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SENSOR-BASED EVALUATION OF CIRCADIAN MOTOR BEHAVIOR IN PEOPLE WITH DEMENTIA. DEVELOPMENT AND VALIDATION OF ANALYSIS STRATEGIES.

Tesi in
Elaborazione di dati e segnali biomedici LM

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Alla mia cara famiglia,
a Luca,
agli amici: quelli di sempre,
quelli nuovi e quelli ancora da scoprire

Contents

Sommario

Introduzione: La demenza consiste nel deterioramento, spesso progressivo, dello stato cognitivo di un individuo. Chi è affetto da demenza, presenta alterazioni a livello cognitivo, comportamentale e motorio, ad esempio compiendo gesti ossessivi, ripetitivi, senza uno scopo preciso. La condizione dei pazienti affetti da demenza è valutata clinicamente tramite apposite scale e le informazioni relative al comportamento vengono raccolte intervistando chi se ne occupa, come familiari, il personale infermieristico o il medico curante. Spesso queste valutazioni si rivelano inaccurate, possono essere fortemente influenzate da considerazioni soggettive, e sono dispendiose in termini di tempo. Si ha quindi l'esigenza di disporre di metodiche oggettive per valutare il comportamento motorio dei pazienti e le sue alterazioni patologiche; i sensori inerziali indossabili potrebbero costituire una valida soluzione, per questo scopo. L'obiettivo principale della presente attività di tesi è stato definire e implementare un software per una valutazione oggettiva, basata su sensori, del pattern motorio circadiano, in pazienti affetti da demenza ricoverati in un'unità di terapia a lungo termine, che potrebbe evidenziare differenze nei sintomi della malattia che interessano il comportamento motorio, come descritto in ambito clinico. Lo scopo secondario è stato quello di verificare i cambiamenti motori pre- e post- intervento in un sottogruppo di pazienti, a seguito della somministrazione di un programma sperimentale di intervento basato su esercizi fisici.
Materiali e Metodi: I dati per lo studio sono stati acquisti su 82 pazienti affetti da demenza e ricoverati nella clinica LVR di Colonia in Germania, di età compresa tra i 55 e i 95 anni, tramite un sensore inerziale indossabile indossabile posizionato in regione lombare, in prossimità di L5 e sviluppato dall'Università di Bologna (sistema uSense). I segnali sono stati elaborati in Matlab ed è stato sviluppato un software per la misura di diverse quantità di interesse per la valutazione dell'attività motoria e per evidenziare la struttura temporale del pattern di attività. Sono state estratte informazioni sui periodi di riposo, di attività, di sedentarietà e di cammino e, dalla distribuzione e disposizione dei diversi periodi nelle ore del giorno, sono state

calcolate misure di complessità (entropia di Shannon, complessità di Lempel e Ziv, Sample Entropy, Recurrence Period Density Entropy); è stata applicata l'analisi frattale (Fano Factor Analysis e Detrended Fluctuation Analysis), e la Cosinor analysis. L'analisi della varianza è stata impiegata per il confronto tra sotto-gruppi di pazienti.
Risultati: Attraverso opportuni criteri di inclusione ed esclusione, il campione complessivo è stato ridotto a 64 pazienti per l'analisi della baseline e di 44 soggetti per il confronto tra pre e post intervento sperimentale. La classificazione clinica è apparsa da subito poco accurata e l'analisi si è concentrata sui profili motori ottenuti tramite le metodiche di valutazione oggettiva per la quale si sono ottenuti risultati coerenti con la descrizione e l'interpretazione clinica delle diverse categorie di pazienti. Nel confronto dei pazienti pre e post intervento non sono invece state evidenziate differenze significative.
Conclusioni:A valle dei risultati ottenuti è possibile affermare che la valutazione e la classificazione dei comportamenti motori dei pazienti affetti da demenza, tramite sensoristica inerziale indossabile, le metriche di entropia e la struttura delle serie temporali, è possibile ed è in grado di evidenziare le caratteristiche specifiche dei profili patologici descritti in clinica. Queste metodiche possono essere impiegate come supporto alla decisione clinica. L'analisi del pre e post intervento non ha invece mostrato effetti significativi; possibili fattori che hanno avuto un peso nello studio di intervento sono la grande eterogeneità del campione e l'aderenza al trattamento che è stata molto variabile tra i soggetti.

Abstract

Introduction: Dementia involves deterioration, often progressive, of a person's cognitive status. Those who suffer from dementia, present alterations in cognitive and motor behavior, for example performing obsessive and repetitive gestures, without a purpose. The condition of patients suffering from dementia is clinically assessed by means of specific scales and information relating to the behavior are collected by interviewing caregivers, such as the family, nurses, or the doctor. Often it turns out that these are inaccurate assessments that may be heavily influenced by subjective evaluations and are costly in terms of time. Therefore, there is the need for objective methods to assess the patients' motor behavior and the pathological changes; wearable inertial sensors may represent a viable option, so this aim. The main objective of this thesis project was to define and implement a software for a sensor-based assessment of the circadian motor pattern in patients suffering from dementia, hospitalized in a long-term care unit, which could highlight differences in the disease symptoms affecting the motor behavior, as described in the clinical setting. The secondary objective was to verify pre- and post-intervention changes in the motor patterns of a subgroup of patients, following the administration of an experimental program of intervention based on physical exercises.
Materials and Methods: Data for the study were collected on 82 patients suffering from dementia and admitted to the LVR clinic in Cologne, Germany, between 55 and 95 years old, through a wearable inertial sensor developed by the University of Bologna (uSense system) positioned on the lower back, in proximity of L5. Signals were processed in Matlab and a software has been developed for the measurement of different quantities of interest, for the evaluation of general mobility and to highlight the temporal structure of the pattern of activities. Information about rest intervals, activity, sedentariness and gait were extracted and, from the distribution and arrangement in different periods during the day, complexity measures were calculated (Shannon's entropy, Lempel-Ziv complexity, Sample Entropy, Recurrence Period Density Entropy); the fractal analysis (Fano Factor Analysis and Detrended

Fluctuation Analysis) and the Cosinor Analysis were applied. The analysis of variance was used for comparison between subgroups of patients.
Results: Through appropriate inclusion and exclusion criteria, the finall sample was of 64 patients for the baseline analysis and of 44 subjects for the comparison between the pre- and post- experimental intervention. The clinical classification appeared immediately inaccurate and the analysis has been focused on the motion profiles obtained through the objective assessment, for which results were consistent with the description and interpretation of the different clinical patients categories. However, in the comparison of patients before and after the intervention, no significant differences have been shown.
Conclusions: Based on obtained results, it can be stated that the assessment and classification of motor behavior in patients with dementia, using wearable inertial sensors, metrics of entropy and the structure of time series, is possible, and it is able to highlight the specific characteristics of pathological profiles described in the clinic. These methods can be used to support clinical decision. The analysis of pre- and post- intervention, instead, showed no significant effects; possible factors that played a role in the study of intervention are the great sample heterogeneity and the highly variable adherence to treatment among subjects.

Chapter 1

Introduction

With the progress of medicine, an aging population and the prevalence of age-related diseases are a rising factor in next decades. Among them, the number of cases of dementia will continue to rise and the behavioral and psychological symptoms, such as aggressive behaviors, day-night rhythm disturbances, and restlessness are the most clinical features seen during the late course of dementia. A handling of symptoms is required because they place a particular burden on caregivers and family [47]. This project searches for strategies that are more suitable to quantify the circadian behavior in people suffering from dementia who live in a long-term care unit, and which highlight clinically relevant differences among the patients, providing an objective support to the current methods used by clinicians. Since a link between physical inactivity and behavioral disturbances is described in literature [30, 51], it is aimed also to find out whether it is possible to quantify, with the chosen methods, a change in behavior after a physical exercise protocol. To answer the questions, it has been chosen to use an inertial measurement unit (IMU), worn by each subject analysed in the project and to develop a software in Matlab, for the analysis of the collected data. The IMU recorded the motor behavior for three days both at the baseline and in the post-intervention, starting from the hour of the sensor placement on the lower back. Data have been acquired from inpatients in the Department of Old Age Psychiatry at the LVR-Hospital in Cologne, by means of a hybrid body worn motion sensor, the uSense-sensor, developed by the University of Bologna, at the Department of Electrical, Electronic and Information Engineering «Guglielmo Marconi» (DEI). The project has been performed in collaboration with the Institute of Movement and Sport Gerontology of the German Sport University (DSHS): as partners in FARSEEING EU project, DSHS and DEI investigated the effects of tailored interventions on mobility and motor behavioural disturbances in elderly people, with the aid of ICT. Ethical approval was

obtained by the Ethical Committee of the German Sport University Cologne and the North-Rhine Medical Chamber [30].

1.1 Project Background

1.1.1 Dementia

Dementia is not a specific disease, but a collective term to describe a wide range of symptoms, associated with the decline of memory or other thinking skills, severe enough to reduce a person's ability to perform activities of daily living [3, 5, 7]. Dementia has multiple types: Alzheimer's disease, vascular dementia, vitamin deficiency and thyroid related problems; symptoms of dementia can vary greatly. The illness is caused by damaged brain cells and the different types are associated to specific brain regions involved [17]. Therefore, different kinds of behavioral and psychological symptoms occur, not only related with cognitive skills, but also with motor skills, like pacing back and forth, wandering around, night-time wakefulness, rummage around, and restlessness.

1.1.2 State of art and clinical assessment

In dementia care units, physicians assess patient's behavior interviewing caregivers and the nursing staff. The usual clinical assessment includes three main evaluation scales: the Neuropsychiatric Inventory (NPI), the Cohen-Mansfield Agitation Inventory (CMAI), and the Clinical Global Impression of Change (CGIC) that, together with other tests, provides an insight into patient's behavior over a week spent in the ward. What is evaluated, is the frequency and severity of pathological behavior (e.g. obsessions, restlessness, wandering, aberrant motor behavior), and the caregiver's burden. Additional details about the clinical assessment in dementia are given below:

- The NPI: the Neuropsychiatric Inventory is used for assessing neuropsychiatric symptoms and psychopathologies in patients with neurodegenerative disorders. The questionnaire has been developed for providing a brief assessment of neuropsychiatric symptomatology in clinical settings. Ten behavioral and two neurodegenerative areas are included in the NPI, where two items are about the aberration in the motor behavior (item 10: aberrant motor behavior, and item 1 in neurodegenerative area: sleep and night-time behavior disorders) [2]. This inventory is based on the answers of an informed caregiver, who is able to observe the patient at least 4 hours a day, at least for 4 days per

week, with the patient. Questions are about changes in behavior; frequency and severity rating of the symptoms (1=rarely; 2=sometimes; 3=often; 4=very often and 1=mild; 2=moderate; 3=severe); neurodegenerative changes; and caregiver distress (0=not at all; 1=minimally; 2=mildly; 3=moderately; 4=severely; 5=extremely).

- The CMAI: The Cohen-Mansfield Agitation Inventory is a 29-item scale to assess agitation [19, 20, 21]. The CMAI is completed by interviewing nursing staff or family caregivers and the 29 items are rated on a 7-point scale of frequency (1. Never; 2. Less than once a week but still occurring; 3. Once or twice a week; 4. Several times a week; 5. Once or twice a day; 6. Several times a day; 7. Several times an hour.). Ratings pertain to the two weeks preceding the administration of the CMAI [18, 19]. In addition, the rater is asked to give information as to how disruptive each behavior is. The rating scale is a 5-point scale of disruptiveness (1 = never, 5 = extremely). This scale relies on subjective information given by the rater but inter-rater reliability is not known for judging disruptiveness [25].

- The CGIC: the clinical global impression of change is intended to be used as a measure of clinically meaningful change. The CGIC focuses on clinicians' observations of change in the patient's cognitive, functional, and behavioral performance since the beginning of a trial. Scoring is based on an interview with the caregiver and examination of the patient by an independent evaluator, without consulting other information such as cognitive test results [17, 24].

- ICD-10: the "International Classification of Diseases, Injuries and Causes of Death" is used in statistic and epidemiologic studies. Description of dementia patients is in chapter V, F00.1* (dementia in Alzheimer's disease with late onset), sub-category G30.1+ (after the age of 65) and F07.8 (Other organic personality and behavioural disorders due to brain disease, damage and dysfunction: Right hemispheric organic affective disorder) [31].

- The MMSE: The Mini-Mental State Examination is used to measure cognitive impairment. It is also used as a screening tool for dementia, and neuropsychological syndromes of different nature. MMSE has been designed for pathologies symptoms with cognitive impairment (such as Alzheimer's disease) while subjects suffering from diseases with executive impairment (such as Parkinson's disease) may not show any deterioration, except in very advanced stages of the disease [32, 33].

- B-ADL: the Bayer Instrumental activities for daily living evaluates subjects' ability to perform daily life activities. It is mainly used to test elderly people's social life or to determine their self-sufficiency, but is also useful in home care [34]. A patient is classified as disabled if he does not perform or cannot perform the task analysed, or the inability is due to health problems [35].

A limit of the above mentioned clinical tools is that the scoring is mostly based on subjective observations. This could lead to an over- or underestimation of pathological behaviours and aberration in patient's activity pattern [7, 8]. Clinical decision-making could be strongly influenced by biased or inaccurate information.

1.1.3 Quantitative assessment: The Inertial sensors

A possible way to monitor human motor behaviour in everyday life is the use of one or more wearable inertial sensors placed on relevant body segments: measurement of the segments' velocity, relative position and orientation allows assessing users' mobility pattern and functional capacity [8, 11, 16, 44, 45]. Inertial measurement units (IMU) embed a triaxial accelerometer, gyroscope and magnetometer, to measure acceleration, angular velocity and local magnetic field. A reliable sensor-based assessment would allow a continuous and objective monitoring of the patient's motor behaviour in real life conditions. The use of wearable inertial sensors requires intelligent signal processing and appropriate methods for activity recognition but outcomes usually outdo those of the actigraphy approach. Indeed, actigraphy outcomes are limited to the information on absence/presence of movement and its intensity [46, 47, 48]. Moreover actigraphs are usually worn on the wrist like a watch and demented patients often reacts badly removing it at the earliest opportunity [49]. IMU are usually fixed on anatomical landmarks such as the lower back, hip, thigh, leg [26, 27, 44, 45, 50]: the lower back is a promising anatomical landmark since the patient does not see it and may forget about it if it is small and comfortable enough. A detailed description of the sensors embedded into an IMU is reported in the following paragraphs.

1.1.3.1 The Accelerometer

The accelerometer measures the proper acceleration and it behaves as a damped mass on a spring: when the sensor is subject to acceleration, the mass is displaced to the point that the spring accelerates it at the same rate as the case. The displacement is measured and the acceleration is given by

solving a second order differential equation:

$$K_s \cdot x_0 + B \cdot \dot{x_0} = M \cdot (a - \ddot{x_0}) \tag{1.1a}$$

$$\ddot{x_0} + \frac{B}{M} \cdot \dot{x_0} + \frac{K_s}{M} \cdot x_0 = a \tag{1.1b}$$

Where M is the mass; K_s is the spring constant; B is the damping constant; x_0 is the displacement and a, is the acceleration to be measured with the accelerometer. Single and multi-axis models are available to detect magnitude and direction of acceleration as a vector quantity and can be used to sense:

- Linear acceleration along the measurement axis;
- Inclination with respect to the gravity line;
- Vibration;
- Shock.

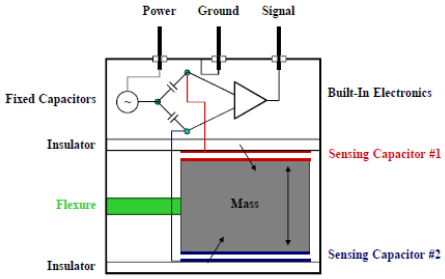


Figure 1.1: capacitive accelerometer model

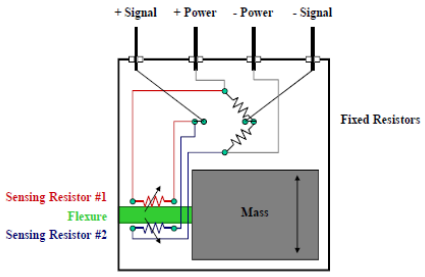


Figure 1.2: resistive accelerometer model

Images from: Kinematic sensors – Prof. Angelo Cappello – teaching material of "Bioengineering rehabilitation"

In resistive accelerometers (Figure 1.2), voltage output of the resistor bridge changes proportionally with applied acceleration; in capacitive ones (Figure 1.1), frequency modulation technique is used through varying the capacitor bridge. Nowadays accelerometers are usually small micro electro-mechanical systems (MEMS, Figure 1.3), consisting of a cantilever beam with a proof mass [26, 27].

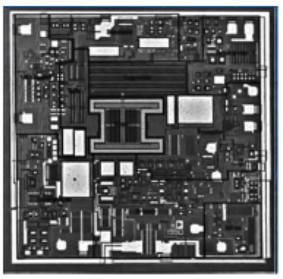


Figure 1.3: polysilicon MEMS

Images from: Kinematic sensors – Prof. Angelo Cappello – teaching material of "Bioengineering rehabilitation"

1.1.3.2 The Gyroscope

The gyroscope is a device for measuring angular velocity based on the principle of the angular momentum conservation. A MEMS gyroscope takes the idea of the Foucault pendulum and uses a vibrating element: a vibrating object tends to continue vibrating in the same plane as its support rotates (Figure 1.4). This type of device is also known as a Coriolis vibratory gyroscope because, as the plane of oscillation is rotated, the response detected by the transducer results from the Coriolis term in its equations of motion ("Coriolis force"). The Coriolis Effect is an apparent acceleration that arises in a moving element in a rotating body: considering a particle traveling with velocity v and the coordinate system rotating around the z-axis with angular velocity Ω, a hypothetic observer sees the particle moving toward the x-axis with acceleration:

$$\vec{a_{cor}} = 2v \times \Omega \tag{1.2}$$

The Coriolis acceleration is a modulated signal: frequency range is from several kHz to tens of kHz, while amplitude is in the sub-mg range. When a mechanical element is made to oscillate by the application of an alternating force, and the oscillating body is placed in a rotating reference frame, the Coriolis force produces a secondary oscillation perpendicular to the primary oscillation motion. The vibrating structure can be driven by electrostatic, electromagnetic or piezoelectric force, while capacitive, piezoresistive or piezoelectric sensors can detect the Coriolis induced vibrations, so, the transducer, needs to be driven into oscillation in order to function as a sensor. The governing equation of motion for a gyroscope device with a resonating

mass in the y-axis, rotated about the z-axis is given by the following second order differential equation:

$$\ddot{x_0} + \frac{B}{M}\dot{x_0} + \frac{K_s}{M}x_0 = a_{cor} = 2\Omega_z\dot{y} \tag{1.3}$$

Where Ω_z is the rate of rotation and y is the linear velocity of the structure due to the drive.

