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Jaime Ibáñez Pereda

Development of EEG-based technologies for the characterization and treatment of neurological diseases affecting the motor function

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Director/es

Mínguez Zafra, Javier
Castillo Sobrino, María Dolores del
Serrano Moreno, José Ignacio

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DEVELOPMENT OF EEG-BASED TECHNOLOGIES FOR THE CHARACTERIZATION AND TREATMENT OF NEUROLOGICAL DISEASES AFFECTING THE MOTOR FUNCTION

Autor

Jaime Ibáñez Pereda

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María Dolores del Castillo Sobrino

José Ignacio Serrano Moreno

Javier Mínguez Zafra

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Development of EEG-based technologies for the characterization and treatment of neurological diseases affecting the motor function

Jaime Ibáñez Pereda

Thesis submitted in fulfillment of the requirements for the degree of Doctor of Philosophy in Computer Science and Systems Engineering

Supervised by:

María Dolores del Castillo Sobrino

José Ignacio Serrano Moreno

Javier Mínguez Zafra

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Resumen

La electroencefalografía, o registro de potenciales eléctricos generados por el cerebro mediante electrodos superficiales colocados sobre el cuero cabelludo, es una técnica ampliamente utilizada a nivel clínico, siendo tradicionalmente útil para un primer diagnóstico en alteraciones en la corteza cerebral, trastornos del sueño o para la búsqueda de focos epilépticos en pacientes con este tipo de crisis. En las últimas décadas, la incursión de las tecnologías de la información y comunicación en los campos clínicos y, en este caso, de estudios electrofisiológicos, han contribuido a que este tipo de herramientas hayan sido propuestas para un gran número de aplicaciones, entre las que destacan los estudios de búsqueda de correlatos neuronales de la actividad motora en los seres humanos y las interfaces cerebro-computador que proporcionan una línea directa de interacción entre la actividad cerebral y sistemas automatizados. Las propiedades óptimas en cuanto a resolución temporal de la señal de electroencefalografía hacen que esta técnica permita conocer, sin prácticamente retraso en el tiempo, las características de los procesos eléctricos de poblaciones de neuronas en la corteza motora. Estos procesos pueden desencadenarse como consecuencia de la realización de una acción voluntaria o ser provocados por el comportamiento patológico del cerebro, causando dificultades en el control motor. De este modo, se abre la puerta al desarrollo de nuevas técnicas que caracterizan los procesos corticales patológicos y sanos asociados con el procesamiento motor, como puede ser la ejecución, visualización o imaginación de un movimiento voluntario, la realización de tareas funcionales por parte de pacientes con alteraciones cerebrales causadas por una lesión, o la manifestación de movimientos involuntarios que alteran la capacidad funcional del paciente. En todos estos casos, la señal de electroencefalografía puede presentar patrones, observables en las variaciones de las actividades oscilatorias o de baja frecuencia de ciertas componentes de la señal, que permiten conocer información relevante acerca de los procesos corticales que desencadenan el movimiento.

Este trabajo de tesis presenta un conjunto de estudios en los que se aplican técnicas de procesamiento de la señal y de minería de datos en sistemas en tiempo real para el registro, caracterización y condicionamiento de la actividad de la corteza motora en sujetos sanos y en pacientes con desórdenes neurológicos que afectan a la capacidad motora. En concreto, la presente tesis incluye estudios con pacientes de dos de las patologías de origen neurológico más extendidas: pacientes con temblor esencial y pacientes que han sufrido un accidente cerebrovascular. Los mecanismos neuronales de acción y tecnologías para el tratamiento de ambas patologías son en la actualidad ampliamente investigados por numerosos grupos en todo el mundo. A lo largo de los capítulos que conforman este trabajo de tesis se presentan resultados sobre la actividad cortical normal relacionada con la planificación y ejecución de acciones motoras con el miembro superior, y ésta se contrapone a la actividad patológica que los pacientes presentan y que está directamente relacionada con la incapacidad motora que se puede observar y cuantificar por medio de técnicas de estimación de la actividad muscular y/o de movimiento. En los capítulos iniciales se presenta una revisión de los conceptos básicos del papel de la corteza cerebral en el control motor y de cómo la actividad electroencefalográfica permite su análisis y su condicionamiento, se propone un estudio de interacción cortico-muscular a la frecuencia del temblor en pacientes con temblor esencial con el objetivo de conocer los efectos de un fármaco en estos pacientes y, por último, se presenta un estudio basado en algoritmos evolutivos para la identificación de patrones corticales asociados con la planificación de tareas motoras realizadas con un mismo brazo. En la segunda parte del trabajo se presentan dos propuestas de interfaces cerebro-computador para ser utilizadas en entornos de rehabilitación en pacientes con temblor esencial o con un ictus. En la primera propuesta se plantea el uso de un sistema de electroencefalografía para anticipación de movimientos voluntarios como parte integrada de una plataforma multimodal de estimación y supresión del temblor. En la segunda propuesta se plantea un paradigma de condicionamiento basado en la identificación de la intención motora con precisión temporal para pacientes con ictus, y éste es evaluado en un grupo de pacientes durante un intervalo de un mes a lo largo del cual se realizan hasta ocho intervenciones.

De este modo, el objetivo general de esta tesis es proponer soluciones tecnológicas que permitan profundizar en el conocimiento de los mecanismos neuronales que permiten la generación de la acción motora voluntaria, la caracterización de la actividad cortical patológica en pacientes con desórdenes motores causados por afecciones nerviosas, la búsqueda de técnicas óptimas para la estimación de la planificación e intencionalidad motora y la propuesta de nuevas formas de rehabilitación de pacientes con las patologías previamente indicadas. Se espera que los resultados aquí presentados sirvan de base para el posterior desarrollo de plataformas cercanas al ámbito clínico y que supongan un avance en el diagnóstico, pronóstico y tratamiento de patologías del sistema nervioso central que conllevan alteraciones en el control motor.

