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Master's Degree in **Biomedical Engineering**

Exploring Data Analysis To Assess The Effects Of Telerehabilitation For People With Parkinson's Disease

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Abstract

Parkinson's disease (PD) is a common neurodegenerative and progressive disorder affecting millions of people world wild, that was firstly described in 1817 by Dr. James Parkinson. Even though more than 200 years have passed from the PD discovery, an effective cure, able to slow down, stop or modify the disease course, has not been found yet, meaning that all the pharmacological medications available nowadays are destined to alleviate the main PD motor and nonmotor symptoms. Currently, physical activity and exercise are achieving greater relevance as promising and effective alternative treatments to complement the prescribed drug therapy, thanks to many demonstrated benefits that they could induce in those affected. However, due to the many restrictions imposed by the recent COVID-19 emergency, PD patients could not get any more access to fundamental visits and cares, including physical rehabilitation. To respond to the changed healthcare needs imposed by the pandemic, RAPIDO ("teleReabilitatione per I mAlati di Parkinson In qualsiasi staDIO") has proposed and developed a telerehabilitation and telemonitoring systems destinated to people suffering from PD, relying on easy-to-access and economically-sustainable devices. In particular, a common Samsung A7 tablet delivers the rehabilitation services, while a Garmin smartwatch continuously collect daily and nocturnal patient-related data. Basing on the gathered information about the enrolled subjects, this experimental dissertation aims to define a data analysis method to assess whether the telerehabilitation protocol, proposed by RAPIDO, has induced some changes in the state of health of enrolled PD patients, supporting the scale-bases clinical evaluations effectuated by medical doctors. Specifically, the presented analysis approach involves, firstly, a statistical analysis to identify the variables that significantly change throughout the telerehabilitation period and, secondly, an unsupervised clustering technique that could provide further insights about the progression of the disease during the RAPIDO program. The obtained results suggest that the proposed method has not been able to depicts any variation of the processed data during the telerehabilitation period for any of the considered patients. Nonetheless, these outcomes seem to be in line with subjects' actual medical conditions; indeed, the evaluated clinical parameters indicate that the patient's states of health have remained stable throughout the entire at-home rehabilitation program, despite the strong degenerative nature of the disease itself. In conclusion, the training services proposed by RAPIDO, in combination with an effective pharmacological treatment, seems to contribute the slowdown of the PD course even in patients characterized by different initial disease stages.

Chapter 1

Introduction

Parkinson's disease (PD) is a common neurodegenerative and progressive disorder affecting millions of people world wild [1]. As the second most spread neurodegenerative syndrome after Alzheimer [2], PD affects 1%-2% of population over 65 years. However, this percentage increases up to 4% in those individuals with more than 80 years, showing how age represents one of the main risk factors for the disease.

PD was firstly introduced by Dr. James Parkinson in 1817 in his "Essay on the Shaking Palsy" [3], in which he methodically described six cases of patients that suffered from a particular syndrome that he termed "Shaking Palsy". The contribution of Dr. Parkinson was the fundamental starting point that has encouraged the research conducted in the following years, thanks to which a more exhaustive knowledge about PD is nowadays available.

In recent years, many studies have sought the possible causes of PD origins; nonetheless, its neuropathological picture has not been fully understood yet, since it involves many complex and synergic molecular mechanisms, some of them are still unclear. Certainty, it has been proved, through postmortem autopsies, that PD is marked by an elective loss of dopaminergic neurons in the substantia nigra pars compacta [4], a key anatomical component of the substantia nigra, located in the midbrain [5,6]. This hallmark is typically accompanied by an accumulation of the so-called Lewy bodies [7] and neurites, generally referred to as Lewy pathology, which can also affect many nondopaminergic nuclei.

These neurological changes induced by PD are responsible for the peculiar manifestations of this syndrome that can be identified in the affected population. Motor symptoms are the most recognizable ones, the reason why they are typically used as clinical markers for PD assessment. They include bradykinesia, muscular rigidity and resting tremor [2, 8], as well as postural and gait impairments and difficulties in speaking and swallowing [2]. However, there is an increasing awareness about recurrent nonmotor manifestations of PD, encouraged by many studies that have recognized them as the main determinants of poorer quality of life in people with PD [9]. Furthermore, it has been shown that they may present even years before the appearance of the PD motor features [10], thus, currently, research and clinical practice are shifting their interest closer to nonmotor manifestations [9] since they may represent important biomarkers for pre-symptomatic identification of PD [10].

As mentioned before, the clinical assessment of PD is based on the evaluation of the main motor manifestations, which is typically performed by means of standardized scales and questionnaires. The first ones are filled in by the clinician during a medical interview, in order to estimate the disease

severity and progression; the questionnaires are instead completed by patients themselves, providing important insights about quality of life and their perceptions of the disease that can't be easily deduced during the clinical examinations. However, although these scales and questionnaires have gathered a broad agreement, they present undeniable limitations. Firstly, it has been shown that assessment scales tend to reflect a more advanced level of severity of PD that is not in fact experienced by the patients, suggesting that they could not be fully appropriate for studying progression in PD from its early stages [11]. Besides, the rating of the items in the scales strictly depends on the clinician expertise and, most importantly, they only provide a snapshot of patients' condition, reflecting only short-term effects that are irrelevant to the overall progression of the disease [12, 13].

In order to overcome the main limitations associated to PD scales, novel strategies using sophisticated devices are reaching a greater approval from the scientific community [14]. Specifically, wearable sensors have demonstrated to be promising in the characterization of motor functions in patients with PD [12, 14], and it is believed that they could become a cost-effective alternatives to the current diagnosis tools and techniques, as well as an efficient way to detect early PD patients [12].

Even though more than 200 years have passed from the PD discovery, currently an effective cure, able to slow down, stop or modify the disease course, has not been found yet, meaning that all the treatments available nowadays are only able to provide symptomatic relief [2, 8]. These includes both pharmacological and nonpharmacological therapies. The mainstay of current PD treatments is Levodopa-based preparations, aiming to replace the dopamine in the depleted tissues [15].

However, although the benefits induced by Levodopa are noticed quickly, it comes with significant side effects that constitute an important part of the illness experienced by the patients, especially in more advanced stages [15]. For this reason, alternative options that could overcome or at least reduce these issues are emerging. Among these, physical activity and exercise are demonstrating to be promising. Indeed, the latter, besides being one of the main protective factors against PD, are emerging as crucial components of the treatment regimen, thanks to many demonstrated benefits that they could induce in those affected [16]. First of all, it has been shown that exercise has PD-specific symptomatic effects; indeed, it attenuates motor symptoms [17] and possibly improves health-related quality of life [24]. Furthermore, a body of publications has pointed out that dopaminergic neurons are highly responsive to exercise and inactivity [18-21]. This suggests that introducing planned physical activity at earlier stages of PD could slow down its progression; thus, exercise should be considered as a universally available, side effect-free medicine that should be prescribed to vulnerable populations as a preventive measure, but also to PD patients as an important component of treatments [22].

It is following this guideline that RAPIDO ("teleReabilitatione per I mAlati di Parkinson In qualsiasi staDIO") project was initiated in 2021 from the collaboration among Università Politecnica delle

Marche, Università di Verona and Revolt s.r.l. company. In fact, this project also responds to the many fragilities faced by territorial healthcare systems dedicated to PD, revealed by COVID-19 emergency. Indeed, due to the many restrictions imposed by the pandemic, PD patients could not get any more access to fundamental visits and cares, including physical rehabilitation. Therefore, the territorial healthcare facilities have realized that was necessary to find out new operative modalities to ensure PD subjects a sufficient and adequate assistance. In this context, RAPIDO represents an innovative tool to cope with these changed needs. This project aims to develop a telerehabilitation and telemonitoring system destined to people suffering from PD, guaranteeing an effective integration, thus, differentiating from many other analogous systems that usually supply telemonitoring services independently from the training ones, and vice versa. In this way, it is possible to provide, via a single platform, telemonitoring and telerehabilitation tools that can be easily accessed by both patients and direct assistance operators, involved in the treatment of PD and in at-home rehabilitation. The integrated telerehabilitation and telemonitoring system proposed by RAPIDO is composed by suitable wearable and noninvasive sensors (i.e., sensors embedded in a commercial smartwatch) that collect patient-related data which are then partially and locally processed by a specific app (accessible both from mobile devices and personal computers), thereby making the elaborated outcomes available to clinicians. So that, the latter can possibly implement some changes in the rehabilitative schedule in order to adapt it to the specific needs of each patient. Thanks to these wearables, it is also possible to monitor the main subjects' vital parameters during the rehabilitative treatment, providing important feedbacks on the training intensity and reducing the risk of adverse effects. Furthermore, it is believed that this system may provide a significant contribution in the improvement of the patients' quality of life, promoting economic sustainability of long-term management of PD and reducing the consumption of health resources, as well as caregivers stress and responsibility.

Once the main technical aspects of the RAPIDO system have been described, this experimental dissertation aims to propose a method to analyze data collected from wearable sensors (i.e., the smartwatch) in order to assess whether the proposed telerehabilitation protocol has induced some changes in the state of health of enrolled PD patients, possibly supporting the scale-bases clinical evaluations effectuated by medical doctors. Specifically, the presented analysis approach involves, firstly, a statistical analysis to identify the variables that significantly change throughout the telerehabilitation period and, secondly, an unsupervised clustering technique that could provide further insights about the progression of the disease during the RAPIDO program.

Chapter 2

Parkinson's disease

Parkinson's disease (PD) is a common neurodegenerative and progressive disorder that affects millions of people world wild [1], the second after Alzheimer disease [2]. PD does not only damage the human central nervous system, but also the peripheral and enteric ones [7], causing its cardinal symptoms that have both motor (e.g., resting tremor and bradykinesia) and nonmotor (e.g., depression, cognitive decline and sleep disturbances) manifestations [23,3].

2.1 Historic background

The first insight about PD dates back to 1817, when James Parkinson published his "Essay on the Shaking Palsy" [3]. In this essay, Parkinson methodically describes six cases of patients that suffered from a particular syndrome characterized by a degenerative nature, that he termed *"shaking palsy"*, which was defined as:

> *"Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace: the senses and intellects being uninjured."*

Indeed, Parkinson noticed that the first symptoms that could reveal the presence of the disease are a slight sense of weakness accompanied by a tendency to trembling in some specific parts, most commonly in one of the hands or arms [3].

Parkinson also recognized the importance of non-motor symptoms [24]. He observed that, due to the degenerative nature of the syndrome, the tremors tend to exacerbate, leading to negative changes in many aspect of the patients' daily life. Indeed, he reported that the sleep becomes much more disturbed, and normal actions, such eating and speaking, become arduous.

All these observations systematically and objectively presented by Parkinson feed his central point presented in the essay, which is the need to distinguish the *"shaking palsy"* from other disease with which it can be confused [3]. Indeed, he pointed out how frequently the term *"shaking palsy"* had been improperly applied in other cases by physicians of the time, who usually considered the key signs of PD as separate diseases [24].

Although more than 200 years are passed from his publication, the contribution of James Parkinson is still considerable. Indeed, the many features described in the essay continue to underpin the diagnostic

process [24]. He laid the foundations of a disease that nowadays affects and dramatically change the life of millions people. His evidence and hopes have pushed all the research conducted in the following years, thanks to which a more exhaustive knowledge about PD is nowadays available, crucial for the development of efficient treatments and for an improvement in the quality of life of those affected.

2.2 Neuropathology

From a neuropathological point of view, PD is marked by an elective loss of dopaminergic neurons in the substantia nigra pars compacta (SNc) [4], a key anatomical component of the substantia nigra (SN), located in the midbrain [5,6]. Indeed, although the latter appears as continuous band, it can be anatomically divided in two different parts, each one shows peculiar connections and functions [25]. One of these two is the previously mentioned SNc that mainly serves as projection to the basal ganglia circuit, providing dopamine to the striatum [25]. The other part of the substantia nigra is generally referred to as pars reticulata (SNr), which instead is deputed to the transmission of signals from the basal ganglia to numerous other brain structures [25].

The SNc is constituted by densely packed dopaminergic neurons that are clearly recognizable in humans because of their high content in neuromelanin, a byproduct of dopamine autooxidation [5], which typically undergoes to a depigmentation process caused by Parkinson's disease [6].

As mentioned before, an important hallmark for PD is a represented by a loss of neuromelanin-laden dopaminergic projection cells in the SNc, which is responsible for the well-known motor symptoms of PD. However, it has become evident that these neuronal symptoms are not sufficient to fully describe the origin of PD. Indeed, the deterioration of SNc is typically accompanied by an accumulation of the so-called Lewy bodies [7] and Lewy neurites because of deposition of phosphorylated α-synuclein (αSyn), the major protein marker of PD [26]. This phenomenon is generally referred to as Lewy pathology, which can also affect many nondopaminergic nuclei, including the locus coeruleus, reticular formation of the brain stem, raphe nucleus, dorsal motor nucleus of the vagus, basal nucleus of the Meynert, amygdala, and hippocampus, resulting in some of the nonmotor symptoms of PD [7].

However, the neuropathological picture of PD is much more complicated, since it involves many other molecular mechanisms, some of them still remain unclear. Among them, oxidative stress plays a pivotal role in the understanding of the loss of dopaminergic neurons in PD [2]. Although the source of the oxidative stress is still questioned and argued, there is an increasing belief that the major contribution is given by an increased radical formation originating from mitochondria [2, 27, 28].

Specifically, due to the presence of genes responsible for PD, there is a decrease in the mitochondrial protection against oxidative stress, which in turn increases mitochondrial dysfunction [2] (Figure 1).

Therefore, the neuropathology of PD involves extremely complex and multifactorial participants, whose roles and origins have not found a complete explanation yet. Indeed, the mechanisms currently used to explain pathogenesis in PD may just be the downstream consequence of a so far unknown trigger [2].

2.3 Epidemiology

The distribution of the PD in the population strictly depends on different factors.

Age is a significant determinant, indeed the percentage of people affected by PD tends to increase with age, from 1% to 2% in those over 65 years of age to 4% of the population over 80 [2, 29], with a mean age of onset approximately around 60 years [2]; instead, PD is considered rare before age of 50 years [30].

Due to the rising of life expectancy, the number of people with PD is assumed to grow more than 50% by 2030 [29]. Other reports have hypothesized that this increased occurrence of PD in the population may be related to other determinants than age, such as the dramatic changes in smoking behavior observed in the last part of the twentieth century and the intensification of traffic-related air pollution [30-32].

Another important factor to be considered in the epidemiology of the PD is gender, indeed different studies have demonstrated that men tend to be more affected by PD than woman, with a male-to-female ratio of 3:2 [2, 29, 30].

Eventually, Caucasians are more commonly affected than African, Americans or Asians [29].

2.3.1 Risk factors

Evidence has confirmed that the age is the most important risk factor for the disease [2, 29, 30].

Gender is a risk determinant to be take into account, as well; specifically, the male gender confers a moderate risk [29]. However, there are also environment factors that augment the probability to contract the syndrome [2]. These ones include pesticides and rural living, together with other substances such as 1-methyl-4-phenyl tetrahydropyridine (MPTP) and annonacin which can induce nigrostriatal cell death and a form of atypical parkinsonism, characterized by clinic and pathological features different from classic PD. This list of dangerous substances can be extended by toxic levels of manganese, trichloroethylene and carbon monoxide [2, 29].

Family history is a risk factor as well, indeed familial form of PD account for 5% to 15% of cases [29].

Eventually, one last risk factor worthy of note is head trauma [2].

2.3.2 Protective factors

Contrary to what could be expected, cigarette smoking has a significant protective effect against the development of PD, which has been well documented and reproduced by many observational studies [2, 29, 31]. Similarly, caffeine intake appears to be protective against the development of PD [2, 29].

Other protective factors are not so well documented, however there is an increased evidence about the inverse association between the risk of PD and calcium channel blockers, nonsteroidal anti-inflammatory drugs and antilipidemic, whilst contrasting [2, 29].

Lastly, the link between physical activity and reduced risk of PD is noteworthy. Indeed, epidemiological data does not only support the fact that exercise may slow down the progression of the syndrome, reducing the entity of its motor symptoms, but, more importantly, that may exist an inverse relationship between the risk of developing PD and the amount of physical activity [33, 34, 22]. More precisely, it seems that exercise could limit the alteration in dopaminergic neurons in the substantia nigra and could contribute to optimal functioning of the basal ganglia involved in motor commands and control by adaptive mechanisms involving dopamine and glutamate neurotransmission [34]. These findings have significant implications in the treatment and prevention of PD, especially in vulnerable population [22].

2.4 Parkinson's disease manifestations

As a consequence of the complex molecular mechanisms that are triggered by PD in human brain, characteristic manifestations of this syndrome can be recognized in the affected population (Table 1). The most persisting and most disabling ones dramatically alter the motor functions. That is why the motor limitations caused by PD are typically used to make a clinical diagnosis of the syndrome [2]. However, recurring nonmotor symptoms can also be identified in people suffering from PD. The latter are receiving much more importance in the last years, since they have been recognized as the key determinants of poorer quality of life in people with PD [9].

2.4.1 Motor symptoms

James Parkinson methodically described the major motor manifestations caused by PD already in 1817, when he published his “Essay on the shaking palsy” [7]. These motor symptoms have become nowadays the key clinical features for the PD diagnosis. They include primary bradykinesia (i.e., slowness of movement and speed), muscular rigidity and resting tremor [2, 8], which can be accompanied by postural and gait impairments that typically manifest as festination (i.e., rapid shuffling steps with a forward-flexed posture when walking). Motor manifestations can also affect many aspects of the daily life, such as speaking and swallowing [2].

Bradykinesia can be easily recognized since it causes a slowed initiation of voluntary movement [8]. In the early stage of PD, it is reflected in smaller arm swing, slower turns and a reduction in step length. As the disease progresses, bradykinesia leads to a more unstable gait and possible episode of freezing of gait, that is defined as a subjective feeling that the feet seem to be “glued to the ground” [35]. It is worth to remark that these events may be rare or even absent during the clinical assessment, therefore it is important to evaluate the presence and severity of these phenomena through histories or questionnaires.

All these motor manifestations are worsened by a general muscle weakness caused by impaired basal ganglia that have an inadequate effect on the cortical motor centers, leading to a lower activation of motor neurons [18].

A direct consequence of the motor symptoms caused by PD is the related increase of falling, which is a problem that should not be underestimated since it might have a great impact on the health care system in the coming decades [36]. Indeed, it has been shown that people with PD are three times more likely to sustain a hip fracture as a result of a fall when compared to those without the condition [18].

Therefore, it can be deduced that motor symptoms, especially muscular weakness, gait and balance impairments, are the major contributors to the decreased quality of life of people suffering from PD [37].

2.4.2 Nonmotor symptoms

Although the motor manifestations remain the key factors of PD diagnosis, awareness for nonmotor symptoms associated to PD has increases considerably in the last years [38], since it is now well known that they largely contribute to the patients’ quality of life, especially in the advanced stages of the disease [9, 37, 39]. Brain imaging studies also support the crucial role of nonmotor involvement showing that loss of non-dopaminergic neurotransmitters plays an important role in the pathophysiology of various nonmotor manifestations in PD [23]. Moreover, it has been recognized that the nonmotor symptoms may present even years before the appearance of the classic motor

features used to PD diagnose [39] (Figure 2). Thus, this increased awareness has encouraged the PD research and clinical practice, as well, to shift their main focus closer to nonmotor manifestations of PD [9], since they may represent important biomarkers for pre-symptomatic identification of PD [39].

Nonmotor features of PD typically include sensory dysfunction, neuropsychiatric impairment, sleep disorders and autonomic dysfunction [39].

Typically, sensory disfunctions involve olfactory deficits, which develops in more than 90% of patients with PD, and visual disturbances, such as hallucinations, which typically increases with the disease progression and are probably linked to the presence of Lewy bodies in the occipital lobe and in the retinal neurons [39].

Anxiety and depression are common neuropsychiatric impairment. They both have been correlated with disease duration, severity of motor symptoms and level of dopamine medication. However, it is important to highlight that depression in PD is actually a complex phenomenon that may not represents a direct consequence of PD pathology, but rather a reaction to PD-associated disability or even a complete separate phenomenon [39]. Neuropsychiatric features also include cognitive deficit and dementia which are usually considered a component of late-stage PD. These impairments do not have a basal ganglia origin but are associated with Lewy bodies in posterior cortical regions, notably, the parietal and temporal lobes [39].

Disturbances in sleep and wakefulness affect most patients with PD, and their prevalence increases with the duration of disease. Specifically, it is possible to distinguish between daytime somnolence, “sleep attacks” and nocturnal sleep disturbances. The latter include insomnia, which can be disease-related or drug-related, involving sleep fragmentation and frequent, prolonged awakening. Moreover, the wearing off period of medication can exacerbate these sleep disturbances [39].

Eventually, autonomic disfunctions can concern the gastrointestinal tract with excessive salivation, dysphagia, impaired gastric emptying, constipation and impaired defecations, but also the cardiovascular system with changing in its general functioning [39].

2.5 Parkinson’s disease diagnosis

As mentioned before, although great achievements in the understanding of PD have been made during the over 200-year history of PD research, the diagnostic criteria for PD are still mainly based on the identification of motor symptoms [40], that typically include tremor, rigidity and bradykinesia [1, 29, 40]. Specifically, the bradykinesia is regarded as “obligate symptom” and it must occur in combination with rest tremor, rigidity or both [29]. In fact, the criteria for PD diagnoses do not include exclusively motor manifestations, but also nonmotor aspects of the disease, which, in more recent years, are acquiring greater importance, since they may appear even years before the motor

manifestation, giving a significant contribution in the early diagnoses of PD [39]. In more detailed terms, a diagnosis of "clinically established PD" requires at least two supportive criteria, the absence of absolute exclusion criteria, and no red flags. The supportive criteria include both motor and non-motor aspects of the disease, namely effects of dopaminergic therapy, presence of levodopa-induced dyskinesia, asymmetric rest tremors and positive tests on cardiac sympathetic denervation or olfactory loss. Absolute exclusion criteria are cerebellar abnormalities, supra nuclear gaze palsy, frontotemporal cognitive changes, slow progression, use of anti-dopaminergic therapy, absence of levodopa response, cortical findings like apraxia, and normal DAT scan. Red flags are early gait impairment, absence of progression, early bulbar dysfunction, inspiratory respiratory dysfunction (most frequently seen in MSA), severe autonomic failure during the first year of the disease, recurrent falls due to reduced balance, early antecollis, pyramidal tract signs, bilateral symmetric parkinsonism throughout the disease course and absence of any of the common non-motor features seen in PD like sleep dysfunction, autonomic dysfunction or hyposmia [29].

Therefore, it becomes evident how the PD diagnoses is an undoubtedly intricate procedure that depends mostly on the clinicians' expertise [12] and ability of identifying a specific pattern of significant symptoms, that could be directly related and connected with the characteristic pathogenesis of PD.

However, studies have demonstrated that, even if the diagnostic criteria are correctly applied, cases of misdiagnosis and delayed diagnosis of PD have been recognized and their rate is quite high, probably due to substantial clinical overlap among parkinsonian disorders [15, 41]. These two represent real issues that militate against the therapeutic benefits of disease modifying therapies which should not be underestimated [40]. That is why, in more recent years, the discovery and identification of reliable and accurate biomarkers for PD has become an urgent need that has gained the attention of much clinical research [40].

2.5.1 Biomarkers for Parkinson's disease

According to National Institutes of Health Biomarkers, a biomarker is:

> "*a measurable indicator of some biological state or condition that is objectively measured and evaluated to examine normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention*" [42].

Biomarkers can be classified according to their functional characteristics:

- susceptibility risk biomarkers, representing the potential for developing PD;
- diagnostic biomarkers, typically used to confirm the presence of PD;
- prognostic biomarkers, indicating disease progression, treatment-associated changes, or disease recurrence.

Robust and accurate diagnostic biomarkers can help in the recognition of PD before the onset of motor symptoms or when the motor or non-motor signs are inadequate to make the clinical diagnosis. They are also useful to make a differential diagnosis between PD and other neurological disorders, especially when it is necessary to differentiate idiopathic PD from other forms of parkinsonism. Furthermore, biomarkers may address many of the critical issues in clinical trials, such as the selection of appropriate participants and the assessment of treatment effects [40].

Currently, biomarkers for PD mainly focus on its symptomatic evaluation, specific neuroimaging changes and biochemical measurements of biofluids. Specifically, non-motor symptoms such as rapid eye movement sleep behavior disorder, hyposmia, constipation, and mood disorders are referred to as promising biomarkers in the detection of prodromal PD. Similarly, α-synuclein, the major protein component of Lewy bodies, has been proposed as surrogate biomarkers for the assessment of the drugs' efficacy.

Although some of these biomarkers have shown high diagnostic performance and predictive values for PD, only few biomarkers have been translated into clinical practice [40, 43]. Therefore, to improve the diagnostic accuracy of individual biomarkers, an increasing number of studies have focused on searching for a particular combination of biomarkers that, after a suitable and precise validation, could bring new insights on the prediction and diagnosis of PD, opening to new opportunities for clinical trials, personalized treatments and primary or secondary prevention [40].

2.6 Parkinson's disease assessment

There are generally two kinds of measures used for the assessment of PD. The first one is subjective, inferential, based on rater-based interview and examination or patient self-evaluation, and typically consist of rating scales and questionnaires. These estimations provide an assessment of the major symptoms of PD, scored according to an ordinal scale. On the contrary, the second type of measure is objective, factual, based on technology-based devices which are able to capture physical characteristics of the pathological phenomena. A typical example is represented by sensors that measure the frequency and amplitude of tremor. These instrumental evaluations furnish appraisals with real numbers on an interval scale for which a unit exists [44].

Subjective and objective assessment methodologies both include a broad variety of tools. In the following sections, the most used ones will be introduced and briefly discussed.

2.6.1 Subjective clinical assessment

The subjective clinical assessment of PD relies on standardized scales and questionnaires. The first ones are filled in by the clinician during the many periodic medical visits, with the specific purpose of evaluating and monitoring the impact and progression of PD in a variety of domains [38]. On the other hand, the questionnaires are directly completed by the patients themselves, providing important information about patients' quality of life and their perceptions of the disease that can't be easily deduced during the clinical examinations [45].

2.6.1.1 Unified Parkinson's Disease Rating Scale (UPDRS)

The Unified Parkinson's Disease Rating Scale (UPDRS) was originally developed in the 1980s to capture different aspects of PD and has become the most widely used and globally accepted compound scale in PD (pdf) [38, 46]. The present version of UPDRS is characterized by four components covering different domains and aspects of the disease. Specifically, the part I concerns mentation, behavior and mood; the part II rates activities of daily living; part III evaluates the motor symptoms; eventually, part IV involves possible complications of therapy [38].

The UPDRS is the most frequently applied instrument in clinical settings and scientific trials in PD and has been shown to respond to changes in the course of disease, motor fluctuations and interventional studies. Clinimetric properties have been described in detail and a teaching videotape is easily available in order to promote inter-rater reliability [38].

2.6.1.2 Movement Disorder Society sponsored Unified Parkinson's Disease Rating Scale (MDS-UPDRS)

In 2001, the Movement Disorder Society (MDS) sponsored a critique of the UPDRS, and this document lauded the strengths of the scale but identified a number of ambiguities, weaknesses, and areas in need of inclusion to reflect current scientific developments. The summary conclusions recommended the development of a new version of the UPDRS that would retain the strengths of the original scale, while resolving the identified problems and especially incorporating a number of clinically pertinent PD-related measures, poorly captured in the original version. Based on this critique, the MDS published a new version, termed the MDS sponsored UPDRS revision (MDS-UPDRS) [46]. Currently, MDS-UPDRS is considered the gold standard means for the clinic assessment and progression of PD [47, 13] (pdf).

2.6.1.3 39-Item Parkinson's Disease Questionnaire (PDQ-39)

The 39 item Parkinson's disease questionnaire (PDQ-39) is the most widely used self-reported questionnaire for the assessment of quality of life of patients suffering from PD and its impact on their daily lives [48, 49] (pdf). The PDQ-39 was developed on the basis of in-depth interviews with PD patients and a number of large-scale surveys. Initially, this has led to the development of 65 items, but, after a careful statistical analysis, the questionnaire was summarized and reduced to the final and current form characterized by 39 items and eight dimensions [49].

2.6.1.4 Ambiguities in Parkinson's disease scales and questionnaires

Although the wide use and the broad agreement achieved by PD scales and questionnaires, a number of limitations exist. In particular, the analysis conducted by Regnault et al. [11] suggests that many items in the MDS-UPDRS scale, especially those belonging to the sections dedicated to the daily activities (part II) and evaluation of motor symptoms (part III), tend to reflect a more advanced level of severity of PD that is not in fact experienced by the patients. It has been shown that this misfit occurs more frequently in the early stages of the disease. Therefore, it is unclear if MDS-UPDRS is appropriate for studying advancement of PD, especially when examining progression from its first stages. Since measuring severity in the early, least severe stages of PD is particularly important when considering how to evaluate and demonstrate the benefits of new therapies for PD, especially disease-modifying therapies, it could be concluded that different assessment methods may be more appropriate for the achievement of this specific purpose [11]. Certainly, these limitations arise the need of additional research in order to address and, possibly, resolve this significant gap in the assessment of progression of PD from the less severe stages. Moreover, since the rating of the items in the scale strictly depends on the clinician expertise, the final score provided as output is subjected by inter- and intra-rater variability [13].

Another important limitation affecting the PD scales is that patients' visits to the doctor only provide a snapshot of their condition and is therefore prone to reflect short-term effects that are irrelevant to the overall progression of the disease [12, 13].

For what concern the questionnaires, they depend a lot on the subjective patients' interpretations, which could be not reliable and not always useful for clinical evaluation. Furthermore, the grouping of items into questionnaires tends to appear overly complex and the meaning of scores is quite unclear, hampering their interpretation. Thus, questionnaires derived endpoints should be decoded and selected cautiously [48].

2.6.2 Objective clinical assessment

In order to overcome the main limitations associated to PD scales, novel strategies using sophisticated devices are reaching a grater approval from the scientific community [14]. Specifically, wearable sensors, such as accelerometers and gyroscopes, as well as balance boards and optical motion capture systems, have demonstrated to be promising in the characterization of motor functions in patients with PD [12, 14]. It is believed that they could become a cost-effective alternative to the current diagnosis tools and techniques as well as an efficient way to detect early PD patients [12]. Moreover, the same device can provide multiple neurophysiological signals and features that may guarantee a better characterization of PD [14]. Many studies have applied these devices in a controlled environment, asking the patient to perform a standardized motor tasks which reflect a specific characteristics of certain PD symptoms in order to differentiate between healthy and PD-affected patients. However, other publications report the application of these devices in a real-world environment to monitor the patients during their daily activities. This approach has demonstrated to be suitable in the evaluation of effectiveness and possible side effects of PD medications [12], which is instead more difficult with traditional methods, such as PD scales and questionnaires.

It is also important to highlight that this kind of objective approach could not be reliable without the employment of machine learning techniques, that in recent years are substituting the traditional statistical analysis and are becoming the pillar for classification and prediction problems [50].

Although their promising role, the tools used for objective assessment of PD encounter some limitations. The first problem is that clinical scales are still most frequently used as the “gold standard” in most publications, such as the UPDRS score, despite they are non-linear, provide only a snapshot of the condition and have high inter-rater variability. This implies that it is difficult to find a reference and standardized device system to which compare the results of objective assessments obtained with different technologies [12]. This main issued could be the consequence of another important limitation characterizing these systems. Indeed, some lab-based equipment, such as the ‘force plate system’ and ‘pressure sensitive walking mats’, are expensive and limited to only a subset of PD symptoms [12]. Eventually, these objective measuring system lack of representative measures, as most of the multi-dimensional motions are presented in the form of separate physical parameters [12].

Therefore, although great progress has been made in recent years, there is still much room for improvement. Nevertheless, it is reasonable to believe that in the near future, the objective measuring systems of motor symptoms will be widely used for the assessment of severity and progression of PD [12].

2.7 Treatments of Parkinson's disease

From 1817, year in which PD was methodically defined for the first time by James Parkinson as a complex and distinguished syndrome, much research has been conducted in order to better understand the precise neuropathology that stands behind and determines the characteristic features of the disease. Nonetheless, Parkinson's hopes that an understanding of the pathology underlying PD would lead to effective therapy began to materialize only in the second half of the 20th century [24]. From that, the treatments for PD have not changed substantially. Specifically, any of the treatments proposed until now is designated to provide symptomatic relief and minimize the debilitating symptoms [2, 8]. It means that at the present time there are no established treatments able to slow, stop or modify the disease course [15].

The available cures for alleviating the main symptoms of PD involve both pharmacological and non-pharmacological treatments.

2.7.1 Pharmacological treatments

In the following sections, the main pharmacological treatments are presented, pointing out their major strengths and side effects as well.