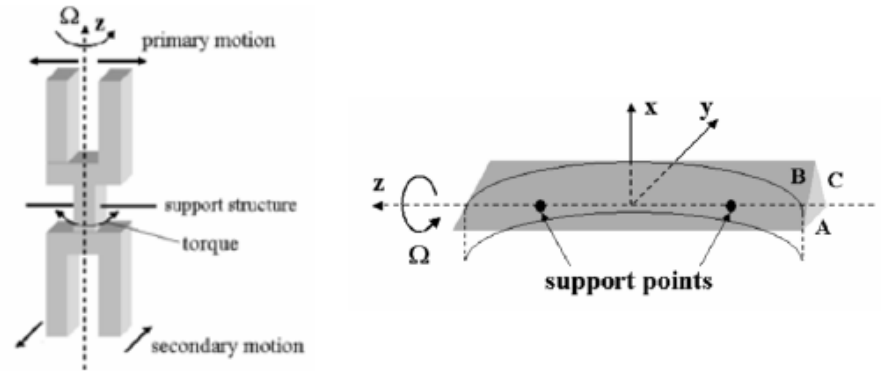


Figure 1.4: example of vibrating gyroscopes

Images from: Kinematic sensors – Prof. Angelo Cappello – teaching material of "Bioengineering rehabilitation"

MEMS gyroscopes present high impedance output and integrates measurements obtained from accelerometers, increasing accuracy in detecting subject shift.

1.1.3.3 The Magnetometer

Magnetometers are devices for measuring magnetic field and they can be divided into scalar magnetometers, which measure magnetic field module, and vector magnetometers, which measures one specific magnetic field direction component. The definition of three components along three independent directions allows defining a unique magnetic vector in the point where measure is taken. Magnetometers are sensors able to generate a difference in potential, depending on the magnetic field they are subjected to, so the electric signal in output will be proportional to its intensity. In absence of an external magnetic field, it is capable of measuring the Earth's magnetic field

vector, that assumes orientation and different intensities depending on the location on the globe, but that can be considered a constant reference in the laboratory environment. For example, the magnetometers whose operation principle is based on the Hall effect in a crystal semiconductor, they are most versatile and with greater sensitivity. Considering the charge carriers moving longitudinally in a semiconductor crystal, with speed v, immersed in a magnetic field B, which acts perpendicularly to them, one can observe a cross potential difference V, generated by the interaction of B with I (Hall effect). The total force acting on the electric charge is given by:

$$\vec{F} = q\vec{E} + q\vec{v} \wedge \vec{B} \tag{1.4}$$

which yields the electric field:

$$\vec{E} = -\vec{v} \wedge \vec{B} = -\frac{\vec{J}}{nq} \wedge \vec{B} \tag{1.5}$$

which produces a potential difference V proportional to current intensity and to magnetic field and inversely proportional to the thickness and the charges per volume unit:

$$V = \vec{E}\vec{I} = \frac{\vec{B}\vec{I}}{nqs} \tag{1.6}$$

So is possible to achieve high sensitivity:

$$S = \frac{dV}{dB} \tag{1.7}$$

in samples of low thickness with high resistivity. Hall Effect magnetic field sensors are particularly affected by the temperature changes that alter mobility of electrons in semiconductor crystal. It's also clear that, to make a correct measurement of Earth's magnetic field, it should be avoided as much as possible the presence of ferromagnetic materials and electronic equipment in the proximity of the sensor [28, 29]. Magnetic sensors define the component of the local magnetic field along an axis heard, producing a significant electric signal. In the analysis of movement, the measure of the Earth's magnetic field is needed for horizontal detection to complete the detection of vertical accelerometers, so to allow monitoring in three dimensions orientation.

1.2 Project Purposes

Measuring behavior provides important information on the patient's clinical evaluation. As reported in section 1.1.2, such information is usually obtained from a formal or informal caregiver who is familiar with the patient's behavior. Evaluator perception may introduce highly subjective factors, which have an impact on medical decisions. It is therefore important to introduce novel objective tools for the assessment of dementia symptoms and behavior [30]. A possible solution is the use of a wearable inertial sensor for measuring the patient's mobility pattern in the long-term care unit, and to identify specific symptoms like restlessness, wandering phenomenon, and aberration in the circadian motor behaviour [49]. The need to have an objective assessment tool becomes now even more relevant since clinicians are starting to take into account the use of different support therapies for replacing antidepressants, antipsychotics and mood stabilizers, because of their side effects. An alternative approach to pharmacological treatment, currently explored at the LVR clinic in Cologne (Germany), is the physical exercise; therefore, physical activity monitoring could address both needs: assess the post-intervention motor changes and assess the circadian motor behaviour [16, 50]. The main aim of the project is to develop and implement an objective, sensor-based assessment of the circadian motor patterns, for evaluating patients' living habits in the hospital, and to classify different disease symptoms affecting the motor behaviour. The secondary aim is to verify pre- and post-intervention changes in a subgroup of patients involved in the experimental exercise program performed at the LVR clinic, after two weeks of physical exercises in addition to Treatment as Usual (TaU) [30]. To address the main aim of the project, a software has been implemented in Matlab, for the circadian rhythmicity evaluation and classification of different motor behaviors in people with dementia. A statistical analysis has been performed for addressing the secondary aim, to investigate the effects of a day-structuring exercise program on dementia patients in the LVR hospital in Cologne. The hypothesis of the experimental exercise program is that the intervention group (IG), carrying out a 2-week-structuring exercise intervention in addition to TaU, will show a reduction in the behavioural and psychological symptoms of dementia in the post-intervention, while the control group (CG), only receiving social stimulation in addition to TaU, will not show such changes.

Chapter 2

Materials and Methods

2.1 Overview

2.1.1 Clinical assessment and intervention

Eighty-two patients between 55 and 95 years old and with different diagnosis of dementia (table 2.1), were recruited based on the diagnosis of dementia, according to ICD-10 criteria [31], and, after being screened by two external psychiatrist, stayed one week in the clinic before the enrolment, to familiarize with the environment and to exclude delirium. All patients enrolled were able to perform the Timed Up and Go Test (TuG). Patients excluded from the study presented non-vascular or non-neurodegenerative dementia, cardiac diseases that deny exercise participation and aggressive behavior that deny participation to group activities. The group allocation to create the control (CG) and intervention (IG) clusters has been done with the free online software Qminim, to minimize differences between the tested clumps. Group allocation has been performed according to sex, age, MMSE [32, 33] and B-ADL [34]. Baseline characteristics have been recorded within the geriatric assessment, carried out by nurses and doctors of the LVR-Hospital, including age, sex, BMI, type of dementia [31], MMSE score [32,33], clock-drawing-test score, cognitive reserve capacity, the 10 meter gate speed (TuG) and B-ADL[34,35]. Patients who took part in the intervention with physical exercises, had TaU (exercise therapy for 45 minutes twice a week) and an additional 2-week exercise program: on three non-consecutive days of the week, they were offered of 4-exercises sessions a day, but each session was not compulsory. If patient refused or were unable to participate, instructor invited him/her at the next scheduled exercise session, while if positive feedback was given, patient carried out a 20-minute session, followed by a rest period of an hour (table 2.2). For participation to be rated as complete, more

than 50% of scheduled exercise time, intensity and repetitions were required. Two exercise sessions included endurance exercises on seated ergometers for upper and lower limb; other two focused on strengthening, with wrist and ankle worn weights. The sessions included 2 minutes of warm up at the beginning and two minutes of cool down at the end [30]. The control group followed psychosocial stimulation at the time the experimental one had the physical activity (table 2.3).

Table 2.1: ICD-10 code explanation

Type of Dementia	**ICD-10 Code**
Dementia in Alzheimer's disease	F00/G30
Vascular Dementia	F01
Dementia in other diseases classified elsewhere	F02
Unspecified Dementia	F03
Other specified degenerative diseases of nervous system [Lewy-body Dementia]	G31.8
Primary psychiatric diagnoses	
Organic hallucinosis	F06.0
Organic delusional [schizophrenia-like] disorders	F06.2
Organic mood [affective] disorders	F06.3
Organic anxiety disorder	F06.4
Other organic personality and behavioral disorders due to brain disease, damage and disfunction	F07.9
Severe depressive episode without psychotic symptoms	F32.2
Secondary diagnosis	
Progressive vascular leukoencephalopathy [Binswanger's disease]	I67.3
Parkinson's disease	G20.00

Table 2.2: example of scheduled activities

	a.m.						**p.m.**						
Time	**9:00**	**9:30**	**10:00**	**10:30**	**11:00**	**11:30**	**00:00 to 02:00**	**2:00**	**2:30**	**3:00**	**3:30**	**4:00**	**4:30**
Groups													
Group 1	I			II			Lunch Break	III			IV		
Group 2		I			II				III			IV	
Group 3			I			II				III			IV

Table 2.3: example of participation

	Int-day 1				Int-day 2				Int-day 3				Int-day 4				Int-day 5				Int-day 6			
DD.MM	16.03				18.03				20.03				23.03				25.03				27.03			
exerc. session	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
ID 25	X	S	X	X	X	X	X	X	X	O5	O3	X	O2	X	X	O4	O5	X	O2	X	O2	X	O4	X

x = participation (20 min. net exercise time)
S = sleep/advanced tiredness
O2= overlap with other therapies
O3=overlap with nursing services
O4=overlap with visiting relatives
O5=overlap due to other

2.1.2 Dataset acquisition

After the feasibility assessment [49], the uSense sensor has been fixed in proximity of L5, on the lower back, to avoid any sense of presence of the sensor for the patients and for avoiding the early removal. The uSense recorded each patient's activities for more than 60 hours at the pre-intervention (three days before the start of the exercises) and additional 60 hours at the post-intervention, the following three days after 2-weeks of exercises (Figure 2.1). The sensor was attached to the patient in the period from 8:00 until 11:00 in the morning, and the recording time was about 72 hours. A Java-compiled software (WMU_sw8, Figure 2.2) and a docking station have been used to download the raw data and convert them into a TXT format. Six or more .txt files were generated by the Java software containing eight hours of recording each (Figure 2.4); log files reported nine columns of values (Figure 2.5). Details on the uSense system are reported in the next paragraph.

Figure 2.1: schedule of body-fixed sensor assessment of patient motion behavior: T0=baseline; Int0=beginning of intervention; Int1=end of intervention; T1=after intervention

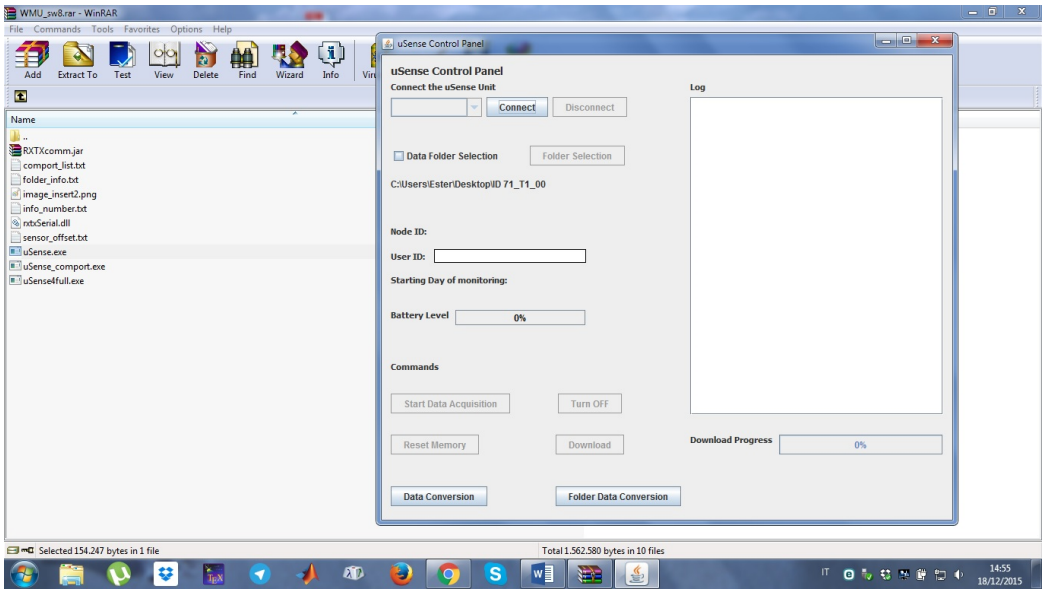


Figure 2.2: Java-compiled software GUI for downloading and raw data conversion

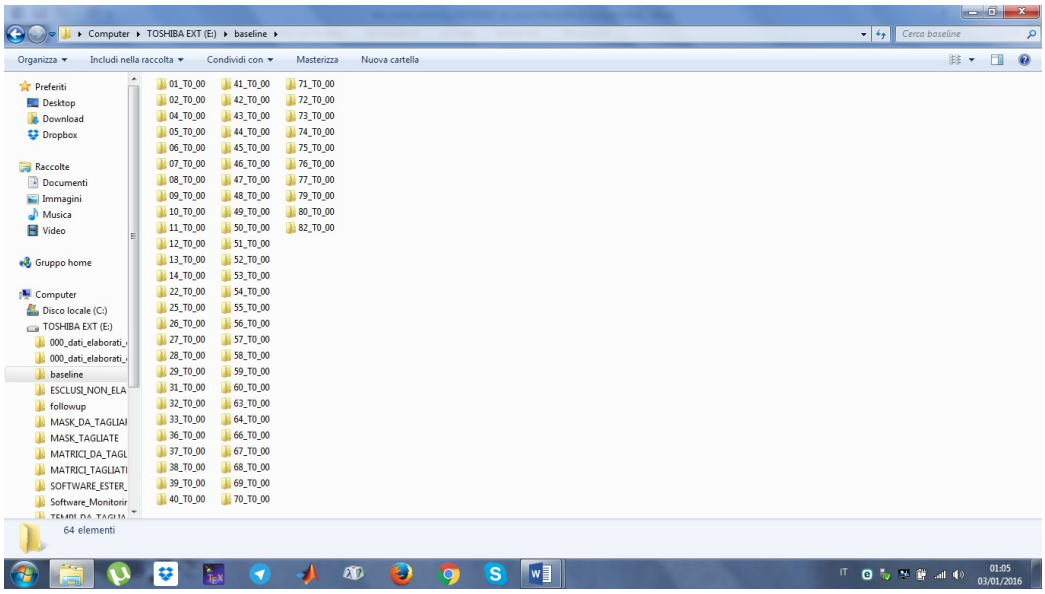


Figure 2.3: output from the java-compiled software for the raw data conversion

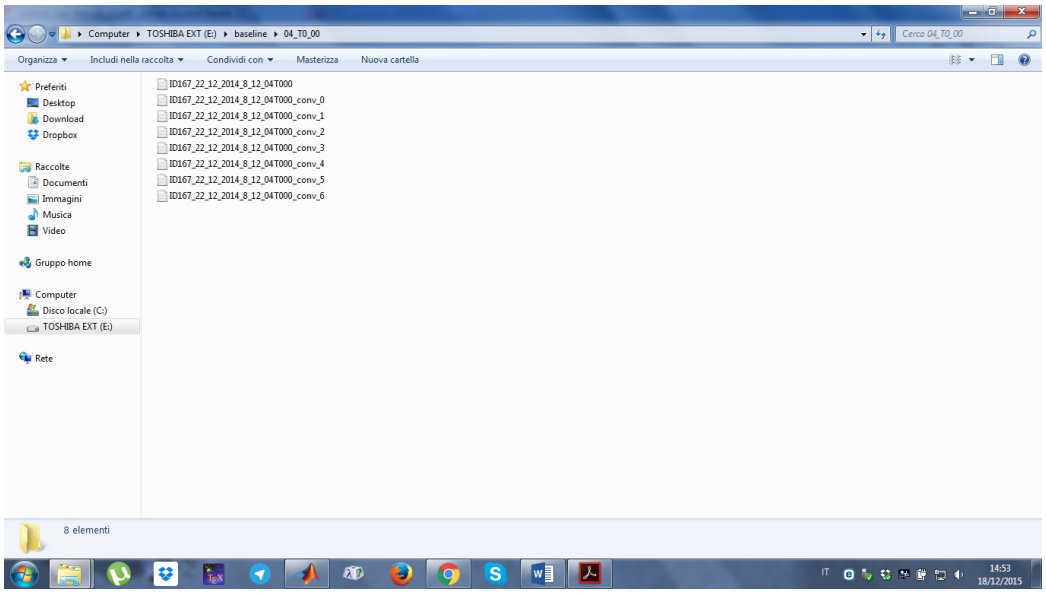


Figure 2.4: log file converted in 8-hours files

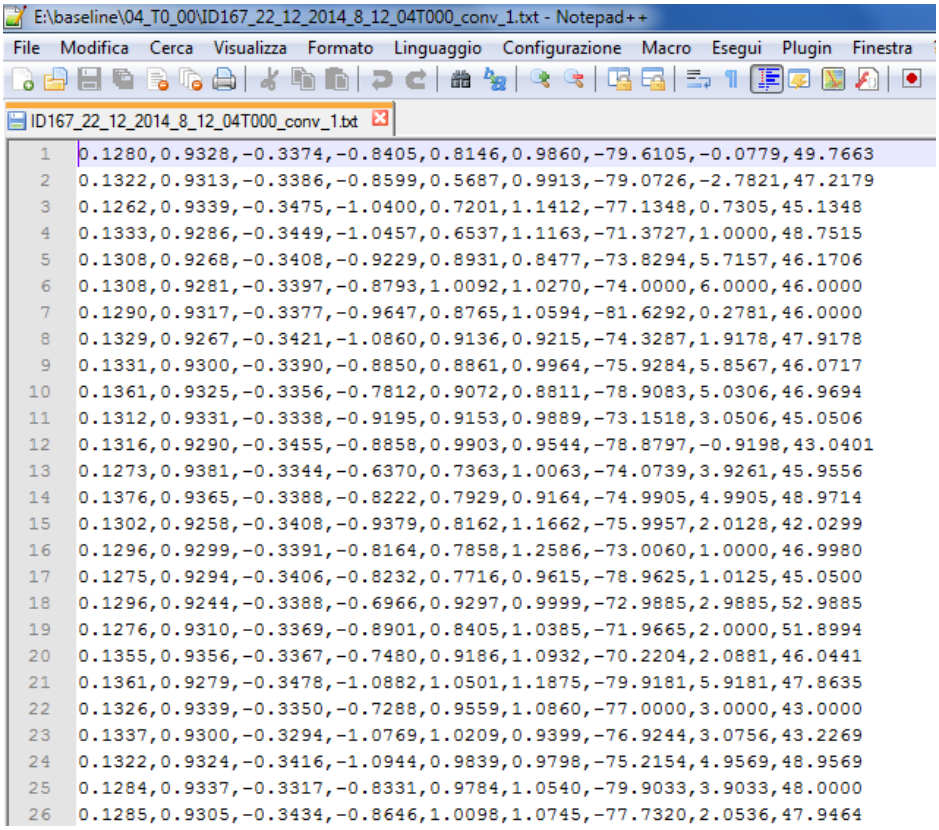


Figure 2.5: data recorded

2.1.2.1 The uSense sensor system

The printed circuit board of the wearable unit, designed and developed by DEI at University of Bologna, mounts the following components:

- Microcontroller AT32UC3A4256-C1UR, manufactured by Atmel Corporation (`www.atmel.com`);
- Memory MT29F8G08ABACA-H4 by Micron Semiconductor Products (`www.micron.com`);
- SENSOR1 – MPU-9150 - manufactured by InvenSense Inc. (`www.invensense.com`);
- Embedded temperature sensor;
- On-a-chip oscillator;
    - Gyroscope features: user-programmable full-scale range of ±250, ±500, ±1000 and ±2000°/s, sensitivity 131-16.4 LSB/(°/s);
    - Accelerometer features: programmable full scale range of ±2g, ±4g, ±8g, ±16g, sensitivity 16.4-2 LSB/g;
    - Magnetometer features: Full-scale measurement range is ±1200 μT, resolution 0.3 μT
- SENSOR2 – LSM330DTR – manufactured by STMicroelectronics (`www.st.com`)
    - Gyroscope features: user-programmable full-scale range of ±250, ±500, ±1000 and ±2000°/s, sensitivity 8.75-70 m(°/s)/digit FARSEEING(288940);
    - Accelerometer features: programmable full scale range of ±2g, ±4g, ±8g, ±16g, sensitivity 1-12 mg/digit;
- Battery – LP383560-PCM-LD – manufactured by EEMB (`www.eemb.com`).

