POLITECNICO DI TORINO

Corso di Laurea Magistrale in Ingegneria Biomedica

Tesi di Laurea Magistrale

Innovative indicators of muscle fatigue in Multiple Sclerosis

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Luglio 2018

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Acronimi

25FWT 25- Foot Walking Test

AR Area Ratio

CMAP compound muscle action potential

CMCT Central Motor Conduction Times

CNS Central Nervous System

DTW Dynamic Time Warping

EDSS Expanded Disability Status Scale

EP Evoked Potentials

FHB Flexor Hallucis Brevis

HVES High Voltage Electrical Stimulation

ITV Inter-Trial Variability

K-channels potassium voltage-dependent channels

MEP Motor Evoked Potentials

MS Multiple Sclerosis

PCT Peripheral Conduction Time

PL Peroneus Longus

6MWT 6- Minutes Walking Test

TA Tibialis Anterior

TMS Transcranial Magnetic Stimulation

VL Vastus Lateralis

VM Vastus Medialis

Summary

Multiple Sclerosis is one of the most widely diffused neurodegenerative diseases. Since the severity of its symptoms, that involve many aspects of daily life, researches and clinical trials are fundamental instruments to attenuate its disturbs, to provide innovative monitoring procedures and to improve quality of life in patients. The problem faced in this study is to support clinicians in the evaluation of phenomenon of fatigue in Multiple Sclerosis patients that are object of clinical trial with Fampyra drug. The group of patients is heterogeneous and involves subjects with different levels of disability. Methods adopted in study aim to perform a complete clinical picture of fatigue progression in each patient. The work takes into a count results provided by gait analysis (25- Foot Walking Test and 6- Minutes Walking Test) and from the elaboration of both central and peripheral evoked potentials. All data are stored before and after Fampyra administration and finally all of them, with information of EDSS scale, are used to assert an improvement or worsening in patients condition. To obtain reliable results, the algorithm implemented is able to face problems of data instability. Results show coherency among the different indicators proposed and are also consistent with medical reports provided by neurologists of Azienda Ospedaliero-Universitaria San Luigi Gonzaga of Orbassano (TO). The main aspect of the study is represented by the important rule of signal morphology: literature demonstrates that clinical studies about evoked potential in Multiple Sclerosis are always centred on parameters affected by problems of data stability so, as a consequence, give importance to morphology of signal represents a pioneering approach.

Chapter 1

Introduction

1.1 Multiple Sclerosis

Multiple Sclerosis (MS) is a neurodegenerative disease characterized by injuries at the Central Nervous System (CNS). These kind of injures are damages of myelin sheaths around nerve axons and are caused by a reaction of immune system: it begins an attack to myelin areas and leads to an inflammatory process against oligodendrocytes, specialized cells responsible of myelin production. Attached areas, called plaques, can be localized in many positions in cerebral hemispheres, mostly optical nerves,cerebellum and spinal cord, justifying the disease name.[1]

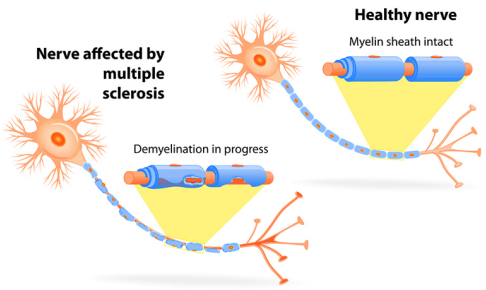

Figure 1.1: Consequences on nerve morphology during demyelinating process.[2]

The development of MS consist in an early inflammatory phase (1.1) where first injuries appear, followed by a second chronic phase where plaques are completely evolved in "scars". MS is mainly diagnosed in adults between 20 and 40 years, despite people can be affected in every moment of life. Many studies show that the number of female subjects affected in this age is almost twice that of man one.[1]

1.1.1 MS Causes

Researchers are still making studies about possible causes and exact mechanisms by which MS acts on immune system. As mentioned above, immune system altered reaction is the main responsible of MS onset, because it recognizes as "pathogen agent" some areas of myelin sheaths and acts destroying them through antibodies release or other chemical mechanisms. This mechanism of damage is defined as "autoimmune" or, more in general "disymmune". More in details, these substances have to overcome blood brain barrier,a complex capillary network which keeps the cerebral blood flow separated from entire body's bloodstream to protect it.The barrier role is to avoid that external or dangerous molecules interact with one of the most important areas of human body, so it is normally passed only by necessary nutrients for CNS cells. In these terms the altered behaviour of immune system is let macrophages penetrate the barrier and cause an inflammatory attack to Myelin Basic Protein (MBP), one of the basic components of myelin itself.

Factors that play a fundamental role in MS occurrence are:

- environment and ethnicity (latitude,temperate climate,Caucasian origin,toxic agents,vitamin D low levels);
- exposures to infective agents (bacteria and viruses);
- A genetic predisposition has been recognized although MS is not properly genetic disease;

These factors normally cooperate together in the break out of autoimmune mechanism due to the MS advent justifying the multiple origin of the disease.[1]

1.1.2 MS Types

MS symptoms can change among subjects, but in the early stage of disease some of them recur very often:

- impaired vision in terms of rapid decline of visual acuity, nocontrolled eyes movements and problematic double vision (dyplopy);

- disorders of sensibility including persistent tingling,numbness of limb,loss of touch sensitivity and problems in distinguishing cold and warm;
- loss of muscular strength and limiting fatigue in daily activities.

According to "Defining the clinical course of multiple sclerosis: the 2013 revision", a document compiled by Fred D.Lublin, it is possible to classify the different clinical courses of this neurodegenerative disease identifying:

- RR-MS (Relapsing Remitting-MS).It is commonly diagnosed in the 85% of cases and it is characterized by alternation of acute episodes to silent periods of the illness;

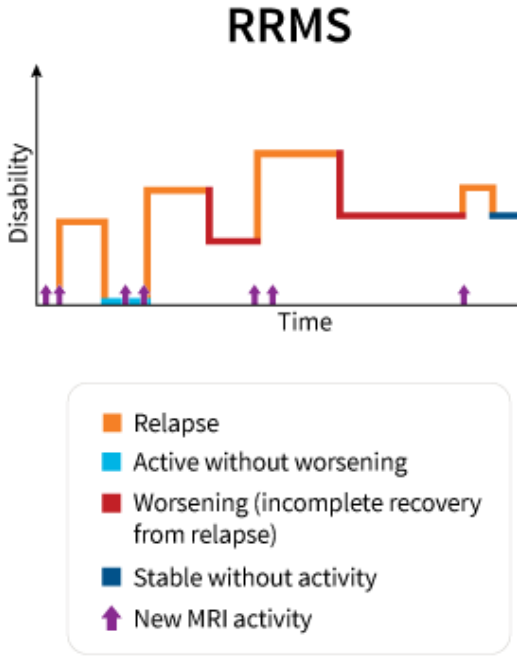

Figure 1.2: RR MS.[3]

- SP-MS (Secondary Progressive-MS).It usually represents the evolution of the previous one and it consists in a gradual development of disability which leads to always worsening conditions;

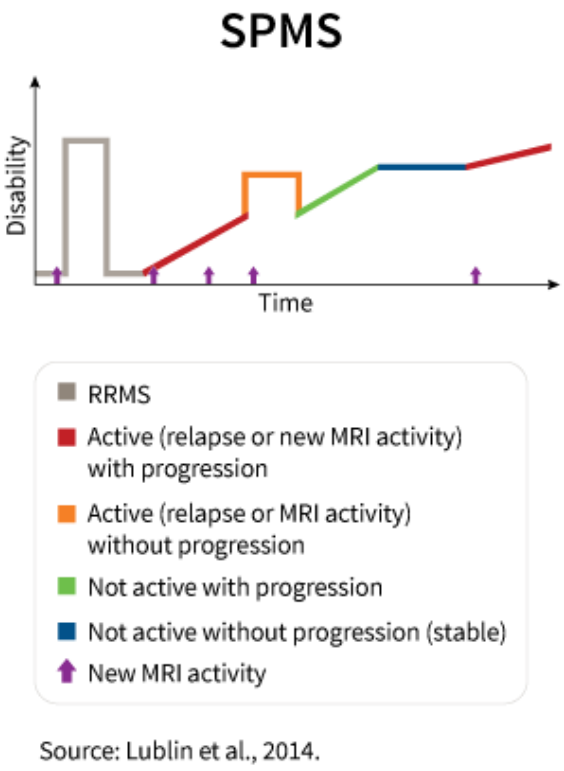

Figure 1.3: SP MS.[3]

- PP-MS(Primary Progressive-MS).It is commonly diagnosed in the 15% of cases and it is characterized by progressive impairment of neurological functionality since the early phases of the disease; [1]

1.1.3 MS drug treatments

Despite treatments that completely defeat MS are not yet available,nowadays there are several solutions to reduce the incidence and the severity of acute phases in daily life of patient.Treatments main purpose is to prevent irreparable damages at myelin sheaths axons, to modify the normal course of disease since the early stages (immediately after the diagnosis and the evident anatomic compromising) and to reduce the possibility of progressively worsening relapses.

Many pharmacological treatments are based on anti-inflammatory steroidal drugs, such as methylprednisolone. Their action decreases the duration and severity of the

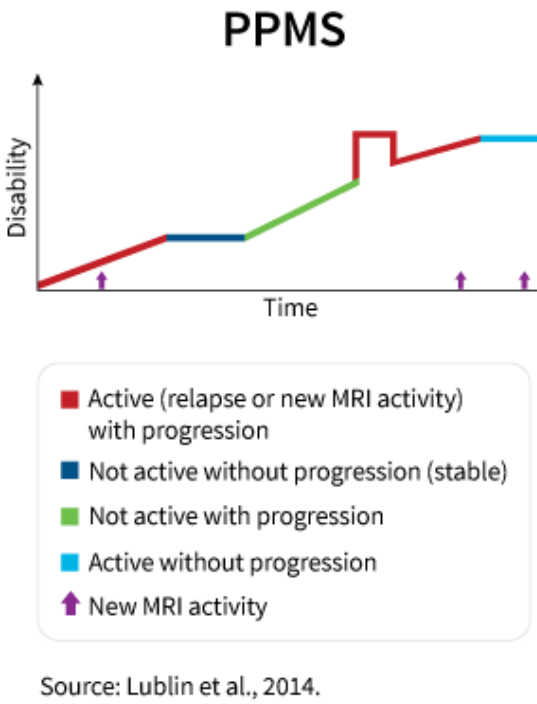

Figure 1.4: PP MS.[3]

attack even though patient response to cortison component is not always predictable and varies by individual and relapses.

These kind of drugs may be administered by orally tablets, intramuscular injection,or most commonly by intravenous infusion for 3-5 days. Since the period of administration is very short, treatments are usually well-tolerated. It is possible to classify long-term and symptomatic treatments: the first ones are pharmacological therapies described above and they play a role on basic mechanisms of MS at various level of immune system. The second ones are both pharmacological and rehabilitative treatments aiming at reducing the impact of MS symptoms and improve quality of daily life.