2.7.1.1 Levodopa

The mainstay of current PD treatments is levodopa-based preparations, produced to replace the dopamine in the depleted striatum [44]. Indeed, dopamine cannot be directly administered to patients since it is unable to cross the blood-brain barrier (BBB), meaning that it cannot be used to successfully treat PD. On the contrary, the dopamine precursor, levodopa, is able to cross the BBB. Specifically, after absorption and transit across the BBB, it is converted into dopamine through a decarboxylation process that takes place in the pre-synaptic terminal [15].

Levodopa can be administrated with different modalities. Usually, it is given in table form multiple times per day, but it can also be given in by duodenal infusion in patients with advanced disease [51]. The administered dose strictly depends on the specific needs of each patient. It is usual practice for patients to be commenced on a low dose of levodopa, with the dose being titrated up based on the patient's response to treatment, balanced against the adverse effects experienced [15].

Generally, the clinical effect of levodopa is noticed quickly, and may last for several hours, particularly in the early stages of disease. However, as disease becomes more advanced, the effect of the drug usually wears off after shorter durations, and an increased frequency of dosing is often required [15]. That's why clinicians should delay prescription of levodopa as long as possible because its effectiveness diminishes with time [8].

Levodopa, though effective, comes with significant side effects that constitute an important part of the illness experienced by the patient, particularly in advanced disease [15]. Some of its associated side effects result from the conversion of levodopa to dopamine outside of the central nervous system. This peripheral conversion can be minimized by administering levodopa in combination with the so-called carbidopa, which inhibits peripheral breakdown of levodopa, thereby allowing a greater proportion of levodopa to correctly act at the level of central nervous system [8, 15]. However, the most important levodopa limitation relates with its prolonged used, which typically results in significant motor complications, including severe on-off motor fluctuations and dyskinesias [8, 15, 51], defined as involuntary twisting hyperkinetic movements, which usually occur when the drug is at peak dose but may also occur during the drug wearing-off phase [15]. Generally, the development of these side effects can be related to different determinants, such as the severity of dopaminergic neurodegeneration (more severe, greater the risk), the dose of levodopa (>400 mg daily), female sex and low weight (relates to dose/kg) [51]. As these motor complications become more frequent and disturbing, many aspect of patients' daily life could significantly worsen; thus, they should be adequately controlled. Typically, a motor relief could be obtained by reducing and further fractionating the levodopa dose, meaning that a difficult balance must be struck between optimizing the control of the motor symptoms, while minimizing the adverse effects [15]. Other important side effects induced by levodopa include gastrointestinal disturbances, such as nausea and vomiting, orthostatic hypotension and neuropsychiatric problematics, involving anxiety and hallucinations [15].

2.7.1.2 Dopamine agonist

Dopamine receptor agonists came into the market for the treatment of PD in 1978 [15]. Their main function is stimulating the activity of dopamine system by binding to the dopaminergic receptors and, unlike levodopa, do not need to be converted into dopamine. Dopamine agonists are often prescribed as initial therapy for PD, particularly in younger patients, since they typically allow for a delay in the use of levodopa, thereby reducing the impact of the problematic motor complications. Although they may be less effective than levodopa in controlling the motor symptoms, dopamine agonists can be useful in patients with minor symptoms, in those that are unable to tolerate levodopa, or as an adjunct to levodopa therapy [15]. The dose required strictly depends on the specific characteristics and needs of each patients. In general, the dose is usually gradually increased, based on the patient's response and the side effects experienced [15].

Their effect in reducing the incidence and severity of dystonia, motor fluctuations, and dyskinesia seems to be promising and even more effective than levodopa. Moreover, some preclinical and imaging studies have suggested that dopamine agonists may lead to reduced loss of dopaminergic neurons, though there is no convincing evidence that these drugs offer a disease-modifying effect [15].

Nonetheless, they may cause other severe adverse effects. Common side effects include nausea and vomiting, dry mouth, insomnia, peripheral edema, constipation, fainting, hallucinations, and sleepiness. Perhaps, the most important adverse effect of dopamine agonists is the development of compulsive and impulsive behavioral problems, such as hypersexuality, gambling, binge eating and compulsive buying/shopping. Another important consideration is the risk of dopamine agonist withdrawal syndrome, which may occur when a person with compulsive or impulsive behavior either stops taking or reduces the dosage of dopamine agonists, inducing the development of persistent symptoms like anxiety, panic attacks, insomnia and irritability. [15].

2.7.1.3 Other pharmacological treatments

Other PD medications work by inhibiting the enzymes involved in dopamine metabolism, which preserves the levels of endogenous dopamine. Monoamine oxidase B and catechol-O-methyl transferase are part of this class of pharmacological therapies. Their use relieves motor symptoms in PD patients, and as with dopamine agonists they may be used as an initial treatment option, to delay the need for levodopa therapy, to reduce the risk of levodopa-induced motor complications [15, 51].

Differently, there are a small number of drugs used in the treatment of PD that act through non-dopaminergic mechanisms. One such class of drugs are the anticholinergics, which may offer some benefits in improving rigidity and tremor in PD. They are particularly effective drugs for young patients at early stages of the syndrome, giving relief to mild movement symptoms. Instead, anticholinergics are generally avoided in elderly patients or those with cognitive problems, due to an increased risk of confusion with this class of drug [15].

2.7.1.4 Emerging pharmacological treatments

Although there are still no disease-modifying treatments for PD, a variety of promising novel approaches are currently under investigation and testing phase. These include gene therapies and stem cell approaches aiming to restore dopaminergic activity in the striatum in a more physiological fashion than what is currently achieved with dopaminergic medications, theoretically with a reduced risk of the adverse effects of levodopa [15].

2.7.2 Nonpharmacological treatments

As pointed out before, despite the pivotal and beneficial role played by pharmacological treatments in alleviating the major symptomatic features of PD, it is undeniable that each patient suffering from PD has to deal with disturbing side effects caused by such treatments. That is why non-pharmacological interventions are increasingly being recognized as valuable treatment options to help overcome or

reduce these functional problems. Nowadays, a wide range of non-pharmacological treatment options is available. Even though they have not been studied extensively yet, the supportive scientific evidence for these treatments is increasing. Moreover, it is reasonable to think that nonpharmacological management might be particularly important for advanced-stage PD patients, because in this specific phase many symptoms no longer respond adequately to pharmacological treatment [52].

In the following sections, the more promising nonpharmacological treatments will be explained.

2.7.2.1 Deep brain stimulation (DBS)

Deep brain stimulation (DBS) is a nonpharmacological option for treating advanced PD. It is based on the use of chronic, high-frequency direct electrical current on a specific target area of the brain, dependently on the clinical features of each patient. The mechanism of action of DBS seems to rely on both excitatory and inhibitory effect. Specifically, a current hypothesis is that DBS exerts its therapeutic effects by dissociating input and output signals in the stimulated target and disrupting the abnormal information flow through the cortico-basal ganglia loop. In order to achieve a positive outcome of DBS, different variables should be carefully considered and examined. Among them, patient selection is the most crucial one, a procedure that should be performed by multidisciplinary team experienced in DBS. Other important aspects to consider are the disease duration, age, levodopa responsiveness, type and severity of levodopa-unresponsive symptoms, cognitive and psychiatric issues, comorbidities, and brain MRI findings. Although most of the studies have been performed in advanced PD, there is an emerging trial, called EARLSTIM, which suggested that DBS might be useful in patients with recent onset of levodopa-induced motor complications [51].

2.7.2.2 Physical activity and exercise

As mentioned previously, there is much evidence that underlies the importance of physical activity in reducing the risk of developing PD [33, 34, 22, 18]. Indeed, exercise limits the alteration in dopaminergic neurons in the substantia nigra and contributes to optimal functioning of the basal ganglia involved in motor commands and control by adaptive mechanisms involving dopamine neurotransmission [33]. In fact, exercise has emerged as one of the most important components of the treatment regimen for patients with PD, thanks to many demonstrated benefits that it could induce in PD-suffering patients [16].

Exercise is the general term for physical activity that is planned, structured, and repetitive for the purpose of conditioning any part of the body [48]. First of all, it has been shown that exercise has PD-specific symptomatic effects; indeed, it attenuates motor symptoms [49] and possibly improves health-related quality of life [18]. More in general, it has been shown that exercise can also have more

global effects on factors that influence brain health. These include blood flow through vascularization and angiogenesis and activation of beneficial effects of the immune system [53]. As well, evidence about the benefits induced by physical activity on gait is encouraging. Indeed, according to [37], specific balance training, gait training and strength and flexibility training can be effective for improving mobility and some important gait parameters (e.g., gait velocity, stride and step length) in patients affected by PD. Furthermore, a body of publications regarding the positive effects of exercise in terms of neuroplasticity and the ability of the brain to self-repair is keep growing in the recent years [6, 19, 20, 21]. Fox et al. [21] have suggested that there are some key principles of exercise that enhance neuroplasticity in relation to PD. Firstly, activities should be sufficiently intense and complex to promote greater structural adaptation and maximize synaptic plasticity; secondly, activities that are rewarding can increase dopamine levels and thereby can promote learning/relearning. Another important consideration pointed out in this study is that dopaminergic neurons are highly responsive to exercise and inactivity. This suggests that introducing planned physical activity at earlier stages of the PD could slow down its progression. Based on this increasing evidence, exercise should be considered as a universally available, side effect-free medicine that should be prescribed to vulnerable populations as a preventive measure and to PD patients as an important component of treatment [22]. For this reason, physicians need to be informed about these important effects induced by physical activity so that they can encourage their PD patients to incorporate it into their health routine [16]. Nevertheless, future research is required in order to establish what elements constitute an optimal exercise intervention for people with PD such as the dosage, component parts of intervention, and the targeted stage of the disease. This is of particular importance given the deteriorating nature of this condition [18].

2.8 Socio-economic impact of Parkinson's disease

PD is a neurodegenerative disorder that affect a wide portion of world-wild populations. As highlighted before, currently there is not cure for PD, meaning that any of the treatments nowadays available can act on the originating causes, but they mainly aim to provide symptomatic relief to patients, reducing, as much as possible, the main motor manifestations of PD. This ongoing reality together with the degenerative and progressive nature of the syndrome have significant economic and social implications for patients affected by PD. Certainly, the economic cost escalates as the disease becomes more severe [54], since more healthcare resources are required by patients. These include medications, need of assistance, increased risk of falling or get injured as the muscular strength worsen, and needs of constant physiotherapy or physical activity [35, 55]

Nonetheless, the PD causes important consequences on the social aspects of patients' life that should not be underestimated. In fact, it has been shown that PD does not only affect the domain of motor activity and mobility, but it is also correlated to nonmotor manifestations, that in recent years are acquiring much more importance, due to their significant impact on the patients' quality of life. According to the Global Parkinson's Disease Survey [56], the major influence on quality of life in PD is indeed the emotional status, especially depression, whose consequences do not only socially affect patients and caregivers, but they have also been associated with increased economic cost of illness [54]. Furthermore, thanks to the positive effects induced by modern pharmacological therapy, the life expectancy of PD patients is increasing and does not differ greatly from healthy age-matched individuals. As results, people may live many years with PD, suggesting that the financial burden is destinated to dramatically rise over time [54].

However, this summary represents only a general picture of the actual socio-economic burden of PD. Indeed, there are very few studies that have focused on this topic, and, above all, none of them specifically describe the Italian situations nor in global terms. Therefore, further research should be conducted to better understand an important aspect of PD, that should not be underestimated.

Chapter 3

Telehealth in Parkinson's disease

From the previous initial description of the main aspects surrounding this complex syndrome, it has become evident that PD is characterized by several motor and nonmotor features, which significantly affect patients' daily life. Levodopa has demonstrated to be an effective pharmacological therapy in reducing the major motor manifestations of the disease (e.g., bradykinesia, rigidity and tremor). On the other hand, a prolonged use of this medication causes significant side effects which adversely impact on the quality of life of those afflicted. In particular, levodopa-induced dyskinesia and motor fluctuations represent real issues, especially in more advanced stages of PD, which should be both managed and limited with suitable and effective interventions.

All these negative effects of drugs, together with the PD-related motor and nonmotor symptoms, need to be clinically evaluated in order to estimate the disease severity and, accordingly, the progression of the disease, as well as the effectiveness of prescribed pharmacological therapy. This assessment is typically performed by standardized clinical scales which aim to provide a measure of many aspects of PD, ranging from motor disability to behavioral features. Nowadays, MDS-UPDRS is considered the gold standard thanks to its good clinometric properties. Nonetheless, recent studies have shown that this scale tend to reflect a more advanced level of severity of PD that is not in fact experienced by patients. Though, it is believed that the primary limitation, associated with these scales, rests in the subjective manner by which they are applied and the lack of continuous, real-time assessment [50]. Indeed, they can only provide a snapshot of patients' conditions, making difficult for the physicians to get the full scope of disease advancing [12]. Furthermore, the progressive nature of the disease, together with the expected increase in afflicted population, will lead to an enormous burden on healthcare system and national economies, both in terms of direct and indirect costs [57]. In fact, PD has a significant economic impact in those afflicted too. Indeed, patients need to frequently travel to medical centers for the periodic clinical evaluations, which could be expensive, since not all the patients are lucky enough to live in the proximity of healthcare facilities, but it could also be stressful and laborious especially in more advanced stages of the disease. Consequently, patients-clinicians contact becomes highly troublesome in terms of care, monitoring and interventions [57]. It is in this multifactorial context related to PD that the need to switch to alternative types of care, monitoring and assessment is becoming urgent.

An efficient solution is provided by telehealth, that is increasingly spreading out in the last years, thanks also to the many logistic difficulties that the recent COVID-19 pandemic have given birth to. Indeed, during this emergency, the health service for chronic patients was suddenly interrupted, inevitably generating a sense of loss and abandonment due to the lack of dedicated medical and psychological support [55].

By definition, telehealth is the distribution of health-related services using electronic technologies and, in this set, it can improve the continuity of care in patients with chronic neurodegenerative disorders, like PD. In fact, telehealth has several facets that include telemedicine, telecoaching and telecare [57]. The term telemedicine refers more specifically to the use of information technologies and electronic communications to provide remote clinical services to patients (e.g., video consultations, evaluation of medical imaging). Telecoaching, instead, means the process of mentoring the use of devices and patient's management. Finally, telecare comprises assistive technologies and services tailored to individual needs. It monitors activity changes over time and can call for help in emergencies [57]. These innovative approaches can be realized employing different technologies, including wearable sensors and computer interface, which have demonstrated to ensure sufficient accuracy, portability and sensitivity by many recent publications. Such device and protocols could provide a more tailored approach to treating PD patients, but they could also provide wider insights necessary for its early diagnosis and its progression assessment [12, 50, 58].

3.1 Literature review

One of the first work in which technology has been used for health-related purposes in PD patients dates back to 2009. Giuffrida et al. [59] developed the first wireless portable automated system, designed for clinical use, made by a finger-worn sensor and wrist-worn command module. This innovative system collected arm kinematic data from 60 PD subjects, who were asked to complete a subset of the UPDRS upper extremity motor exam, including rest, postural and kinematic tremor. Thanks to data processing, they were able to extract quantitative variables representative of tremor severity, and highly correlated to clinical UPDRS score. Thus, this particular system represented one of the first clinical tool that provided a novel and automated method for tremor assessment in PD patients. Since then, many other studies have focused on finding alternative solutions based on wearable sensors to assess different aspects of PD. Yang et al. [60] found that a single, small tri-axial accelerometer attached to the belt buckle enabled real-time estimation of multiple gait parameters such as cadence, step regularity, stride regularity and step symmetry, allowing for immediate quantification of gait. Klucken et al. [61] also reported the use of a small, heel-clipped device that achieved a classification accuracy of 81% differentiating between PD patients and healthy controls.

More recently, a study of insole sensors enabled detection of PD-related freeze of gait episodes with 90% accuracy [62] and wrist-worn accelerometers demonstrated to be efficient in discriminating between treatment-caused changes and motor symptoms [63]. Besides, it has been shown that objective measurement based on inertial sensors is a promising cost-effective way to detect early PD patients who have shown minimal motor abnormalities with practically normal UPDRS. It is generally accepted that mild motor dysfunction has started before the appearance of motor symptoms of PD, therefore inertial sensors can provide an advantage over the naked eye due to its sensitivity [12]. Mancini et al. found jerk (the derivative of acceleration with respect to time) to be a particularly discriminative measure, exhibiting a high classification rate between subjects of early diagnosed PD and healthy controls [64]. Analogously, in the study carried out by Tien et al., they mounted an inertial measuring system on the subject's foot, providing numerical measures of gait performance. With the help of classifiers, the objective measuring system was able to discriminate early-stage PD from control group with a sensitivity of 80% and a specificity of 86% [65].

Though some of these studies were conducted in laboratory settings, the collective results indicate that patients could wear similar devices at home, enabling remote mobility assessment. In particular, in-home monitoring became even more practical after the spreading out of smartphones and other smart devices. Recently in 2020, van Brummelen et al. tested seven consumer product accelerometers in smartphones (e.g., iPhone 7) and consumer smart devices (e.g., Huawei watch) and found that these products performed comparably to laboratory-grade accelerometers when assessing the severity of certain PD symptoms [66]. Further expansion of smart devices came with the advent of user-friendly mobile applications such as the Fox Wearable Companion, app developed by the Michael J. Fox Foundation [67].

Use of smartwatches in conjunction with such mobile applications also allows for cloud-based data storage, thereby enabling research and clinical teams to more effectively monitor symptom progression and severity in real time [67]. In 2021, Powers et al. [68] developed the "Motor fluctuations Monitor for Parkinson's Disease" (MM4PD) system that used continuous monitoring from an Apple Watch to quantify resting tremor and dyskinesia. MM4PD strongly correlated with evaluations of tremor severity, aligned with expert ratings of dyskinesia, and matched clinician expectations of patients 94% of the time. Monitoring fluctuations using smart devices can be particularly useful, as the device can document what a patient was doing when symptoms worsened.

Finally, multiple studies have proposed using technologies other than accelerometers and gyroscopes (either stand-alone or in smartphones). Instead, some studies used computer vision-based algorithms to assess data from video cameras, time-of-flight sensors, and other motion devices [69-71].

Other intriguing developments of telehealth and telemedicine include speech and physical telerehabilitation. Already in 2009, Howell et al. [72] developed a tailored voice treatment for PD patients delivered by webcam, which allowed for similar beneficial outcomes when compared to face-

to-face treatment in three subjects. These non-inferiority results were confirmed by other studies that compared remote voice treatments to conventional in-person approaches [73,74]. Moreover, it has been shown that speech assessment can be reliably performed online. For example, already in 2010, Constantinescu and colleagues [75] evaluated the level of agreement between an online and face-to-face assessments of speech features, finding that, for the majority of parameters, there were no significant differences between the two approaches. These findings were confirmed in 2015 by Dias et al. [76], who investigated the efficacy of their proposed vocal telerehabilitation approach. Specifically, their analysis revealed a decrease in magnitude of voice quality changes after the intervention, indicating an improvement of vocal pattern. Besides, all patients reported satisfaction and preference for telerehabilitation compared to face-to-face rehabilitation.

Regarding physical telerehabilitation, different methodologies have been proposed. In the last 10 years, virtual reality (VR) telerehabilitation has reached increasing growth and acceptance by the scientific community. In 2011 treadmill training and VR were proposed to be viable in PD and to significantly improve physical performance, gait during complex challenging conditions and certain aspects of cognitive function [77]. More recently, Isernia and colleagues [78] have proposed a new multidimensional telerehabilitation protocol for neurological disease, named Human Empowered Aging and Disability (HEAD) program, which relies of VR setting to enhance motor and cognitive abilities, and quality of life. Thirty-one people with PD were included in the study. Firstly, all participants underwent 1 month of HEAD program in clinic (clinicHEAD), which mainly served as supervised and training period for the following step of the rehabilitation protocol. Indeed, the patients then proceeded with the HEAD protocol at home (homeHEAD). Both clinic and home HEAD showed high acceptability (> 80%) from the subjects involved. More interestingly, study's results reflected the positive influence of a multidimensional rehabilitation protocol approach to be performed at home, by underlining its effect on both motor and nonmotor functioning. Other studies addressed the efficacy and safety of commercially available systems, such as Nintendo WiiTM Fit equipped with balance board, suggesting that a home-based balance program using this kind of tools can improve the static and dynamic balance, mobility and functional abilities of people affected by PD [79-82]. A recent review concludes that despite suggestions that VR can provide a more effective and less labor-intensive rehabilitation than non-VR rehabilitation, little evidence exists to date to support these claims [83]. These authors suggest the development of personalized assessments and rehabilitation using VR in order to adapt to individual changes over time and optimize motor learning. Other telerehabilitation approaches that have demonstrated to be feasible and effective for PD patients include exergaming [84] and partnered remote dance class (e.g., tango class) [85].

Telemedicine may also bring many benefits to nonmotor manifestation of PF, such as depression and anxiety. A randomized controlled trial [86] proved the feasibility of telephone-administered Cognitive Behavioral Therapy (CBT) to tackle these nonmotor features. Dobkin and colleagues [87], who tested

telephone-based cognitive-behavioral treatment (T-CBT), further confirmed these results, reporting significantly improved depression scores and a persistent benefit over a six-month follow-up. Another study [88] explored both the feasibility and patients' satisfaction with telepsychiatry services of 33 PD subjects who completed 119 telepsychiatry and 62 in-person visits. It came out that patients were overall satisfied, even though some technical aspects needed further optimization.

Furthermore, another important advantage of telemedicine is the related considerable resource saving that could be achieved [57]. Cubo et al. [89] confirmed the cost-effectiveness of home-based motor monitoring plus standard in-office visits compared to in-office visits alone in 35 PD patients. Specifically, the home-based care model was cost-effective in terms of functional status, motor impairment, and motor complications, as evaluated by UPDRS II, III, and IV. Accordingly, another study [90] examined the feasibility, effectiveness, and economic advantages of this remote approach. The authors performed a randomized controlled trial in 20 patients, 11 with in-person visits and nine with specialist care via telemedicine. Each telemedicine visits saved participants, on average, 100 miles of travel, with a relevant economic value.

Even though many advantages can be observed, telemedicine programs' implementation and use have raised concerns regarding the doctor-patient relationship. Some studies have evaluated patients' perception. Qiang JK and Marras [91] administered to 34 users and 103 non-users of telemedicine services a satisfaction questionnaire. 29/34 users were interested in continuing with telemedicine, and non-users (55/103) were interested in using telehealth, either partially or wholly replacing in-person visits. Interest in the use of telemedicine was also confirmed in a survey conducted by Spear and colleagues in 2016 [92], whose results individuated as main advantages of remote care the access of specialists, convenience and time saving. Therefore, these studies suggest that the doctor-patient relationship is not affected by telemedicine.

Surely, the impact of COVID-19 pandemic has led the scientific community to redefine and improve telemedicine's role in the healthcare system. For instance, recent guidelines and recommendations [93, 94] have highlighted the importance of telemedicine in substituting outpatients' visits. Expanding telehealth could reduce person-to-person contact, thus lowering the risk of exposure for patients. Substantial innovations are currently being implemented, and the Telemedicine Study Group of the International Parkinson and Movement Disorders Society has updated a guide to telemedicine to tackle these recent challenges [57].

In spite of the clinical benefits, telehealth intervention has faced some challenges that deserve attention. Firstly, there is the issue of user retention, meaning that some user interfaces and user experiences may not be suitable for PD patients. Therefore, it is pivotal to make a suitable choice of telecommunication technology for patients, according to their specific condition [95]. Eventually, additional research is warranted to further elucidate both benefits and limitations of telemedicine in PD [57].

Chapter 4

RAPIDO: teleReabilitatione per I mAlati di Parkinson In qualsiasi staDIO

RAPIDO ("teleReabilitatione per I mAlati di Parkinson In qualsiasi staDIO") is a project that was initiated in 2021 from the collaboration between Università Politecnica delle Marche, Università di Verona and Revolt s.r.l. to respond to the fragilities, faced by territorial healthcare systems dedicated to PD, revealed by COVID-19 emergency. Indeed, due to the many restrictions imposed by the pandemic, PD patients could not get any more access to fundamental visits and cares, including physical rehabilitation. Therefore, territorial healthcare facilities realized that was necessary to find out new operative modalities to ensure PD subjects a sufficient and adequate assistance. In this context, RAPIDO represents an innovative tool to cope with these changed needs.

This project aims to develop a telerehabilitation and telemonitoring system destinated to people suffering from PD, guaranteeing an effective integration. In this way, it is possible to provide, via a single platform, telemonitoring and telerehabilitation tools that can be easily accessed by both patients and direct assistance operators involved in the treatment of PD and in at-home rehabilitation.

At the basis of this novel project there is a heterogeneous team composed by different professionals, including, first of all, medical doctors, specialized in neurorehabilitation, who are essential in the evaluation of disease severity, its progression and eligibility of different patients to the clinical study. Engineers also take part in this team, who have developed the overall system and continuously handle and manage all the technical aspects, encompassing data collection and analysis.

The integrated telerehabilitation and telemonitoring system proposed by RAPIDO is composed by suitable wearable and noninvasive sensors that collect patient-related data which are then partially and locally processed by a specific app (accessible both from mobile devices and personal computers), thereby making the elaborated outcomes available to clinicians. So that, they can possibly implement some changes in the rehabilitative schedule in order to adapt it to the specific needs of each patient. Thanks to these wearables, it is also possible to monitor the main subjects' vital parameters during the rehabilitative treatment providing important feedbacks on the training intensity, lowering the risk of probable adverse effects. Furthermore, it is believed that this system may provide a significant contribution in the improvement of the patients' quality of life, promoting economic sustainability of long-term management of PD and reducing the consumption of health resources, as well as caregivers

stress and responsibility. Indeed, it is reasonable to think that the empowerment of patients may correspond to a diminution of complications and to a positive impact on the progression of disability.

4.1 Technical aspects

RAPIDO telemonitoring and telerehabilitation system includes two main subsystems: a local edge/fog computing system and a remote server that exposes RESTful services (Figure 3). Specifically, the local (near to the user) system consists of a wrist-worn smartwatch (Garmin Vivosmart 4) equipped with several onboard sensors to collect raw data about patient's physiological status, including sleeping, fitness and activity variables, as well as wrist-based heart rate and stress information. All this data collected by the smartwatch are tracked, analyzed and shared through Garmin Connect TM, a user-friendly application (mobile or web) which is installed in a Samsung A7 tablet, the other fundamental component of the local subsystem. This device essentially represents an edge/fog node which, thus, receive all the collected data from the smartwatch via Bluetooth, compute some aggregated and higher-level variables, communicating them to the remote subsystem. The latter is a server application (hosted by Italian company Aruba Spa) that follows a Software-As-A-Service paradigm, designated to deliver and keep track of rehabilitation therapies. Besides, it ensures the storage of collected data received from edge/fog node, which periodically synchronizes with the server through POST requests, sharing health data and summaries which are typically grouped by days in anonymous form, in compliance with the General Data Protection Regulation (GDPR). These data can be possibly downloaded by the engineer team or by clinician in order to conduct different analyses, possibly adjusting the rehabilitation protocol, if needed.

The combination of these two subsystems, local and remote, ensures that each patient can log into a reserved area by means of anonymous and unique username, which presents the assigned rehabilitation therapy together with the reached progress (in terms of percentage of completion). The exercises, composing the rehabilitation protocol, are retrieved through https GET requests from the database and shown to the patient with a brief description. So that, each patient can easily start a new training session through a user-friendly interface that automatically presents the next scheduled exercise and guides the patient throughout the rehabilitation program.

4.2 Clinical study

In order to join the clinical study, patients need to respect precise and rigid inclusion criteria (Table 2) that are evaluated during an initial enrollment session at the healthcare facility of reference.

On the other hand, any subject that shows at least one of the conditions included in the exclusion criteria (Table 3) will be ruled out.

During the enrollment session (T_0), patients are also evaluated from a more global point of view. By means of a specifically tailored medical record, demographic and clinic data related to the first PD manifestations are collected, together with information about symptoms evolution, motor and nonmotor features, ongoing pharmacological and rehabilitative treatments, potential comorbidity, social-aid aspects, quality of life and previous medical complications connected to PD or treatment side effects. For this purpose, specific clinical scale and questionnaires, e.g., UPDRS, NonMotor Symptoms Scale (NMSS) [96], PDQ-8, are used. In addition, main walking parameters have been extrapolated from Timed Up and Go (TUG) test [97]. This initial evaluation is also required in order to assign an appropriate rehabilitation protocol, tailored according to the specific health status and disease severity of each patient.

If medical doctors officially declare the suitability for the clinical study, patients then meet the engineers' team in order to be informed about the correct use of both telemonitoring and telerehabilitation systems. First of all, subjects are instructed to wear the smartwatch continuously, 7 days a week, 24 hours a day for the entire duration of telerehabilitation protocol. Besides, the technical team takes care of illustrating how to correctly access to the telerehabilitation reserved area, in which each subject can retrieve videos explaining all the different exercises belonging to the assigned rehabilitation protocol.

Specifically, four different rehabilitation programs have been specifically designed for this clinical study, on the basis of the different stages of the disease and the presence/absence of freezing episodes.

- The first protocol is indicated for patients in the early stage of the disease, where the main limitations deriving from it are not present yet. The protocol is mainly focused on the performance of strengthening, mobility and coordination exercises performed while standing, as well as on the maintenance/improving of ambulation, possibly increasing the aerobic capacity.
- The second protocol is developed for patients in the intermediate stage of the disease, but that have not experienced any freezing episode yet. Analogously to the first one, this second program is centered on the performance of strengthening, mobility and coordination exercises performed while standing, as well as exercises to improve the step quality. The main difference with the first protocol is in its initial difficulty and progression.
- The third protocol is reserved for patients in the intermediate stage of the disease with daily-recurrent freezing episodes. For this reason, this program is focused on the exercise and strategies that can possibly reduce freezing.
- The fourth protocol is indicated for patients in advanced stages of the disease, especially for those that are compelled in bed or wheelchair most of the day. This protocol specifically

involves exercises performed at bed or while sitting, aiming to reinforcement, coordination and mobility of some postural passages.

Each protocol is composed by different series of exercises, oriented to train skills belonging to four different domains: postural alignment skills (Domain 1), strategies for overcoming freezing and preventing falls (Domain 2), ability to articulate speech (Domain 3), compensatory postures for swallowing (Domain 4). The exercises of each domain are proposed in levels of increasing complexity and based on the risk of falling, evaluated with the item postural instability of the UPDRS part III, allowing a better personalization of the training experience and promoting motivation to the exercise regularity. The at-home rehabilitation program has a duration of three months, during which patients should periodically train in sessions of 45 minutes/day for at least 3 times/weeks (for no less than 27 total sessions, corresponding to 1200 minutes of training). In fact, during the very first week of these 3 months, patients are asked to solely wear the smartwatch for the entire day, without performing any of the proposed exercises, in order to make possible the recording of pre-therapy baseline values that could be helpful in the data analysis. Thus, only after one week from the devices' delivery, subjects are allowed to begin the telerehabilitation protocol, according to the previously specified modalities. Furthermore, during the entire rehabilitation period, participants are supported by regular (every 15+3 days) video calls from clinicians in order to verify the correct use of the devices, the level of adherence of exercise program, as well as to agree on the adaptation of the training program to the progression of the user's skills.

At the end of the 3-months training trials, patients need to undergo a new clinical evaluation (T_3) in order to assess their health status, highlighting possible improvements determined by the at-home rehabilitation. A final clinical session is scheduled after six months from the baseline visit (T_6).

However, it is important to underly that the fixed duration for the telerehabilitation protocol is actually only the minimum and recommended duration; indeed, it could happen that the trial prolongs over the three months for many causes. First of all, patients could not be able to strictly respect the suggested training frequency, since they may be occupied by other scheduled appointments or may be indisposed due to several healthy issues. Besides, the 45-minutes exercises sessions could be too heavy for certain subjects, thus they could prefer to divide it among different days. In addition, it is not always certain that T_3 is exactly scheduled immediately after the conclusion of the telerehabilitation program. Thus, the telemonitoring continues and data keep being collected and available for data analysis.

At least one hundred subjects (50 subjects in each clinical center) will be enrolled. Considering a dropout quota of less than 20%, the sample available for evaluating the outcome will be eighty subjects. The sample size was calculated using the confidence interval method (95% CI), the exact Clopper-Pearson method, and a 95% confidence level.

At the present time, the clinical study is in the trial phase, required to establish if the proposed telerehabilitation program could be efficiently applied and extended in a wider population of people affected by PD. For this purpose, 5 patients have been enrolled, specifically:

- 3 subjects out of 5 have concluded the three-months program,
- 2 subjects out of 5 have handed back the devices before the suggested endpoint.

This clinical study is submitted for approbation to the Regional Ethics Committee (CERM). Any adverse events reported by the patients or detected by healthcare professionals will be recorded and reported to CERM, as required by local regulations. Importantly, it is conducted in full compliance with the current revision of the Declaration of Helsinki, and it is designed to ensure adherence to the principles of Good Clinical Practice (GCP) and compliance with Italian law. Any changes to the protocol will require the approval of the CERM before the implementation of such changes.