Accelerometer range is set at 2g, gyroscope range is set at 250°/s, sampling rate is 100 Hz, battery life is between 69 and 72h. The case is made with hypoallergenic material and is water-resistant, weight is 36g, dimensions are $10 \times 42 \times 68$ mm. The uSense system is composed by three main components: a software application, the sensing unit (uSense sensor) and a docking station.

The docking station is used to connect the sensing unit with the software application. The uSense software application is used to manage the Sensing Unit and it allows performing the following actions:

- start/stop the data recording;
- download the data stored in the internal sensor memory;
- reset the memory (this operation is needed before starting a new monitoring session);
- convert the raw data;
- turn off the Sensing Unit.

The inertial raw data are collected and converted in .txt files of 8 hours each, formatted as a table with nine columns: each row contains nine comma-separated values: three values for the 3-axis accelerometer, three values for the 3-axis gyroscope and three values for the 3-axis magnetometer. Each row is the equivalent of one single sample, i.e.:

acc X, acc Y, acc Z, gyro X, gyro Y, gyro Z, mag X, mag Y, mag Z .

acc X: accelerometer raw signal captured on the X axis;
acc Y: accelerometer raw signal captured on the Y axis;
acc Z: accelerometer raw signal captured on the Z axis;

gyro X: gyroscope raw signal captured on the X axis;
gyro Y: gyroscope raw signal captured on the Y axis;
gyro Z: gyroscope raw signal captured on the Z axis;

mag X: magnetometer raw signal captured on the X axis;
mag Y: magnetometer raw signal captured on the Y axis;
mag Z: magnetometer raw signal captured on the Z axis.

Data stored in the log file are the raw signal captured from each sensor (i.e. 16-bit resolution). Formulas to convert raw data are as follows:

Accelerometer:
Accelerometer Data range: +/- 2g
Accelerometer Raw Data range: +/- 32768
Conversion formula (for each axis):

g = (Accelerometer_raw_value)/ (32768/2)

Gyroscope:
Gyroscope Data range: +/-250 degree/sec
Gyroscope Raw Data range: +/-32768
Conversion formula (for each axis):
ω [degree/sec] = (Gyroscope_raw_value) / (32768/250)

Magnetometer:
Magnetometer Data range: +/-1200 μT
Magnetometer Raw Data range: +/-32768
Conversion formula (for each axis):
H[μT] = 0.007629 μT $\times$ (Magnetometer_raw_value) [10].

2.2 Signal processing and feature extraction

The uSense log files were loaded in Matlab and used as an input to a MatLab software developed and validated by DEI at the University of Bologna. The Matlab software performs signal processing and activity recognition distinguishing four categories: "lying", "sedentary", "active", and "walking". Software output also includes: the time of the day, the activity duration and other advanced parameters like the energy expenditure and gait cadence in a matrix format (Figure 2.6). Two additional vectors are given as an output: the time series of activity categories and the time vector with the time of the day both sampled at 100 Hz. Since it is important to observe exactly the same time frame for the analysis of the circadian motor behaviour and for making statistical comparisons between different patients groups, a Matlab function has been implemented to cut the recording into blocks of exactly 48 consecutive hours from 12:00 to 12:00 (with apposite function *cut_output.m*). Another function was used to select the subjects who were observed in this time frame (with function *select_48_hours.m*). Patients without 48 hours of continuous recording from 12:00 to 12:00 were excluded from the analysis.

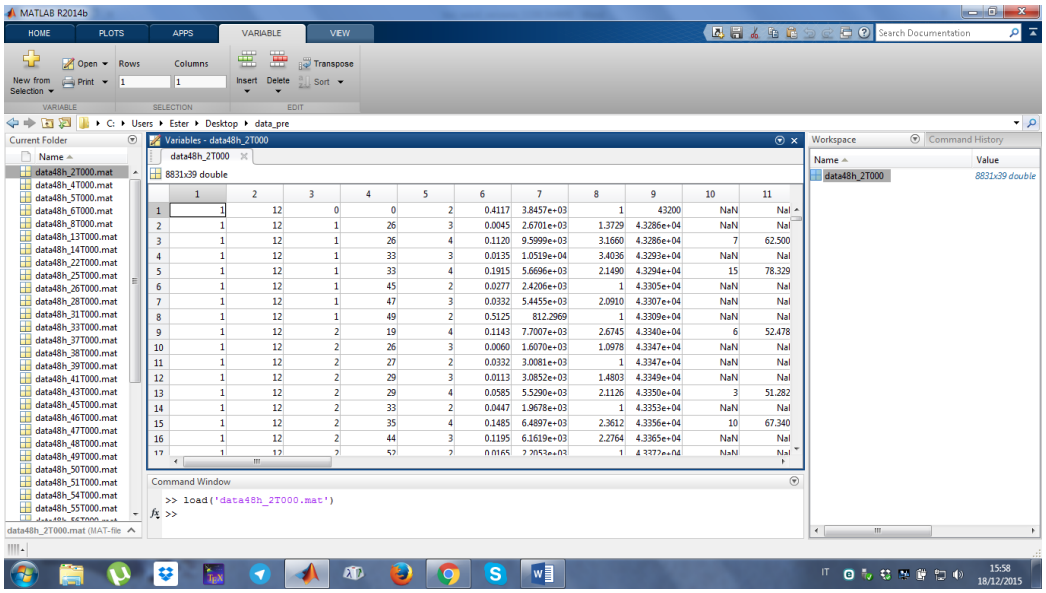


Figure 2.6: software output matrix

To understand and evaluate patients' circadian patterns, a review of the scientific literature has been performed in order to select the most promising metrics and related algorithms have been developed and implemented in Matlab. The use of fractal and cosinor analysis, barcoding, and complexity measures has been studied and validated in different clinical research projects and their ability to discriminate different patterns in motor behavior or other biologic time-series have been proven [4, 6, 11, 12, 14, 16, 36, 37, 38, 39, 40, 41, 43, 52]. Anisoara Ionescu et al., with a different inertial sensors setup, developed an 18-levels encoding, with thresholds on acceleration of body segments, gait cadence and duration of episodes (lying, sitting, standing and walking). Applying the Sample Entropy, Shannon's entropy and Lempel-Ziv complexity algorithms to the encoding obtained from the analysed patterns, they were able to assess differences in circadian motor behavior between healthy subjects and chronic-pain patients. As well, the barcoding technique was useful in the visualization of the motor patterns, to have an immediate understanding of differences [16]. In a different study, Anisoara Ionescu et al. used the fractal analysis, such as the Fano Factor Analysis and the Detrended Fluctuation Analysis to analyse chronic pain patients treated with spinal cord stimulation (SCS). Thanks to these mathematical tools, it has been possible to see a significant difference in the activities performed by the chronic-pain patients, compared with the healthy subjects [11]. The Cosinor Analysis has been widely used in the analysis of circadian behavior.

Refinetti et al. and Cornelissen et al. defined the Cosinor technique as a good mathematical tool to understand circadian phenomena with a 24 hours periodicity [12], and applied it to several field. For what concerns the circadian rhythm, Refinetti et al. employed the Cosinor Analysis to study the behavior of populations from several countries, to understand the socioeconomic development [52].

Furthermore, the aforementioned analysis strategies have been used in the field of biological phenomena. Nagarajan used the Lempel-Ziv complexity to find sub-patterns in the uterine contraction during labour [14]. Richmann and Moorman used the Sample Entropy to analyse the cardiovascular time-series, finding recurrences and discriminating pathological from healthy cardiovascular profiles [4]. Little et al. demonstrated that DFA and RPDE are sensible in detecting speech disorders and pathologies, highlighting significant differences from the normal speech, and in detecting abnormal cardiac patterns [36, 37]. Cornelissen et al. applied the Cosinor Analysis to the ambulatory blood pressure monitoring [39] and to the study of chronobiological phenomena that occur in unicellular and multicellular organisms [38]. Peng et al. utilized the DFA, while Viswanathan et al. the DFA and FFA, to distinguish people with congestive heart failure from healthy subjects [40, 41]. Baddeley et al. applied the FFA in the field of neural networks, to study neurons responses in primary and inferior temporal visual cortices, to videos stimulation [43].

However, these methodologies have never been used for investigating the motor behaviour of people suffering from dementia. What is expected from these metrics is the ability to discriminate different motor pattern within the patients group allowing identifying specific clusters with a clinical meaning. Details about selected metrics are reported in the next paragraphs.

2.2.1 The encoding

The output matrix of the signal processing software (section 2.2, Figure 2.6) is used for the encoding (or its visual representation, the barcode. See section 2.2.3) of the activities. In analogy to [16], different features of the Physical Activity (PA), type, intensity, and duration, were used to define PA states:

- if the PA type was identified as “lying”, two PA states were defined and encoded with “0”,”1”:
    - if patient has been inactive/resting for more than 30 minutes, than the activity has been identified by “0”;

- if patient has been inactive/resting for less than 30 minutes, than the activity has been identified by “1”;

- if the PA type was identified as “sedentary”, two PA states were defined and encoded with “2”,”3”:
  - if the patient has been poorly active/sitting for more than 5 minutes, than the activity has been identified by “2”;
  - if the patient has been poorly active/sitting for less than 5 minutes, than the activity has been identified by “3”;

- if the PA type was identified as “active”, then 4 PA states were defined and encoded with digit from “4” to “7”:
  - active for less than 5 minutes with mild to moderate intensity (metabolic equivalent less than 2.5 , so less than 7000 counts/min) = “4”;
  - active for more than 5 minutes with mild to moderate intensity = “5”;
  - active for less than 5 minutes with moderate to high intensity = “6”;
  - active for more than 5 minutes with moderate to high intensity = “7”;

- if the PA type was identified as “walking”, then 4 PA states were defined and encoded with digit from “8” to “11”:
  - Mild to moderate gait intensity (MET $<$ 3,5) for less than 5 minute = “8”;
  - Mild to moderate gait intensity for more than 5 minutes = “9”;
  - Moderate to high gait intensity (MET $>$ 3,5) for less than 5 minutes = “10”;
  - Moderate to high gait intensity for more than 5 minutes = “11”.

Thresholds on activity duration have been suggested by the clinicians on the basis of their experience in behavioural assessment considering a reasonable time to distinguish between a brief rest or a sleep (th_{d1}= 30 min), and a reasonable duration for typical indoor activities like walking in the corridors, going to the toilet, watching TV, etc. (th_{d2}= 5 min). METs thresholds were selected taking into account the metabolic equivalent range for gait (th_{met2}=

3.5) and other activities (th_{met1}= 2.5); threshold for gait was higher than for other activities because gait usually requires more energy for this kind of patients. The time series of PA states was obtained encoding the data from the 48 recording hours, from 12:00 to 12:00 (Matlab function named *12_ levels_ encoding.m*). The encoded time series was used to measure the complexity of the pattern and to measure the time-structure of the pattern.

2.2.2 Complexity measures

Complexity measures have been selected for their ability to reveal clinically relevant features of movement behavior [16]. The meaningful information resides in the variety, temporal dynamics, and duration of PA states and these differences can be quantified using structural complexity measures, as structural-static and structural-dynamic measures[1]. Structural-static measures allow the quantification of the amount of different PA states while structural dynamic measures are sensible to the order of PA states in the sequence, allowing the quantification of the amount of different subsequences, and the description of transition between states. Four complexity measures have been applied to the PA states time series.

2.2.2.1 Information Entropy

Information entropy is a structural-static complexity measure that has high/low values when there are many/few types of PA states in the time series. The information entropy is calculated as:

$$H = \sum_{i=1}^{a} p(i) log_2(p(i)) \tag{2.1}$$

where a is the amount of digit to define states in the "alphabet" (in this case a=12) and *p(i)* is the probability to have the i-th symbol. The normalized entropy is defined as:

$$Hn = H/log_2(a) \tag{2.2}$$

and varies between 0 and 1. This measure is sensitive to the diversity of PA states in the code but insensitive to the dynamical structure of it. Information entropy is calculated for each time series by means of the Matlab function named *entropy.m* expressly implemented for the purpose. This measure has been applied to both the sequence of PA states (section 2.2.1) and the time series of the PA state sampled at 100Hz (hence keeping the information about the PA states duration).

2.2.2.2 Lempel-Ziv complexity (LZC)

Lempel-Ziv complexity is a structural dynamic measure that takes into account the number of sub patterns identified in the sequence as it evolves. It is related to Kolmogorov complexity, but Lempel and Ziv linked the concept of complexity to the generation rate of new sub patterns along a sequence of symbols S, of length N, with an alphabet size a; the LZC measure is calculated as:

$$LZC = \frac{(c(S(N,a)))}{(N/log_a(N))} \tag{2.3}$$

where c is the number of sub patterns in the decomposition of S [1, 6, 9, 14, 16]. The Lempel-Ziv complexity measure has been computed implementing an algorithm that follows the flowchart provided by Kaspar and Schuster [6]. The Matlab function *lzc.m* created, implements the measure as it is reported in the flowchart in Figure 2.7; first the number of sub patterns is identified as described in the flowchart and then the LZC formula is applied.

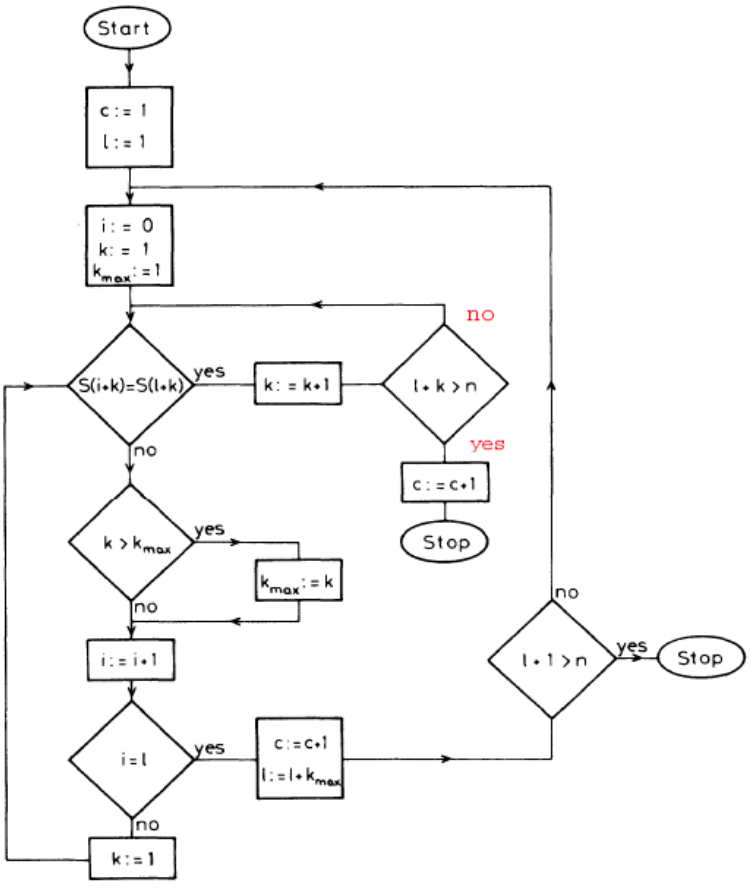


Figure 2.7: LZC algorithm by Kaspar and Schuster

2.2.2.3 Sample Entropy

Sample entropy is a structural-dynamic parametric measure that quantifies the regularity of a symbolic sequence by analysing the presence of similar sub patterns in data sequence. It is defined as the negative natural logarithm of probability that two sub patterns similar for m points remain similar to the next point *m+1*. To calculate the sample entropy, the symbolic sequence is divided into overlapping sequences of length m and the probability that two sub patterns are matched for m points is calculated taking into account the average number of sub pattern pairs for which the Euclidean distance is lower than a tolerance r. Same is applied to *p(m+1)*. Sample entropy is calculated as:

$$SampEn = -ln\frac{p_{m+1}(r)}{p_m(r)} \tag{2.4}$$

Algorithm description is provided by Richman and Moorman [4], and implementation is available on Mathworks – file exchange (Copyright I 2012, Kijoon Lee – All rights reserved.). It provides a non-negative finite index (between 0 and 1) where high values are associated with high complexity, irregularity and unpredictability in the sequence. Parameters m and r have been set as m=2 and r=1, in analogy with [16], in order to speed up the computation but also because the PA time series show many sub-patterns and the tolerance r=1 is the best value for comparing two sub sequences [16]. The Matlab function *SampEn.m* implements this measure.