Abstract

The electroencephalography consists in the recording of electric potentials generated in the brain acquired by means of surface electrodes distributed on the scalp. This technique is widely used in the clinical field, and it is of relevance for the first diagnosis of damages in the brain cortex, the study of sleep disorders or the localization of seizure foci in patients with epilepsy. During the last decades, the use of the information and communication technologies in the clinical field, and in this case in electrophysiological studies, has contributed to broaden the field of applications of the electroencephalographic systems. Among these, studies on the neural correlates of the motor activity in human beings and the development of brain-computer interfaces (providing an interaction line between the brain activity and automatic systems) stand out. Due to the optimal properties in terms of temporal resolution of the electroencephalographic signal, it is now possible to study, with almost no temporal delay, the characteristics of the electrical processes produced by neuronal populations in the motor cortex. These processes may appear as a consequence of the execution of a certain voluntary action, or may be caused by the pathological function of the brain, leading to an affected motor function. As a result of these advances in electroencephalographic systems new techniques are developed, studying the movement-related healthy and pathological cortical processes during the execution, visualization or imagination of a voluntary movement, the performance of functional tasks by patients suffering brain damages due to a certain lesion, or the presence of involuntary movements, such as tremors. In all these cases the electroencephalographic signal presents certain patterns, observed in the variations of the oscillatory or low-frequency components of the signal, that may allow the extraction of relevant information regarding the cortical processes giving rise to the studied movement.

This thesis presents a set of studies applying signal processing and data mining techniques in real-time working systems to register, characterize and condition the movement-related cortical activity of healthy subjects and of patients with neurological disorders affecting the motor function. Patients with two of the most widespread neurological affections impairing the motor function are considered here: patients with essential tremor and patients who have suffered a cerebro-vascular accident. The neurophysiological action mechanisms and treatment technologies for both pathologies are currently under extensive research by a number of groups around the world. The different chapters in this thesis present results regarding the normal cortical activity associated with the planning and execution of motor actions with the upper-limb, and the pathological activity related to the patients' motor dysfunction (measurable with muscle electrodes or movement sensors). The initial chapters of the book present i) a revision of the basic concepts regarding the role of the cerebral cortex in the motor control and the way in which the electroencephalographic activity allows its analysis and conditioning, ii) a study on the cortico-muscular interaction at the tremor frequency in patients with essential tremor under the effects of a drug reducing their tremor, and finally iii) a study based on evolutionary algorithms that aims to identify cortical patterns related to the planning of a number of motor tasks performed with a single arm. In the second half of the thesis book, two brain-computer interface systems to be used in rehabilitation scenarios with essential tremor patients and with patients with a stroke are proposed. In the first system, the electroencephalographic activity is used to anticipate voluntary movement actions, and this information is integrated in a multimodal platform estimating and suppressing the pathological tremors. In the second case, a conditioning paradigm for stroke patients based on the identification of the motor intention with temporal precision is presented and tested with a cohort of four patients along a month during which the patients undergo eight intervention sessions.

To summarize, the general objective of this thesis is to propose technological solutions that lead to i) a better understanding about the neuronal mechanisms that mediate voluntary motor actions, ii) the characterization of the cerebral cortical activity in patients with neurological affections, iii) the search of optimal techniques to estimate the motor planning and intention, and iv) the proposal of new rehabilitation strategies in patients with the aforementioned pathologies. It is expected that the results presented become the basis for future developments of technological platforms that can be integrated in the clinical practice and allow an improved diagnosis, prognosis and treatment of pathologies of the central nervous system.

Chapter 1

Introduction

Exploring the nervous system implies studying the essence of human beings. It entails understanding the mechanisms through which two people perceive in a different way the same song [Ramachandran et al., 2001], how a child's personality is conditioned by the mechanisms of language acquisition [Pinker and Jackendoff, 2005], or how is it possible to achieve, by means of intensive practise, that a tennis forehand results in a winner point by slightly touching the side line of the opponent's field [Kandel et al., 2000].

Clocks tick, skyscrapers and bridges vibrate... and neurons oscillate [Buzsáki, 2006], and with their oscillation they communicate with other neurons, giving rise to highly complex associations that result into all kinds of mental processes, from which we consciously recognize a small fraction [Dijksterhuis and Nordgren, 2006].

Discovering the correlates between electrical processes observed in the brain and observable or measurable human acts leads to understanding the neuronal principles that rule human behaviour and to further describing the neurophysiological mechanisms of neurological disorders. Nowadays there exist different windows on the brain, covering many and complementary spatial regions and time intervals. The electroencephalogram provides a window on the mind, albeit one that is often clouded by technical and other limitations [Nunez and Srinivasan, 2006]. Since Hans Berger placed in 1924 the first scalp electrodes to observe alpha rhythms [Berger, 1929] up to now, the number of possibilities that electroencephalographic systems provide has grown exponentially. Indeed, the electroencephalography is now an essential tool in any neurology department and new potential applications are expected to be a reality in the near future, allowing an improved analysis and treatment of certain neurological pathologies.

The analysis of the nervous system and the description of how it works may be carried out from, *a priori*, independent research fields such as medicine, informatics, robotics, physiotherapy, chemistry, etcetera. This thesis aims at being a small contribution in the neuroscience field from the biomedical engineering perspective. To that end, a group of four independent studies using electroencephalographic systems are proposed in the framework of the analysis and treatment of neurological diseases causing motor disabilities. The global objectives of the entire work are to further understand the cortical mechanisms of voluntary movement planning and execution, how they may be affected by the pathological brain structures of patients with neurological diseases (specifically patients with essential tremor and patients who have suffered a stroke) and, eventually, how functional recovery may be achieved either with assistive technologies taking advantage of the online characterization of the motor cortex, or using conditioning paradigms of the cortical activity that elicit plastic changes resulting in an improvement of the motor function. In order to meet these goals, advanced signal processing techniques and data mining algorithms are used to characterize the cortical changes of subjects performing movement actions, and the observed results are used to characterize the action mechanisms and evolution of the two studied pathologies. Additionally, and of special relevance in this thesis, real-time systems characterizing the cortical activity related to motor-planning online are programmed and used to implement brain-computer interfaces that allow the patients to use the brain activity to control external neuroprosthetic devices.

