruction video first.

A common usability problem observed with the Self-Tandem, and also mentioned by many of the participants in the interviews, was the discrepancy between the instructions and actual duration required to stand in the tandem position. The instructions state that the participant is supposed to place the feet in tandem, hold the phone against the chest, and, after hearing the start signal, keep as still as possible for 15 seconds. What often happened in the current version, however, was that the app tried to detect and verify the position of the smartphone after the participant had been instructed to place the feet in a tandem position. The TTS then instructed the participant to hold the tandem position and keep as still as possible for 15 seconds, until the end signal. Depending on how fast they placed the phone against the chest, the participant could thus stand up to 25 seconds in total. However, if the instructions had said that the participant should assume the tandem position after hearing the start signal, different people would likely need a different amount of time to get into the correct position, thereby risking that we would get less than 15 seconds of actual tandem balancing. The outcome measure in Self-Tandem is mediolateral sway, which was found to be a strong predictor of age-related decline in a study in which an eyes-open condition was used [14]. We therefore designed the test in a way that would ensure, or at least increase the chance, that we would have at least 15 seconds of the participant standing in tandem.

A limitation with the Self-Tandem test is that we cannot infer whether the participant was keeping the correct tandem position for the entire 15 seconds from the inertial sensor signals. This is not true for the Self-STS and Self-TUG tests, where the correct performance of all phases of the test can be identified reliably from the signal. A potential solution could be to implement a pop-up question where the user self-reports whether they actually held the position for the entire duration. Such a solution has been implemented in the mHealth app “Steady” [14]. Steady is a falls risk app that consists of a health history questionnaire, 4 balance tasks (eyes open, eyes closed, tandem, and single leg), and a 30-second sit-to-stand test. The binary outcome measure of whether a user is able to complete a static steady-state balance task in various conditions and durations, such as those used in Steady, has been used extensively in studies assessing healthy young seniors [15].Therefore, adding this feature could potentially increase the Self-Tandem’s diagnostic/prognostic abilities.

Implications and Future Work

The 3 iterations of usability testing described in this chapter were sufficient to identify all major usability problems with the self-tests. The only problem remaining after the third cycle is the real-time counting in the Self-STS, described earlier in the discussion, which can easily be fixed.

We have demonstrated what challenges can be expected when developing app-based tests of physical function for seniors and how solutions to specific usability problems identified in one iteration affected the same problems in the next iterations (Tables 2-5). In addition, we described the perspectives of the seniors regarding their experience of using the apps to self-administer the tests (Multimedia Appendix 3). Another interesting insight is how going from the lab to a home-setting influenced the type of usability problems observed, in particular those related to the test setup. In the lab setting, the setup was prepared beforehand, whereas in the home setting, participants needed to follow the instructions in the app describing how to measure the walkway in the TUG, secure the chair for Self-STS, and perform the Self-Tandem in a spot with a secure object within hands reach, without any guidance from the assessor.

The next step in the developmental process of the apps is to implement the solutions proposed in Multimedia Appendix 3 to address the remaining usability problems and conduct new usability tests to ensure that the apps are ready to be used by the target group to self-administer the tests safely and correctly. Furthermore, the algorithms used for signal processing in Self-TUG and Self-STS need to be validated with the changed placement of the smartphone from the lower back (version 1) to the thigh (versions 2 and 3). Although we experienced some issues with this new placement in the usability testing (eg, some trousers were too loose), with the smartphone tilting down on either side of the thigh and making the trial invalid, we nevertheless believe that this solution offers the best trade-off between motion detection ability on one side and ease of use on the other side.

Our app-based tests of physical function could be applicable in many contexts, and different contexts may require different test outcomes. In the current version of the apps, the results presented to the user after performing the tests are total durations for the Self-TUG and Self-STS and sway path distance in the Self-Tandem. As discussed, however, these might not be feasible to exploit from an unsupervised test, where correct test set-up cannot be verified. The data processed by the inertial sensors within the smartphone provide additional features, and we aim to review existing literature to identify which of the signal features from instrumented versions of the TUG, Five Times STS, and standing tandem are the most predictive of functional decline in seniors. Given that these features can be reliably measured with the smartphone worn in the trouser pocket, they will be exploited as outcomes presented to the app users.

Although many tests of physical function have been instrumented by the use of smartphones, the authors are only aware of one other app that is developed for unsupervised self-assessment, the Steady app [14].

What separates the Steady app from ours is the type of tests implemented in the app. In addition to static balance and repeated sit-to-stands, we integrated the instrumented TUG. Furthermore, we performed usability assessments of the app in the participants' own homes, in contrast to Steady, where an unoccupied apartment was used for all non-lab test sessions in order to mimic a home environment.

Limitations

In our first 2 usability tests, the apps were tested by 189 and 134 participants, respectively. Although this was very useful for identifying what did and did not work well, we might have achieved similar results with fewer participants. Earlier studies have suggested that as few as 12 test users can be sufficient to detect the majority of usability problems [16]. Thus, with shorter and faster test cycles, the apps could potentially have been at a more mature stage today.

The participants in the summative usability evaluation differed to those from the PreventIT study in terms of age and smartphone experience. This makes it more difficult to say something about the impact that each app improvement had, as opposed to testing all app versions in 3 different, but homogenous, cohorts. However, we see it as an advantage that the apps are also tested in a slightly older cohort, as these participants can help us identify problems that could be more relevant to how they experience the usability of the apps, as compared to seniors that are younger or more experienced with technology in their daily life. Furthermore, the self-tests have not been validated in persons with tremor or pathologies; thus, the results do not necessarily generalize to these populations.

ISO's definition of usability comprises 3 main aspects: effectiveness, which is the accuracy and completeness with which users achieve certain goals; efficiency, which is the relationship between the accuracy and completeness with which users achieve certain goals and the resources expended in achieving them; and satisfaction, which is the user's comfort with and positive attitudes towards the use of the system [17]. Efficiency was not measured in our usability studies. It is often measured as task completion time or learning time, but in the context of testing physical function, where the time spent on completing a task also depends on the person's physical abilities, we did not consider task completion time to be an appropriate outcome measure of usability, but rather of functional level of the participant.

Although we have assessed the usability of these apps and identified solutions to the remaining usability problems, the validity of the outcome measures from the tests also needs to be further investigated before being made available to end users. Another point worth mentioning is that the correct use of the apps and, accordingly, valid test results could be ensured by giving the end users a one-time demonstration of how to use apps and perform the tests correctly. This could be given in a home visit or in an appointment at the lab or clinic, depending on the context of use.

Conclusion

The study results suggest that the apps have the potential to be offered as a solution for self-testing of physical function in a non-supervised, home-based setting. Participants found the apps easy to use. The summative user evaluation in a home setting revealed important usability problems that were not identified in the lab, highlighting the importance of utilizing both test settings when assessing app usability. The current version of the apps has some remaining usability problems that can affect the test results, indicating that the apps need to be further improved and then validated before being made available to end users.

Multimedia Appendix 1

Video instruction available within version 3 of the Self-TUG app, demonstrating how to perform the Self-TUG, with voiceover in Norwegian.
MP4 File (MP4 Video), 21012 KB

Multimedia Appendix 2

Detailed description of usability problems.
DOCX File , 16 KB

Multimedia Appendix 3

Sub-themes within perceived ease of use and sample quotes from participant interviews following the third iteration of usability testing and proposed solutions.
DOCX File , 15 KB

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Section II - Clinical Assessment Solutions

Chapter 7

"Ecological, Obstructed Walking paradigm to assess the effects of Audio-Visual Scanning Training (AViST) in Hemianopic subjects"

Most of the content of this chapter has been Published in:

M. Corzani, S. De Silvestri, A. Ferrari, D. Braghittoni, E. Ladavas, L. Chiari. "Ecological, Obstructed Walking paradigm to assess the effect of Audio-Visual Scanning Training (AViST) in Hemianopic subjects". Proceedings of the XX SIAMOC Congress, Bologna, Italy. p. 120 (2019). DOI: http://doi.org/10.6092/unibo/amsacta/6260

Ph.D. candidate's main Contribution:
Designed the walking protocol and data analysis, performed/processed part of the experiment/data analysis.

Abstract

Homonymous hemianopia (HH) is a condition that originates from a visual field loss on the right or left side of both eyes (right HH, left HH). This impairment compromises the ability to produce effective saccades leading to increased difficulty in functional activities. For this reason, patients with HH undergo specific treatments, such as the Audio-Visual Scanning Training (AViST), to learn to respond to audio-visual stimuli with more effective saccades, with a better exploratory ability. Usually, patients fill in questionnaires to judge their ability in carrying out such activities before and after the rehabilitation treatment. This study used an innovative walking paradigm to quantify the subjects' behaviour while walking and avoiding vertical obstacles. Ten subjects with HH and six healthy controls (HC) performed the walking paradigm. Using the Gait Tutor system (mHealth Technologies, IT), the aims of this study are: 1) explore differences in movement between groups; 2) quantify the effect of AViST through a longitudinal analysis in HH subjects.

Introduction

Homonymous hemianopia (HH) is a condition that originates from a visual field loss on the right or left side of both eyes (right HH, left HH) due to post-chiasmatic lesions on the contralateral retinogeniculostriate pathway. This impairment compromises the ability to produce effective saccades leading to increased difficulty in functional activities, like walking in a crowded environment [1].

For this reason, patients undergo specific treatments. In collaboration with the Cesena Centre of Cognitive Neuroscience (CNC), in this study, we used Audio-Visual Scanning Training (AViST), a 4 h/day for 2 weeks treatment used to train subjects with HH to respond to audio-visual stimuli with more effective saccades, contributing to a better exploratory ability [2]. The AViST apparatus consisted of a semicircular structure in which the visual and the acoustic stimuli were spatially located. The apparatus was made of a plastic horizontal arc (height 30 cm, length 200 cm) fixed on the table surface. The auditory stimuli were produced by eight piezoelectric loudspeakers (0.4 W, 8 Ω), located horizontally at the subject's ear level, at an eccentricity of 8°, 24°, 40°, and 56° both in the hemianopic hemifield and in the intact hemifield. The loudspeakers were covered by a strip of black fabric, attached to the arc, preventing any visual cues about their position. The sounds were created by a white-noise generator (80 dB). Six visual stimuli were located directly in front of the loudspeakers: the light displays, poking out of the black fabric, were placed at an eccentricity of 24°, 40° and 56° to either side of the fixation point. Note that we refer to the auditory positions by labels A1–A8 moving from left to right, and similarly, we described the corresponding visual stimuli positions by labels V1–V6 (**Figure 1**).

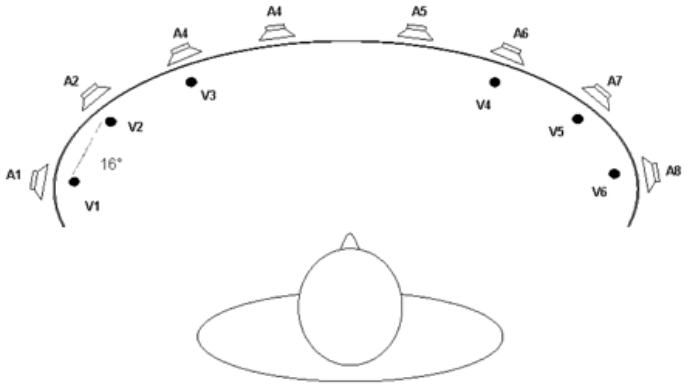
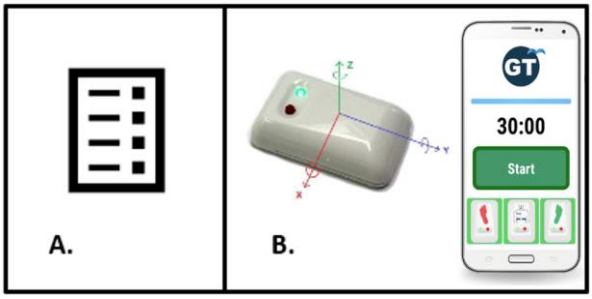


Figure 1. Bird's eye schematic view of the position of loudspeakers and light displays. Source [2].

Usually, patients are asked to fill in (A.) questionnaires to assess their ability to carry out functional activities before and after the rehabilitation treatment. In this study, we used (B.) the Gait Tutor (mHealth Technologies, IT) to quantify the subjects' motor behavior while walking, avoiding vertical obstacles [3] in the future perspective of providing the neuropsychological staff with a tool for objective assessment of visuospatial exploration in a motor task.



In this scenario, the aims of this study are:

1. Explore differences between *HH* and healthy control subjects (*HC*) in performing the walking test;
2. Quantify the effect of AViST in *HH* subjects by a longitudinal analysis.

Methods

Twelve subjects with HH (8 right-HH, 4 left-HH) and six HC walked three times through a corridor avoiding three vertical obstacles, **Figure 2**. Nine HH-subjects performed the test before and after they performed AViST.

In our walking paradigm, the Gait Tutor system was used with two inertial sensors applied to the feet to detect trajectories and spatiotemporal gait parameters. One sensor is worn on the forehead to detect the head's left-right movement (yaw angle).

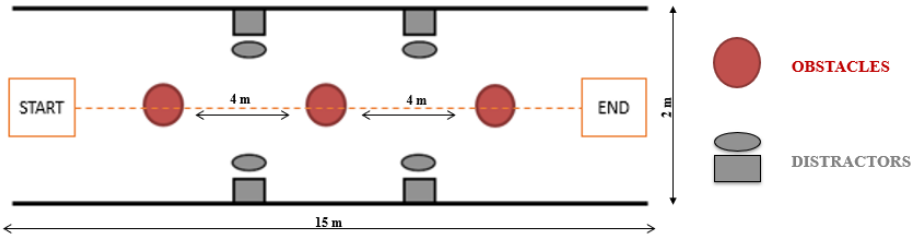


Figure 2. Set-up of the walking paradigm.

Data are transmitted via Bluetooth to the Gait Tutor app. For the sake of this study, the Gait Tutor system provided the following outputs: trajectory estimates from the right foot; raw data from magneto-inertial sensors: 3-D accelerometer, 3-D gyroscope, and 3-D magnetometer (sampling frequency: 100 Hz); Spatiotemporal gait parameters.

From the trajectory, we calculated frontal and lateral distances between the subject and each obstacle during their circumvention (semi-axes of the approximating ellipse [3]), **Figure 3**.

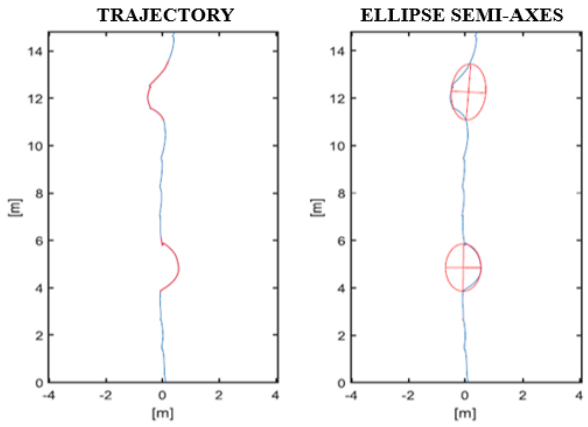


Figure 3. Methods to extract ellipse semi-axes.

An on-site recording was performed to calibrate the magnetometer while the head sensor was rotated around all possible directions. Then, to obtain an attitude and heading reference system (AHRS) for the head, we used the Madgwick filter, which needs tuning of parameter Beta (0.005).

We extracted features from the yaw angle, namely: the maximum angle between head direction and central line; variance during the test; observation of the subjects with hemianopia behavior suggested that segments of 1.5 m preceding every obstacle could carry more significant information, thus mean frequency of the yaw spectrum in those segments was added to the analysis (n = 8).

For each outcome, we averaged the values obtained during the three repetitions of the test. We used unpaired non-parametric statistics to examine differences between HC and HH groups and paired non-parametric statistics to assess the effect of AViST.

Results

The statistical analysis showed that the HH group requires more time and takes smaller steps to perform the protocol than HC subjects (**Table 1**). Looking at the absolute median value, we observed greater variance and maximum yaw angle (Max_Angle) in HH compared to the HC group. Instead, the semi-axes drawn by subjects to circumvent the obstacles were similar between the groups.

Regarding the effects of AViST (**Table 2**), the paired analysis showed that subjects after the treatment tend to walk farther from the obstacles and with higher yaw mean frequency while approaching them.

Group Effect	**Time [s]**	**Stride Length [m]**	**Minor axis [m]**	**Major axis [m]**	**Max_Angle [°]**	**Variance [°^2]**	**Mean Freq. [Hz]**
HH (n=12)	17.0 (14.0-18.3)	0.98 (0.92-1.18)	0.37 (0.32-0.39)	1.12 (0.83-1.25)	24.4 (18.1-30.7)	80.3 (55.0-104.5)	0.17 (0.09-0.21)
HC (n=6)	11.0 (9.4-13.1)	1.24 (1.16-1.26)	0.35 (0.24-0.38)	1.33 (1.19-1.38)	16.6 (13.6-19.0)	44.7 (25.5-66.3)	0.23 (0.16-0.30)
P-value	***p < 0.001***	***p = 0.007***	p = 0.750	p = 0.066	p = 0.083	p = 0.150	p = 0.150

Table 1. Results of the Group effect.

AViST Effect	**Time [s]**	**Stride Length [m]**	**Minor axis [m]**	**Major axis [m]**	**Max_Angle [°]**	**Variance [°^2]**	**Mean Freq. [Hz]**	**Mean Freq. Segm. [Hz]**
Pre-HH (n=9)	16.7 (14.2-19.3)	0.99 (0.88-1.18)	0.36 (0.32-0.38)	1.06 (0.75-1.17)	23.9 (18.1-35.4)	79.3 (57.1-88.1)	0.17 (0.11-0.21)	0.39 (0.26-0.70)
Post-HH (n=9)	17.0 (13.8-18.0)	0.93 (0.90-1.18)	0.39 (0.36-0.43)	0.77 (0.73-1.06)	24.8 (17.6-29.3)	72.5 (54.7-106.5)	0.20 (0.17-0.25)	0.61 (0.44-1.01)
P-value	p = 0.250	p = 0.820	***p = 0.039***	p = 0.496	p = 0.652	p = 0.910	p = 0.203	***p = 0.008***

Table 2. Results of the AViST effect.

Discussion

Differences in total time and stride length between groups show that this walking paradigm was more challenging for the HH subjects participating in the study. Besides, greater variance and maximum yaw angle seen in HH subjects seem to support the hypothesis that they rely on head rotation to compensate for the blind hemifield. Still, these effects were not confirmed by statistical analysis.

Results obtained in the longitudinal analysis indicated that there are only a few parameters that changed significantly after AViST. In particular, the increase in yaw means frequency when approaching obstacles, could reflect behavioral strategies employed when subjects explore a scene.

These parameters can discriminate between the two groups, but the analysis should be performed on a larger sample to detect small effects. Moreover, by focusing on other segments of the walking trajectory, different

behavioral patterns may be highlighted. In the future, the subjects' anthropometric characteristics could be considered in the analysis, and the reliability of the features should be assessed. Finally, from using this protocol to assess objective changes due to AViST, concurrent validity with other neuropsychological assessment tools should be tested.

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Section III - Neuromotor Rehabilitation Solutions

Chapter 8

"Motor Adaptation in Parkinson's Disease During Prolonged Walking in Response to Corrective Acoustic Messages"

Published:

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Ph.D. candidate's main Contribution:
Designed the analysis and processed the data.

Abstract

Wearable sensing technology is a new way to deliver corrective feedback. It is highly applicable to gait rehabilitation for persons with Parkinson's disease (PD) because feedback potentially engages spared neural function. Our study characterizes participants' motor adaptation to feedback signaling a deviation from their normal cadence during prolonged walking, providing insight into possible novel therapeutic devices for gait re-training.

Twenty-eight persons with PD (15 with freezing, 13 without) and 13 age-matched healthy elderly (HE) walked for two 30-minute sessions. When their cadence varied, they heard either intelligent cueing (IntCue: bouts of ten beats indicating normal cadence) or intelligent feedback (IntFB: verbal instruction to increase or decrease cadence).

We created a model that compares the effectiveness of the two conditions by quantifying the number of steps needed to return to the target cadence for every deviation. The model fits the short-term motor responses to the external step inputs (collected with wearable sensors). We found some significant differences in motor adaptation among groups and subgroups for the IntCue condition only. Both conditions were instead able to identify different types of responders among persons with PD, although showing opposite trends in their speed of adaptation. Increasing rather than decreasing the pace appeared to be more difficult for both groups. In fact, under IntFB the PD group required about seven steps to increase their cadence, whereas they only needed about three steps to decrease their cadence. However, it is important to note that this difference was not significant; perhaps future work could include more participants and/or more sessions, increasing the total number of deviations for analysis. Notably, a significant negative correlation, $r = -0.57$ (p-value = 0.008), was found between the speed of adaptation and number of deviations during IntCue, but not during IntFB, suggesting that, for people who struggle with gait, such as those with PD, verbal instructions rather than metronome beats might be more effective at restoring normal cadence.

Clinicians and biofeedback developers designing novel therapeutic devices could apply our findings to determine the optimal timing for corrective feedback, optimizing gait rehabilitation while minimizing the risk of cue dependency.

Introduction

Parkinson's disease (PD) is a neurodegenerative disorder predominantly characterized by the depletion of dopamine and dopaminergic neurons in the basal ganglia (BG) [1]. The disease affects different neural networks and neurotransmitters, leading to impaired ability to learn and express automatic actions, such as walking [2]. The use of external sensory cues (e.g., auditory, visual) to reinforce attention toward the task [3] is an effective gait-rehabilitation strategy for persons with PD; the cues stimulate the executive voluntary component of action [4]–[6] by activating the attentional-executive motor control system and bypassing the dysfunctional, habitual, sensorimotor BG network [2], [4], [5], [7]–[11]. This strategy helps people with PD improve gait consistency and rhythmicity. In the past, auditory cueing during gait has typically been provided continuously in an open loop (regardless of gait performance). However, continuous cueing may result in cue-dependency and habituation on external stimuli [12]–[15].

One of the most innovative developments in the quantitative assessment and management of PD symptoms is the use of wearable technologies during gait [16], which are able to provide customized cueing: stimuli are triggered when gait deviates from normal, thus providing patients with immediate feedback on their performance. These closed-loop stimuli [audio [17]–[19], visual [20], [21], audio-visual, [22] or proprioceptive [23]] are known as intelligent inputs [18], [19]. In contrast to open-loop systems, in closed-loop systems the external information does not necessarily become part of the participants' movement representation (as explained by the “guidance hypothesis”), thus possibly decreasing the development of cue-dependency [12]. Wearable systems also permit data collection in a more naturalistic environment [17], [22].

Two previous studies [18], [19] compared the effects of intelligent auditory cueing (IntCue) and intelligent verbal feedback (IntFB) on gait as alternatives to traditional open-loop continuous cueing (ConCue) (see **Figure 1**). Those studies showed that both IntCue and IntFB conditions were at least as effective as ConCue for optimizing gait in PD. For example, the first study showed that IntFB was most effective at maintaining normal cadence at the end of a 30-minute-long gait exercise, although it also increased the gait variability (deviations from the target pace) in persons with PD compared to healthy controls. Furthermore, during IntCue, the number of deviations was actually smaller than during the no-input condition in PD [18].