2.2.2.4 Recurrence period density entropy (RPDE)

It is applied in dynamical systems theory, stochastic processes and time series analysis, for determining the periodicity or repetitiveness of a signal [36, 37]. It is useful for characterizing the extent to which a time series repeats the same sequence, and is therefore similar to linear autocorrelation and time delayed mutual information, except that it measures repetitiveness in the phase space of the system, and is thus a more reliable measure based upon the dynamics of the underlying system that generated the signal. It has the advantage that it does not require the assumptions of linearity, Gaussianity or dynamical determinism. The RPDE value *Hnorm* is a scalar in the range from zero to one. For purely periodic signals, *Hnorm* = 0, whereas for purely Independent and identically distributed random variables, *Hnorm* is approximately near 1. The RPDE method first requires the embedding of a time series in phase space, which, according to stochastic extensions to Taken's embedding theorems, can be carried out by forming time-delayed

vectors:

$$X_n = \{x_n, x_{n+t}, x_{n+2t}, ..., x_{\left(n+(m-1)t\right)}\} \tag{2.5}$$

for each value xn in the time series, where m is the embeding dimension, and t is the embedding delay. These parameters are obtained by systematic search for the optimal set; in this study, m has been set to 2 and t has been set to 1. For each point xn in the phase space, an epsilon-neighbourhood (an m-dimensional sphere of epsilon radius) is determined, and every time the time series goes inside the sphere, the time difference T between serial passages is recorded in a histogram. This histogram is normalized to 1, obtaining an estimate of the recurrence period density function *P(T)*. The normalized entropy of the density is calculated as:

$$H_{norm} = -[ln(T_{max})]^{-1} \sum_{t=1}^{Tmax} P(t) ln(P(t)) \tag{2.6}$$

where $Tmax$ is the largest recurrence value (typically on the order of 1000 samples). RPDE has the ability to detect subtle changes in natural biological time series such as the breakdown of regular periodic oscillation in abnormal cardiac function, which are hard to detect using classical signal processing tools such as the Fourier transform or linear prediction. The recurrence period density is a sparse representation for nonlinear, non-Gaussian and nondeterministic signals, whereas the Fourier transform is only sparse for purely periodic signals [36, 37]. Algorithm for RPDE is available on file exchange on Mathworks (Copyright I 2007 Max Little). Calculation of RPDE uses a set of Matlab functions: *rpde.m, close_ret.c, close_ret.mexw64*.

2.2.3 The Barcode

To visualize the behavioral pattern of each patient during the continuous monitoring a colour code has been associated to PA states (section 2.2.1). For each symbol, a colour has been selected (Figure 2.8) following the rule that inactivity or sedentary activities is associated to cold colours (blue and light blue), activities to transition colours (green, yellow), and gait to warm colours (orange and red), and activity duration gives a different shade and is reflected in the width of the colour bar. This visual strategy allows a quick and intuitive representation of the motor pattern during the 48 hours of recording; in the x-axis of the barcode was reported the time of the day. The Matlab function *12_levels_barcode.m* has been implemented for generating all the figures of the subjects' behavioural pattern. Figure 2.9 shows a couple of examples of activity barcodes created with data recorded in two patients with very different behaviors.

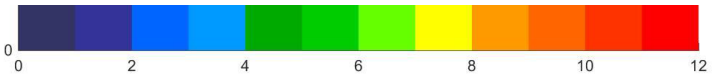


Figure 2.8: color barcode legenda

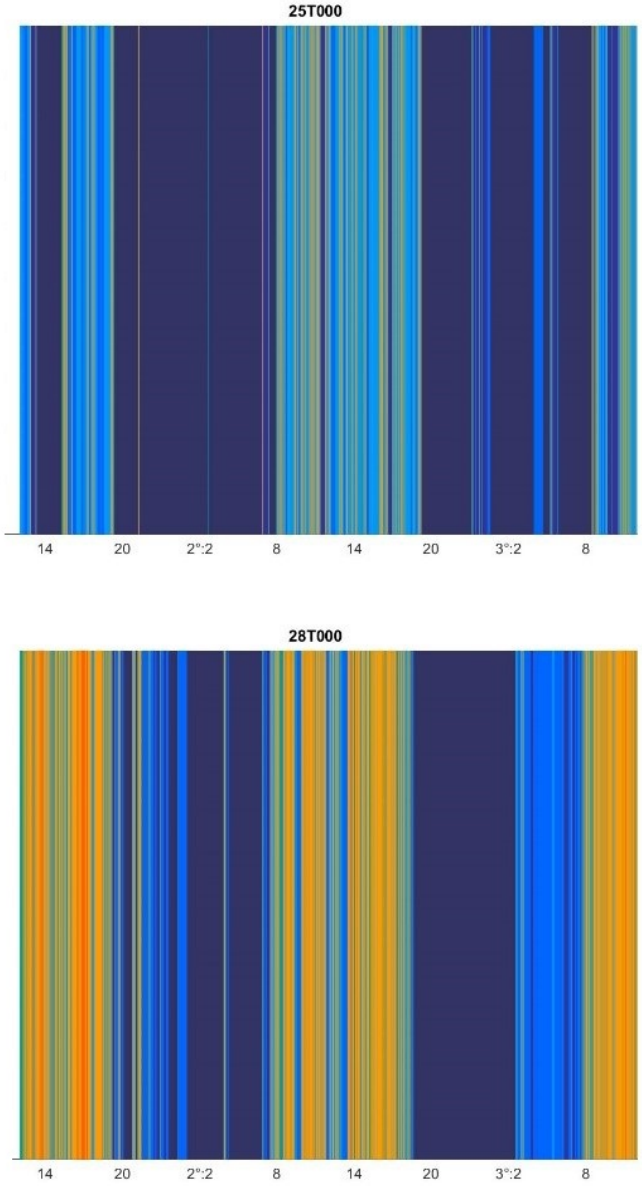


Figure 2.9: Examples of barcodes: (top) sedentary inpatient subject with dementia and no sleep problems or wandering behavior; (bottom) active inpatient subject with dementia and wandering behavior during the day and sleep problems

2.2.4 Fractal analysis

2.2.4.1 Detrended fluctuation analysis (DFA)

DFA is a method in fractal analysis that can quantify fluctuations in a given nonstationary time series by a single scaling exponent α, the self-similarity parameter that represents the long-range power-law correlation properties of the signal [11, 40, 41]. Alpha is obtained by computing the root-mean-square of the fluctuation *F(n)* of an integrated and detrended time series at different observation windows of size n and plotting *F(n)* against n on a log-log scale. Fractal signals are characterized by a power law relation:

$$F(n) \sim n^{\alpha} \tag{2.7}$$

The slope of regression line relating $log_2(F(n))$ to $log_2(n)$ determines the scaling exponent alpha. For a value of $\alpha = 0.5$, the signal is random; for $0.5 < \alpha \leq 1$ indicates a rising power law scaling behaviour and the presence of long-range correlations. According to [11,40], a proper scaling range for assessment of a power law behaviour is $5 \leq n \leq L/10$, where L is the data length of the time series. This method allows detecting intrinsic self-similarity embedded in a seemingly nonstationary time series and avoids spurious detection of apparent self-similarity, which may be an artefact of extrinsic trends [11]. This method has been used by Rutschmann et al. [11], Little et al. [36, 37] and by Peng et al. [40]. The code was implemented in two Matlab functions: *DFA.m* and *DFA_main.m* in agreement with the description reported in literature [11, 36, 37, 40, 41].

2.2.4.2 Fano Factor analysis

The Fano Factor is a useful statistical measure to test whether the fluctuations of activity-rest or rest-activity transitions counts N occur randomly or are of fractal nature and so invariant in the time-scale. The Fano factor, *Ff(t)*, is defined as the event-number variance divided by the event number mean:

$$F_f(t) = \frac{< N^2(T) > - < N(T) >^2}{< N(T) >} \tag{2.8}$$

where T is the time length of the window and N is the number of transition between values of inactivity ("lying" and "sedentary") and activity ("active" and "walking"). The Fano factor curve is obtained by plotting *Ff(T)* as a function of the window size T on a log-log scale. T is progressively increased from a minimum of 5 seconds to 10 times *Tmax*, where *Tmax* is the block data length, so that at least ten non overlapping windows are used for each

measure of *Ff(T)*. For a random Poisson process, *Ff(T)* is close to 1 for all windows sizes; for a periodic process, *Ff(T)* is instead close to 0, due to the decrease in variance as the windows size increases, while for a fractal-rate stochastic point process, *Ff(T)* assumes a power law form for large T:

$$F_f(T) = 1 + \frac{T}{T0}^{\alpha_F} \tag{2.9a}$$

$$0 < \alpha < 1 \tag{2.9b}$$

where *T0* is the fractal onset time and marks the lower limit for significant scaling behaviour in the *Ff*. The power law relationship appears as a straight line on the log-log scale with a positive slope; the slope, α_F is defined as the fractal-scaling exponent. Linear regression is used to calculate α_F [11, 41, 42, 43]. For the computation of the Fano Factor two Matlab functions (*fano.m* and *FanoFactor.m*) have been implemented.

2.2.5 Cosinor analysis

The Cosinor analysis uses a cosine function (Figure 2.10) as a model for biological and circadian rhythms [12, 38, 39, 52]; it is characterized by the following parameters:

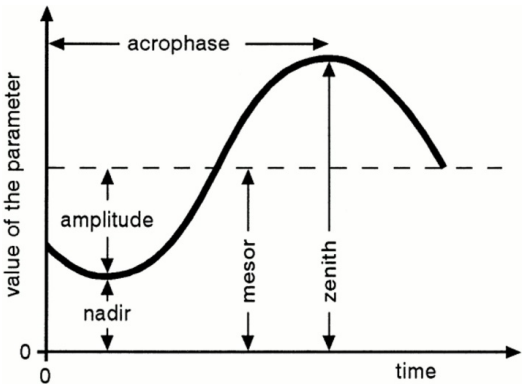


Figure 2.10: Cosinor wave explanation

M = MESOR: Midline Estimating Statistic Of Rhythm, that is the value around which oscillation occurs;
A = amplitude: half the difference between the highest and lowest value, or the distance between MESOR and the highest (lowest) value;
ω = angular frequency: the coefficient to translate from hours to degrees;
ϕ = acrophase: the time at which the higher value occurs;
t= the time, which is the independent variable.

In studies of circadian rhythms, it is indeed possible to assume that the period is known, being synchronized to the external 24-hour cycle. The regression model for a single component can be written as:

$$Y(t) = M + A \cdot cos(\omega t + \phi) + e(t) \tag{2.10}$$

where *e(t)* is the error term and

$$\omega = 2\pi$$

radians/24 hours. The model can be rewritten as:

$$Y(t) = M + \beta x + \gamma z + e(t) \tag{2.11}$$

where:

$$\beta = Acos\phi; \;\; \gamma = -Asin\phi; \;\; x = cos(\omega t); \;\; z = sin(\omega t) \tag{2.12}$$

The principle underlying the least squares method is the minimization of the residual sum of squares (*RSS*), that is the sum of squared differences between measurements Yi (obtained at times *ti*, *i=1, 2, ..., N*) and the values estimated from the model at corresponding times:

$$RSS = \sum_i [Yi - (\hat{M} + \hat{\beta} xi + \hat{\gamma} zi)]^2 \tag{2.13}$$

This approach is valid when all individual standard deviations are equal, as is often the case. Estimates for M, β, and γ are obtained by solving the normal equations, obtained by expressing that *RSS* is minimal when its first-order derivatives with respect to each parameter are zero. Normal equations are:

$$\sum(Yi) = MN + \beta \sum(xi) + \gamma \sum(zi) \tag{2.14a}$$

$$\sum(Yixi) = M \sum(xi) + \beta \sum(xi^2) + \gamma \sum(xizi) \tag{2.14b}$$

$$\sum(Yizi) = M \sum(zi) + \beta \sum(xizi) + \gamma \sum(zi^2) \tag{2.14c}$$

or, in matrix form: $d = S \cdot u$, where $u = [M \;\; \beta \;\; \gamma]'$. Estimates of M, β and γ are thus obtained as $u = S^{-1}d$. Estimates for the amplitude and acrophase can be derived from the estimates of β and γ by the following relations:

$$A = (\beta^2 + \gamma^2)^{1/2}; \tag{2.15}$$

$$\varphi = arctg(-\gamma/\beta) + K\pi; \tag{2.16}$$

where K depend upon the sign of β and γ themselves:

- if β is positive and γ is positive then K = 0
- if β is positive and γ is negative then K= -2π
- if β is positive and γ is negative then K = -π
- if β is negative and γ is positive then K = -π

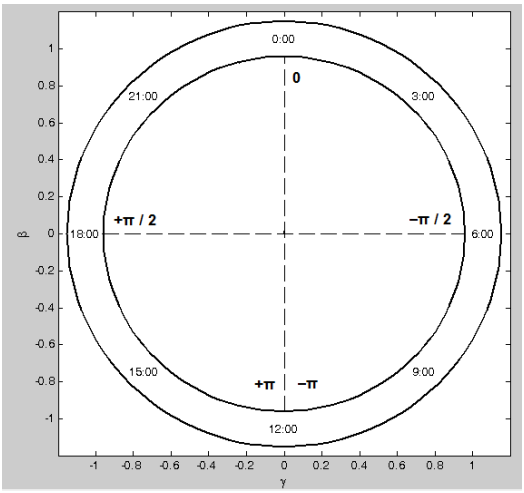


Figure 2.11: Cosinor clock

Hours run clockwise, as usual, while degrees, that normally are measured counter clockwise, here are from 0 to -2π, so acrophase is positive between π and $\pi/2$ (corresponding to -3$\pi/2$) and between -3$\pi/2$ and -2π; while negative between 0 and -π [39] (Figure 2.11). Acrophase is represented as the hand of the clock showing at which hour of the day the patient has the peak of physical activity. The model is statistically significant when the model sum of squares is large related to the residual sum of squares, as determined by the F-test:

$$F0 = (MSS/2)/(RSS/(N-3)) \tag{2.17}$$

Where *2* and *N-3* are the numbers of degrees of freedom attributed to the model *(k = 3 parameters – 1)* and to the error term *(N – k)*. The null hypothesis (*H0*) that there is no rhythm (the amplitude is zero) is rejected when *F0 > F (1-*α*, 2, N-3)*, where α relates to the chosen probability level for testing *H0* (α=0.05). For this study, *F(1-*α*, 2, N-3)* taken from Fisher's tables, is 3.69. Cosinor analysis is performed over each single continuous recording of a patient's physical activity and becomes important for assessing the circadian motor pattern since disruptions in a person's circadian

rhythm are used for diagnostic purposes. Indeed, it must be performed on every single monitoring in order to estimate the Mesor M and parameters β and γ [39]. Cosinor Analysis has been implemented in Matlab in agreement with Cornelissen's article [38]; the ad hoc Matlab function is named *cosinor3.m* . Cosinor analysis has been applied to two datasets: the time series of the 4 main activity categories ("Lying", "Sedentary", "Active", "Walking") and on the 12 PA state time series (section 2.2.1) obtained by applying the Matlab functions *obtain_alphabet.m*, *obtain_12_levels_alphabet_mask.m*, *find_beginning_and_end_indexes_of_integer_mask.m*, and *measures_on_12_levels_mask.m*, which give a 100Hz sampled vector of the encoding.

2.2.6 Steps count and percentage of activities

In addition to the features described in previous paragraphs, other variables have been included in the analysis: the number of steps and the percentage of time spent in each activity type, which are traditionally used for the assessment of physical activity. Those features are calculated on both daytime and night-time. Daytime is defined as the period between 6:00 and 00:00 while night-time is defined as the period between 00:00 and 6:00. These variable are implemented in the Matlab functions *compute_steps.m* and *process_data_without_encoding.m* : the first function provide as output the number of steps in 24 and 48 hours; the second function provide as output the percentage of time spent in the four activities, "Lying", "Sedentary", "Active", and "Gait", for both daytime and night-time.

2.3 Statistical analysis

Three groups of patients have been defined by clinicians on the basis of clinical scores and scales: "aberrant and wandering motor behavior"; "sleep problems"; and "normal motor behavior". A first statistical analysis has been performed on these three clinically defined groups by means of a one-way anova for comparing the groups. Since clinical criteria allows patients to be in more than one group, those patients exhibiting both aberrant/wandering behaviour and sleep problems have been assigned to the "sleep problem" group, to underline this last characteristic.

To pursue the main aim of the project, namely developing an objective sensor-based criterion to assess patients' living habits in the hospital, and before applying statistical analysis, subjects have been divided into 4 mutually exclusive groups on the basis of activities revealed by the software: "Lying"

activity, coded as 1, "Sedentary" activity, coded as 2, "Active", coded as 3, and "Gait", coded as 4. The amount of each activity in the time series served as criterion to classify the patients. Two thresholds have been defined on the mean value of this time series for daytime (06:00 to 00:00) and night-time (00:00 to 06:00). The threshold for the daytime activities has been set to 2 (equal to the value associated with the sedentariness) and the threshold for night-time has been set to 1.3 (close to the value associated with lying periods but allowing short active periods for usual visits to the bathroom). By means of these two thresholds it was possible to define four groups: "mostly regular", patients who were active during the day and inactive during the night; "poorly active", patients who were mostly sedentary during the day and inactive during the night; "always active": patients who were active during both the day and the night; and "day inactive/night active", active during the night and inactive/mostly sedentary during the day" (d. i. n. a.). One-way anova with multiple comparison has been used for comparing these four groups. The Matlab function *subgroups_subdivision_of_included.m* was used for assigning the patients to these four groups.

To pursue the secondary aim of the project, namely verifying pre- and post-intervention changes in a subgroup of patients, statistical comparison (one-way anova) has been performed between CG and IG in the pre-intervention (baseline) and between CG and IG in the post-intervention. A cross-comparison (one-way anova and multiple comparison correction) between pre and post intervention of both CG and IG has been performed for investigating possible trends in the output variables in these groups.

Chapter 3

Results

From the total starting sample involved in the project, 18 out of 82 patients were excluded at the baseline: n=6 patients had more than 48 hours of recording but it was not possible to select the time period between 12:00 and 12:00; n=8 patients removed the sensor before completing the 48 hours starting at 12:00; n=3 patients had recording problems; and n=1 patient refused to wear the sensor. A sample of 64 patients was available for the analysis.

3.1 Results via clinical classification criteria

With respect to the statistical comparison at the baseline among the groups defined by means of the clinical criteria, n=38 patients were assigned to the "aberrant + wandering motor behaviour" group; n=20 patients were assigned to the "normal behaviour" group and n=6 patients were assigned to the "sleep problems" group. Since the "sleep problems" group was too small, the anova was performed only on the first two groups. Statistically significant differences were found only for two features (Figure 3.1 and 3.2): the number of steps and the percentage of walking episodes at daytime ($p < 0.05$). Figure 3.1 shows the graph focused on the values of interest, for better observing dissimilarities. Differences were not significant for all the other features ($p > 0.05$).