1.1 Purpose

The past decades have witnessed the achievement of important advances in the electrophysiological study of the nervous system, both in terms of advances in the technology used to acquire neurophysiological information and in terms of new algorithms developed to process this information. These advances have allowed the acquisition, storage, characterization and even the conditioning of the nervous system activity at a local level (measuring neurons spike trains) or at a global level (considering the activity of populations of neural networks), and focusing on the central nervous system (brain and spinal cord) or the peripheral nervous system (characterising the activity of motor neurons, reflexes etc.). All these achievements provide new opportunities to analyse the function and the structure of the nervous system associated with the execution of daily-living activities by the human beings.

Focusing on the applications using electroencephalographic (EEG) systems to analyse and treat neurological diseases affecting the motor function, a wide variety of studies have been published during the last two decades. These studies can be divided in two generic research lines: neurophysiological studies characterising the motor cortex processes associated with neurological conditions and treatments, and experiments aimed to validate rehabilitation technologies for the motor function. In the first case, the goal is to relate the neurological pathologies and their evolution with altered cortical activation patterns in the patients, so that it becomes possible to find precise descriptions of the neurological mechanisms that lead to affected motor control. Examples among the large amount of studies in this field are the experiments analysing the cortico-muscular interaction at the tremor frequency in patients suffering from tremor-related pathologies (see for example [Hellwig et al., 2001; Timmermann et al., 2002]), or the experiments characterizing the altered cortical activation patterns in patients with brain damages to provide ways of predicting the degree of recovery (see [Burghaus et al., 2007]).

The second group of EEG-based applications for patients with motor disorders are those in which the main goal is to provide new means of achieving functional rehabilitation of the patients. In this case the main objective is to develop brain-computer interfaces (BCIs), *i.e.* devices using the electrical activity acquired from specific scalp regions to provide a feedback (typically visual or proprioceptive) to the patient. This group of EEG-based applications may in turn be further divided into BCIs for motor compensation and BCIs for motor recovery. In the first case, BCI systems extract information from the cortical activity and convert it into control signals used to operate external devices such as robotic or prosthetic arms, wheelchairs or spellers. An illustrative example in this field may be taken from BCI technologies providing a communication channel for patients with complete locked-in syndrome, which constitutes a significant gain in the possibilities of these patients to interact with the environment [Hinterberger et al., 2003; Birbaumer, 2006]. On the other hand, BCI systems aimed to recover the lost motor capacity are mainly focused on finding ways to condition the neural activity of specific cortical regions, resulting in an improvement of the patient's motor function. In this line, the main area of research at present is oriented towards new interventions for patients suffering from a spinal cord injury or with a stroke [Silvoni et al., 2011; Ramos-Murguialday et al., 2013].

The purpose of this thesis is to evaluate the potential uses of EEG-based systems for the analysis and treatment of neurological diseases affecting the motor capacity. To that end, four studies associated with the aforementioned research lines with EEG systems (neurophysiological studies of the normal and pathological motor function and studies of BCI technology either assisting or recovering the lost motor capacity) are presented and validated with control subjects and patients. The critical validation of the potential applications of this type of systems is built upon the obtained results and reached conclusions.

1.2 Research lines and projects giving rise to this thesis

Currently, one of the most active research areas with EEG systems is the development of applications for patients with neurological disorders affecting the motor function. In this regard, EEG systems provide a window on the cortical electrical activity with high temporal precision, which is a critical factor when trying to study and model the nervous system. In addition, EEG systems are widely used in neurophysiological fields due to their advantages as compared to other alternatives: EEG systems are cost-effective practical systems for clinical environments that do not require ample rooms or restrictive conditions in terms of vulnerability against electrically noisy environments. All these factors have made these systems an attractive solution to carry out experimental procedures studying the neurophysiological characteristics of movement disorders and developing neurorehabilitation technologies, which has in turn received an important economical support from funding institutions in these research lines, both in the national and European domains. This thesis is the result of studies carried out in the framework of some of these funded projects.

The first experiments performed for this thesis were carried out in the framework of the TREMOR European project (FP7-ICT-2007-224051, An ambulatory BCI-driven tremor suppression system based on functional electrical stimulation). This project proposed for the first time (to the author's knowledge) the use of a multimodal brain-neural-computer interface integrating information regarding the EEG activity with information about muscular activation with surface electromyography (EMG) and information regarding the actual movement of the arm (using gyroscopic and accelerometric sensors). The interface combined the information gathered from these different sensors to achieve a robust characterization of the involuntary tremor before voluntary movements started, so that it could be cancelled by means of electrical stimulation of the muscles only when intended actions were performed. The experiments carried out to validate the proposed multimodal interface demonstrated the potential benefits of using a set of sensors with partially recurrent and complementary information regarding the planning and execution of voluntary movements to distinguish intended actions from the undesired tremor. The project provided in addition the first demonstration of tremor reduction using electrical stimuli on the arm muscles of the patients while they performed daily-living tasks.

Following the line started in the TREMOR project, the NEUROTREMOR project (ICT-2011.5.1-287739, NeuroTREMOR: A novel concept for support todiagnosis and remote management of tremor) aimed to develop novel systems for understanding, giving support to diagnosis, and remotely managing tremors. The results obtained in one of these studies are included here as a chapter. In it, the therapeutic effects of a drug (alprazolam) on cortical activity and tremors in patients with essential tremor (ET) are studied. Together with the other studies developed in the framework of the NEUROTREMOR project, these results provided a deeper understanding about the neurophysiological mechanisms of tremor generation in ET.

In parallel with the NEUROTREMOR project, the HYPER project (Hybrid NeuroProsthetic and NeuroRobotic Devicesfor Functional Compensation and Rehabilitation of Motor Disor-ders, CSD2009-00067) started and gave rise to BCI experiments aimed to provide innovative therapies for the motor rehabilitation of patients with spinal cord injury or patients who have suffered a stroke. In the case of stroke patients, the main objectives of the EEG experiments in the HYPER project were to understand the way in which neurological lesions affect the normal functioning of the cortex, and to look for clinically feasible ways to induce activity-dependent cortical plasticity leading to functional recovery of the lost function in the damaged limbs of these patients. In the framework of this project, experiments were carried out to develop an EEG-based BCI intervention for stroke patients focusing on upper-limb voluntary movements.