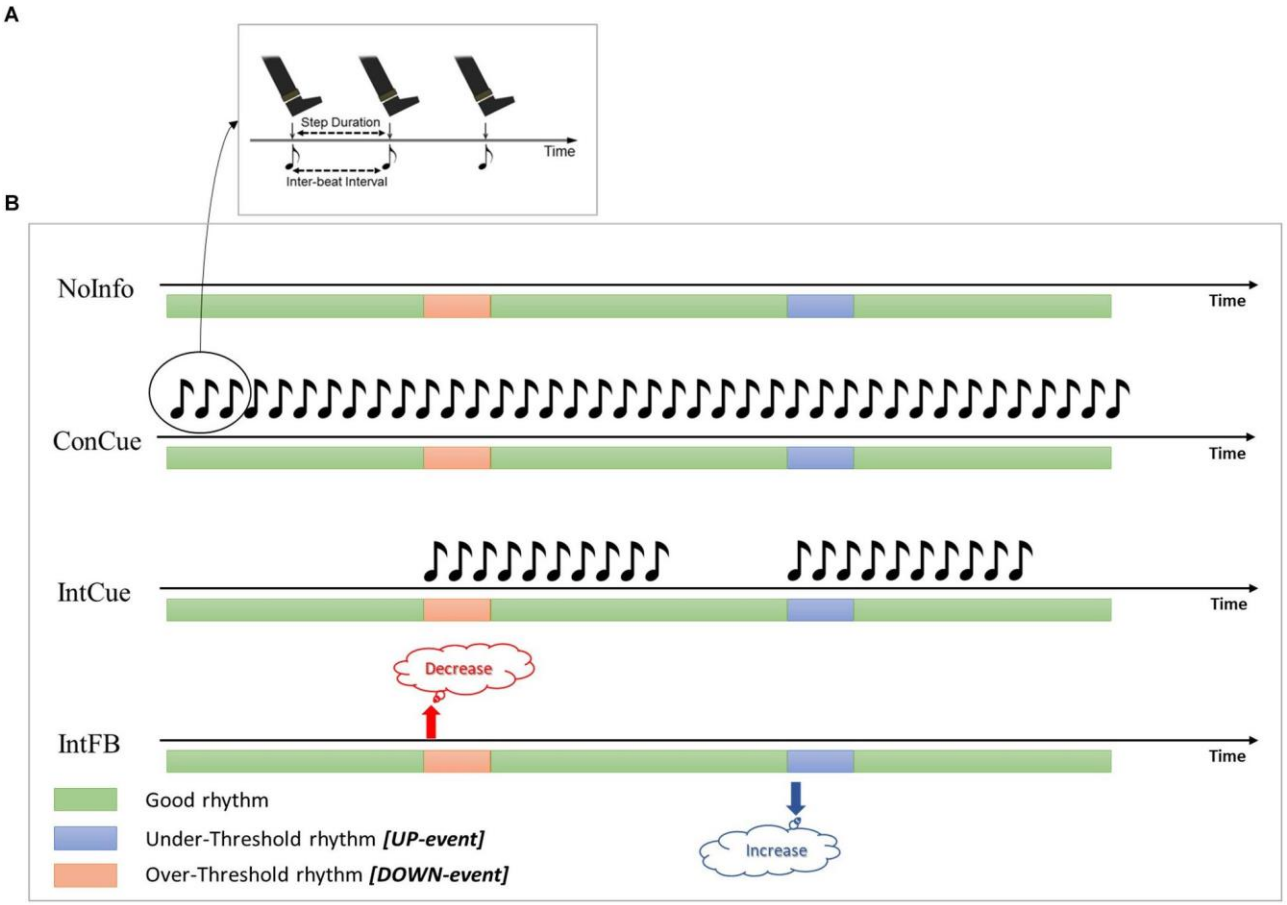

Figure 1. (A) During ConCue and IntCue the participants were instructed to follow the rhythm by stepping to the beat of the metronome set at the mean cadence of the reference walk. **(B)** Schematic representations of the different intelligent inputs used in the protocol. Green, blue and red bars represent the periods during which the cadence is good, deviates below the threshold, or deviates above the threshold, respectively. NoInfo: no external information was given during the entire walk; ConCue: during the entire walk, participants received the auditory rhythm set at the mean cadence of the reference walk; IntCue: participants received the same auditory rhythm as in ConCue, but only for ten beats and only when the cadence deviated from the reference cadence; IntFB: participants received verbal feedback to "Increase the rhythm" or "Decrease the rhythm" when the cadence was more than 5% slower or faster (respectively) than the reference cadence.

In the second one, persons with and without freezing of gait (FOG+ and FOG-) were compared [19]. The results show that the FOG+ group benefits less from intelligent inputs than the FOG- group, probably due to more affected motor and cognitive functions [19]. In addition, the former had significantly more gait deviations than the latter during IntCue and IntFB conditions, but not when continuously cued. Although these findings suggest that ConCue was more effective in supporting prolonged gait in the FOG+ group, the majority of these persons favored the IntFB condition [19].

These two works [18], [19] adopted a macro approach to analyze the effect of wearable sensors and external inputs on continuous gait in PD: they did not quantify the individual motor responses to the corrective messages. However, since many factors are at play during a prolonged walking trial, such as fatigue and learning, a micro-analysis is more appropriate, because it quantifies the motor adaptations during the

participants' immediate response to the IntFB and IntCue conditions. Thus, the cadence of the subjects' first steps following each corrective acoustic message can be quantified.

The aim of this study is to characterize motor adaptation in response to corrective acoustic messages during prolonged walking in order to gain insight on how to better design novel therapeutic devices for gait re-training in PD (FOG- and FOG+). To this end, we propose a new model for fitting the short-term motor responses to external inputs (collected with wearable sensors). Using this model we determine the number of steps needed to adapt gait patterns following corrective acoustic messages. We investigated adaptation speed during IntFB and IntCue conditions for the following groups: healthy elderly (HEg), persons with PD (PDg), and PD subgroups with (FOG+g) and without (FOG-g) freezing of gait. We hypothesized that IntFB would lead to a more effective adaptation than IntCue, due to its verbal nature. In fact, the IntFB has an explicit nature with a clear direction of change to adapt the gait, compared to IntCue, which requires some processing time to elaborate the direction of adaptation leading to a delay in the motor response. Furthermore, because persons with PD struggle to maintain a normal gait [24], we expected that slowing down would be easier than speeding up. For both conditions, they would adapt more quickly when they were directed to slow back down to their reference cadence (because they had speed up) than when they were directed to speed up (because they had slowed down).

To assess the effect of the clinical characteristics of the participants, we investigated the relationship that links motor adaptation with their disease severity and their cognitive status. Furthermore, to match our micro-analysis with the macro results of previous work [18], [19], we also evaluated the relationship between motor adaptation speed and the number of deviations of each subject, to determine if persons who struggled more to walk consistently were slower to adapt to the corrective stimuli.

Materials and Methods

The present study consists of a sub-analysis of another study that compared persons with PD to age-matched healthy subjects on several gait characteristics throughout 30 min of walking during four different auditory input conditions [18]. These sections briefly describe the participants and protocol of the previous study before presenting the motor adaptation model and statistical analysis.

Original Study – Participants, Protocol, and Materials

Twenty-eight persons with PD were recruited from the Movement Disorders clinic of the University Hospitals Leuven based on the following inclusion criteria: (1) idiopathic PD, diagnosed according to the United Kingdom Brain Bank criteria; (2) Hoehn and Yahr stage I–III; and (3) stable PD medication for the past month and anticipated for the following 2 months. Exclusion criteria were: (1) cognitive deficits (Mini Mental State

Examination <24/30); (2) subjectively unable to walk unassisted for 30 min; (3) fluctuating response to levodopa; (4) musculoskeletal or neurological conditions other than PD affecting gait; and (5) severe hearing problems precluding headphone use for auditory information. Participants were categorized into freezers, FOG+ (n = 15), and non-freezers, FOG- (n = 13), based on a score of one or higher on the New Freezing of Gait Questionnaire (NFOG-Q). All persons with PD were tested in their subjective ON-medication state, an average of 1 h after the medication intake. It is important to note that no freezing episodes occurred during the study.

Thirteen age-matched HE were recruited from a database of voluntary study participants. The study design and protocol were approved by the local Ethics Committee of the KU Leuven and performed in accordance with the requirements of the International Council of Harmonization (Declaration of Helsinki, 1964). Written informed consent was obtained from each participant prior to the experiment. Over a period of 6 weeks, participants performed four 30-minute walks, with at least one week between walks, around an elliptical track measuring 24 m by 9 m. Prior to each 30-minute walk, the reference walk consisted of a fixed duration of a 1-min walk at a comfortable pace was recorded, to obtain the reference cadence. Participants started the 30-minute walk randomly in a clockwise or anti-clockwise direction, after which the starting direction was kept identical per person over the four sessions. After 15 min of walking, participants changed their walking direction (by crossing the trajectory diagonally) to counteract possible effects of disease dominance. In a randomized order, participants experienced one of the following conditions for the entire 30-minute walk: (1) continuous cueing (ConCue); (2) intelligent cueing (IntCue); (3) intelligent feedback (IntFB); and (4) no information (NoInfo). Cueing and feedback were provided by an adaptive wearable system [25] through headphones (Sennheiser RS160, Sennheiser, Germany). During IntCue, for every deviation, participants received an auditory rhythm, consisting of ten beats at the reference cadence—whether it was a DOWN event (cadence over the threshold) or a UP event (cadence below the threshold). The threshold which triggered the stimulus was set as a variation of more than 5% from the reference cadence, calculated from the mean cadence of five consecutive steps. During IntFB, participants received a verbal instruction to “increase rhythm” or “decrease rhythm” based on the same criteria as during IntCue. The values for the IntCue and IntFB settings, as well as the duration of the 1-min reference walk, were based on user acceptability, determined during pilot testing prior to the study. All the conditions are shown in **Figure 1**. All walks were performed in the same hall at the same time and day of the week to minimize the effects of time and PD medication. Demographic information and clinical test results were collected: in particular, the Movement Disorders Society Unified Parkinson's Disease Rating Scale—Motor Part (MDS-UPDRS III) [26], Scale for Outcomes in Parkinson's Disease-Cognition (SCOPA-Cog) [27], and Montreal Cognitive Assessment (MoCA) [28]. All the clinical tests were collected during the ON phase of medication before the start of the walking task to avoid the potential influence of fatigue. Clinical tests were evenly distributed over the different assessment days.

Participants wore two foot-mounted inertial measurement units (IMUs) attached to the tops of their shoes using Velcro straps. The IMUs (EXLs1, EXEL srl, Italy) contained a tri-axial accelerometer, gyroscope, and magnetometer, sampled at 100 Hz and wirelessly streaming via Bluetooth to a computer. A custom Matlab (Mathworks Inc., United States) software application, using the algorithms currently implemented in the commercially available system Gait Tutor (mHealth Technologies, IT), processed the signals in real-time during each 30-minute walk. The algorithm (validated for PD [17], [29]) and described elsewhere [25] computed cadence from the raw IMU data and registered any deviations from the pre-recorded reference cadence.

Motor Adaptation Model

This section describes the analysis we performed for IntCue and IntFB conditions in order to evaluate motor adaptation after intelligent inputs.

Cadence for all conditions was calculated by combining the data from both feet. The system in the original study only retained the average cadence for every five steps of each foot, while to obtain better sensitivity we recreated the original cadence for every trial.

Next, adaptation (in response to both UP and DOWN events) was quantified by fitting a single-term exponential model (Eq. 1) to the cadence of the ten steps following a deviation. In Eq. (1), y is the fitted cadence expressed as a percentage of the difference with respect to the reference cadence, k is the exponential decay/growth rate [step–1], x is the number of steps after intelligent input (from 0 to 9), and M is the under-/over-threshold value [%].

$$y = \pm M e^{-kx} \qquad (1)$$

The primary outcome was the exponential decay/growth rate k estimated for each UP or DOWN deviation (for all participants). **Figure 2** shows a representation of the mathematical model in response to both DOWN and UP events. To better illustrate the role of k, each graph in **Figure 2** reports three responses with different k values. A higher value of k corresponds to a faster adaptation, as is clear in **Figure 2**. Next, we evaluated the relative step constant (intrinsic to an exponential decay/growth model), $\tau = 1 / k$, which (as shown in the graph) intercepts the curve at a value for M of 63%. This characteristic parameter is defined in our study as the number of steps required to reduce M sufficiently that participants are in the correct range. (Note that this percentage supposes a reasonable M). Therefore, τ represents what we can call a refractory period: the number of steps needed to bring the cadence back within the reference range following verbal/acoustic feedback, during which providing a new corrective message may have no effect.

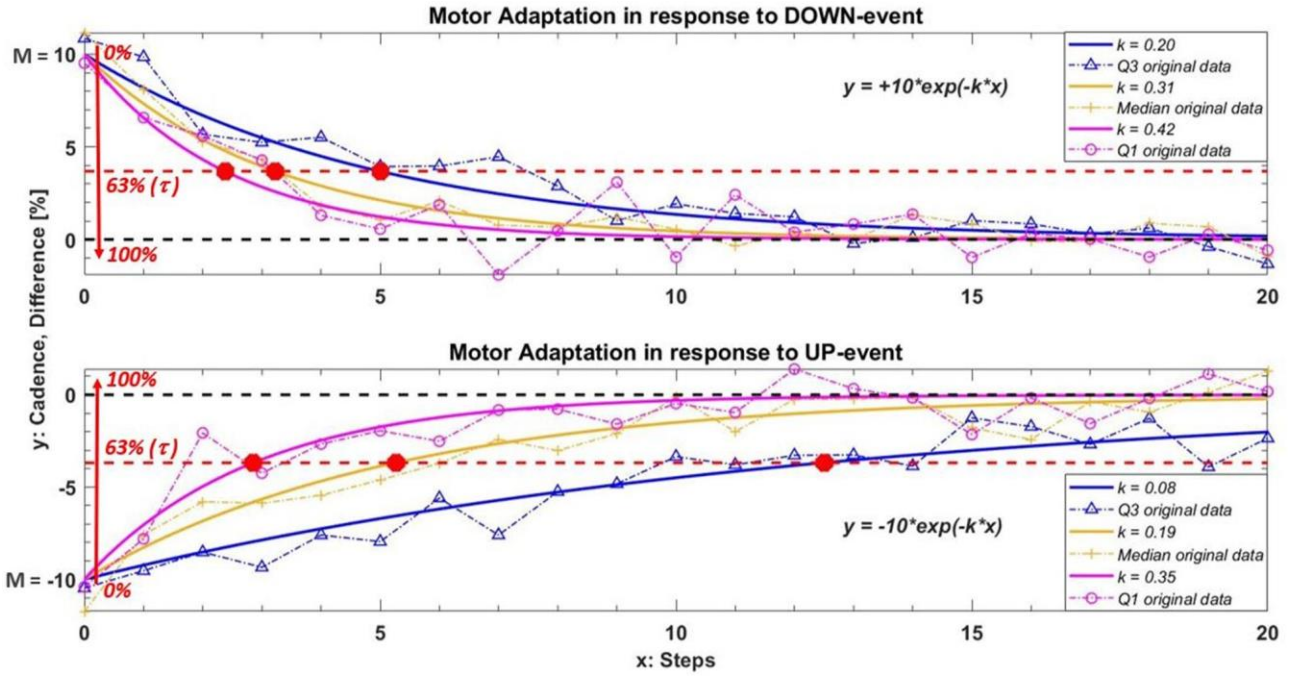

Figure 2. Example of the model used to quantify motor adaption in response to DOWN and UP events. In this example, the under/over threshold value M is ± 10 and we used three different values of k to better understand the role of this parameter. The curves in orange, blue, and magenta represent the median and relative interquartile values (Q3 in blue; Q1 in magenta) of the exponential fitting model obtained among all participants during IntFB condition. The orange plus, the blue triangles, and the magenta circles are an example of the original cadence with the same k adaptation rate in one subject. The red circles in the graph show the relative τ value of each curve. This value indicates the steps needed to adapt gait pattern increasing/decreasing M of 63% toward the reference cadence following a corrective feedback. A higher value of k (or a smaller value of τ) corresponds to a faster motor adaptation.

Statistical Analysis

A preliminary qualitative analysis compared the average responses to corrective stimuli between PDg, HEg, and FOG-g, FOG+g. We used our fitting model to quantify motor adaptation in terms of k, the exponential decay/growth rate during all the corrective acoustic messages received by the participants. We calculated the absolute median values and the relative interquartile range among all groups and subgroups.

Next, we used paired non-parametric statistics (Wilcoxon Signed Rank test) to evaluate the condition effect (IntCue vs. IntFB) and the task effect (UP event vs. DOWN event), analyzing differences in the average k rate of each subject only within the PDg, due to the small sample available. However, the resulting average differences do not say anything about specific motor responses [30]. On the other hand, situations where people show a high level of motor adaptation reflect their best possible performance and are thus of specific therapeutic interest. To identify the best performances, we investigated the 90th-percentile values of each subject in addition to the average k rate. Clearly, a paired test requires subjects who had corrective messages in both conditions or in both tasks (depending on the analysis).

Unpaired non-parametric statistics (Mann-Whitney U tests) were used to examine differences in the value of k between groups HEg and PDg (group effect) and subgroups FOG+g and FOG-g (subgroup effect). In addition, we performed an exploratory analysis to assess whether subjects who had only UP events responded differently than those who had both UP and DOWN events. We assumed that for those subjects who tend to slow down, it may be more difficult to increase their rhythm in response to corrective acoustic messages—compared to subjects who tend to both slow down and speed up. The relations between adaptation speed and clinical data were explored by correlating the participants' scores on SCOPA-Cog and MoCA (cognitive aspect) and MDS-UPDRS III (disease severity) with their median k rate using Spearman rank correlation coefficients. The median k rate was also correlated with the number of deviations for each subject. Matlab (Mathworks Inc., United States) was used for all statistical analyses, with $\alpha = 0.05$.

Results

Demographics

For simplicity, the demographic analysis (available from previous studies) is reported in **Table 1** [18], [19] PDg and HEg were well matched for age, body height, body weight, cognitive ability (MoCA), total self-reported daily physical activity (LAPAQ Total), and self-reported daily walking time (LAPAQ Walking). The PD group had significantly lower cognitive scores (SCOPA-Cog). Freezers (FOG+) and non-freezers (FOG-) were well matched for age, body morphology (weight, height, and leg length), self-reported daily walking, and total daily activity time (LAPAQ), as well as for Hoehn and Yahr stage. The FOG+g had a significantly longer disease duration, lower cognitive scores (MoCA), and more reported gait difficulties on the 12-item gait scale (12G) than the FOG-g.

	PD (n = 28)	HE (n = 13)	Sign.	FOG+ (n = 15)	FOG− (n = 13)	Significant
Age (years)	62.04 (6.91)	60.23 (6.07)	$p = 0.42$	62.80 (6.91)	61.15 (7.08)	$p = 0.54$
Gender (M/F)[a]	23/5	7/6	$p = 0.07$	14/1	9/4	$p = 0.09$
Body weight (kg)	82.73 (15.83)	74.39 (14.63)	$p = 0.12$	79.93 (14.56)	85.95 (17.20)	$p = 0.33$
Body height (cm)	174.00 (8.37)	169.85 (7.99)	$p = 0.14$	173.07 (5.61)	175.08 (10.89)	$p = 0.56$
Leg length left (cm)	92.54 (5.99)	90.15 (4.20)	$p = 0.21$	92.13 (3.72)	93.00 (8.01)	$p = 0.73$
Leg length right (cm)	92.14 (5.77)	90.46 (4.35)	$p = 0.36$	91.80 (3.26)	92.54 (7.88)	$p = 0.76$
Disease duration (years)	10.57 (6.71)	/	/	13.20 (5.55)	7.54 (6.84)	**$p = 0.03$**
H and Y (1/2/2.5/3)[a]	1/12/7/7	/	/	0/6/4/5	1/7/3/2	$p = 0.14$
MDS-UPDRS III (0–132)	34.57 (14.37)	/	/	37.93 (14.39)	30.69 (13.88)	$p = 0.19$
LEDD (mg/24 h)	517.42 (312.97)	/	/	622.98 (338.51)	395.62 (238.12)	$p = 0.05$
MoCA (0–30)	26.36 (2.18)	27.46 (2.22)	$p = 0.14$	25.27 (2.15)	27.62 (1.45)	**$p = 0.003$**
SCOPA-Cog (0–42)[b]	29.50 (26.00–31.25)	34.00 (32.00–35.00)	**$p = 0.001$**	29.00 (22.25–30.00)	31.00 (27–31.25)	$p = 0.29$
LAPAQ walking (min/day)[b]	14 (5–30)	11 (7–21)	$p = 0.71$	8.57 (0.89–32.86)	15.00 (6.43–20.00)	$p = 0.53$
LAPAQ total (min/day)[b]	127 (56–198)	207 (105–326)	$p = 0.14$	117.14 (67.14–181.07)	136.43 (52.14–322.86)	$p = 0.86$
12 G (0–87)[b]	9.50 (5.75–14.50)	0 (0–0)	**$p < 0.001$**	13.00 (9.50–19.50)	6.00 (3.00–9.00)	**$p = 0.007$**

Bold numbers indicate significant differences between groups and subgroups. MDS-UPDRS III Movement Disorders Society Unified Parkinson Disease Rating Scale-Motor Part, LEDD levodopa equivalent daily dosage, MoCA Montreal Cognitive Assessment, LAPAQ LASA Physical Activity Questionnaire, 12G 12 item gait scale, SCOPA-Cog Scale for Outcomes in Parkinson's Disease-Cognition. All the clinical tests were collected during the ON phase. [a] Chi-squared statistics. [b] Non-parametric statistics were applied.

Table 1. Results are reported as mean (standard deviation) in the case of parametric statistics and as median (quartile 1– quartile 3) in the case of non-parametric statistics.

Qualitative Adaptation Plots

In this preliminary analysis, we qualitatively highlighted the average behavior of the participants following the corrective acoustic messages. We compared the average cadence between HEg and PDg and subgroups FOG+g and FOG-g, from five steps before the deviation until 20 steps after. **Figure 3** shows the average original cadence responses to all corrective acoustic messages received by HEg and PDg during both conditions.

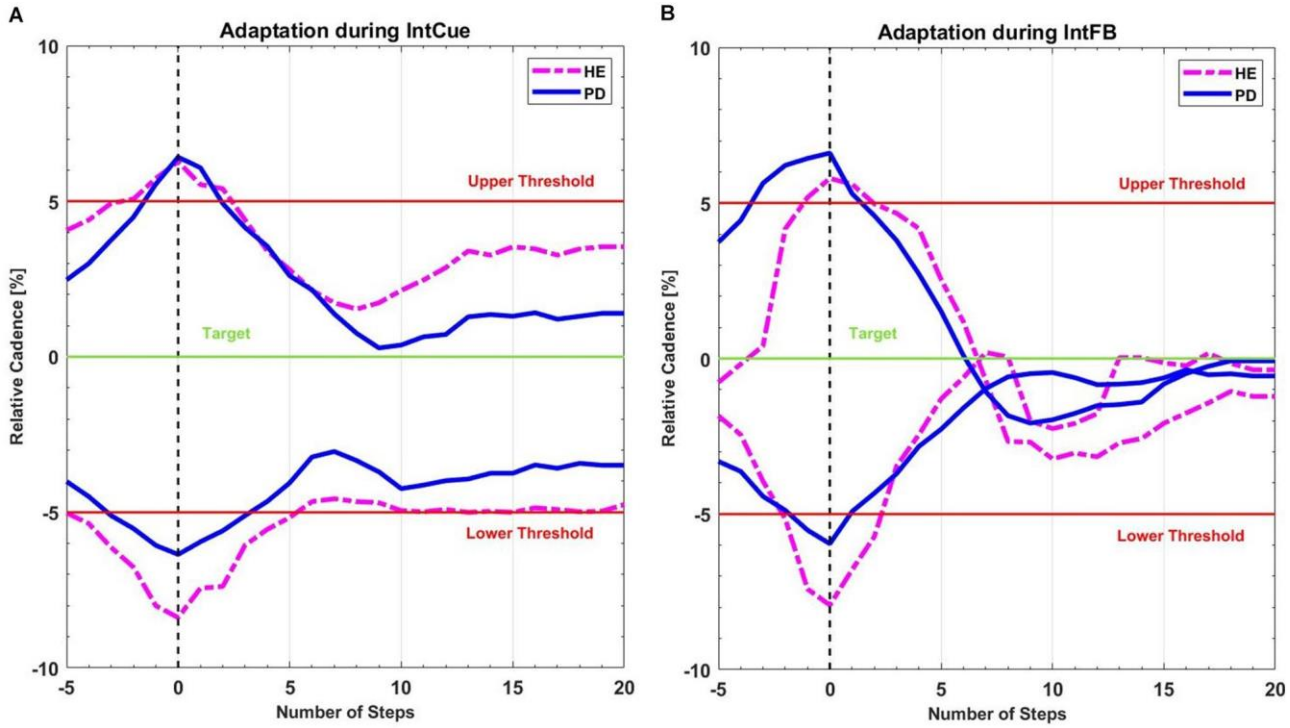

Figure 3. Mean recreated cadence of all PDg (full lines in blue) and all HEg (dashed lines in magenta) after all corrective acoustic messages **(A)** during IntCue and **(B)** during IntFB condition, starting 5 steps before until 20 steps after the deviation. The vertical black dashed line represents the onset of corrective input. The green target line represents the stepping rhythm recorded during the 1-min reference walk. The red lines mark the 5% deviation levels above and below the target line.

Figure 4 reports the same analysis as **Figure 3**, comparing FOG- and FOG+ subgroups in both conditions.