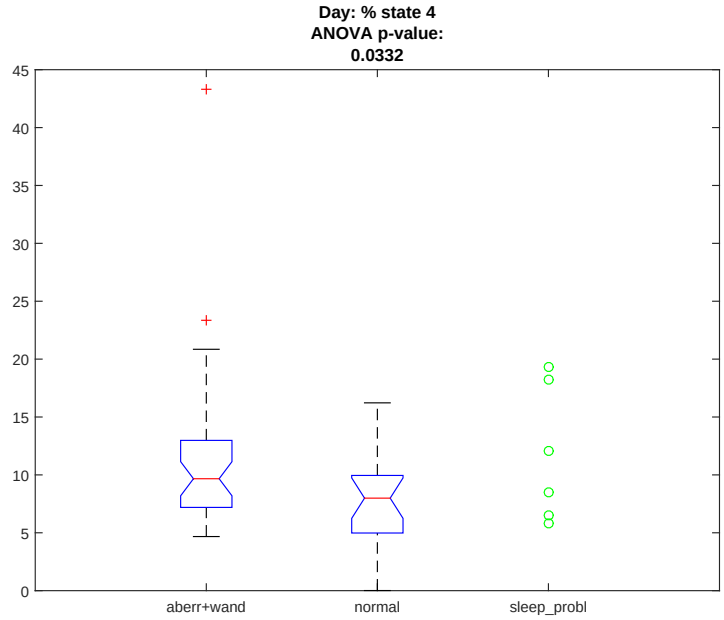


Figure 3.1: one-way anova for gait activity (labeled as 4) during the day time frame (06:00-00:00)

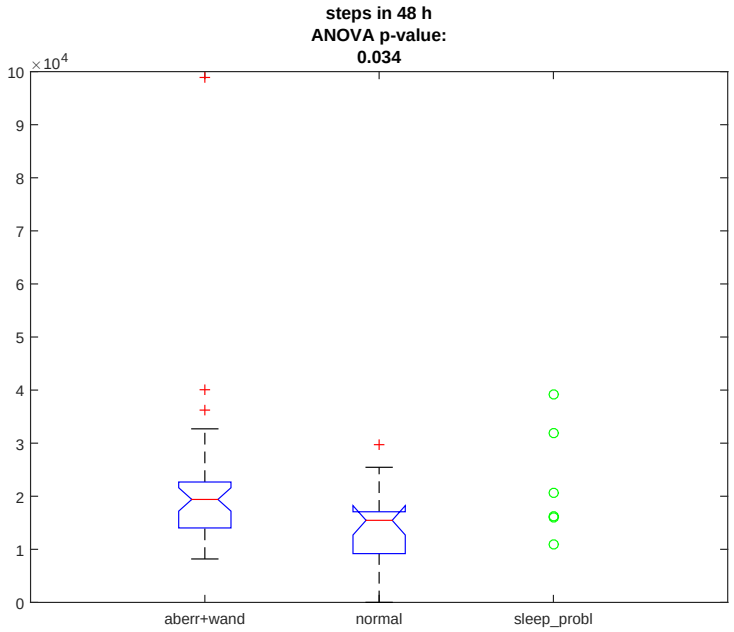


Figure 3.2: one-way anova on the steps number during the 48 hours recorded

As expected, the "aberrant + wandering motor behaviour" group had more steps and spent more time walking during the day with respect to the "normal behaviour" group. Anyway, mesor from the Cosinor analysis (on both the time series of the four activity categories, Figure 3.3 and the time series of the 12 PA states, Figure 3.4) and the time spent walking during night-time (Figure 3.5) were not significantly different in the two groups ($p > 0.05$). The "sleep-problems" did not show any difference with respect the other two groups. Figures show the graphs focused on the values of interest, for a better observation.

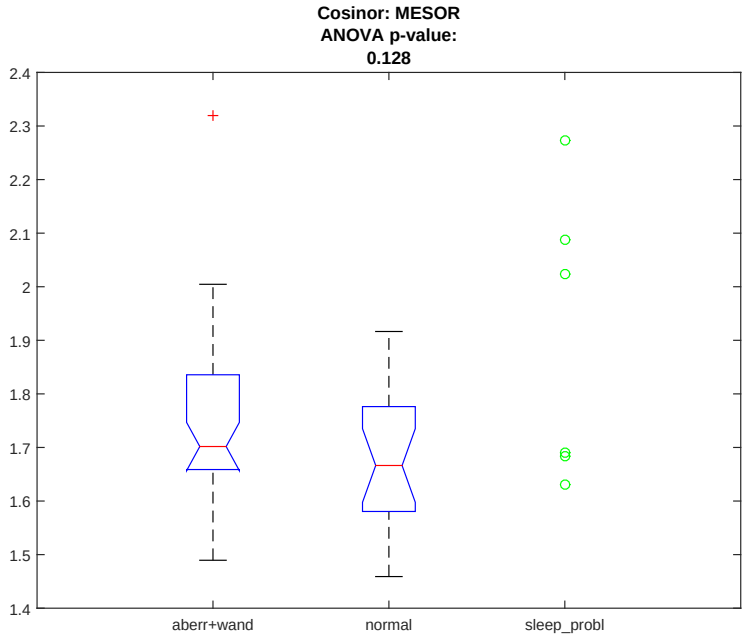


Figure 3.3: one-way anova on mesor evaluated on the 4 activity categories

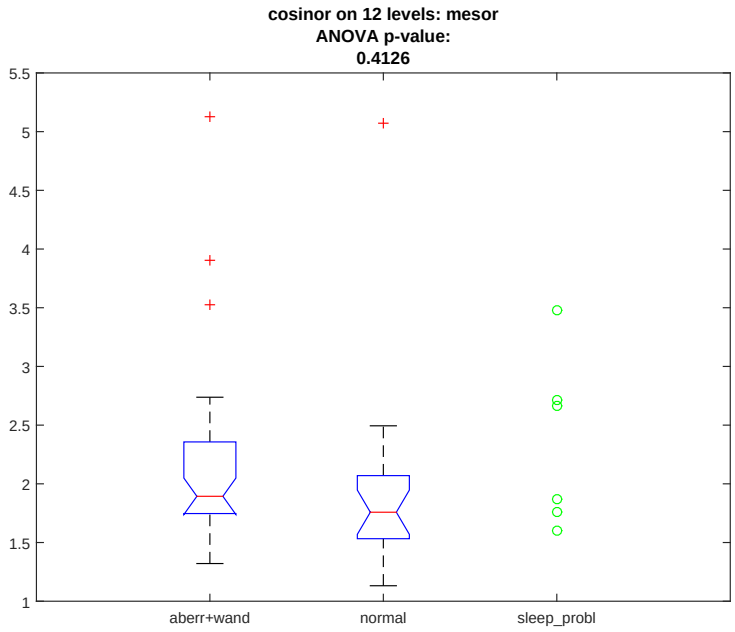


Figure 3.4: one-way anova on mesor evaluated on the PA states

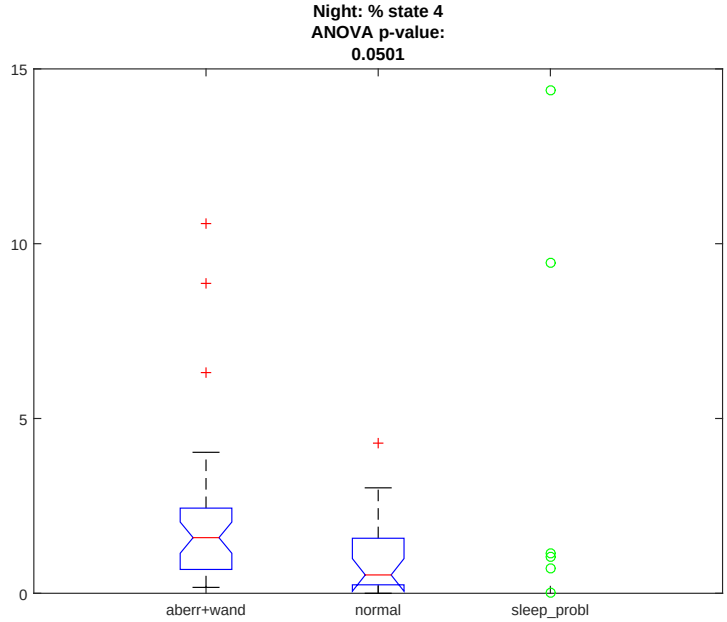


Figure 3.5: one-way anova for gait activity (labeled as 4) during the night

3.2 Results via classification based on activities

With respect to the analysis of the four groups defined by the instrumental features, n=38 patients were assigned to the "poorly active" group, n=7 patients were assigned to the "mostly regular" group, n=9 patients were assigned to the "always active" group, and n=10 patients were assigned to the "day inactive/night active" group (Figure 3.6). Statistics about the features extracted from signals at the baseline are reported in Table 3.1 and 3.2. Cosinor analysis applied to the time series of the 4 activity categories is significant for mesor, amplitude and F0 ($p < 0.05$, Figure 3.7, 3.8, 3.9); Cosinor analysis applied to the time series of the PA states is also significant ($p < 0.05$, Figures 3.17, 3.18, 3.19). The percentage of time for the four activity categories at night-time (Figure 3.13, 3.14, 3.15, and 3.16) were all significantly different among the groups; also the percentage of time for "Lying", "Active", and "Gait" during daytime (Figures 3.10, 3.11, 3.12) were significantly different among the groups ($p < 0.05$). Information entropy computed on the 100 Hz sampled encoding of PA states (Figure 3.20) was significantly different ($p < 0.05$) as well as the number of steps (Figure 3.21). Looking at the specific groups, in the multiple comparison, differences are found for the Cosinor analysis of the time series of PA states regarding the amplitude (Figure 3.18) and F0 (Figure 3.19) between the "poorly active" and the "day inactive/night active" (d.i.n.a) groups, and between the "mostly regular" and the "d.i.n.a." groups; this means that the fitting of the model was better in those groups with respect the "d.i.n.a." group. Mesor was significantly different between the "poorly active" group and the "always active" group meaning that the latter had a higher activity level (Figure 3.17). Similar results have been obtained for the Cosinor analysis applied to the time series of the four activity categories (Figures 3.7, 3.8, 3.9): looking at table 3.2, significant differences in the model fitting are between the "poorly active" and "d.i.n.a." groups, and "mostly regular" and "d.i.n.a." groups. Mesor is not significant, for these two comparisons, but it is between "poorly active" and "always active" groups. During the day, the percentage of "Lying" activity is higher in the "poorly active" group with respect to the "always active" group and the "mostly regular" group (Figure 3.10). As expected, the "mostly regular" group had a higher percentage of active time with respect to the "poorly active" group (Figure 3.11). Gait time is higher in the "mostly regular" group and in the "always active" group with respect to the other two groups (Figure 3.12). During the night, the "mostly regular" and the "poorly active" groups present about the same amount of lying activity and are significantly different from the "d.i.n.a." and the "always active" groups (Figure 3.13); these last two groups are usually awake at night, showing sedentary activities and gait episodes

(Figures 3.14, 3.15, 3.16). In general, the "d.i.n.a." group is similar to the "poorly active" group during the day, but similar to the "always active" group during the night (tables 3.1, 3.2 and 3.3). Information entropy computed on the 100Hz sampled encoding is significantly different between the "poorly active", the "mostly regular", and the "always active" groups: "poorly active" group present a less complex behavioural pattern due to the poor variety of activities (Figure 3.20); this is also confirmed by the total number of steps and percentage of each activity in this group, with respect the others. The "mostly regular" group was the one walking more than the others followed by the "always active" group (Figures 3.21 and 3.16). The graphs shown are focused on the values of interest. No significant differences were found for the other metrics, see table 3.2.

Table 3.1: mean values and standard deviations of outcomes in the total baseline dataset

	Poorly active (n=38)	Mostly regular (n=7)	Day inactive/night active (n=10)	Always active (n=9)
Alpha FFA Mean ± std	0.64±0.05	0.66±0.05	0.62±0.04	0.63±0.04
Alpha DFA Mean ± std	0.48±0.08	0.53±0.06	0.51±0.07	0.53±0.06
4-states Mesor Mean ± std	1.63±0.08	1.91±0.09	1.74±0.09	2.02±0.17
4-states Amplitude Mean ± std	0.60±0.14	0.74±0.09	0.38±0.05	0.51±0.34
4-states Acrophase Mean ± std	2.44±0.94	2.56±0.20	1.95±1.84	1.48±2.32
4-states F0 Mean ± std	3.88e+6±1.89e+6	3.95e+6±1.09e+6	1.41e+6±4.63e+5	2.33e+6±2.85e+6
12-levels Mesor Mean ± std	1.92±0.86	2.44±0.24	1.92±0.22	2.67±0.48
12-levels Amplitude Mean ± std	1.50±0.45	2.00±0.26	1.01±0.16	1.43±0.92
12-levels Acrophase Mean ± std	2.23±1.20	2.55±0.19	1.91±1.81	1.49±2.28
12-levels F0 Mean ± std	3.49e+6±1.86e+6	4.22e+6±1.22e+6	1.42e+6±4.97e+5	2.67e+6±3.17e+6
Information entropy Mean ± std	0.48±0.03	0.47±0.01	0.47±0.02	0.48±0.01
Lempel-Ziv complexity Mean ± std	0.27±0.04	0.28±0.01	0.26±0.04	0.28±0.02
HRPD Mean ± std	0-28±0.04	0.27±0.01	0.28±0.04	0.28±0.02
Sample entropy Mean ± std	0.47±0.11	0.51±0.04	0.43±0.11	0.49±0.04
Entropy on 100Hz sampled encoding Mean ± std	0.53±0.046	0.59±0.04	0.55±0.03	0.58±0.05
Day: Lying Mean ± std	38.2%±10.36%	20.6%±7.53%	31.9%±8.37%	21.4%±6.57%
Day: Sedentary Mean ± std	50.7%±11.82%	58.5%±10.59%	59.2%±8.82%	58.8%±14.82%
Day: Active state Mean ± std	2.6%±1.34%	4.2%±1.48%	2.5%±1.19%	3.9%±2.07%
Day: Gait Mean ± std	8.5%±3.46%	16.7%±5.02%	6.4%±1.89%	16.0%±10.90%
Night: Lying Mean ± std	92.0%±5.80%	90.1%±5.44%	60.3%±10.11%	46.8%±28.33%
Night: Sedentary Mean ± std	6.4%±5.34%	8.0%±5.70%	34.7%±11.24%	46.2%±25.15%
Night: Active state Mean ± std	0.5%±0.40%	0.7%±0.64%	1.6%±1.36%	2.3%±2.63%
Night: Gait Mean ± std	1.1%±1.08%	1.2%±1.08%	3.4%±3.52%	4.6%±4.58%
Steps in the 48 h Mean ± std	16'108±7'083	29'160±8'479	13'716±5'041	31'841±26'423