1.3 Motivation

The concept of this thesis is the consequence of a practical and theoretical interest in the neuroscience field. The main motivation to conceive and carry out the studies integrating this thesis arises from the curiosity about how the brain and the nervous system work, and in particular, the way in which the nervous system provides the necessary mechanisms to interact with the environment through movement. Two aspects are of special relevance in the definition of the experimental studies carried out for this thesis.

On the one hand, from the perspective of learning relevant aspects about the human brain function, research using neuroimage techniques, such as the EEG, allow the design of experiments addressing a wide variety of processes defining the function of the central nervous system. The possibility of analysing in real-time (*i.e* with a high enough temporal resolution to observe the studied phenomenon) the changes in the cortical activity associated with the planning and execution of motor tasks, leads to a deeper knowledge regarding relevant issues associated with the fact that the human being is interacting with the environment. This, in turn, provides elements to rise abstract questions regarding wilfulness in movement intention or the conscious perception of it. The development of new technologies conditioning the electrical activity of specific brain regions as a result of the online characterization of the movement-related cortical activity opens a way to study the plasticity mechanisms at the neural network level and to analyse the neurophysiological processes associated with the acquisition of skills to perform motor tasks. In the same line, it is also of interest to characterize the oscillations of cortical networks to carry out studies about the interaction between different regions of the nervous system, which provides new ways to study higher order cognitive functions that allow humans to process stimuli and interact with the environment.

On the other hand, the development of neurophysiological techniques to study the function of the nervous system and the neural mechanisms allowing motor control has a direct application from the clinical point of view. Studies as the ones proposed in this thesis are expected to be beneficial in the clinical field, both to improve diagnosis and prognosis of specific neurological pathologies and to propose innovative techniques to rehabilitate the impaired motor functions. This aspect is of special relevance considering the expected increase in the population that will benefit from these technologies in the near future. The increase of population over sixty years old, and the incidence growth of neurological affections due to bad lifestyle habits and toxic factors in the modern society will lead to an increased amount of population demanding optimized healthcare systems and treatments in the decades to come [Feigin et al., 2003; Wenning et al., 2005; Bloom et al., 2011]. Finding effective metrics about the patients' clinical conditions and expected evolution, increasing the knowledge about neurological diseases and achieving a deeper understanding on the neural reorganization mechanisms associated to good and bad recovery of the patients are general goals that need to be pursued during the following years in order to satisfy the present and future demand from the patients.

1.4 Objectives

As aforementioned, in a broad sense, this thesis aims at further validating the use of EEG systems to study and treat patients with motor disabilities caused by the pathological function of the nervous system. To do so, a platform integrating EEG, EMG, gyroscopic and functional electrical stimulation (FES) devices is developed and used in a set of experiments to propose and test novel movement-related neurophysiological analyses and BCI applications in four studies sharing an essential link: the description of the cortical activity associated to voluntary and pathological movements and its use to develop systems for the rehabilitation of the motor function. The specific objectives of this thesis are developed in the following lines.

Firstly, since the proposed general objectives have a marked clinical focus, a significant part of the experimental procedures carried out to achieve them is done with patients. Two specific pathologies are considered in this thesis: essential tremor (ET) patients and patients with stroke. It has been shown that movement-related cortical patterns in these two groups of patients are typically altered, especially in stroke patients, due to the change in the cortical organization that these patients present [Tamás et al., 2006; Fang et al., 2007, 2009; Lu et al., 2010]. For these groups of patients the intrinsic technological and neurophysiological challenges associated with measuring their EEG activity either during resting or movement conditions need to be considered. On the one hand, during the resting states of ET patients, a certain degree of resting tremor, which originates centrally (in the cerebello-thalamo-cortical relay), may be present in the peripheral limbs, and this tremor can in turn produce a proprioceptive stimulation altering the cortical basal activity [Moazami-Goudarzi et al., 2008]. This can also occur in stroke patients with clonus episodes (involuntary, rhythmic, muscular contractions and relaxations and is particularly associated with upper motor neuron lesions involving descending motor pathways). On the other hand, during movements, the low signal-to-noise ratio of the EEG and its low spatial resolution are limiting factors that need to be overcome in order to validate BCI applications especially in patients like the ones considered here. ET patients typically present an increased tremorgenic activity of their limbs and head when they begin a movement [Louis et al., 2007], which can affect the quality of the acquired EEG signal. In patients with stroke, on the other hand, compensatory movement strategies when trying to perform simple tasks are typically observed and they may distort the EEG signal as well. Moreover, stroke patients tend to have slower and altered EEG signal activity in the damaged regions of the brain, which makes the analysis of movement-related cortical processes in these patients even more complicated [Niedermeyer and da Silva, 2005]. According to all these potential difficulties in the recording and characterization of EEG activity related to movement in ET and stroke patients, it is identified as a major objective of this thesis to further explore the capacity of EEG-based systems to characterize the cortical activity related to voluntary and pathological movements in these two groups of patients.

Secondly, previous studies analysing the EEG signal to characterize mental processes related to the voluntary motor function have been able to describe certain spatio-temporo-frequential characteristics of cortical changes (see for example [Simonetta et al., 1991; Pfurtscheller and da Silva, 1999; Bai et al., 2005; Pfurtscheller et al., 2006; Jochumsen et al., 2013]). These findings have been used in other studies to either characterize the neurological condition of patients with neurological disorders by describing alterations in the observed patterns [Cunnington et al., 1995; Hellwig et al., 2000; Magnani et al., 2002; Daly et al., 2006; Fang et al., 2007; Müller-Putz et al., 2007; Fang et al., 2009; Stepien et al., 2010; Cremoux et al., 2013], or to develop new control signals for brain-machine interfaces [Pfurtscheller et al., 2006; Morash et al., 2008; Bai et al., 2011; Delgado Saa and Cetin, 2013]. In line with these experiments, this thesis also aims to i) study the characteristics of movement-related cortical activation and deactivation patterns, especially in the time intervals preceding voluntary movements and in patients with neurological conditions, to use them as control signals in BCI systems, and ii) to propose novel experimental studies and analysis methods to find new identifiable correlates between the cortical oscillatory activity and mental states related to motor planning of different kinds of movements performed with a single limb. In short, with the experiments proposed in this thesis it is intended to further demonstrate how informative the EEG signal can be to characterize the mental processes associated with movement-related aspects as movement intention, planning, and execution, and to demonstrate whether it is possible to introduce new control signals in BCI systems assisting the motor function.