Despite each subject needs a different therapy and treatment along the course of disease, better results are achievable with an early as possible and efficient therapeutic project. [1]

1.2 Fatigue

Many studies report that about the 95 % of people of MS are affected by fatigue problems with considerable effects on their life.[4]

Definition of fatigue provided by the Multiple Sclerosis Council for Clinical Practical Guidelines in 1998 is: "A subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities"[5]. From this definition it is possible to define fatigue as a very complex symptom that, from a clinical point of view, consist in a persistent feeling of tiredness and weakness for no apparent reasons.[4]

Researchers suggest that possible causes of fatigue in MS are related to alterations in central nervous system that has to face demyelinating events and consequently injuries at brain cells with an irreversible reduction in glucose metabolism. As described above, alterations in immune system response influence the situation in terms of increase the level of perception.Moreover hormonal changes should be consider as further contribution in MS experience. [6]
MS fatigue can be distinguished in Primary Fatigue and Secondary fatigue as shown in (1.5)

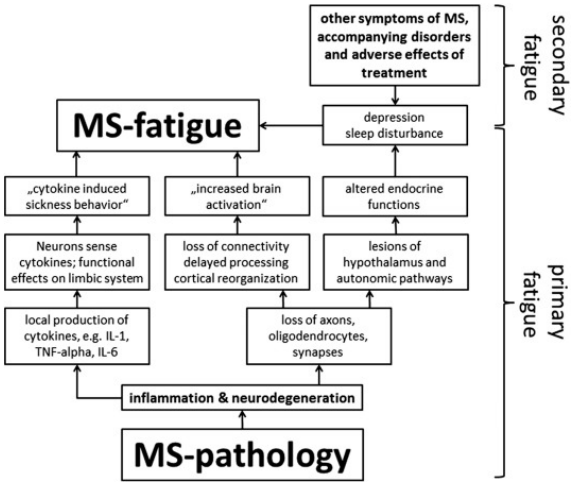

Figure 1.5: Primary and Secondary Fatigue in MS.[2]

Primary fatigue is a type of fatigue that is not solved with sleep or rest.It is a mentally and physically weakness that worsens with temperature rise or when a single muscle group is used for a short period of time.It is defined as primary because causes

have to be searched at central level in demyelinating process. Secondary fatigue is a consequence of MS symptoms or its treatments.It consists in insomnia,depression and leg restless and all of them are serious side effects of drug therapies that increase episodes of spasms,sleep disorders and tremor.[7]

1.3 Motor Evoked Potentials

Evoked Potentials (EP) are electric potential recordings that represent CNS response at external stimulations (sensory,visual,motor and acoustic) and they are located along peripheral nerves, spinal cord and brainstem. Motor Evoked Potentials (MEP)s are EPs that allow to evaluate motor system functionality because they are recorded at muscular level immediately after electric or magnetic stimulation of the cerebral cortex or spinal cord (1.6).[8] MEPs are fundamental in the assessment

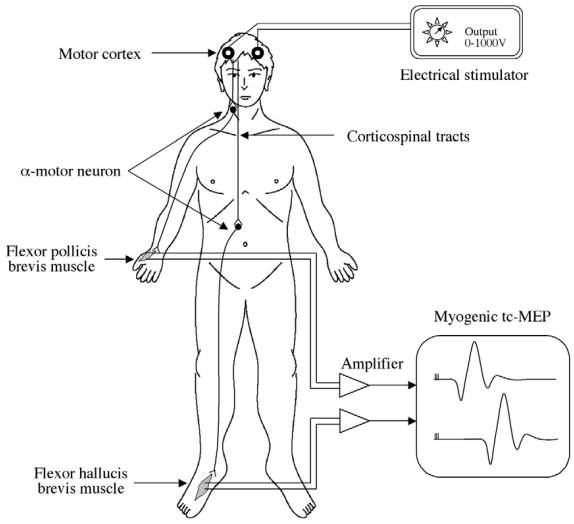

Figure 1.6: Schematic Representation of MEP provided by no-invasive technique.[9]

of motor conduction in CNS pathologies: to record electric signals means to be able of estimating their temporal propagation, providing important information about nerve conduction. The presence of pathology at neuromuscular level, such as MS, induces a delay in electric impulse propagation along nerves that can be detected estimating motor conduction time of the MEP. MEPs are often used in diagnosis

of many disorders that have implications at motor level: MS, motor neuron disease, spondylotic myelopathy, stroke, ataxia and spastic paraplegias. [8]

Chapter 2

State of the Art

2.1 Fampyra

Fampyra is a drug, available as tablets, used in the treatments of motor symptom in MS patients. The active substance is 4-amino-pyridine, a slow release molecule that blocks potassium voltage-dependent channels (K-channels) on nerve fibres surfaces. [1]

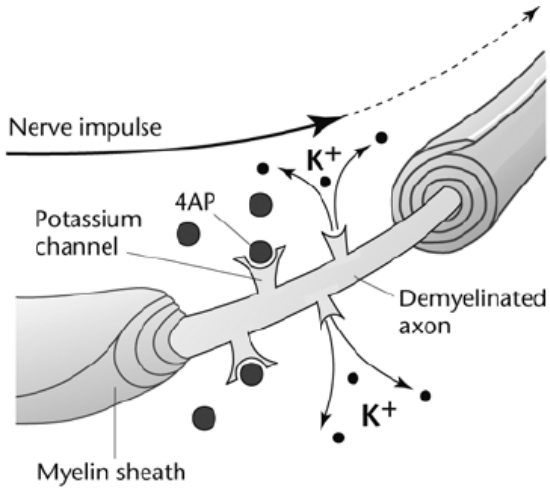

Figure 2.1: K - channels along axon surface.[10]

Numerous studies have demonstrated that K-channels are expressed in demyelinated neuronal membranes (typical condition in MS) and their presence induces a delay in electric signal propagation. K-channels activity is directly correlated to electric conductivity of signal to muscles and, as a consequence, is responsible of many impairments at motor level. The ability of 4-amino-pyridine to block K-channels activity is important in the re-establishment of conduction along axons, improving signal transmission and muscle contraction. Molecule efficiency is not present in all

of subjects but reliable results have been demonstrated in the three types on MS described above. [11]

The working principle of Fampyra leads to an improvement in MS symptoms related to motor fatigue; in fact its performance have been tested in deambulation at clinical levels employing two types of tests: Time 25 Foot Walk Test and 12-item MS Walking Scale.
Frequent side effects of Fampyra are infections of urinary tracts,insomnia,anxiety, dizziness, headache and breathlessness. Normally Fampyra is prescribed for gait improvement in patients with different severity levels of de ambulation disorders. [1]

2.2 Clinical Exams

In this work the clinical condition of patients is properly assessed considering information related to motor and central fatigue.Data are provided by clinical exams to which patients have been submited: Transcranial Magnetic Stimulation, High Voltage Electric Stimulation and Gait Analysis.

2.2.1 Transcranial Magnetic Stimulation

Transcranial Magnetic Stimulation (TMS) is a non invasive and safe technique that provides MEPs.The method is based on the electromagnetic induction principle: a powerful transient magnetic field induces electric currents in brain, producing the direct cortical brain stimulation. In this work, TMS is used to obtain Central Motor Conduction Times (CMCT) of MEPs recorded in the same muscular districts of compound muscle action potential (CMAP)s. Bilateral stimulation is induced using a double cone coil (110mm of diameter) in correspondence of the deep cortical regions related to the lower limbs. Stimuli are delivered with an intensity that guarantees MEPs with amplitude from 50 to 200 μV in almost all recording sites. In each patient 5 activated MEPs are obtained.
In order to reduce variability of MEP, they are recorded using a well defined protocol of controlled voluntary muscle activation; for each district, five MEPs are averaged. The protocol consist in a pre-determined pattern with 3 movements of both legs that

the patient must perform in rapid sequence supported by two devices that assets the correctness of the procedure.[12]

The protocol is shown in **??**.

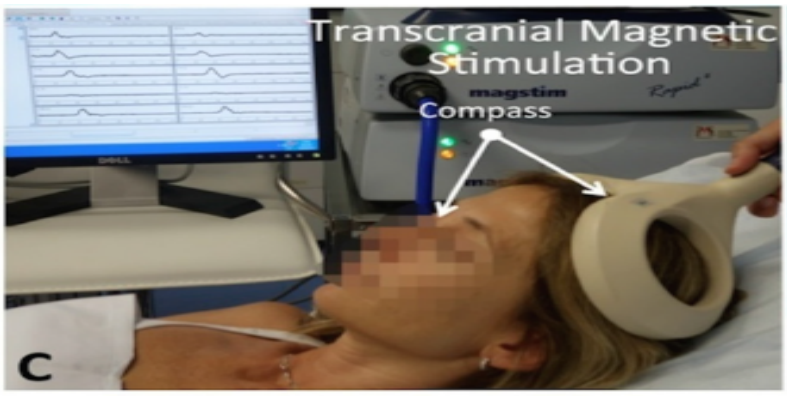

Figure 2.2: Transcranial Magnetic Stimulation.

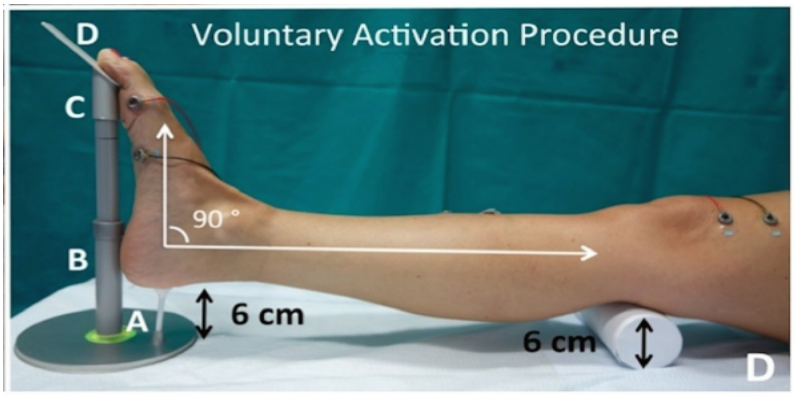

Figure 2.3: Voluntary Activation Procedure

2.2.2 High Voltage Electric Stimulation

High Voltage Electrical Stimulation (HVES) is a technique that allows to record CMAPs. CMAPs are the sum of few simultaneous action potentials related to muscle fibres located in a specific district. CMAPs are normally elicited by stimulation of the motor nerve [13]. In this specific work, HVES of lumbosacral nerve roots is

employed.

Multiple electrode array on spinal cord (dorsolumbar position) let clinicians to find the optimal vertebral stimulation sites that ensure sub maximal responses simultaneously in all recording sites. As a result stimulation is induced with an appropriate stimulus at vertebral level, while recording sites are in distal and proximal muscles: Flexor Hallucis Brevis (FHB), Peroneus Longus (PL), Tibialis Anterior (TA), Vastus Lateralis (VL), Vastus Medialis (VM).[12] The correct position of electrode in recording sites is a procedure described in [14].

Fig.**??** shows the electrode montage.

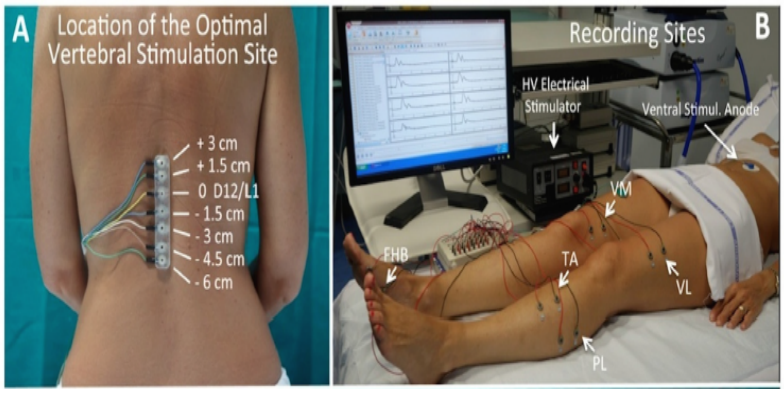

Figure 2.4: Neurophysiology of mapping for signals recording. [12]

Simulation is performed using Digitimer D 185-Mark IIa (Digitimer Ltd., UK)as high voltage electrical stimulator. It is able to produce a rectangular pulse stimulus of current with an suitable amplitude to achieve the best response from CMAP in all limb sites. The impulse has normally 600V and 1100mA. Latencies of root CMAP recorded are then used to estimate Peripheral Conduction Time (PCT). [12]

2.2.3 Gait Analysis

Alterations during walk are important indicators of fatigue progression and motor impairment in many neurodegenerative disorders like MS. Despite MS leads injuries at central level, the most impacting symptoms in daily life are at motor level: about

76% of patients need an ambulatory support and about 52% need bilateral aid al least. Asymmetry in strength of leg, decrease of speed in somatosensory conduction and alterations in control of motor pathway, are presumed responsible of loss in walk abilities. Studying gait of patients, evidences are related to the attitude of subjects to walk slowly, take no long steps, and try to increase the time of foot support. [15].

In this work tests performed to study gait impairments, namely:

- 25- Foot Walking Test (25FWT). In this test patients have to safely walk for 25 feet as quickly as possible for two times. The duration of the test begins when patients starts the task and ends when she reaches a distance of 25-foot mark.

- 6- Minutes Walking Test (6MWT): the test measures the distance performed by patients in 6 minutes walking as fast as possible. The goal is to evaluate the ability to perform efforts. Moreover, signals form accelerometers on feet are recorded and many physiological parameters are provided by sensors. [15]

In both tests patients can use aid devices.