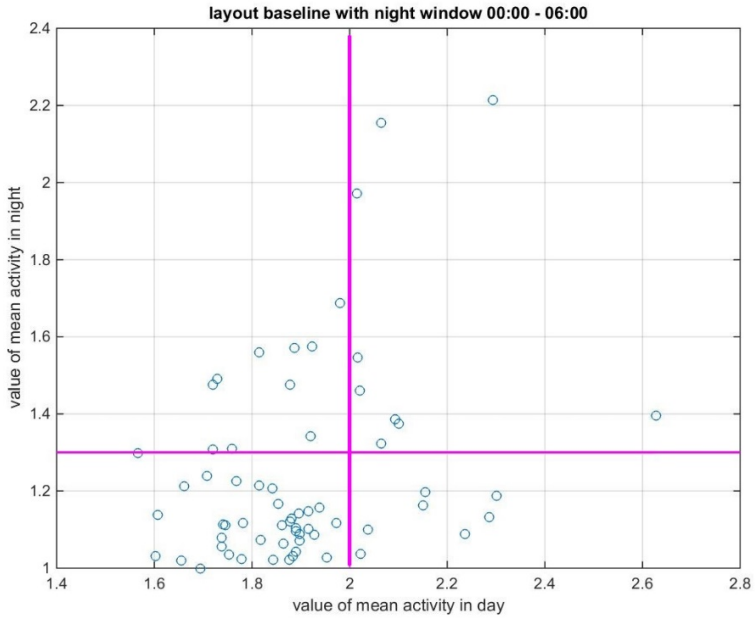


Figure 3.6: Total dataset layout

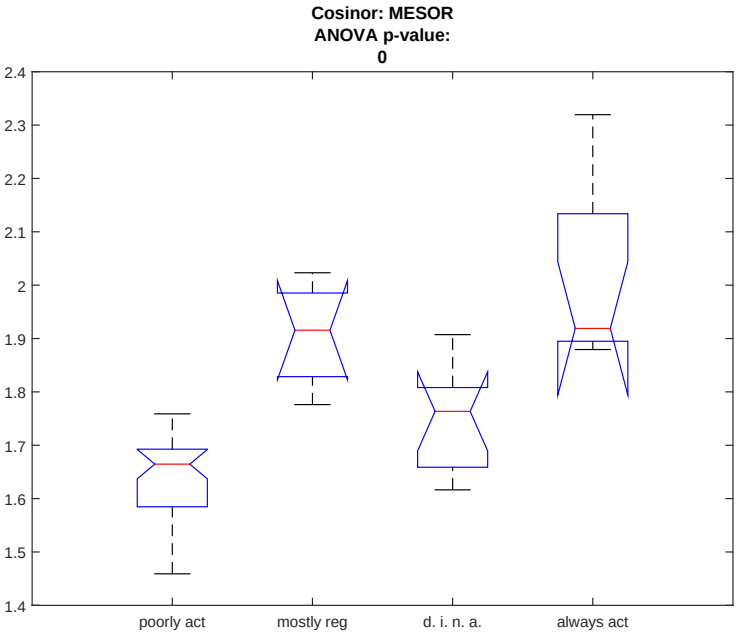


Figure 3.7: one-way anova on mesor evaluated on the 4 activity categories

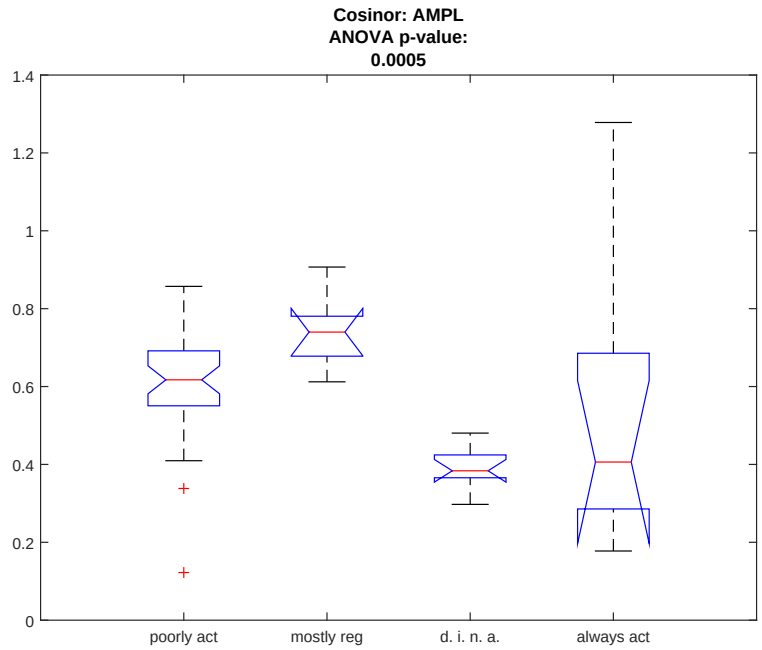


Figure 3.8: one-way anova on amplitude evaluated on the 4 activity patterns

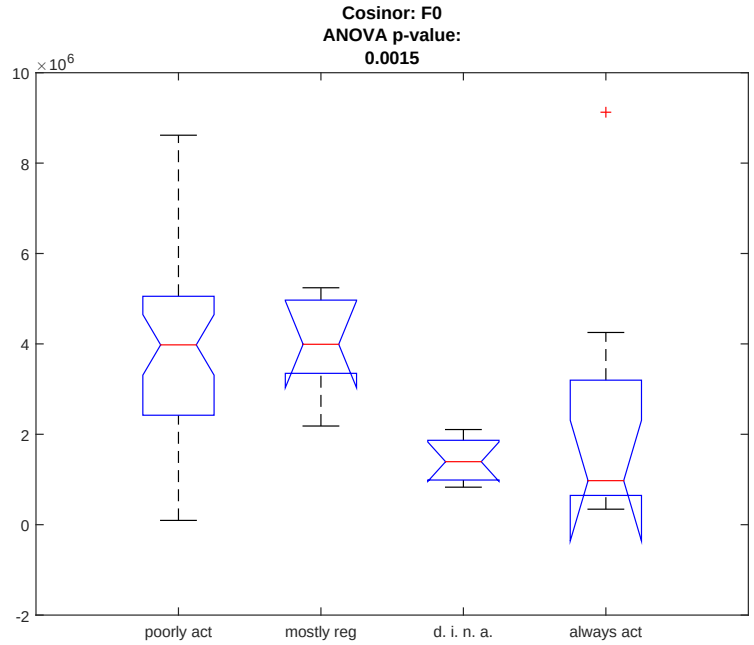


Figure 3.9: one-way anova on F0 evaluated on 4 activity patterns

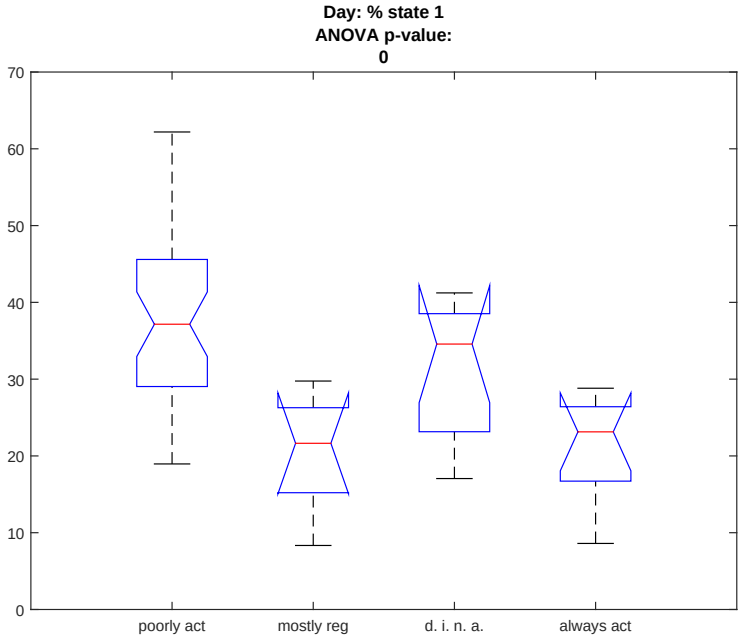


Figure 3.10: one-way anova on lying activity during the day

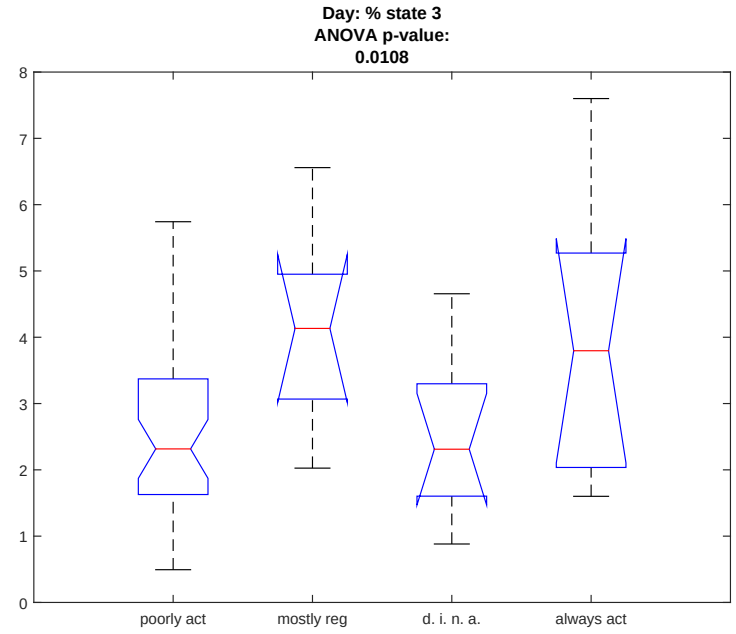


Figure 3.11: one-way anova on "active" state during the day

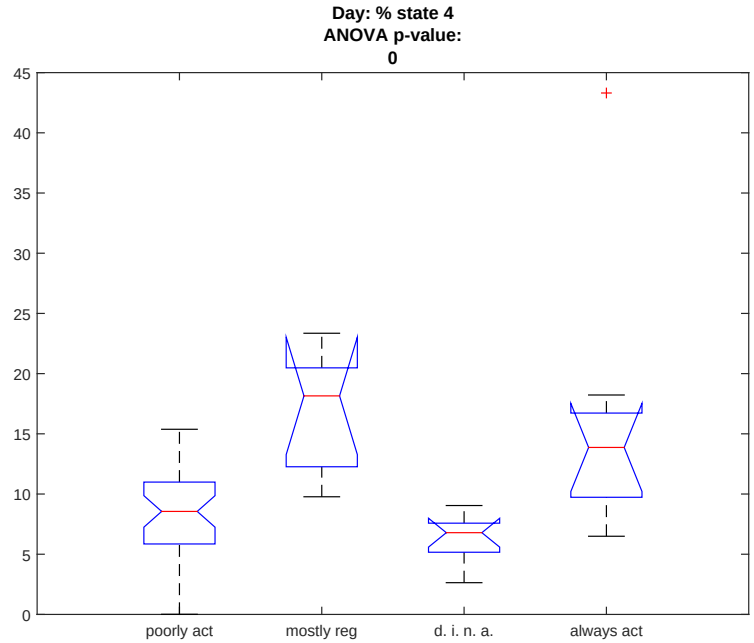


Figure 3.12: one-way anova on gait activity during the day

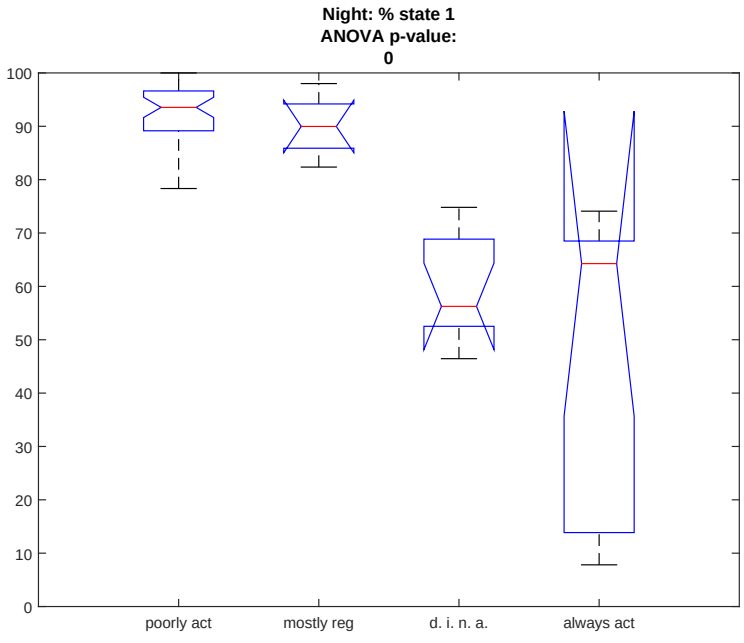


Figure 3.13: one-way anova on the lying activity at night-time

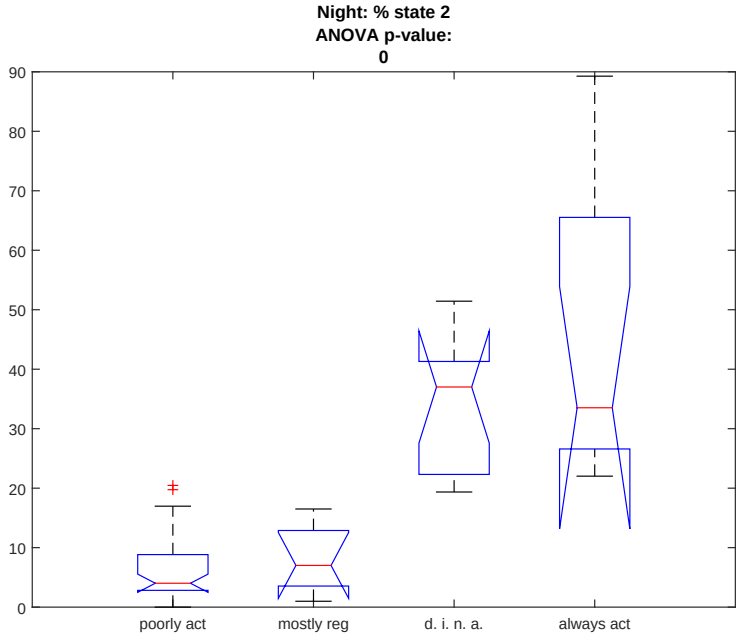


Figure 3.14: one-way anova on sedentariness at night-time

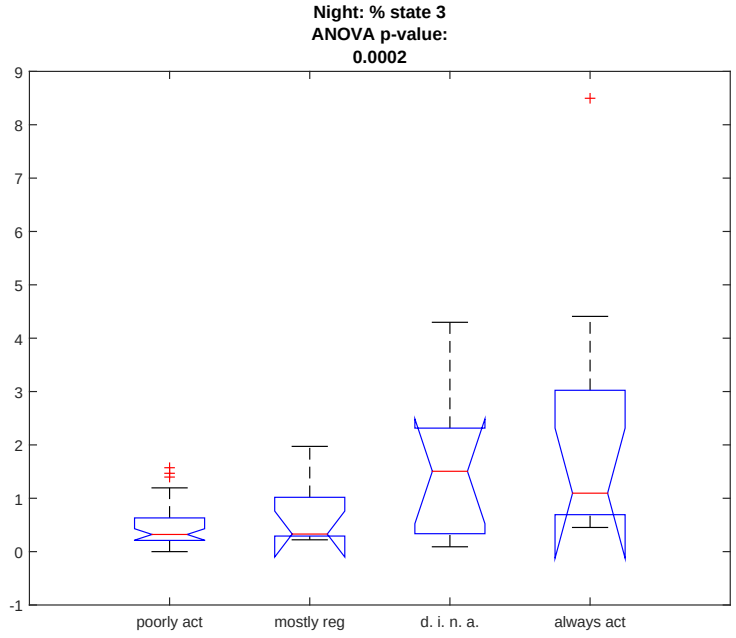


Figure 3.15: one-way anova on state “active” at night-time

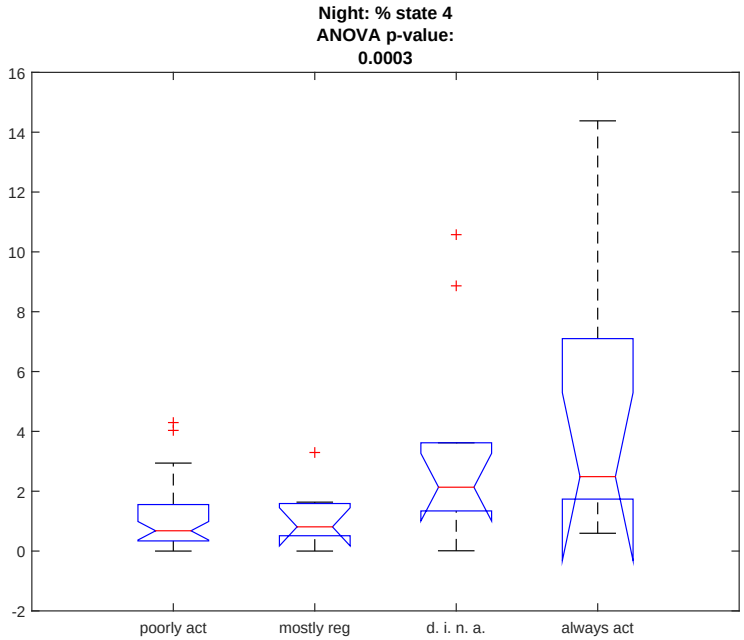


Figure 3.16: one-way anova on gait activity at night-time

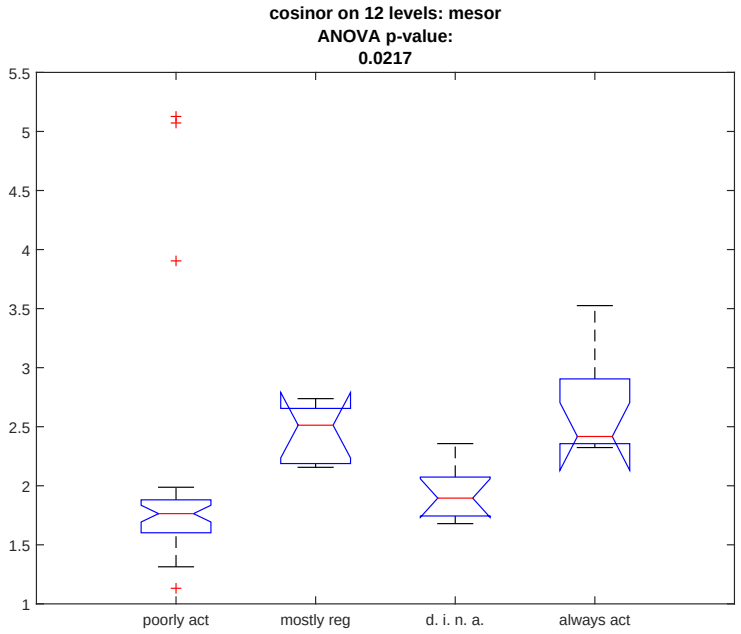


Figure 3.17: one-way anova on mesor evaluated on the PA states

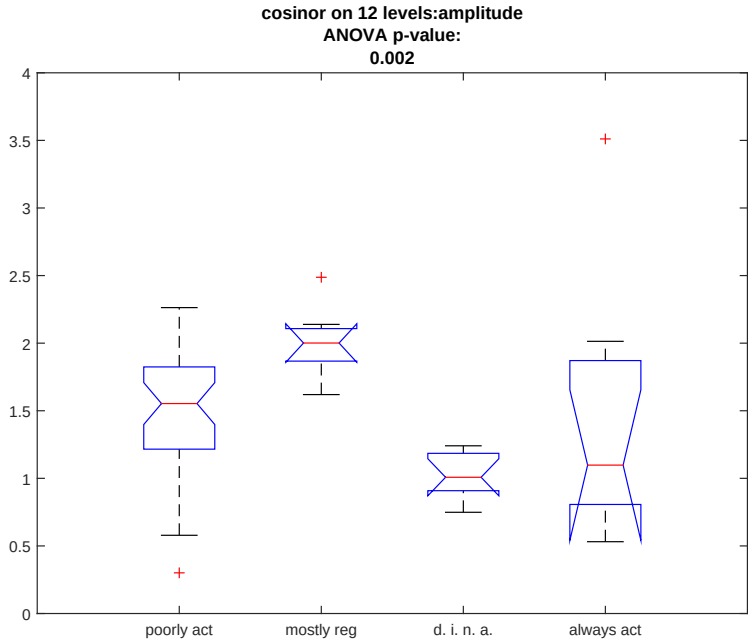


Figure 3.18: one-way anova on amplitude evaluated on the PA states

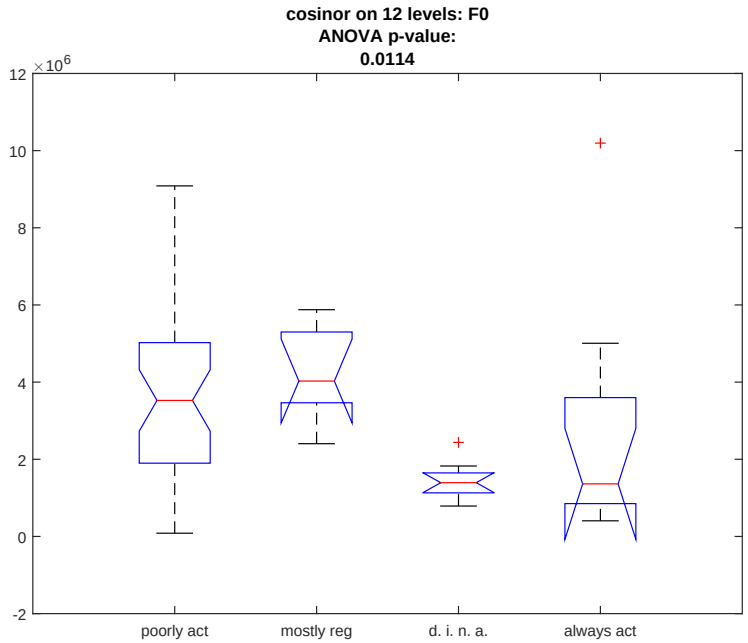


Figure 3.19: one-way anova on F0 evaluated on the PA states

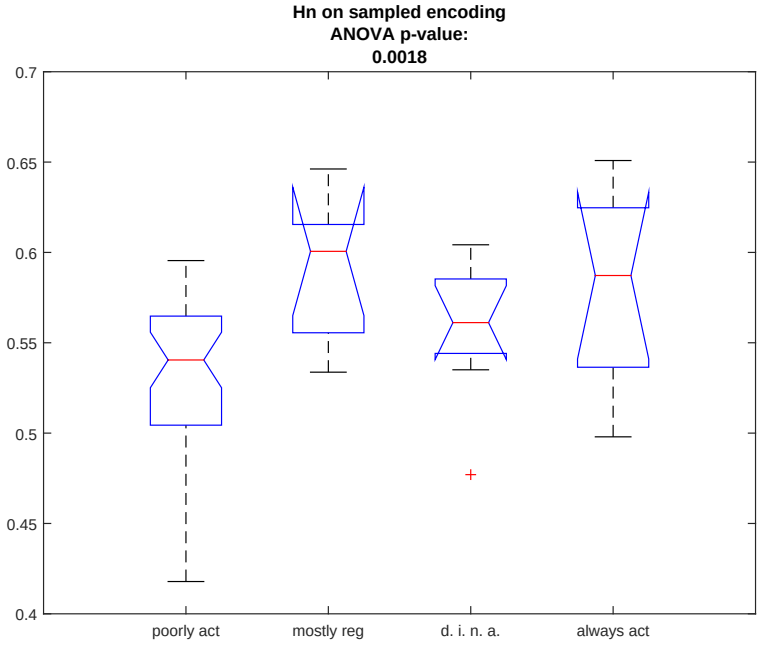


Figure 3.20: one-way anova on information entropy computed on the 100 Hz sampled encoding of PA states