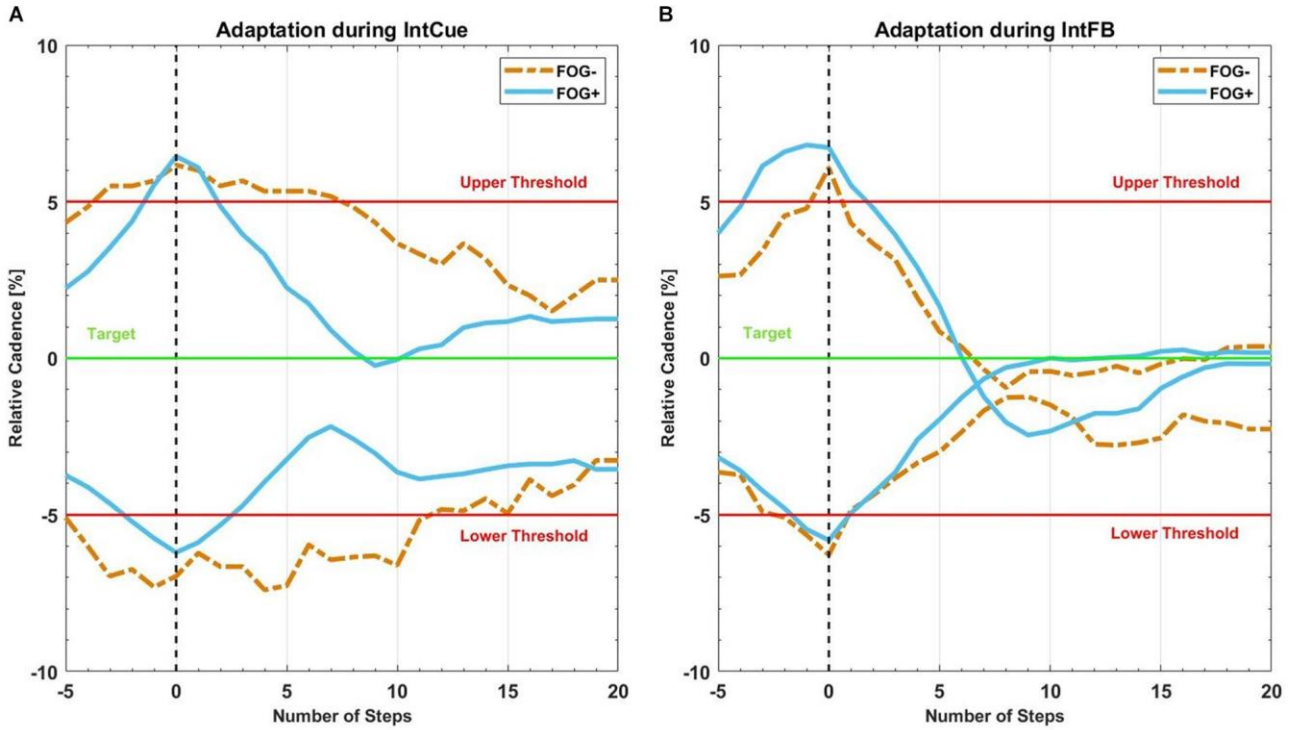

Figure 4. Mean recreated cadence of all FOG+g (full lines in light blue) and all FOG-g (dashed lines in yellow) after all corrective acoustic messages, **(A)** during IntCue and **(B)** during IntFB condition, from five steps before to 20 steps after the deviation. The vertical black dashed line represents the corrective input onset. The green target line represents the stepping rhythm recorded during the 1-min reference walk. The red upper and lower thresholds mark the 5% deviation levels above and below the target line.

Number of Deviations

To improve the interpretability and readability of our analysis, in **Table 2** we reported the total number of deviations, already presented and discussed in the original study [18], [19].

A		
Deviations UP-event	**IntCue**	**IntFB**
HE	54	9
PD	119	139
FOG+	95	96
FOG-	24	43

B		
Deviations DOWN-event	**IntCue**	**IntFB**
HE	13	6
PD	62	88
FOG+	54	81
FOG-	8	7

IntCue, intelligent auditory cueing; IntFB, intelligent verbal feedback; UP event, cadence under the threshold – Increase rhythm; DOWN event, cadence over the threshold – Decrease rhythm; PD, people with Parkinson's disease; HE, healthy elderly; FOG+, people with Parkinson's disease with freezing of gait; FOG-, people with Parkinson's disease without freezing of gait.

Table 2. Total number of deviations received by the groups in response to UP **(A)** and DOWN **(B)** messages.

Condition Effect: IntCue vs. IntFB

As can be seen in **Table 3**, although the fastest median k rate (i.e., larger median k rate) occurred during IntFB, the differences in k rates for the two types of conditions were not significant for PDg. It is important to note that, to perform a paired analysis, we had to exclude some subjects: only 12 of the 28 PD subjects received at least one UP message during the two conditions, and only four subjects received at least one DOWN message.

A

k UP-event	IntCue	IntFB	Mean Condition effect	90th Condition effect
HE	0.06 (0.00–0.10)	0.21 (0.18–0.38)	–	–
#deviators	#5	#6		
PD	0.13 (0.06–0.18)	0.15 (0.07–0.35)	$p = 0.260$	$p = 0.151$
#deviators	#14	#16	($n = 12$)	($n = 12$)
FOG+	0.13 (0.08–0.18)	0.20 (0.10–0.36)	–	–
#deviators	#10	#11	($n = 9$)	($n = 9$)
FOG-	0.08 (−0.02–0.18)	0.12 (0.05–0.30)	–	–
#deviators	#4	#5		

B

k DOWN-event	IntCue	IntFB	Mean Condition effect	90th Condition effect
HE	0.23 (0.18–0.26)	0.28 (0.22–0.35)	–	–
#deviators	#2	#3		
PD	0.21 (0.07–0.44)	0.33 (0.19–0.45)	$p = 0.250$	$p = 0.625$
#deviators	#8	#11	($n = 4$)	($n = 4$)
FOG+	0.24 (0.09–0.49)	0.31 (0.18–0.45)	–	–
#deviators	#6	#7	($n = 3$)	($n = 3$)
FOG-	0.01 (−0.01–0.06)	0.36 (0.24–0.44)	–	–
#deviators	#2	#4		

IntCue, intelligent auditory cueing; IntFB, intelligent verbal feedback; UP event, cadence under the threshold – Increase rhythm; DOWN event, cadence over the threshold – Decrease rhythm; #deviators participants who have at least one deviation; PD, people with Parkinson's disease; HE, healthy elderly; FOG+, people with Parkinson's disease with freezing of gait; FOG-, people with Parkinson's disease without freezing of gait. Mean Condition effect, paired analysis using the average k rate of each subject; 90th Condition Effect, paired analysis using the 90th percentile value k rate of each subject. n, number of participants included in the paired analysis.

Table 3. Condition effect. Index of adaptation k is reported as median (quartile 1– quartile 3) among all groups in response to UP (A) and DOWN (B) messages.

Next, a subgroup evaluation was carried out (see Table 3). No statistical analysis was performed for HEg, FOG+g or FOG-g, due to the small number of paired samples, which would increase the possibility of a type II error. In line with the PDg findings, this analysis suggested a slightly faster adaptation during IntFB than IntCue looking at the absolute median value.

Group Effect: PDg vs. HEg; SubGroup Effect: FOG+g vs. FOG-g

Differences in motor adaptation between the groups (HEg vs. PDg) and subgroups (FOG+g vs. FOG-g) were analyzed during IntFB (Tables 4A-1, A-2) and IntCue conditions (Tables 4B-1, B-2). During the IntCue condition, PDg had a significantly faster adaptation than HEg in response to the UP event (p-value < 0.000) and FOG+g adapted significantly faster than FOG-g in response to the DOWN event (p-value = 0.006).

A-1					A-2			
k **IntFB**	**UP-event**	**DOWN-event**	**Mean Task effect**	**90th Task effect**	***k*** **IntFB**	**UP-event**	**DOWN-event**	**Task effect**
HE	0.21 (0.18–0.38)	0.28 (0.22–0.35)	–	–	FOG+	0.20 (0.10–0.36)	0.31 (0.18–0.45)	–
#deviators	#5	#3			#deviators	#11	#7	(*n* = 5)
PD	0.15 (0.07–0.35)	0.33 (0.19–0.45)	*p* = 0.630	*p* = 0.195	FOG-	0.12 (0.05–0.30)	0.36 (0.24–0.44)	–
#deviators	#16	#11	(*n* = 8)	(*n* = 8)	#deviators	#5	#4	
Group effect	*p* = 0.255	*p* = 0.734			**SubGroup effect**	*p* = 0.101	*p* = 0.460	
B-1					**B-2**			
k **IntCue**	**UP-event**	**DOWN-event**	**Mean Task effect**	**90th Task effect**	***k*** **IntCue**	**UP-event**	**DOWN-event**	**Task effect**
HE	0.06 (0.00–0.10)	0.23 (0.18–0.26)	–	–	FOG+	0.13 (0.08–0.18)	0.24 (0.09–0.49)	–
#deviators	#6	#2			#deviators	#10	#6	(*n* = 4)
PD	0.13 (0.06–0.18)	0.21 (0.07–0.44)	*p* = 0.156	*p* = 0.312	FOG-	0.08 (–0.02–0.18)	0.01 (–0.01–0.06)	–
#deviators	#14	#8	(*n* = 5)	(*n* = 5)	#deviators	#4	#2	
Group effect	***p* < 0.000**	*p* = 0.872			**SubGroup effect**	*p* = 0.073	***p* = 0.006**	

IntCue, intelligent auditory cueing; IntFB, intelligent verbal feedback; UP event, cadence under the threshold – Increase rhythm; DOWN event, cadence over the threshold – Decrease rhythm; #deviators participants who have at least one deviation; PD, people with Parkinson's disease; HE, healthy elderly; FOG+, people with Parkinson's disease with freezing of gait; FOG-, people with Parkinson's disease without freezing of gait. Mean Task effect, paired analysis using the average k rate of each subject; 90th Task effect, paired analysis using the 90th percentile value k rate of each subject. Group effect, unpaired analysis between HE and PD groups. SubGroup effect, unpaired analysis between FOG+ and FOG- groups. Bold numbers indicate significant differences in the task (UP vs. DOWN event), groups (PD vs. HE), and subgroups effect (FOG+ vs. FOG-). n, number of participants included in the paired analysis.

Table 4. Task and group effect. Index of adaptation k is reported as median (quartile 1– quartile 3) among all groups for (A-1, A-2) IntFB condition, (B-1, B-2) for IntCue condition.

Task Effect: UP Event vs. DOWN Event

Although the fastest median k rate occurred following a DOWN event, the differences in k rates for the two types of the event were not significant for PDg (**Tables 4A-1, B-1**). This finding also holds true within the HEg, FOG+g, and FOG-g (Table 4), but here no statistical analysis was performed because of the small number of paired samples. Moreover, only eight persons with PD experienced at least one of each event type during the IntFB condition and only five during the IntCue condition.

We performed an exploratory analysis to assess whether members of PDg who had only UP events responded differently than those who experienced both UP and DOWN events. The results indicate a different trend for each condition. During IntCue, those who only had UP events adapted faster (p-value = 0.039). In contrast, during IntFB those who experienced both DOWN and UP events adapted faster than those who experienced only UP events (p < 0.000) (**Table 5**).

k UP-events	only UP	UP+DOWN	Sign.
IntCue	0.13 (0.10–0.18)	0.06 (0.02–0.17)	**$p = 0.039$**
#deviators	#9	#5	
IntFB	0.10 (0.05–0.15)	0.28 (0.14–0.48)	**$p < 0.000$**
#deviators	#8	#8	

In the first column the group who received only UP events, while in the second column the group who received both UP and DOWN inputs during the 30 min of walking. Bold numbers indicate significant differences between groups.

Table 5. Exploratory analysis on different responders. Index of adaptation k in response to UP events is reported as median (quartile 1– quartile 3) for IntCue and IntFB conditions among PDg.

Correlation Analysis

The participants' SCOPA-Cog, MoCA, and MDS-UPDRS III scores did not correlate significantly with the median k rate during either condition or either task. However, as can be seen in **Table 6**, the median k rate correlated significantly with the number of deviations during the IntCue UP event (r = −0.57; p-value = 0.008), indicating that those with the slowest adaptations had the most deviations throughout the 30-minute walk. No significant correlations were observed for the IntCue DOWN events or any of the IntFB events.

Spearman's *r*	UP-event	DOWN-event
IntFB	−0.15 ($p = 0.525$)	0.24 ($p = 0.398$)
#deviators	#21	#14
IntCue	**−0.57 ($p = 0.008$)**	0.13 ($p = 0.731$)
#deviators	#20	#10

Spearman rank correlation coefficient r and relative p-value are shown in the table. Bold numbers indicate significant correlation.

Table 6. Correlation between the number of messages received (#deviations) and the median k rate of each subject during IntFB and IntCue conditions in response to UP-event and DOWN-event.

Refractory Period During IntFB in PDg

Focusing on the PD group, the relative step constant τ = 1 / k, with the k values reported in **Table 3**, indicates the refractory period of about seven steps for the UP event and three steps for the DOWN event during the IntFB condition. Higher values of τ are observed during the IntCue condition: about eight steps for the UP event and about five steps for the DOWN event. In **Table 7** we report the values of τ.

[step] (PD group)	UP event	DOWN event
IntFB	6.7	3.0
IntCue	7.7	4.8

τ represents the refractory period in response to UP and DOWN events and indicates the number of steps needed to adapt gait pattern and bring the cadence within the reference range following verbal/acoustic feedback.

Table 7. Refractory period. The relative step constant τ = 1 / k [step] in the PD group.

Discussion

This study investigated the effects of intelligent auditory cueing (IntCue) and verbal feedback (IntFB) on motor adaptation in HE, PD, and PD subgroups (with and without FOG.) We introduced an innovative model to quantify motor adaptation speed following the two different acoustic messages. Thanks to our novel

adaptation model, which applies a decay/growth exponential model to gait biofeedback for the first time, we can define the refractory period as the value of the relative step constant τ. This value indicates the steps needed to bring the cadence within the reference range following verbal/acoustic feedback.

Our results from the IntFB condition indicate a refractory period of about seven steps for the UP event and about three steps for the DOWN event for PD subjects. We found a similar (only slightly higher) refractory period for the IntCue condition. Clinicians and biofeedback developers designing novel therapeutic devices could apply our findings to determine the optimal timing for corrective feedback, optimizing gait rehabilitation while minimizing the risk of cue dependency. In this way, the system could provide optimal corrective feedback in maintaining the proper gait pattern.

We hypothesized that the verbal and explicit nature of IntFB could speed up the motor response [31], compared to IntCue which is more implicit and may thus require some processing time to elaborate the direction of adaptation. In contrast to what assumed, our analysis could not detect different adaptations between IntFB and IntCue conditions. Nevertheless, in line with our expectations, the absolute median values of the decay/growth rate k for IntFB are larger than for IntCue in all groups and subgroups. This is consistent with the qualitative indications of the adaptation plots and is in line with the visual exploration performed in a previous study [19]. Furthermore, when looking at the adaptation plots (**Figure 3**) it can be observed that there is an overshooting in IntFB only, which may be explained by the reference cadence indicated only during the IntCue condition.

We also expected that increasing the pace to the reference level would be a more difficult task than decreasing it. However, this trend is not confirmed within PDg by the statistical analysis. This lack of significance could be due to the small number of deviations recorded.

The group effect analyses yielded two results during IntCue: PDg had faster adaptation than HEg in response to UP events and FOG+g adapted faster than FOG-g in response to DOWN events. These results could be unexpected because HEg and FOG-g have better gait stability (fewer deviations) than PDg and FOG+g, respectively, as indicated in previous work [18], [19]. However, this is in line with previous work that showed a higher reliance on external input in PD compared to healthy subjects [32].

There were no differences in motor adaptation between the groups (HEg vs. PDg) or subgroups (FOG+g vs. FOG-g) during IntFB. In this regard, contradictory results can be found in the literature. Some authors [33] found that PD and HE adapted similarly, during the first strides after exposure to a split-belt gait pattern. On the other hand, others [34] showed that FOG+ have more difficulties than FOG- and HE to adapt their gait to a split-belt treadmill over a short time period.

Our exploratory analysis revealed that during 30 min of walking, subjects who had only UP events adapted more slowly than those who had both UP and DOWN events during IntFB condition. This result is in agreement with our hypothesis: for those subjects who tend to slow down, it may be more difficult to increase their rhythm in response to corrective acoustic messages—compared to subjects who tend to both

slow down and speed up. Instead, for IntCue we had the opposite trend, maybe because the metronome cues were more difficult to understand for those who received both up and down messages.

No significant correlations were found between our adaptation speed results and cognitive ability. In this protocol, the subjects had to walk maintaining a determined cadence, without turning or avoiding obstacles. This steady-state walking, with a reduced cognitive load, can be the reason for the lack of correlations found. In addition, the fact that all participants had an MMSE ≥ 24/30, conform to the study's inclusion criteria, suggests that further study is needed in a cohort with a wider cognitive spectrum. On the other hand, the original study found a correlation between gait stability (number of deviations) and the MoCA scale (with the same dataset) [19].

The relationship between our micro-analysis and the macro approach adopted in previous works [18], [19] was evaluated by correlating the adaptation speed with the number of deviations. We found a negative trend only, during IntCue in response to UP events. During IntCue in response to DOWN events, as well as during IntFB, no significant correlations were observed. This finding seems to indicate that motor adaptation might be more effective during IntFB for all subjects, including those who require a lot of assistance through intelligent messages. In fact, the previous work reported that subjects preferred verbal feedback [19]. The negative trend found could also be explained by the slower adaptation leading to an increased number of deviations. In fact, participants may not yet be within the threshold values, triggering the feedback again. As expected, in response to DOWN events we did not find correlations in any conditions, suggesting that decreasing cadence is a relatively simple task that can be done fairly quickly.

A critical re-analysis of our results might suggest that an interesting solution could be the use of a combined-cue system, i.e., verbal feedback to increase or decrease cadence followed by the rhythmic cues to specify the target rate. This combined solution could trigger adaptation similar to the IntFB system, because of its explicit nature. On the other hand, due to the target rate indicated by the cueing, the combined-cue system may avoid the overshooting observed in part during the IntFB condition in the preliminary qualitative analysis. In any case, the joint use of IntFB and IntCue conditions could increase the overload of sensory and cognitive functions.

Future Work

Effective tools for PD rehabilitation should allocate attention appropriately and lighten cognitive load [35]. The use of multisensory stimuli improves the learning process [36], [37], thanks to a reduced cognitive load and easier storage in short-term memory [38], [39]. A multisensory approach also enhances perceptual processing [37], known to be reduced in PD subjects with FOG [40]. [41] demonstrated the effectiveness of this approach in a study that used video and synthesized sounds to help PD subjects with FOG relearn gait movements and reduce freezing episodes.

Following this principle, it might be useful to add another sensory input to the IntFB condition. Proprioceptive feedback (such as vibrational stimuli) which require little or no cognitive processing or attention [42], might greatly improve motor adaptation in response to intelligent inputs. In fact, proprioceptive stimuli, in a closed-loop system [23], are already commonly used for gait rehabilitation in PD.

Future work also needs to address the long-term effect of gait rehabilitation on adaptation speed. It could be important to quantify the dynamics of adaptation during a trial and any possible motor-learning effect [i.e., the formation of a new motor pattern, in response to intelligent inputs, that occurs via long-term practice [43]]. It would also be useful to evaluate motor adaptation through a prolonged, home-based training period, which would provide naturalistic data. Finally, it would be interesting to explore the use of different parameters (stride length, gait speed) instead of cadence to trigger the feedback.

It should be noted that further exploration of our model would benefit from ensuring that sufficient data are obtained to validate the qualitative and quantitative findings.

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Section III - Neuromotor Rehabilitation Solutions

Chapter 9

"Smartphone-delivered augmented auditory feedback for gait training in persons with Parkinson's disease: A retrospective comparison of different feedback variables"

Ph.D. candidate's main Contribution:
Designed the analysis and processed the data.

Abstract

Wearable sensing technology consents to deliver corrective feedback. It is highly applicable to gait-rehabilitation for persons with Parkinson's disease (PD) because feedback potentially engages spared neural function.

Our study investigated in daily-life the role of different verbal-biofeedback strategies in PD subjects. Eighteen persons with PD undertook gait training for 30 min, three times per week, for six weeks using CuPiD-system in a free-living scenario. When Stride Length (SL), Gait Speed (GS), or Cadence (CAD) varied, they received verbal instruction to increase or decrease them.

We evaluated the provided feedback's effectiveness by counting how many times the subjects returned within their therapeutic window following a deviation. We compared it with a sham condition without biofeedback (no-BF). An exploratory analysis was performed to visualize long-term effects by showing how SL and GS changed during the protocol. We reached a high level of coherence between the verbal-biofeedback and the relative motor response using SL and GS as biofeedback variables.

Excluding CAD, using this gait rehabilitation system led to the best response than the no-BF condition (*p-value < 0.000*). Notably, we achieved the best coherence using GS as a biofeedback-variable, rather than SL (*p-value = 0.015*). The exploratory analysis revealed a slight presence of long-term effects.

1. Introduction

One of the most innovative and promising developments in the assessment and management of PD symptoms is the use of wearable technologies during gait [1], [2], which allows collecting behavioral data in a more naturalistic environment [3], [4], and may provide customized cueing for home-based rehabilitation [9]. In the latter case, stimuli are, e.g., triggered when gait deviates from normal, thus providing patients with immediate feedback on their performance. The use of external sensory cues (e.g., auditory or haptic) to reinforce attention toward the task has been shown to enhance motor learning [5] and is an effective gait-rehabilitation strategy for persons with PD [6], [7]. The cues stimulate the voluntary executive component of action [8]–[10] by activating the attentional-executive motor control system and bypassing the dysfunctional, habitual, sensorimotor BG network [11]–[16]. This strategy helps people with PD improve gait consistency and rhythmicity.

The current study builds on some of the data collected during the former EU-funded CuPiD-project. Innovatively, and in line with recent evolutions [17], the project designed a gait training application not only with a team of engineers and physiotherapists, but also with the active participation of persons with PD. The CuPiD technology integrates three main functions: 1) measurement of gait in real-time; 2) auditory feedback on one or more spatiotemporal gait parameters [18]; and 3) rhythmical auditory cueing to prevent or overcome FOG episodes [19]. The resulting system (from now on referred to as the CuPiD system) represents a relevant example of the application of wearable technologies for home-based rehabilitation of persons with PD. The system allows the therapists to design personally tailored rehabilitation programs based on individual patient evaluation, clinical history, cognitive aspects, primary symptoms, patient's expectation, and medical knowledge.

The CuPiD system is a smartphone-based virtual trainer exploiting spatio-temporal gait parameters monitored through shoe-worn inertial sensors [18], [20]. Through augmented feedback, the system makes persons with PD better aware of their gait performance and helps them to correct their pathological gait patterns in real-time. Sensory augmentation is achieved through verbal biofeedback (BF) on gait performance which is subject-specific thanks to a personalized training plan and a functional calibration trial in which the patient is asked to walk at her/his best, during which individual reference values for the spatio-temporal parameters are estimated. During the training sessions, corrective BF is then provided to the user each time a deviation in the gait parameter(s), preselected by the therapist as BF variable, occurs. On the contrary, if the person can maintain the BF variable within the therapeutic window defined by the therapist, the system generates praising messages, to reinforce the behavior.

The CuPiD system was used in a previous study [21] to characterize the motor response of persons with PD during prolonged indoor walking in response to different corrective acoustic messages. Results suggested that, for people who struggle with gait, such as those with PD, verbal instructions rather than metronome

beats might be more effective at restoring normal cadence after a deviation [21]. This indoor study used cadence as the sole BF variable unlike the previous pilot randomized controlled study [4], through which we demonstrated the feasibility and effectiveness of the system for home-based training of gait, that used multiple BF variables.

The selection of the most appropriate BF variable for a specific rehabilitation task or exercise is essential, although relatively unexplored [22]. For this reason, this study aimed to retrospectively compare the effectiveness of different BF variables in enhancing the real-life locomotor performance of persons with PD during a 6-week rehabilitation program reanalyzing, with this specific focus, the data collected for [4]. To this aim, we compared, at multiple time scales, the effectiveness of the BF variables that were used most frequently in that study: Stride Length (SL), Gait Speed (GS), and Cadence (CAD).

2. Materials and Methods

The present chapter analyzes the data collected in the intervention group of a previous multicenter and randomized feasibility study run in Leuven and Tel Aviv between March and December 2014 [4]. The study was approved by the local ethics committee of the University Hospitals Leuven and Tel Aviv Sourasky Medical Center. All participants gave written consent according to the declaration of Helsinki.

2.1. Participants, Protocol, and Materials

Participants were included if they were able to walk for 10 min continuously; had a score of 24 or higher on the Montreal Cognitive Assessment (MoCA); were in Hoehn & Yahr Stage (H&Y) II to III in ON state and were on stable PD medication. Twenty persons with PD undertook gait training with the CuPiD system during a period of 6 weeks [4], [20]. We excluded two subjects, because of incomplete data. Therefore, eighteen participants were included in the analysis, who performed 332 training trials in total. They were: 15 Males and 3 Females, Age: 64 ± 9 years, Height 173 ± 6 cm, Weight 82 ± 17 kg, Disease Duration 12 ± 6 years, H&Y 2.3 ± 0.4, MoCA 27.2 ± 2.5, MDS-UPDRS-III [0–132] 38 ± 14, NFOG-Q New Freezing Of Gait Questionnaire 8.9 ± 9.0, LEDD Levodopa Equivalent Daily Dose 572.6 ± 403.3 mg, ON L-Dopa.