Chapter 5

Methods

For the study purpose, only patients that have completed the 3-month telerehabilitation protocol have been considered. Therefore, data acquired from a total of 3 patients have been used to conduct the data analysis, which consists of two main phases: data processing and data clustering. Both of these two steps have been performed offline and implemented in Python 3.10. The latter is an object-oriented, high-level programming language with dynamic semantics. Its build-in data structures, combined with dynamic typing and binding, make Python extremely appealing and suitable for database analysis and visualization, as well for machine learning applications. Moreover, Python interpreter and its many standard libraries are open source, thus free to be downloaded. All these peculiarities have drove and motivated the choice of using this specific programming language, among others.

5.1 Data acquisition

Real-life raw data have been collected by means of Garmin Vivosmart 4 smartwatch, worn by each patients during the entire training period, according to the assigned telerehabilitation protocol. During the program, patients should have worn the smartwatch 24 hours/day in order to obtain information not only about daily activities (including the exercise sessions), but also details related to their sleep behavior. Indeed, although the main manifestations of PD are related to motor impairments, sleep routine could be severely affected by the syndrome. Therefore, night recordings might provide wider insights about the patients' health condition, as well as the disease progression, possibly giving a significant contribution to the achievement of the final study goal.

As mentioned before, data are then sent via Bluetooth to the Samsung tablet, which serves as edge/fog node making possible the transfer of recordings to the remote server, specifically implemented for the RAPIDO project. So that, data of interest can be downloaded in the form of summary records. The latter represent updates containing aggregated variables, computed by Garmin Connect app, which provide a broad variety of information including wrist-based heart rate, daily and physical activity, stress and sleep.

Specifically, data used in this study are retrieved in the form of the following summaries:

- Dailies summaries: dailies summaries offer a high-level view of the user's entire day. They generally correspond to the data found on the "My Day" section of Garmin Connect. The main parameters offered by dailies summaries are reported in Table 4.
- Sleep summaries: sleep summaries are data records representing how long the user slept and the automatically classified sleep levels during that sleep event (e.g., light, deep periods) based on data generated by the user's device. Unlike Daily summaries, which are associated with a given day on a midnight-to-midnight basis, sleep summaries are associated with a user's overnight sleep range. Most will start on one calendar day and end on the next calendar day, but it is possible for two different sleep summaries to begin on the same day if, for example, the user goes to bed after midnight, wakes up, and then goes to bed prior to midnight the next evening. The main parameters offered by sleep summaries are reported in Table 5.
- Stress summaries: stress summaries contain the user's stress level values for a given day. Stress levels are provided as 3-minute averages of the real-time stress scores generated on the device with values ranging from 1 to 100. A value of -1 means there was not enough data to detect stress, and -2 means there was too much motion (e.g., the user was walking or running). Scores between 1 and 25 are considered "rest" (not stressful), 26-50 as "low" stress, 51-75 "medium" stress, and 76-100 as "high" stress. These numbers are derived based on a combination of many device sensors and will automatically adjust to the wearer of the device and gain accuracy over time as the stress algorithms learn the user's natural biometric norms. The main parameters offered by stress summaries are reported in Table 6.

5.2 Data processing

Data processing involves an initial phase, required to create dataframes starting from the many JSON (JavaScript Object Notation) files acquired by Garmin smartwatch, which is then followed by a second step where statistical analysis has been performed in order to determine the features that have significantly changed during the telerehabilitation protocol.

5.2.1 Dataframe creation and organization

Data recorded by Garmin smartwatch are made available from the web application to the implemented server in JSON-format files. JSON format is an open standard file format and data interchange format that uses human-readable text to store and transmit data objects, consisting of attribute-value pairs and arrays. For each day of acquisition, there are different JSON files, each of which is related to different domains. For the purpose of this study, three JSON files have been

considered for each days: the first one is the JSON file belonging to daily activities domain, the second one is the JSON file containing information about sleep domain, while the last one provides information about stress levels and condition. So that, due to this huge amount of available data for each patient, it becomes clear the necessity to find an alternative and lighter approach in order to quickly and efficiently analyze all this information.

Indeed, once the folders containing the different JSON files have been downloaded locally for each patient, a customized function has been implemented in Python to correctly load and aggregate all these different JSON files in a unique dataframe. Specifically, for each patients three dataframes, which reflect the three chosen informative domains, have been created: a dailies summaries dataframe, a sleeps summaries dataframe and a stress summaries dataframe. These dataframes are essentially tables in which each row corresponds to a specific daily acquisition, while each column contains a specific feature, matching one single entry of JSON file. Therefore, cells of the table house the values that each feature assumes daily. In fact, as it can be seen in the Table 4, Garmin smartwatch is also able to collect daily wrist-based heart rate ("timeOffsetHeartRateSamples"), which is typically provided as vector of samples recorded with a sampling frequency of 0.066 Hz (1 sample every 15 seconds) contained in the daily summaries. Similarly, each stress JSON file (Table 6) contains two variables ("timeOffsetStressLevelValues" and "timeOffsetBodyBatteryValues") whose values are collected every 3 minutes. However, the actual number of available samples for these variables strictly depends on the real time that a certain patient has worn the smartwatch. Thus, in order to construct dataframes that always have the same number of columns, facilitating the development of the following analysis, but without losing significant information, it has been opted to compute descriptive measures for each day of acquisition, for each of the previous mentioned features. These include maximum, mean, minimum and standard deviation for "timeOffsetHeartRateSamples", while maximum, mean, median, 25 and 75 quantiles, and minimum for "timeOffsetStressLevelValues" and "timeOffsetBodyBatteryValues". All these computed measures are then inserted in the daily dataframe and stress dataframe respectively for each patient. All the variables taking part in each constructed dataframe are summarized in Table 7.

Once the dataframes have been set, data have been organized according to the different weeks of acquisition. In other words, each row has been labeled with an integer number, corresponding to the acquisition week of belonging. This organizing procedure is required to correctly perform the statistical analysis that will be discussed below. By the same token, any row containing NaN values has been eliminated.

5.2.2 Statistical analysis: features selection

One-way analysis of variance (ANOVA) test has been applied to each created dataframe to find out those features whose values change significantly among different weeks. Indeed, since this study primarily aims to determine whether the proposed telerehabilitation protocol could bring changes in the health condition of subjects affected by PD, it is reasonable to disregard those variables that do not show any statistically significant difference among weeks, possibly improving the informative content of available data, thereby leading to more reliable results.

ANOVA is a technique, based on the evaluation of variability measures, for analyzing the way in which the mean of a variable is affected by different types and combinations of factors. It gives a single overall test to determine whether there are differences between more than two populations. One-way analysis of variance is the simplest form [98], in which there is one categorial independent variable (also known as factor) and normally distributed, continuous, dependent variables. This method provides a rule for deciding whether to reject the null hypothesis (H_0), which states that there is no significant difference among groups:

$$H_0 : \mu_1 = \mu_2 = \mu_3 = \ldots = \mu_k$$

where μ is the group mean and k is the number of groups.

This decision is based on the evaluation of the so-called p-value. When interpreting the p-value, it can be concluded that there is a significant difference between groups if the p-value is smaller than a fixed cut-off value (α), defined as significance level, that represents the probability of a type I error (i.e., the probability to reject the $H_0$when in fact $H_0$is true). Typically, α=0.05, therefore, a p-value <0.05 means that there is sufficient evidence to reject the H_0 and consequently accept the alternative hypothesis (H_1), according to which there are at least two means in the population that are significantly different. One-way ANOVA test is based on four fundamental assumptions:

1. An ANOVA can only be conducted if there is no relationship between the sample in each group (e.g., independent samples/between-groups).
2. The different groups/levels must have equal sample sizes.
3. An ANOVA can only be conducted if the dependent variable is normally distributed. However, it has been demonstrated that ANOVA test is still robust even if this assumption is not verified, as long as the sample size is sufficiently large. It means that test results should not be severely affected by violation of normality [99, 100]. Generally, there are mainly two kinds of approach to investigate the normality of the dependent variable. The first one relies on visualization techniques, such as histograms or Quantile-Quantile (Q-Q) plots. The latter allows to compare graphically two probability distribution by plotting their quantiles against each other [101]. Specifically, if the data points fall along a straight diagonal line, then the samples likely follow a normal distribution. Statistical test can be also used to prove the

normality condition. One of the most common is the so-called Shapiro-Wilk test, which essentially aims to verify the null hypothesis, according to which a sample come from a normally distributed population.

4. Population variances must be equal (i.e., homoscedastic). Similarly, also in this case there are two main kinds of approached that can be adopted to investigate the homoscedasticity. The first one checks the assumption visually using boxplot. Alternatively, it is possible to use formal statistical tests, like Levene's test. It aims to verify the validity of null hypothesis, according to which the population variances are equal. In general, a one-way ANOVA is considered to be fairly robust against violations of the equal variances' assumption as long as each group has the same sample size.

Specifically, for the purpose of the study, the vector containing all integer numbers, corresponding to the different weeks, is considered as the independent and categorical variable, that drive the entire statistical analysis.

However, the major setback associated with ANOVA is that it only compares the means between groups, but it does not categorize the exact information such as which particular pairs of means are significant. Therefore, in order to specifically understand which are the couples of weeks that are statistically different, it is necessary to adopt specific post-hoc tests that allows to compare all possible combination of mean values between pairs of groups. Thus, once one-way ANOVA has confirmed an overall statistically significant difference in weeks means, Tukey Honestly Significant Difference (HSD) test has been chosen to perform the pair wise comparison. The main idea of Tukey HSD is based on the computation of the HSD between two means using a statistical process, which gives the exact information and identifies the major difference between means of a set of group from the population under consideration [102]. The HDS for each pair of mean is calculated according to the formula below [102]:

$$HSD = \frac{M_i - M_j}{\sqrt{\frac{MS_w}{N}}}$$

where $M_i - M_j$ is the difference between the pair of means, MS_w is the means square within and N is the number of the group.

The results provided by Tukey HSD test are not only useful to confirm what has emerged from ANOVA, but also to understand if there is a pattern followed by the pair wise comparisons that could indicate a change over time of the features belonging to the constructed dataframes.

Therefore, thanks to the insights provided by one-way ANOVA test, and confirmed by Tukey HSD multi-comparison, only the features that have demonstrated statistically significant differences throughout the weeks have been selected. Then, all these variables, even if coming from the three

different dataframes, have been incorporated in a unique and new table, which, thus, contains all the informative data required for the following step of data analysis.

5.3 Data clustering

At this point of the analysis, it becomes evident the necessity to find out an effective method that could demonstrate changes in the selected features during successive weeks. It has been though that the possible evolution of these variables could have brought to a redistribution of the available data points in a certain number of separated groups, reflecting a specific weekly range. In order to objectively validate this hypothesis, a Principal Component Analysis (PCA) has been applied to the elected data as initial investigative procedure. Indeed, PCA is not only a useful mathematical algorithm that reduces the dimensionality of the data, while retaining most of the variation in the dataset, but it allows also for an exemplified representation of data samples, making it possible to visually assess similarities and differences, as well as determine whether samples can be grouped [103]. These peculiarities of PCA make it a useful first step before clustering.

PCA is one of the older and most popular multivariate technique, which has a wide range of applications. Its main goal is to extract the important information from the data table and to express this information as a set of new orthogonal variables called Principal Components (PC) [104]. The latter are linear combination of the original variables, each of which can be interpreted as the direction, uncorrelated to previous components, that maximizes the variance of the samples when projected onto the component [104]. Generally, the first PC is required to have the largest possible variance, meaning that this component will extract, or explain, the largest part of the variance of the dataframe. The second component is computed under the constraint of being orthogonal to the first component and to have the largest possible variance. The other components are computed likewise. Once the PCs have been set, the algorithm proceeds with the computation of the so-called *factor scores* which can be interpreted geometrically as the projections of the observations onto the PCs. The latter are obtained applying the singular values decomposition (SVD) to the original data table (X), which can thus be expressed as the product between 3 matrixes:

$$X = P \cdot \Delta \cdot Q^T$$

where P is the $I \times L$ matrix of left singular vectors, Q is the $J \times L$ matrix of right singular vectors, and Δ is the diagonal matric of singular values. Specifically, Q gives the coefficients of the linear combinations used to compute the factors scores. It can also be interpreted as a projection matrix because multiplying X by Q gives the values of the projections of the observations on the PCs, that can be summarized is the matrix F [105]:

$$F = X \cdot Q$$

The just described PCA steps are graphically described by the Figure 4.

Once the implemented PCA algorithms has been run, its results have been evaluated and interpreted graphically.

Accordingly, the analysis has proceeded with actual division of the data in different clusters, which could possibly reflect an improvement in the health condition of patients. Since all the available samples are unlabeled, thus not associated with any identifying characteristic or property, it demonstrates necessary to adopt an unsupervised clustering technique. Specifically, K-means clustering has been elected as designated approach.

Generally, clustering is a useful tool for finding group structures in a data set that are characterized by the greatest similarity within the same cluster and the greatest dissimilarity between different clusters. From statistical viewpoint, clustering methods are generally divided as probability model-based approaches and nonparametric approaches. The probability model-based approaches follow that the data points are from a mixture probability model so that a mixture likelihood approach to clustering is used. For nonparametric approaches, clustering methods are mostly based on an objective function of similarity or dissimilarity measures, and these can be divided into hierarchical and partitional methods. Among the latter, K-means is one the oldest and most used one [105]. Specifically, it is a distance-based clustering method that finds locally optimal solutions basing on dissimilarity (or distance) between a points and a cluster centroid [106]. However, since in this specific case the data are unlabeled, the number of clusters (K) cannot be a-priori known. Therefore, the first problem that needs to be faced with the implementation of this algorithm is the choice of a suitable number of clusters. There have been a number of different proposals in the literature for choosing the right K, which are typically based on the measure of a certain validity index computed iteratively in multiple runs of K-means. For the specific case of this clinical study, the so-called *elbow method* has been chosen. It is a visual method that is particularly suitable for relatively small K values. The rationale followed by elbow method relies on an iterative procedure in which at each step the K-means is run with a different K and the sum of squared distance (SSD) between centroids and the data present in that cluster is computed. The following equation provides the mathematical formula for computing SSD.

$$SSD = \sum_{k=1}^{K} \sum_{x_i \in S_K}^{\square} \left\| x_i - c_k \right\|^2$$

where c_k is the i-th cluster center, x_i is the i-th data in the k-th cluster.

The K is made change in a specified range of integer numbers, typically starting from K=2. As the K value increases, the number of samples contained in each category decreases, and the samples are closer to the centroid. As a consequence, the SSD decreases as the number of clusters increases, reaching its theoretical minimum when K equals the number of data points. However, although the SSD is minimized, a too elevated K would not be useful for an effective classification process. According to the elbow method, the most suitable number of clusters can be deduced by plotting the

SSD for each of evaluated K. In particular, the desired K is that one for which the rate of reduction of SSD begins to decline, meaning that adding extra clusters would not help in obtaining enough clarity in groups separation that could justify this addition.

Once the most suitable K has been selected, it is possible to proceed with the actual implementation of the K-mean algorithm for unsupervised clustering, that follows these main steps:

1. Initialization of the centroids: K distinct data points are selected. These will provide the initial coordinates (centroids) to initially position the different clusters.
2. Assignment of data points: all the remaining data points are assigned to the nearest cluster centroids, depending on their distance. Specifically, firstly the algorithm computes all the possible distances between a certain data point and each centroids. It selects the minimum one in order to decide which is the cluster of belonging. This procedure is repeated for every data points. There are several distance metrics that can be adopted for this purpose. The most common one remains the Euclidean distance, computed as:

$$d\left(x_i, c_i\right)=\sqrt{\sum_{i=1}^{N}\left(x_i-c_i\right)^2}$$

   where c_i is the i-th cluster center, x_i is the i-th data in the i-th cluster, N is the number of data points in i-th clusters.
3. Re-initialization of the centroids: the algorithm computes the mean value of all data point for each cluster, that will represent the new cluster center:

$$c_i=\frac{1}{N}\sum_{j=1}^{N} x_j$$

   where c_i is the i-th cluster center, x_j is the j-th data in the i-th cluster, N is the number of data points in i-th clusters.
4. Re-assignment of data points: again, all the remaining data points are re-assigned to the nearest cluster centroids computed in the step 3.
5. Repeat step 4 and 3: the algorithm repeats the step 3 and 4 until there are any centroids re-initializations and points re-assignments. Eventually, each point must belong to one cluster, and more importantly, each point can only belong to one and only one cluster.

Although the logic followed by the K-means is quite simple, the positioning of the initial centroids can be challenging and should not be underestimated since it directly impacts on the overall run time and especially on the algorithm performance [105, 106]. The traditional way is to select the centroids randomly, however this is a very time-consuming process, since the number of steps required to obtain the correct centroids significantly increases with the dataset complexity. For this reason, other methods have been proposed to limit this issue. In this case, K-means ++ [107] has been selected as an alternative procedure to achieve a more effective clusters initialization. The idea is to push the

centroids as far as possible one from another, that can be achieved following simple successive steps. Let $D(x)$ denote the shortest distance from a data point to the closest center that has already be chosen. Then:

1. Take one center c_1, chosen uniformly at random from the entire set of points X.
2. Take a new center c_i, choosing a point $x \in X$ with probability $\frac{D(x)^2}{\sum_{x \in X} D(x)^2}$.
3. Repeat step 2 until k center have taken altogether.

After that, it is possible to proceed with the standard K-means algorithm, thanks to which it is possible to obtain the vector containing integer numbers specifying the different groups of belonging for each row of data.

On the other hand, it is important to remind that K-means is an unsupervised algorithm, meaning that it does not identify groups, rather it is useful to discover potential labels, whose interpretation is up to the user, basing on the knowledge of the available data. Therefore, in order to give a possible explanation to the algorithm output, a copy of the initial dataframe has been created and it has been homogenously divided depending on the K value obtained through the previously mentioned elbow method. As results, two dataframes are now available:

- Testing dataframe, that is the dataframe in which the columns represent the statistically significant features determined by ANOVA, while the rows represent the daily acquisitions of those features. Furthermore, each row is associated with a label provided by the application of K-means algorithm.
- Actual dataframe, that is an exact copy of the testing dataframe, but each row is assigned to a label that has been *"*manually*"* created according to the previously specified criterion, which provides information on the specific K-period of the telerehabilitation protocol in which the data point was recorded.

So that, the performance metrics can be computed by comparing these two dataframes. These include:

- Confusion matrix: it is a specific table in which each row represents the instances in an actual class, while each column represents the instances in a predicted class, or vice versa.
- Accuracy: it presents the number of correctly classified data instances over the total number of data instances.

$$Accuracy = \frac{True\ Negative + True\ Positive}{N\ data}$$

- Precision: it measures how many positive predictions are actually true.

$$Precision = \frac{True\ Positive}{True\ Positive + False\ Positive}$$

- Recall (or sensitivity): it is the fraction of relevant instances that have been successfully retrieved.

$$Recall = \frac{True\ Positive}{True\ Positive + False\ Negative}$$

- F1-score: it is a measure of test's accuracy, calculated starting from the precision and recall of the test.

$$F1 - Score = 2 \cdot \frac{Precision \cdot Recall}{Precision + Recall}$$

Basing on the results provided by these indexes, it is possible to prove whether the potential labels provided by K-means could reflect a changing throughout the weeks of the selected features and, thus, a possible improvement in the patients' health condition, determined by the application of the telerehabilitation protocol.

Chapter 6

Results

In this section, the results obtained from the application of the data analysis are presented.

For patient 1:

- The number of acquired samples and weeks for each dataframe (dailies summary, stress summary, and sleeps summary) are explained in Table 8.
- The dailies variables that present statistically significant differences (p-value <0.05) throughout the weeks, according to ANOVA test, are shown in Table 9.
- The significant (p-value <0.05) pair-wise comparisons between couple of weeks for the significant dailies' variables, according to Tukey HSD test, are described in Table 10.
- The stress variables that present statistically significant differences (p-value <0.05) throughout the weeks, according to ANOVA test, are shown in Table 11.
- The significant (p-value <0.05) pair-wise comparison between couple of weeks for the significant stress variables, according to Tukey HSD test, are described in Table 12.
- The summary of the selected features for each dataframe, according to the result provided by ANOVA and Tukey HSD tests, are presented in Table 13.
- The distribution of data points on 2 principal components is represented in Figure 5.
- Figure 6 represents the percentage of explained variance as function of the number of principal components.
- The sum of squared distance between each data point and cluster centers as function of the number of K-means cluster are displayed in Figure 7.
- The distribution of the features labeled with the clusters predicted by K-means algorithm on 2 principal components is illustrated in Figure 8.
- The values of the correlation of each data frame's feature with the groups predicted by K-means algorithm are shown in Figure 9.
- The distribution of actual features on 2 principal components is illustrated in Figure 10.
- Figure 11 shows the distribution of acquired weeks on 2 principal components.
- Table 14 summaries the main performance metrics related to K-means algorithm.
- Table 15 explains the confusion matrix and the accuracy of proposed K-means algorithm.

For patient 2:

- The number of acquired samples and weeks for each dataframe (dailies summary, stress summary, and sleeps summary) are explained in Table 16.
- The dailies variables that present statistically significant differences (p-value <0.05) throughout the weeks, according to ANOVA test, are shown in Table 17.
- The significant (p-value <0.05) pair-wise comparisons between couple of weeks for the significant dailies' variables, according to Tukey HSD test, are described in Table 18.
- The stress variables that present statistically significant differences (p-value <0.05) throughout the weeks, according to ANOVA test, are shown in Table 19.
- The significant (p-value <0.05) pair-wise comparison between couple of weeks for the significant stress variables, according to Tukey HSD test, are described in Table 20.
- The summary of the selected features for each dataframe, according to the result provided by ANOVA and Tukey HSD tests, are presented in Table 21.
- The distribution of data points on 2 principal components is represented in Figure 12.
- Figure 13 represents the percentage of explained variance as function of the number of principal components.
- The sum of squared distance between each data point and cluster centers as function of the number of K-means cluster are displayed in Figure 14.
- The distribution of the features labeled with the clusters predicted by K-means algorithm on 2 principal components is illustrated in Figure 15.
- The values of the correlation of each data frame's feature with the groups predicted by K-means algorithm are shown in Figure 16.
- The distribution of actual features on 2 principal components is illustrated in Figure 17.
- Figure 18 shows the distribution of acquired weeks on 2 principal components.
- Table 22 summaries the main performance metrics related to K-means algorithm.
- Table 23 explains the confusion matrix and the accuracy of proposed K-means algorithm.

For patient 3:

- The number of acquired samples and weeks for each dataframe (dailies summary, stress summary, and sleeps summary) are explained in Table 24.
- The dailies variables that present statistically significant differences (p-value <0.05) throughout the weeks, according to ANOVA test, are shown in Table 25.
- The significant (p-value <0.05) pair-wise comparisons between couple of weeks for the significant dailies' variables, according to Tukey HSD test, are described in Table 26.

- The stress variables that present statistically significant differences (p-value <0.05) throughout the weeks, according to ANOVA test, are shown in Table 27.
- The significant (p-value <0.05) pair-wise comparison between couple of weeks for the significant stress variables, according to Tukey HSD test, are described in Table 28.
- The summary of the selected features for each dataframe, according to the result provided by ANOVA and Tukey HSD tests, are presented in Table 29.
- The distribution of data points on 2 principal components is represented in Figure 19.
- Figure 20 represents the percentage of explained variance as function of the number of principal components.
- The sum of squared distance between each data point and cluster centers as function of the number of K-means cluster are displayed in Figure 21.
- The distribution of the features labeled with the clusters predicted by K-means algorithm on 2 principal components is illustrated in Figure 22.
- The values of the correlation of each data frame's feature with the groups predicted by K-means algorithm are shown in Figure 23.
- The distribution of actual features on 2 principal components is illustrated in Figure 24.
- Figure 25 shows the distribution of acquired weeks on 2 principal components.
- Table 30 summaries the main performance metrics related to K-means algorithm.
- Table 31 explains the confusion matrix and the accuracy of proposed K-means algorithm.

The main clinical parameters measured by medical doctors during T_0, T_3 and T_6 are reported in bar plots. Specifically:

- Figure 26 represents the bar plot related to the assigned UPDRS scores for each patient.
- Figure 27 represents the bar plot related to the assigned NMSS scores for each patient.
- Figure 28 represents the bar plot related to the assigned PDQ-8 scores for each patient.
- Figure 29 show the bar plot related to the state of health of each patient.
- The global walking time measured for each patient is summarized in the bar plot depicted in Figure 30.
- The turning time measured for each patient is summarized in the bar plot depicted in Figure 31.
- The step velocity measured for each patient is summarized in the bar plot depicted in Figure 32.
- The step symmetry evaluated for each patient is summarized in the bar plot depicted in Figure 33.

Chapter 7

Discussion

This dissertation attempts to propose a method that could objectively estimate the effects of a telerehabilitation on the state of health of patients affected by Parkinson's disease, possibly supporting the scale-based clinical assessments carried out by clinicians. Indeed, the newly born RAPIDO project has designed a specific and unique system that could manage, at the same, the continuous telemonitoring of subjects' main health parameters during the entire course of the day, and the delivery of specifically tailored at-home rehabilitation protocols, composed by series of different exercises, which are exemplified by short videos and text descriptions. This peculiar integration between telemonitoring and telerehabilitation reached by RAPIDO allows the latter to stand out from all the other similar systems that have been proposed in literature, which, instead, supply the telemonitoring services independently from the training ones, and vice versa. RAPIDO relies on easy-to-use and easy-to-access devices, meeting the particular needs of PD patients, which, dependently on the syndrome stage, may face some difficulties even when performing simple actions. Moreover, the telemonitoring is carried out without employing any invasive or limiting wearable sensors, but by means of a common smartwatch that is given to the patients during the enrollment examination. Indeed, it is important that subjects, who often have to deal with mental stress, anxiety and depression induced by the disease itself, do not suffer from the pressure of being under continuous observation, but rather feel unconstrained and comfortable as if they are wearing a canonical bracelet or watch, so that they can perform all their daily actions, including the telerehabilitation, as they usually do. This is also crucial to keep the patients motivated, in order to possibly achieve a good adherence to the telerehabilitation protocol which can thus lead to more positive effects on their general health condition and quality of life. Besides, the remote delivery of rehabilitation services proposed by RAPIDO could furnish the access to healthcare to a wider PD-affected population, including especially those that need to travel longer distances to reach the nearest medical center, as well as those that are in more advanced stages and, thus, moving from home could become very arduous. As a consequence, economic sustainability can be promoted with this project, as well as reduction of caregivers' load and the amount of wasted time. The latter is a key factor that can significantly determine the success of any rehabilitation protocol. Indeed, Ellis et al. [108] have demonstrated that the lack of time to exercise is perceived by the PD subjects as one of the major barrier against a constant physical activity routine.

Although the data collected by the smartwatch are only qualitative and descriptive data, that cannot be compared with that one extrapolated with more advanced sensors, they provide a broad variety of information about many aspects of patients' daily routine, including physical activity, resting heart rate, stress condition and sleep behavior, which can be as well useful to gain a summary picture of their medical condition. Definitely, the lack of quantitative variables would make the data analysis more difficult and more subjected to errors, however, it is a necessary trade-off to promote a long-term participation of subjects to this clinical study and sustain the main philosophy underlying the RAPIDO project, according to which by promoting an active lifestyle, it is possible to pursue a slowdown in functional decline, while by improving the health literacy of patients, greater resilience is expected towards functional deficits (freezing, postural instability, dysphagia), as well as an effective prevention against many serious PD complications.

These collected data belong to three main domains: dailies, stress and sleeps. The number of observations in each domain should be the same for a certain patient and should be equal to the duration in days of the telerehabilitation protocol for that specific patient. However, there could be some discrepancies depending on whether the subject has respected the recommended indications of wearing the smartwatch 24 hours/day, 7 days/week for the entire duration of the rehabilitation program.

Currently, this clinical study is on its trial phase, required to understand the major strengths, as well as the main pitfalls of the proposed methodology, thereby refining those aspects that are not perfectly in line with the achievement of the final study purpose. So that, in the near future, the telemonitoring and telerehabilitation protocols proposed by RAPIDO could be extended to a wider population of people affected by PD.

Having regard the small number of available patients, it has been opted for an intra-subject approach for the data analysis. Actually, this particular choice is also motivated by the fact that each of the considered patients was characterized by rather different initial clinical pictures, which have determined the consequent assignment of distinct rehabilitative programs. On the same grounds, the obtained analysis results will be discussed separately for each trial patient.

For each subject, it will be also shown the evolution of their clinical picture during the rehabilitation process, necessary to better understand the results emerged from of the data analysis. Indeed, since an unsupervised clustering algorithm has been applied to actual patient data, it is absolutely important to relate these outcomes to the specific clinical parameters evaluated during the successive medical visits. The latter involve the walking measures extracted from the TUG test (e.g., global walking time, turning time, step velocity and step symmetry), the score values assigned according to UPDRS, NMSS, PDQ-8 and the state of health.

7.1 Patient 1

Patient 1 is a male of 72 years old at the 4th stage of the disease, according to Hoehn and Yahr Scale [109], who thus needs the assistance of a caregiver.

Patient 1 has joined the training protocol proposed by RAPIDO for approximately 6 months and 3 weeks, exceeding the established period of telerehabilitation of about 3 months. Indeed, the patient 1 who was enrolled 01/04/2022, handed back the devices only 12/10/2022, probably due to a lower training frequency than the recommended one.

As can be seen in Table 8, 27 weeks (corresponding to 189 samples) have been recorded for both dailies and stress summaries, while for sleeps summary only 25 (corresponding to 175 samples) weeks are available, suggesting that the patient 1 did not wear the smartwatch on every night of the 6-months period of telerehabilitation.

As can be deduced from Table 9, 13 out of 21 dailies variables show statistically significant (p-values < 0.05) differences among the weeks, according to ANOVA test. In particular, these results suggest that wrist-based heart rate characteristics, as well as stress and some physical activity aspects, may have experienced some changes during the course of at-home rehabilitation program.

Nonetheless, a wider and more complete comprehension of these variations are provided by the Tukey HSD test. Specifically, according to Table 10, it can be at first noticed that only 9 features out of 13, that were identified by ANOVA, effectively exhibit statistically significant differences among weeks. Indeed, for the variables named "*steps*", "*distanceInMeters*", "*activeTime*", "*minHeartRate*", "*HR_std*", the chosen multicomparison test has demonstrated that any changes that was depicted by ANOVA test can be in fact explained only due to chances. Furthermore, by specifically analyzing the first two columns of the Table 10, it is possible to highlight that for these 9 features not all pairwise comparisons show statistically significant differences, making it difficult to find a certain trend that could reflect a temporal evolution during the telerehabilitation period of the analyzed dailies variables. This deduction may be supported by the mean difference values, reported in the third column of the Table 10, that do not vary importantly, or even remain unvaried, for several pairwise comparisons. Besides, the confidence intervals for each of the considered variables are quite wide for the vast majority of the couples of weeks juxtaposed by Tukey HSD test, indicating that the estimations may be characterized by not too high accuracies. Nonetheless, the combination of ANOVA and Tukey HSD test has allowed to identify those dailies features that do not significantly vary statistically as the weeks of telerehabilitation passed, which are, thus, disregarded in the following steps of the analysis.

Repeating the same statistical analysis on stress variables, it is possible to notice that, according to ANOVA, only 5 out 10 stress features show statistically significant differences among weeks (Table 11), but then the "*std_BodyBatteryValues*" is excluded by the Tukey HSD test. Even in this case,

Table 12 suggests that analogous considerations to that of dailies features can be as well deduced for the stress ones, meaning that the results provided by both ANOVA and Tukey HSD cannot be easily related to a certain time tendency, reflecting a change in the health condition of the patient 1 during the course of the telerehabilitation.

Finally, ANOVA test on sleeps dataframe has revealed that any of the 5 features show statistically significant differences as the at-home rehabilitation proceeded, which can be determined by the lower number of samples and variables that are available for this specific table.

It is worth to remark that, in this specific study, ANOVA and Tukey HSD tests are performed as easy-to-implement and reliable investigative procedures, useful to understand whether there are statistically significant changes on the features values throughout the protocol's weeks, that can be further deepen whit other kinds of techniques. Therefore, although the just discussed results provided by Tukey HSD test seems to be quite instable, the latter can be considered as sufficiently valid and reliable to motivate the attempt to proceed with a clustering technique, considering only those features that have shown statistically significant differences among the weeks, in order to possibly demonstrate a progression in the state of health of the patient 1.

Thus, the selected features, reported in Table 13, have been joined in a unique dataframe to be tested in the clustering algorithm.

The PCA applied to the test dataframe has confirmed that the data points seem to distribute in different groups. Indeed, as can be seen graphically in the Figure 5, which depicts all the data points redistributed in two PCs, it is possible to recognize some separated clusters of samples. For this patient, two PCs are able to explain about the 55% of the total variance of analyzed dataframe, as can be deduced from Figure 6. Although a greater number of PCs would have allowed to describe a higher percentage of variance, choosing two PCs looks reasonable for this specific purpose. Indeed, in this case, the PCA is not implemented with the primary objective to obtain an effective dimensionality reduction of the initial dataframe, which would have requested a higher explained variance; rather, it is used as explicative procedure though which it is possible to graphically and easily discern the possible presence or absence of groups of data.