2.3 Clinical Fatigue Indicators

Fatigue quantification is a very difficult task for clinicians because the highly subjective aspect of the problem among patients.As a consequence, there are not reliable methods of measurement universally accepted. Despite this,many alternative methods have been developed in order to support doctors in the evaluation of MS progression. Some of them try to measure "subjective" fatigue, such as Fatigue Scales,others try to obtain data from the morphology of MEP performing a totally objective description, finally some exams try to measure the decrease in the ability of performing a particular task, such gait analysis. [4]
In this work fatigue scales, innovative morphological clinical indicators and results from gait analysis are considered in order to evaluate progression of MS in ten patients.

2.3.1 Fatigue Scales

In order to diagnose fatigue and distinguish it from physiological one,specific instruments have been proposed as alternatives to common clinical exams: fatigue scales. They are specific tools that provide a global picture of situation in the course of MS to clinicians considering questionnaires filled in patients. Questionnaires and scales are limited because they provide only subjective evaluation, in fact they give information based on individual perceptions of the patient [16]. Some of scales most commonly used are described below.

- Fatigue Severity Scale (FSS). It estimates the severity of symptoms. Neurologists ask the patient to comment a list of 9 voices about sensation they feel about fatigue, with a score between 1 (strongly disagree) and 7(strongly agree). The global result of the test allow clinician to express about patient fatigue progression. [16].Proposed items are reported in 2.6.

- Modified Fatigue Impact Scale (MFIS). It describes how fatigue influences daily activities and it is proposed to patients by physiatrists, physical therapists and by occupational therapists. There are 21 items about sensations felt during ordinary tasks and patients have to give a score related their frequencies (never, rarely, sometimes, often, very often) in 4 weeks.[16].Proposed items are reported in 2.7.

- Visual Analogue Scale (VAS). It consists of a line of 10cm with a starting point marked with ”1” (absence of pain) and a ending point marked with ”10” (the worst pain ever felt).The patient have to indicate a point related to the intensity of pain he/she feels. An example is provided in 2.8.

Another scale, that is not specific to fatigue, is Expanded Disability Status Scale (EDSS).It is a no subjective scale,showed in Fig.2.5, that tries to give a score about level of disability in person with MS; it starts at 0, corresponding to normal neurological exam, and gradually increases until 10 that represents the maximum level of disability.Inside this interval there are all intermediate situations.Global score is obtained by the sum of all partial values.EDSS scale is largely used in many centres for treatments of MS because it allows simple evaluation of disease evolution and demonstrates the efficiency of one specific therapy. [1]

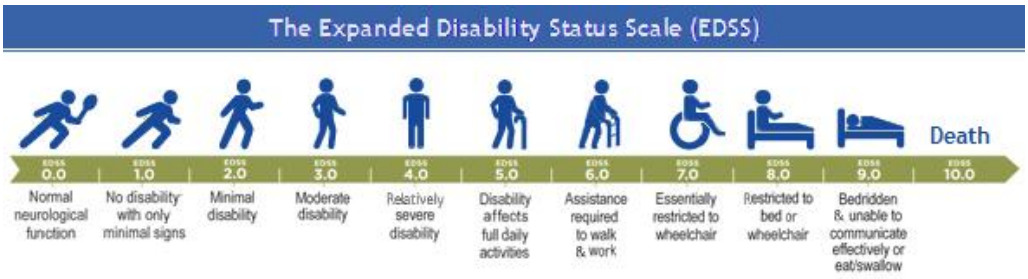

Figure 2.5: EDDS scale for disability progression of Multiple Sclerosis.[3]

	Scores 1 = Strongly Disagree; 7 = Strongly Agree						
1. My motivation is lower when I am fatigued.	1	2	3	4	5	6	7
2. Exercise brings on my fatigue.	1	2	3	4	5	6	7
3. I am easily fatigued.	1	2	3	4	5	6	7
4. Fatigue interferes with my physical functioning.	1	2	3	4	5	6	7
5. Fatigue causes frequent problems for me.	1	2	3	4	5	6	7
6. My fatigue prevents sustained physical functioning.	1	2	3	4	5	6	7
7. Fatigue interferes with carrying out certain duties and responsibilities.	1	2	3	4	5	6	7
8. Fatigue is among my three most disabling symptoms.	1	2	3	4	5	6	7
9. Fatigue interferes with my work, family, or social life.	1	2	3	4	5	6	7

Figure 2.6: FSS scale for fatigue progression of Multiple Sclerosis.[17]

1. I have been less alert.
2. I have had difficulty paying attention.
3. I have been unable to think clearly.
4. I have been clumsy and uncoordinated.
5. I have been forgetful.
6. I have had to pace myself in my physical activities.
7. I have been less motivated to do anything that requires physical effort.
8. I have been less motivated to participate in social activities.
9. I have been limited in my ability to do things away from home.
10. I have had trouble maintaining physical effort for long periods.
11. I have had difficulty making decisions.
12. I have been less motivated to do anything that requires thinking.
13. My muscles have felt weak.
14. I have been physically uncomfortable.
15. I have had trouble finishing tasks that require thinking.
16. I have had difficulty organizing things.
17. I have been less able to complete tasks that require physical effort
18. My thinking has been slowed down.
19. I have had trouble concentrating.
20. I have limited my physical activities.
21. I have needed to rest more often or for longer periods of time.

Figure 2.7: MFIS scale for fatigue progression of Multiple Sclerosis

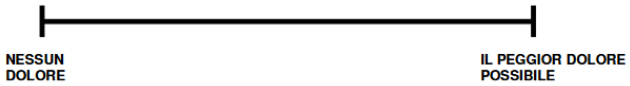

Figure 2.8: MFIS scale for pain progression of Multiple Sclerosis

2.3.2 Latencies and Areas

In many studies on MEPs,latencies and areas are the first measures evaluated by neurologists.In Fig.2.9 the biphasic morphology of the signal is shown. Latency is defined as the time between the impulse of stimulation and the appearance of related response under electrodes localized on muscle in exam.Latency is measured in [ms] and is very important to understand how much time an impulse takes to search the muscle, overall in MS where injures are manly present at nerve conduction level.

Area,instead,is an energy indicator defined as the portion of the space under the signal. In this work,which takes inspiration from Di.Sapio et. al [18], these two parameters are evaluated from MEP and CMAP signals using MATLAB 2018a software and considering:

- Latency: instant of time when MEP is 3% of its maximum value;
- Area—Energy: product between time and square of the signal;

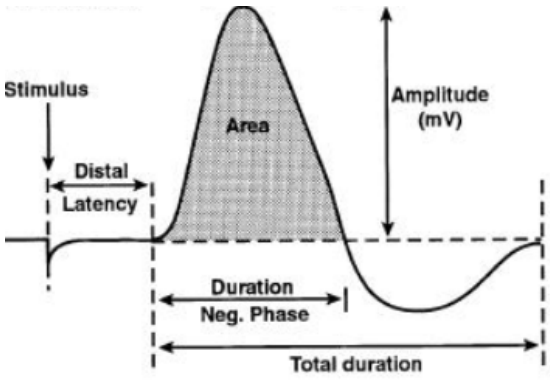

Figure 2.9: Morphology of Evoked Potential.[19]

Considering this information, directly measured on peripheral and central signals, Di.Sapio et.al [18] have selected the following variables to characterized conduction in patients:

- PCT:calculated from CMAPs provided by HVES described later;
- CMCT: subtraction of PCT to MEP, assuming that there are not peripheral alterations due to MS;
- Area Ratio (AR): ration between areas of central and peripheral MEPs;

2.3.3 Inter trial Variability

In order to establish the effect of a therapy on a patient, make evaluation about a variable before and after therapy is the better approach. From this point of view the use of Inter-Trial Variability (ITV) for latencies and areas has been proposed. ITV computation is implemented from signals recorded using a standardized pattern of voluntary activation,and elaborated considering an average of a few rectified potentials. According to [18],ITV for latencies is defined in 2.1 as:

$$Lat\_ITV = 100 \cdot \frac{Lat_{post} - Lat_{pre}}{< Lat_{post}, Lat_{pre} >} \tag{2.1}$$

where Lat_{post} and Lat_{pre} are the latencies of signal after and before drug administration. For areas,ITV is defined in 2.2 as:

$$A\_ITV = 100 \cdot \frac{A_{post} - A_{pre}}{< A_{post}, A_{pre} >} \tag{2.2}$$

where A_{post} and A_{pre} are areas of signal after and before drug administration. In this case the problem of variability impairs data reliability, so a normalized form of ITV called norm-ITV is introduced, defined as:

$$norm\_ITV = A\_ITV \cdot \frac{(100 - (Cv \cdot \Delta))}{100} \tag{2.3}$$

where Cv represents the ITV component inversely related to area for unit of area (1mV*ms), and Δ is provided by the subtraction of mean area (between A_{post} and A_{pre}) from theoretical value (as the mean area values from their population + 3SD) [20]. Values of ITV can be calculated for CMCT and AR too.[18]

Chapter 3

Materials and Methods

3.1 Patients and Signal Acquisition

The study is conducted on a group of patients with MS composed by 7 men and 3 women. The mean age is 48.4 and subjects have values of EDSS between 1 and 6.5 (mean EDSS=4.5). All of them are treated with drug Fampyra by clinicians of Azienda Ospedaliero-Universitaria San Luigi Gonzaga of Orbassano (TO). Lower limb muscles involved in study are: FHB (Flexor Hallucis Brevis), PL (Peroneus Longus), TA (Tibialis Anterior), VL (Vastus Lateralis), VM (Vastus Medialis) for both sides.
The complete procedure consist in TMS to record MEPs, HVES,to evaluate CMCT and gait analysis. Each patient performs these tests twice: before starting the drug therapy and after two week of treatment with Fampyra.
This work aims to automatizing the task of doctors in elaboration of information provided by recorded signals in measure of areas and latencies, and in evaluation of ITV. For these reason, signal processing is implemented by an algorithm (MATLAB, version 2018a for Windows 10) that yields as output information about patient after drug administration. Results are then compared and completed by gait analysis test data and fatigue scales scores.

Patients data, taken from the computer used for signal acquisition,are in ASCII format.

The algorithm allows one to choose central and peripheral data of patient to be analysed, elaborate them and provides as output ITV of latencies and areas, CMCT and AR.

3.2 Signal Processing

As previously mentioned, signal acquisition has been done following the procedure proposed in Di Sapio et al. [18], which is different for peripheral (called RAD) and central activation signals. RAD requires a protocol with two electrical stimuli by HVES where only the last epoch is considered for the subsequent analysis. For what concerns central activation signals, five magnetic stimuli are delivered and as the final epoch the average of last five simulations is considered.
Once final epochs of signals are obtained, information about peripheral and central conduction before and after two week of drug therapy are available for preprocessing phase:

- subtraction of mean value;
- subtraction of first value (signal starts from zero);
- rectification of the signals;
- low-pass FIR filtering to remove signal fluctuations.

Results of signal processing are shown in **??** for central signals and in **??** for peripheral ones.

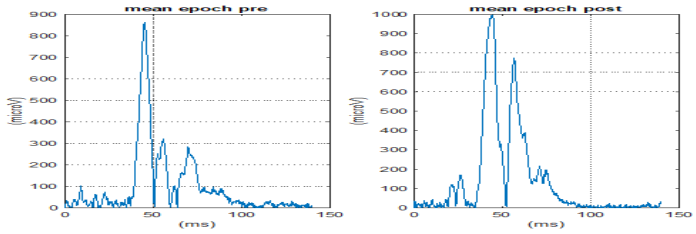

Figure 3.1: Central signals before filtering in TA.

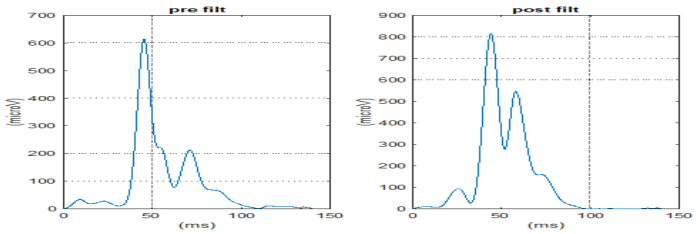

Figure 3.2: Central signals after filtering in TA.

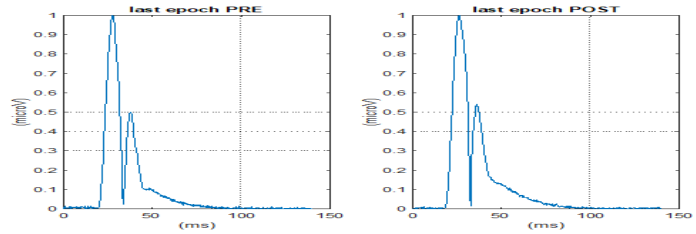

Figure 3.3: Peripheral signals before filtering in TA.