A third objective of this thesis deals with the validation of the EEG signal for the neurophysiological characterization and understanding of movement disorders. To this end, experiments are performed with ET patients, a disease in which the exact mechanisms of tremor generation are nowadays still unknown [Elble and Deuschl, 2009; Louis et al., 2013]. While previous studies in this regard have extensively characterised the tremor properties in these patients and the interaction between central and peripheral neural information [Hellwig et al., 2001; Raethjen et al., 2007], no studies up to date have investigated the temporal dynamics of tremor manifestation and how the cortical and muscular activities interact as a result of a pharmacological treatment. With this kind of studies, the present thesis intends to validate the EEG signal in the clinical environment as a powerful tool to study, along time, how tremor in ET can be modified through drug-induced changes in the brain activity.

In the framework of BCI technologies and applications, the studies proposed here aim at improving the function of online and real-time asynchronous interfaces, *i.e.* interfaces in which no external cue stimulus is used, and the user is the one who dictates the timing of the communication commands to the controlled device [Mason and Birch, 2000; Townsend et al., 2004]. New metrics are proposed to evaluate the performance of these technologies in assistive and rehabilitation BCI systems and new signal processing and classification methods are developed to improve the temporal estimations of the times at which specific mental states occur, taking advantage of techniques proposed in previous studies by other authors [Bai et al., 2011; Niazi et al., 2011]. The advantages of implementing adaptive designs of BCI systems working along different days to overcome problems associated with non-stationarities of the EEG signal [Shenoy et al., 2006] are also addressed.

The fusion of voluntary movement-related information recorded from different types of sensors placed on the body (such as EEG, EMG, movement sensors etcetera) provides a detailed description of inner body processes of motor planning and execution. Therefore, this thesis includes innovative ways to integrate the EEG information with other movement-related sensor modalities (such as EMG) to improve the behaviour of human-machine interaction by achieving more natural interfaces between users and devices.

Finally, and by applying the developed techniques in BCI systems for asynchronous applications, the experiments in this thesis also aim to propose and test novel rehabilitation interventions for stroke patients promoting associative facilitation between the cortex and the peripheral muscles. The thesis presents an analysis of how EEG systems allow the online acquisition of reliable information regarding motor intention in functional tasks with the upper-limb, and how this information can be used to implement BCI-based interventions for stroke patients inducing functional improvements after a reduced number of sessions. Despite the large amount of BCI systems that can be found in the literature in this regard, little is still know about the single-trial characterization of upper-limb motor intentions in stroke patients and the way in which BCI interventions using this information to drive external proprioceptive stimuli can improve the patients' motor function. For this reason, these proposed objectives are fully in line with the current work of a number of BCI groups around the world.

1.5 Methodology

As the purpose of this thesis entails both technical development and studies from the clinical perspective, the followed methodology to reach the goals is based on two fundamental blocks:

- Theoretical study of the neurophysiological processes giving rise to the experimental paradigms and hypotheses proposed in the thesis. This block entails different aspects:
  - Detailed study about the cortical patterns described by previous experiments and related to movement tasks, analysing the structures giving rise to these cortical patterns and how they relate to concepts as movement conception, planning, and execution.
  - Review the state of the art to develop real-time processing techniques for motor-related cortical patterns, to extract relevant information from single movements that can be used to achieve a robust control of BCI systems
  - Bibliographic analysis of experiments with EEG technology studying plasticity mechanisms caused by conditioning paradigms and how they may benefit the motor function
  - Study of the neurophysiological basis describing the tremor in essential tremor and its implications in the studies proposed in this thesis
  - Study of the neurophysiological basis describing the cerebro-vascular accident and its implications in the studies proposed in this thesis
- Technological and experimental development to address the objectives in the studies of the thesis. The identified subtasks are
  - To integrate non-invasive measurements of different parts of the body associated with the movement generation such as the EEG signal over the sensorimotor cortex, the surface EMG activity of specific muscles and gyroscopic information of the limb segments involved in the movement.
  - Use and development of signal processing algorithms and data mining techniques to characterise and model mental states related to specific cortical activation patterns.
  - Development of an integrated platform processing in real-time the acquired cortical, muscular and gyroscopic activity and generating in turn proprioceptive feedback by means of electrical stimulation.

- Interaction with clinical environments supporting them in the design of ethical committees for the proposed studies, in the definition of patients inclusion criteria and in the recruitment of patients for the experiments.

1.6 Chapters description

The thesis is organized around four chapters, each of which related to the four proposed studies. Preceding these four chapters, Chapter 2 presents the neurophysiological basis and EEG-related knowledge regarding cortical control of the movement, which is used in the subsequent parts of the document. In the beginning of this chapter, a brief description of the basic nervous system structures involved in the generation of voluntary movements and how they interact with each other to achieve motor control of the body limbs is reviewed. After this description, the advantages and disadvantages of EEG technology as compared to other electrophysiological measurements of the brain are presented, thus justifying its use in the subsequent chapters. BCI systems for motor rehabilitation are briefly described in the end of the chapter.

The first study is presented in Chapter 3 and it explores, using healthy subjects, the possibilities of modelling cortical activation patterns related to different analytical motor tasks with spatially close somatotopic representations. The methods section of this chapter describes in detail the data mining methodology used to this end. Results show both, the performance of a classifier of these movements and a set of tests to evaluate the validity of the results obtained. The final part of the chapter presents a critical analysis of the obtained results and describes possible scenarios in which the presented EEG-based application may be of interest.