In a first session (pre-test), in- and exclusion criteria were checked, and baseline values of selected gait variables were collected in a laboratory. The same outcomes were assessed after the 6-weeks intervention (post-test) and after a 4-week (follow-up) period by the same assessor at each clinical center. Measurements' order was standardized within the test procedure and conducted when participants were optimally medicated, about one hour after the PD medication intake. In particular, participants were asked to walk for one minute over an instrumented walkway at a comfortable speed (PKMAS, Protokinetics, USA) [4].

The CuPiD system consisted of a smartphone app running on a Galaxy S3-mini (Samsung, South Korea), a docking station, and two IMUs (EXLs3, EXEL srl., Italy) connected via Bluetooth to the smartphone and with a sampling frequency of 100 Hz. Technical features and signal processing algorithms embedded inside the app were first validated for their sensitivity and robustness in the detection of gait abnormalities against standard gait analysis systems [18].

Corrective or praising messages were provided via earphones or the smartphone's speaker according to the results of the real-time comparison between an individual's current and 'optimal' gait performance. 'Optimal' performance was defined as the best performance that was reasonable to achieve on a specific patient asking her/him to walk at her/his best with the supervision of the therapist, in a given moment of the rehabilitation program. The recording of such an optimal performance was performed during the initial visit in the lab and repeated twice at the patient's home over the 6-week study period to calibrate the app. Reference values of the spatiotemporal parameters were, on average, four times adjusted by the researcher/clinician during weekly visits [4]. The therapeutic window for each BF variable was then chosen by the therapist as a fixed percentage around the personal best (see Fig. S1 in Supplementary Materials). The larger the therapeutic window, the higher the percentage tolerance and the easier the task.

The CuPiD system identifies a deviation whenever the percentage difference between the median value of the BF variable(s) computed on the last five steps and the respective reference value computed during the optimal performance is above an upper or below a lower threshold (i.e. outside the therapeutic window set by the therapist). Following a closed-loop approach, augmented verbal feedback was then provided to patients: either positive, when gait remained within the therapeutic window, or negative, when gait parameters fell outside the therapeutic window (see Fig. S1.A in Supplementary Materials). For example, when GS was used as the BF variable if its value was above (below) the therapeutic window, the subject would accordingly receive verbal feedback to "Walk Slower" ("Walk Faster") (see Fig. S1.B in Supplementary Materials). Verbal messages about the performance were given in Dutch or Hebrew, according to the testing site. Their frequency would decrease following an exponential law to prevent feedback overload and maximize motor learning. In particular, the CuPiD system dynamically looks for an operating point corresponding to a training level, neither too demanding and verbose, with an excessive number of vocal messages per unit time, nor too loose and silent, with too few messages [20].

Study participants received weekly home visits from the researchers/clinicians during the six weeks of intervention and were invited to adopt an ecological approach for their training. They were indeed invited to train at least three times per week for 30 min in their daily life environment, which typically involved walking outside in their neighborhoods. They were taught how to wear the IMUs on their shoes and how to use the app, which provided feedback on some gait parameters, preselected on a daily basis according to a personalized rehabilitation program determined by the patient's clinician. During the training sessions, the smartphone was carried in a pocket of the participant's clothing. A booklet with pictures and personalized

instructions was left in the home and consultation by telephone was offered in case of difficulties using the system. At the end of the study, participants were asked to fill in an ad-hoc questionnaire similar to QUEST [23].

2.2. Usage of BF variables

The English version of the list of messages triggered by the actual value of each BF variable is shown in Table 1. The CuPiD system randomly picked one of the sentences from the list, according to the current state of the subject in relation to the active BF variable(s) (SL, GS, CAD) and needed Instruction (Praise, Increase, Decrease). The BF variables used in each trial and each individual BF message generated during the training sessions were stored in a log file of the app. This allowed us to compute the number of subjects and trials where each BF variable was used at least once, and the relative frequency of the instructions.

2.3. Coherence between verbal BF and motor responses

Given the ecological set-up of the protocol, which introduces some contextual uncertainties (e.g. a slowdown message might be produced when crossing a road), for each BF variable, we examined the coherence between the verbal instruction and the motor response both qualitatively and quantitatively.

2.3.1 Grand average motor responses

We visually inspected the trend of the selected spatio-temporal gait parameters in the five steps before and the five steps following a corrective/praising BF message. The CuPiD system only retained the median value of each BF variable for consecutive batches of five right and left steps. To achieve better time resolution, we reconstructed the original step-by-step value for each BF variable. This was possible by combining the right and left foot's raw data for each spatio-temporal gait parameters of interest with their calibration value. We then estimated the average motor response (and 95% confidence intervals) to each possible verbal message (i.e., any cells in the 3x3 matrix of Table 1) from all trials performed by all subjects. Observing these responses can tell us if the subjects responded, and in what ways, to incoming verbal messages.

2.3.2 Effectiveness

We evaluated the percentage effectiveness of each BF variable by counting how many times on the total, following a deviation (persistence) in the variable and the respective corrective (praising) message, the subjects correctly returned (remained) within their therapeutic window. Correct responses were computed, analyzing the BF variable's median in the five steps following immediately the corrective (praising) message, see **Figure 1**, and comparing it with the upper and lower limits of the therapeutic window. In the example

shown in **Figure 1** and relative to corrective messages about GS, the change in the variable in response to a DOWN (UP) message will be classified as an appropriate response if the median value of GS in the five steps after the message will lie below (above) the Upper (Lower) limit of the therapeutic window. For each subject, the average effectiveness was calculated on all performed trials.

We also investigated the difference between the three BF variables (BF Variable Effect) to evaluate whether some gait parameters are more effective than others in restoring an 'optimal' gait pattern. We compared the effectiveness of CuPiD with a sham condition without BF (no-BF). Besides, we also compared the effectiveness of responding to messages to increase or decrease the selected BF variable (Instruction Effect). Analyzing these comparisons can tell us if some BF variables perform better than others, and whether it is easier to increase or decrease them.

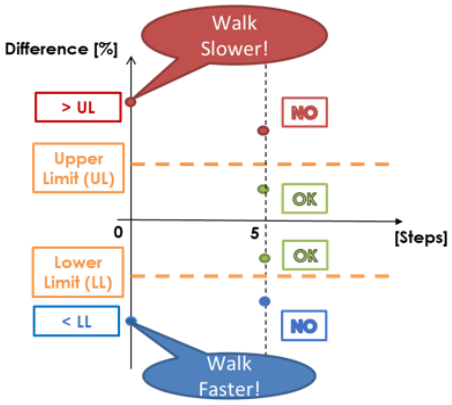


Figure 1. Schematic representation to illustrate how the effectiveness was calculated in response to a deviation (in GS in this example).

2.4 Long-term effects

To investigate long-term effects, we analyzed the inter-trials trend of effectiveness. Firstly, we calculated the effectiveness percentage in each trial performed by each subject. Then, we derived its linear regression, considering all trials performed by each subject. In addition, to quantify the reliability of this data, we also calculated its standard deviation. However, this method may not be indicative of assessing long-term effects. The CuPiD-system works by updating the initial therapeutic window set by the therapist using an automatic adaptive algorithm introduced to prevent feedback overload (e.g., if in a given day a subject is particularly stiff or clumsy) and maximize motor learning (introducing some elements of variability in the rehabilitation program to obtain behaviors more resistant to extinction). Thus, therapeutic window limits may change during the trials. In particular, the CuPiD-system can automatically increase or decrease the task's difficulty to follow a patient's performance. For example, every time the patient can remain within the therapeutic window for a certain amount of steps (set by the clinician), the upper and lower limits are progressively decreased to a certain extent (set by the clinician), providing a more challenging exercise [18]. Taking this

into account, to assess long-term effects we explored the changes in SL and GS during the entire protocol. For this analysis, we included only sessions with BF on SL or GS and decided to report the results of one representative subject with enough trials. When BF was on CAD, no sufficient trials were indeed available. To do so, we analyzed the average values of GS and SL in each minute of the trials performed by this subject, excluding the first and the last minute, to remove transients related to the start and end of the walking session. To this aim, firstly, we calculated the average value of the GS or SL in each trial performed by the subject, then we extracted its median value.

2.5. Statistical Analyses

Results on effectiveness were reported as the median and interquartile range because of the non-normal distribution of the data. The non-parametric right-tailed Wilcoxon signed-rank test (one sample) was used to evaluate if the percentage effectiveness of each BF variable was larger than 33.3%, assumed as the effectiveness of the sham no-BF condition. Due to the absence of a real no-BF walking session within the CuPiD-project, in retrospect, we made this hypothesis since it is reasonable to assume that when the BF variable falls outside the therapeutic window, in the lack of a corrective message the subject can, with equal probability: a) keep the variable (almost) unchanged, b) increase it, or c) decrease it. So, only in one case out of three (33.3%), the subject with no feedback would return within her/his therapeutic window.
The Wilcoxon signed-rank test (paired) was used to determine the significance ($p < 0.05$) of the differences in the effectiveness of the three BF variables (BF Variable Effect). We evaluated each possible pair: SL vs GS, SL vs CAD, and GS vs CAD, introducing the Bonferroni correction for multiple comparisons. The Wilcoxon signed-rank test (paired) was also used to evaluate the significance ($p < 0.05$) of the difference in responding to increasing or decreasing BF messages (Instruction Effect). Statistical analyses were performed using Matlab (version 2018a, Mathworks Inc., United States).

3. Results

Participants with PD were in the early and mid-stages of the disease with mild to moderate motor symptoms and they were all physically independent and able to use the CuPiD-system [20]. In general, participants were very positive about the system, as scores on user-friendliness were on average above 4 on a 5-point scale [4]. The dosage of the intervention actually delivered to participants and estimated from the logs of the CuPiD app is summarized in **Table 1**.

CuPiD Dosage Individual average values over the 6 weeks	
Number of training sessions	19
Distance travelled per session	1.3 km
Average duration of each session	18 min
Total number of left plus right strides	2129
Cadence	116 steps/min
Stride Length	1.3 m
Gait Speed	1.21 m/s
Number of praising messages	61
Number of correcting messages	21

Table 1. The dosage of the CuPiD intervention

3.1. Usage of BF variables

As shown in **Table 2**, SL and GS were the BF variables most frequently selected by therapists during the protocol. Both variables were used for 17 out of 18 subjects, totaling 175 and 133 trials, respectively. CAD was prescribed to 6 subjects only, over the course of 24 trials.

	INSTRUCTION				
BF VARIABLE	**Gait Parameters**	**PRAISE**	**INCREASE**	**DECREASE**	**Subjects** *(Trials)*
	Stride Length (SL)	"Well done!" "Very well!" "Great, keep going!"	"Lengthen your steps" "Take longer steps" "Take long and well-stretched steps"	"Shorten your steps" "Take shorter steps" "Reduce the length of your steps"	**17** *(175)*
	Gait Speed (GS)	"Well done!" "Very well!" "Great, keep going!"	"Speed up" "Walk faster" "Increase your walking speed"	"Slow-down" "Walk more slowly" "Walk slower"	**17** (*133)*
	Cadence (CAD)	"Well done!" "Very well!" "Great, keep going!"	"Take your steps with a stronger pace" "Increase the pace of your steps" "Raise the rhythm of your steps"	"Take your steps at a slower pace" "Slow the rhythm of your steps" "Decrease the pace of your steps"	**6** (*24)*

Table 2. Verbal feedback (BF) messages received by the participants for each BF variable (Stride length, Gait Speed, Cadence) and Instruction (praising, increasing, and decreasing). The last column presents the number of subjects and the total number of trials across all subjects in which at least one praising/corrective message for that BF variable was displayed.

Eighteen participants received a total of 28673 verbal messages, (median values and interquartile range messages per participant of 1260 (602; 2478)), with a prevalent number of praising messages (22251; 77%). As expected, due to PD-related hypokinesia, the majority of corrective messages were encouraging larger rather than smaller amplitude or speed in gait-related movements (4473; 70% vs 1949; 30%). The larger usage of SL and GS as the BF variables, as also shown in **Figure 2**, influenced the number of messages targeting their control: 15347 for SL; 11878 for GS; 1448 for CAD.

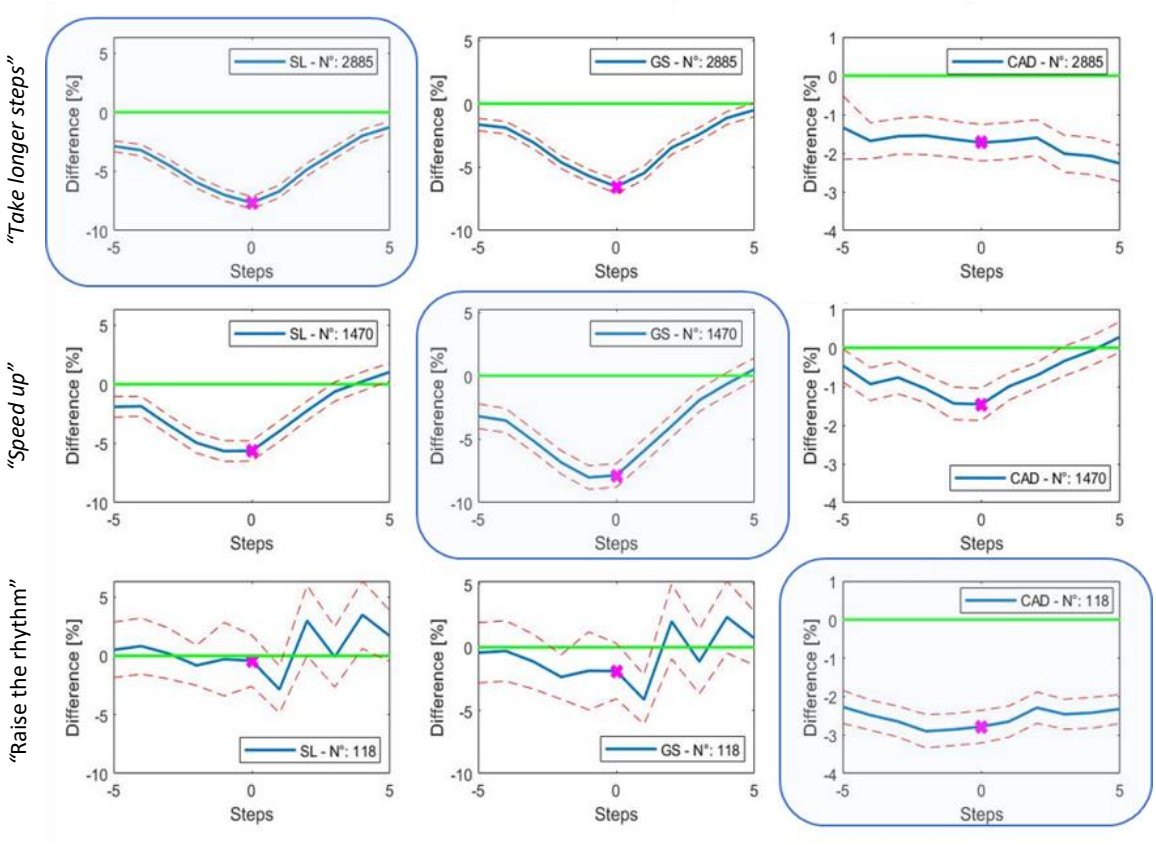
3.2. Coherence between verbal BF and motor responses

3.2.1 Grand average motor responses

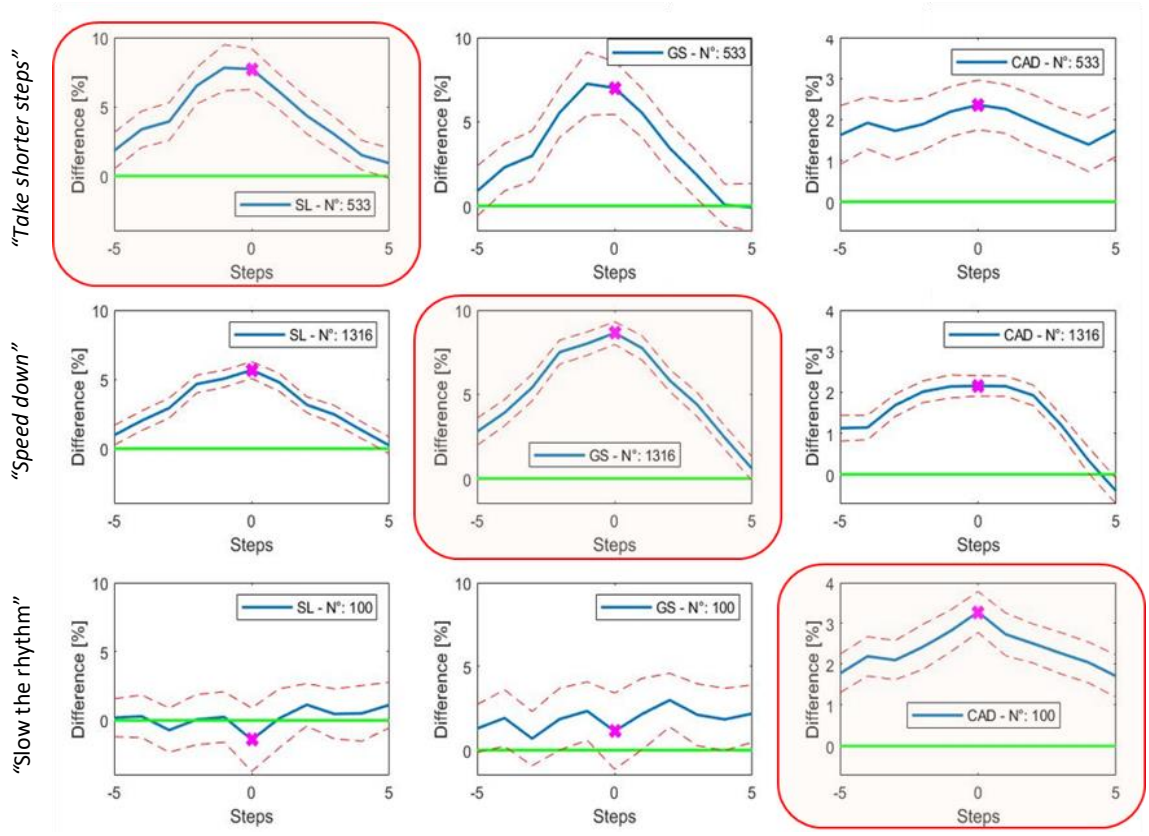
In this analysis, we qualitatively assessed the motor responses of the participants across the different BF states they experienced during the trials. To do so, we computed and plotted the grand average motor responses and corresponding 95% confidence intervals for each pair (BF variable, Instruction). To investigate the carryover effects among BF variables, we also analyzed the changes in selected spatio-temporal gait parameters when they were not used as the BF variable. Such an approach produces 27 subplots, corresponding to the observation of 3 spatio-temporal gait parameters (SL, GS, CAD) when each one of the 3 is set as the BF variable (SL, GS, CAD) and can generate messages along with three different instructions (increasing, decreasing, praising), i.e., 3x3x3. **Figure 2** presents an overview of these motor responses.
Displayed on the main diagonal, the selected BF variables, in the presence of corrective messages (**Figure 2.A** and **Figure 2.B**), disclose the expected behavior: they tend to increase (**Figure 2.A**) or decrease (**Figure 2.B**) when prompted. In the case of SL and GS, within 5 steps after the message they are back to their reference value, or very close to it. In such timeframe, participants proved to be, on average, well responding to the incoming verbal message, demonstrating the ability to keep focused on the training even in a naturalistic environment and to produce a 5-to-10% recovery in the BF variable. Even if qualitatively consistent, the ability to react to errors in CAD was instead milder and slower.

Motor responses to praising messages (**Figure 2.C**) confirmed their protective effect, showing that all variables, after the message, remained in the therapeutic window, getting even closer to their reference value.
An overview of the different columns of the matrix plot in **Figure 2** demonstrates apparent carryover effects among gait variables, particularly strong between SL and GS.

(A)


"Take longer steps"
"Speed up"
"Raise the rhythm"
SL - N°: 2885
GS - N°: 2885
CAD - N°: 2885
SL - N°: 1470
GS - N°: 1470
CAD - N°: 1470
SL - N°: 118
GS - N°: 118
CAD - N°: 118
Difference [%]
Steps

(B)


"Take shorter steps"
"Speed down"
"Slow the rhythm"
SL - N°: 533
GS - N°: 533
CAD - N°: 533
SL - N°: 1316
GS - N°: 1316
CAD - N°: 1316
SL - N°: 100
GS - N°: 100
CAD - N°: 100
Difference [%]
Steps

(C)

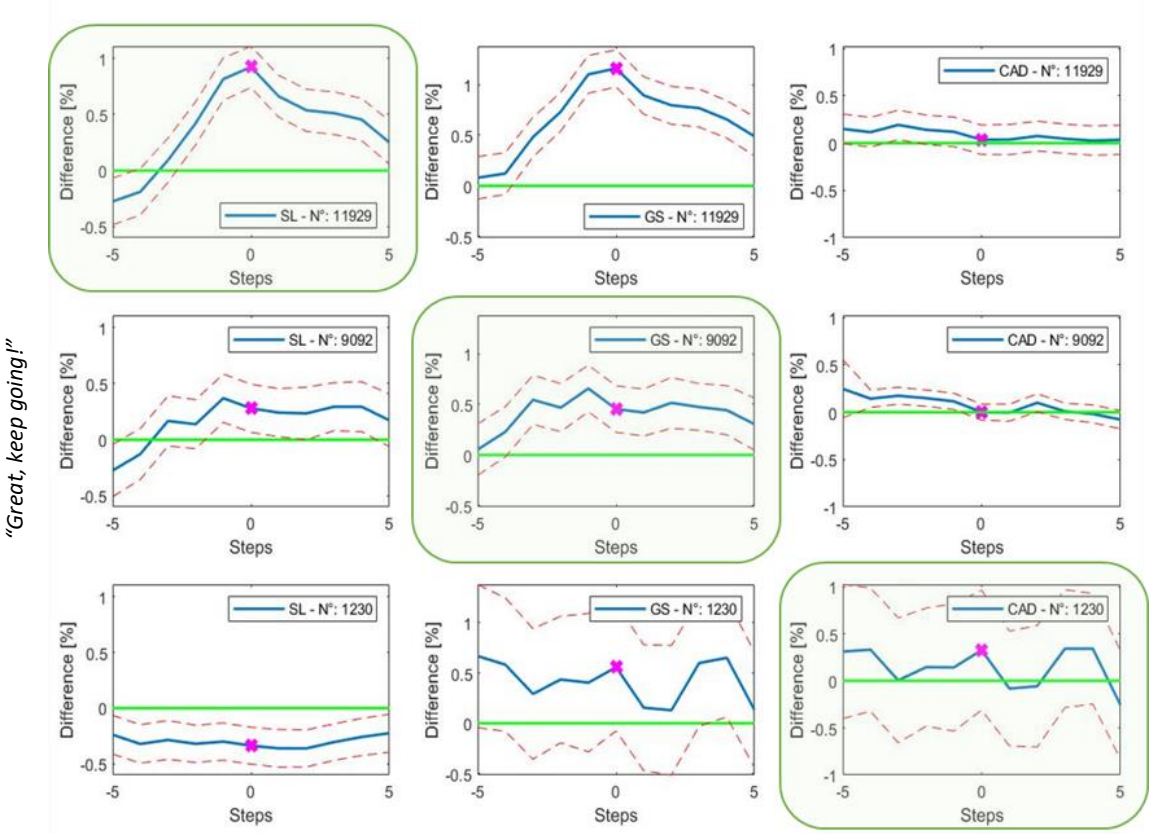


Figure 2. Grand average motor response (solid blue line) and 95% confidence interval (dotted red lines) as a result of increasing **(A)**, decreasing **(B)**, and praising **(C)** messages. The first row in each matrix plot shows the responses when SL was the BF variable; the second row when it was GS; the third row when it was CAD. Corresponding legends document the overall number of BF messages for each pair (BF variable, Instruction) and hence the number of motor responses that were averaged in each respective subplot (e.g., first row in box **(A)** presents the average of 2885 motor responses when the BF variable was SL, and the Instruction was 'Increase'). Off-diagonal elements in the matrix plots show the carryover effects on the other BF variables (e.g., the second and third subplots in the first row present the corresponding changes in GS and CAD when the BF variable was SL, etc.). Values are reported as percentage differences with respect to the current reference value (green line) for that variable, estimated during the functional calibration of the CuPiD-system. Subplots in each column, referring to the same gait parameter, have the same scale. Step 0, marked with a magenta cross, indicates the instant when the verbal BF message was displayed.