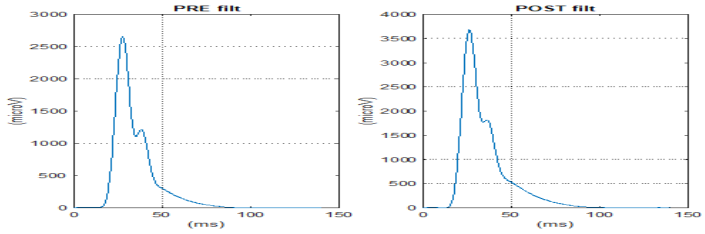

Figure 3.4: Peripheral signals after filtering in TA.

At the end of these operations, measure of parameters mentioned above can be done.

3.3 Problems of Data Stability

Observing the recorded signals, some considerations about data stability and reliability can be done. First of all signal with a peak value lower than 50 μV are present in central registrations ones. According to clinicians and material found in literature, if a neurological signal has a maximum under this value, it is not meaningful. Reasons of this assumption are attributed to the impossibility to say if signal has amplitude totally covered by noise or if it is completely absent. The first case denotes a situation in which axon damage is very important and nerve conduction is completely compromised; in this condition drug therapy,alone,is not able to improve patient conditions and the analysis is useless. In the second case, instead, problems or artifacts in signal acquisition have definitively deleted the signal and it is possible only to record noise. Moreover in this study, peaks under 50 μV are observed in MEPs probably because MS lesions of these patients are located more common in central regions. As a consequence, the algorithm marks these signals as "non-classified" and excludes them from further analysis. An example of non-classified signal is presented in 3.5.

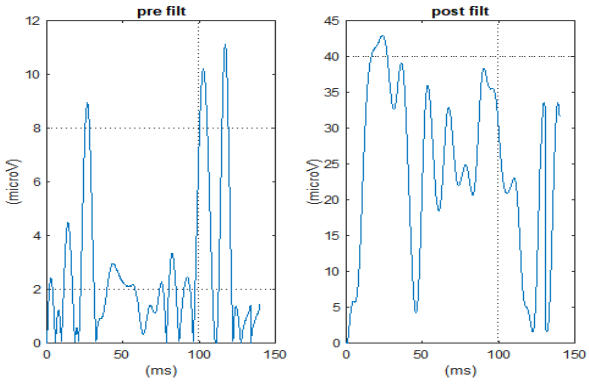

Figure 3.5: MEP signal with amplitude under 50 μV.

In sections 3.3.1 and 3.3.2 other considerations about artifacts due to wrong signal acquisition are discussed.

3.3.1 Peaks Amplitude

Important information related to nerve functionality is provided by amplitude of MEP and CMAP.In particular,the amplitude of the main peak of the signal is closely correlated to the number of axons and fibres involved in muscle activation. Abnormal values of peak amplitude allow to diagnose diseases that induce loss af nervous fibres such as neurodegenerative pathologies, block of conduction,muscular dystrophy ecc. It is possible to say that is a very important indicator in the evaluation of clinical situation of a subject with MS, but at the same time is not totally usable cause of its huge variability.

Processing both central and peripheral signals, amplitude of peak is observed: in some cases there is a huge difference in maximum values before and after Fampyra administration, sometimes it is more than twice. Reasons of this are not neurologically explainable by doctors because,despite their physiological morphology, these signals are not reliable since Fampyra cannot induce such an improvement in signal amplitude. Finally,since causes are not clear, hypothesis of errors during signal acquisition have been done like the malposition of stimulation recording site.
In Fig. **??** an example is reported.

To establish patients improvement, a problem of this entity has a great impact because peak amplitude heavily influences area of signals and, of course, ITV measures. For all this reasons the algorithm has been structured to automatically recognize problematic peak difference situations and exclude that muscle activations from discussion.

3.3.2 Morphology

Elaboration of signals reveals other situations related to anomalous signal morphology that appear indifferently in either central or peripheral both signals and with the same incidence before and after Fampyra administration. It makes impossible to identify the standard waveform that characterizes EPs and the value of latency. From a neurological point of view, these signals are of no interest since they do not carry available information, rather they have to be excluded because their areas,and

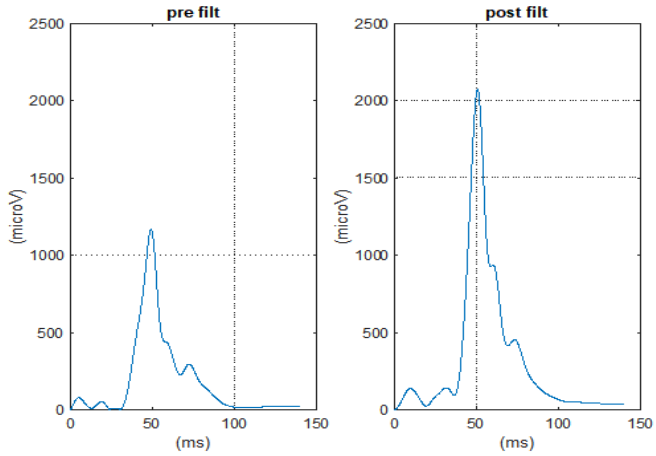

Figure 3.6: Example of huge difference amplitude in MEPs.

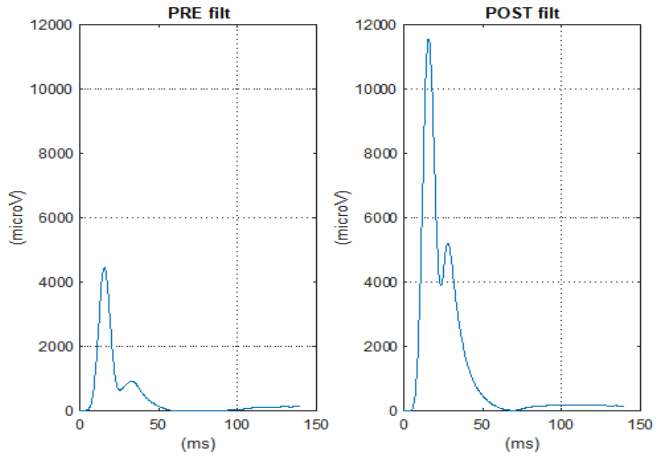

Figure 3.7: Example of huge difference amplitude in RAD

as a consequence,their ITV values could influence patient final response. Also with this artifact, errors in the procedure of signal acquisition have been assumed.
In Fig. 3.9 an example is reported.

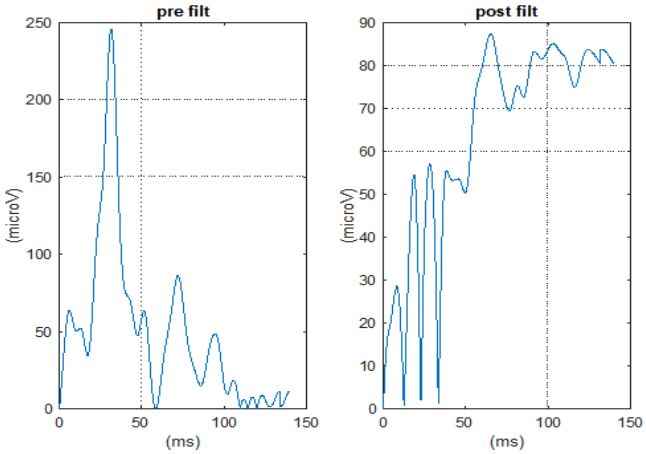

Figure 3.8: Example of anomalous morphology in MEPs.

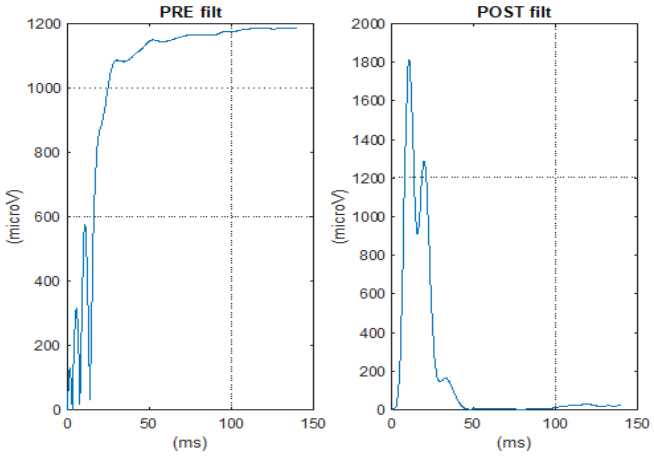

Figure 3.9: Example of anomalous morphology in RAD.

Other situations observed are related to final fluctuations of signal that after peak does not return to zero. An example is reported in Fig.3.10

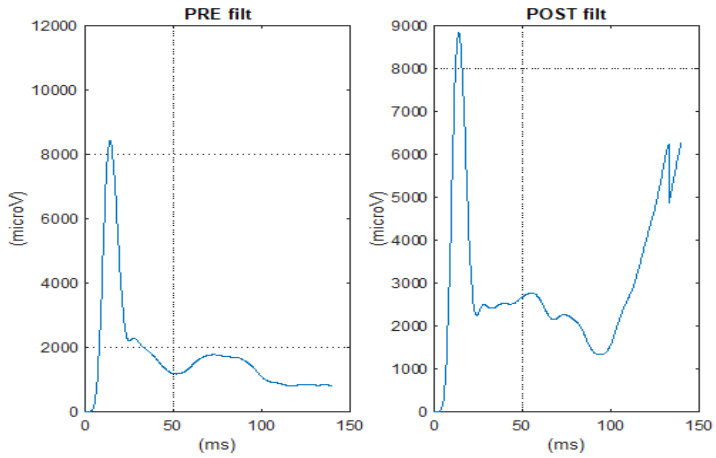

Figure 3.10: Example of RAD signal that does not return to zero

Also in this case specialists were not able to provide a exhaustive explanation, because in physiological condition such behaviour of evoked potential is completely impossible. Different from the situation described above, in this case it is possible to recognize the standard waveform and latencies, but also these signals are considered unreliable because they provide altered values of ITV. As a result algorithm have to recognize this kind of situations and leave out related muscle activation from study.

3.4 Methods

3.4.1 Automation of algorithm

Algorithm works on one patient at a time elaborating his/her central and peripheral signals before and after drug therapy.For each signal it is able to recognize if it is affected by one of the data instability situations described in section 3.3. First of all, for what concerns signals with maximum amplitude under 50 μV, a threshold criteria has been implemented: all signals with peak lower than a threshold of 50 μV are considered not classified and immediately excluded. Respective pre/post and MEP/RAD ones are not considered too. Problems about peaks values and

morphology are faced using a statistic approach.

Peaks: A variable ΔP is introduced defined as:

$$\Delta P = |P_{pre} - P_{post}| \tag{3.1}$$

where P_{post} and P_{pre} are the maximum values of signal after and before therapy. This variable is calculated for all signals and total data are stored distinguishing the peripheral group and the central one. The objective is to identify a threshold value above which the couple of signals "before/after" is considered not suitable for the reasons described in 3.3.1. The identification of this value can not be supported by literature or physiological considerations, so a plot of data distribution and relative box plot is performed. For central signals, 80 signal are available.

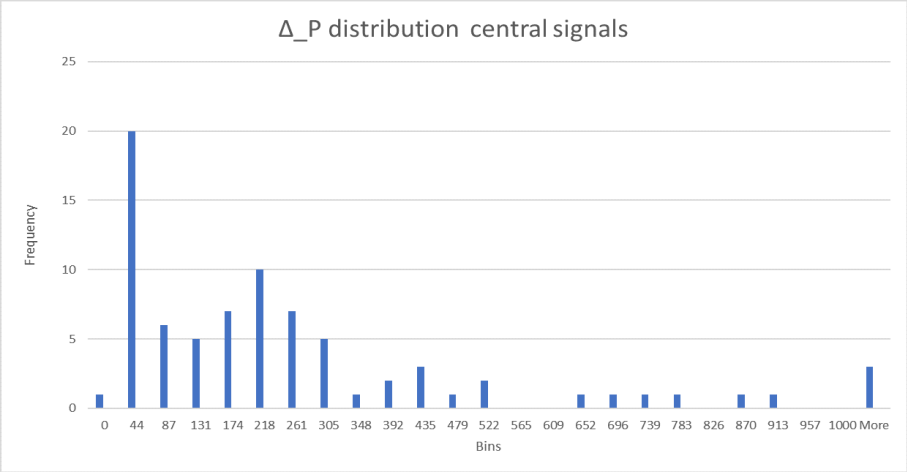

Figure 3.11: Distribution of MEPs values of ΔP.