Therefore, the results obtained from PCA has encouraged to proceed with the execution of K-mean algorithm to divide the features' samples in distinct groups, whose number has been selected according to an acceptable trade-off between the technical aspects, provided by the elbow method, and the necessity to demonstrate an evolution in time of the variables' values. In particular, as depicted by Figure 7, the optimal number of clusters should be two, nonetheless, choosing a K=3 seems more convenient to obtain a better representation of eventual changes in time of the selected variables, while achieving acceptable values of the sum squared distance. Based on that, it has been opted for a division of the data points in three separated groups.

In order to make more understandable the results provided by the K-means, the samples, labeled with the corresponding cluster assigned by the algorithm, have been plotted on two PCs, as can be seen in Figure 8. It appears that the clustering method has arranged the data in three well-distinguished groups, significantly correlated especially with those features carrying information about the stress condition of the patient 1 (Figure 9). However, due to the unsupervised nature of the algorithm, it is not possible to a-priori know the exact meaning of the assigned labels. That is why the K-means has been run with the so-called *actual dataframe*, in which each row is associated to a label equal to an integer number representing the acquisition week of belonging. On the contrary, in this case there is not a delineated separation between the different labels, as demonstrated by the Figure 10, in which the labeled data points seem to be randomly distributed on the PCs space. In fact, this trend is confirmed by the Figure 11 that shows the distribution of the samples colored on the basis of the acquisition week of belonging. These results suggest that the clustering algorithm has assembled the data points according to other kinds of similarities that fall outside the specific purpose of this study. Even the performance metrics (Table 14) and the confusion matrix (Table 15), constructed on the basis of the comparison between the *testing dataframe* and *actual dataframe*, confirms that the K-means might not been able to catch any changes of the selected features during the at-home rehabilitation protocol.

In order to better understand the obtained outcomes, it is important to also analyze the clinical picture of the patient. Specifically, as mentioned before, this subject has a 4^{th} stage PD. In these advanced stages of the syndrome, although the disease itself is quite stable, the motor and nonmotor clinical conditions of those affected tend to strongly fluctuate in time due to the irregular functioning of pharmacological therapy; this means that it is possible to detect significant medical changes among different months or even days. Partly, this could explain the random distribution of the labeled samples in the PCs space, highlighted previously. Nonetheless, by precisely analyzing the UPRDS score assigned by the medical doctors, it can be noticed that UPDRS outcomes, reported in Figure 26, have not changed during the 6-months period, proving that, thanks to the proposed training protocol, a certain stability in the clinical status of the subject has been achieved, despite the degenerative nature of the PD. This conclusion is as well sustained by the clinical measures of the walking parameters that have not substantially deviated after 6 months. Specifically, the global walking time (Figure 30) and the turning time (Figure 31) have practically remained unchanged; the step velocity (Figure 32) has even slightly improved, contrary to the step symmetry (Figure 33), which, instead, has been subjected to small worsening at 3 months, reaching back the starting values at 6 months. Accordingly, the patient state of health (Figure 29), despite a slight worsening at 3 and 6 months, has not dramatically changed in the course of the overall period of at-home rehabilitation, as well as the score assigned by PDQ-8 (Figure 28) and by NMSS (Figure 27). In particular, the latter scale has recorded a small improvement in the nonmotor symptoms both at 3 and 6 months.

7.2 Patient 2

Patient 2 is a male of 63 years old at the 1st stage of the disease, according to Hoehn and Yahr Scale [109], who thus is still physically active and fully independent.

Patient 2 has joined the training protocol proposed by RAPIDO for approximately 9 months, exceeding the established period of telerehabilitation of about 6 months. Indeed, the patient 2 who was enrolled 08/04/2022, handed back the devices only 24/01/2023, probably due to a lower training frequency than the recommended one.

As can be seen in Table 16, 36 weeks (corresponding to 252 samples) have been recorded for both dailies and stress summaries, while for sleeps summary only 9 (corresponding to 63 samples) weeks are available, suggesting that the patient 2 did not wear the smartwatch on every night of the 9-months period of telerehabilitation.

As can be deduced from Table 17, 17 out of 21 dailies variables show statistically significant (p-values < 0.05) differences among the weeks, according to ANOVA test. In particular, these results suggest the activity parameters, together with wrist-based heart rate and stress characteristics, may have experienced some changes during the course of at-home rehabilitation program. Nonetheless, a wider and more complete comprehension of these variations are provided by the Tukey HSD test.

Specifically, according to Table 18, it can be at first noticed that 14 features out of 17, that were identified by ANOVA, effectively exhibit statistically significant differences among weeks. Indeed, for "*floorClimbed*", "*maxStressLevel*", "*HR_std*" the multicomparison test has demonstrated that any changes that was depicted by ANOVA test can be in fact explained only due to chances. Analogously to the case of patient 1, it is difficult to find a certain trend that could reflect a temporal evolution during the telerehabilitation period of the analyzed dailies variables, according to the mean difference values and the 95% confidence intervals provided by Tukey test HSD, as shown in Table 18. Nonetheless, the combination of ANOVA and Tukey HSD test has allowed to identify those dailies features that do not vary statistically as the weeks of telerehabilitation passed, which are thus disregarded in the following steps of the analysis.

Repeating the same statistical analysis on stress variables, it is possible to notice that, according to ANOVA, only 8 out 10 (Table 19) stress features show statistically significant differences among weeks, but then the "*min_StressLevelValues*", "*mean_StressLevelValues*" are excluded by the Tukey HSD test (Table 20). Even in this case, Table 20 suggests that analogous considerations to that of dailies features can be as well deduced for the stress ones, meaning that the results provided by both

ANOVA and Tukey HSD cannot be easily related to a certain time tendency, reflecting a change in the health condition of the patients during the course of the telerehabilitation.

Finally, ANOVA test on sleeps dataframe has revealed that any of the 5 features show statistically significant differences as the at-home rehabilitation proceeded, which can be determined by the significant the lower number of samples and variables that are available for this specific table.

At this point, the selected features, reported in Table 21, have been joined in a unique dataframe to be tested in the clustering algorithm.

Even in this case, the PCA applied to the test dataframe has confirmed that the data points seem to distribute in different groups. Indeed, as can be seen graphically in the Figure 12, which depicts all the data points redistributed in two PCs, it is possible to recognize some separated clusters of samples. For this patient, the percentage of variance explained by two PCs is slight lower than the one obtained for the patient 1 (Figure 13), nonetheless, such number of PCs is suitable for allowing an immediate visualization of the data points distribution.

Therefore, the results obtained from PCA has encouraged to proceed with the execution of K-mean algorithm to divide the features' samples in three distinct groups, even though, also in this case, the optimal number of clusters should be two, on the basis of the sum of squared distances provided by the elbow method (Figure 14). However, it seemed more convenient to follow the same trade-off made for patient 1, obtaining more comparable outcomes.

In order to make more understandable the results provided by the K-means, the samples, labeled with the corresponding cluster assigned by the algorithm, have been plotted on two PCs, as can be seen in Figure 15. It appears that the clustering method has arranged the data in three well-distinguished groups, significantly correlated especially with those features providing information about the daily activities, as well as wrist-based heart rate (Figure 16). In order to understand the possible meaning of the different clusters, the K-means is run with the *actual dataframe*, confirming the trend emerged for the patient 1. Indeed, there is not a delineated separation between the different labels, as demonstrated by the Figure 17, in which the labeled data points seem to be randomly distributed on the PCs space. In fact, this tendency is confirmed by the Figure 18 that shows the distribution of the samples colored on the basis of the acquisition week of belonging. These results suggest that the clustering algorithm has assembled the data points according to other kinds of similarities that fall outside the specific purpose of this study. Even the performance metrics (Table 22) and the confusion matrix (Table 23), constructed on the basis of the comparison between the *testing dataframe* and *actual dataframe*, confirms that the K-means might not been able to catch any changes of the selected features during the at-home rehabilitation protocol.

Certainly, to achieve a complete interpretation of the obtained outcomes, the latter need to be also evaluated in function of the evolution of the patient clinical picture during the at-home rehabilitation period. First of all, it is important to remind that this specific patient is at the 1st stage of the syndrome

in which the motor and nonmotor manifestations are still trivial, without compromising the performance of normal daily actions. Indeed, this patient, even before joining the project, was fully active and completely autonomous. However, contrary to what it may be though, the first stages of the PD are the most evolutive ones, meaning that it is in this particular phase that the more significant deteriorations can be appreciated. That is mainly because a suitable combination of drugs has not been found yet, therefore the patient medical condition could be more unstable. Effectively, by looking at the UPDRS score (Figure 26), the latter has slightly worsened at 3 months, just like to the step velocity (Figure 32) and step symmetry (Figure 33). However, all these measures have improved significantly at 6 months; specifically, the UPDRS score has risen back to the initial value, while the walking velocity and step symmetry have even surpassed the starting points. Conversely, the other two walking parameters, e.g., global walking time (Figure 30) and turning time (Figure 31), have firstly got better at 3 months, and then they have come back to the initial conditions, although these changes are quite trivial. On the whole, it can be said that the patient 2 has remained reasonably stable, despite the degenerative nature of the PD, which especially characterize the first stages of the syndrome itself. This general trend can be confirmed by the values assigned for the health status (Figure 29), the PDQ-8 (Figure 28), as well as the NMSS (Figure 27), which have almost remained unvaried in each of the three medical visits.

On the basis of the just discussed consideration about the clinical picture of the patient 2, the inability of K-means algorithm to create distinct clusters of data reflecting a possible change in time of the selected features could be explained by the fact that effectively the patient medical condition has not substantially changed during the protocol, but rather, thanks to the contribution given by the constant telerehabilitation, it has been possible to achieve a stabilization of the disease, avoiding significant worsening.

7.3 Patient 3

Patient 3 is a male of 68 years old at the 3rd stage of the disease, according to Hoehn and Yahr Scale [109], who, despite the advanced phase of the syndrome, is active and independent.

Patient 3 has joined the training protocol proposed by RAPIDO for approximately 6 months, exceeding the established period of telerehabilitation of about 3 months. Indeed, the patient 3 who was enrolled 08/04/2022, handed back the devices only 13/10/2023, probably due to a lower training frequency than the recommended one.

As can be seen in Table 24, 12 weeks (corresponding to 252 samples) have been recorded for both dailies and stress summaries, while for sleeps summary only 8 (corresponding to 63 samples) weeks

are available, suggesting that the patient 2 did not wear the smartwatch on every night of the 6 months-period of telerehabilitation.

As can be deduced from Table 25, 9 out of 21 dailies variables show statistically significant (p-values < 0.05) differences among the weeks, according to ANOVA test. In particular, these results suggest that wrist-based heart rate and stress characteristics may have experienced some changes during the course of at-home rehabilitation program. Nonetheless, a wider and more complete comprehension of these variations are provided by the Tukey HSD test.

Specifically, differently from the previous two patients, all the 9 features identified by ANOVA effectively exhibit statistically significant differences among weeks, as shown in Table 26, even though in very few pairwise comparisons. Besides, according to the previous cases, the values of the mean difference do not vary importantly, as well as the confidence intervals are still quite wide for the vast majority of the couples of weeks juxtaposed by Tukey HSD test, indicating that the estimations may be characterized by not too high accuracies.

Nonetheless, the combination of ANOVA and Tukey HSD test has allowed to identify those dailies features that do not significantly vary statistically as the weeks of telerehabilitation passed, which are thus disregarded in the following steps of the analysis.

Repeating the same statistical analysis on stress variables, it is possible to notice that, according to ANOVA, only 7 out 10 (Table 27) stress features show statistically significant differences among weeks, but then the "*mean_StressLevelValues*" is excluded by the Tukey HSD test (Table 28). Even in this case, Table 28 suggests that analogous considerations to that of dailies features can be as well deduced for the stress ones, meaning that the results provided by both ANOVA and Tukey HSD cannot be easily related to a certain time tendency, reflecting a change in the health condition of the patients during the course of the telerehabilitation.

Finally, ANOVA test on sleeps dataframe has revealed that any of the 5 features show statistically significant differences as the at-home rehabilitation proceeded, which can be determined by the lower number of samples and variables that are available for this specific table.

Thus, the selected features, reported in Table 29, have been joined in a unique dataframe to be tested in the clustering algorithm.

The PCA applied to the test dataframe has confirmed that the data points seem to distribute in different groups. Indeed, as can be seen graphically in the Figure 19, which depicts all the data points redistributed in two PCs, it is possible to recognize some separated clusters of samples. For this patient, two PCs are able to explain about the 65% of the total variance of analyzed dataframe (Figure 20), which is certainly an acceptable value, especially considering that, in this specific case, the PCA is implemented with the primary objective to obtain an immediate and explicative representation through which easily discern the possible presence or absence of groups of data.

Therefore, the results obtained from PCA has encouraged to proceed with the execution of K-mean algorithm to divide the features' samples in three distinct groups, even though, also in this case, the optimal number of clusters should be two, on the basis of the sum of squared distances provided by the elbow method (Figure 21). However, it seemed more convenient to follow the same trade-off made for patient 1 and 2, obtaining more comparable outcomes. In order to make more understandable the results provided by the K-means, the samples, labeled with the corresponding cluster assigned by the algorithm, have been plotted on two PCs, as can be seen in Figure 22. It appears that the clustering method has arranged the data in three well-distinguished groups, significantly correlated especially with those features providing information about the stress characteristics (Figure 23). By comparing these outcomes with those reported in Figure 24, the trends emerged for both patient 1 and 2 seems to be confirmed; indeed, there is not a delineated separation between the different labels, which appears to be randomly distributed on the PCs space. In fact, the Figure 25, that shows the distribution of the samples colored on the basis of the acquisition week of belonging, sustains this tendency. These results suggest that the clustering algorithm has assembled the data points according to other kinds of similarities that fall outside the specific purpose of this study. Even the performance metrics (Table 30) and the confusion matrix (Table 31), constructed on the basis of the comparison between the *testing dataframe* and *actual dataframe*, validates that the K-means might not been able to catch any changes of the selected features during the at-home rehabilitation protocol.

By specifically looking at the clinical picture of patient 3, he is in the 3rd stage of PD, which is quite advanced phase that, however, do not imply severe impediments; indeed, the subject is still independent and able to move without significant symptomatic side effects. Nonetheless, due to the quite advanced stage of the disease, more fluctuations on the motor and nonmotor conditions are expected. Effectively, UPDRS and NMSS scales, reported in Figure 26 and Figure 27 respectively, highlight strong worsens after 3 months which are then fully recovered at 6 months. Actually, these deteriorations are determined by the fact that the patient, in the first period of telerehabilitation protocol, has experienced for the first-time hallucinations, which is a negative experience that leave a deep mark in the subject emotional status and that requires the assignment of a new compensatory pharmacological therapy. Nonetheless, the clinical outcomes clearly show that the patient 3 has been able to fully recover, finally reaching score values that are absolutely comparable with the starting one, demonstrating the effectiveness of the synergic combination of both drugs and rehabilitation. Probably, these significant variations might have negatively influenced the accuracy reached by the K-means algorithm in discriminating a possible evolution in time of the selected features, whose data points tend, instead, to randomly distribute across the considered time period. On the whole, it can be concluded that the patient 3 has remained quite stable from the clinical point of view. In fact, all the walking parameters sustain this point of view; specifically, the global walking time (Figure 30), the turning time (Figure 31) and step velocity (Figure 32) can be considered stationary in the 6-months

period, while the step symmetry (Figure 33) has even observed an improvement at 6 months. The state of health results (Figure 29) and the PDQ-8 scores (Figure 28) keep showing that patient 3, despite the hallucination event at 3 months, has not undergone to significant worsening.

7.4 Summary considerations

The patients who took part in this clinical trial started from completely different clinical conditions that cannot be put on the same level. Indeed, each stage of PD has its own peculiar characteristics that can even change from subject to subject depending on several factors, such as, age, lifestyle and presence of comorbidities. In general, all three patients already had a fairly high level of independent physical activity before the beginning of the telerehabilitation protocol, which has been maintained until the end of the trial, as shown by the evaluated clinical parameters. This fact already fulfils an important objective set by a telerehabilitation for people suffering from PD, that is to keep patients as active as possible and, thus, educating them on the importance of continuous exercise to counteract the motor and non-motor symptoms induced by the disease. Furthermore, it is important to stress out that the telerehabilitation proposed for this specific study is not an intensive rehabilitation, which is usually prescribed in case of more acute events such as falls or pneumonia, but rather it is a maintenance rehabilitation aiming at maintaining the patients' state of health as stable as possible.

The clinical evaluations provided by medical doctors show that this objective has been fully achieved, since the measured parameters have not undergone to significant changes during the 6-month trial. Even the results of the implemented analysis seem to support this trend for all three patients, despite starting from completely different disease stages. Therefore, at the moment, these results are very encouraging precisely because, due to the strong degenerative nature of PD, one could have expected a deterioration in the patients' health status. On the contrary, the fact that their condition has been kept stable gives important hopes that a maintenance rehabilitation, like the one proposed in this clinical study, in combination with proper pharmacological therapy, can slow down, or at least hinder, the progress of PD.

Chapter 8

Conclusion

In recent years, several studies have pointed out that constant physical activity can mitigate the main motor and nonmotor symptoms induced by PD. In fact, exercise is not only an important protective factor against the syndrome, but it also represents an effective, side-effect-free therapy that can slow the progression of the disease. Thanks to the increasingly widespread use of technology, several solutions, based on the employment of wearable sensors, have been designed for patients with PD, providing fundamental contributions to early disease diagnosis, assessment of its severity and its main symptoms, but also to the achievement of continuous monitoring and rehabilitation purposes. In the latter context, the project described in this dissertation also takes part, which proposes an integrated telemonitoring and telerehabilitation system specifically dedicated to PD patients, relying on user-friendly devices. In particular, a tablet allows the access to the rehabilitative protocols, while a smartwatch continuously collects patient-related data, through which it is possible to continuously monitor the most important health parameters, possibly adjusting the training program and avoiding undesired complications.

This thesis attempts to define a method to analyze data collected from the smartwatch onboard sensors to assess whether the proposed telerehabilitation protocol has induced some changes in the state of health of enrolled PD patients, possibly supporting the scale-based clinical evaluations effectuated by medical doctors. In particular, this analysis involves, firstly the selection of most relevant data based on the statistically significant differences identified by ANOVA and Tukey HSD tests and, secondly, data clustering based on K-means algorithm in order to possibly recognize changes of the selected variables, which could reflect potential improvements in the patients' state of health induced by the at-home rehabilitation program.

The obtained results suggest that the proposed method was not able to depict any variation in time of the processed data. Although the interpretation of the outcome provided by an unsupervised algorithm could be challenging, it can be deduced that the obtained results actually comply with the patients' clinical picture. Indeed, even though each patient started with a different disease stage, their overall state of health has not worsened or improved, but rather has remained stable, suggesting that the synergic combination between an effective pharmacological treatment and at-home rehabilitation could slow down the progression of the PD. Even though the main dissertation aim seems to be unfulfilled, these results are instead promising, especially considering the strong degenerative nature

that characterizes the syndrome. Certainly, the proposed method should be further tested with a wider population of PD subjects in order to verify the actual reliability and repeatability of the involved algorithm and techniques.

In conclusion, although the proposed project is still in the testing phase, the obtained results bring hope to the possibility of making available to PD patients an easy-to-access and economically sustainable therapy that can maintain the subjects sufficiently trained, possibly slowing down the course of the disease.

Figures

Figure 1 | Key molecular mechanisms that are widely accepted to contribute to the neurodegenerative process in dopaminergic neurons in the substantia nigra in Parkinson's disease. Blue double-headed arrows indicate molecular mechanisms that may not only be toxic in their own right but importantly may also influence other molecular mechanisms known to be features in Parkinson disease. Double helix structures identify some of the common gene mutations found in familial PD and brown arrows indicate where the altered protein may interfere with cell function and overlap with known mechanisms of cell death in sporadic Parkinson disease. ROS stands for reactive oxygen species.

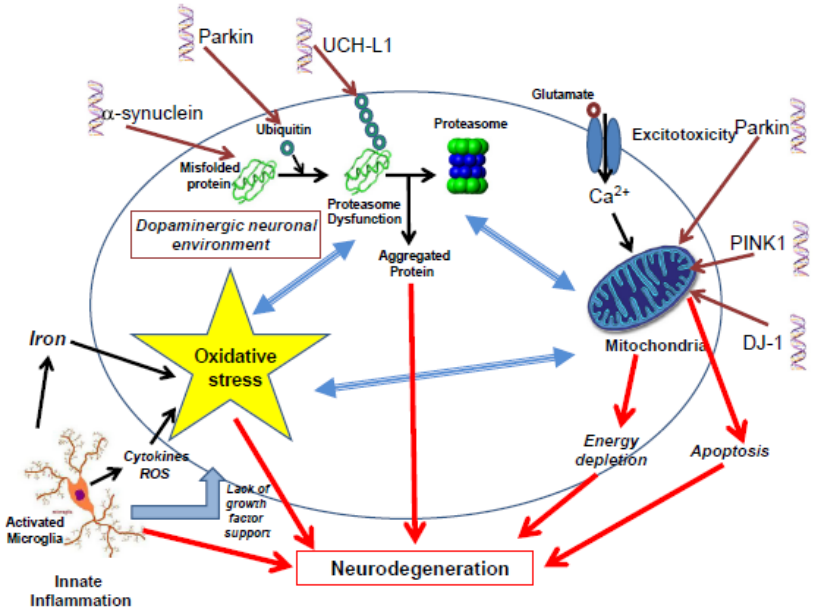


Figure 2 | Time courses of the onset of the motor and non-motor features of Parkinson disease.

a) A schematic representation of the potential timeline by which the non-motor features of Parkinson disease (PD) may manifest.

b) This part is a graphic depiction of the rates of development and progression of the motor and non-motor features of PD, and the decline in dopaminergic neuronal function.

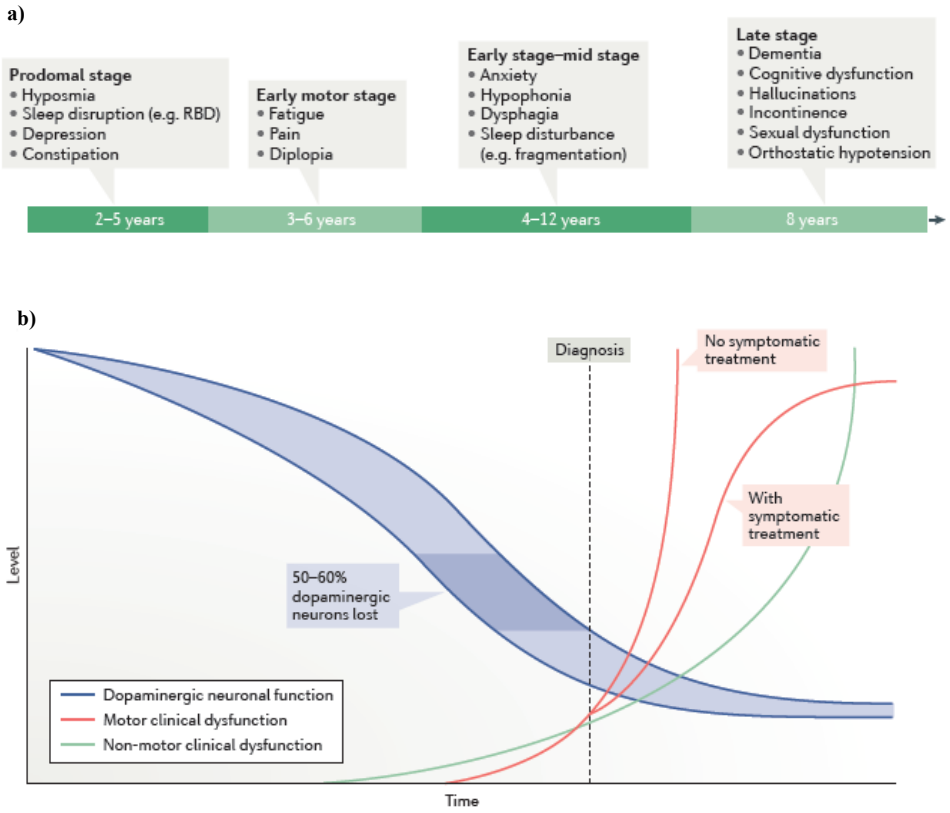


Figure 3 | Schematic representation of the general architecture of RAPIDO telerehabilitation and telemonitoring systems

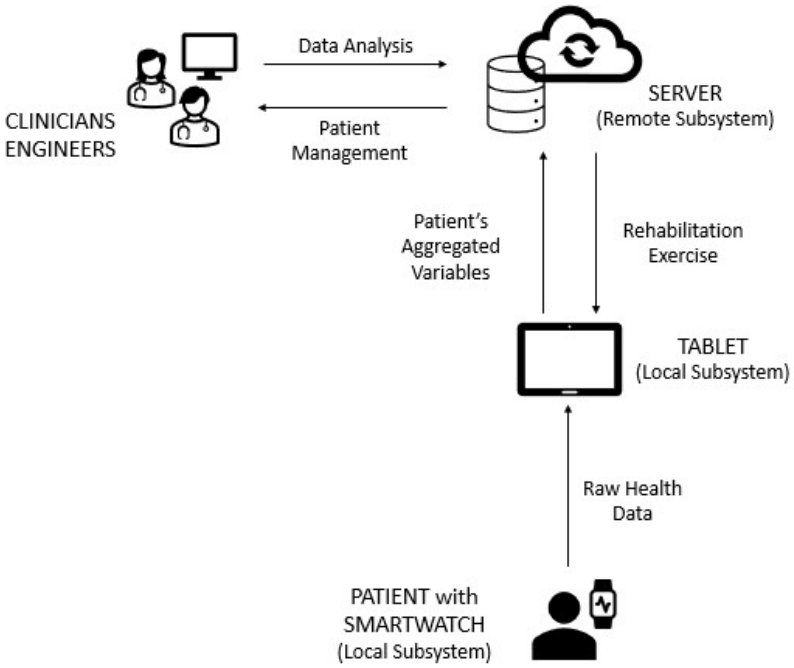


Figure 4 | The geometric steps for finding the components of a principal component analysis.

a) To find the components center the variables then plot them against each other.

b) Find the main direction (called the first component) of the cloud of points such that we have the minimum of the sum of the squared distances from the points to the component. Add a second component orthogonal to the first such that the sum of the squared distances is minimum.

c) When the components have been found, rotate the figure in order to position the first component horizontally (and the second component vertically), then erase the original axes.

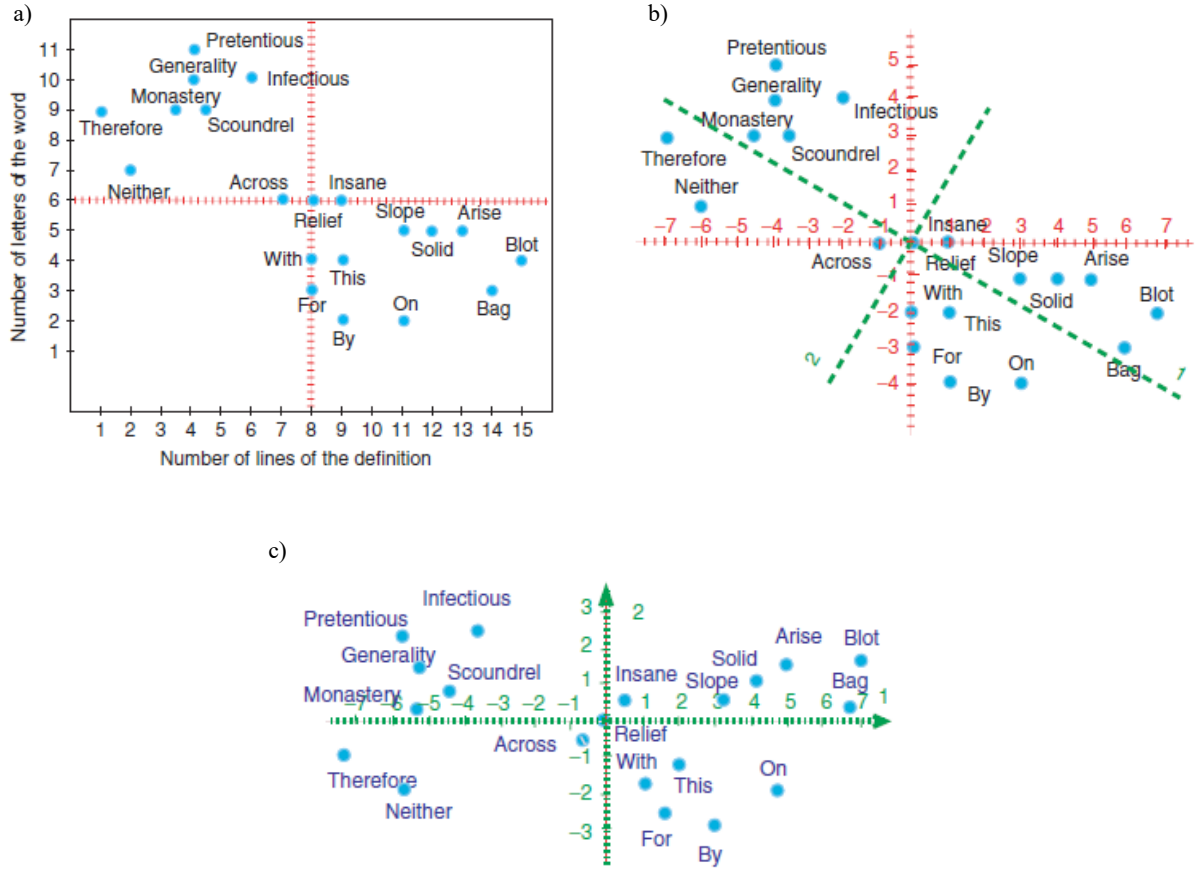


Figure 5 | Distribution of the patient 1 data point on 2 Principal Components.

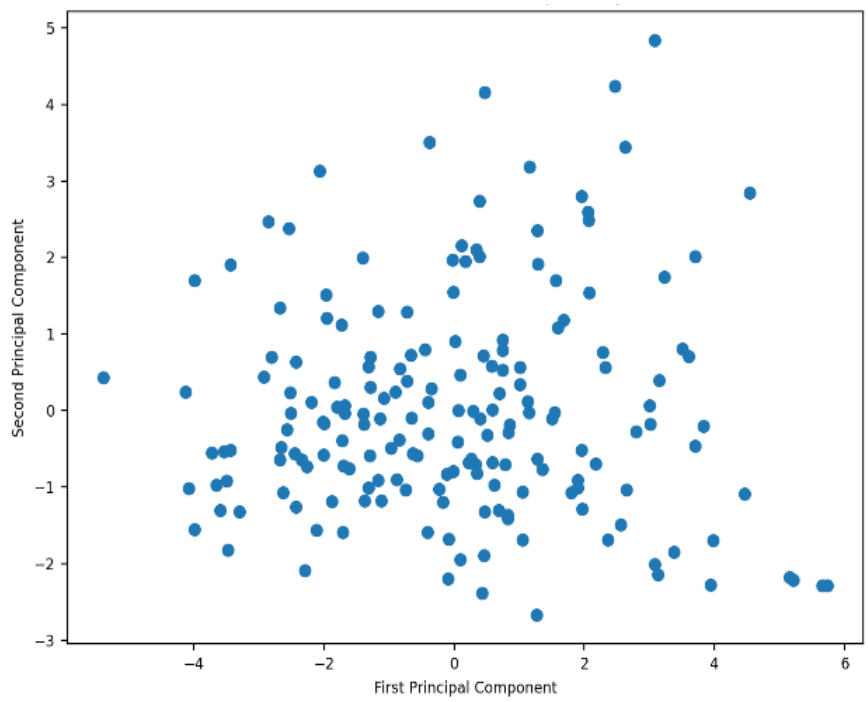


Figure 6 | Percentage of the explained variance as a function of the number of Principal Components, obtained by applying iteratively the Principal Component Analysis to patient 1 selected data.