3.2.2 Effectiveness

Table 3 reports the percentage effectiveness achieved using the three BF variables SL, GS, and CAD. Across participants, the most effective variable was GS with a median value of 66.5% (so, two out of three times, after corrective feedback, the subject correctly returned within the therapeutic window). The effectiveness of SL was only slightly smaller (60.6%), while CAD was not as good (34.6%). When comparing the percentage effectiveness of the BF with the sham no-BF condition, we obtained that both SL and GS but not CAD introduced significant responses. As far as the choice of the BF variable may affect the results, **Table 3** shows

that GS led to significantly higher effectiveness compared to SL (p-value = 0.015, with a Bonferroni-corrected significance level of 0.017). No significant differences were found for the paired comparisons with CAD. **Figure 3** shows the data behind the Wilcoxon signed-rank test for paired comparisons between individual patient values of percentage effectiveness when using different BF variables.

	BF on **SL**	BF on **GS**	BF on **CAD**	*BF variable **SLvsGS***	*BF variable **SLvsCAD***	*BF variable **GSvsCAD***
EFFECTIVENESS [%] Median (Q1;Q3)	*60.6 (57.2;71.1)*	*66.5 (62.2;77.7)*	*34.6 (22.7;66.7)*	***p = 0.015*** *(n=16)*	*p = 0.094 (n=6)*	*p = 0.063 (n=6)*
Median vs 33.3%	***p = 0.000***	***p = 0.000***	*p = 0.656*			

Table 3. Percentage effectiveness in response to corrective messages regarding each BF variable (SL - Stride Length; GS - Gait Speed; CAD - Cadence). Median values and interquartile range obtained across participants are reported. Statistical significance values are reported for paired comparisons among BF variables and between BF variables and sham no-BF condition, when it is assumed that percentage effectiveness is 33.3%. Bold numbers indicate significant differences after the Bonferroni correction. n, number of participants included in the paired analysis.

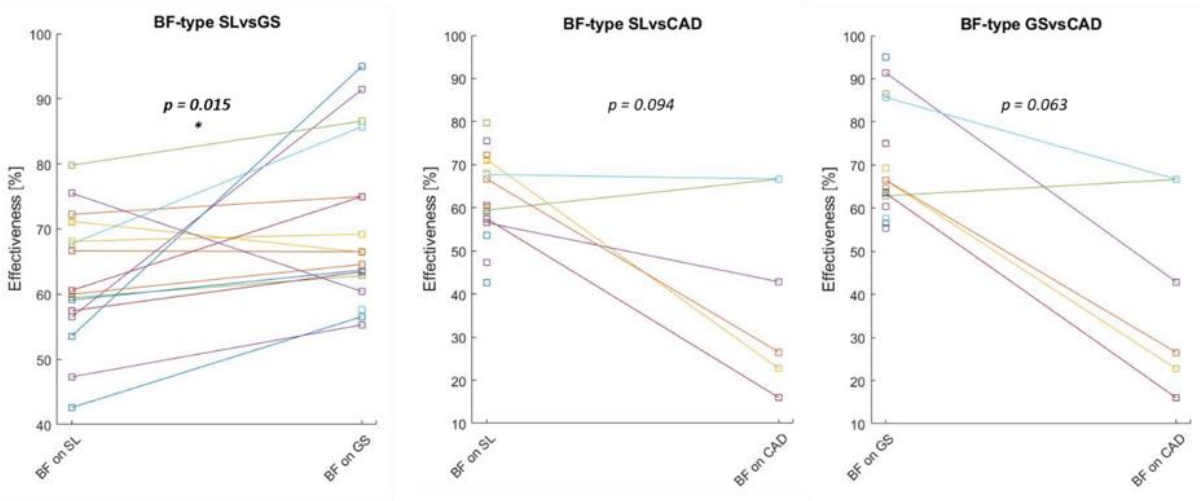


Figure 3. BF Variable Effect: paired comparisons between the effectiveness median value using BF on the different spatio-temporal gait parameters (SL, GS, and CAD). We evaluated each possible pair: SL vs GS, SL vs CAD, and GS vs CAD, introducing the Bonferroni correction for multiple comparisons.

Table 4 compares the effectiveness of the motor response in the presence of opposite corrective instructions. Wilcoxon signed-rank test disclosed the lack of any significant difference in effectiveness between messages aimed at increasing or decreasing the value of each of the BF variables.

EFFECTIVENESS [%] Median (Q1;Q3)	BF on **SL**	BF on **GS**	BF on **CAD**
INCREASE	65.3 (58.6;72.4)	65.9 (61.1;77.9)	36.4 (20.0;63.6)
DECREASE	66.7 (55.1;75.0)	71.4 (63,1;87.9)	36.8 (12.7;63.8)
Instruction Effect	*p = 0.804 (n=16)*	*p = 0.227 (n=17)*	*p = 0.813 (n=5)*

Table 4. Percentage effectiveness in response to opposite corrective messages (Increase; Decrease) on the three BF variables. Median values and interquartile range obtained across participants are reported. The last row reports the results of the Wilcoxon signed-rank test of the three paired comparisons. n, number of participants included in the paired analysis.

3.3. Long-term effects

Table 5 reports the inter-trials linear regression and standard deviation of the effectiveness percentage in each trial performed by each subject. Across participants, the inter-trials trend is close to zero as the median value, with a high standard deviation (more than 20%). It seems that, along with the treatment, subjects not improve their efficacy in response to BF.

	BF on **SL**	BF on **GS**	BF on **CAD**
TREND Inter-Trials [%/Trials] Median (Q1;Q3)	*0.06 (-3.33;0.66)*	*0.20 (-3.38;2.02)*	*3.03 (-18.9;17.4)*
STD Inter-Trials [%] Median (Q1;Q3)	*23.3 (19.7;30.0)*	*23.5 (19.7;30.5)*	*36.3 (26.5;37.7)*

Table 5. In the table, the inter-trials linear regression and standard deviation of the effectiveness percentage in each trial performed by each subject. Median values and interquartile range obtained across participants are reported.

However, this method may not be indicative of assessing long-term effects. The CuPiD-system can automatically increase or decrease the task's difficulty to follow a patient's performance. **Figure 4** illustrates how the SL and GS values changed for one subject over the 6-week protocol in the trials when they were selected as the BF variables. As shown, the number and the scheduling of the trials performed using the two BF variables were different, as in some days the therapist designed the treatment focusing on SL while in others the focus was on GS. **Figure 4** shows a trend towards improvement (larger SL and higher GS) for this subject during the treatment. For GS, there also seems to be a reduction in variability over time, showing a possible increase in efficacy and motor learning [24] effect as a result of the treatment.

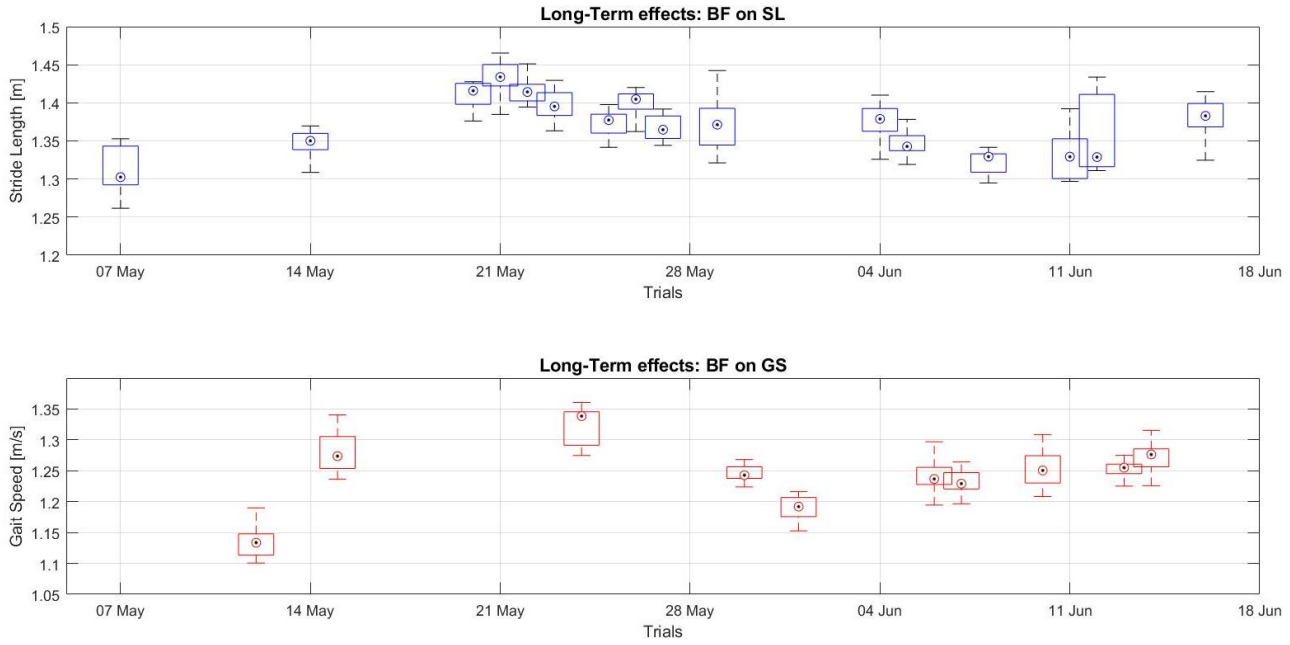


Figure 4. Single-subject analysis of the long-term effects of the BF training. Upper panel: 6-week time course of SL (in [m]) recorded by the CuPiD system during the trials in which SL was set as the BF variable. Lower panel: 6-week time course of GS (in [m/s]) recorded by the CuPiD system during the trials in which GS was set as the BF variable.

4. Discussion

This study improved the knowledge on the effectiveness of different biofeedback-based, therapeutic strategies in PD subjects outside the laboratory, exploring in a real-life context the role of varying biofeedback variables used in the CuPiD gait-rehabilitation system. Eighteen participants with PD in the early and mid-stages of the disease were able to use CuPiD-system. The subjects could react with a coherent increasing or decreasing pattern to BF messages based on spatio-temporal gait parameters (GS and SL). Despite the ecological set-up of CuPiD's protocol, which could make it harder to follow instructions concerning a supervised environment, a high level of coherence was reached (Effectiveness > 60%) between the verbal feedback and the relative motor response using SL and GS as biofeedback variables. For these two variables, a biofeedback system led to significantly better motor control than a no-feedback condition. The BF-type Effect reported the best coherence using GS, although near the limits of significance. No sign of Instruction Effect was found; thus, interestingly, the subjects were equally able to increase or decrease their performance. Moreover, we performed a first exploratory analysis of the long-term pattern for SL and GS of the whole 6-week protocol in a single subject. This subject showed a lower gait performance in the first training sessions, with a performance increase towards the last session, indicating a possible motor learning effect. This is true especially for GS, where a reduction in variability across the median value was shown, possibly related to a more effective way for the patient to keep her/his speed inside the therapeutic window.

4.1. Usage of BF variables

The CuPiD-system consists of straightforward instructions, as indicated in Table 2; thus, the first stage of the motor learning process, the cognitive phase, can be achieved by participants during the system's initial familiarization. SL and GS were the most frequently used biofeedback variables during the protocol. Clinician's directive may have led to this result: the gait impairments in PD are characterized by small shuffling steps and general slowness of movement [25]–[28]. Thus, to help maintain optimal gait, clinicians mainly decided to use BF on SL and GS.

4.2. Grand average motor responses - Effectiveness

We reached a high level of coherence between the verbal feedback and the relative motor response using SL and GS as biofeedback variables, less with CAD. This is a significant result considering the ecological (out of the lab) set-up of CuPiD's protocol. Both qualitative and quantitative analysis suggested this aspect. The superiority of GS and SL might be found in the type of verbal sentences used. For example, in response to SL, subjects can only act on the length of the steps to change it without the risk of misinterpretation (for CAD, this could be less straightforward). Still, there is then always to keep in mind that fewer subjects and fewer trials were analyzed for CAD.

The quantitative statistical analyses confirmed the qualitative trend: the effectiveness of CuPiD was significantly higher than a walking session without BF only during BF on SL and GS, where after a deviation in two out of three responses, the subjects return within their therapeutic window. Furthermore, GS led to best effectiveness percentage over SL (66.5% vs 60.6%, *p-value = 0.015*), thus possibly leading to a better motor control. However, it is important to highlight that this difference was close to the limit after the Bonferroni correction. No significant differences were found for the other coupled comparisons, although CAD achieved the worst percentage in absolute value. This lack of significance could be due to the small number of participants involved in the paired analysis when CAD was implied.

Regarding the instruction of the feedback, the statistical analysis (Instruction Effect) reported that the subjects were able to increase or decrease their performance in response to the BF messages. In a previous work [21], characterizing the motor response of people with PD during prolonged indoor walking in response to different corrective acoustic messages (on CAD), it was also found that no significant difference existed between the two directions in people with PD.

Interestingly, looking at the qualitative trend, after praising messages and only during BF on SL, we noticed that the subjects slightly decrease their performance, maybe as a contentment effect in response to the praise message. We can also see the carryover effect between SL and GS to confirm the linear relation between these parameters [29], [30].

As expected, the highest number of messages was received during praising BF; instead of looking inside the corrective BF, the highest number of messages were received during increasing BF. This is because persons with PD struggle to maintain a normal gait [27], [28].

4.3. Long-term effects

The inter-trials linear regression of the effectiveness percentage is close to zero as the median value, with a high standard deviation. Thus, along with treatment, there seems to be high variability and no motor improvement in response to BF. We already stressed the limitation of this analysis considering the challenging nature of the CuPiD-system, besides, Table 2, indicated that the trials and subjects available are not sufficient to analyze CAD data.

Moving on to the results of the exploratory analysis, for a single subject, there seems to be a trend towards improvement in SL and GS values along with the 6-weeks treatment, thus possibly showing a slight presence of motor learning. This is just a single subject, which was chosen because he/she presented a structure of the training sessions with both GS and SL, which were also well distributed over time. Different subjects could have other chosen training parameters (e.g., only SL), distributed in very different ways along with the 6-weeks protocol. With the few subjects of this study, it was no possible to consider all subjects for this exploratory analysis, which would have had too many co-founding factors. This analysis should be repeated on a much larger sample size.

4.5. Limitations and future work

To compare the effectiveness percentage of CuPiD with a virtual walking session without BF, we compared the effectiveness of a no-BF scenario to be 33.3%. We used this value because we hypothesized that the subjects in a no-BF scenario would return within their therapeutic window only in one case out of three. This value is obtained through a simplification and therefore does not cover all possible cases and could be improved. For example, after a deviation, even if the subject modified her/his performance in the right direction, it is not sure that the deviation could be enough to return within his therapeutic window. Still, the optimal solution would be achieved by performing an additional walking session without BF within the protocol.

Moreover, it is essential to note that only Gait Speed and Stride Length reached more than ten subjects. Future work should include more participants and more trials, increasing the total number of messages received in each condition.

Furthermore, to investigate long-term effects, we averaged responses and events of different trials. This is a limitation because values might come from different statistical distributions with different means.

In addition, to better investigate the motor learning process, a different study set-up should be outlined. For example, as done by Nieuwboer et al. [31], a randomized controlled trial study may be ideal for measuring the effects of long-term training with functional testing before and after the intervention. Besides, each participant's disease stage and the fatigue contribution within each trial should be integrated and handled as confounding factors. In particular, a study is in progress to assess the feasibility, patient compliance, and potential efficacy of a long-term training program of 9-months using the same CuPiD-system in the home environment: twenty persons with PD, 10 in Italy and 10 in Israel, are undertaking gait training in the ON therapy condition for 30 minutes, 3 times per week for 9-months. Participants are evaluated with functional tests before treatment, after treatment, and after 3- and 6-months of training.

Another aspect to mention is the automatic adaptive therapeutic window of the CuPiD-system, together with the possibility to manually modify the temporal resolution of the feedback, which are essential aspects to customize and tailor the rehabilitation treatment for PD. In general, this resolution was fixed, and feedback was triggered every five steps, but it could be set in a range between 4 to 7 steps. To analyze the temporal resolution effect, we should test the data with a different and ad hoc protocol.

Supplementary Materials

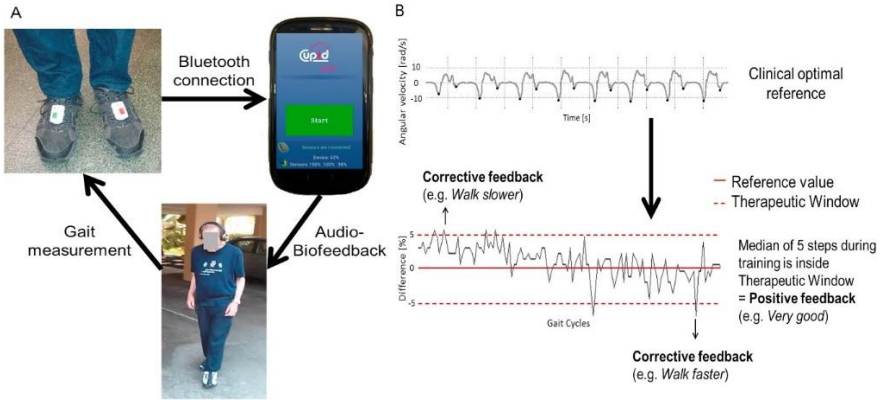


Figure S1 [9]. **(A)** Illustrates the CuPiD system with the foot-mounted IMUs and the single large touchscreen button on the smartphone; **(B)** shows a schematic overview of the CuPiD-gait app with at the top a recording of a clinical optimal reference walk, which was captured under the therapist's supervision. The median value is then used as the reference value (full horizontal line). The pre-set therapeutic window (dotted horizontal lines) are the percentages above and below the reference value as determined by the therapist.

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Section III - Neuromotor Rehabilitation Solutions

Chapter 10

"Innovative mHealth system to provide Multimodal Feedback during Gait Rehabilitation in persons with Parkinson's disease"

A selection of the content of this chapter has been accepted in:

S. Imbesi, M. Corzani, G. Lopane, F. Petrocchi, L. Chiari, G. Mincolelli. "User-Centered Design of Cues with Smart Glasses for Gait Rehabilitation in People with Parkinson's Disease: A Methodology for the Analysis of Human Requirements and Cues Effectiveness". Accepted for 12th International Conference on Applied Human Factors and Ergonomics (AHFE). Sheraton Times Square, Manhattan, New York, July 25-29, 2021.

A selection of the content of this chapter has been submitted as:

M. Corzani, S. Imbesi, G. Lopane, L. Chiari, G. Mincolelli. "Multimodal Cues for Gait Rehabilitation with Smart Glasses in persons with Parkinson's Disease: A Methodology for the selection of Effective Design Solutions". Submitted for the International Conference on Ambulatory Monitoring of Physical Activity and Movement (ICAMPAM) 1st Virtual Conference, June 23-24, 2021.

Ph.D. candidate's main Contribution:
Developed the Smart Glasses (SG) app and the Smartphone app that acts as a remote control to exchange data with SG. Performed and Designed the Human-Centered testing phase. Processed the data.

Abstract

Persons with Parkinson's disease (PD) are affected by cognitive and motor impairments that compromise their autonomy, independence, and self-esteem. To face gait problems peculiar to this disease, recent advances in mobile technology have shown that augmented sensory feedback can be leveraged to improve walking. An existing smartphone-based gait rehabilitation system (CuPiD system) makes persons with PD better aware of their gait performance through augmented verbal feedback. Thanks to smart glasses (SG), real-time visual and haptic feedback are also possible: this Chapter describes an innovative mHealth system obtained by integrating the smartphone-based CuPiD system with an Android SG.

As an alternative to the technical industrial mindset, User-Centered Design has proven to be an effective tool to realize products and services for the Healthcare sector. This Chapter also reported a specific Human-Centered testing phase on five subjects not belonging to a particular category of users. This pilot-trial investigates how sensory feedback influences the user's gait and identifies the most efficient cues to improve the user's performance and acceptance of the mHealth system. We proposed sensory cues suggesting a rhythm to be followed: auditory by wireless earphones, visual and haptic by the SG. We analyzed the subjects' qualitative and quantitative responses from an interview and a specific gait analysis protocol, respectively. Then, we applied an alternative version of the Quality-Function-Deployment (QFD) design tool to manage the complexity of collected data and guide the analysis.

While visual BF improves spatial gait parameters, auditory and somatosensory BF improve temporal gait features (cadence). Our QFD's results confirm the role of sensory BF on gait rehabilitation: auditory and haptic BF reach a higher efficacy than the visual one. Some critical aspects emerged: the gap between the user's cadence and the target one; the subjects' sensory preferences. In the next testing phase, the target cadence will be subject-specific, and questionnaires should be used to evaluate subjects' sensory preferences and integrate them into the QFD matrix.

Introduction

This work was developed to provide gait training to people with Parkinson's disease (PD), which markedly impacts their functional independence, well-being, and health-related quality of life [1]. In particular, parkinsonian gait is generally expressed as reduced step length and gait speed, increased asymmetry and double support time, and increased variability in step/stride time and length [2]. It is known that the use of external sensory cues (e.g., auditory, visual) to reinforce attention toward the task [3] is an effective gait-rehabilitation strategy for persons with PD; the cues stimulate the voluntary executive component of action [4], [5] by activating the attentional-executive motor control system and bypassing the dysfunctional, habitual, sensorimotor basal ganglia network [4], [6]. In the past, auditory cueing during gait has typically been provided continuously in an open loop (regardless of gait performance) [7], [8]. In the therapeutic context, people are instructed to match foot strike with each beat of the auditory rhythm: these so-called 'cues' [9] facilitate the movement initiation or continuation. Recent advances in wearables and mobile technology offer promising new ways to provide closed-loop feedback to people with PD during gait [10], which can overcome traditional open-loop cue, providing customized cueing: stimuli are triggered in real-time when gait deviates from normal, thus providing patients with immediate feedback on their performance. Casamassima et al. [11] developed a unique wearable and smartphone-based system (CuPiD system) that provides verbal feedback to improve the dynamic balance and gait performance of people with PD, as described in the previous Chapters 8 and 9. During the former EU-funded CuPiD-project, Ginis et al. [12] tested this system's feasibility in a real-life context: they discovered that the wearable system was well-accepted and seemed to be a practical approach to promote gait training in PD subjects.

It is known that proprioceptive feedback (such as vibrational stimuli) requires little or no cognitive processing or attention [13]. Besides, a multi-sensory approach enhances perceptual processing [14], known to be reduced in PD subjects [15]. Therefore, using a different combination of sensory inputs may significantly change the motor response's effectiveness and efficiency to the feedback. Thanks to advances in technologies, visual feedback is possible through Smart Glasses (SG) [16]. SG represents an ideal modality to provide personalized feedback and assistance to people with PD in daily living situations. Indeed, McNaney et al. [17] reported that participants with PD were generally positive about SG as an everyday assistive device; however, usability issues and social stigma still hinder its general acceptance.

This work aims to develop an innovative wearable gait rehabilitation solution by integrating the Vuzix Blade SG [18] into the smartphone-based CuPiD system [11]. Blade SG can augment reality by overlaying pertinent information on top of the user's visual field: projecting a bidimensional image on the right lens. Besides, it also can trigger dual vibratory feedback on its right and left temples. **Figure 1** shows a schematic operation of the CuPiD mHealth system and its possible future scenarios.

However, to accelerate the shift toward the brave new world of mHealth solutions, it is necessary that technology, is appropriately designed with end-users' aid. Many innovative technologies have failed to innovate the current clinical practice because they ignored the interaction between technology, human characteristics, and socio-economic environment [19]. As an alternative to the technical industrial mindset, User-Centered Design has proven to be an effective tool to realize products and services for the Healthcare sector. User-Centered approach has to be included in the design process since the starting phases to develop a product or system that is effective due to the close relationship with the users' requirements and the high capacity of satisfaction of their needs [20]–[22].

Thus, this Chapter describes the innovative mHealth system obtained by integrating the smartphone-based CuPiD system with an Android SG. Secondly, this Chapter also reports a specific Human-Centered testing phase performed on five subjects. This pilot-trial investigates how sensory feedback influences the user's gait and the better cues to improve the user's performance and acceptance of the mHealth system. We proposed sensory cues suggesting a rhythm to be followed: auditory by wireless earphones, visual and haptic by the SG. We analyzed the subjects' qualitative and quantitative responses from an interview and a specific gait analysis protocol, respectively. Then, we applied an alternative version of the Quality-Function-Deployment (QFD) design tool to manage the complexity of collected data and guide the analysis.