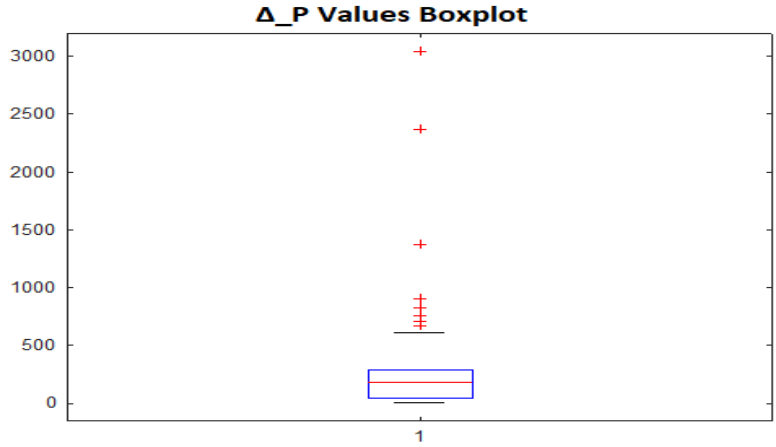

Figure 3.12: Boxplot of MEPs value of ΔP.

For peripheral signals, 80 signal are available too.

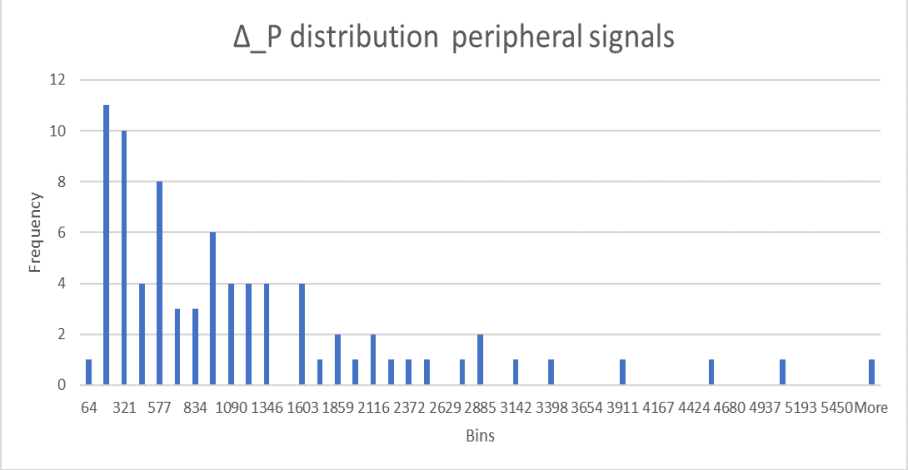

Figure 3.13: Distribution of RAD values of ΔP.

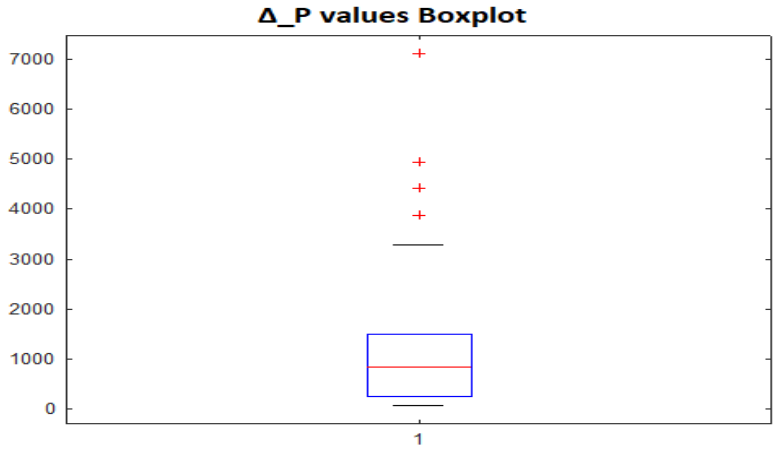

Figure 3.14: Boxplot of RAD value of ΔP.

The assumption is remove all pairs of signals for which ΔP value represent an outlier of the sample distribution, so a value that is anomalous or aberrant respect others. To recognize them, threshold is calculated considering:

$$T = Q_3 + 1.5 \cdot (Q_3 - Q_1) \tag{3.2}$$

where Q_1 is the $25^{th}\%$ and Q_3 is the $75^{th}\%$ of intervals.

As a result, all those pairs of pre/post of central signals whose ΔP is higher than 650 μV have been removed for a total of eight pairs.For peripheral signals, instead, all that pairs whose difference in peaks amplitude is lower than 3 mV are accepted (four signal are removed).

Morphology: In order to recognize signals with a morphology different from the standard one another variable,called Error of Energy, has been introduced:

$$\Delta E = |E_{pre} - E_{post}| \tag{3.3}$$

with E_{post} and E_{pre} energy values of signal after and before therapy, calculated as:

$$E = \sum_{k=1}^{N} T \cdot (A)^2 \tag{3.4}$$

where N is the number of samples in signal recording and T and A are, respectively, the instant of time and the amplitude of signal of the n^{th} sample.

Certainly,the higher it is ΔE, the higher is the area difference before and after Fampyra administration.Since highest values of ΔE are related to situation in which difference in areas are not explainable as a drug effect,all cases described in section 3.3.2 can be identified because are not physiologically possible.

As a result, the same approach used for difference in peaks value is adopted to recognize the optimal threshold for both signal categories.

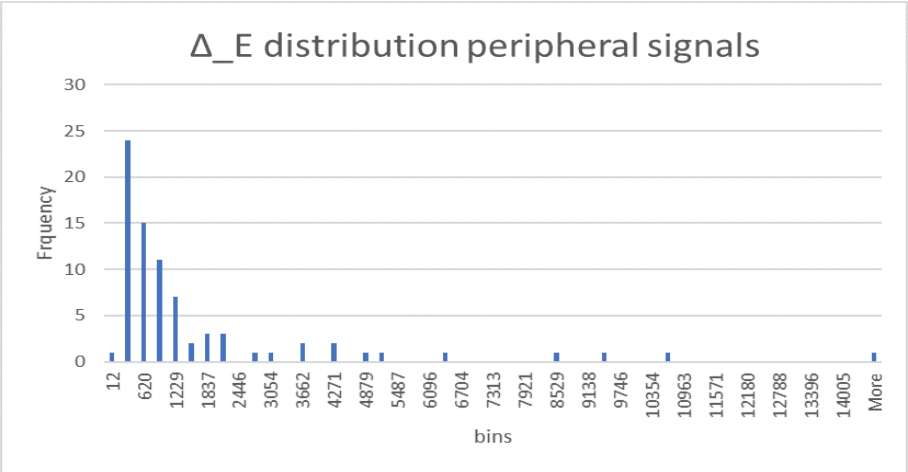

Figure 3.15: Distribution of MEP values of ΔE.

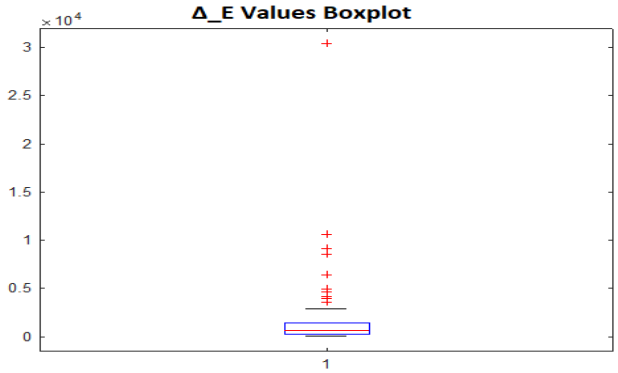

Figure 3.16: Boxplot of MEPs value of ΔE.

For peripheral signals, 80 signal are available.

After having identified outliers of ΔE distribution, of all those pair "pre/post" of central signals for which ΔE is higher than 3 $s \cdot mV^2$ have been removed for a total of eight couples.For peripheral ones, instead, all those pairs, which difference in energy was lower than 1,4 $s \cdot mV^2$ are delete (four signal are removed).

3.4.2 Elaboration of parameters

Starting from a total of 100 central signals and 80 peripheral signals, after removing all ones that could not provide reliable results, the algorithm proceeds in the

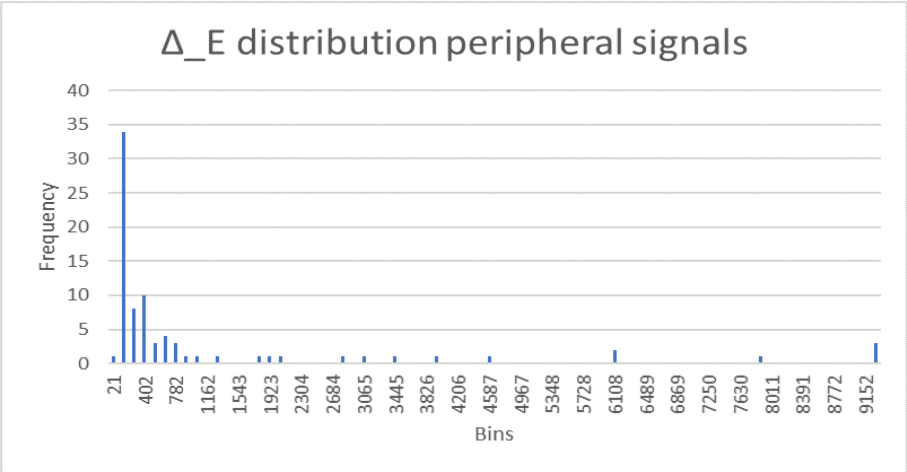

Figure 3.17: Distribution of RAD values of ΔE.

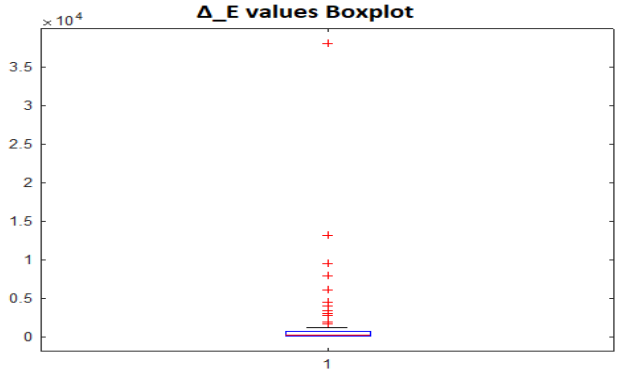

Figure 3.18: Boxplot of RAD value of ΔE.

calculation of clinical fatigue indicators.

As explained in 2.3.2,first measures to perform are related to areas and latencies.

This work presents a variation from that conducted by Di Sapio et al.[18], because instead of areas, a measure of signals energy $[ms \cdot mV^2]$ has been chosen. This choice is equivalent,because a measure of area is always representation of a measure of energy in signal processing. Once that measures of energy are obtained, the same parameters proposed by Di Sapio et al. and described in section 2.3.3, have been calculated.

- AR;

- norm_ITV according to equation 2.3 ;

For what concern latencies, the algorithm returns the instant of time in which peripheral and central signals have reached the 3% of their peak amplitude. In Fig **??**, some examples are reported.

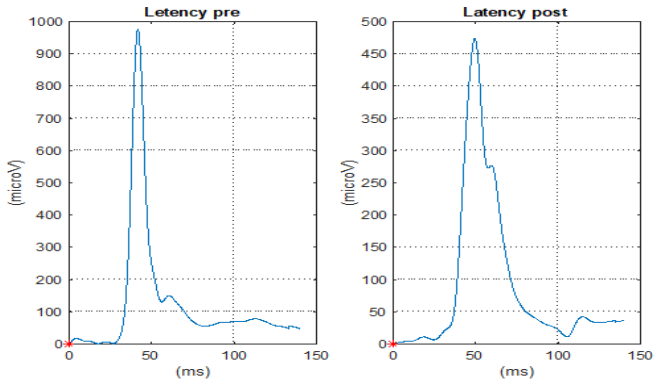

Figure 3.19: Latency instant in red stars in MEPs.