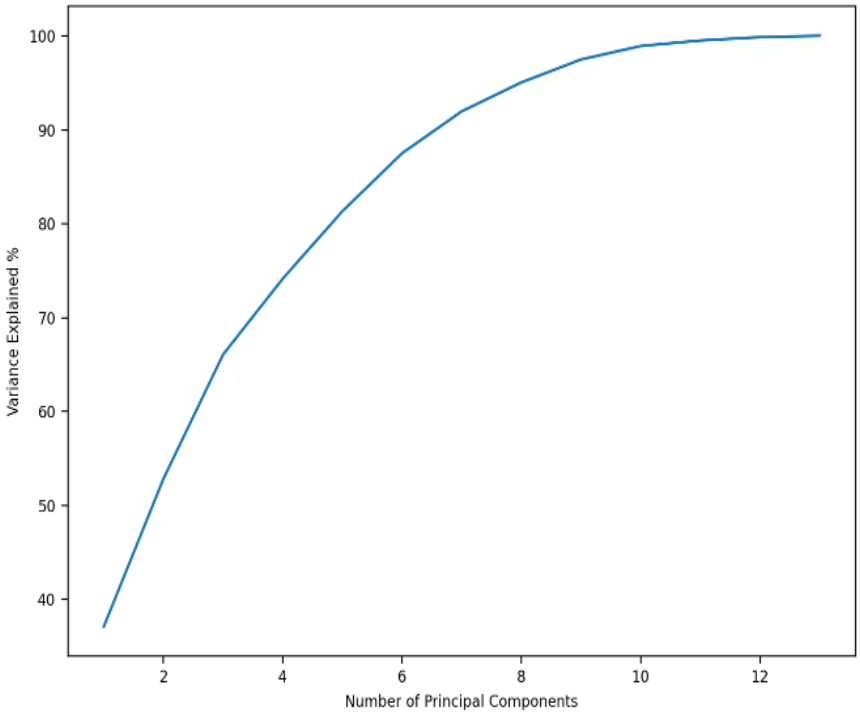


Figure 7 | Sum of squared distances expressed as a function of the number of clusters (K) obtained applying iteratively the K-means algorithm with patient 1 data.

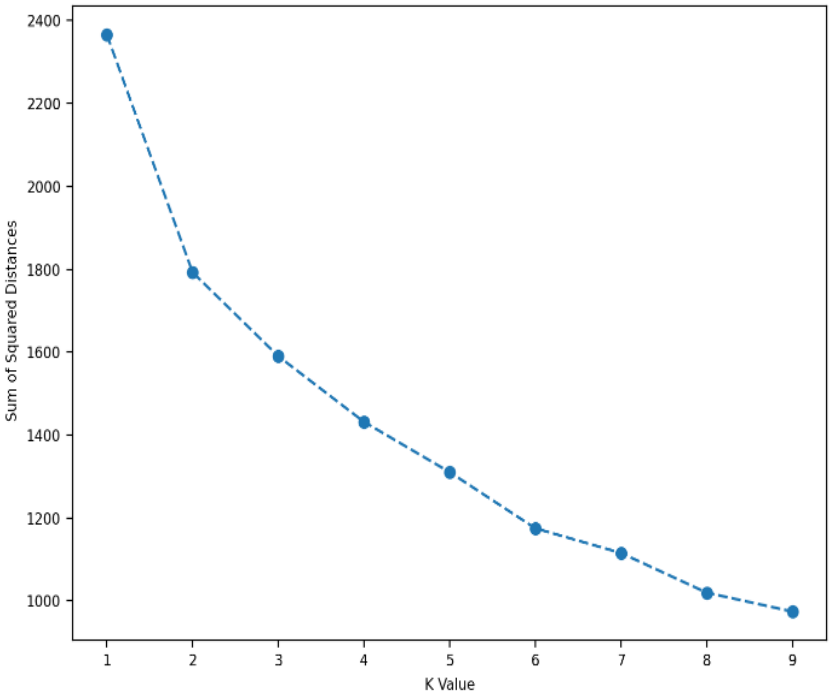


Figure 8 | Distribution of patient 1 data points on 2 Principal Components, colored according to the cluster of belonging predicted by K-means algorithm.

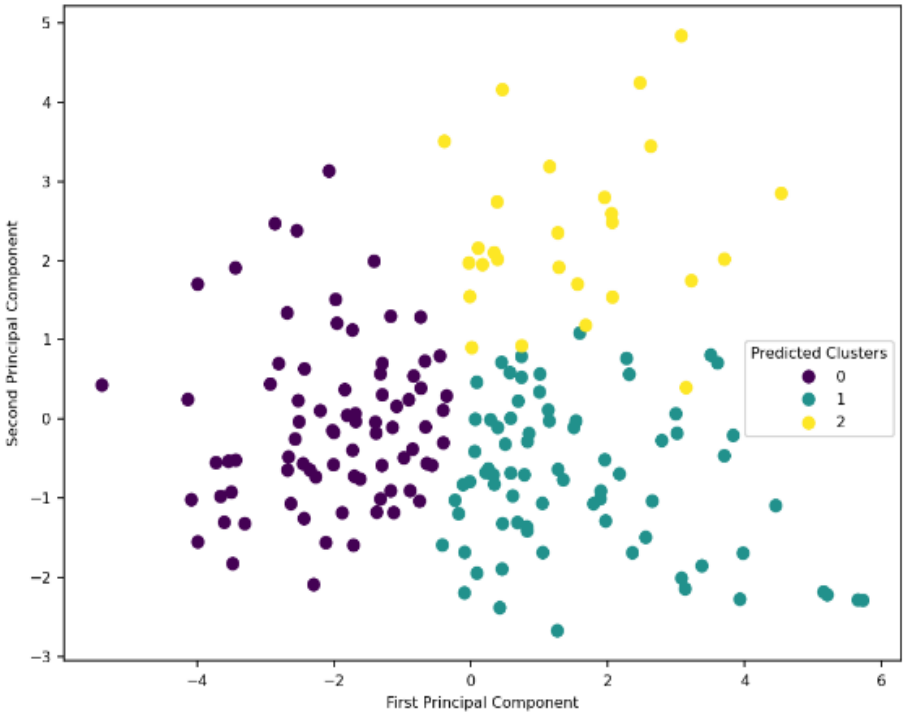


Figure 9 | Values of the correlation of each dataframe feature with the groups predicted by K-means algorithm, applied on patient 1 data.

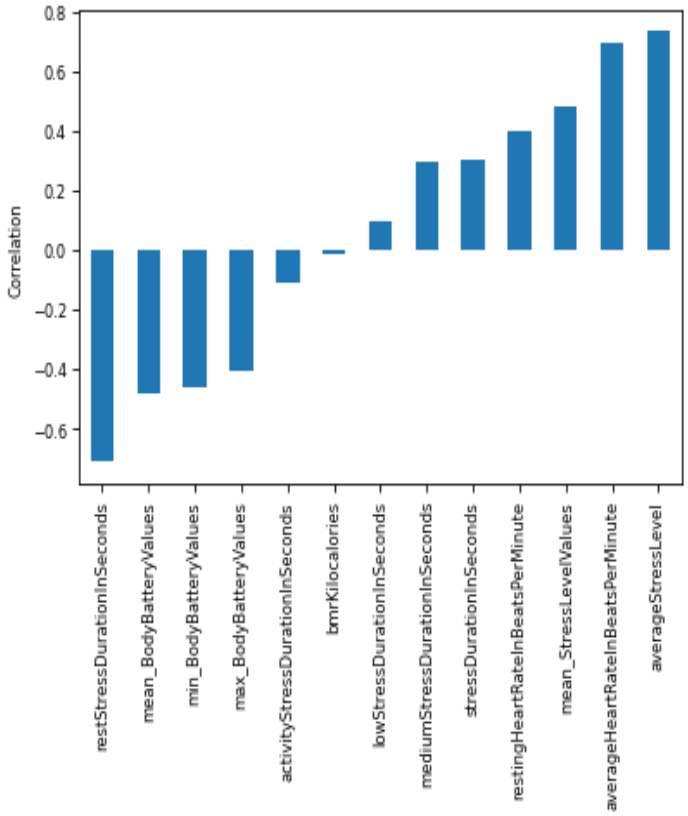


Figure 10 | Distribution of patient 1 data points on 2 Principal Components, colored according to the labels assigned to each row of the "Actual dataframe".

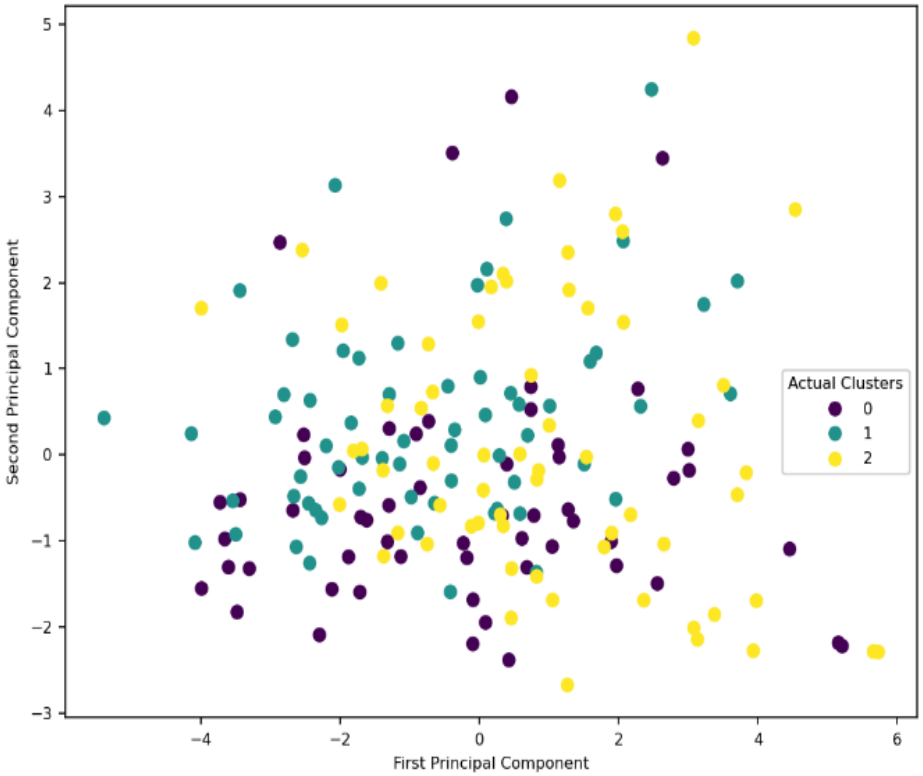


Figure 11 | Distribution of patient 1 selected data points on two Principal Components, colored dependently on the acquisition week of belonging.

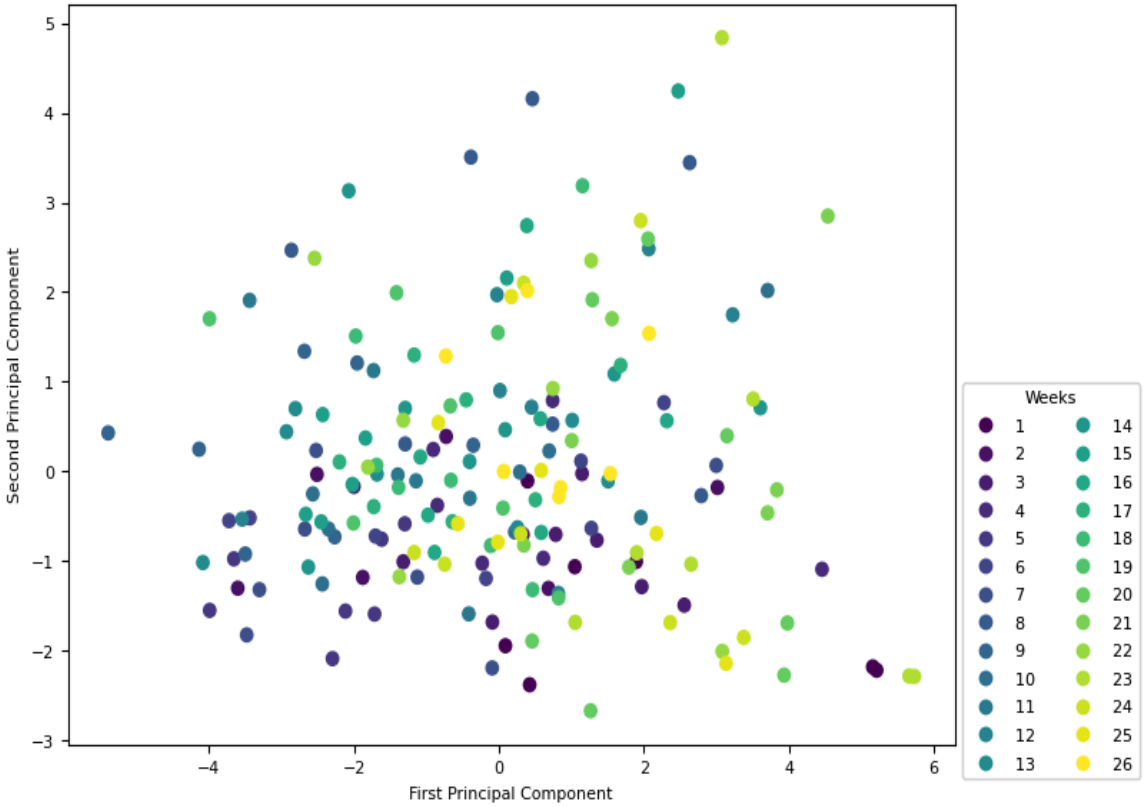


Figure 12 | Distribution of the patient 2 data point on 2 Principal Components

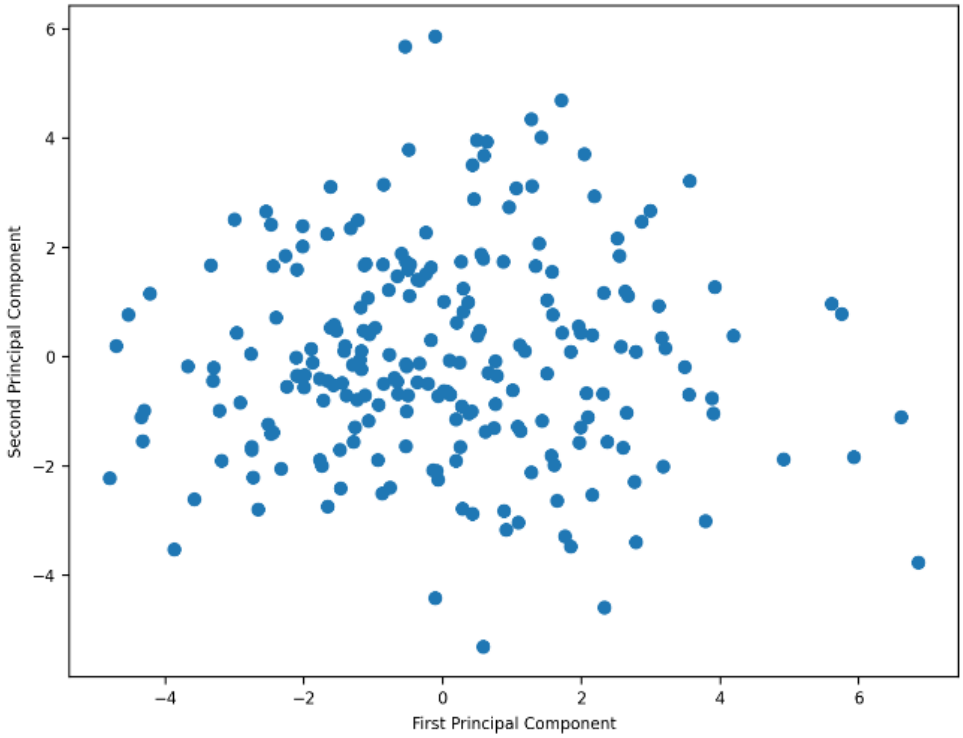


Figure 13 | Percentage of the explained variance as a function of the number of Principal Components, obtained by applying iteratively the Principal Component Analysis to patient 2 selected data.

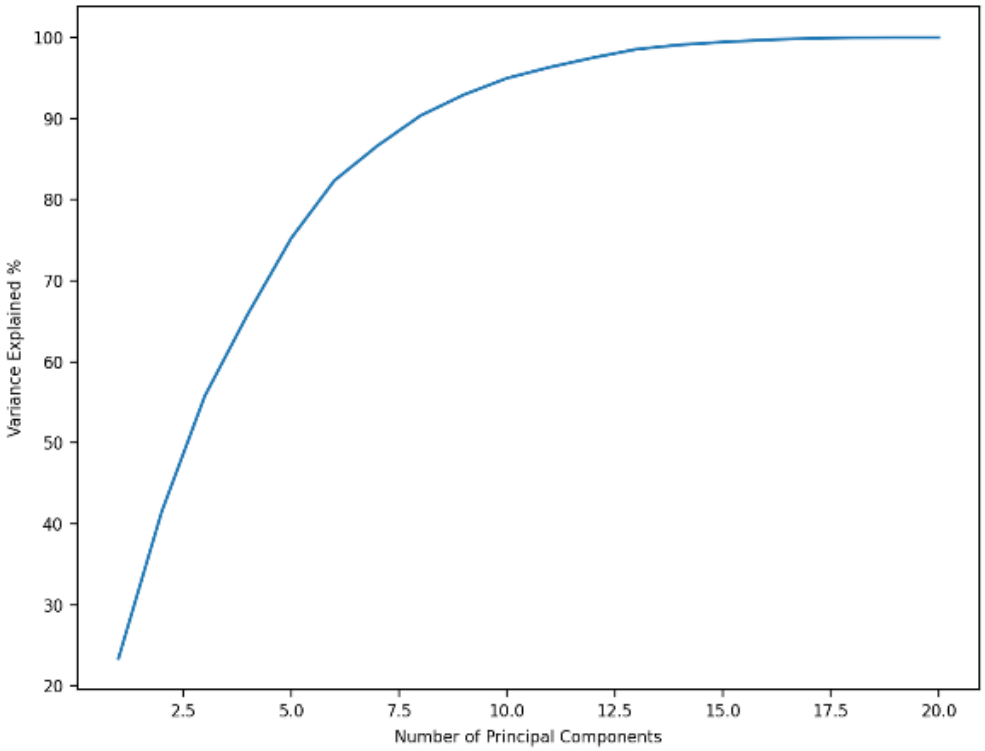


Figure 14 | Sum of squared distances expressed as a function of the number of clusters (K) obtained applying iteratively the K-means algorithm with patient 2 data.

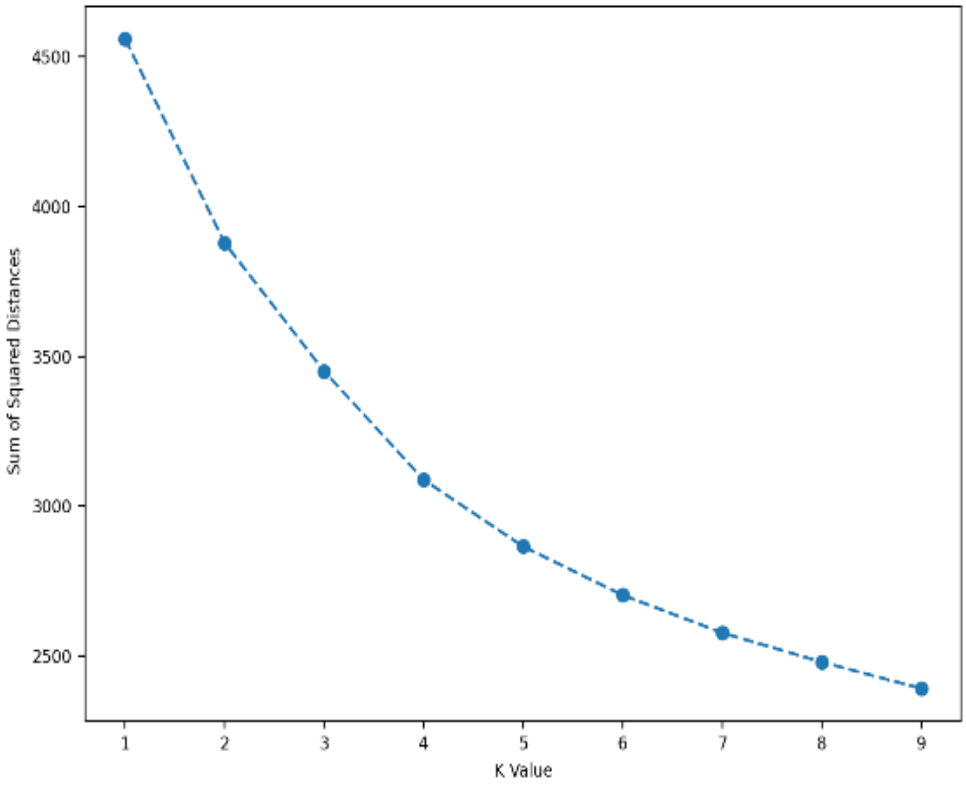


Figure 15 | Distribution of patient 2 data points on 2 Principal Components, colored according to the cluster of belonging predicted by K-means algorithm.

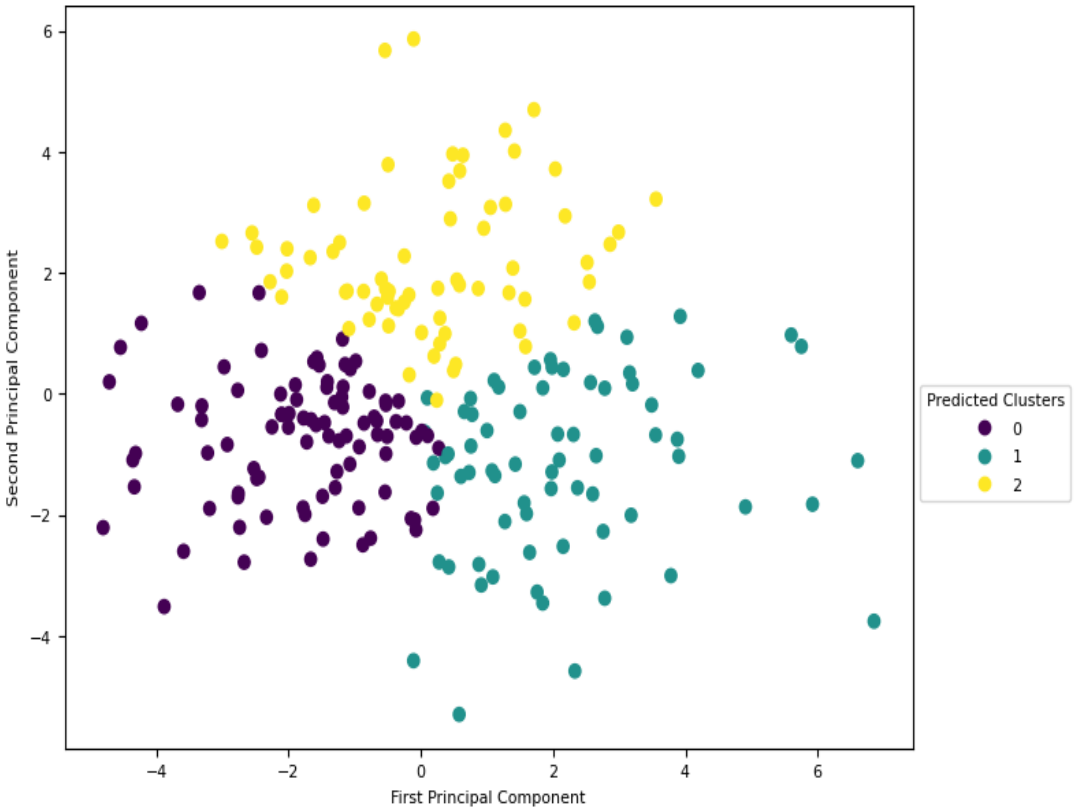


Figure 16 | Values of the correlation of each dataframe feature with the groups predicted by K-means algorithm, applied on patient 2 data.

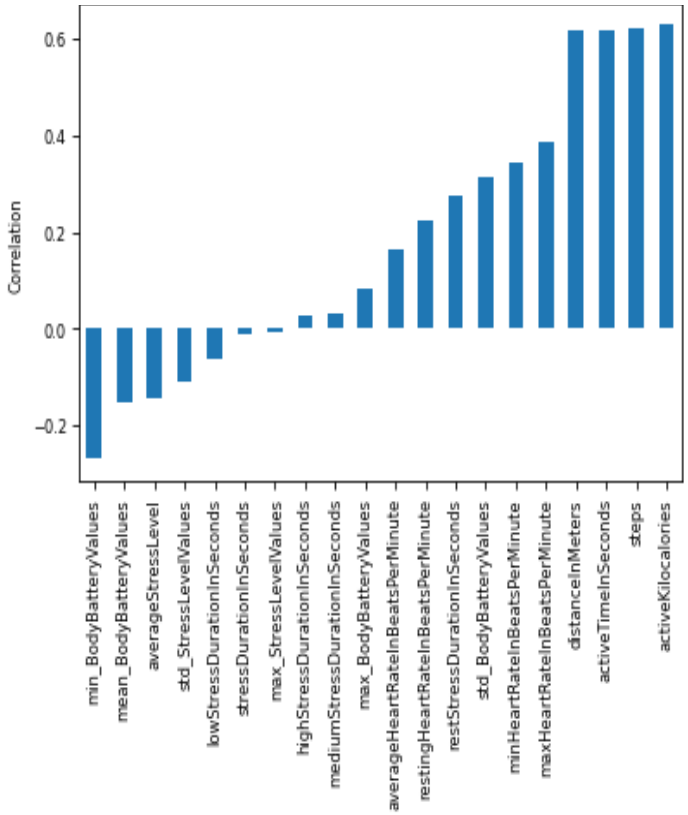


Figure 17 | Distribution of patient 2 data points on 2 Principal Components, colored according to the labels assigned to each row of the "Actual dataframe".

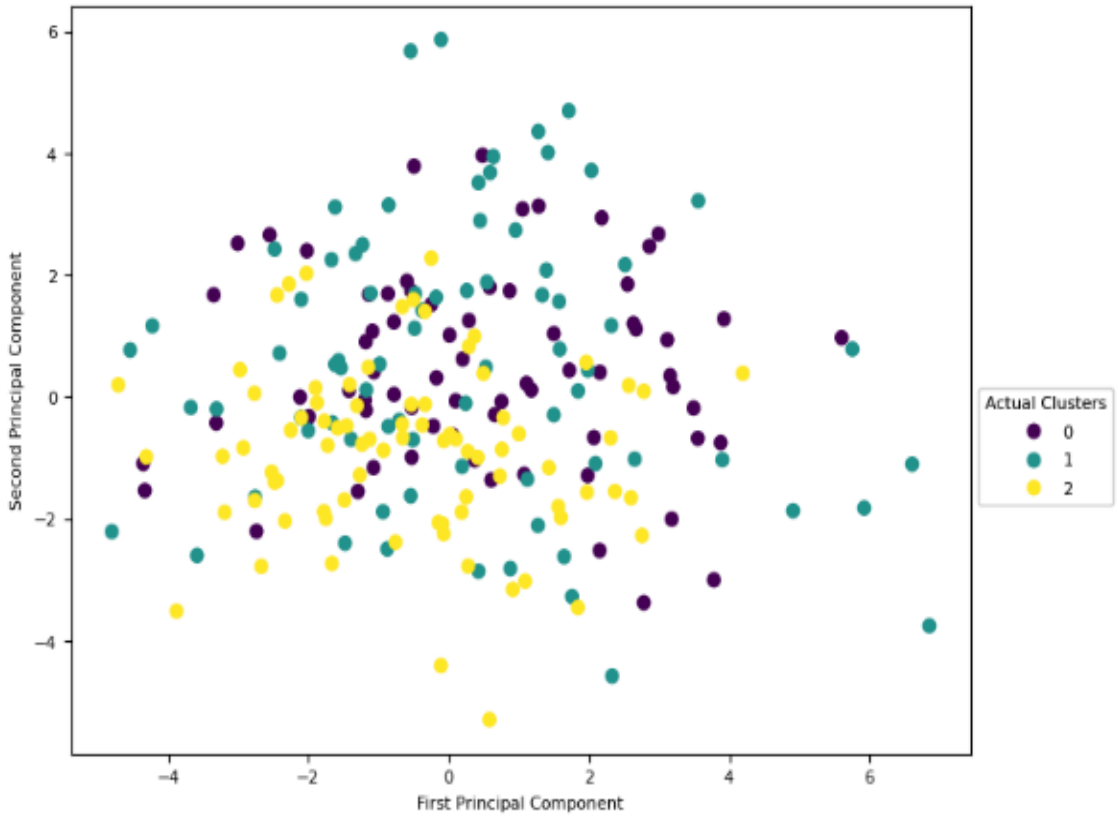


Figure 18 | Distribution of patient 2 selected data points on two Principal Components, colored dependently on the acquisition week of belonging.

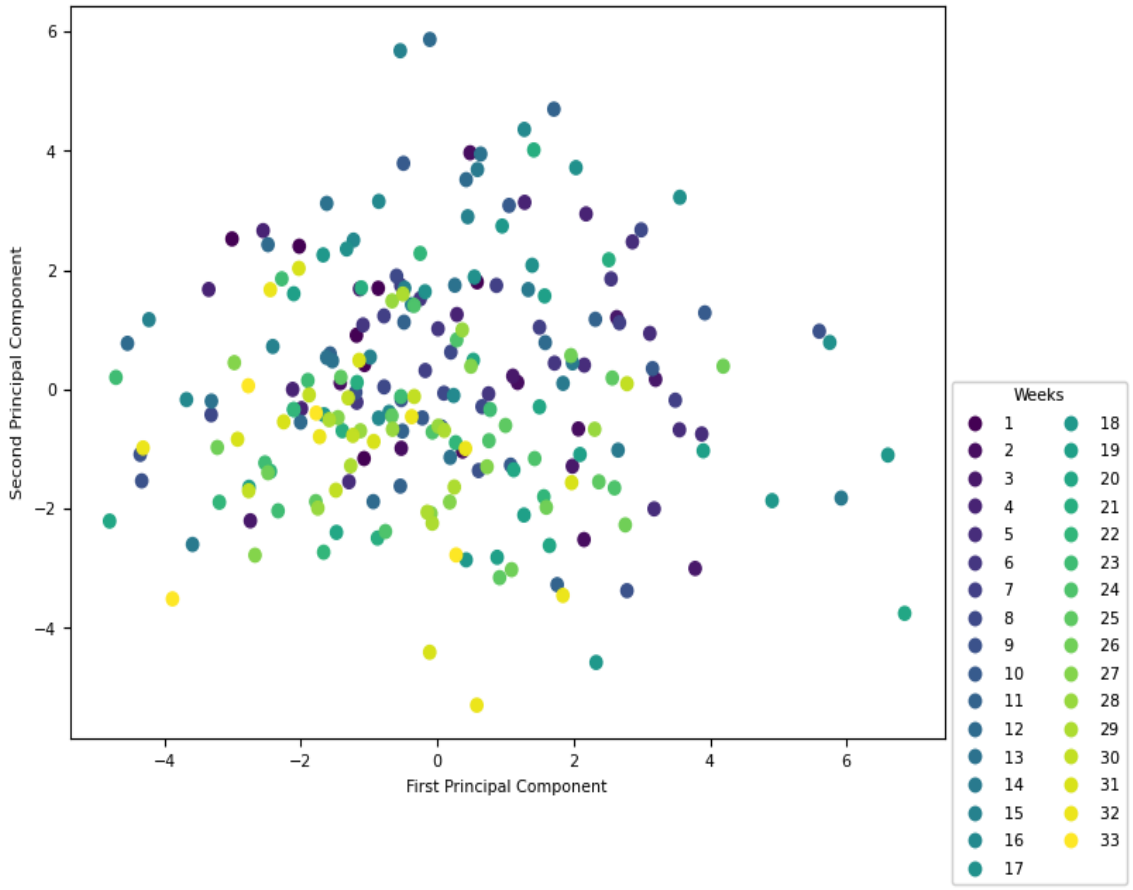


Figure 19 | Distribution of the patient 3 data point on 2 Principal Components

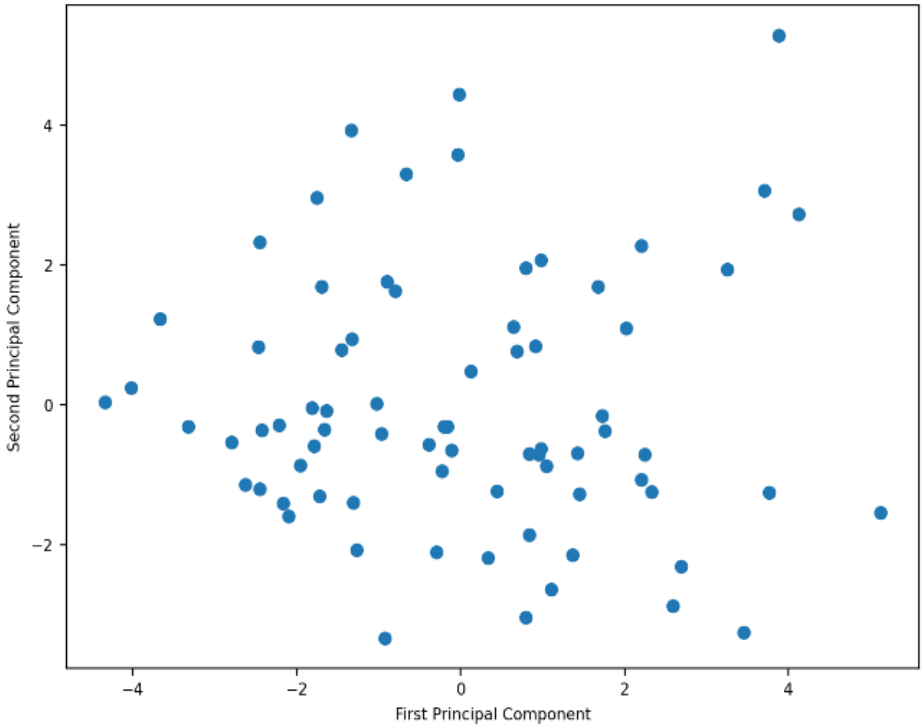


Figure 20 | Percentage of the explained variance as a function of the number of Principal Components, obtained by applying iteratively the Principal Component Analysis to patient 3 selected data.