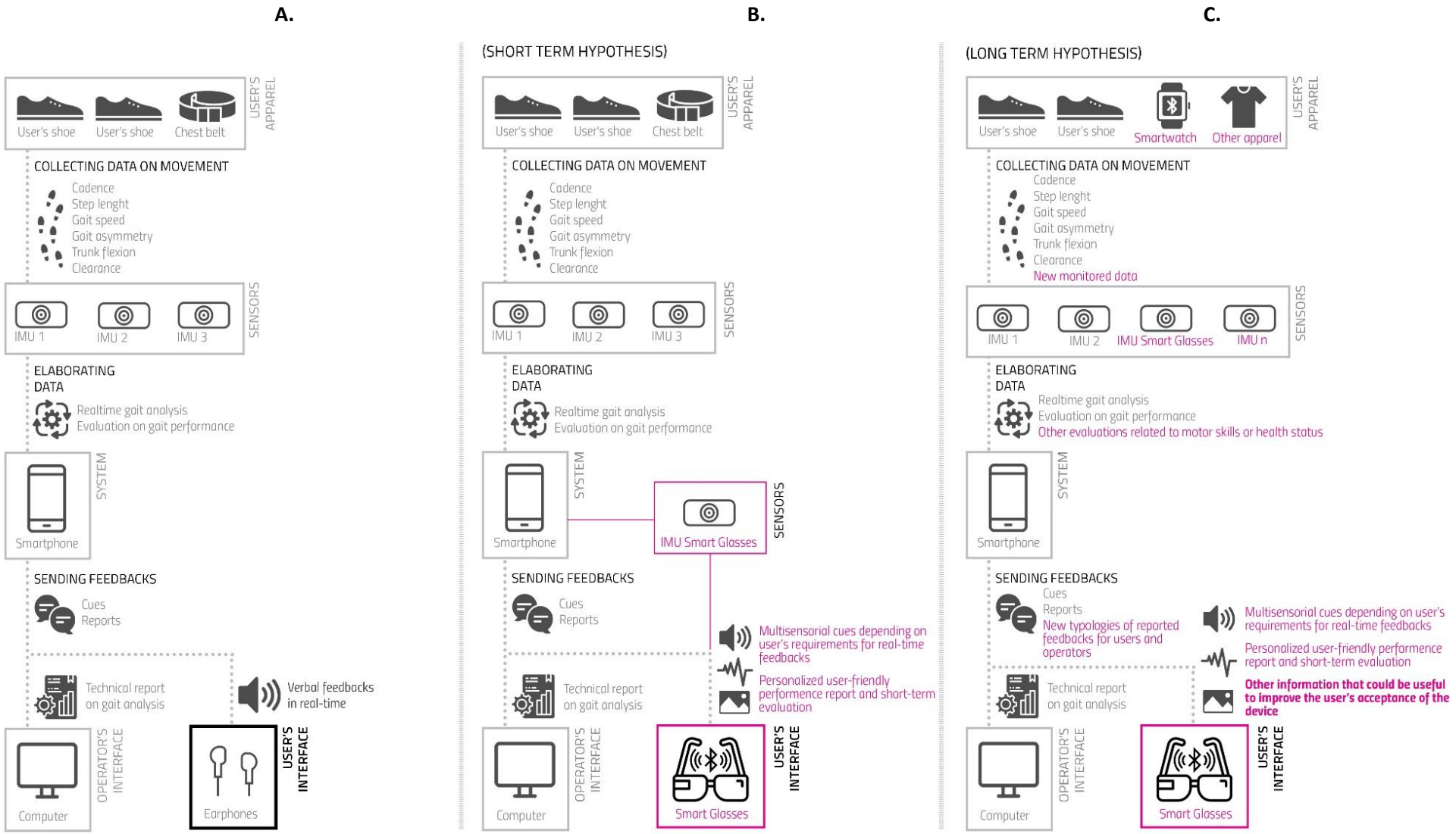

Figure 1. ***A)*** Schematic operation of the CuPiD System. ***B)*** The mHealth system developed integrating the CuPiD system with the Smart Glasses. ***C)*** A possible future scenario where other devices and sensors should be integrated to extend the system capability. The added features are shown in magenta. Adapted from [11].

mHealth system: Concept and Design

This study was developed to optimize gait rehabilitation in PD subjects further using the CuPiD system. During training, the information returned to the user aims to mirror the verbal instructions normally provided to the patient by the therapist during traditional rehabilitation trials. In the intended scenario of use, the CuPiD system uses shoe-worn inertial sensors [11], [23] to make persons with PD better aware of their gait performance and helps them to correct their pathological gait patterns in real-time through augmented feedback. The innovative nature of the mHealth solution that we are proposing here is that it lies in a multisensory approach, where visual and proprioceptive stimuli complement the auditory feedback. To achieve such multisensory feedback, we integrated the CuPiD system with commercial smart glasses for augmented reality applications.

The mHealth system presented in this study is essentially composed of three elements:

1. The inertial sensor nodes: two worn on the shoes and one on the trunk;
2. An Android Smartphone (SP) app with onboard algorithms able to compute gait features (and generate verbal feedback);
3. An Android SG app to generate the augmented multisensory feedback (visual and proprioceptive).

mHealth system – Inertial Sensors and Smartphone (SP) app

The description of the inertial sensors and the SP app has been introduced earlier in this thesis (Chapter 8 and Chapter 9) and was described in detail here [11], [23], [24]. The CuPiD system has been implemented into a standalone Android app installed on the SP, which processes data streamed from the sensor nodes via Bluetooth, and computes gait parameters to trigger real-time feedback on gait, **Figure 2**. It was tested on different smartphones, consistently achieving real-time performance and running without delay [11].

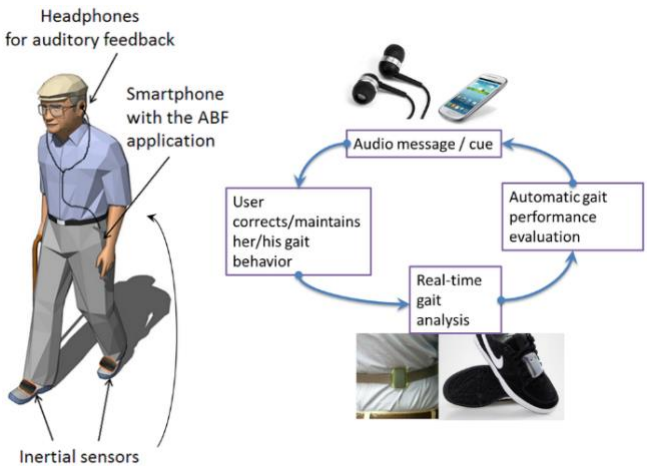

Figure 2. Schematic representation of the CuPiD system. Source [11].

More detailed information can be found in [11]. Innovatively, we modified the Android SP app to allow information exchange via Bluetooth with the SG. In particular, when the SP app triggers verbal instructions, it also sends the message to the SG app to handle multisensory feedback/cues.

mHealth system – Smart Glasses (SG) app

The Vuzix Blade is the SG adopted in our solution, **Figure 3**.

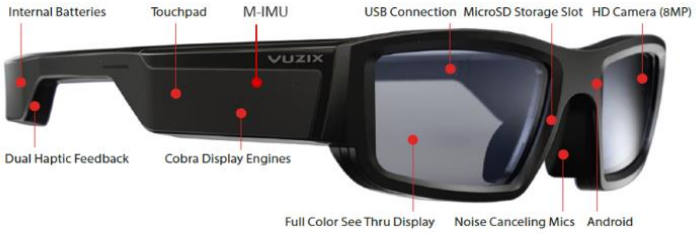

Figure 3. Vuzix Blade smart glasses. Adapted from [18].

It loads the Android 5.1.1 operating system and weights 90 gr [18]. It contains many of the capabilities of a standard Android SP in an unobtrusive head-mounted form factor. Blade-SG can augment reality by overlaying pertinent information on top of the user's visual field: projecting a bidimensional image on the right lens, which is the display user interface. Besides, their embedded camera and microphone can capture information about the user environment and handle voice control, while inertial sensors can track the user's head movement. Interestingly, it also can trigger dual haptic/proprioceptive feedback on its right and left temples. In **Figure 4**, the schematic representation of the mHealth system. The custom SG app is always active in the background when the SG power is on. As soon as it receives the incoming feedback messages from the CuPiD-SP app (via Bluetooth), the user receives visual and/or haptic cues in real-time and without any action needed.

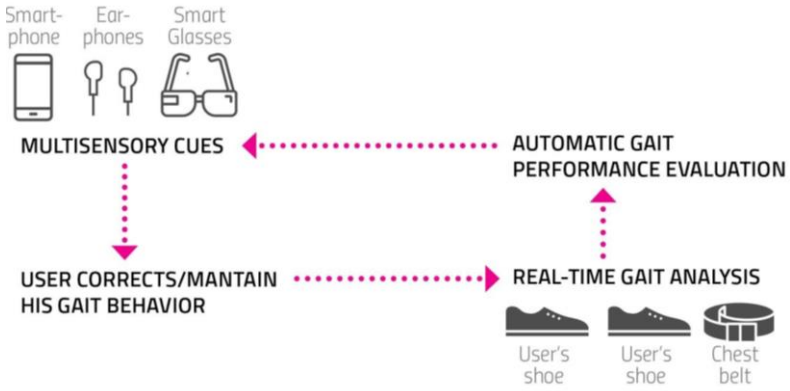

Figure 4. Schematic representation of the mHealth system. Adapted from [11].

Similar to the verbal feedback, there will be specific visual and haptic cues to help patients correct their pathological gait patterns in real-time. In the next section, we described the Human-Centered testing phase, which is the first step necessary to select the most effictive and accepted types of feedback/cues.

Human-Centered Testing phase

We used the mGait system, a CE-marked medical device from mHealth Technologies [25], to evaluate the spatio-temporal gait parameters. In our walking paradigm, the mGait system was used with two inertial sensors applied to the feet, and data is transmitted via Bluetooth to the mGait smartphone app. In designing significant and effective cues to be tested with people with PD, it was first decided to plan a pilot-trial on a sample not belonging to a particular category of users. Thus, we tested the preliminary feedback developed following a Human-Centered approach to guide a selection of the most effective ones for further experimentations with persons with PD. We proposed three sensory stimuli: auditory by wireless earphones, visual and vibratory by the Vuzix Blade SG [18].

Designing Sensory Cues

The first decision was to design signals suggesting a rhythm to be followed rather than incrementing and decrementing specific gait features [12], [26]. This rhythm was made coincident with the walking cadence and set at the average value of 100 steps/min, as suggested by Tudor-Locke et al. [27]. Thus, we elaborated stimuli that are easy to understand and interpret, not compromising the focus on gait. As reported in Figure 9, the sensory cues' patterns aimed to mirror the Gait Cycle Pattern (Cadence = 100 steps/min; Gait Cycle duration of 1200 ms).

The scientific literature on visual feedback developed for people with PD reveals that static and dynamic cues significantly contribute to body balance, standing, and walking when conditions of equilibrium are compromised [28]. Considering the Vuzix Blade's functionalities, it was decided to elaborate static patterns composed of two figures and dynamic patterns with six figures (in both cases played in a loop following the established cadence). For all patterns, to avoid complex icons and written parts, it was preferred to use simple figures that do not involve interpretation, **Figure 5**.

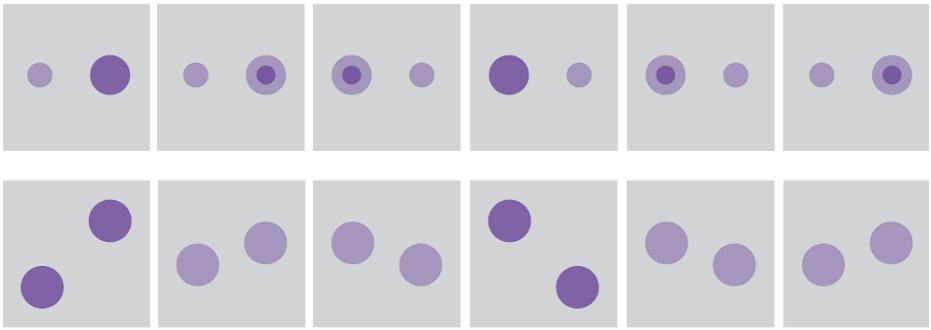

Figure 5. This image presents two examples of the elaborated dynamic patterns, based on the circle, suggesting the rhythm to be followed while walking.

Also, vibratory cues impact gait parameters, especially if associated with the cadence [29]. In this experiment, vibrations are provided by the SG temples. The only design choice is related to the stimuli duration, while the location or intensity of the stimuli cannot be modified. Besides, the right and left temples of the SG can be set to induce a right or left vibration independently. Following these constraints, we produced several vibratory patterns to be submitted to the users.

The field of auditory feedback is the one that has undoubtedly been more investigated in the scientific literature [8], [9]. As previously described, there have been many experiments testing the effect of auditory cues on persons with PD, most of them using rhythmic patterns [30]. Moore et al. suggest using musical cues [31] that have been shown to impact the human brain, including areas that are responsible for movement, language, attention, memory, executive function, and emotion [32]. The authors created a basic melody, then reproduced it in various versions using one or more musical instruments or electronic sounds. Those pathways were registered at 100 bpm, corresponding to 100 steps/min. In the supplementary materials there are all the cues used.

Test Protocol – Materials

The path has a total length of 25 m, is linear and free of physical and perceptive obstacles (unevenness, carpets, floor changes, sudden changes of lighting). The environment has a minimum width of 2 meters without obstructions (furniture, walls, etc.) immediately before the start or immediately after the end. The user wears IMUs on his/her shoes connected to the mGait system, and starts with a walk that will be the reference for the following ones. Then, the user wears the SG and the earphones to perform the other protocol tests. Cues' administration starts between 5 and 9 meters from the beginning of the path, and the stimuli are interrupted at the end of the path, **Figure 6**.

Figure 6. Schematic representation of the path for the test.

We developed a specific SP app for the testing phase. This SP app acts as a remote control. It mimics the verbal feedback sent by the CuPiD system (**Figure 1**): using the SP app, an operator selects the sensory cue to be tested, then, clicking on a specific button, the selected sensory cue is triggered on the SG app. In submitting the stimuli, attention is paid to the correct synchronization between the incoming signal and the user's cadence: the cue is sent to the subject while its heel touches the floor. Besides, the operator can write this step in a specific field of the SP app, which saves this information in a ".txt" file.

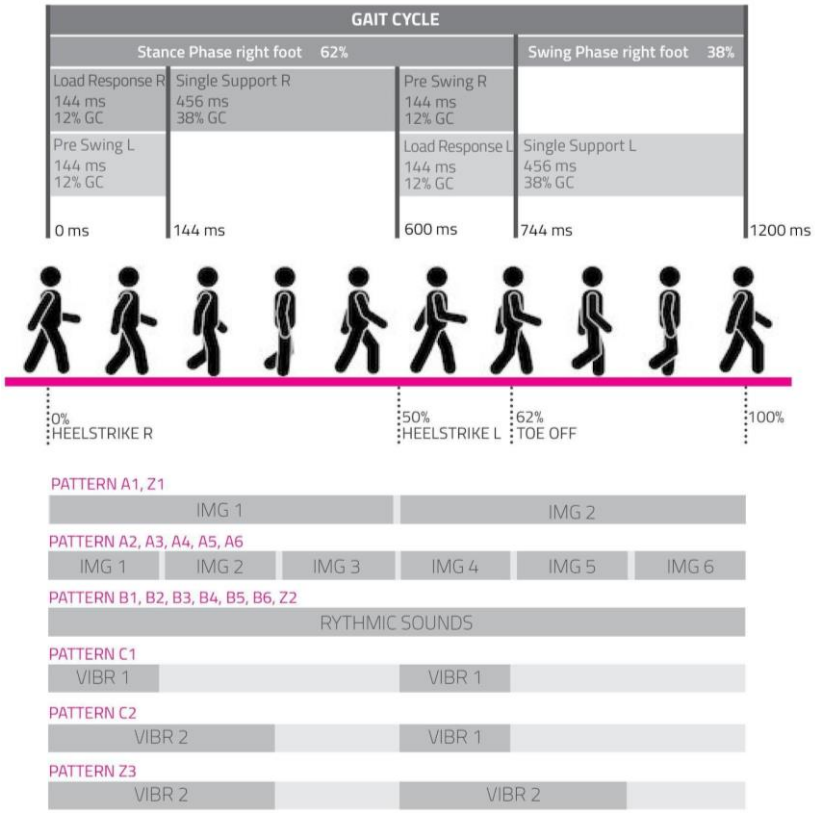

Figure 7. The scheme represents the different phases of the Gait Cycle and the correspondence between the phases and the submitted cues' timing. Adapted from [33].

Five subjects - 4 M and 1 F, 29.4 (1.7) years and 180.6 (5.7) cm - performed 21 walking tests following this scheme:

- 1 Baseline Trial without stimuli, as a reference;
- 3 Unisensory Tests (visual, vibratory, auditory) with randomized administration order (Z1, Z2, Z3);

- 14 Unisensory Tests (6 visual, 2 vibratory, 6 auditory) and 3 Multisensory Tests (1 visual+vibratory, 1 auditory+vibratory, 1 visual+auditory+vibratory) with randomized order (A1: A6, B1: B6, C1: C2, D1: D3).

The second, third, and fourth tests are carried out without providing information to the user on the type of signal that will be received, not to conditionate the user's behavior. The aim is to verify the perceptual impact of these unisensory stimuli. Subsequently, in the last 17 tests, the user is invited to synchronize his/her footsteps with the cadence suggested by the uni- or multisensory stimuli that will be transmitted, **Figure 7**. After each test, the user answers a few questions to evaluate the perceptual and functional quality of the cues he/she has received, with scoring from 1 to 5. At the end of all tests, the user answers a short interview on his/her perception of the SG, their wearability, ease of use, etc. In the supplementary materials there is the questionnaire used.

Data Analysis

From interviews and the gait analysis results, we developed and applied an alternative and innovative version of the Quality-Function-Deployment (QFD) design tool to manage the complexity of collected data and judge every cue's functionality and usability. Usually, QFD is used to express relationships between needs and product specifications: the sensory cues in our case. All the outcomes obtained from the qualitative and quantitative analysis were included as needs for the QFD matrix, **Table 1**. Each need's absolute importance weight was assigned accordingly to the importance of the outcome itself (1 to 5).

CODE	NEED	USER EXPRESSING THE NEED	KIND OF RESPONSE	RELATED PARAMETER	WEIGHT
US01	I don't want it to be invasive and annoying	Test User	Qualitative	Interview	5
TO01	If it is invasive and annoying, I want all users to perceive it in the same way	Technical operator	Qualitative	Interview	2
US02	I don't want it to be difficult to follow the suggested rhythm	Test User	Qualitative	Interview	3
TO02	If it is difficult to align to the signal, I want all users to perceive it in the same way	Technical operator	Qualitative	Interview	1
TO03	I want the user's cadence to align with the target one	Technical operator	Quantitative	Difference between users' cadence and the target one	5
TO04	I want all users to have the same cadence when they receive the signal	Technical operator	Quantitative	Difference between users' cadence and the target one	2
TO05	I want the user to reach the target with few steps	Technical operator	Quantitative	Number of steps to align to the rhythm	5
TO06	I want all users to reach the target cadence with the same amount of steps	Technical operator	Quantitative	Number of steps to align to the rhythm	3
TO07	I want the user to reduce the cadence variability in his gait	Technical operator	Quantitative	Cadence Variability	4
TO08	I want the user's gait to be more balanced and symmetrical in right and left cadence (ASYM_CAD)	Technical operator	Quantitative	Asymmetry Index on Cadence	1
TO09	I want the user's gait to be more balanced and symmetrical in right and left stride length (ASYM_SL)	Technical operator	Quantitative	Asymmetry Index on Stride Length	2

Table 1. Needs for the QFD matrix.

Results

This testing phase aimed to detect qualitative and quantitative responses from the users, respectively obtained from the interviews and the specific gait analysis protocol.

Qualitative Response

Thanks to a questionnaire and an interview, it was possible to collect users' point of view on the designed cues' perception.

1. **CUES' PERCEIVED INVASIVITY** *[Users were asked, after each test, to answer the question "How invasive and annoying was this cue?". They assigned to every cue a score from 1 not invasive to 5 very invasive]*

Figure 8. Graphical representation of users' answers on how invasive and annoying were the cues. Magenta squares represent the median value, and grey bars the interquartile range (Q3-Q1).

2. **CUES' PERCEIVED EFFECTIVENESS** *[Users were asked, after each test, to answer the question "How difficult it was to follow the rhythm suggested by this cue?". They assigned to every cue a score from 1 not invasive to 5 very invasive]*

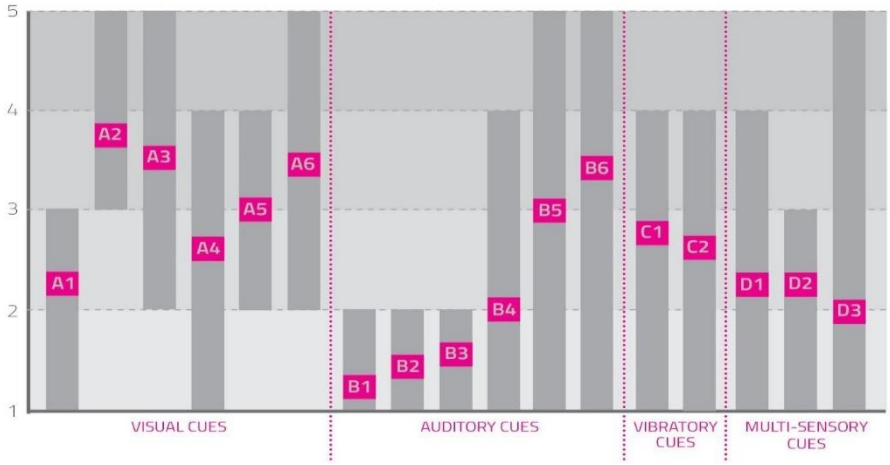

Figure 9. Graphical representation of users' answers on how difficult it was to follow the rhythm suggested by each cue. Magenta squares represent the median value, grey bars the interquartile range (Q3-Q1).

Quantitative Response

Several gait features were computed from the wearable inertial sensors. They were used to analyze and compare the relationship between different cues and performance improvement.

1. **USERS' CADENCE**

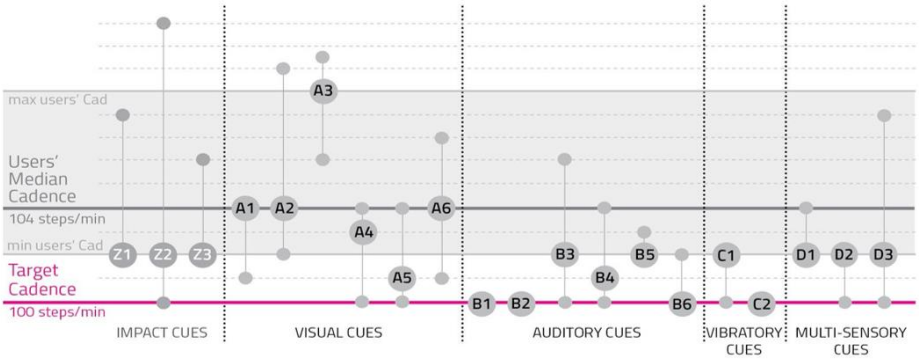

Figure 10. Graphical representation of the users' Cadence obtained during each test. Gray squares represent the median value, grey bars the interquartile range (Q3-Q1). Magenta line represents the target cadence imposed by the cues (100 steps/min), grey line the users' median cadence obtained during the Baseline Test.

2. **NUMBER OF STEPS TO REACH THE TARGET CADENCE** *[Number of steps needed to hold the users' cadence within a value of 95-105 steps/min (5% of the target cadence) for at least 5 steps. The results show the first step of the 5 consecutive steps. If there is no alignment during the test, we reported a value of 30 steps, consistent with the maximum number of steps taken after the signal]*

$$Step_{Treact} = (Cad >= 95 \,\&\, Cad <= 105)_{at\ least\ 5\ steps}$$

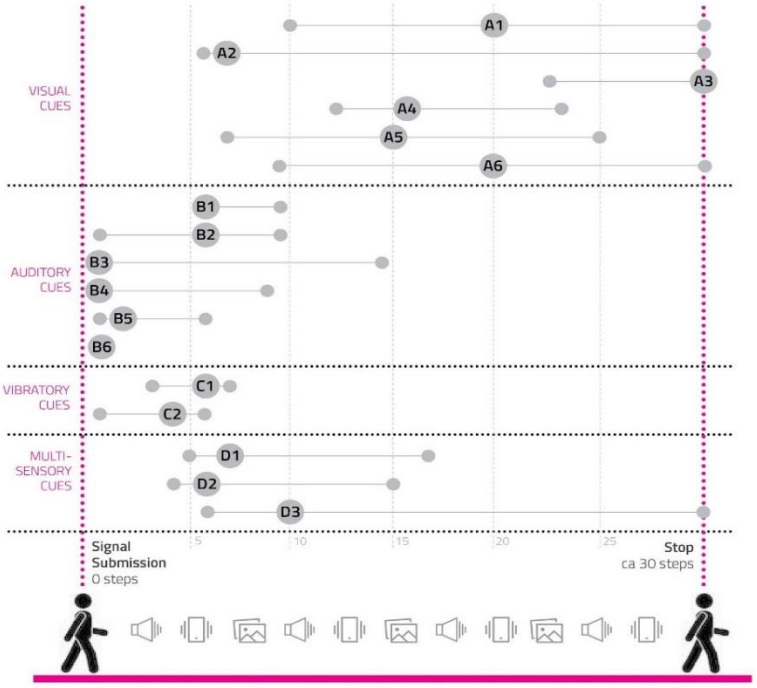

Figure 11. Graphical representation of the number of steps needed to the user to reach the target. Gray squares represent the median value, grey bars the interquartile range (Q3-Q1).