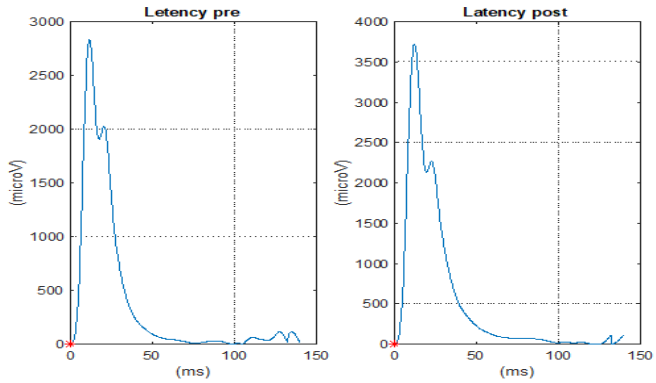

Figure 3.20: Latency instant in red stars in RAD signals.

As in Di Sapio et. al [18] the follow parameters are calculated:

- CMCT;
- Lat_ITV according to equation 2.1;
- ITV of CMCT;

3.4.3 Score assignment

Improvement of patient conditions are evaluated giving a score to each muscle depending on its signal before and after drug administration. In particular:

- -1 worsened muscle condition;
- 0 stable muscle condition;
- +1 improved muscle condition;

Considering the work of Di Sapio et. al [18], the score is decided comparing all parameters, output from algorithm, to the respective reference range of values.In the work of W. Troni et al. [12], for each muscle a range between 5TH and 95TH percentile of the different indicators was established **??** (RIV,Relative Inter trial Variation). In the Fig **??**, results from work presented in [18] are reported.

Finally,for all patients a score is assigned for each indicator resulting from the sum of marks on residual muscles.This score, compared to the ones of all other parameters, can help clinician in the assessment of patient state. Having excluded from the analysis a significant number of muscles, the patient final score, in case not all muscles are reliable, is evaluated as:

$$S = \frac{10 - NC}{10} \tag{3.5}$$

where NC is the number of muscles for which the algorithm has not calculate indicators. Considering relation 3.5, the maximum value of each indicators is "+10" if in all muscles of the patient there is improvement. On the contrary, the minimum value is "-10" if worsening is globally observed. Of course the latter condition is very unlikely because drug should not induce impairment in patient condition, at worst keeps stable situation.

Recording site	RIV5th-95thPercentile	RIV5th-95thPercentile	RIV5th-95thPercentile
VM	-9.6 / +9.1	-6.4 / +6.7	-12.2 / +15.1
VL	-9.7 / +13.6	-6.4 / +6.1	-14.9 / +11.5
TA	-6.4 / +5.2	-5.9 / +5.6	-14.8 / +13.8
PL	-6.7 / +6.9	-5.8 / +4.2	-12.4 / +12
FHB	-6.5 / +4.1	-7.6 / +3.5	-13.1 / +16

Figure 3.21: RIV range values for latency, ITV_lat and ITV_CMCT.

Recording site	RIV5th-95thPercentile	RIV5th-95thPercentile	RIV5th-95thPercentile
VM	-29.1 / +26.6	-26.0 / +37.1	-25.3 / +32.2
VL	-37.8 / +36.5	-21.3 / +35.0	-22.0 / +31.0
TA	-21.7 / +28.0	-34.5 / +30.5	-25.2 / +30.0
PL	-24.8 / +24.1	-24.1 / +34.8	-20.9 / +26.3
FHB	-23.3 / +17.5	-31.7 / +24.5	-15.0 / +17.4

Figure 3.22: RIV range values for energy,E_ITV, AR_ITV and $normE\_ITV$.

Chapter 4

Alternative indicators

The search of alternative indicators with to as proposed by Di Sapio et. al [18], is manly due to the excessive variability of ITV values. Their dependency from the area of signals make them not totally reliable leading to possibly wrong statements by neurologists.In this view new indicators independent of area but based only on morphology changes of MEP before and after drug administration are proposed.

4.1 Morphologic approch

The idea at the base of this approach is related to the damage that MS can induce at nerve conduction level.Normally, in healthy adult subjects values of speed in transmission of nervous impulse range between 40m/s as 75 m/s. In literature, many studies confirm that these values can be modified in relation to:

- proximal vs distal areas (proximal areas have higher values of conduction speed respect to distal areas);
- age of subject;
- metabolic factors such as poor vascularization of the area in exam and increase in body temperature;

Clinicians confirm that demyelinating processes in MS are responsible for a huge series of metabolic changes in human body and, together, induce a reduction in speed conduction. A consequence, measures of speed conduction are indices of the state of pathologies of myelin sheaths or conduction block at different levels of nerves.

Starting from these clinical evidences, in this work hypotheses of morphology of a MEP before and after the assumption of drug have to been done. In particular,

knowing that a therapy with Fampyra should improve nerve conduction, after two week of administration it is expected an improvement in motor conduction. In terms of morphology, this statement is translated into a faster signal with higher and less wide peak. In other words the MS should induce a âĂİ stretching âĂİ in healthy signal, and so quantifying it can be an alternative way to characterize the effect of drug. A qualitative representation of idea is proposed in figure.

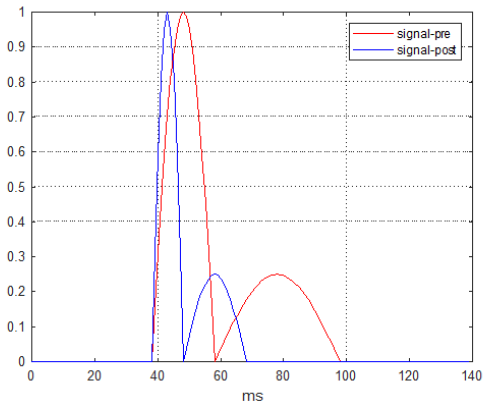

Figure 4.1: Synthetic signal expected Pre/Post administration .

Signals in Fig. 4.1 are normalized to 1 because the approach does not consider information about the peak amplitude due their instability.

Parameters introduced are based on the considerations made above. They are described more in details in the following sections.

4.2 Peak width

From Fig.4.1 it is evident that information about peak width is directly related to improvement in speed nerve conduction and of course to effect of therapy on patients. The measure of peak width is performed by function $find - peaks$ of Matlab2018a in signals before and after administration. In Fig. 4.2 an example is reported.

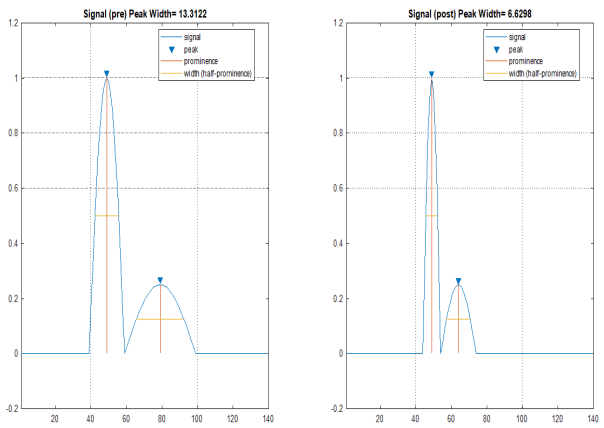

Figure 4.2: Function Find-peaks applied to synthetic signal expected Pre/Post administration with measure of width.

According to qualitative aspects, if a patient benefits from therapy, it is expected an improvement in nerve conduction and a slight decrease of peak width after Fampyra. The algorithm evaluates peak width for all signals and compares results before and after Fampyra therapy.

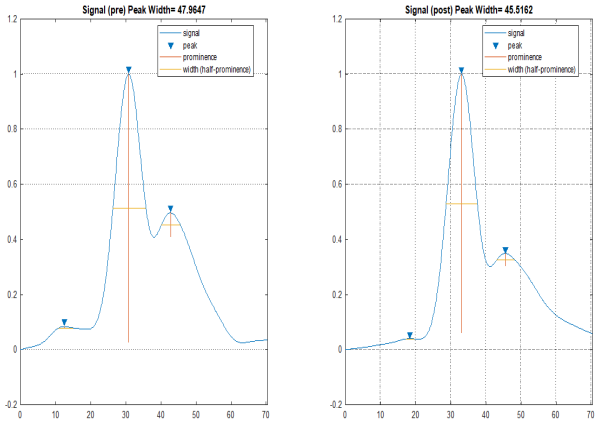

Figure 4.3: Find-peaks application to MEPs.

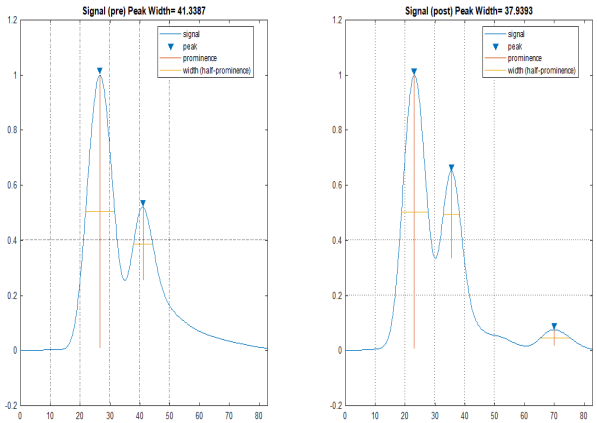

Figure 4.4: Find-peaks application to RAD signals.

4.3 Distance between signals

From Signal Processing Toolbox of Matlab2018a, the function that implements Dynamic Time Warping (DTW) has been employed.

DTW is an algorithm that implements the alignment of two sequences returning the optimum value of distance between them. It is very useful to examine signals

which components change in time because it is able to find a optimum correspondence through a nolinear distortion respect to time (independent variable). The method is mostly used in speech recognition and gait analysis for the identification of specific repeated cycles. [20]

The function works stretching two input signals into a common set of instants: each element of signals is repeated as many times as necessary to report the two signals at the same duration. In Fig 4.5 the result of function when inputs are two synthetic signal is shown.

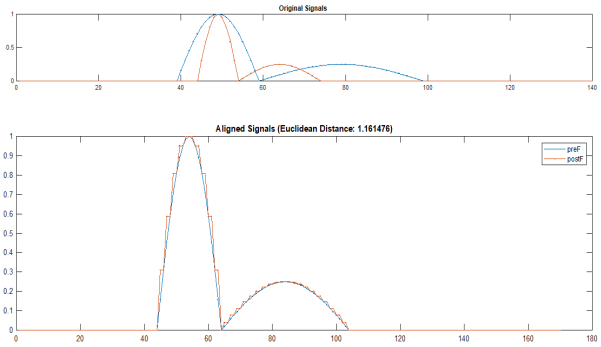

Figure 4.5: Synthetic signal expected Pre/Post administration.

The parameter returned as output is the smallest value of the sum of Euclidean distances between each point of both signal. In other words, returned distance is the optimal way to align signals stretching them the least possible. Application to signals in analysis are shown in **??**.

Applying DTW to signal before and after drug administration, the value of distance returned can be an index of how is morphology is changed.

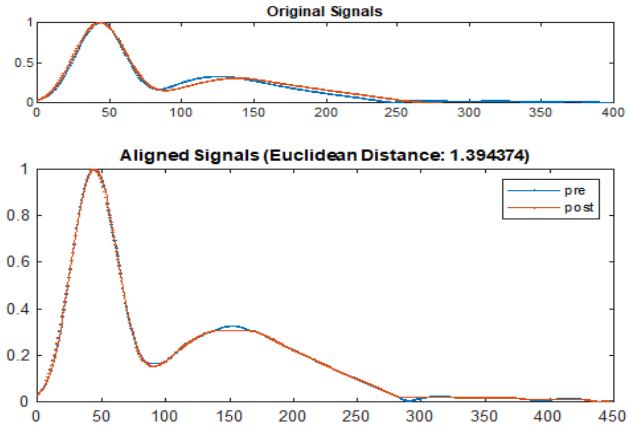

Figure 4.6: DTW application to MEPs in VM muscle.

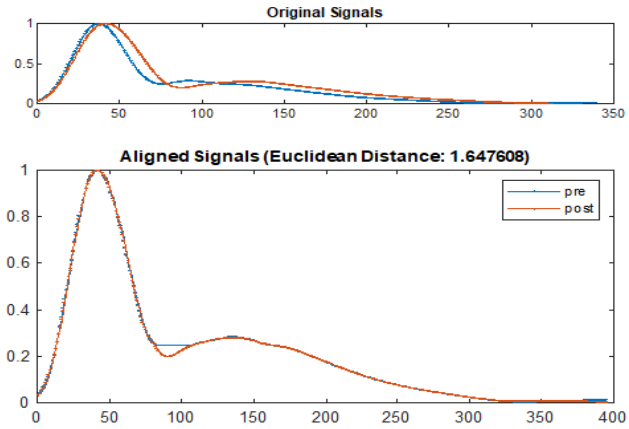

Figure 4.7: DTW application to RAD signals in VM muscle.