In Chapter 4 a novel application of EEG systems in ET patients is presented. In this case, a neurophysiological study of the effects of a therapeutic drug (alprazolam) in the tremor manifestation and in specific cortical oscillations in patients with ET is carried out. The first part of the chapter provides an up-to-date summary of neurophysiological studies in patients with ET, presenting the main hypotheses of the mechanisms and structures leading to tremor manifestation. Next, the experimental design used to analyse the effects of the drug along a certain time after its intake is described, and results are presented, which lead to establishing a hypothesis regarding the way in which alprazolam reduces the tremor: the increased presence of fast cortical rhythms (specially in the beta band) in patients with ET caused by a single dose intake of a benzodiazepine is tightly related with tremor reduction. The critical discussion of these results, comparing them with previous studies by other authors, as well as the presentation of the main technical limitations of the study are included in the final part of the chapter.

Chapter 5 presents the development of a multimodal brain-neural-computer interface in which EEG technology is integrated with other movement-related sensors to predict voluntary movements. In order to justify the proposed system concept, the potential benefits of a multimodal interface to control a tremor-compensation neuroprosthesis are exposed. After this, the global architecture of the multimodal interface is presented, giving special relevance to the EEG-based subsystem, and preliminary results with healthy subjects and ET patients are shown. In addition, results of the multimodal interface are included, in order to provide a proof of concept of the cooperative interaction between different subsystems combining information from cortical, muscular and gyroscopic sensors. A critical evaluation of the reached results and the future lines of study are included in the final part of the chapter.

In Chapter 6, the last of the four proposed studies is presented. This study is aimed to develop an EEG-based BCI intervention for the motor recovery of the upper-limbs of stroke patients. To achieve this, the first part of the chapter includes a brief review of related studies in the field. The proposed intervention integrates 4 different technologies: an EEG amplifier, an EMG amplifier, inertial sensors and an electrical stimulator. The experimental set-up and the used protocol are presented in the chapter. After this, preliminary results of the system function are presented. The chapter also includes results of a small clinical validation carried out with the system with four patients during eight sessions. The critical analysis of the obtained results and the possible therapeutic effects of the BCI system are presented in the final part of the chapter.

Finally, the general results obtained in the proposed studies are summarized in the last chapter (Chapter 7). This chapter also includes a detailed discussion regarding the achieved results here, the main limitations that have been found throughout the process of carrying out the thesis and the future research lines that may continue what has been here proposed and tested.

Chapter 2

EEG-based systems to study the motor function and BCI technologies in the neurorehabilitation field

This chapter presents the theoretical basis supporting the starting points of the subsequent chapters with the four studies included in the present thesis. The first part of the chapter describes the main regions of the central nervous system that are involved in the generation of voluntary movements. After, the use of EEG technology in neurophysiological studies of the human motor cortex is justified according to its advantages as compared to other alternatives. Finally, the chapter presents the basic concepts regarding BCI systems and refers to some of the most important published studies up-to-date using BCI technology for rehabilitation purposes.

2.1 Structures of the central nervous system involved in the generation of volitional movements

The adult human brain weights around 1.3 kg and it is comprised of around 10^{11} neurons with approximately $2 * 10^{14}$ connection points between them. The neuron is the basic cell of the nervous system, and there exist at least over one thousand different kinds of neurons, although they all share a basic architecture. The complexity of human behaviour does not rely on the neural specificity, but on the ability of these cells to wire together, building highly precise anatomical circuits. Four main aspects of the nervous system are essential to understand its function: the mechanisms by which the neurons produce signals, the connection patterns between neurons, the relationship between this connection patterns and human behaviour and the means by which neurons and connections are modified through experience [Kandel et al., 2000].

Macroscopically, the central nervous system has seven main parts: spinal cord, medulla oblongata, pons, cerebellum, midbrain, diencephalon and cerebral hemispheres. The most important parts of the central nervous system, according to size and development, are the cerebral hemispheres, which consist of the cerebral cortex (outermost part of the brain formed by neural tissue) and three deep lying structures: the basal ganglia, the hippocampus and the amygdaloid nuclei. The two hemispheres of the human brain can be further divided into four different regions separated by the so-called cerebral sulci: the frontal lobe, the parietal lobe, the occipital lobe and the temporal lobe (see Fig. 2.1). Cortical neurons are highly interconnected, giving rise to human behavior through functions such as sensory processing, movement planning, preparation and execution, language processing, memory retrieval and many other cognitive functions. Among the different regions in the cerebral cortex, the primary motor and somatosensory cortices are located anterior and posterior to the Rolandic fissure, which divides the frontal and parietal lobes.

Elaborating a motor strategy to perform a voluntary action is a complex task (see Fig. 2.1). The first step in a volitional movement is intent generation and planning. The prefrontal cortex is connected to many other cortical regions. This allows accessing to all required information for decision making and associated motor action. The prefrontal cortex receives information about past experience stored in memory from the temporal cortex. This information is consciously kept available, thus allowing the subject making inferences and predictions about the outcome of the tentative action. The parietal cortex, area 7, receives in turn information from vision-related cortical areas. This allows the planning of the action in space. In addition, area 5 of the parietal cortex can access information about body situation in space. Considering this whole network, the subject is self-aware and perceives himself as an agent who can act in the environment, predicting the outcomes of his actions based on his past experience.

Performing the planned action is still an even more complex process among interacting brain areas. Once the decision of performing an action is made, the upper motor controller (prefrontal cortex) let the fine-grained control to other frontal areas, such as the premotor and supplementary motor areas. Then, the primary motor area receives commands about the sequence of movements to perform the intended action and projects relevant movement commands directly to the motorneurons through the corticospinal tract and indirectly through the extrapyramidal system (specially through the rubrospinal tract for upper-limb movements). Descending projections to the muscles are also generated from other cortical regions such as the premotor and somatosensory cortices, thus building a complex model of motor control. The motor information travelling along these complex network defines the beginning and end of motor sequences, and on-line corrections. For this on-line correction, sensory information (visual, haptic, proprioceptive) is collected and introduced into the control model.

Certain subcortical regions are also involved in the beginning of a motor sequence. These subcortical regions are the basal ganglia and the cerebellum.