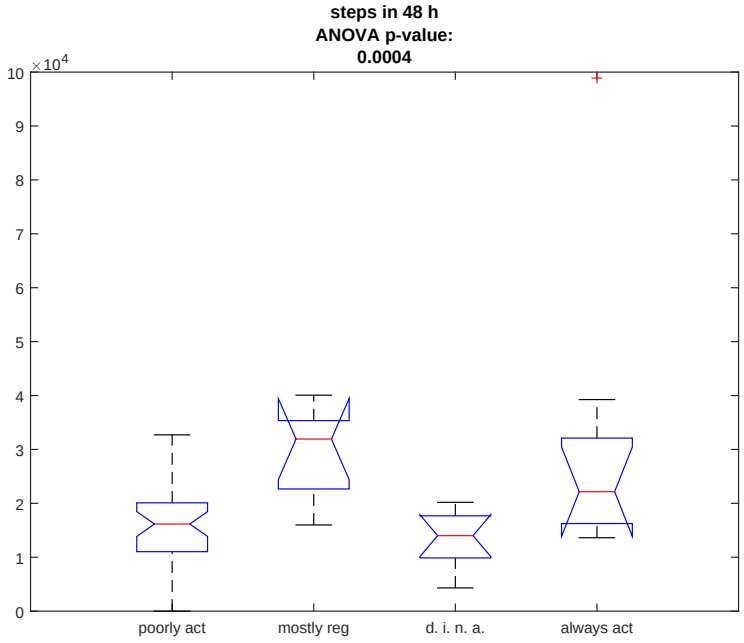


Figure 3.21: one-way anova on the number of steps

Table 3.2: p-value from multiple comparison on the complete baseline dataset

	Poorly active(n=38) vs Mostly regular (n=7)	Poorly active(n=38) vs D. inac./N. act. (n=10)	Poorly active(n=38) vs Always active (n=9)	D. inac./N. act.(n=10) vs Mostly regular (n=7)	Always active(n=9) vs Mostly regular (n=7)	D. inac./N. act.(n=10) vs Always active (n=9)
Alpha DFA	0.39	0.69	0.17	0.95	0.99	0.84
Alpha FFA	0.77	0.25	0.80	0.15	0.47	0.89
4-states Mesor	**5.20e-8**	**0.02**	**3.76e-9**	**0**	0.13	**5.96e-7**
4-states Amplitude	0.22	**0**	0.49	**6.20e-4**	0.05	0.39
4-states Acrophase	0.99	0.73	0.22	0.79	0.38	0.86
4-states F0	0.99	**0**	0.12	**0.03**	0.32	0.69
12-levels Mesor	0.28	1.00	**0.03**	0.45	0.92	0.11
12-levels Amplitude	0.07	**0.03**	0.98	**9e-4**	0.11	0.27
12-levels Acrophase	0.95	0.92	0.51	0.81	0.47	0.92
12-levels F0	0.79	**0.01**	0.65	**0.02**	0.38	0.49
Day: Lying	**1.70e-4**	0.25	**6.42e-5**	0.08	0.99	0.08
Day: Sedentary	0.39	0.19	0.26	0.99	1.00	0.99
Day: Active state	**0.04**	0.99	0.08	0.09	0.97	0.16
Day: Gait	**0**	0.65	**0**	**7.40e-4**	0.99	**8.10e-4**
Night: Lying	0.98	**7.17e-9**	**3.77e-9**	**3.11e-5**	**1.36e-8**	0.08
Night: Sedentary	0.98	**1.21e-8**	**3.77e-9**	**5.12e-5**	**3.56e-8**	0.12
Night: Active state	0.96	**0.03**	**4.11e-4**	0.39	**0.03**	0.55
Night: Gait	0.99	**0.04**	**8.12e-4**	0.24	**0.02**	0.63
Information entropy	0.95	0.97	0.99	0.99	0.94	0.97
Lempel-Ziv complexity	0.96	0.98	0.84	0.91	0.99	0.78
HRPD	0.92	0.99	0.99	0.98	0.98	1.00
Sample entropy	0.68	0.83	0.88	0.42	0.98	0.61
Entropy on 100Hz sampled encoding	**0.01**	0.31	**0.01**	0.53	0.99	0.66
Steps in the 48 h	**0.04**	0.93	**0**	**0.04**	0.96	**0**

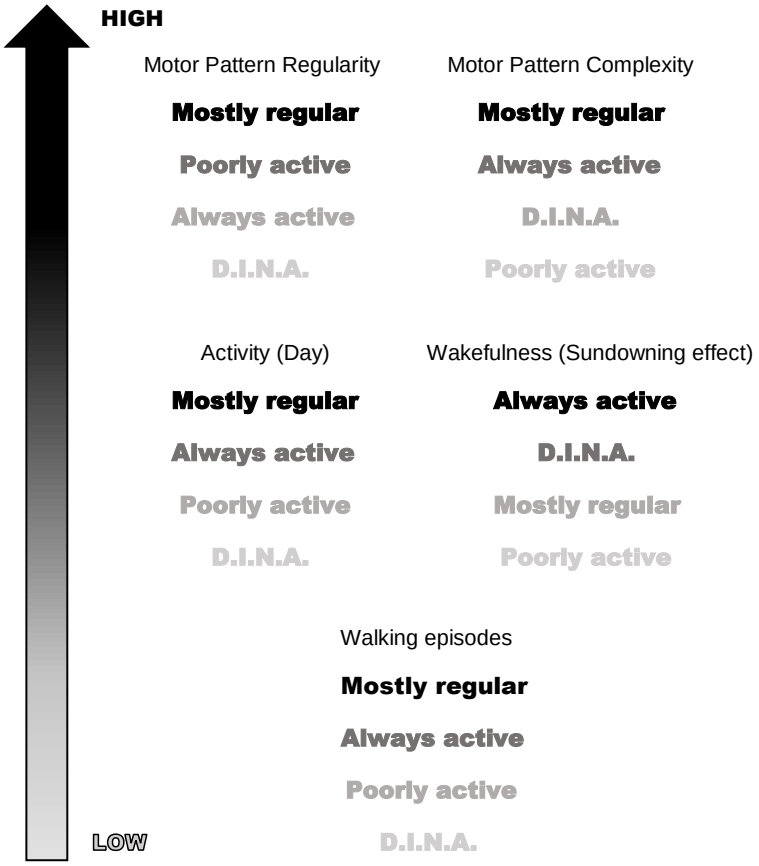


Figure 3.22: Qualitative summary of the obtained results

3.2.1 Results from patients included in the experimental protocol

Out of 64 patients, 44 had the follow up available and it was possible to perform the pre-post intervention analysis. Groups defined by means of the instrumental features were: n=27 patients in the "poorly active" group; n=5 patients in the "mostly regular" group; n=6 patients in the "d.i.n.a" group; and n=6 patients in the "always active" group (Figure 3.23). Statistics about the features extracted from the signals are reported in Table 3.3.

Table 3.3: mean values and standard deviations at the baseline of included sample in the pre/post analysis

	Poorly active (n=27)	Mostly regular (n=5)	Day inactive/night active (n=6)	Always active (n=6)
Alpha FFA Mean ± std	0.65±0.05	0.66±0.05	0.60±0.05	0.64±0.04
Alpha DFA Mean ± std	0.48±0.08	0.51±0.07	0.53±0.09	0.53±0.06
4-states Mesor Mean ± std	1.63±0.08	1.93±0.09	1.74±0.06	1.98±0.17
4-states Amplitude Mean ± std	0.60±0.11	0.74±0.11	0.40±0.05	0.58±0.37
4-states Acrophase Mean ± std	2.33±1.09	2.51±0.21	1.55±2.33	2.66±0.24
4-states F0 Mean ± std	3.84e+6±1.72e+6	4.18e+6±1.24e+6	1.53e+6±4.59e+5	2.92e+6±3.31e+6
12-levels Mesor Mean ± std	1.82±0.69	2.49±0.26	1.93±0.19	2.55±0.47
12-levels Amplitude Mean ± std	1.57±0.36	2.00±0.32	1.07±0.17	1.63±1.00
12-levels Acrophase Mean ± std	2.17±1.30	2.50±0.19	1.53±2.30	2.65±0.25
12-levels F0 Mean ± std	3.78e+6±1.78e+6	4.45e+6±1.39e+6	1.62e+6±4.82e+5	3.34e+6±3.68e+6
Information entropy Mean ± std	0.48±0.03	0.47±0.01	0.47±0.03	0.48±0.01
Lempel-Ziv complexity Mean ± std	0.27±0.04	0.28±0.01	0.27±0.04	0.29±0.02
HRPD Mean ± std	0.28±0.04	0.27±0.01	0.28±0.04	0.29±0.02
Sample entropy Mean ± std	0.48±0.09	0.52±0.04	0.41±0.11	0.51±0.04
Entropy on 100Hz sampled encoding Mean ± std	0.54±0.04	0.59±0.04	0.57±0.02	0.59±0.05
Day: Lying Mean ± std	38.0%±10.20%	17.5%±6.36%	32.4%±8.91%	23.7%±3.83%
Day: Sedentary Mean ± std	51.0%±12.25%	61.8%±10.79%	58.6%±9.72%	55.6%±14.73%
Day: Active state Mean ± std	2.5%±1.21%	3.7%±1.27%	2.8%±1.37%	3.6%±1.82%
Day: Gait Mean ± std	8.5%±3.56%	17.0%±5.94%	6.1%±2.09%	17.1%±13.02%
Night: Lying Mean ± std	91.7%±5.20%	88.8%±5.13%	59.4%±6.77%	54.9%±24.82%
Night: Sedentary Mean ± std	6.8%±4.99%	9.8%±5.60%	35.7%±10.12%	41.5%±25.74%
Night: Active state Mean ± std	0.4%±0.31%	0.5%±0.38%	1.8%±1.63%	1.1%±0.78%
Night: Gait Mean ± std	1.1%±0.98%	0.9%±0.68%	3.1%±3.88%	2.5%±1.97%
Steps in the 48 h Mean ± std	15'878±7'076	29'192±1'006	12'973±5'782	33'589±32'431

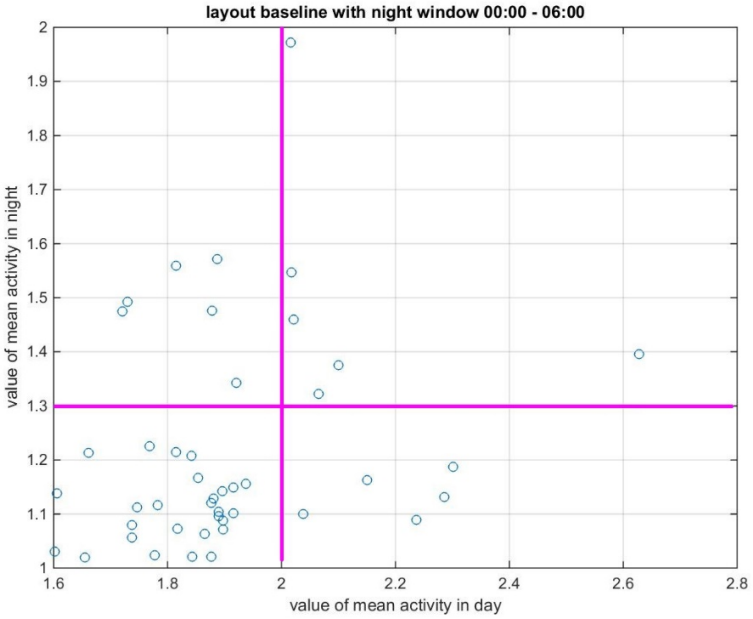


Figure 3.23: layout of included sample for the pre-post intervention analysis

3.3 Results of pre-post intervention analysis

The pre-intervention dataset was divided into CG (n=20) and IG (n=24) by means of randomization. Sub-groups were defined as CG pre-intervention (CG pre), CG post-intervention (CG post), IG pre-intervention (IG pre), and IG post-intervention (IG post). As regards the statistical comparison, CG pre and IG pre were not statistically different ($p > 0.05$ for all the measures), confirming the two groups were properly randomised; as expected CG pre was not statistically different from CG post ($p > 0.05$ for all the measures). However, this remained valid also for the comparison between IG pre and IG post and between CG post and IG post ($p > 0.05$ for all the measures). Results from the multiple comparison are reported in table 3.4. Possible reasons for this lack of differences in the two groups could be the relatively short duration of the intervention, the different participation among the patients or the effectiveness of the intervention itself. Another possible explanation could be the groups' heterogeneity. In order to investigate further this last hypothesis CG and IG were also divided into the four motor behavior groups ("mostly regular", "poorly active", "always active", and "d.i.n.a."); in this way, eight subgroups were defined for both pre- and post-intervention.

Looking at the trends in the features pre and post the intervention, in both CG and IG, an interesting trend was present only in two of the instrumental features: the "poorly active" IG increased sedentary activities and decreased the lying activity during the day in the post-intervention with respect to the pre-intervention (Figure 3.24, 3.25). As it is possible to observe from the barcoding of PA and the Cosinor analysis (Figures 3.26 (a) and (b)) some patients show a more time-structured circadian behavior, while, for other patients, activities are spread in the 48 hours also at the night-time. If we look at the barcode images in Figure 3.26(a), at the post intervention (right side), illustrated subjects present more light blue and green bars respect to the baseline (left side on the same row), meaning an increase in activities, while the dark blue bars stating the lying activity, are less than in pre-intervention, or are almost absent. However, the light blue and green bars are illustrated in the window belonging to the daytime, but in the window belonging to the night-time as well. This means patients are probably awake in a period during which lying position, meaning rest, was expected. Barcodes results are confirmed from the Cosinor images: the 4 activity patterns fitted by the cosine wave (in the top of each cosinor picture), underline some activities during the night. Indeed, the lying position (value 1) was expected, but the signal in the top of the image shows values 2 (sedentariness), 3 (active state) and 4 (gait episodes) frequently. The clock in the bottom of each cosinor picture states the time with the peak of activities, obtained from the cosinor model. Looking at figure 3.26(b), patients illustrated are, contrary to Figure 3.26(a), improved in their activity patterns, showing more lying activity when expected, namely the night. Indeed, barcodes show wider dark blue bars (meaning rest) and less light bars (meaning activities) in the night, reporting activities during the day, while cosinor has value 1 in the night-time and values 2, 3, and 4 during the day, meaning an improve in the sleep and night behavior. Therefore, a unique trend is not present among the experimental group; the exercise program procures different results in the IG.

Table 3.4: p-value from multiple comparison on CG-IG comparison

	CG pre vs. CG post	CG pre vs. IG pre	CG post vs. IG post	IG pre vs. IG post
Alpha FFA	0.69	0.67	0.98	0.97
Alpha DFA	0.82	0.99	0.99	0.84
4-states Mesor	0.99	0.99	0.99	0.78
4-states Amplitude	0.99	0.99	0.99	0.98
4-states Acrophase	0.50	0.98	0.99	0.78
4-states F0	0.97	0.99	0.99	0.98
12-levels Mesor	0.89	0.69	0.73	0.47
12-levels Amplitude	0.99	1.00	0.93	0.95
12-levels Acrophase	0.18	0.70	0.99	0.74
12-levels F0	0.96	1.00	0.93	0.99
Information entropy	0.15	0.21	0.99	0.98
Lempel-Ziv complexity	0.42	0.60	0.99	0.96
HRPD	0.30	0.33	0.99	0.99
Sample entropy	0.86	0.81	0.95	0.96
Entropy on 100Hz sampled encoding	0.94	0.97	1.00	0.99
Day: Lying	0.67	0.99	0.93	0.40
Day: Sedentary	0.36	0.86	0.97	0.48
Day: Active state	0.77	0.43	0.98	0.99
Day: Gait	0.89	0.92	0.98	0.99
Night: Lying	0.95	1.00	0.96	0.99
Night: Sedentary	0.94	1.00	0.96	0.99
Night: Active state	0.75	0.93	0.98	0.85
Night: Gait	0.99	0.98	0.99	0.93
Steps in the 48 h	0.88	0.92	0.99	0.99

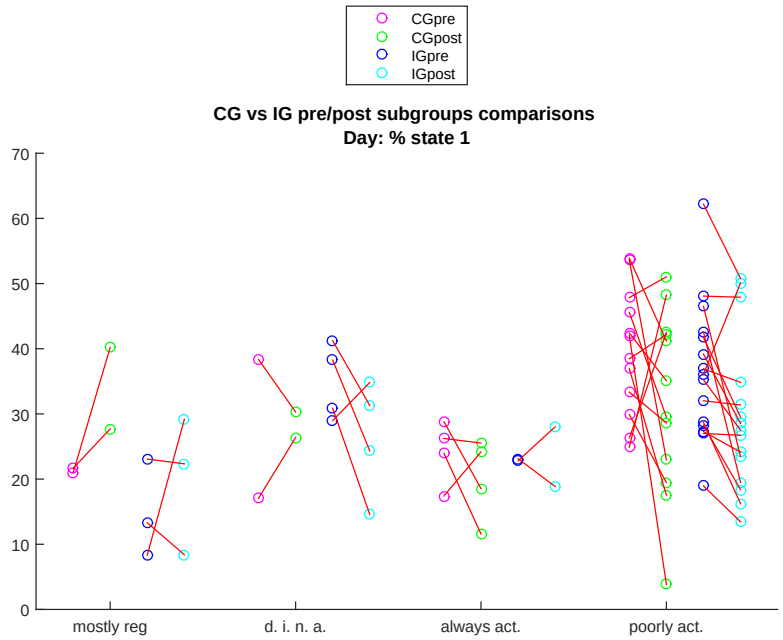


Figure 3.24: pre-post intervention comparison of lying activity during the day in the CG and IG subgroups