3. **USERS' CADENCE VARIABILITY** *[To analyze users' cadence variability, we extracted its standard deviation, std]*

$$Cad_{std} = \sqrt{\frac{1}{\mathrm{N}-1} \cdot \sum_{\mathrm{k}=1}^{\mathrm{N}} \left(Cad_k - \overline{Cad}\right)^2}$$

N: number of steps

$\overline{Cad}$: average Cad

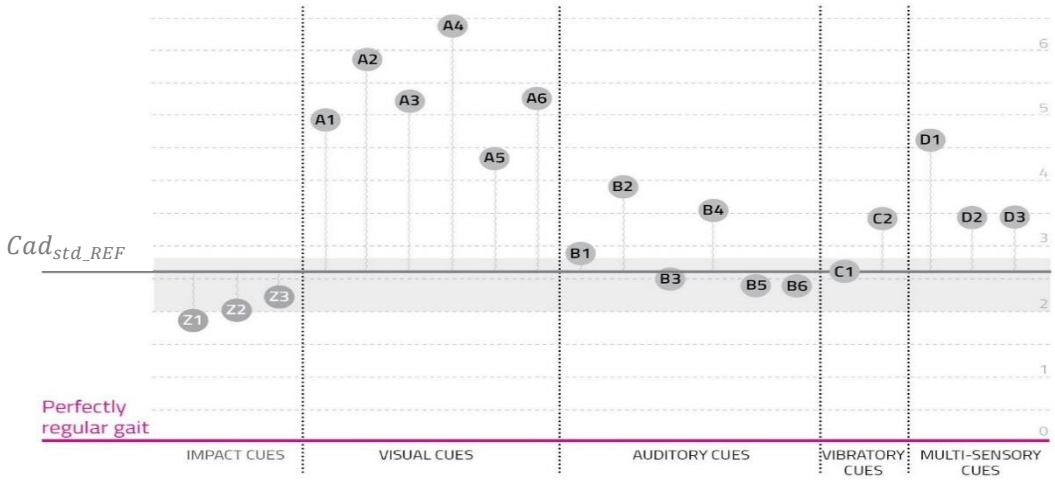

Figure 12. Graphical representation of the users' Cadence Variability. Gray squares represent the median value, grey bars the interquartile range (Q3-Q1). Magenta line represents the perfect regular gait (std = 0), grey line the users' median value obtained during the Baseline Test (Cad_{std_REF}).

4. **RHYTHMIC ASYMMETRY, USERS' ASYMMETRY INDEX ON CADENCE** *[Percentage variation between the average right and left cadence]*

$$Cad_{Asym} = abs\left(\frac{\overline{Cad}_{Right} - \overline{Cad}_{Left}}{0.5 * [\overline{Cad}_{Right} + \overline{Cad}_{Left}]} * 100\right)$$

$\overline{Cad}$: average Cad

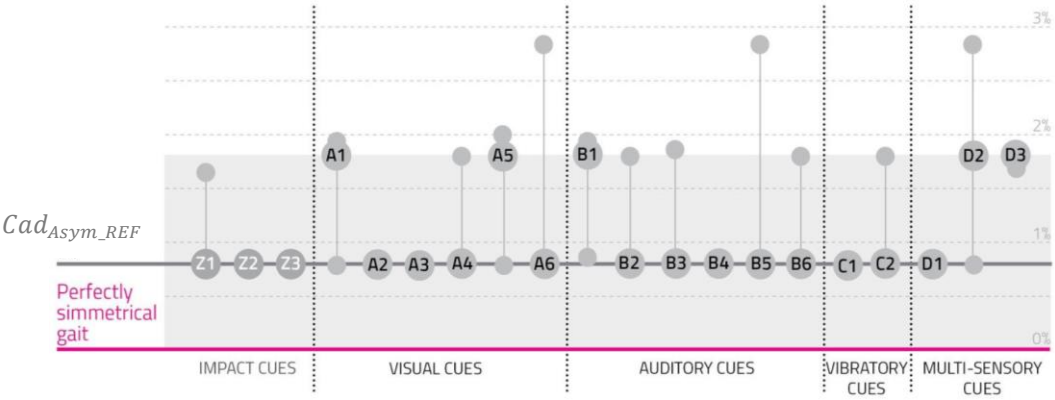

Figure 13. Graphical representation of the users' asymmetry index on Cadence. Grey squares represent the median value, grey bars the interquartile range (Q3-Q1). Magenta line represents the perfect symmetric gait ($\boldsymbol{Cad_{Asym}}$ = 0), grey line the users' median value obtained during the Baseline Test ($\mathrm{Cad_{Asym\_REF}}$).

5. **SPATIAL ASYMMETRY, USERS' ASYMMETRY INDEX ON STRIDE LENGTH** *[Percentage variation between the average right and left stride length]*

$$SL_{Asym} = abs\left(\frac{\overline{SL}_{Right} - \overline{SL}_{Left}}{0.5 * [\overline{SL}_{Right} + \overline{SL}_{Left}]} * 100\right)$$

$\overline{SL}$: average Stride Length

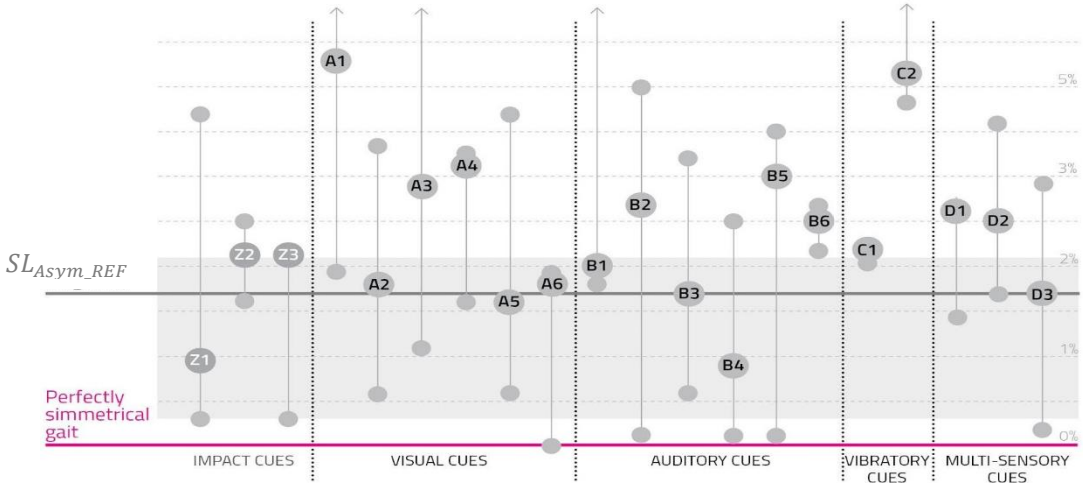

Figure 14. Graphical representation of the users' asymmetry index on Stride Length. Grey squares represent the median value, grey bars the interquartile range (Q3-Q1). Magenta line represents the perfect symmetric gait (SL_{Asym} = 0), grey line the users' median value obtained during the Baseline Test (SL_{Asym_REF}).

QFD matrix

From the relationships between needs and cues expressed in the QFD matrix, we obtained a hierarchization of the cues' effectiveness considering all the qualitative and quantitative data, **Figure 15**.

NUM	CODE	NEED	Absolute Importance	Relative Importance	SENSORY CUES															
					A1	A2	A3	A4	A5	A6	B1	B2	B3	B4	B5	B6	C1	C2	D1	D2	D3
B01	US01	I don't want it to be invasive and annoying	5	15%																	
B02	US02	I don't want it to be difficult to follow the suggested rhythm	3	9%																	
B03	TO01	If it is invasive and annoying, I want all users to perceive it in the same way	2	6%																	
B04	TO02	If it is difficult to align to the signal, I want all users to perceive it in the same way	1	3%																	
B05	TO03	I want the user's cadence to align with the target one	5	15%																	
B06	TO04	I want all users to have the same cadence when they receive the signal	2	6%																	
B07	TO05	I want the user to reach the target with few steps	5	15%																	
B08	TO06	I want all users to reach the target cadence with the same amount of steps	3	9%																	
B09	TO07	I want the user to reduce the cadence variability in his gait	4	12%																	
B10	TO08	I want the user's gait to be more balanced and symmetrical in right and left cadence	1	3%																	
B11	TO09	I want the user's gait to be more balanced and symmetrical in stride length	2	6%																	
		Absolute Importance			49	50	37	45	89	34	180	201	219	193	204	186	137	179	79	86	110
		Relative Importance			2%	2%	2%	2%	4%	2%	9%	10%	11%	9%	10%	9%	7%	9%	4%	4%	5%

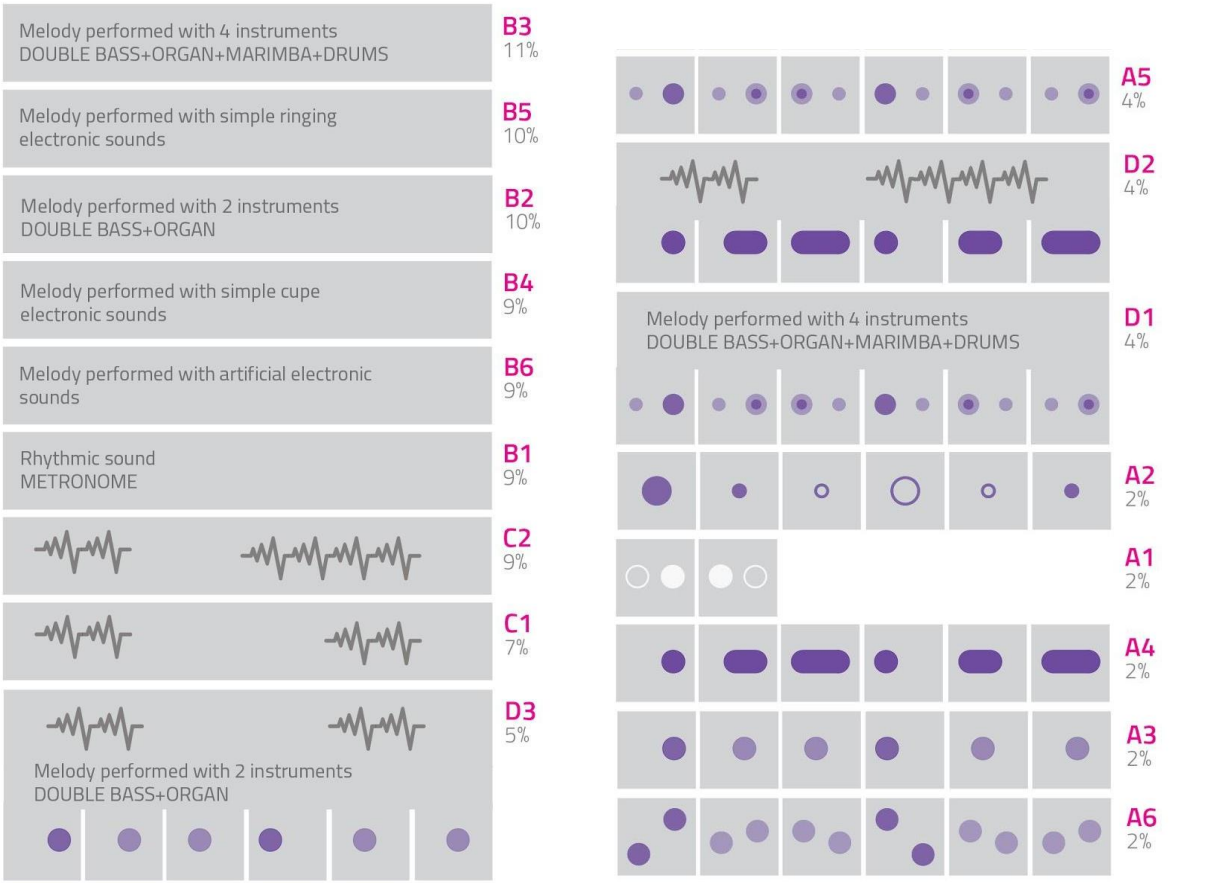

Figure 15. QFD matrix (top) and hierarchization of the cues' effectiveness (below) following QFD results. A1:A6 Visual cues; B1:B6 Auditory cues; C1:C2 Haptic cues; D1:D3 Multimodal cues.

Discussion

The first three unisensory tests (Z1, Z2, Z3) are performed without providing information to the user on the type of signal received, not to conditionate the user's behavior. Interestingly, the results suggested that the participants implicitly got close to the rhythm imposed by the unimodal feedback (**Figure 10**). Furthermore, their cadence variability appears to be reduced compared to their reference walk (**Figure 12**).

It is known that different cueing modalities have a differential effect on gait rehabilitation. While visual cueing mainly improves spatial gait parameters (e.g., stride length), auditory and somatosensory cueing primarily improve temporal gait features (e.g., gait speed and cadence) [34], [35]. Our QFD's outcomes are in line with these indications: all the auditory and vibratory cues reach a higher percentage than to the visual one (**Figure 15**). Also, our results indicated that unimodal feedback is more effective than the multimodal one. This aspect is partially linked to the choice of a simple walking paradigm in which the subject had to walk on a linear path without obstacles trying to follow the suggested cadence. In a complex motor task, multimodal feedback can be better suited to exploit each modality's specific advantages. In particular, the characteristic of visual stimuli to display alerts and improve the spatial aspects of the gait, against the ability of haptic and auditory stimuli to enhance the temporal aspects [34].

Limitations and Future Works

We identify these main critical points from this first testing phase: the gap between the user's cadence and the one proposed by the system; the extent that each subject is visually-, auditory-, or somatosensory-dependent. The nervous system uses augmented sensory information differently, depending primarily on individual proclivities to rely on a sensory channel over another to control motor behavior [36].

To overcome them, in the next testing phase, the target cadence will be subject-specific. In particular, during gait training with the CuPiD system, the target cadence can be based on the one detected during the user's reference gait of the CuPiD system [11]. Alternatively, to comply with the therapeutic needs, the target cadence should be a modified version of that recorded during the user's reference gait.

Besides, questionnaires or automated assessment methods should evaluate patients' sensory preferences and integrate them into the QFD matrix.

Importantly, even SG must be personalizable in their physical dimension according to the user's requirements: most people with PD are over 50 and have vision problems. Thus SG must be compatible with prescription lenses. This feature is possible with the SG used [18].

Gait and balance impairments afflict most persons with PD and impact their quality of life and independence [37]. With their sensors and feedback capabilities, SG may help alert the patient to correct this behavior and provide support via visual, auditory, or vibratory cues, instructional videos, or step-by-step verbal instructions.

Although the potential of real-time feedback systems in gait rehabilitation through wearable devices is underexploited [38], these new real-time systems seem to increase adherence to treatment, self-management, and quality of life [39], allowing also personalized and tailored rehabilitation on the individual patients' needs [12].

In conclusion, SG has the potential to empower persons with PD. However, more research is necessary to ensure safety, efficacy, usability, and social acceptance.

Supplementary Materials

In the following link, there are all the cues used in the Human-centered testing phase.

https://drive.google.com/drive/folders/1qQU0cwB9wR8wnMF0--5fyy0CXpRBa-81?usp=sharing

In the following link, there is the questionnaire used in the Human-centered testing phase.

https://drive.google.com/file/d/1F9oYJw1J9f2TgR4-aBHRT0lTGo87GDLh/view?usp=sharing

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Section III - Neuromotor Rehabilitation Solutions

Chapter 11

"Innovative ‘Smart Crutches’ integrated with an Exoskeleton for Aiding and Rehabilitating Paraplegic patients' gait"

“Proof of Concept”, unpublished results

Ph.D. candidate's main Contribution:
Developed the Smartphone app and processed the data.

Abstract

This chapter presents a proof of concept concerning the use of innovative smart crutches with an active, powered, and wearable lower-limb exoskeleton for aiding and rehabilitating paraplegic patients' gait disorders resulting from severe central nervous system lesions.

In the current version of the proof of concept, two sensorized crutches measure the intensity of the force applied by the user to the ground and the crutches' orientation. Thanks to an Android app, the two smart crutches communicate with a smartphone, worn on the chest with a belt, that can estimate the trunk's orientation in real-time. In the future, the exoskeleton will communicate with the smartphone to handle these data in a biomechanical model to improve the exoskeleton's effectiveness and action.

Firstly, we briefly describe the integrated mHealth system; secondly, the validity of real-time orientation is tested using stereophotogrammetry as the gold standard: the preliminary results of the validation disclosed acceptable RMSE values.

Introduction

Gait disorders imply a reduction in autonomy and in the ability to move independently. They can result from serious central nervous system (CNS) lesions due to spinal cord injury (SCI), cerebrovascular accident (CVA), cerebral palsy, and infectious diseases [1], [2]. Usually, the patient is forced to rely on a wheelchair for mobility and often requires support from a caregiver. Over time, patients may also develop secondary complications such as hypertension, osteoporosis, and bedsores. These comorbidities severely limit the individual's ability to carry out daily living activities, restrict social participation, and affect the quality of life and mood [3]. Novel neurorehabilitation approaches based on robotic devices have been proposed in recent years. These approaches are referred to as neurorobotic or neuroprosthetic training and may include devices such as an exoskeleton [4]. Robotics-assisted powered exoskeletons represent a relatively new technology that is safe and effective in helping individuals with complete motor paraplegia to stand and walk [5]. Some exoskeletons developed to assist paraplegic patients in their lower limb movements are passive [6]; that is, the exoskeleton moves the patient's body on a predefined trajectory, regardless of what the patient is doing [7]. Other exoskeletons are active [8] since they enable patients to move together with the robot in the desired direction [7]. These allowed patients with motor disorders to stand to bolt upright and move autonomously in their environment. Exoskeletons have been used to assist patients with SCI by restoring their functional abilities [9].

In collaboration with the Rehab Technologies - INAIL-IIT Lab [10], in this proof of concept, we developed a mHealth system integrating innovative smart crutches with an active, powered, and wearable lower-limb exoskeleton for aiding and rehabilitating paraplegic patients' gait disorders resulting from severe CNS lesions. The Rehab Technologies - INAIL - IIT Lab developed the Twin exoskeleton [11], intending to become a personal device that allows spinal lesioned patients to walk autonomously, through a design approach that emphasizes ease of use, wearability, and transportability of the exoskeleton. Through this innovative system component, we aimed to improve the exoskeleton's effectiveness and safety.

In the current version of the proof of concept, two sensorized crutches measure the intensityof the force applied by the user to the ground and the crutches' orientation. Thanks to an Android app, the two smart crutches communicate with a smartphone (SP), worn on the chest with a belt. The SP can then estimate the trunk orientation in real-time. In the future, the exoskeleton will communicate with the smartphone to handle these data in a biomechanical model.

Firstly, we briefly describe the integrated mHealth system; secondly, we report preliminary results of the validation of real-time orientation estimation of the user's trunk and the crutches using stereophotogrammetry as the gold standard.

Materials and Methods

Smart Crutches

Figure 1 shows the individual components of the smart crutches and their interconnections. In **Table 1**, we report the details of the individual components. All electronics and batteries are contained in the white PLA case. The case containing the electronics and battery and the foot for housing the load cell were designed on CAD and printed with a 3D printer. The case is made of Polylactate (PLA), while the support of the case on the rod of the crutch and the foot are made of Thermoplastic Polyurethane (TPU), **Figure 2**.

The Arduino board (see **Table 1** and **Figure 1**) is equipped with an open-source microcontroller and a chip for Bluetooth BLE 5.0 communication. The reprogramming of the board is possible through the micro-USB connector accessible on the bottom of the case, while the reset button and the power lever are accessible on the top of the case (**Figure 2**). The board integrates an IMU LSM9DS1 of the ST Microelectronics iNEMO family of inertial modules and comprises a triaxial accelerometer, gyroscope, and magnetometer. The accelerometer has a programmable range of ± 2, ± 4, ± 8, ± 16g, the gyroscope has a programmable range of ± 245, ± 500, ± 2000 degrees per second, and the magnetometer has a programmable range of ± 4, ± 8, ± 12, ± 16 Gauss. In the current configuration, the accelerometer range is set at ± 2g, while the gyroscope range is set at ± 245 degrees per second. Sample frequency was fixed in the Arduino system at 30 Hz.

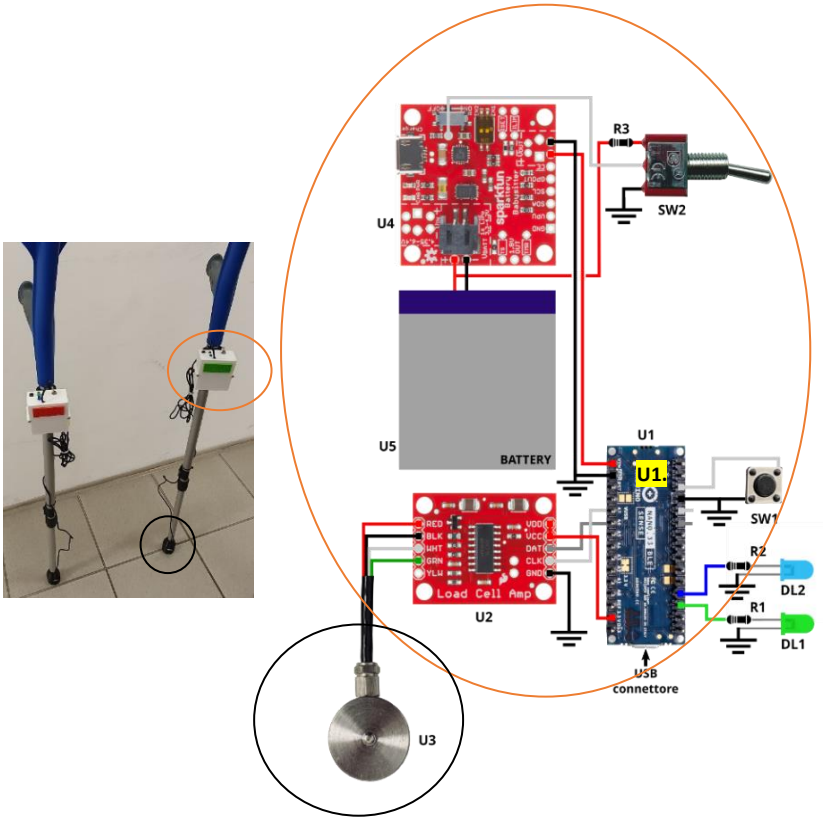

Figure 1. System components and their interconnection. The identification code (ID) of the individual components refers to the list shown in Table 1.

Component	Description	Link	ID
Arduino Nano 33 BLE Sense	Mainboard for the acquisition, processing, and data transmission via BLE 5.0 of IMU signals and load on the crutch.	Official page: https://store.arduino.cc/arduino-nano-33-ble-sense Datasheet: https://www.mouser.it/datasheet/2/34/Arduino_06052019_ABX00031-1601141.pdf Microcontroller datasheet: https://content.arduino.cc/assets/Nano_BLE_MCU-nRF52840_PS_v1.1.pdf	**U1**
IMU LSM9DS1	Inertial module composed of 3-axis accelerometer, 3-axis gyroscope, 3-axis magnetometer. In the current configuration, the ACC range is set at ± 2g, while the GYRO range is set at ± 245 degrees per second. Sample Frequency **30 Hz**	Datasheet: https://www.st.com/resource/en/datasheet/lsm9ds1.pdf	**U1.1**
SparkFun Load Cell Amplifier - HX711	Amplifier board for interfacing microcontroller with Wheatstone bridge load cell.	Datasheet: https://cdn.sparkfun.com/assets/b/f/5/a/e/hx711F_EN.pdf	**U2**
Load Cell	Wheatstone bridge load cell, with a maximum capacity of 50 Kg. Sample Frequency **30 Hz**	Official page: http://www.htc-sensor.com/products/151.html	**U3**
SparkFun Battery - LiPo Battery Manager	Board for managing a LiPo battery.	Official page: https://www.sparkfun.com/products/13777	**U4**
Lithium-ion Polymer Battery	3.7 V, 1400mAh Li-ion battery.	Datasheet: https://www.olimex.com/Products/Power/BATTERY-LIPO1400mAh/resources/JA803450-Spec-Data-Sheet--J-A.pdf	**U5**
Contact switch	To reset the Arduino board without directly accessing the board.	Datasheet: https://www.te.com/commerce/DocumentDelivery/DDEController?Action=srchrtrv&DocNm=1825910&DocType=Customer+Drawing&DocLang=English&PartCntxt=1-1825910-4&DocFormat=pdf	**SW1**
Toggle switch	Switch off/on of the device.	Datasheet: https://www.te.com/commerce/DocumentDelivery/DDEController?Action=srchrtrv&DocNm=1825138&DocType=Customer+Drawing&DocLang=English&PartCntxt=3-1825138-7&DocFormat=pdf	**SW2**
Green LED	Device power-on signal.		**DL1**
Blue LED	BLE connection signal.		**DL2**

Table 1. Electronic Components and datasheet of the smart crutches.