4.4 Tracts of Index Repetitions

DTW has been used also to obtain information about how many indices of one signal needed repetitions to perform the alignment to the other one. Function return also the ”warping path” that means a monotonically increasing sequence in which the elements of the corresponding signal are repeated the necessary number of time.

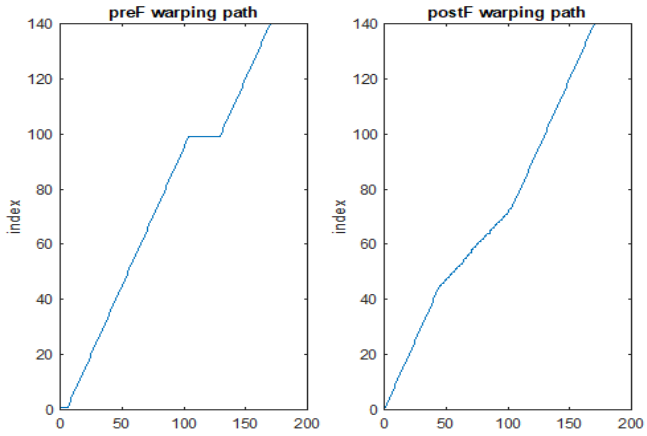

Figure 4.8: Warping path.

It is important to note that the warping path on the left of Fig 4.8 is related to the stretching that post signals have to be subject to be aligned to the pre one.Evidences from this warping path are related to the fact that there are two constant lines in linear increasing: this means that,in order to identify post signals tighter than pre ones, at least two constant tracts have to be recognized in their warping path.

In the work the parameter that is used to achieve information about patient state is the number of tracts related to repetition of the same index: for each pre/post pair this number has been computed. Tracts considered informative are those related to index repeated more than three times. As it is possible to appreciate from in Fig. **??**, warping paths of signal analysed exhibit the same trend of synthetic ones both in MEPs and CMAPs respect to the number of constant tracts.

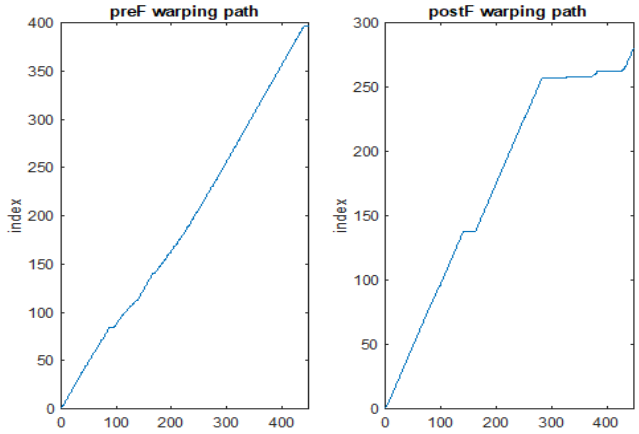

Figure 4.9: Warping path resulted from DTW application to MEPs in VM muscle.

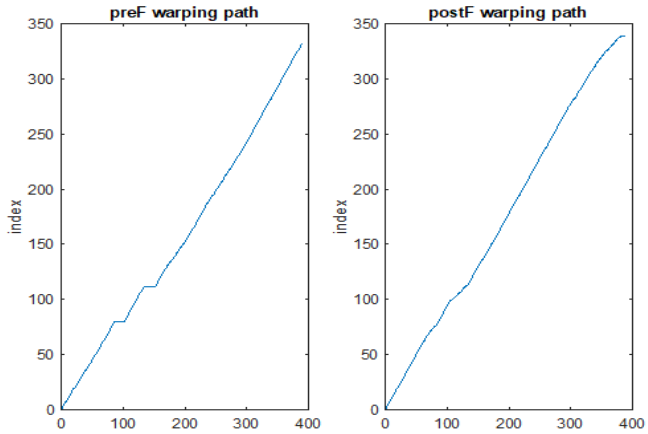

Figure 4.10: Warping path resulted from DTW application to RAD in VM muscle.

Chapter 5

Results

In this section an overview about patients situation of Fampyra trial are proposed. Evaluations are based on information provide by all the indicators returned from the algorithm, EDSS scale and gait analysis results.Finally, an assessment of patient state is defined. A patient with a score larger than 3 has been considered improved; if results shown a score lower than -3, patient has been considered worsened and intermediate score is associated to stationary conditions. For what concern 6MWT, only if patient has walked more than 30 metres after drug administration, he/she is considered as improved. Cause of privacy reasons the name of each patient is replaced by a number. The overview consists in tables that summarize all parameters described below:

- Value of EDSS scale;
- Results of 25FWT before and after Fampyra administration;
- Results of 6MWT before and after Fampyra administration;
- ITV_lat;
- ITV_A;
- ITV_CMCT;
- ITV_AR;
- n_m number of activation muscles considered;
- T_RAD total score on RAD signals;
- T_MEP total score on MEP signals;

- *widt_pre* (average values on *n_m*);
- *width_post* (average values on *n_m*);
- *C_Tracts* (average values on *n_m*);
- Distance returned by DTW (average values on *nm*);

The first three sections contain evaluations on patients for which results from group of Azienda Ospedaliero-Universitaria San Luigi Gonzaga of Orbassano (TO) are available too, so a comparison is performed.

5.1 Patient 1

EDSS: level 6

	25MWT	6MWT
Pre	16”89	91.2m*
Post	13”99	7.6m*

Table 5.1: Patient1-Results from Gait Analisys.

Alternative Indicators

	widt_pre	*widt_post*	*C_Tracts*	*Distance*
RAD	52.10	51.1	2.5	2.11
MEP	60.27	49.85	6.57	1.03

Table 5.2: Patient1-Alternative Indicators elaborated by algorithm for MEP and RAD signals.

Clinical Indicators

RAD		MEP		Global		
ITV_A	*ITV_lat*	*ITV_A*	*ITV_lat*	*ITV_CMCT*	*ITV_AR*	*n_m*
-1.8	-1.2	3.6	4.5	0.6	3.6	6
-2	**-1**	**5**	**2**	**3**	**4**	**10**

Table 5.3: Patient1-Clinical indicators proposed by Di Sapio et al. [18]

Patient 1 has a high EDSS level, so it is a very compromised motor condition.Results in Table 5.1 shown the severity of situation,in fact the subject was not able to complete 6MWT, moreover after Fampyra treatment he has only walked for 7.6m, 80% less of the previous test.
Clinical and alternative indicators instead report different situations between RAD and MEP signals: values of ITV_A, ITV_lat and changes in peak width denote a stationary condition for RADs. Respective MEP values, instead, shown a significant improvement confirmed also by ITV_CMCT and ITV_AR.
This evaluation is in agreement with clinicians one, in fact there is total coherence with their results reported in second line of Table 5.3. Different from them, results of the algorithm probably can be considered more reliable because it has recognized four signals as morphologically inappropriate for the analysis.

Finally, it possible to assert that, according to clinicians, the patient is improved at central level and has a stationary situation at peripheral one, despite results of 6MWT.

5.2 Patient 2

EDSS: level 5.5

	25MWT	6MWT
Pre	9”71	42.4m
Post	7”19	30.4m

Table 5.4: Patient2-Results from Gait Analisys.

Alternative Indicators

	$widt\_pre$	$widt\_post$	C_Tracts	$Distance$
RAD	42.56	41.75	3.22	2.54
MEP	54.13	49.88	5.13	3.42

Table 5.5: Patient2-Alternative Indicators elaborated by algorithm for MEP and RAD signals.

Clinical Indicators						
RAD		MEP		Global		
ITV_A	ITV_lat	ITV_A	ITV_lat	ITV_CMCT	ITV_AR	n_m
4	2	0.8	0	-0.8	-2.4	8
2	**4**	**-2**	**-1**	**-2**	**-2**	**10**

Table 5.6: Patient2-Clinical indicators proposed by Di Sapio et al. [18]

According to the EDSS value, result shown in Table 5.4 denoting complicated motor conditions in fact the patient is able to walk only for 30 metres in six minutes even after Fampyra administration.

Looking at the different parameters, the situation appears substantially stationary: RAD values report a slight tendency to improvement while MEP ones tend to get worse. This is not reflected in the alternative indicators that present a positive result in peak width only for MEPs.

Also in this case results from Orbassano are coherent, rather they evidence a more appreciable worse in central conduction because their study consider ten muscles in total. Again, results provide by the algorithm implemented,instead, could be considered more reliable because two muscles affected by morphology problems are excluded.

Summarizing patient condition can be considered as stationary.

5.3 Patient 3

EDSS: level 3.5

	25MWT	6MWT
Pre	4”39	409m
Post	4”41	458m

Table 5.7: Patient3-Results from Gait Analisys.

Alternative Indicators

	widt_pre	*widt_post*	*C_Tracts*	*Distance*
RAD	38.29	38.85	2.4	1.64
MEP	62.32	77.18	5.13	4.22

Table 5.8: Patient3-Alternative Indicators elaborated by algorithm for MEP and RAD signals.

Clinical Indicators

RAD		MEP		Global		
ITV_A	*ITV_lat*	*ITV_A*	*ITV_lat*	*ITV_CMCT*	*ITV_AR*	*n_m*
-4	-3	1.6	0	0.8	4	8
-5	**-2**	**+2**	**2**	**2**	/	**10**

Table 5.9: Patient3-Clinical indicators proposed by Di Sapio et al. [18]

Patient condition appear improved looking results of 6MWT and 25FWT shown in Table 5.7. The subject, in fact has walked for more than 30 meters more after Fampyra treatment. Moreover, the level of disability is not very severe.

For what concern values of *ITV_CMCT* and *ITV_AR*, considered as the most indicative of central conduction injuries, they denote a slight improvement. This is confirmed also by values of area and latency and by clinicians team. *RAD* signals do not present the same situation, rather they appear very worse in both studies. It is evident that a patient in which there is so discordance between central and peripheral signals, need further clinical investigations.

Alternative indicators do not confirm as said but denote an improvement in central condition according to the morphological indicators that suggest an appreciable change in signals before and after Fampyra administration.

Lastly a condition of stationary is proposed for this patient too.

5.4 Patient 4

EDSS: level 6.5

	25MWT	6MWT
Pre	13”49	168m
Post	8”87	268m

Table 5.10: Patient4-Results from Gait Analisys.

Alternative Indicators

	widt_pre	*widt_post*	*C_Tracts*	*Distance*
RAD	/	/	/	/
MEP	54.36	57.21	2	9.09

Table 5.11: Patient4-Alternative Indicators elaborated by algorithm for MEP and RAD signals.

Clinical Indicators

RAD		MEP		Global		
ITV_A	*ITV_lat*	*ITV_A*	*ITV_lat*	*ITV_CMCT*	*ITV_AR*	*n_m*
/	/	-0.4	-0.4	/	/	2

Table 5.12: Patient4-Clinical indicators proposed by Di Sapio et al. [18]

For patient 4 *RAD* signals are not available, so is not possible to compute values of *ITV_A* and *ITV_lat* and the more important *ITV_CMCT* and *ITV_AR*. For a complete clinical picture it is important to report that among ten signals of muscle activation, only two are considered reliable, the other in fact, were excluded due their peaks values. Eight signals presented a maximum peak value under 50 μV, so they are classified as noise or due to absence of conduction.
Respect to information available, values of *ITV_lat* and *ITV_A* for central signals, do not denote significant changes before and after Fampyra.
Alternative indicators, instead, both peak width and *Distance* in Table.5.11 shown appreciable differences after therapy (*Distance*=9.09). According to them also results from gait analysis suggest an improvement in patient condition because he has walked 100 metres more the second time. This is a very significant improvement corresponding about to the 50%, despite it is very discordant with the level of disability (EDSS=6.5).

5.5 Patient 5

EDSS: level 6.5

	25MWT	6MWT
Pre	14”29	133.4m
Post	13”43	140.4m

Table 5.13: Patient5-Results from Gait Analisys.

Alternative Indicators

	$widt\_pre$	$widt\_post$	C_Tracts	$Distance$
RAD	42.03	45.30	3.2	2.0
MEP	53.22	52.94	5.3	4.44

Table 5.14: Patient5-Alternative Indicators elaborated by algorithm for MEP and RAD signals.