The basal ganglia consist of the striatum (caudate nucleus plus putamen), the globus pallidus, the subthalamic nucleus and the substantia nigra. The basal ganglia, and specially the striatum, receive information from the whole sensory and motor cortex. Therefore, the striatum integrates and overlaps the sensory and motor images of the self body. Those images split in the striatum, representing body parts in a redundant way. When relating pieces of sensory information to pieces of motor actions (such as muscle area activations), the striatum builds action plans coherent with the sensory signaling pattern. The internal globus pallidus inhibits paths that link the thalamus and the frontal cortex. The external globus pallidus and the subthalamic nucleus reinforce the globus pallidus activation. Therefore, the output path from the striatum is double. There is a direct path that inhibits the internal globus pallidus, thus allowing movement, and there is also an indirect path that activates the external globus pallidus and the subthalamic nucleus, which in turn reinforces the internal globus pallidus and blocks movement. Finally, the substantia nigra provides flexibility to motor plans by the connection to the striatum. If the motor plan has been successful then the substantia nigra does not activate the path to the striatum. Otherwise, if the motor plan failed the substantia nigra activates the path to the striatum. This produces the release of dopamine in the striatum, making it more plastic and sensitive to be modified and corrected.

The cerebellum modulates movement and posture indirectly, adjusting the outputs of

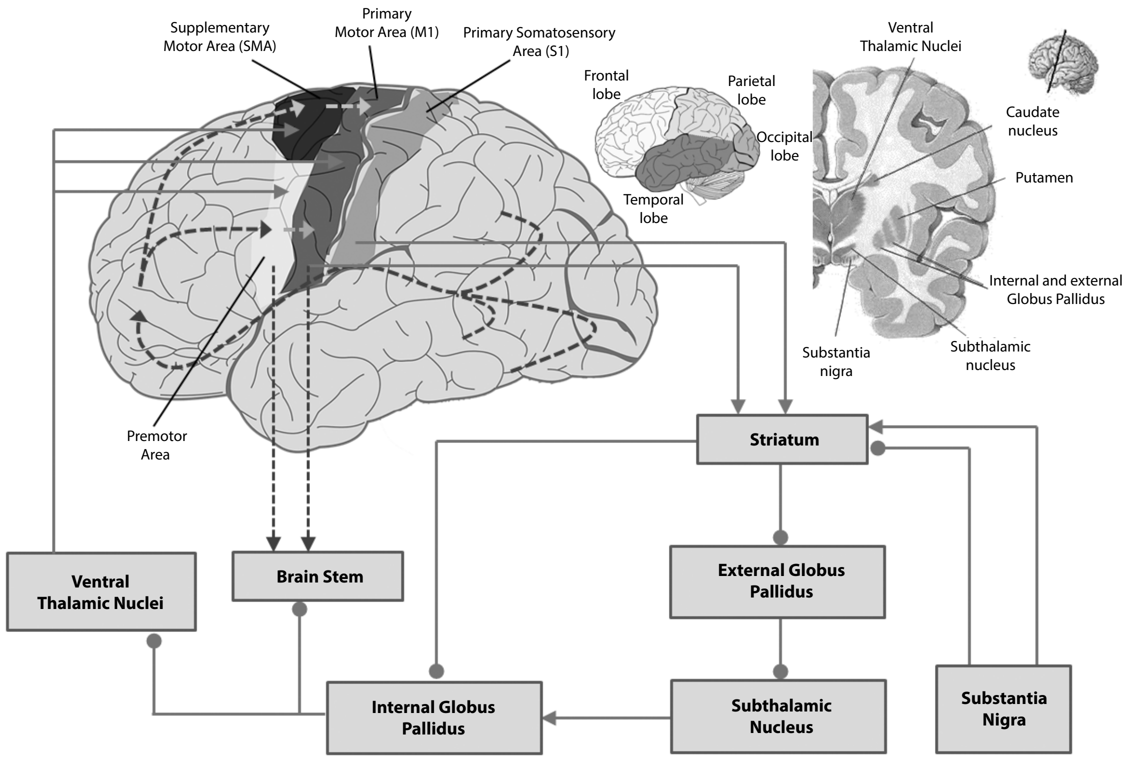


Figure 2.1: Depiction of cortico-cortical (dashed lines) and cortico-subcortico-cortical (solid lines) information flow between brain regions in movement planning and execution. Brain stem projects fibers to muscles. Lines ending with arrows denote excitatory connections. Lines ending with dots denote inhibitory connections.

the main encephalic motor structures. It acts as an online comparator between projected and performed movements, and it is therefore mainly involved in the on-line modulation of the movement, once it has already started.

2.2 The use of the EEG signal to extract cortical activity related to the movement

There are a number of techniques that allow the acquisition of the cortical and subcortical electrophysiological activity. The main difference among these alternatives is the size and location of the neural population that is being “listened to”. This way, it is possible to measure

- the spiking activity of single neurons;
- the local field potentials reflecting the summation of nearby synaptic and neuronal activity;

- the electrical activity directly measured from the cerebral cortex;
- the EEG activity, which is the cortical signal obtained from electrodes placed on the scalp;
- the magnetoencephalographic (MEG) activity, acquiring the magnetic fields elicited by cortical dipole sources tangentially oriented to the head surface;

From this list, only MEG and EEG systems are non-invasive solutions characterizing cortical processes. The main advantages of using the EEG signal are the fact that it is a non-invasive technique, commercially available, easy to set-up and robust to possible external interferences, which makes it perfectly suitable in clinical environments and with wearable robotic systems. The main handicap of the EEG signal is its low spatial resolution caused by the fact that cortical signals are acquired from electrodes on the scalp, a few millimetres away from the actual cortical surface.