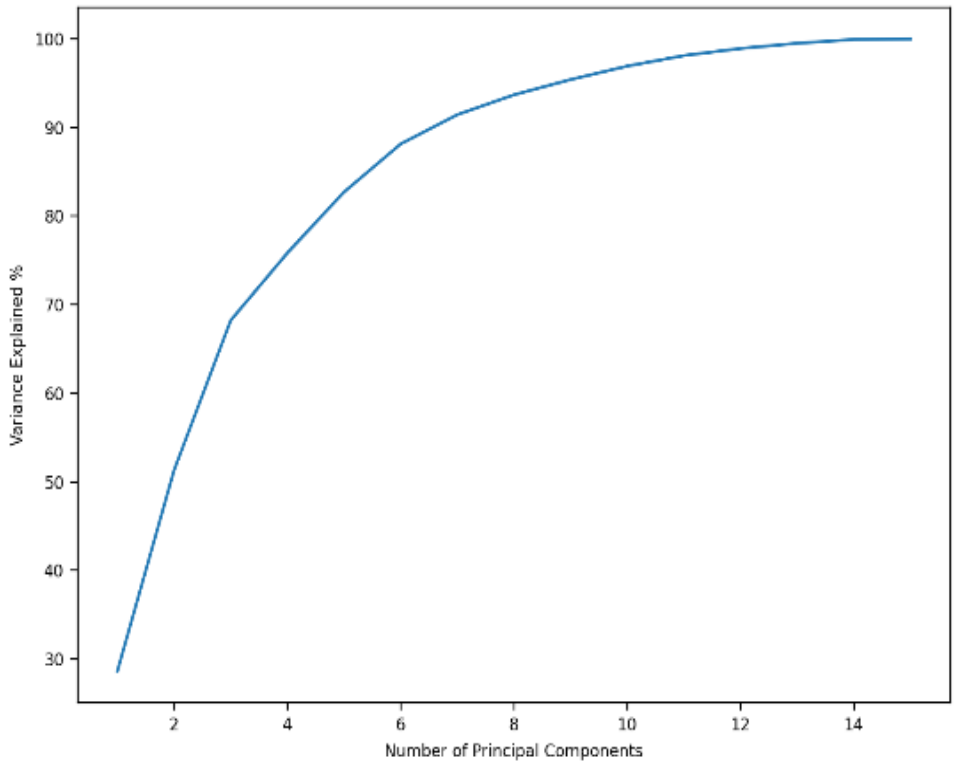


Figure 21 | Sum of squared distances expressed as a function of the number of clusters (K) obtained applying iteratively the K-means algorithm with patient 3 data.

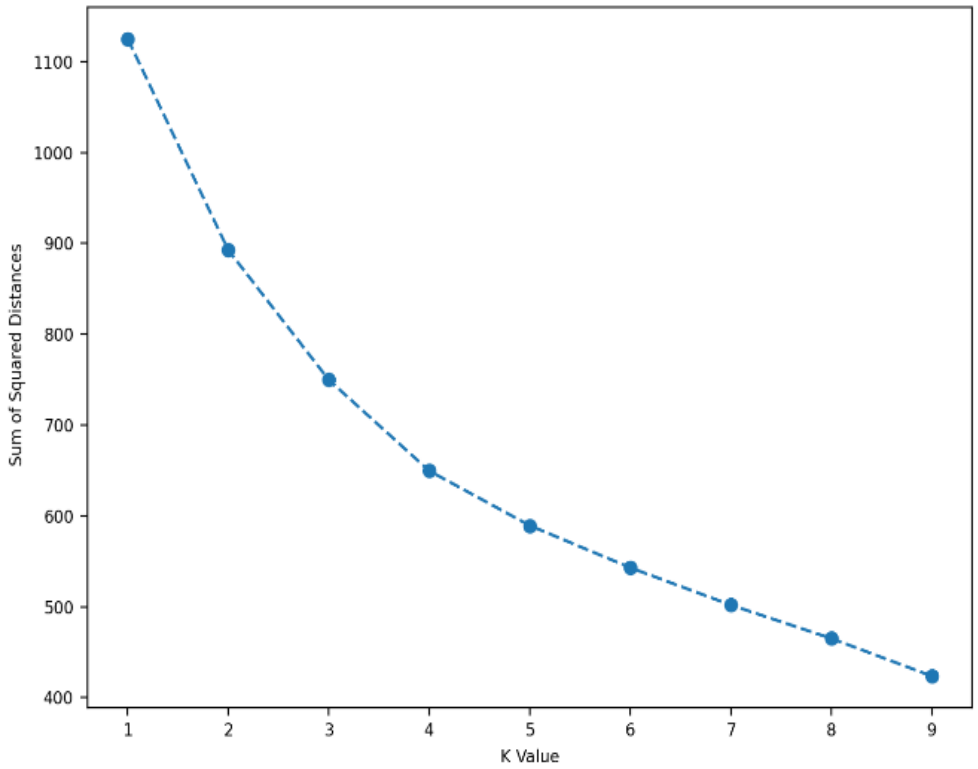


Figure 22 | Distribution of patient 3 data points on 2 Principal Components, colored according to the cluster of belonging predicted by K-means algorithm.

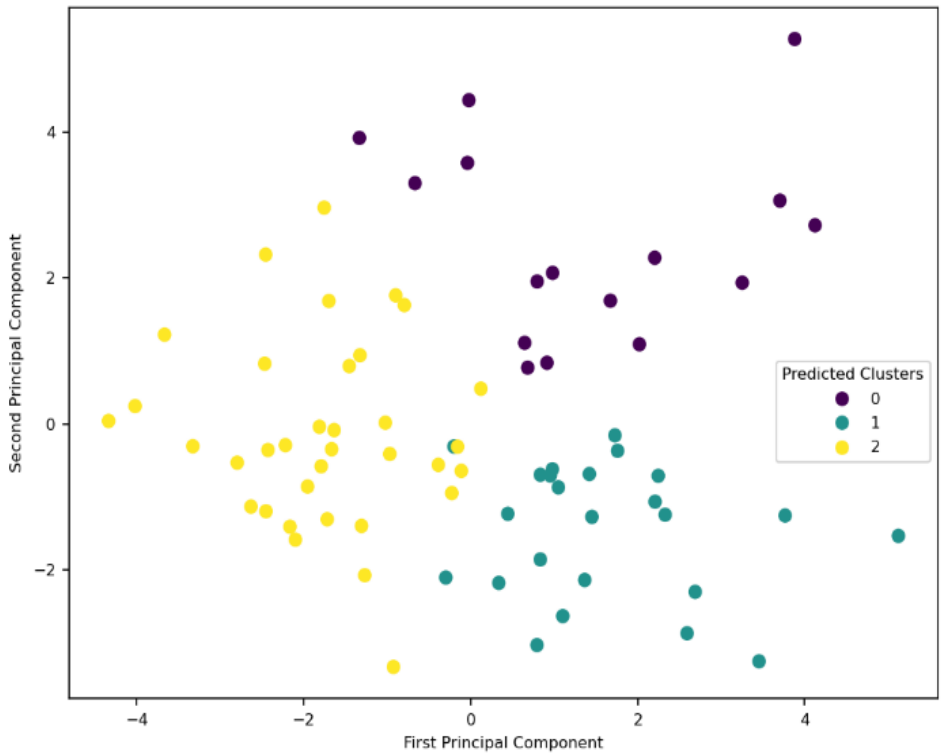


Figure 23 | Values of the correlation of each dataframe feature with the groups predicted by K-means algorithm, applied on patient 3 data.

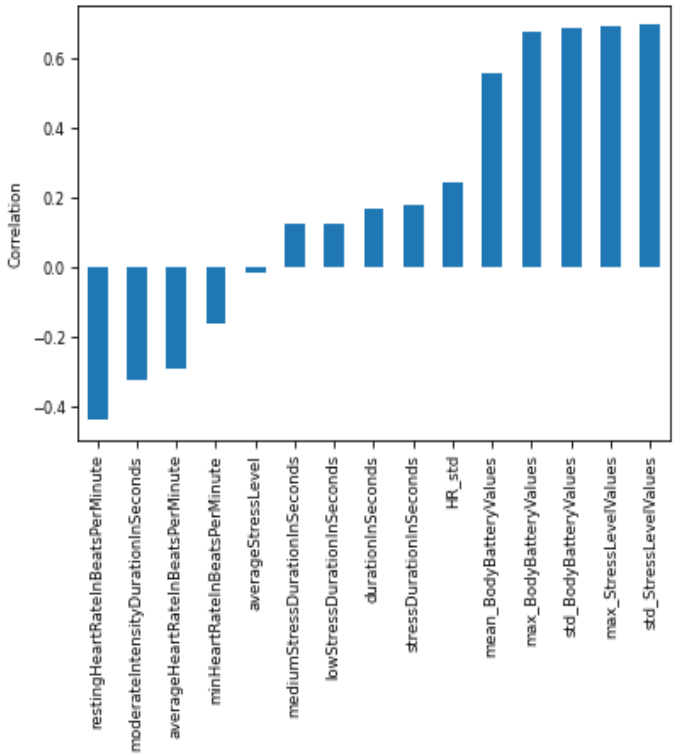


Figure 24 | Distribution of patient 3 data points on 2 Principal Components, colored according to the labels assigned to each row of the "Actual dataframe".

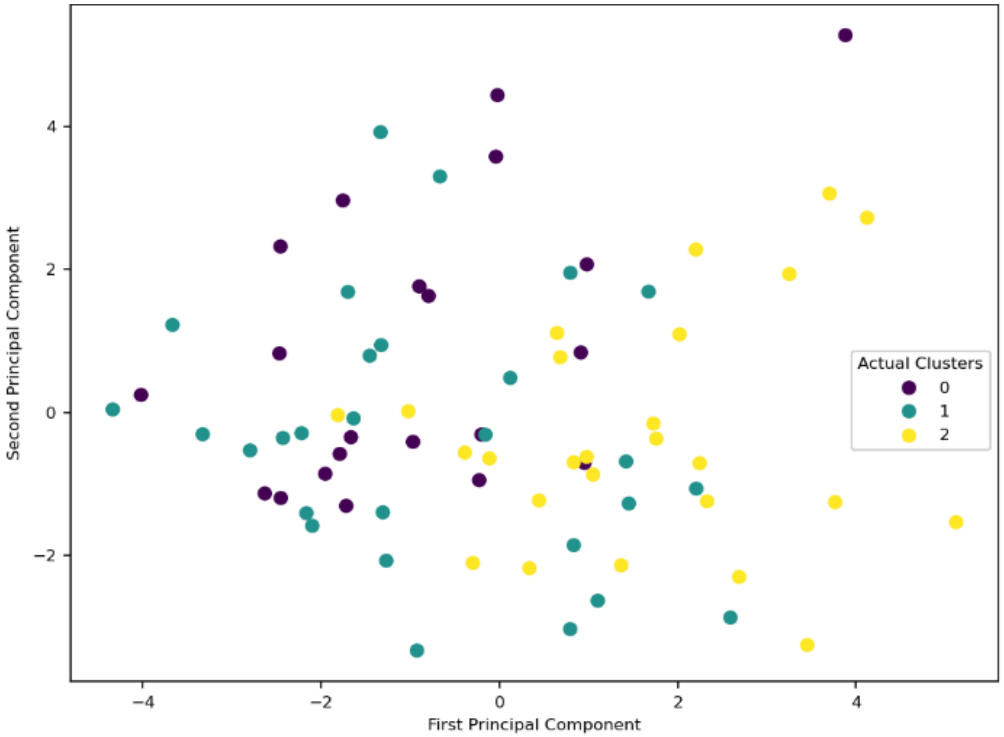


Figure 25 | Distribution of patient 3 selected data points on two Principal Components, colored dependently on the acquisition week of belonging.

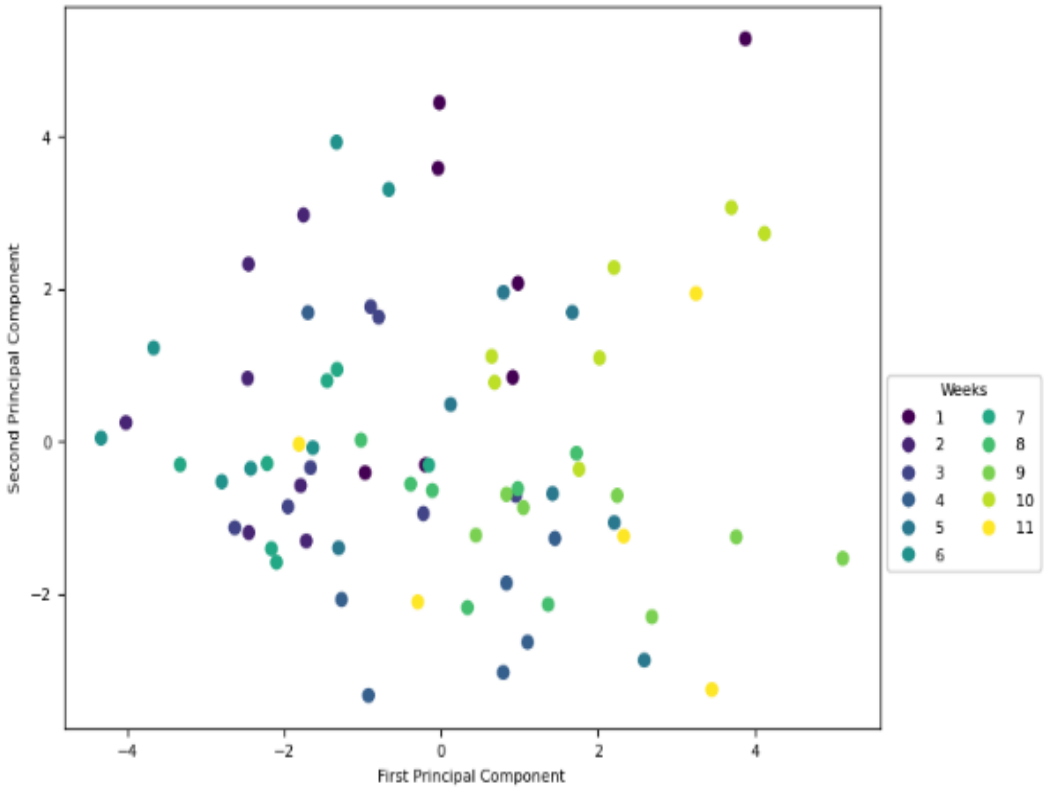


Figure 26 | Bar plot representing the UPDRS scores assigned during T0, T3, T6 for each patient.

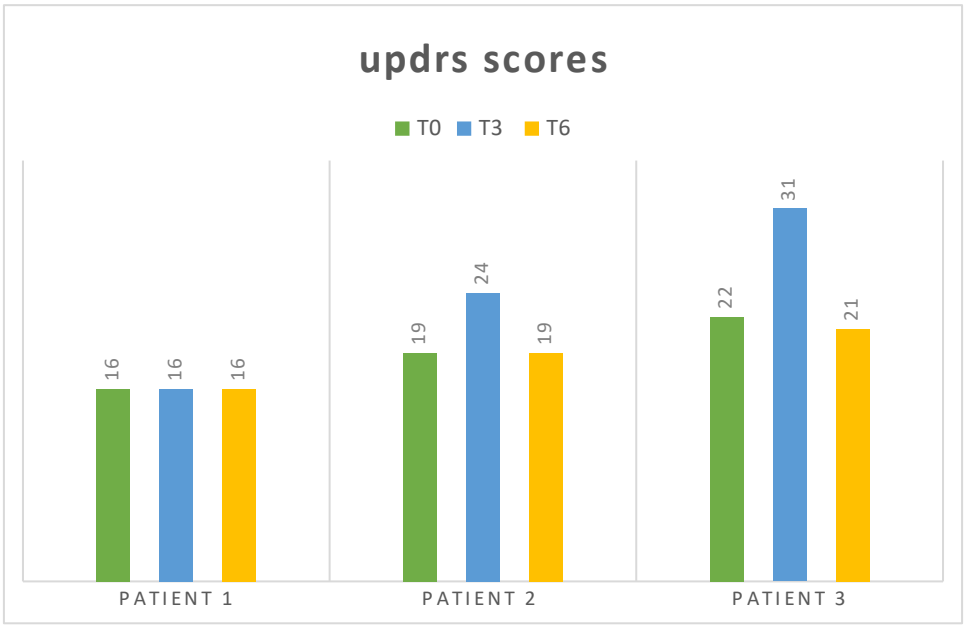


Figure 27 | Bar plot representing the NMSS scores assigned during T0, T3, T6 for each patient.

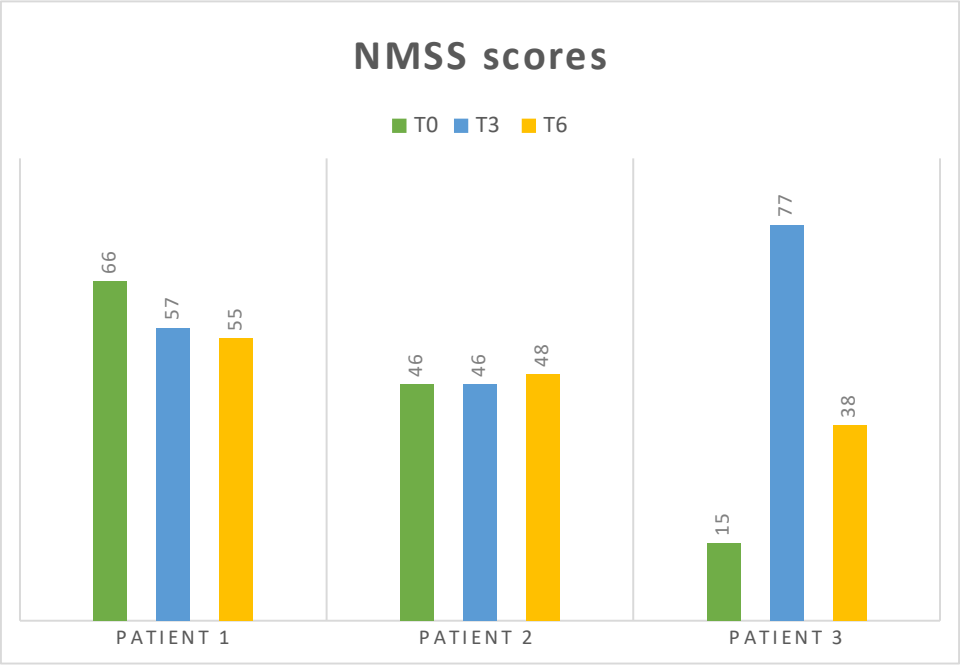


Figure 28 | Bar plot representing the PDQ-8 scores assigned during T0, T3, T6 for each patient.

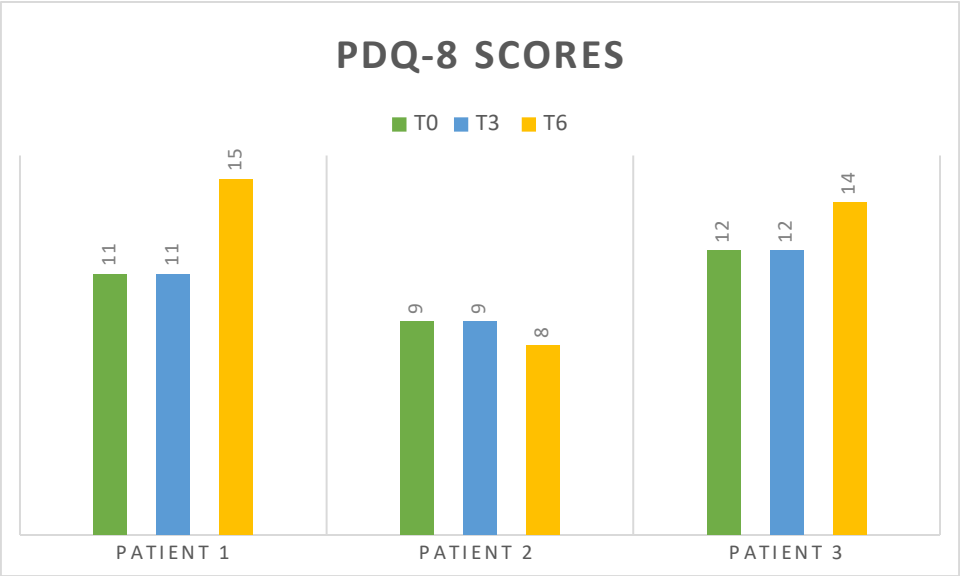


Figure 29 | Bar plot representing the state of health measured during T0, T3, T6 for each patient.

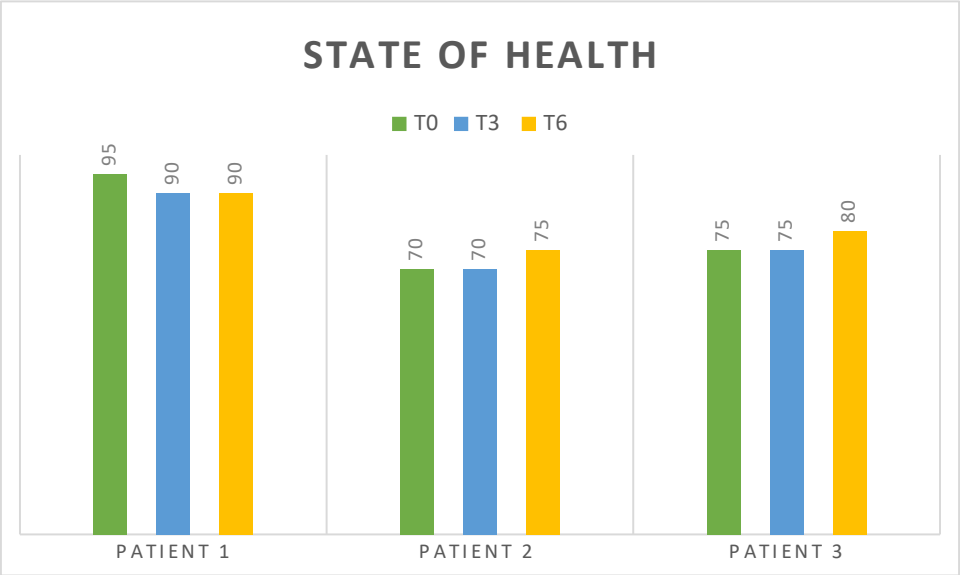


Figure 30 | Bar plot representing the global walking time measured during T0, T3, T6 for each patient.

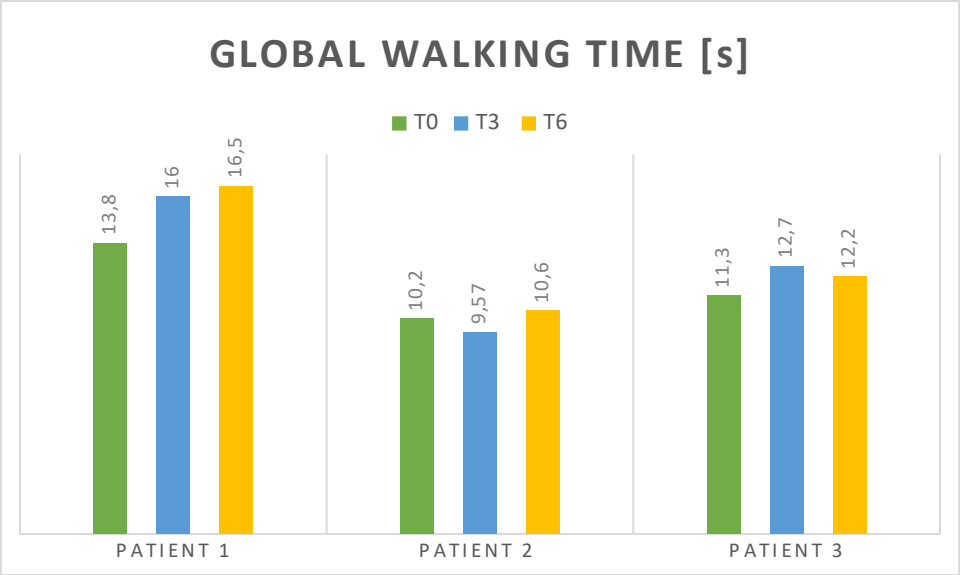


Figure 31 | Bar plot representing the turning time measured during T0, T3, T6 for each patient.

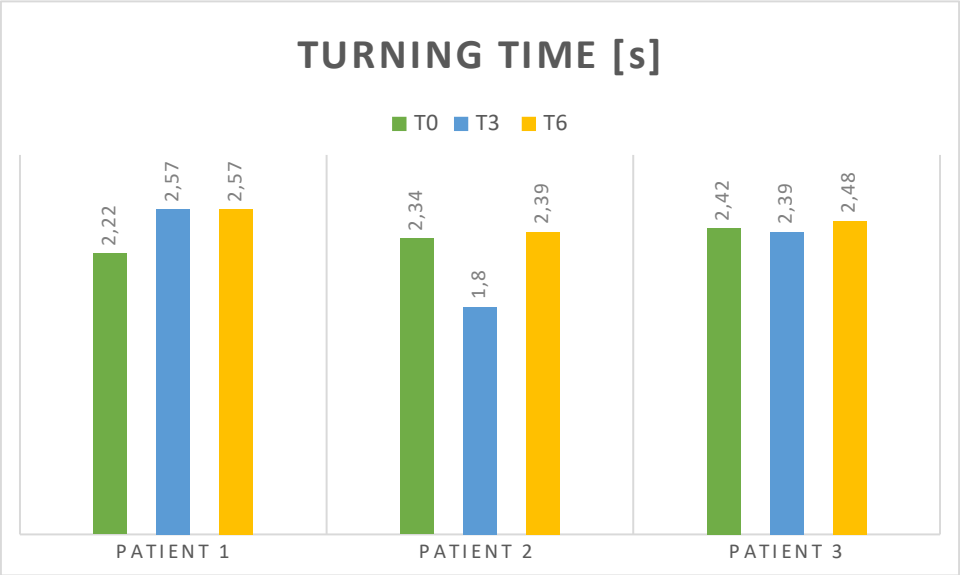


Figure 32 | Bar plot representing the step velocity measured during T0, T3, T6 for each patient.

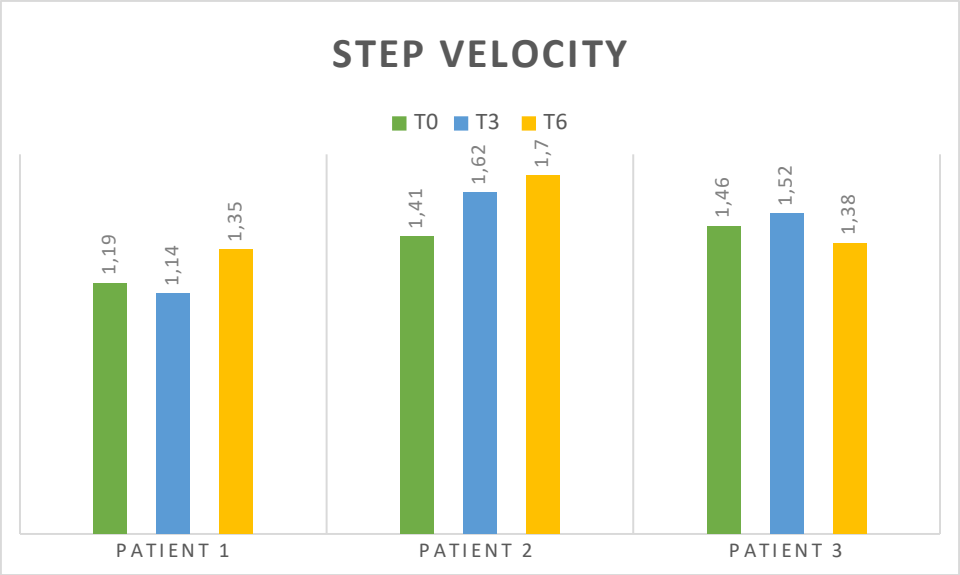
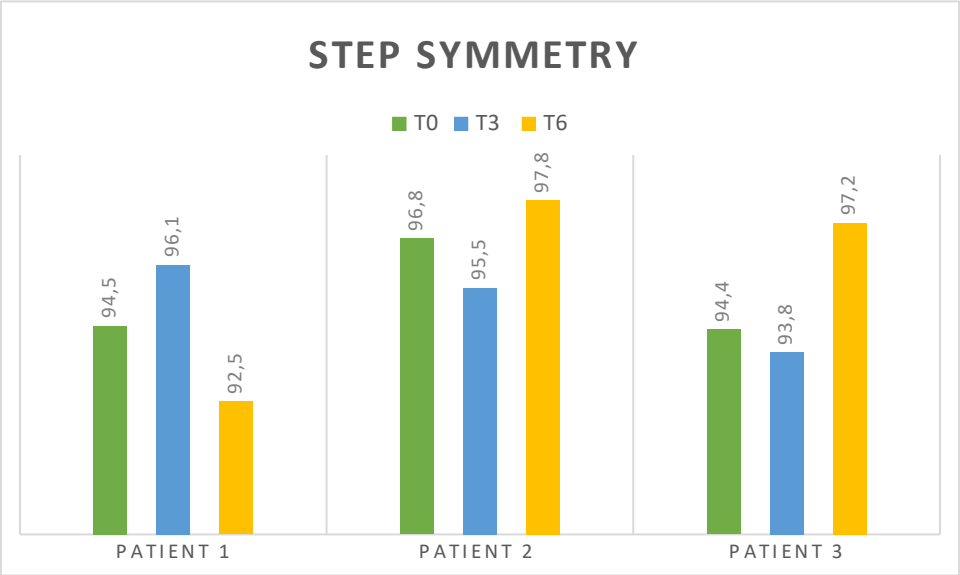


Figure 33 | Bar plot representing the step symmetry evaluated during T0, T3, T6 for each patient.



Tables

Table 1 | Common signs and symptoms of Parkinson's disease.

Motor Manifestations	Nonmotor Manifestations
Tremor	Staring appearance
Bradykinesia	Flat affect
Postural instability	Excessive salivation
Falls	Anosmia
Shuffling gait	Depression/anxiety
Stooped posture	Psychotic symptoms
Dyskinesia	Sleep disruption
Muscle rigidity	Fatigue
“Freezing” episodes	Autonomic dysfunction
Micrographia	Cognitive impairment
	Constipation
	Dysphagia
	Urinary incontinence
	Dysarthria; Difficult pronunciation
	Unexplained pain

Table 2 | Clinical study’s inclusion criteria.

Condition 1	Each subject needs to be at least 18 years old (either male or female)
Condition 2	PD needs to be diagnosed according to Movement Disorder Society criteria
Condition 3	Every subject must give they written and informed consent

Table 3 | Clinical study’s exclusion criteria.

Condition 1	Moderate-to-severe cognitive impairment (MoCA $\leq$ 18) or other known factors interfering with the ability to interact with the platform (e.g., poor visual acuity, lack of family support)
Condition 2	Comorbidities impact survival and autonomy or contraindicate the performance of physical exercise (e.g., neoplastic severe, cardiovascular diseases that are not pharmacologically controlled, including hypertension or arterial hypotension, cardiac arrhythmias, heart failure, musculoskeletal diseases, vertiginous syndrome)

Condition 3	Depression or other severe neuropsychiatric disorders
Condition 4	Change in drug therapy regimen for less than four weeks

Table 4 | Description of dailies summary parameters provided by Garmin Connect App in JSON format.