Clinical Indicators

RAD		MEP		Global		
ITV_A	ITV_lat	ITV_A	ITV_lat	ITV_CMCT	ITV_AR	n_m
-4	0	-1	4	3	3	10

Table 5.15: Patient5-Clinical indicators proposed by Di Sapio et al. [18]

Despite the level of disability is very high, all signals have been recorded with acceptable requisites respect criteria of data stability proposed.

In this patient almost indicators provide by algorithm suggest a modest improvement in MEP values considering their morphology (C_tracts=5.3 and $Distance$=4.44,Table.5.14). A more significant consideration about improvement can be done looking ITV values on area and CMCT, both equal to three. Only parameter related to area ITV of RAD signal is very discordant but the anomalous value can be justified by variability that affected area indicators. To validate the assumption of the slightly improvement results shown in Table.5.13 can be evaluated both for 25FWT and 6MWT. Finally, it is possible to assert that patient result improved after Fampyra therapy.

5.6 Patient 6

EDSS: level 6

	25MWT	6MWT
Pre	6”95	302.6m
Post	6”44	325.4m

Table 5.16: Patient6-Results from Gait Analisys.

Alternative Indicators

	widt_pre	*widt_post*	*C_Tracts*	*Distance*
RAD	/	/	/	/
MEP	64.81	86.01	6.57	1.03

Table 5.17: Patient6-Alternative Indicators elaborated by algorithm for MEP and RAD signals.

Clinical Indicators

RAD		MEP		Global		
ITV_A	*ITV_lat*	*ITV_A*	*ITV_lat*	*ITV_CMCT*	*ITV_AR*	*n_m*
/	0/	0.7	-0.7	/	/	7

Table 5.18: Patient6-Clinical indicators proposed by Di Sapio et al. [18]

For patient 6 *RAD* signals are not available, moreover other three signals have been excluded from analysis because their peaks values was under 50 μV. Give the higher value of disability probably there could be absence of conduction in some areas.
In this patient the results provided in Table. 5.16 are not reliable respect to values of EDSS scale. A patient with level six of disability could not reach distances of hundreds of meters (6MWT) or walk so fast (25FWT),so, as a consequence these information will not take into a count to perform the complete clinical state of patient.

Looking at *ITV* of latency and areas, they do not denote interesting changes but remain stationary. It is possible to observe a slight aggravation looking at alternative indicators in Table 5.17: both differences of width peak and *C_tracts* shown a worse in central conduction. This is only a qualitative assumption because, in order to

quantize morphology changes and give detailed indications about the worsening, there should be undertaken further studies on more signals.

5.7 Patient 7

EDSS: level 3

	25MWT	6MWT
Pre	4”02	391m
Post	4”13	440.8m

Table 5.19: Patient7-Results from Gait Analisys.

Alternative Indicators

	widt_pre	*widt_post*	*C_Tracts*	*Distance*
RAD	46.3	46.7	3	1.9
MEP	61.10	54.81	8	4.73

Table 5.20: Patient7-Alternative Indicators elaborated by algorithm for MEP and RAD signals.

Clinical Indicators

RAD		MEP		Global		
ITV_A	*ITV_lat*	*ITV_A*	*ITV_lat*	*ITV_CMCT*	*ITV_AR*	*n_m*
1	0	-0.6	1.8	-0.6	-2	6

Table 5.21: Patient7-Clinical indicators proposed by Di Sapio et al. [18]

Patient 7 has an acceptable motor disability in fact he/she is able to walk for 400 meters in six minutes as a healthy subject. From data provide by Gait Analysis a significant improvement of 50 meters is visible in 6MWT. To confirm this, alternative indicators in Table 5.20 have to be considered: an improvement mostly in MEP signals is observed looking at difference width peaks. C_tract value for MEPs is height so, surely, signals are very different respect to previous ones denoting that signals are very changed before and after Fampyra administration. All parameters for RAD signal denote, instead, a situation of stability.

The improvement in MEP signal is not coherent with results of ITV calculated in particular for areas ratio: it is equal to -2 that denotes a situation which tends to worse. Since this is the only discordant value of indicators, it is possible to assert that in this case the ITV_AR could be affected by variability depending on the peak values. Looking at n_m in fact, four signals are excluded for anomalous peak maximum values, so it is possible that algorithm is not still robust enough to avoid that other residual situations affect area indicators.
In conclusion a stationary situation tending to improvement is report to patient 7.

5.8 Patient 8

EDSS: level 1

	25MWT	6MWT
Pre	4”15	397.7m
Post	4”30	389.4m

Table 5.22: Patient8-Results from Gait Analisys.

Alternative Indicators

	$widt\_pre$	$widt\_post$	C_Tracts	$Distance$
RAD	52.74	47.06	2.4	2.26
MEP	70.06	57.31	4.56	3.68

Table 5.23: Patient8-Alternative Indicators elaborated by algorithm for MEP and RAD signals.

Clinical Indicators

RAD		MEP		Global		
ITV_A	ITV_lat	ITV_A	ITV_lat	ITV_CMCT	ITV_AR	n_m
3	0	-0.9	0	3.6	-1.8	9

Table 5.24: Patient8-Clinical indicators proposed by Di Sapio et al. [18]

Disability level of patient 8 is comparable with the one of a healthy subject in fact he/she is able to walk for almost 400 meters and does not have symptoms. More in

details, looking to results in Table.5.22 an almost insignificant worse (about 4%) is present both in 6MWT and in 25FWT. This is immediately denied by ITV_CMCT that reports a reliable improvement in central conduction (ITV_CMCT=3.6), confirmed also by alternative indicators in Table.5.23. Both in MEP and RAD signals improvements are recognized. More over only one signal has been excluded by analysis so globally it is possible to say that results are reliable and a final improvement statement about patient condition can be proposed.

5.9 Patient 9

EDSS: level 4.5

	25MWT	6MWT
Pre	6”35	328.5m
Post	5”40	328.6m

Table 5.25: Patient9-Results from Gait Analisys.

Alternative Indicators

	$widt\_pre$	$widt\_post$	C_Tracts	$Distance$
RAD	39.94	45.93	3.0	2.83
MEP	50.59	94.20	7.33	19.91

Table 5.26: Patient9-Alternative Indicators elaborated by algorithm for MEP and RAD signals.

Clinical Indicators

RAD		MEP		Global		
ITV_A	ITV_lat	ITV_A	ITV_lat	ITV_CMCT	ITV_AR	n_m
4.5	-2.7	1.2	0	0	-0.4	4

Table 5.27: Patient9-Clinical indicators proposed by Di Sapio et al. [18]

Only four signals of Patient 9 are used for the study. All of that available in fact, were completed affected by morphological problems. An example is reported in Fig 5.1

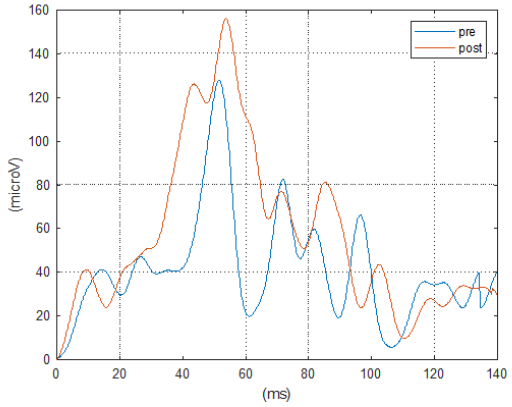

Figure 5.1: Example of *MEP* signals available for Patients 9.Signal activation of PLsx before and after drug administration.

It is evident that algorithm could be improved in order to recognize also these signals and exclude them because take them in consideration means work with totally unreliable data.

Among parameters involved in the study, *Distance* is the only one that has assumed an anomalous value. The mean value of *Distance* for patient 9 in fact is 19.91, more than four times common values for all other patients. In these terms, *Distance* could be an important indicator of reliability of signal in future development.

The only indicators that are not affected by problems of data stability are the ones in Table 5.25. Looking them the final and partial evaluation about patient 9 denote a situation completely stationary.

5.10 Patient 10

EDSS: level 4.5

	25MWT	6MWT
Pre	7”94	203.6m
Post	7”96	212.8m

Table 5.28: Patient10-Results from Gait Analisys.

Alternative Indicators

	widt_pre	*widt_post*	*C_Tracts*	*Distance*
RAD	50.99	53.22	34	4.81
MEP	/	/	/	/

Table 5.29: Patient10-Alternative Indicators elaborated by algorithm for MEP and RAD signals.

Clinical Indicators

RAD		MEP		Global		
ITV_A	*ITV_lat*	*ITV_A*	*ITV_lat*	*ITV_CMCT*	*ITV_AR*	*n_m*
0.4	0.8	/	/	/	/	4

Table 5.30: Patient10-Clinical indicators proposed by Di Sapio et al. [18]

Patient 10 has a very complicated situation too. The algorithm is forced to exclude MEP signals because all of them are under 50 μV and six of RAD signal for elevated value of ΔE. An example is reported in Fig 5.2

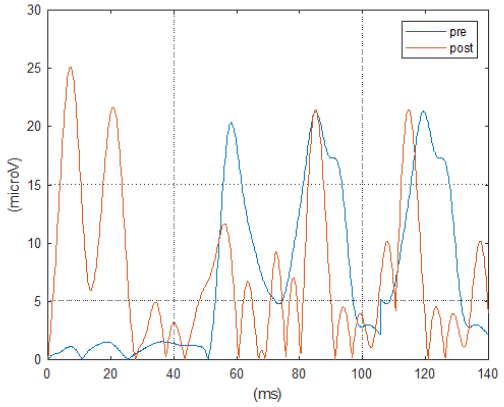

Figure 5.2: Example of MEP signal of Patient 10 before and after drug administration in muscle VL dx.

From Fig 5.2 assumptions about central conductivity can not be done because there are no enough elements to establish if it is a situation of lack of conductivity or errors in signal acquisition. In both cases parameters calculated on these data are not reliable, so final and partial evaluation can be made only looking Table 5.28.

Results provided by 6MWT and 25FWT denote a situation in which patient has not seen substantially changes in motor ability before and after Fampyra treatments.

Chapter 6

Conclusion and Future

Purpose of the study is to provide a complete and reliable clinical picture of subjects with MS considering some stability criteria in order to be more confident in results manly provide by analysis of evoked potentials.

Introduction of these criteria was necessary since about more than 20% of signals available were affected by serious problems of instability that had a significant impact in related parameters and in clinical response. It is evident that larger population of both MEP and RAD signals would improve hypothesis at the base of these criteria improving their efficiency. Moreover, have more signals means to provide results on a higher number of muscles and so a more stable and sure clinical statement about patient improvement.

Useful developments of the algorithm implemented could concern methods to measure the width of peaks and latency instants: currently some simple Matlab functions provide these kinds of information, but in the perspective of a less qualitative study, better system of measure can be structured.

For what concern alternative clinical indicators introduced in the study, it is possible to assert that they are only a first, basic and not complete developed approach to avoid uncertainties coming to variability of parameters related to areas or energy of evoked potentials. According to this, respect the previous section of results, it is evident that ITV calculated on areas, are very often discordant with the totality of the other indicators.

An innovation in the study is represented by the employment of DTW, normally used only in gait analysis trials. Information provided by DTW, in fact, have been

valuable for two reasons: first of all the value of *Distace* gives the possibility to recognize signals morphologically unreliable as shown in Fig 5.1 for patient 9. Secondly, it is important to evidence that the use of DTW has enabled the quantification of how single signal is changed before and after Fampyra administration. An appropriate use of *Distance* and C_Tracts can be done realizing a study with more signals to identify a very useful range of tolerance to compare results.
A second innovation can be found in the important rule given to signal morphology in the structure of study: literature demonstrates that clinical studies about evoked potential in MS are always centred of evaluation about latency, speed conduction, peak amplitude and areas/energy of signals. Mostly last two ones often report instability even if normalized parameters are computed ($norm\_ITV$) , so as a consequence, the increasing of researches that promote morphology approach is observed in last years.

In conclusion idea at the base of the study can be adaptable to numerous situations: the first phase consisting in exclusion of unreliable data, follow by a further evaluation about changes in morphologies, allows elaborating signals of patient with many other motor conduction disorders. In other words, knowing how signal have to change its aspect after an improvement in patient condition, it is possible to establish an improvement or worsening searching the ideal and improved waveform of signal after drug treatments.

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