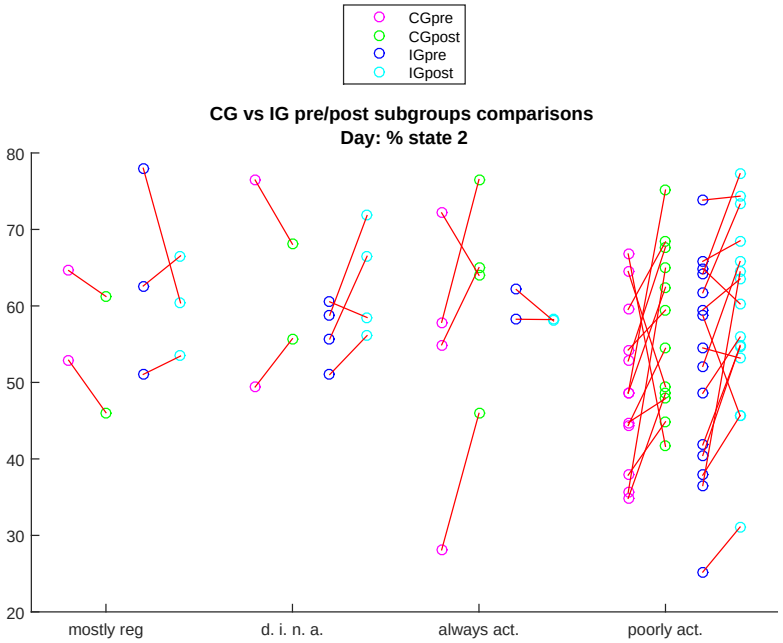
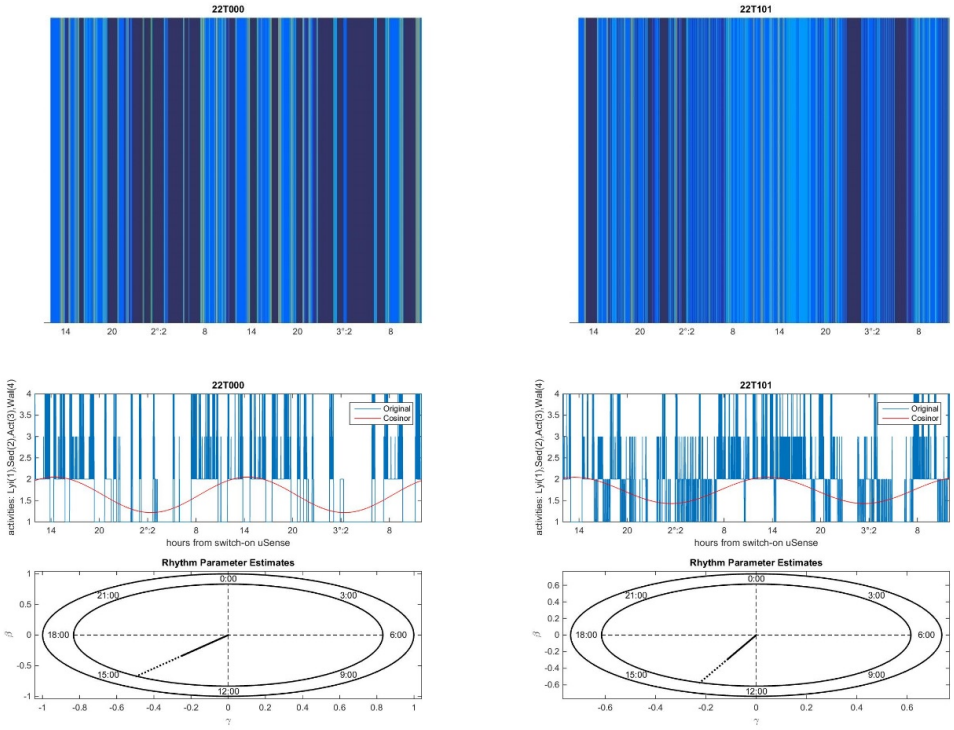
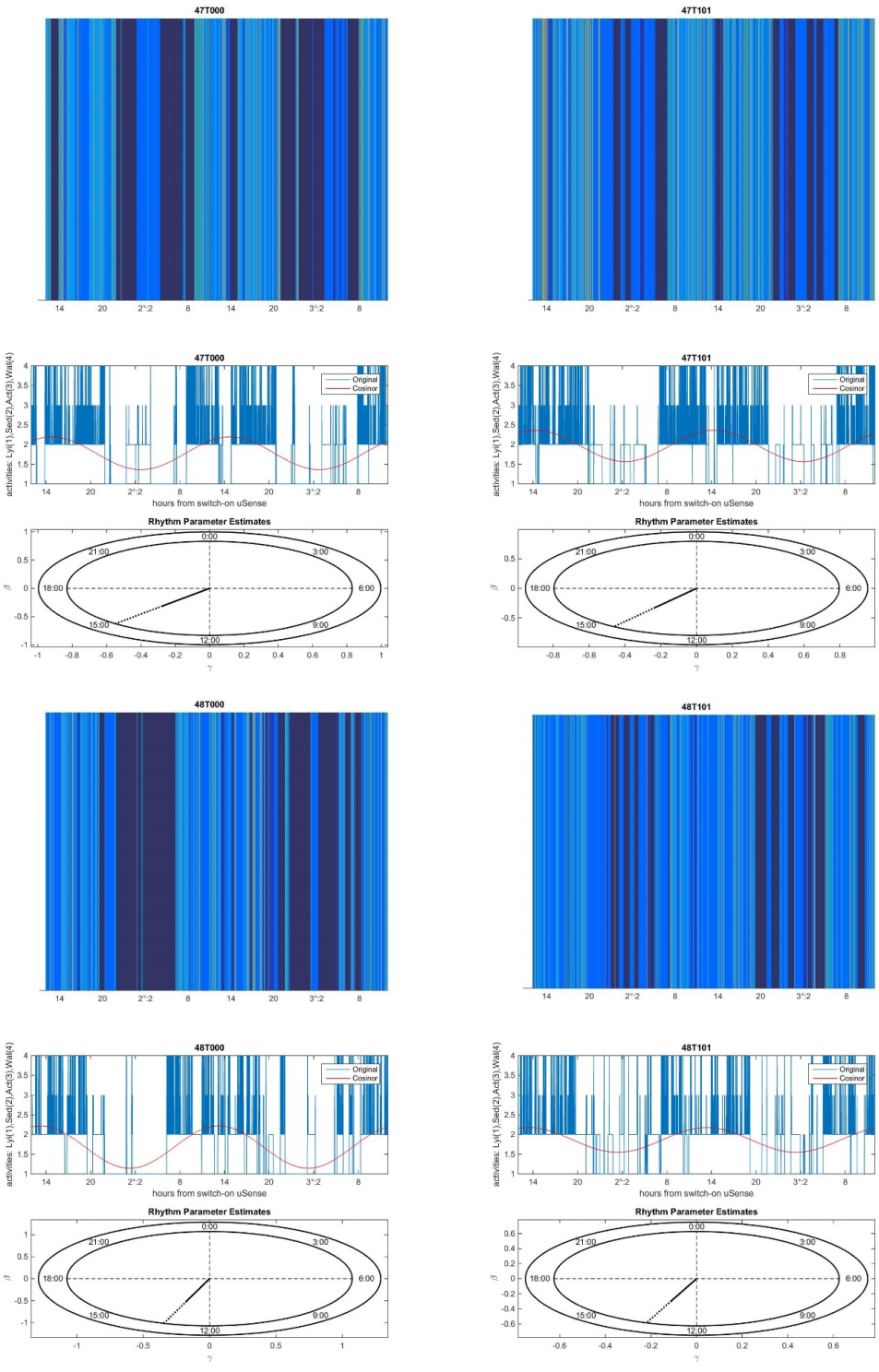


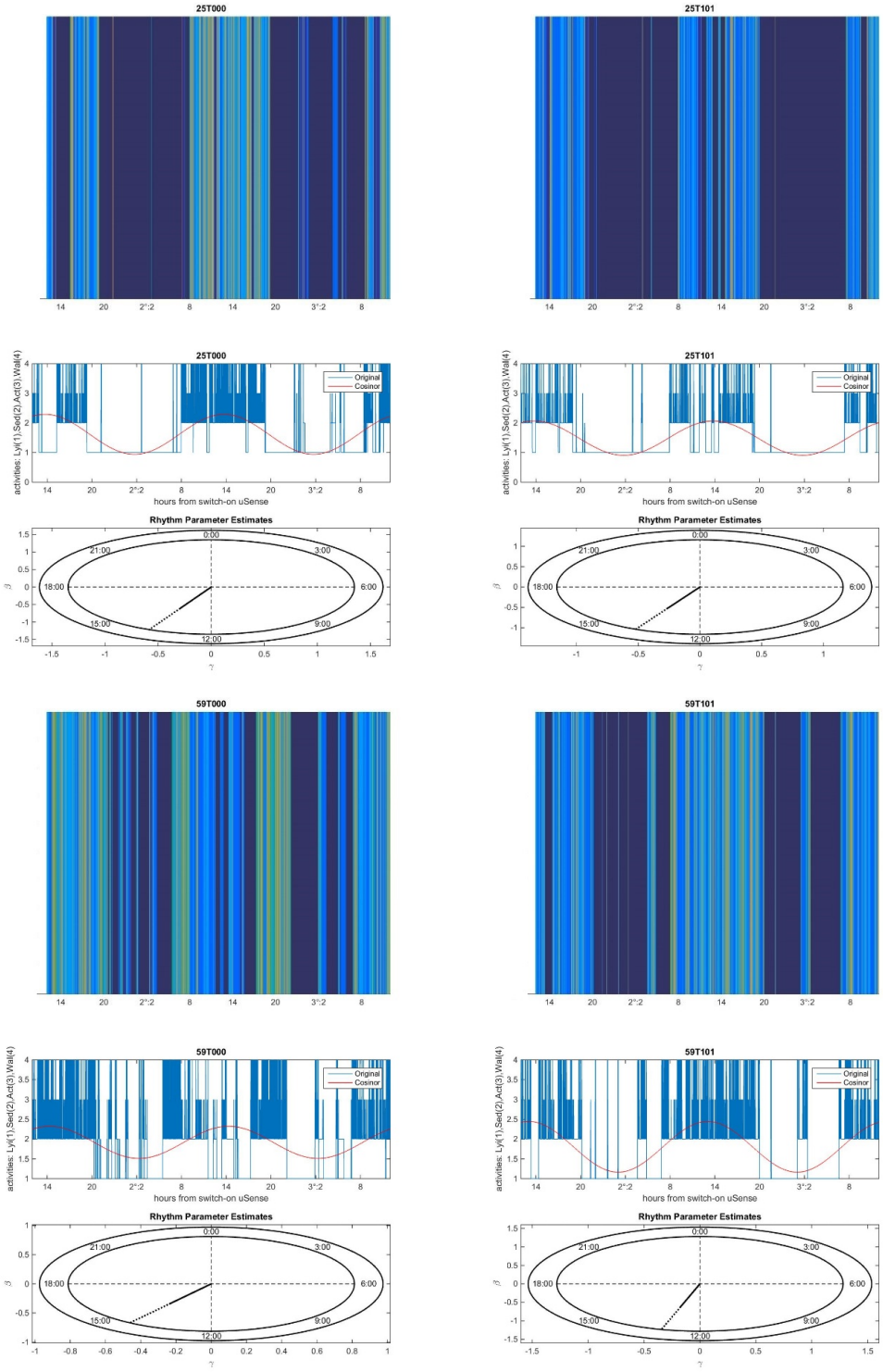
Figure 3.25: pre-post intervention comparison of sedentariness during the day in the CG and IG subgroups

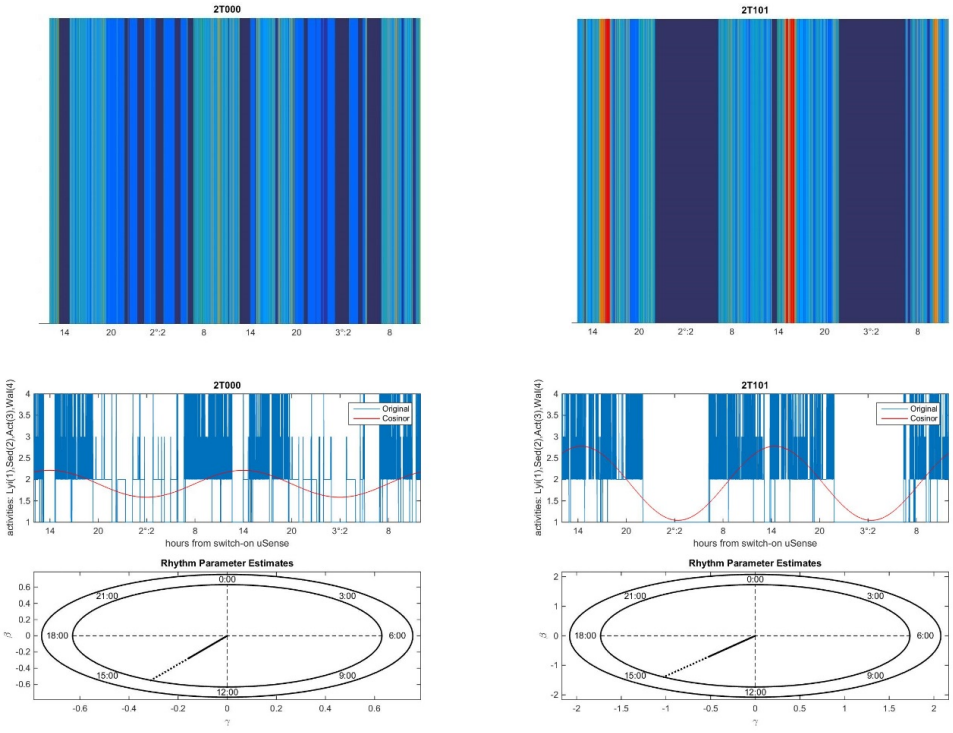
Figure 3.26: Example of barcodes (images with coloured bars) and cosinor images (with clock and cosine fitting wave) from a few patients belonging to IG. Each cluster of 4 images represents a patient: on the left side is reported the pre-intervention (defined as T000 on the title of each image) barcode and cosinor images; on the right side, the post-intervention (T101). IDs 22, 47 and 48 (group a) worsen at the post intervention, becoming more active also in the night; IDs 25, 59 and 2 (group b) become more regular, improving the night behavior




47T000
47T101
activities: Ly(1),Sed(2),Act(3),Wal(4)
Original
Cosinor
hours from switch-on uSense
Rhythm Parameter Estimates
48T000
48T101
0:00
3:00
6:00
9:00
12:00
15:00
18:00
21:00

(a)


25T000
25T101
25T000
25T101
Original
Cosinor
activities: Lyi(1),Sed(2),Act(3),Wal(4)
hours from switch-on uSense
Rhythm Parameter Estimates
0:00
3:00
6:00
9:00
12:00
15:00
18:00
21:00
59T000
59T101
59T000
59T101


2T000
2T101
14 20 2°:2 8 14 20 3°:2 8
2T000
2T101
activities: Ly(1),Sed(2),Act(3),Wal(4)
Original
Cosinor
hours from switch-on uSense
Rhythm Parameter Estimates
0:00
3:00
6:00
9:00
12:00
15:00
18:00
21:00

(b)

Chapter 4

Discussion

The potentials of the sensor-based assessment are already clear looking at the characteristics of the previously defined groups of patients. The division of the sample into the clinically defined groups “aberrant and wandering motor behaviour", “sleep problems” and “normal motor behaviour”, on the basis of the information reported from the caregivers, gives overlapping results, even though two features were found statistically significant. The number of steps and the percentage of walking time during the day, showed significant differences, coherently with the clinical observation, but any other feature reported a statistically significant result.
On the contrary, the division of the sample into four sub-groups by means of the instrumental features, it allowed defining groups which are in agreement with the clinical description of dementia symptoms. Outcomes of the statistical analysis suggest that the Cosinor analysis on both the four activities time series and the PA states time series; percentages of daytime and nighttime activities; the number of steps, and the Information Entropy on the 100 Hz sampled PA time series, are able to identify specific motor patterns with a clear clinical description. These measures are sensitive to differences in the circadian motor behaviour of patients who belong to the same clinical category. The other metrics selected for the analysis, like the fractal analysis and the complexity measures, do not seem to have the same discriminative ability, at least not in this specific group of patients.
Clinical judgment is central for the assessment and management of dementia patients; a caregiver familiar with the patient is able to assess the severity of the symptoms and the distress connected to those symptoms. However, the project provides evidence that an objective PA monitoring tool is able to characterise and measure the patient's motor behaviour, overcoming the limits of over- or underestimation of symptoms due to a subjective evaluation and discrepancies with the effective behavior of the analysed subjects.

Following the patient in his daily movements with an IMU would allow a better insight in the progression of the disease, and could be helpful for the diagnosis and prognosis stated by physicians. Results are in agreement with the clinical understating and interpretation of the disease. Mesor values are higher in patients assigned to the "mostly regular" and the "always active" groups; cosinor model fits better the "mostly regular" and the "poorly active" groups since they have a more time-structured pattern, while who is mostly active at night-time (Sundowning effect) and who is always active did not show time structure. Patients in the "d.i.n.a" group have a motor behaviour which is similar to the "always active" group in the time frame 00:00-06:00 but more similar to the "poorly active" group during the time frame 06:00-00:00; the "mostly regular" group has high values of activity and gait during the day and long resting period at night; as expected the "poorly active" group was the most sedentary and the "always active" group was the most active during the night.
With regard to the secondary aim in the project, the comparison between the CG and IG, the division into the four different sub-groups was useful for assessing specific trends of the instrumental feature but no significant differences between the two groups were found. Therefore, it is not possible to conclude that interventions bring to specific effects in the experimental group (IG), since there are many confounding factors in the study: the sample was very heterogeneous (table 2.1), the duration of the intervention was relatively short (2 weeks with exercise sections on alternate days), intervention was not patient-specific [30], and, from information provided by the physiotherapy personnel, the exercise program was not compulsory and adherence varied greatly. To understand the intervention effectiveness these confounding factors should be avoided.

Chapter 5

Conclusions

The main objective in the project was to develop and implement a sensor-based assessment tool of the circadian pattern to determine objectively the motor behaviour and to classify dementia patients based on the PA monitoring. A review of the scientific literature has been performed in order to select the most promising metrics, and algorithms have been developed and implemented in Matlab. Complexity measures and metrics associated with the Circadian rhythm have been selected for their ability to reveal clinically relevant features of movement behaviour. All the metrics selected for the project are validated and described in the literature but are usually applied to other biological signals like EKG, EEG, speech recording or other pathologies, but they have never been applied to the study of dementia and its related motor behaviour. The selection of the same period for every subject was necessary, even the exclusion of some patients from the analysis was required. Indeed, it was important to avoid time-dependent artefacts and biases in the measures; it is also intuitive that selected variables depend on the activity pattern and the pattern depend on the specific hour of the day. In addition to the clinical classification of the patients, which is based on the information provided by caregivers, a sensor-based classification criterion has been applied. Results suggest that the sensor-based criterion can better distinguish between different motor behaviors with respect to the clinical one. Outcomes of the statistical analysis are in agreement with the clinical understating and interpretation of the disease providing evidence that, instrumental features derived from the PA monitoring, are able to assess the circadian motor pattern and are sensitive to different patients' pathological profiles.

The secondary objective was to verify pre- and post-intervention changes in a subgroup of patients involved in the experimental exercise program performed at the LVR clinic in Cologne (Germany). No significant differences

between the intervention and the control group have been found. This means that is not possible to assess clear effects of the scheduled physical exercises, because there were many confounding factors in the study such as a high heterogeneity in the pathologies and the adherence to the exercise carousel varied greatly within the intervention group. Future studies should focus on well defined patient's pathological profiles and pathology-specific exercises.

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