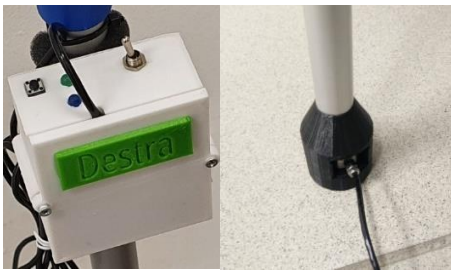

Figure 2 - LEFT: Case made of PLA fixed to the rod of the crutch that contains the electronics and battery of the system. On the upper part of the case, you can see, from left to right: the reset button of the control unit, the status LEDs for switching on (green) and BLE communication (blue), and the system switch on. RIGHT: Foot of the crutch made of TPU for housing the load cell.

mHealth system – Smartphone App

We designed an Android application as the user interface of the prototype, with the aim to automatically start the data acquisition process from the SP and both sensorized crutches. The Android App handles the BLE connection between the two Arduino systems and the SP to have real-time information about the pitch and roll angles in the three systems, **Figure 3**. The vertical force applied to the ground of the two load cells is also reported in the App's user interface. When the acquisition starts, the two Arduino systems automatically stream all the data to the App. We fixed their sample rate at 30 Hz to avoid delays and system overload (which may occur with higher sample rates). In the App user interface, a *RESET* button is available to allow the user to set an initial reference value, **Figure 4**.

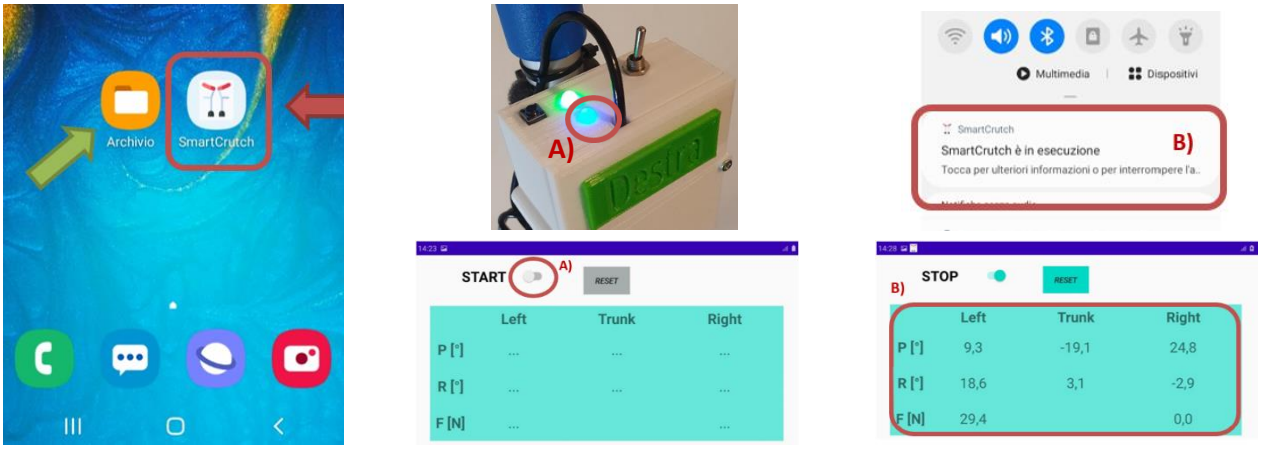

Figure 3. To open the App, the user must click on the "SmartCrutch" icon on the smartphone home. The green arrow indicates the data storage folder of the smartphone. **A)** The App has a simple user interface that allows to save and check all data in real-time by activating the START switch. When the crutches are turned on, and the START switch is activated, the connection and data acquisition is activated automatically after a few seconds. When the Bluetooth connection is active between the smartphone and the stand, the blue status LED is on. **B)** The trunk's pitch and roll angles and the two crutches are displayed in real-time on the interface together with the value read by the load cell for the force applied to the ground in the two crutches. The angles are displayed in degrees and the force in Newton (N). When the process starts a notification is created indicating active data streaming.

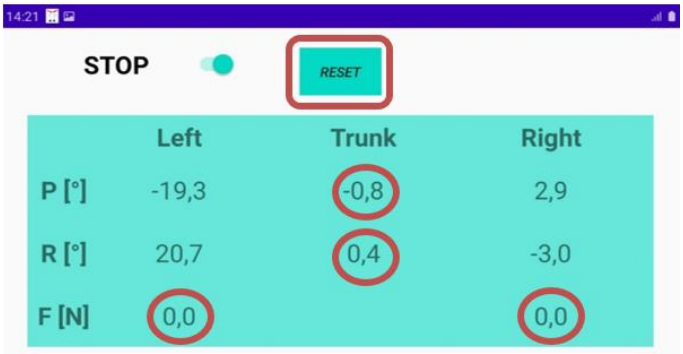

Figure 4. The *RESET* button sets the current value of the forces as zero and the smartphone's pitch and roll angles; is a function implemented to allow the user to set a starting reference value. To end the acquisition, simply activate the STOP switch.

The App saves all data in the smartphone memory in folders organized by date and device. A folder is created with the date for each day on which at least one acquisition is performed. These LOG files are saved in "txt" format to allow off-line elaboration into third-party software, such as Excel or Matlab, **Figure 5**.

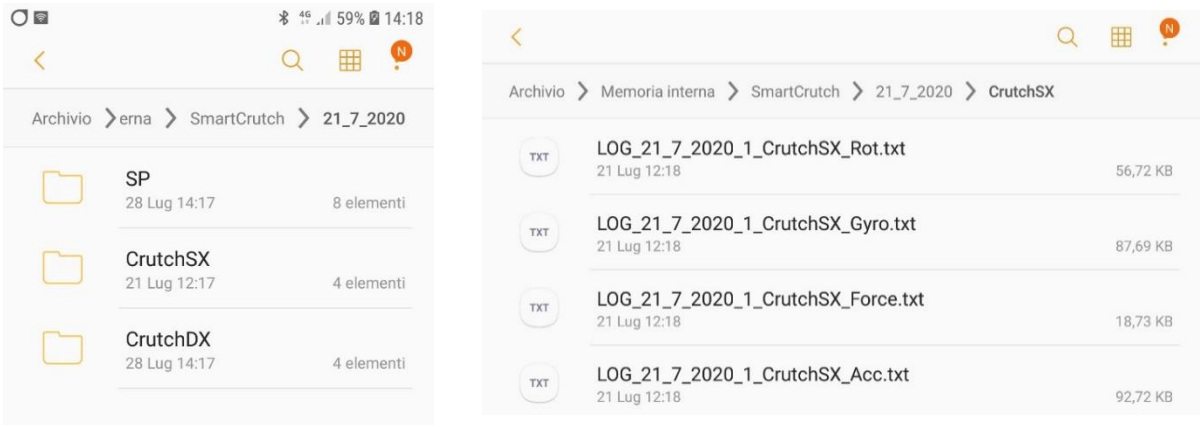

Figure 5. A representation of the App data storage in the smartphone memory. A folder is created with the date for each day on which at least one acquisition is performed. Within this, there are three folders, one for each device: Smartphone (SP), Right crutch (CrutchDX), Left crutch (CrutchSX). All LOG files are saved in "txt" format to allow off-line elaboration into third-party software, such as Excel or Matlab.

In **Table 2**, we report the main details of the SP. It integrates the IMU LSM6DSL of the ST Microelectronics iNEMO family of the inertial module, composed of a triaxial accelerometer and gyroscope. The accelerometer range is set at ± 4g, while the gyroscope range is fixed at ± 1000 degrees per second. The sampling frequency is dynamic as in all Android systems: in this case, it is set around 100 Hz.

Component	Description	Link
Model	Smartphone Samsung A20e	Official Page: https://www.samsung.com/it/smartphones/galaxy-a/galaxy-a20e-blue-32gb-sm-a202fzbditv/
SO	Android 10	
Size and Weight	148mm x 8.3mm x 69.6mm 0.141 kg	
IMU LSM6DSL	Inertial module composed of 3-axis acceleration, 3-axis angular velocity. ACC range is set at ± 4g while the GYRO range at ± 1000 degrees per second. Dynamic Sample Frequency about **100 Hz**	Datasheet: https://www.st.com/resource/en/datasheet/lsm6dsl.pdf

Table 2. Main features of the smartphone.

The orientation estimation involved the gyroscope integration in extracting the angle information and the accelerometer correction when the inertial sensor is 'quite still' (to compensate the temporal linear drift, auto-resetting). Besides, before the angle estimation, signals were low-pass filtered with a real-time filter with a cut-off frequency of 3 Hz. In **Figure 6**, the reference system and axes direction in the two crutches and the smartphone.

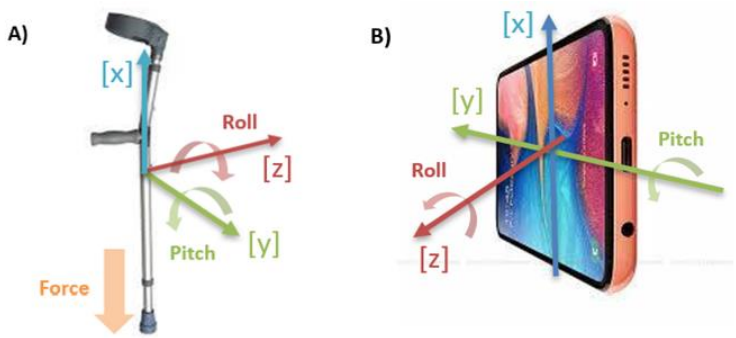

Figure 6. Reference system and Axes direction: A) in the two crutches and B) in the smartphone. Pitch and roll angles are calculated about the vertical direction. When the tip of the crutch or the smartphone in landscape mode is perfectly vertical, the angles are equal to zero, then tilting them forward and to the right, respectively, pitch and roll gets positive (vice-versa negative angles are obtained in the case of motion in the opposite directions).

Stereophotogrammetry Validation

The real-time orientation estimation was tested against stereophotogrammetry, chosen as the gold standard in a demo acquisition with a Twin pilot. The Twin pilot wore a security harness over the torso, underneath the Twin exoskeleton. The smartphone was inserted in a neoprene band and positioned in the center of the upper torso. The pilot walked on a stationary treadmill, and five tests were performed, with short walks of 5/6 steps. The average step length, step time, and step clearance were 60 cm, 1.7 s, and 12 cm. The stereo markers were placed over the pilot and the crutches to compute the angle estimation, as shown in **Figure 7**. To extract the trunk orientation from the stereo, we placed two markers on the shoulders and one on the sternum. Besides, two markers were applied on the hips and one at the L5 vertebrae level. These markers would also help to register the torso movements. To detect crutches' orientation, we placed three markers on the crutch rod along its axial direction.

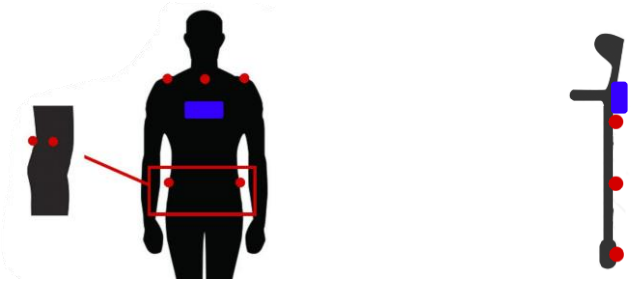

Figure 7. Set-up of the stereo validation. LEFT Smartphone was worn on the chest (blue) and markers (red). RIGHT PLA box attached on the crutch (blue) and markers (red).

Results

In **Figure 8**, we report the trunk estimation result thanks to the SP worn on the chest. The RMSE of both pitch and roll angles were lower than 2°.

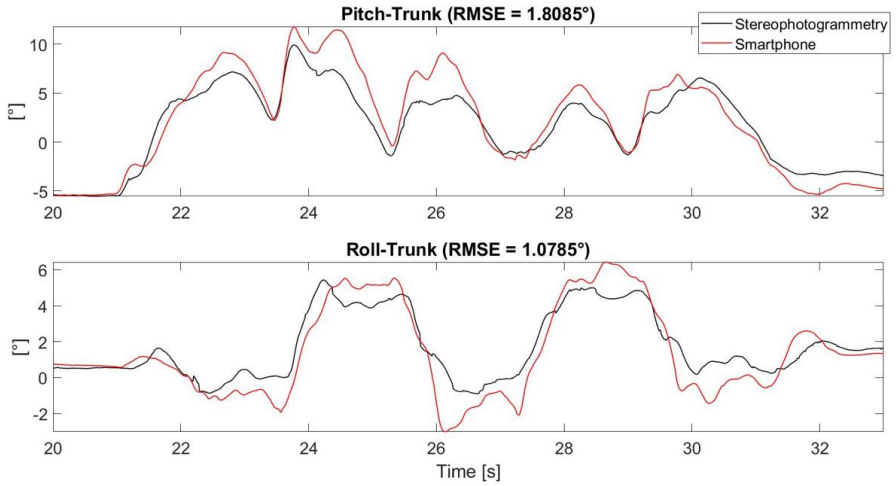

Figure 8. Trunk orientation comparison between smartphone (red line) and stereophotogrammetry (black line). TOP Pitch angle (anteroposterior direction). BOTTOM Roll angle (mediolateral direction).

In **Figure 9**, we reported the right crutch estimation results, with a pitch-RMSE lower than 2° and a roll-RMSE slightly higher than 2°, even though the roll range of motion is limited compared to the pitch.

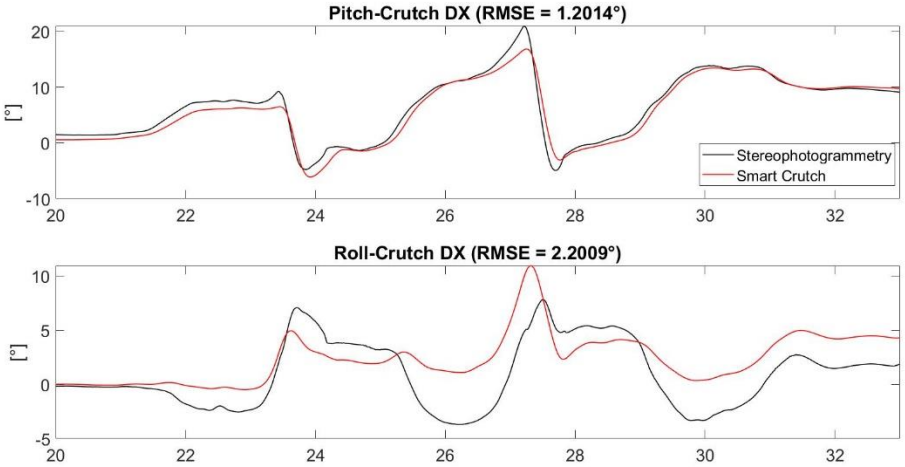

Figure 9. Right-Crutch orientation comparison between smart crutch (red line) and stereophotogrammetry (black line). TOP Pitch angle (anteroposterior direction). BOTTOM Roll angle (mediolateral direction).

Importantly, we noticed that the PLA white box attached to the crutch rod was not fixed firmly, thus during the ground contact of the crutches impact artifacts may corrupt the angle estimation. For this reason, we

modified the location of the IMUs, moving them inside the handle core, **Figure 10**. In the next months, we will validate this new configuration to improve the crutches' angle estimation.

Figure 10. Upgraded version to be tested by moving IMU inside the handle core in a backlash-free rigid fixation.

Discussion

In this proof of concept, the mHealth system developed allows integrating innovative smart crutches with a smartphone. In the future, the goal is to implement a biomechanical model able to improve the effectiveness and safety of the Twin exoskeleton [11]. Thus, knowing the orientation of the trunk and the two crutches, a biomechanical analysis will be possible to optimally handle the Twin exoskeleton functions. Thanks to the load cells, this can be achieved by integrating the information of the force applied by the user on the ground.

An issue we still have to handle is the matching between the load cell and the tip of the crutch. The choice of the foot for housing the load cell is crucial: it strongly influences the sensor's dynamic response and, thus, its use. Besides, the connection between the system developed and the Twin exoskeleton will be established. The preliminary validation reported encouraging results; RMSE was around 2°, even if the torso and crutches' range of motion is limited (± 10°). For our aims, only roll and pitch angles were estimated. Our orientation estimation involved the gyroscope integration and the accelerometer correction when the inertial sensor is 'quite still'. However, more sophisticated methods are required to reduce drift and avoid singularity, including magnetometer information [12]–[14]. We will test an upgraded version of the crutches where the IMU has been moved inside the handle core in a backlash-free rigid fixation.

Interestingly, the technology of this system can easily be adapted to other assistive or rehabilitative scenarios. It is possible to make every object smart by moving the Arduino system inside it. For example, in this proof of concept, a commercial crutch has been made smart.

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Section IV - Conclusion

Chapter 12

"Conclusions and future work"

Considering the pandemic emergency, never as of today, we can say that the integration of mHealth systems in our society may contribute to a new era of clinical practice. This Ph.D. thesis explored a number of different opportunities where new and innovative mHealth solutions could improve Assessment and Rehabilitation strategies for a variety of neuromotor functions and diseases. We described solutions that need a therapist's supervision in a clinical context and others that can be self-administered and require only a smartphone as a stand-alone system.

For the clinical assessment, these new tools overcome the limitations of subjective clinical scales and questionnaires. Creating new mHealth solutions in this work, we investigated the possibility of employing innovative systems for objective clinical evaluation (*Section II*).

- *Chapter 5* presented the Touchscreen Assessment Tool (TATOO), an Android application (app) developed to assess hand skills essential for the interaction with a touchscreen. This pilot study examines the feasibility of using the TATOO app to evaluate touchscreen ability in elderly individuals compared to traditional hand-grip strength tools. Even if no correlation was found between the TATOO variables and prehension strength (grip and pinch strength) or dexterity skills, discriminative validity was demonstrated between the elderly and middle-aged group, showing less accurate and significantly longer movements in the former.
- In *Chapter 6*, we developed three smartphone apps for self-administering an instrumented version of the 'Timed Up and Go' test (Self-TUG), the 'Standing tandem' test (Self-Tandem), and the 'Five times sit-to-stand' test (Self-STS). We were designing all apps with an emphasis on ease of use for the target group. The apps are based on the same structure and, using inertial sensors of the smartphone, they can provide real-time audio- and haptic-feedback to guide the user during the test. The usability test of the apps was performed with target groups of older subjects. The results suggested that the apps can be used to self-test seniors' physical function in an unsupervised home-based setting. The participants reported a high degree of ease of use, even if before being made available to end-users, the apps require further improvements.
- *Chapter 7* proposed an obstructed walking paradigm to quantify the subjects' behavior while walking, avoiding vertical obstacles. With this walking paradigm, our aims are: explore differences in movement between subjects with Homonymous hemianopia (HH) and healthy controls; quantify the effect of the Audio-Visual Scanning Training (AViST) used to train subjects with HH to a better eyes-exploratory ability through a pre-post analysis. Differences in total time and stride length between groups showed that this walking paradigm is more challenging for the HH subjects. The pre-post analysis results indicated that only a few parameters change significantly after AViST. However, this study's sample size was relatively small, and all the analyses should be performed on a larger cohort of patients.

As far as rehabilitation is concerned, we explored the clinical feasibility and effectiveness of mHealth systems. In particular, we developed innovative mHealth solutions with BF capability to allow tailored rehabilitation, focusing on the possible variables to feedback and their different restitution modality (*Section III*).

- In *Chapter 8*, using an innovative gait rehabilitation system in persons with Parkinson's Disease (PD), we characterized participants' motor adaptation to BF signaling as a deviation from normal cadence during prolonged indoor walking. When their cadence varied, they heard either intelligent cueing (bouts of ten beats indicating normal cadence) or intelligent feedback (verbal instruction to increase or decrease cadence). A negative correlation was found between the speed of adaptation and the number of deviations during IntCue, but not during IntFB, suggesting that, for people who struggle with gait, such as those with PD, verbal instructions rather than metronome beats might be more effective at restoring normal cadence.
- In *Chapter 9*, we compared the effectiveness of different BF variables to enhance the real-life gait performance of persons with PD. We compared the effectiveness of the feedback variables that were used most frequently during a home-based rehabilitation protocol of 6-weeks: Stride Length (SL), Gait Speed (GS), and Cadence (CAD). An exploratory analysis was performed to visualize long-term effects by showing how SL and GS changed along with the protocol. We reached a high level of coherence between the verbal-BF and the relative motor response using SL and GS as BF-variables. We achieved the best coherence using GS as the BF-variable. An exploratory analysis revealed moderate long-term effects, but this result should be confirmed on a larger number of participants.
- *Chapter 10* presented an innovative system to deliver multimodal BF during gait rehabilitation in PD subjects. The innovative nature of the mHealth solution developed here is its multisensory approach, where visual and proprioceptive rhythmic stimuli complement the auditory feedback. To achieve such multisensory feedback, we integrated the CuPiD system (shown in *Chapter 9*) with commercial smart glasses. We performed a specific Human-Centered testing phase on five subjects. We analyzed the subjects' qualitative and quantitative responses from an interview and a specific gait analysis protocol, respectively. We applied an ad-hoc redesigned version of the Quality-Function-Deployment (QFD) design tool to manage the complexity of the collected data. Our QFD's results confirm the role of sensory BF on gait rehabilitation: auditory and haptic BF reach a higher efficacy than the visual one.
- In *Chapter 11*, in collaboration with the Rehab Technologies - INAIL-IIT Lab, we contributed a proof of concept concerning the use of innovative smart crutches with an active, powered, and wearable lower-limb exoskeleton for paraplegic patients' gait. Thanks to an Android app, the two smart crutches communicate with a smartphone that can estimate the trunk and crutches orientation in real-time. The preliminary results of the validation reported acceptable RMSE values in the real-time

orientation estimation. Interestingly, the technology of this system can easily be adapted to other assistive or rehabilitative scenarios. It is possible to make every object smart by moving the Arduino system inside it. For example, in this proof of concept, a commercial crutch has been made smart.

One of the main goals that a mHealth system should have is improving the person's quality of life, increasing and maintaining his autonomy and independence. To this end, in the future, inclusive design principles might be useful for designers to collect and elaborate on patients' requirements, next to the technical and technological ones, to improve the project's usability. This is true especially to promote self-administrable solutions for the clinical assessment and the development of personalized mHealth systems in the rehabilitation field.

As we witness a digital transformation of the healthcare system, mHealth technologies are expected to become better integrated into the clinical workflow, especially to provide telemedicine. Thus, thanks to the Internet connection, mHealth systems can increase healthcare access and improve cost-effectiveness. During the COVID-19 pandemic, this transformation of the healthcare system has been dramatically accelerated by new clinical demands, including the need to assure continuity of clinical care services. For example, healthcare professionals could use mHealth systems to monitor patients' conditions remotely and continuously mitigate or prevent hospital surges.

A limitation of most proposed solutions is the lack of telemedicine service: there is no immediate communication between patients and healthcare professionals. For example, when subjects with PD undertake their gait rehabilitation session (Chapter 8, 9, and 10), it would be helpful to inform caregivers in real-time when the walking session starts and finishes. As future work, we may allow telemedicine in each mHealth system here reported, increasing its potential.

In man's continuous aspiration to improve his well-being, we have to face the exponential growth of technology. Thus, we have to deal with unknown challenges, unexpected situations and generate new uncertain solutions. In general, we are used to taking a predictable path, the so-called comfort zone. That is why we are used to choosing the options we already know. The challenge of future research, including the development of mHealth systems, requires a mental shift from linear and predictable to bold and spontaneous, handling the incoming technologies to the best of our abilities.

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