Parameters	Type	Description
summaryId	string	Unique identifier for the summary.
calendarDate	string	The calendar date this summary would be displayed on in Garmin Connect. The date format is 'yyyy-mm-dd'.
startTimeInSeconds	integer	Start time of the activity in seconds since January 1, 1970, 00:00:00 UTC (Unix timestamp).
startTimeOffsetInSeconds	integer	Offset in seconds to add to startTimeInSeconds to derive the "local" time of the device that captured the data.
activityType	string	This field is included in daily summaries for backwards compatibility purposes. It can be ignored and will always default to WALKING.
durationInSeconds	integer	Length of the monitoring period in seconds. 86400 once a full day is complete, but less if a user syncs mid-day.
steps	integer	Count of steps recorded during the monitoring period.
distanceInMeters	floating point	Distance traveled in meters.
activeTimeInSeconds	integer	Portion of the monitoring period (in seconds) in which the device wearer was considered Active. This relies on heuristics internal to each device.
activeKilocalories	integer	Active kilocalories (dietary calories) burned through actual movement and activity during the monitoring period.
bmrKilocalories	integer	BMR Kilocalories burned by existing Basal Metabolic Rate (calculated based on user height/weight/age/other demographic data).
consumedCalories	integer	The number of calories that have been consumed by the user through food for that day (value subtracted from calorie goal). This value is received from MyFitnessPal and is not entered within Connect.
moderateIntensityDurationInSeconds	integer	Cumulative duration of activities of moderate intensity. Moderate intensity is defined as activity with MET value range 3-6.
vigorousIntensityDurationInSeconds	integer	Cumulative duration of activities of vigorous intensity. Vigorous intensity is defined as activity with MET value > 6.
floorsClimbed	integer	Number of floors climbed during the monitoring period.
minHeartRateInBeatsPerMinute	integer	Minimum of heart rate values captured during the monitoring period, in beats per minute.
averageHeartRateInBeatsPerMinute	integer	Average of heart rate values captured during the last 7 days, in beats per minute. The average heart rate value for the monitoring period can be calculated based on the data from timeOffsetHeartRateSamples.
maxHeartRateInBeatsPerMinute	integer	Maximum of heart rate values captured during the monitoring period, in beats per minute.
restingHeartRateInBeatsPerMinute	Integer	Average heart rate at rest during the monitoring period, in beats per minute.
timeOffsetHeartRateSamples	Map	Collection of mappings between offset from start time (in seconds) to a heart rate value recorded for that time, in beats per minute. Each entry is a representative sample of the previous 15 seconds from the given offset. Lack of entry for a given offset should be interpreted as no data available. For example, in the response below, the user had 75 BPM for the first 30 seconds of the daily summary, took off their device until the 3180 second time slice, and took it off again after the 3255 second entry.

averageStressLevel	integer	An abstraction of the user's average stress level in this monitoring period, measured from 1 to 100, or -1 if there is not enough data to calculate average stress. Scores between 1 and 25 are considered "rest" (i.e not stressful), 26-50 as "low" stress, 51-75 "medium" stress, and 76-100 as "high" stress.
maxStressLevel	integer	The highest stress level measurement taken during this monitoring period.
stressDurationInSeconds	integer	The number of seconds in this monitoring period where stress level measurements were in the stressful range (26-100).
restStressDurationInSeconds	integer	The number of seconds in this monitoring period where stress level measurements were in the restful range (1 to 25).
activityStressDurationInSeconds	integer	The number of seconds in this monitoring period where the user was engaging in physical activity and so stress measurement was unreliable. All duration in this monitoring period not covered by stress, rest, and activity stress should be considered Uncategorized, either because the device was not worn or because not enough data could be taken to generate a stress score.
lowStressDurationInSeconds	integer	The portion of the user's stress duration where the measured stress score was in the low range (26-50).
mediumStressDurationInSeconds	integer	The portion of the user's stress duration where the measured stress score was in the medium range (51-75).
highStressDurationInSeconds	integer	The portion of the user's stress duration where the measured stress score was in the high range (76-100).
stressQualifier	string	A qualitative label applied based on all stress measurements in this monitoring period. Possible values: unknown, calm, balanced, stressful, very_stressful, calm_awake, balanced_awake, stressful_awake, very_stressful_awake. This matches what the user will see in Garmin Connect. It is recommended that implementations that use the stressQualifier be tolerant of unknown values in case more granular values are added.
stepsGoal	integer	The user's steps goal for this monitoring period.
netKilocaloriesGoal	integer	The user's goal for net caloric intake (consumed calories minus active calories) for this monitoring period. This field is related to integration with MyFitnessPal and may not be present for many users.
intensityDurationGoalInSeconds	integer	The user's goal for consecutive seconds of moderate to vigorous intensity activity for this monitoring period.
floorsClimbedGoal	integer	The user's goal for floors climbed in this monitoring period.

Table 5 | Description of sleep summary parameters provided by Garmin Connect App in JSON format.

Parameter	Type	Description
summaryId	string	Unique identifier for the summary.
calendarDate	string	The calendar date this summary would be displayed on in Garmin Connect. The date format is 'yyyy-mm-dd'.
startTimeInSeconds	integer	Start time of the activity in seconds since January 1, 1970, 00:00:00 UTC (Unix timestamp).
startTimeOffsetInSeconds	integer	Offset in seconds to add to startTimeInSeconds to derive the "local" time of the device that captured the data.
durationInSeconds	integer	Length of the monitoring period in seconds.
unmeasurableSleepInSeconds	Integer	Time in seconds that the sleep level of the user could not be measured. This may or may not correspond to off-wrist

		time.
deepSleepDurationInSeconds	integer	Time in seconds the user spent in deep sleep during the sleep period.
lightSleepDurationInSeconds	integer	Time in seconds the user spent in light sleep during the sleep period.
remSleepInSeconds	integer	Time in seconds the user spent in REM sleep during the sleep period.
awakeDurationInSeconds	integer	Time in seconds the user spent awake during the sleep period.
sleepLevelsMap	Map	A map of sleep level time ranges, currently deep, light, and awake. Time ranges are represented as unix timestamps in seconds.
timeOffsetSleepRespiration	Map	Collection of key-value pairs where the key is offset in seconds from the startTimeInSeconds and respiration measurement taken at that time. Respiration measurement is in breaths per minute.
timeOffsetSleepSpo2	Map	A map of SpO2 readings, where the keys are the offsets in seconds from the startTimeInSeconds and the values are the SpO2 measurements at that time. Only present if the user's device is SpO2-enabled.
overallSleepScore	Map	A map of overall sleep score, containing the quantitative value and the qualitative description of sleep.
sleepScores	Map	A map of sleep score string descriptions for each type of sleep as well as restless periods and stress levels during sleep. Each entry in the sleepScores will have a qualifierKey value of EXCELLENT, GOOD, FAIR, or POOR that is used as a qualitative description of the user's period of sleep.

Table 6 | Description of stress summary parameters provided by Garmin Connect App in JSON format.

Parameter	Type	Description
summaryId	string	Unique identifier for the summary.
startTimeInSeconds	integer	Start time of the summary in seconds since January 1, 1970, 00:00:00 UTC (Unix timestamp).
startTimeOffsetInSeconds	integer	Offset in seconds to add to startTimeInSeconds to derive the "local" time of the device that captured the data.
durationInSeconds	integer	The duration of the measurement period in seconds.
calendarDate	string	The calendar date this summary would be displayed on in Garmin Connect. The date format is 'yyyy-mm-dd'.
timeOffsetStressLevelValues	Map	Collection of mappings between offset from start time (in seconds) to a stress level value recorded for that time.
timeOffsetBodyBatteryValues	Map	Collection of mappings between offset from start time (in seconds) to a body battery value recorded for that time. Information on and a list of devices that support Body Battery are available here: https://support.garmin.com/ms-MY/?faq=2qczgfbN00AIMJbX33dRq9 .

Table 7 | Number and naming of the features considered in the statistical analysis for each dataframe.

DataFrame	**Number of Features**	**Features**
Dailies	21	'steps', 'distanceInMeters', 'activeTimeInSeconds', 'activeKilocalories', 'bmrKilocalories', 'moderateIntensityDurationInSeconds', 'vigorousIntensityDurationInSeconds', 'floorsClimbed', 'minHeartRateInBeatsPerMinute', 'averageHeartRateInBeatsPerMinute', 'maxHeartRateInBeatsPerMinute', 'restingHeartRateInBeatsPerMinute', 'averageStressLevel', 'maxStressLevel', 'stressDurationInSeconds', 'restStressDurationInSeconds', 'activityStressDurationInSeconds', 'lowStressDurationInSeconds', 'mediumStressDurationInSeconds', 'highStressDurationInSeconds', 'HR_std'
Stress	10	'startTimeInSeconds', 'durationInSeconds', 'max_StressLevelValues', 'min_StressLevelValues', 'mean_StressLevelValues', 'std_StressLevelValues','max_BodyBatteryValues', 'min_BodyBatteryValues', 'mean_BodyBatteryValues', 'std_BodyBatteryValues'
Sleeps	5	'durationInSeconds', 'deepSleepDurationInSeconds', 'lightSleepDurationInSeconds', 'remSleepInSeconds', 'awakeDurationInSeconds'

Table 8 | Number of acquisitions for each dataframe related to patient 1.

Dataframe	**Number of Acquired Samples**	**Number of Acquired Weeks**
Dailies Summary	189	27
Stress Summary	189	27
Sleep Summary	175	25

Table 9 | Statistically significant variables according to ANOVA test performed on patient 1 dailies data.

Dailies Variables	P values
steps	0,033
distanceInMeters	0,027
activeTimeInSeconds	0,029
bmrKilocalories	< 0,001
minHeartRateInBeatsPerMinute	0,013
averageHeartRateInBeatsPerMinute	< 0,001
restingHeartRateInBeatsPerMinute	< 0,001
averageStressLevel	0,005
stressDurationInSeconds	< 0,001
restStressDurationInSeconds	0,010
activityStressDurationInSeconds	0,007
lowStressDurationInSeconds	< 0,001
mediumStressDurationInSeconds	< 0,001

Table 10 | Statistically significant Tukey HSD multicomparison performed for patient 1 dailies selected features, according to ANOVA test.

ACTIVITY STRESS DURATION IN SECONDS						
Week 1	**Week 2**	**meandiff**	**p-adj**	**lower**	**upper**	**reject**
9	23	-14837,1	0,0249	-28872,2	-802,133	TRUE
AVERAGE HEART RATE IN BEATS PER MINUTE						
Week 1	**Week 2**	**meandiff**	**p-adj**	**lower**	**upper**	**reject**
7	16	6,8571	0,0157	0,5802	13,1341	TRUE
7	18	6,2857	0,0492	0,0088	12,5626	TRUE
7	20	6,7143	0,0212	0,4374	12,9912	TRUE
7	22	7,0952	0,0171	0,562	13,6285	TRUE
7	24	6,7619	0,0328	0,2287	13,2951	TRUE
7	26	6,7619	0,0328	0,2287	13,2951	TRUE
AVERAGE STRESS LEVEL						
Week 1	**Week 2**	**meandiff**	**p-adj**	**lower**	**upper**	**reject**
9	20	13,7143	0,0327	0,4684	26,9601	TRUE
9	23	14,1429	0,0217	0,897	27,3887	TRUE
9	24	14,0714	0,0391	0,2847	27,8581	TRUE
BMR KILOCALORIES						
Week 1	**Weeks 2**	**meandiff**	**p-adj**	**lower**	**upper**	**reject**
1	2	-75	0,0001	-127,06	-22,9402	TRUE
1	3	-75	0,0001	-127,06	-22,9402	TRUE

1	4	-75	0,0001	-127,06	-22,9402	TRUE
1	5	-75	0,0001	-127,06	-22,9402	TRUE
1	6	-75	0,0001	-127,06	-22,9402	TRUE
1	7	-75	0,0001	-127,06	-22,9402	TRUE
1	8	-151,286	0	-203,346	-99,2259	TRUE
1	9	-75	0,0001	-127,06	-22,9402	TRUE
1	10	-75	0,0001	-127,06	-22,9402	TRUE
1	11	-75	0,0001	-127,06	-22,9402	TRUE
1	12	-75	0,0001	-127,06	-22,9402	TRUE
1	13	-75	0,0001	-127,06	-22,9402	TRUE
1	14	-75	0,0001	-127,06	-22,9402	TRUE
1	15	-75	0,0006	-132,029	-17,9713	TRUE
1	16	-75	0,0001	-127,06	-22,9402	TRUE
1	17	-75	0,0001	-127,06	-22,9402	TRUE
1	18	-75	0,0001	-127,06	-22,9402	TRUE
1	19	-75	0,0002	-129,186	-20,8144	TRUE
1	20	-75	0,0001	-127,06	-22,9402	TRUE
1	21	-75	0,0001	-127,06	-22,9402	TRUE
1	22	-75	0,0002	-129,186	-20,8144	TRUE
1	23	-75	0,0001	-127,06	-22,9402	TRUE
1	24	-75	0,0002	-129,186	-20,8144	TRUE
1	25	-75	0,0002	-129,186	-20,8144	TRUE
1	26	-75	0,0002	-129,186	-20,8144	TRUE
1	27	-81,5714	0	-133,631	-29,5116	TRUE
2	8	-76,2857	0	-128,346	-24,2259	TRUE
3	8	-76,2857	0	-128,346	-24,2259	TRUE
4	8	-76,2857	0	-128,346	-24,2259	TRUE
5	8	-76,2857	0	-128,346	-24,2259	TRUE
6	8	-76,2857	0	-128,346	-24,2259	TRUE
7	8	-76,2857	0	-128,346	-24,2259	TRUE
8	9	76,2857	0	24,2259	128,3456	TRUE
8	10	76,2857	0	24,2259	128,3456	TRUE
8	11	76,2857	0	24,2259	128,3456	TRUE
8	12	76,2857	0	24,2259	128,3456	TRUE
8	13	76,2857	0	24,2259	128,3456	TRUE
8	14	76,2857	0	24,2259	128,3456	TRUE
8	15	76,2857	0,0004	19,257	133,3144	TRUE
8	16	76,2857	0	24,2259	128,3456	TRUE
8	17	76,2857	0	24,2259	128,3456	TRUE
8	18	76,2857	0	24,2259	128,3456	TRUE
8	19	76,2857	0,0001	22,1001	130,4713	TRUE
8	20	76,2857	0	24,2259	128,3456	TRUE
8	21	76,2857	0	24,2259	128,3456	TRUE
8	22	76,2857	0,0001	22,1001	130,4713	TRUE
8	23	76,2857	0	24,2259	128,3456	TRUE
8	24	76,2857	0,0001	22,1001	130,4713	TRUE

8	25	76,2857	0,0001	22,1001	130,4713	TRUE
8	26	76,2857	0,0001	22,1001	130,4713	TRUE
8	27	69,7143	0,0004	17,6544	121,7741	TRUE
LOW STRESS DURATION IN SECONDS						
Week 1	**Weeks 2**	**meandiff**	**p-adj**	**lower**	**upper**	**reject**
8	21	4088,571	0,009	481,2017	7695,941	TRUE
9	21	3822,857	0,0241	215,4874	7430,227	TRUE
MEDIUM STRESS DURATION IN SECONDS						
Week 1	**Week 2**	**meandiff**	**p-adj**	**lower**	**upper**	**reject**
1	9	-4362,86	0,03	-8548,37	-177,344	TRUE
8	24	4434,286	0,0404	77,8655	8790,706	TRUE
9	24	5728,571	0,0006	1372,151	10084,99	TRUE
14	24	4537,143	0,0303	180,7226	8893,563	TRUE
15	24	4904	0,0331	162,4705	9645,53	TRUE
MEDIUM STRESS DURATION IN SECONDS						
Week 1	**Week 2**	**meandiff**	**p-adj**	**lower**	**upper**	**reject**
1	9	-4362,86	0,03	-8548,37	-177,344	TRUE
8	24	4434,286	0,0404	77,8655	8790,706	TRUE
9	24	5728,571	0,0006	1372,151	10084,99	TRUE
14	24	4537,143	0,0303	180,7226	8893,563	TRUE
15	24	4904	0,0331	162,4705	9645,53	TRUE
RESTING HEART RATE IN BEATS PER MINUTE						
Week 1	**Week 2**	**meandiff**	**p-adj**	**lower**	**upper**	**reject**
2	16	4,8571	0,0441	0,0514	9,6629	TRUE
2	18	5	0,0307	0,1942	9,8058	TRUE
5	16	4,8571	0,0441	0,0514	9,6629	TRUE
5	18	5	0,0307	0,1942	9,8058	TRUE
7	16	5	0,0307	0,1942	9,8058	TRUE
7	18	5,1429	0,0211	0,3371	9,9486	TRUE
RESTING STRESS DURATION IN SECONDS						
Week 1	**Week 2**	**meandiff**	**p-adj**	**lower**	**upper**	**reject**
5	23	-15300	0,0043	-28210,2	-2389,82	TRUE
STRESS DURATION IN SECONDS						
Week 1	**Week 2**	**meandiff**	**p-adj**	**lower**	**upper**	**reject**
1	8	-8862,86	0,0197	-17105,1	-620,598	TRUE
1	9	-10765,7	0,0007	-19008	-2523,46	TRUE
8	24	9577,143	0,0114	998,3278	18155,96	TRUE
9	21	8580	0,0305	337,7411	16822,26	TRUE
9	24	11480	0,0004	2901,185	20058,82	TRUE
13	24	8780	0,0378	201,185	17358,82	TRUE

14	24	8711,429	0,0416	132,6136	17290,24	TRUE

Table 11 | Statistically significant variables according to ANOVA test performed on patient 1 stress data.

Stress Variables	P values
mean_StressLevelValues	0,005
max_BodyBatteryValues	0,003
min_BodyBatteryValues	< 0,001
mean_BodyBatteryValues	< 0,001
std_BodyBatteryValues	0,044

Table 12 | Statistically significant Tukey HSD multicomparison performed for patient 1 stress selected features, according to ANOVA test.

MAX BODY BATTERY VALUES						
Week 1	**Week 2**	**meandiff**	**p-adj**	**lower**	**upper**	**reject**
5	23	-31,1429	0,0082	-58,4557	-3,8301	TRUE
18	23	-27,5714	0,0447	-54,8842	-0,2586	TRUE
MEAN BODY BATTERY VALUES						
Week 1	**Week 2**	**meandiff**	**p-adj**	**lower**	**upper**	**reject**
5	8	-21,6315	0,0382	-42,7882	-0,4748	TRUE
5	14	-21,7712	0,0353	-42,9279	-0,6145	TRUE
5	23	-28,47	0,0003	-49,6268	-7,3133	TRUE
5	24	-22,0461	0,03	-43,2028	-0,8893	TRUE
5	26	-21,2587	0,0472	-42,4154	-0,102	TRUE
7	23	-22,6777	0,0205	-43,8345	-1,521	TRUE
9	23	-25,3151	0,0036	-46,4719	-4,1584	TRUE
15	23	-21,39	0,0439	-42,5468	-0,2333	TRUE
18	23	-21,2443	0,0476	-42,401	-0,0876	TRUE
19	23	-21,3527	0,0448	-42,5095	-0,196	TRUE
MEAN STRESS LEVEL VALUES						
Week 1	**Week 2**	**meandiff**	**p-adj**	**lower**	**upper**	**reject**
9	20	14,7093	0,0397	0,2779	29,1407	TRUE
9	23	14,895	0,034	0,4636	29,3264	TRUE
MIN BODY BATTERY VALUES						
Week 1	**Week 2**	**meandiff**	**p-adj**	**lower**	**upper**	**reject**
1	5	20,8571	0,0092	2,4263	39,288	TRUE
1	9	19,8571	0,0191	1,4263	38,288	TRUE
5	14	-20,1429	0,0156	-38,5737	-1,712	TRUE
5	23	-20,4286	0,0127	-38,8595	-1,9977	TRUE

5	26	-21,7143	0,0047	-40,1452	-3,2834	TRUE
7	26	-19	0,0345	-37,4309	-0,5691	TRUE
9	14	-19,1429	0,0313	-37,5737	-0,712	TRUE
9	23	-19,4286	0,0258	-37,8595	-0,9977	TRUE
9	26	-20,7143	0,0102	-39,1452	-2,2834	TRUE

Table 13 | Summary of the selected features according to the results provided by ANOVA and Tukey HSD tests performed on patient 1 data.

DataFrame	Selected features
Dailies	'bmrKilocalories', 'averageHeartRateInBeatsPerMinute', 'restingHeartRateInBeatsPerMinute', 'averageStressLevel', 'stressDurationInSeconds', 'restStressDurationInSeconds', 'activityStressDurationInSeconds', 'lowStressDurationInSeconds', 'mediumStressDurationInSeconds'
Stress	'mean_StressLevelValues', 'max_BodyBatteryValues', 'min_BodyBatteryValues', 'mean_BodyBatteryValues'
Sleeps	–

Table 14 | Performance metrics related to K-means algorithms performed on patient 1 data with K=3.

Clusters	Precision	Recall	F1-Score
Cluster 0	0,32	0,45	0,37
Cluster 1	0,22	0,27	0,24
Cluster 2	0,56	0,24	0,33

Table 15 | Confusion matrix related to K-means algorithm performed on patient 1 data with K=3.

True Label	Predicted label		
	Cluster 0	Cluster 1	Cluster 2
Cluster 0	25	28	3
Cluster 1	37	17	9
Cluster 2	17	31	15
Accuracy = 0,31			

Table 16 | Number of acquisitions for each dataframe related to patient 2.

DataFrame	Number of Acquired Samples	Number of Acquired Weeks
Dailies Summary	252	36
Stress Summary	252	36

Sleep Summary	63	9

Table 17 | Statistically significant variables according to ANOVA test performed on patient 2 dailies data.

Dailies Variables	P values
steps	0,021
distanceInMeters	0,035
activeTimeInSeconds	0,008
activeKilocalories	< 0,001
floorsClimbed	0,044
minHeartRateInBeatsPerMinute	< 0,001
averageHeartRateInBeatsPerMinute	< 0,001
maxHeartRateInBeatsPerMinute	0,005
restingHeartRateInBeatsPerMinute	0,001
averageStressLevel	< 0,001
maxStressLevel	0,012
stressDurationInSeconds	< 0,001
restStressDurationInSeconds	< 0,001
lowStressDurationInSeconds	< 0,001
mediumStressDurationInSeconds	< 0,001
highStressDurationInSeconds	< 0,001
HR_std	0,030

Table 18 | Statistically significant Tukey HSD multicomparison performed for patient 2 dailies selected features, according to ANOVA test.

ACTIVE KILOCALORIES						
Week 1	**Week 2**	**meandiff**	**p-adj**	**lower**	**upper**	**reject**
9	18	298,4286	0,0056	40,4164	556,4407	TRUE
18	24	-285,976	0,0213	-554,524	-17,4286	TRUE
18	25	-333,714	0,0006	-591,726	-75,7021	TRUE
18	28	-269,857	0,0275	-527,869	-11,845	TRUE
18	30	-269	0,0288	-527,012	-10,9879	TRUE
18	31	-276,429	0,0194	-534,441	-18,4164	TRUE
18	32	-325	0,0011	-583,012	-66,9879	TRUE
18	33	-306	0,0035	-564,012	-47,9879	TRUE
18	34	-301,81	0,0092	-570,357	-33,262	TRUE
18	35	-336	0,0005	-594,012	-77,9879	TRUE
18	36	-374,143	0,0016	-676,689	-71,5968	TRUE
ACTIVE TIME IN SECONDS						
Week 1	**Week 2**	**meandiff**	**p-adj**	**lower**	**upper**	**reject**
18	25	-5719,86	0,0303	-11225,9	-213,801	TRUE
18	36	-7186,86	0,0107	-13643,3	-730,435	TRUE

AVERAGE HEART RATE IN BEATS PER MINUTE						
Week 1	**Week 2**	**meandiff**	**p-adj**	**lower**	**upper**	**reject**
1	22	7,2143	0,0116	0,7012	13,7273	TRUE
1	23	7,8571	0,0011	1,5996	14,1147	TRUE
2	11	8,1429	0,0005	1,8853	14,4004	TRUE
2	13	8,8571	0,0001	2,5996	15,1147	TRUE
2	14	7,5238	0,0057	1,0108	14,0368	TRUE
2	15	7	0,0099	0,7425	13,2575	TRUE
2	16	9,3571	0	2,8441	15,8702	TRUE
2	17	8,8571	0,0002	2,3441	15,3702	TRUE
2	18	9,1429	0	2,8853	15,4004	TRUE
2	20	7,8571	0,0065	1,0024	14,7119	TRUE
2	21	8,1429	0,0005	1,8853	14,4004	TRUE
2	22	10,3571	0	3,8441	16,8702	TRUE
2	23	11	0	4,7425	17,2575	TRUE
2	24	7,6905	0,0038	1,1774	14,2035	TRUE
2	25	6,8571	0,0138	0,5996	13,1147	TRUE
2	26	8,1429	0,0005	1,8853	14,4004	TRUE
2	28	6,8571	0,0138	0,5996	13,1147	TRUE
2	36	7,8571	0,0196	0,5195	15,1947	TRUE
3	16	6,6429	0,0388	0,1298	13,1559	TRUE
3	18	6,4286	0,0352	0,171	12,6861	TRUE
3	22	7,6429	0,0043	1,1298	14,1559	TRUE
3	23	8,2857	0,0004	2,0282	14,5432	TRUE
4	9	6,4286	0,0352	0,171	12,6861	TRUE
4	11	8,5714	0,0002	2,3139	14,829	TRUE
4	12	6,2857	0,0472	0,0282	12,5432	TRUE
4	13	9,2857	0	3,0282	15,5432	TRUE
4	14	7,9524	0,002	1,4393	14,4654	TRUE
4	15	7,4286	0,0035	1,171	13,6861	TRUE
4	16	9,7857	0	3,2727	16,2988	TRUE
4	17	9,2857	0,0001	2,7727	15,7988	TRUE
4	18	9,5714	0	3,3139	15,829	TRUE
4	20	8,2857	0,0025	1,4309	15,1405	TRUE
4	21	8,5714	0,0002	2,3139	14,829	TRUE
4	22	10,7857	0	4,2727	17,2988	TRUE
4	23	11,4286	0	5,171	17,6861	TRUE
4	24	8,119	0,0013	1,606	14,6321	TRUE
4	25	7,2857	0,005	1,0282	13,5432	TRUE
4	26	8,5714	0,0002	2,3139	14,829	TRUE
4	27	6,5714	0,026	0,3139	12,829	TRUE
4	28	7,2857	0,005	1,0282	13,5432	TRUE
4	36	8,2857	0,0085	0,9481	15,6233	TRUE
6	23	6,7143	0,019	0,4568	12,9718	TRUE
8	13	6,6667	0,037	0,1536	13,1797	TRUE

8	16	7,1667	0,0227	0,4078	13,9256	TRUE
8	18	6,9524	0,0205	0,4393	13,4654	TRUE
8	22	8,1667	0,0025	1,4078	14,9256	TRUE
8	23	8,8095	0,0002	2,2965	15,3226	TRUE
13	33	-6,7143	0,019	-12,9718	-0,4568	TRUE
16	33	-7,2143	0,0116	-13,7273	-0,7012	TRUE
17	33	-6,7143	0,0336	-13,2273	-0,2012	TRUE
18	31	-6,2857	0,0472	-12,5432	-0,0282	TRUE
18	33	-7	0,0099	-13,2575	-0,7425	TRUE
22	30	-7,2143	0,0116	-13,7273	-0,7012	TRUE
22	31	-7,5	0,006	-14,013	-0,987	TRUE
22	33	-8,2143	0,001	-14,7273	-1,7012	TRUE
23	30	-7,8571	0,0011	-14,1147	-1,5996	TRUE
23	31	-8,1429	0,0005	-14,4004	-1,8853	TRUE
23	33	-8,8571	0,0001	-15,1147	-2,5996	TRUE
AVERAGE STRESS LEVEL						
Week 1	**Week 2**	**meandiff**	**p-adj**	**lower**	**upper**	**reject**
1	18	19,2857	0,0104	1,9883	36,5832	TRUE
1	21	17,5714	0,0409	0,274	34,8689	TRUE
4	18	20,1429	0,0049	2,8454	37,4403	TRUE
4	21	18,4286	0,0211	1,1311	35,726	TRUE
4	22	18,8571	0,027	0,8534	36,8609	TRUE
12	18	20	0,0056	2,7026	37,2974	TRUE
12	21	18,2857	0,0237	0,9883	35,5832	TRUE
12	22	18,7143	0,03	0,7105	36,718	TRUE
13	18	19,2857	0,0104	1,9883	36,5832	TRUE
13	21	17,5714	0,0409	0,274	34,8689	TRUE
15	18	19,2857	0,0104	1,9883	36,5832	TRUE
15	21	17,5714	0,0409	0,274	34,8689	TRUE
18	25	-18,7143	0,0168	-36,0117	-1,4168	TRUE
DISTANCE IN METERS						
Week 1	**Week 2**	**meandiff**	**p-adj**	**lower**	**upper**	**reject**
18	25	-5093,71	0,0342	-10041,4	-146,059	TRUE
18	36	-6233,29	0,0186	-12034,9	-431,646	TRUE
HIGH STRESS DURATION IN SECONDS						
Week 1	**Week 2**	**meandiff**	**p-adj**	**lower**	**upper**	**reject**
5	12	-2691,43	0,0164	-5174,98	-207,882	TRUE
5	15	-2494,29	0,0474	-4977,83	-10,7393	TRUE
5	25	-2614,29	0,0252	-5097,83	-130,739	TRUE
12	18	2888,571	0,0051	405,025	5372,118	TRUE
12	22	2590	0,0488	5,0429	5174,957	TRUE
13	18	2588,571	0,0289	105,025	5072,118	TRUE
15	18	2691,429	0,0164	207,8822	5174,975	TRUE

17	18	2748,571	0,0217	163,6144	5333,529	TRUE
18	23	-2614,29	0,0252	-5097,83	-130,739	TRUE
18	25	-2811,43	0,0081	-5294,98	-327,882	TRUE
18	33	-2502,86	0,0453	-4986,4	-19,3107	TRUE
LOW STRESS DURATION IN SECONDS						
Week 1	**Week 2**	**meandiff**	**p-adj**	**lower**	**upper**	**reject**
2	11	-8648,57	0,0005	-15278,2	-2018,93	TRUE
2	12	-9154,29	0,0001	-15783,9	-2524,64	TRUE
2	13	-9111,43	0,0001	-15741,1	-2481,79	TRUE
2	15	-8785,71	0,0003	-15415,4	-2156,07	TRUE
2	16	-7554,29	0,014	-14454,6	-653,935	TRUE
2	17	-8694,29	0,0011	-15594,6	-1793,93	TRUE
2	20	-8578,29	0,0038	-15840,7	-1315,88	TRUE
2	22	-7344,29	0,0214	-14244,6	-443,935	TRUE
2	23	-7731,43	0,0048	-14361,1	-1101,79	TRUE
2	25	-7654,29	0,0058	-14283,9	-1024,64	TRUE
2	32	-6728,57	0,0414	-13358,2	-98,9284	TRUE
2	35	-6642,86	0,0488	-13272,5	-13,2141	TRUE
3	12	-6754,29	0,0394	-13383,9	-124,643	TRUE
3	13	-6711,43	0,0428	-13341,1	-81,7855	TRUE
7	12	-6745,71	0,04	-13375,4	-116,071	TRUE
7	13	-6702,86	0,0435	-13332,5	-73,2141	TRUE
MAX HEART RATE IN BEATS PER MINUTE						
Week 1	**Week 2**	**meandiff**	**p-adj**	**lower**	**upper**	**reject**
5	35	-34,7143	0,0247	-67,6511	-1,7775	TRUE
MEDIUM STRESS DURATION IN SECONDS						
Week 1	**Week 2**	**meandiff**	**p-adj**	**lower**	**upper**	**reject**
12	14	7108,571	0,0301	268,4917	13948,65	TRUE
13	14	7468,571	0,0146	628,4917	14308,65	TRUE
14	15	-7477,14	0,0143	-14317,2	-637,063	TRUE
14	16	-7820	0,0127	-14918,3	-721,714	TRUE
14	17	-7140	0,0464	-14238,3	-41,7138	TRUE
14	23	-6937,14	0,0418	-13777,2	-97,0632	TRUE
14	25	-7580	0,0115	-14420,1	-739,92	TRUE
MIN HEART RATE IN BEATS PER MINUTE						
Week 1	**Week 2**	**meandiff**	**p-adj**	**lower**	**upper**	**reject**
10	30	-13,2857	0,0105	-25,2035	-1,3679	TRUE
12	30	-12,2857	0,0336	-24,2035	-0,3679	TRUE
13	30	-13,2857	0,0105	-25,2035	-1,3679	TRUE
16	30	-12,5238	0,0443	-24,9282	-0,1194	TRUE
RESTING HEART RATE IN BEATS PER MINUTE						

Week 1	Week 2	meandiff	p-adj	lower	upper	reject
2	23	10,8571	0,0074	1,3196	20,3947	TRUE
23	33	-11,5714	0,0023	-21,1089	-2,0339	TRUE
25	33	-9,5714	0,0478	-19,1089	-0,0339	TRUE
REST STRESS DURATION IN SECONDS						
Week 1	**Week 2**	**meandiff**	**p-adj**	**lower**	**upper**	**reject**
1	9	-22302,9	0	-37644,7	-6961,06	TRUE
1	10	-23597,1	0	-38938,9	-8255,35	TRUE
1	11	-24642,9	0	-39984,7	-9301,06	TRUE
1	13	-16088,6	0,0265	-31430,4	-746,774	TRUE
1	14	-24798,6	0	-40766,8	-8830,32	TRUE
1	16	-21128,6	0,0004	-37096,8	-5160,32	TRUE
1	17	-17648,6	0,012	-33616,8	-1680,32	TRUE
1	18	-27385,7	0	-42727,5	-12043,9	TRUE
1	20	-18332,6	0,0148	-35138,7	-1526,47	TRUE
1	21	-28097,1	0	-43438,9	-12755,3	TRUE
1	22	-29188,6	0	-45156,8	-13220,3	TRUE
1	23	-17160	0,0099	-32501,8	-1818,2	TRUE
1	24	-22988,6	0	-38956,8	-7020,32	TRUE
1	25	-16568,6	0,0172	-31910,4	-1226,77	TRUE
1	26	-24471,4	0	-39813,2	-9129,63	TRUE
1	27	-26391,4	0	-41733,2	-11049,6	TRUE
1	28	-27162,9	0	-42504,7	-11821,1	TRUE
1	29	-30758,6	0,0003	-53771,3	-7745,88	TRUE
1	30	-25371,4	0	-40713,2	-10029,6	TRUE
1	31	-21685,7	0,0001	-37027,5	-6343,92	TRUE
1	32	-27222,9	0	-42564,7	-11881,1	TRUE
1	33	-26665,7	0	-42007,5	-11323,9	TRUE
1	34	-23628,6	0	-39596,8	-7660,32	TRUE
1	35	-26331,4	0	-41673,2	-10989,6	TRUE
1	36	-25568,6	0,0001	-43558,4	-7578,72	TRUE
2	10	-15754,3	0,0354	-31096,1	-412,488	TRUE
2	11	-16800	0,0139	-32141,8	-1458,2	TRUE
2	14	-16955,7	0,0222	-32924	-987,465	TRUE
2	18	-19542,9	0,0008	-34884,7	-4201,06	TRUE
2	21	-20254,3	0,0004	-35596,1	-4912,49	TRUE
2	22	-21345,7	0,0003	-37314	-5377,47	TRUE
2	26	-16628,6	0,0163	-31970,4	-1286,77	TRUE
2	27	-18548,6	0,0024	-33890,4	-3206,77	TRUE
2	28	-19320	0,0011	-34661,8	-3978,2	TRUE
2	30	-17528,6	0,0069	-32870,4	-2186,77	TRUE
2	32	-19380	0,001	-34721,8	-4038,2	TRUE
2	33	-18822,9	0,0018	-34164,7	-3481,06	TRUE
2	35	-18488,6	0,0026	-33830,4	-3146,77	TRUE
4	9	-21814,3	0,0001	-37156,1	-6472,49	TRUE

4	10	-23108,6	0	-38450,4	-7766,77	TRUE
4	11	-24154,3	0	-39496,1	-8812,49	TRUE
4	13	-15600	0,0404	-30941,8	-258,203	TRUE
4	14	-24310	0	-40278,2	-8341,75	TRUE
4	16	-20640	0,0006	-36608,2	-4671,75	TRUE
4	17	-17160	0,0186	-33128,2	-1191,75	TRUE
4	18	-26897,1	0	-42238,9	-11555,3	TRUE
4	20	-17844	0,0222	-34650,1	-1037,9	TRUE
4	21	-27608,6	0	-42950,4	-12266,8	TRUE
4	22	-28700	0	-44668,2	-12731,8	TRUE
4	23	-16671,4	0,0157	-32013,2	-1329,63	TRUE
4	24	-22500	0,0001	-38468,2	-6531,75	TRUE
4	25	-16080	0,0267	-31421,8	-738,203	TRUE
4	26	-23982,9	0	-39324,7	-8641,06	TRUE
4	27	-25902,9	0	-41244,7	-10561,1	TRUE
4	28	-26674,3	0	-42016,1	-11332,5	TRUE
4	29	-30270	0,0004	-53282,7	-7257,3	TRUE
4	30	-24882,9	0	-40224,7	-9541,06	TRUE
4	31	-21197,1	0,0001	-36538,9	-5855,35	TRUE
4	32	-26734,3	0	-42076,1	-11392,5	TRUE
4	33	-26177,1	0	-41518,9	-10835,3	TRUE
4	34	-23140	0	-39108,2	-7171,75	TRUE
4	35	-25842,9	0	-41184,7	-10501,1	TRUE
4	36	-25080	0,0001	-43069,9	-7090,15	TRUE
6	9	-15522,9	0,0431	-30864,7	-181,06	TRUE
6	10	-16817,1	0,0137	-32158,9	-1475,35	TRUE
6	11	-17862,9	0,005	-33204,7	-2521,06	TRUE
6	14	-18018,6	0,0086	-33986,8	-2050,32	TRUE
6	18	-20605,7	0,0002	-35947,5	-5263,92	TRUE
6	21	-21317,1	0,0001	-36658,9	-5975,35	TRUE
6	22	-22408,6	0,0001	-38376,8	-6440,32	TRUE
6	24	-16208,6	0,0413	-32176,8	-240,323	TRUE
6	26	-17691,4	0,0059	-33033,2	-2349,63	TRUE
6	27	-19611,4	0,0008	-34953,2	-4269,63	TRUE
6	28	-20382,9	0,0003	-35724,7	-5041,06	TRUE
6	29	-23978,6	0,029	-46991,3	-965,875	TRUE
6	30	-18591,4	0,0023	-33933,2	-3249,63	TRUE
6	32	-20442,9	0,0003	-35784,7	-5101,06	TRUE
6	33	-19885,7	0,0006	-35227,5	-4543,92	TRUE
6	34	-16848,6	0,0243	-32816,8	-880,323	TRUE
6	35	-19551,4	0,0008	-34893,2	-4209,63	TRUE
6	36	-18788,6	0,0281	-36778,4	-798,719	TRUE
7	9	-16260	0,0228	-31601,8	-918,203	TRUE
7	10	-17554,3	0,0067	-32896,1	-2212,49	TRUE
7	11	-18600	0,0023	-33941,8	-3258,2	TRUE
7	14	-18755,7	0,0042	-34724	-2787,47	TRUE

7	18	-21342,9	0,0001	-36684,7	-6001,06	TRUE
7	21	-22054,3	0	-37396,1	-6712,49	TRUE
7	22	-23145,7	0	-39114	-7177,47	TRUE
7	24	-16945,7	0,0224	-32914	-977,465	TRUE
7	26	-18428,6	0,0028	-33770,4	-3086,77	TRUE
7	27	-20348,6	0,0003	-35690,4	-5006,77	TRUE
7	28	-21120	0,0001	-36461,8	-5778,2	TRUE
7	29	-24715,7	0,0188	-47728,4	-1703,02	TRUE
7	30	-19328,6	0,0011	-34670,4	-3986,77	TRUE
7	31	-15642,9	0,039	-30984,7	-301,06	TRUE
7	32	-21180	0,0001	-36521,8	-5838,2	TRUE
7	33	-20622,9	0,0002	-35964,7	-5281,06	TRUE
7	34	-17585,7	0,0127	-33554	-1617,47	TRUE
7	35	-20288,6	0,0004	-35630,4	-4946,77	TRUE
7	36	-19525,7	0,016	-37515,6	-1535,86	TRUE
8	9	-18534,3	0,0052	-34502,5	-2566,04	TRUE
8	10	-19828,6	0,0014	-35796,8	-3860,32	TRUE
8	11	-20874,3	0,0005	-36842,5	-4906,04	TRUE
8	14	-21030	0,0009	-37601	-4458,96	TRUE
8	16	-17360	0,0269	-33931	-788,965	TRUE
8	18	-23617,1	0	-39585,4	-7648,89	TRUE
8	21	-24328,6	0	-40296,8	-8360,32	TRUE
8	22	-25420	0	-41991	-8848,96	TRUE
8	24	-19220	0,0053	-35791	-2648,96	TRUE
8	26	-20702,9	0,0006	-36671,1	-4734,61	TRUE
8	27	-22622,9	0,0001	-38591,1	-6654,61	TRUE
8	28	-23394,3	0	-39362,5	-7426,04	TRUE
8	29	-26990	0,006	-50425	-3555,02	TRUE
8	30	-21602,9	0,0002	-37571,1	-5634,61	TRUE
8	31	-17917,1	0,0094	-33885,4	-1948,89	TRUE
8	32	-23454,3	0	-39422,5	-7486,04	TRUE
8	33	-22897,1	0	-38865,4	-6928,89	TRUE
8	34	-19860	0,0029	-36431	-3288,96	TRUE
8	35	-22562,9	0,0001	-38531,1	-6594,61	TRUE
8	36	-21800	0,0041	-40327	-3273,02	TRUE
12	18	-15737,1	0,036	-31078,9	-395,346	TRUE
12	21	-16448,6	0,0192	-31790,4	-1106,77	TRUE
12	22	-17540	0,0133	-33508,2	-1571,75	TRUE
12	28	-15514,3	0,0434	-30856,1	-172,488	TRUE
12	32	-15574,3	0,0413	-30916,1	-232,488	TRUE
STEPS						
Week 1	**Week 2**	**meandiff**	**p-adj**	**lower**	**upper**	**reject**
18	25	-6962,86	0,0355	-13744,5	-181,234	TRUE
18	36	-8495,82	0,0203	-16448	-543,663	TRUE

STRESS DURATION IN SECONDS						
Week 1	**Week 2**	**meandiff**	**p-adj**	**lower**	**upper**	**reject**
2	12	-15805,7	0,0013	-28450,8	-3160,61	TRUE
2	13	-15822,9	0,0012	-28468	-3177,75	TRUE
2	15	-15608,6	0,0016	-28253,7	-2963,46	TRUE
2	16	-14567,1	0,0118	-27728,6	-1405,7	TRUE
2	17	-15237,1	0,0055	-28398,6	-2075,7	TRUE
2	20	-14849,1	0,0193	-28701,2	-997,123	TRUE
2	23	-13937,1	0,0126	-26582,2	-1292,04	TRUE
2	25	-14700	0,0051	-27345,1	-2054,89	TRUE
3	12	-13500	0,0205	-26145,1	-854,893	TRUE
3	13	-13517,1	0,0201	-26162,2	-872,036	TRUE
3	15	-13302,9	0,0254	-25948	-657,751	TRUE
5	12	-12874,3	0,0397	-25519,4	-229,179	TRUE
5	13	-12891,4	0,039	-25536,5	-246,322	TRUE
5	15	-12677,1	0,0484	-25322,2	-32,0362	TRUE
12	18	14262,86	0,0086	1617,751	26907,96	TRUE
13	18	14280	0,0084	1634,893	26925,11	TRUE
15	18	14065,71	0,0108	1420,608	26710,82	TRUE
17	18	13694,29	0,0296	532,8415	26855,73	TRUE
18	25	-13157,1	0,0296	-25802,2	-512,036	TRUE

Table 19 | Statistically significant variables according to ANOVA test performed on patient 2 stress data.

Stress Variables	P values
max_StressLevelValues	0,006
min_StressLevelValues	0,005
mean_StressLevelValues	< 0,001
std_StressLevelValues	< 0,001
max_BodyBatteryValues	< 0,001
min_BodyBatteryValues	< 0,001
mean_BodyBatteryValues	0,001
std_BodyBatteryValues	< 0,001

Table 20 | Statistically significant Tukey HSD multicomparison performed for patient 2 stress selected features, according to ANOVA test.

MAX BODY BATTERY VALUES						
Week 1	**Week 2**	**meandiff**	**p-adj**	**lower**	**upper**	**reject**
3	8	29,3095	0,0002	7,6649	50,9542	TRUE
4	5	-23,1429	0,0106	-43,9384	-2,3473	TRUE

4	36	-23,8	0,0279	-46,5804	-1,0196	TRUE
5	7	23,7143	0,007	2,9188	44,5098	TRUE
5	8	33,3095	0	11,6649	54,9542	TRUE
7	36	-24,3714	0,0197	-47,1518	-1,5911	TRUE
8	10	-22,3095	0,0336	-43,9542	-0,6649	TRUE
8	11	-24,881	0,0061	-46,5256	-3,2363	TRUE
8	21	-23,7381	0,0135	-45,3828	-2,0934	TRUE
8	22	-22,5	0,0489	-44,9617	-0,0383	TRUE
8	27	-26,1667	0,0024	-47,8113	-4,522	TRUE
8	28	-22,5952	0,0282	-44,2399	-0,9506	TRUE
8	30	-22,6667	0,0445	-45,1284	-0,2049	TRUE
8	32	-23,881	0,0122	-45,5256	-2,2363	TRUE
8	33	-22,4524	0,0308	-44,097	-0,8077	TRUE
8	34	-28,3095	0,0004	-49,9542	-6,6649	TRUE
8	35	-22,7381	0,0258	-44,3828	-1,0934	TRUE
8	36	-33,9667	0	-57,5247	-10,4086	TRUE
MAX STRESS LEVEL VALUES						
Week 1	**Week 2**	**meandiff**	**p-adj**	**lower**	**upper**	**reject**
5	17	-16,4286	0,0186	-31,7221	-1,135	TRUE
17	18	16,2857	0,0212	0,9922	31,5792	TRUE
MEAN BODY BATTERY VALUES						
Week 1	**Week 2**	**meandiff**	**p-adj**	**lower**	**upper**	**reject**
1	5	-24,0474	0,0288	-47,1171	-0,9776	TRUE
3	12	26,1023	0,0081	3,0325	49,172	TRUE
5	8	26,8073	0,0101	2,7956	50,8191	TRUE
5	12	29,4935	0,0007	6,4238	52,5632	TRUE
5	23	23,6023	0,0372	0,5326	46,6721	TRUE
MIN BODY BATTERY VALUES						
Week 1	**Week 2**	**meandiff**	**p-adj**	**lower**	**upper**	**reject**
1	6	-32,4286	0,0067	-60,7734	-4,0838	TRUE
3	12	33,5714	0,0036	5,2266	61,9162	TRUE
3	16	29,7143	0,0266	1,3695	58,0591	TRUE
5	12	38	0,0003	9,6552	66,3448	TRUE
5	13	29,1429	0,0348	0,7981	57,4876	TRUE
5	16	34,1429	0,0026	5,7981	62,4876	TRUE
5	20	36,1786	0,0152	2,9414	69,4158	TRUE
5	23	30,7143	0,0163	2,3695	59,0591	TRUE
5	25	31,1429	0,0131	2,7981	59,4876	TRUE
5	35	29,4286	0,0304	1,0838	57,7734	TRUE
6	12	43,2857	0	14,9409	71,6305	TRUE
6	13	34,4286	0,0022	6,0838	62,7734	TRUE
6	14	33,0476	0,0095	3,5454	62,5498	TRUE
6	15	29,2857	0,0325	0,9409	57,6305	TRUE

6	16	39,4286	0,0001	11,0838	67,7734	TRUE
6	17	31	0,0141	2,6552	59,3448	TRUE
6	18	30	0,0231	1,6552	58,3448	TRUE
6	20	41,4643	0,0013	8,2271	74,7015	TRUE
6	21	30,2857	0,0201	1,9409	58,6305	TRUE
6	23	36	0,0009	7,6552	64,3448	TRUE
6	24	30,7143	0,0163	2,3695	59,0591	TRUE
6	25	36,4286	0,0007	8,0838	64,7734	TRUE
6	26	30,1429	0,0216	1,7981	58,4876	TRUE
6	27	29,5714	0,0284	1,2266	57,9162	TRUE
6	28	28,8571	0,0397	0,5124	57,2019	TRUE
6	30	31,5476	0,0199	2,0454	61,0498	TRUE
6	32	32,5714	0,0062	4,2266	60,9162	TRUE
6	35	34,7143	0,0019	6,3695	63,0591	TRUE
7	12	34,7143	0,0019	6,3695	63,0591	TRUE
7	16	30,8571	0,0151	2,5124	59,2019	TRUE
8	12	31,7381	0,0182	2,2359	61,2403	TRUE
BODY BATTERY VALUES STANDARD DEVIATION						
Week 1	**Week 2**	**meandiff**	**p-adj**	**lower**	**upper**	**reject**
1	6	11,042	0,0113	1,0824	21,0015	TRUE
1	7	10,0143	0,0466	0,0548	19,9739	TRUE
1	8	11,3258	0,0143	0,9596	21,692	TRUE
4	16	-10,1985	0,0367	-20,158	-0,239	TRUE
6	10	-10,4982	0,0245	-20,4577	-0,5387	TRUE
6	11	-10,9149	0,0136	-20,8744	-0,9554	TRUE
6	12	-13,9702	0,0001	-23,9297	-4,0107	TRUE
6	13	-13,5309	0,0002	-23,4904	-3,5714	TRUE
6	14	-12,0232	0,0052	-22,3894	-1,657	TRUE
6	16	-14,6952	0	-24,6547	-4,7357	TRUE
6	17	-10,9271	0,0134	-20,8866	-0,9676	TRUE
6	18	-12,0753	0,0023	-22,0348	-2,1158	TRUE
6	20	-15,3459	0,0004	-27,0245	-3,6673	TRUE
6	21	-11,9493	0,0028	-21,9088	-1,9898	TRUE
6	23	-12,9405	0,0005	-22,9	-2,9809	TRUE
6	24	-11,5649	0,0051	-21,5244	-1,6054	TRUE
6	25	-12,8514	0,0006	-22,8109	-2,8919	TRUE
6	26	-10,7763	0,0166	-20,7358	-0,8168	TRUE
6	27	-13,6513	0,0001	-23,6108	-3,6918	TRUE
6	28	-11,5252	0,0054	-21,4847	-1,5657	TRUE
6	30	-12,988	0,0012	-23,3542	-2,6218	TRUE
6	31	-10,8375	0,0152	-20,797	-0,878	TRUE
6	32	-13,5415	0,0002	-23,501	-3,582	TRUE
6	33	-12,3329	0,0015	-22,2924	-2,3734	TRUE
6	34	-13,9289	0,0001	-23,8884	-3,9694	TRUE
6	35	-14,2116	0,0001	-24,1712	-4,2521	TRUE

6	36	-14,7153	0,0002	-25,6254	-3,8052	TRUE
7	12	-12,9425	0,0005	-22,9021	-2,983	TRUE
7	13	-12,5032	0,0011	-22,4628	-2,5437	TRUE
7	14	-10,9956	0,0224	-21,3617	-0,6294	TRUE
7	16	-13,6676	0,0001	-23,6271	-3,708	TRUE
7	18	-11,0477	0,0112	-21,0072	-1,0882	TRUE
7	20	-14,3183	0,0018	-25,9968	-2,6397	TRUE
7	21	-10,9217	0,0135	-20,8812	-0,9622	TRUE
7	23	-11,9128	0,0029	-21,8723	-1,9533	TRUE
7	24	-10,5373	0,0233	-20,4968	-0,5778	TRUE
7	25	-11,8238	0,0034	-21,7833	-1,8643	TRUE
7	27	-12,6237	0,0009	-22,5832	-2,6642	TRUE
7	28	-10,4975	0,0246	-20,4571	-0,538	TRUE
7	30	-11,9603	0,0057	-22,3265	-1,5941	TRUE
7	32	-12,5139	0,0011	-22,4734	-2,5543	TRUE
7	33	-11,3053	0,0076	-21,2648	-1,3457	TRUE
7	34	-12,9012	0,0006	-22,8608	-2,9417	TRUE
7	35	-13,184	0,0003	-23,1435	-3,2245	TRUE
7	36	-13,6877	0,0011	-24,5978	-2,7776	TRUE
8	10	-10,782	0,0297	-21,1482	-0,4158	TRUE
8	11	-11,1987	0,017	-21,5649	-0,8326	TRUE
8	12	-14,254	0,0001	-24,6202	-3,8878	TRUE
8	13	-13,8147	0,0003	-24,1809	-3,4485	TRUE
8	14	-12,307	0,0067	-23,0645	-1,5495	TRUE
8	16	-14,979	0	-25,3452	-4,6128	TRUE
8	17	-11,211	0,0168	-21,5772	-0,8448	TRUE
8	18	-12,3592	0,0031	-22,7253	-1,993	TRUE
8	20	-15,6297	0,0005	-27,657	-3,6025	TRUE
8	21	-12,2332	0,0038	-22,5994	-1,867	TRUE
8	23	-13,2243	0,0008	-23,5905	-2,8581	TRUE
8	24	-11,8488	0,0068	-22,215	-1,4826	TRUE
8	25	-13,1353	0,0009	-23,5014	-2,7691	TRUE
8	26	-11,0601	0,0206	-21,4263	-0,6939	TRUE
8	27	-13,9352	0,0002	-24,3014	-3,569	TRUE
8	28	-11,809	0,0072	-22,1752	-1,4428	TRUE
8	30	-13,2718	0,0016	-24,0293	-2,5143	TRUE
8	31	-11,1213	0,0189	-21,4875	-0,7551	TRUE
8	32	-13,8253	0,0003	-24,1915	-3,4591	TRUE
8	33	-12,6167	0,0021	-22,9829	-2,2505	TRUE
8	34	-14,2127	0,0001	-24,5789	-3,8465	TRUE
8	35	-14,4955	0,0001	-24,8617	-4,1293	TRUE
8	36	-14,9992	0,0003	-26,2817	-3,7166	TRUE
STRESS LEVEL VALUES STANDARD DEVIATION						
Week 1	**Week 2**	**meandiff**	**p-adj**	**lower**	**upper**	**reject**
1	27	5,8507	0,0207	0,3641	11,3372	TRUE

Table 21 | Summary of the selected features according to the results provided by ANOVA and Tukey HSD tests, performed on patient 2 data.

Patient 2	Selected features
Dailies	'steps', 'distanceInMeters', 'activeTimeInSeconds', 'activeKilocalories', 'minHeartRateInBeatsPerMinute', 'averageHeartRateInBeatsPerMinute', 'maxHeartRateInBeatsPerMinute', 'restingHeartRateInBeatsPerMinute', 'averageStressLevel', 'stressDurationInSeconds', 'restStressDurationInSeconds', 'lowStressDurationInSeconds', 'mediumStressDurationInSeconds', 'highStressDurationInSeconds'
Stress	'max_StressLevelValues', 'std_StressLevelValues', 'max_BodyBatteryValues', 'min_BodyBatteryValues', 'mean_BodyBatteryValues', 'std_BodyBatteryValues'
Sleeps	–

Table 22 | Performance metrics related to K-means algorithms performed on patient 2 data with K=3

Clusters	Precision	Recall	F1-Score
Cluster 0	0,2	0,26	0,22
Cluster 1	0,27	0,25	0,26
Cluster 2	0,13	0,11	0,12

Table 23 | Confusion matrix related to K-means algorithm performed on patient 2 data with K=3

True Label	Predicted label		
	Cluster 0	**Cluster 1**	**Cluster 2**
Cluster 0	18	27	25
Cluster 1	24	19	34
Cluster 2	48	24	9
Accuracy = 0,2			

Table 24 | Number of acquisitions for each dataframe related to patient 3.

DataFrame	Number of Acquired Samples	Number of Acquired Weeks
Dailies Summary	84	12
Stress Summary	84	12
Sleep Summary	56	8

Table 25 | Statistically significant variables according to ANOVA test performed on patient 3 dailies data.

Dailies Variables	P values
moderateIntensityDurationInSeconds	0,004
minHeartRateInBeatsPerMinute	0,001
averageHeartRateInBeatsPerMinute	<0,001
restingHeartRateInBeatsPerMinute	<0,001
averageStressLevel	<0,001
stressDurationInSeconds	0,001
lowStressDurationInSeconds	<0,001
mediumStressDurationInSeconds	0,003
HR_std	0,004

Table 26 | Statistically significant Tukey HSD multicomparison performed for patient 3 dailies selected features, according to ANOVA test.

AVERAGE HEART RATE IN BEATS PER MINUTE						
Week 1	**Week 2**	**meandiff**	**p-adj**	**lower**	**upper**	**reject**
1	10	10,8857	0,0004	3,4125	18,3589	TRUE
1	12	12,1	0,0006	3,5384	20,6616	TRUE
2	9	7,2857	0,0264	0,4637	14,1078	TRUE
2	10	11,8571	0	5,0351	18,6792	TRUE
2	11	7,7381	0,0213	0,6375	14,8387	TRUE
2	12	13,0714	0	5,0719	21,071	TRUE
3	10	10,2857	0,0002	3,4637	17,1078	TRUE
3	12	11,5	0,0004	3,5005	19,4995	TRUE
4	10	7,4286	0,0215	0,6065	14,2506	TRUE
4	12	8,6429	0,0234	0,6433	16,6424	TRUE
6	10	9,2857	0,0043	1,8125	16,7589	TRUE
6	12	10,5	0,0051	1,9384	19,0616	TRUE
7	10	10,4524	0,0003	3,3518	17,553	TRUE
7	12	11,6667	0,0006	3,4283	19,9051	TRUE
8	10	7,1429	0,0323	0,3208	13,9649	TRUE
8	12	8,3571	0,033	0,3576	16,3567	TRUE
AVERAGE STRESS LEVEL						
Week 1	**Week 2**	**meandiff**	**p-adj**	**lower**	**upper**	**reject**
4	6	-17,6	0,0182	-33,5226	-1,6774	TRUE
6	9	16,3143	0,0399	0,3917	32,2369	TRUE
6	10	18,0286	0,0139	2,106	33,9512	TRUE
6	12	20,85	0,0124	2,6084	39,0916	TRUE
7	12	17,5833	0,0492	0,0303	35,1364	TRUE
HEART RATE STANDARD DEVIATION						
Week 1	**Week 2**	**meandiff**	**p-adj**	**lower**	**upper**	**reject**
2	10	-4,0234	0,0277	-7,8087	-0,2381	TRUE
8	10	-4,6978	0,0043	-8,4831	-0,9125	TRUE

LOW STRESS DURATION IN SECONDS						
Week 1	**Week 2**	**meandiff**	**p-adj**	**lower**	**upper**	**reject**
1	5	9342,857	0,0085	1421,04	17264,67	TRUE
2	5	7782,857	0,0243	551,2606	15014,45	TRUE
3	5	8057,143	0,0167	825,5463	15288,74	TRUE
5	6	-11310,9	0,0005	-19232,7	-3389,04	TRUE
5	7	-8062,86	0,0256	-15589,7	-535,973	TRUE
5	8	-7962,86	0,019	-15194,5	-731,261	TRUE
5	11	-10872,9	0,0004	-18399,7	-3345,97	TRUE
MEDIUM STRESS DURATION IN SECONDS						
Week 1	**Week 2**	**meandiff**	**p-adj**	**lower**	**upper**	**reject**
4	6	-9886,29	0,0081	-18242,4	-1530,13	TRUE
5	6	-8643,43	0,0364	-16999,6	-287,277	TRUE
MIN HEART RATE IN BEATS PER MINUTE						
Week 1	**Week 2**	**meandiff**	**p-adj**	**lower**	**upper**	**reject**
2	10	15,1429	0,0008	4,2082	26,0775	TRUE
3	10	12,8571	0,0088	1,9225	23,7918	TRUE
4	10	12,4286	0,0133	1,494	23,3632	TRUE
6	10	12,3143	0,0386	0,336	24,2926	TRUE
7	10	13,881	0,0055	2,4998	25,2621	TRUE
MODERATE INTENSITY DURATION IN SECONDS						
Week 1	**Week 2**	**meandiff**	**p-adj**	**lower**	**upper**	**reject**
2	10	4105,714	0,0398	99,7083	8111,72	TRUE
RESTING HEART RATE IN BEATS PER MINUTES						
Week 1	**Week 2**	**meandiff**	**p-adj**	**lower**	**upper**	**reject**
1	10	10	0,0244	0,7069	19,2931	TRUE
1	12	11,25	0,0294	0,6034	21,8966	TRUE
2	10	12,4286	0,0003	3,9452	20,912	TRUE
2	11	9,0952	0,0379	0,2654	17,9251	TRUE
2	12	13,6786	0,0009	3,7309	23,6263	TRUE
3	10	12,8571	0,0002	4,3737	21,3406	TRUE
3	11	9,5238	0,0238	0,694	18,3536	TRUE
3	12	14,1071	0,0006	4,1595	24,0548	TRUE
4	10	11,2857	0,0016	2,8023	19,7691	TRUE
4	12	12,5357	0,0035	2,588	22,4834	TRUE
7	10	10,1667	0,0114	1,3368	18,9965	TRUE
7	12	11,4167	0,0166	1,172	21,6614	TRUE
8	10	9,1429	0,024	0,6594	17,6263	TRUE
8	12	10,3929	0,033	0,4452	20,3405	TRUE
STRESS DURATION IN SECONDS						

Week 1	Week 2	meandiff	p-adj	lower	upper	reject
4	6	-19116	0,013	-35909	-2322,98	TRUE
4	11	-16680	0,0328	-32635,8	-724,175	TRUE
5	6	-20718,9	0,0047	-37511,9	-3925,84	TRUE
5	11	-18282,9	0,0121	-34238,7	-2327,03	TRUE

Table 27 | Statistically significant variables according to ANOVA test performed on patient 3 stress data.

Stress Variables	P values
durationInSeconds	0,015
max_StressLevelValues	< 0,001
mean_StressLevelValues	0,019
std_StressLevelValues	0,005
max_BodyBatteryValues	0,019
mean_BodyBatteryValues	0,002
std_BodyBatteryValues	< 0,001

Table 28 | Statistically significant Tukey HSD multicomparison performed for patient 3 stress selected features, according to ANOVA test.

DURATION IN SECONDS						
Week 1	**Week 2**	**meandiff**	**p-adj**	**lower**	**upper**	**reject**
1	2	23802,86	0,0321	1076,656	46529,06	TRUE
1	3	23220	0,0409	493,7987	45946,2	TRUE
1	5	23802,86	0,0321	1076,656	46529,06	TRUE
1	8	23802,86	0,0321	1076,656	46529,06	TRUE
1	9	23802,86	0,0321	1076,656	46529,06	TRUE
1	10	23802,86	0,0321	1076,656	46529,06	TRUE
MAX BODY BATTERY VALUES						
Week 1	**Week 2**	**meandiff**	**p-adj**	**lower**	**upper**	**reject**
1	7	32,2286	0,0348	1,2079	63,2492	TRUE
MAX STRESS LEVEL VALUES						

Week 1	Week 2	meandiff	p-adj	lower	upper	reject
1	2	23,5714	0,0001	8,473	38,6699	TRUE
1	3	18,2857	0,006	3,1872	33,3842	TRUE
1	4	19,8571	0,0018	4,7587	34,9556	TRUE
1	5	15,2857	0,0446	0,1872	30,3842	TRUE
1	6	22,3095	0,0005	6,5945	38,0245	TRUE
1	7	24,7429	0,0002	8,2033	41,2824	TRUE
1	8	20,7143	0,0009	5,6158	35,8128	TRUE
1	9	16,1429	0,026	1,0444	31,2413	TRUE
MEAN BODY BATTERY VALUES						
Week 1	**Week 2**	**meandiff**	**p-adj**	**lower**	**upper**	**reject**
6	12	-23,5156	0,0248	-45,4118	-1,6193	VERO
7	12	-25,1884	0,0189	-48,0583	-2,3185	VERO
BODY BATTERY VALUES STANDARD DEVIATION						
Week 1	**Week 2**	**meandiff**	**p-adj**	**lower**	**upper**	**reject**
2	5	-11,337	0,0205	-21,7089	-0,965	TRUE
2	9	-10,7237	0,0365	-21,0956	-0,3517	TRUE
2	10	-12,1403	0,0092	-22,5123	-1,7683	TRUE
2	12	-11,9862	0,0299	-23,3481	-0,6243	TRUE
5	6	10,8179	0,0491	0,0224	21,6134	TRUE
5	7	12,5587	0,0181	1,1968	23,9206	TRUE
6	10	-11,6212	0,0242	-22,4167	-0,8258	TRUE
7	9	-11,9454	0,0309	-23,3073	-0,5835	TRUE
7	10	-13,362	0,0087	-24,724	-2,0001	TRUE
7	12	-13,2079	0,0243	-25,4802	-0,9357	TRUE
STRESS LEVEL VALUES STANDARD DEVIATION						
Week 1	**Week 2**	**meandiff**	**p-adj**	**lower**	**upper**	**reject**
1	2	9,3773	0,0223	0,7326	18,022	TRUE
1	7	9,7487	0,0381	0,2789	19,2184	TRUE

Table 29 | Summary of the selected features according to the results provided by ANOVA and Tukey HSD tests performed on patient 3 data.

Patient 3	Selected features
Dailies	'moderateIntensityDurationInSeconds', 'minHeartRateInBeatsPerMinute', 'averageHeartRateInBeatsPerMinute', 'restingHeartRateInBeatsPerMinute', 'averageStressLevel', 'stressDurationInSeconds', 'lowStressDurationInSeconds', 'mediumStressDurationInSeconds', 'HR_std'
Stress	'durationInSeconds', 'max_StressLevelValues', 'std_StressLevelValues', 'max_BodyBatteryValues', 'mean_BodyBatteryValues', 'std_BodyBatteryValues'

Sleeps	–

Table 30 | Performance metrics related to K-means algorithms performed on patient 3 data with K=3.

Clusters	Precision	Recall	F1-Score
Cluster 0	0,31	0,24	0,27
Cluster 1	0,29	0,25	0,27
Cluster 2	0,11	0,15	0,13

Table 31 | Confusion matrix related to K-means algorithm performed on patient 3 data with K=3

True Label	Predicted label		
	Cluster 0	Cluster 1	Cluster 2
Cluster 0	5	2	14
Cluster 1	4	7	17
Cluster 2	7	15	4
Accuracy = 0,21			

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