As previously defined, the EEG consists in the acquisition of the cortical electrical activity with scalp electrodes over specific points of the brain. In its origin, the EEG was developed to analyse mental processes, but its clinical applications rapidly followed. Cortical neurons are connected to thousands of other neurons through excitatory and inhibitory synapses, spreading throughout the dendritic part of the neuron. The transmission of an action potential from one neuron to the next one produces in the latter an excitatory or inhibitory postsynaptic potential. These potentials caused by ionic imbalances are summed in the dendritic bodies of the neurons, giving rise to field potentials in the nearby region. This process is assumed to be one of the main sources of the EEG activity acquired by the scalp electrodes [Niedermeyer and da Silva, 2005]. Therefore, the EEG activity will represent mental processes with sufficiently large enough groups of neurons spiking synchronously, so that the amplified version of their activity can reach the scalp.

The EEG morphology depends on multiple factors such as the age, vigilance, performance of cognitive tasks, motor tasks, etcetera. Its similarity with a chaotic process and its small amplitude (10-100 μV), have definitive influence on the way these signals are analysed. As with other biological signals, the EEG activity presents a number of characteristics that make its analysis a complex task. The EEG signal is nonlinear and it is considered a stochastic and non-stationary process. The high variability present in an EEG signal is caused mainly by the noisy environment and the acquisition techniques used, the neurophysiological phenomena that produce the signal, the biological phenomena that appear in parallel with the studied process and that contribute to the recorded signal and the response of biological mechanisms to external agents.

The EEG signal is traditionally described by means of its power spectrum, characterized by the presence of a number of cortical oscillations (cortical rhythms) associated with different frequency bands. The main rhythms of the brain are located in different frequency bands: the theta band (4-7 Hz), the delta band (1-3 Hz), the alpha band (8-12 Hz), the beta band (13-28 Hz) and the gamma band (29-100 Hz). In addition to these bands, the cortical changes with frequencies under 1 Hz (slow and ultra-slow rhythms) may also to be considered as a relevant source of information, specially in the analysis of movement-related potentials.

2.2.1 Cortical patterns related to the motor function and visible in the EEG signal

Cortical patterns measured with EEG may be classified according to the nature of the stimuli that generate them: they may appear as a response to external stimuli or they may be electrical processes endogenously generated. Cortical patterns can also be classified according to their morphology and the components that form them. In this line, two sources of information may be distinguished: slow cortical changes and information contained in cortical rhythms. The information obtained from the processing of the cortical rhythms can in turn be acquired either by analysing the power changes in a specific cortical region, or by studying how two different regions interact through these oscillations. Attending to these classification criteria, cortical patterns associated with the voluntary movements may be classified in different groups, described in the forthcoming sections.

2.2.1.1 Movement related cortical potentials (MRCPs)

Before and during self-initiated movements of healthy subjects, slow changes (with frequencies under 1 Hz) appear in the EEG activity. In most subjects these changes have amplitudes of few μV and therefore they are difficult to observe in the raw EEG signal. When averaging across a number of similar movements performed by a same subject, a sequence of defined temporal patterns with a specific spatial distributions can be observed. This sequence of patterns is termed movement-related cortical potential (MRCP) [Shibasaki and Hallett, 2006] and it constitutes one of the main sources of information to evaluate certain aspects of the mental activity before and during voluntary movements.

Each of these MRCP components are found either before or after the onset of voluntary movements and are characterized by positive or negative deflections of the EEG signal. The MRCPs in self-initiated actions begin with a slow negative deflection of the EEG signal amplitude starting about 1.5 s before the onset of the movement, called the Bereitschaftspotential (BP). The BP precedes voluntary movements and it has proven to

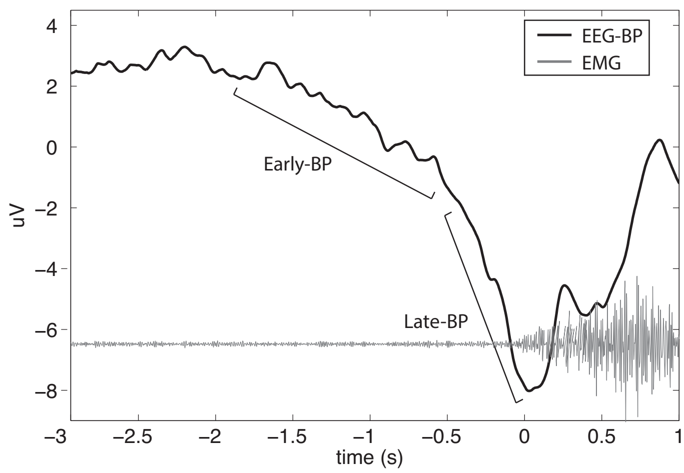


Figure 2.2: Typical BP slope coupled with the EMG signal indicating movement.

supply reliable online estimations regarding movement intentions [Niazi et al., 2011]. In addition, as the pattern precedes the actual movement, it is less dependent on the characteristics of the movement to which it is related (movement speed, complexity, number and size of muscles involved etc.). For these two reasons, the BP is the most studied component of the MRCPs, both in terms of physiological findings and clinical applications. The BP typically presents an “early” part that begins around 1.5 s before the onset of the voluntary movements. During this first stage, a slow decreasing tendency of the signal is observed. About 400 ms before the movement starts, a steeper decay appears, known as “late BP” (see Fig. 2.2). Different cortical regions are responsible for the generation of the “early-” and “late-BP” (Fig. 2.2). In the case of hand movements, the SMA and the lateral precentral gyrus, both bilaterally, are estimated to be the main generator sources for “early-BP”. Cui and Deecke [Cui and Deecke, 1999], based on a high-resolution low-frequency EEG analysis, demonstrated that BP occurs earliest in the medial wall motor areas (SMA and cingulate motor areas), then in the contralateral motor cortex, and lastly in the ipsilateral motor cortex. Fig. 2.3 shows the spatio-temporal distribution of the BP pattern associated to the movement of the right arm in a reaching task.

Similarly to the BP pattern in self-initiated movements, the contingent negative variation [WALTER et al., 1964] is also a slow negative brain potential, but in this case it appears between two successive external stimuli, with the first stimulus serving as a preparatory ’warning’ signal for the second ’imperative’ stimulus, to which a motor response is required. In this case, the contingent negative variation is assumed to represent the neural activity necessary for sensorimotor integration. It is therefore related to planning or execution processes for externally-paced voluntary movements.

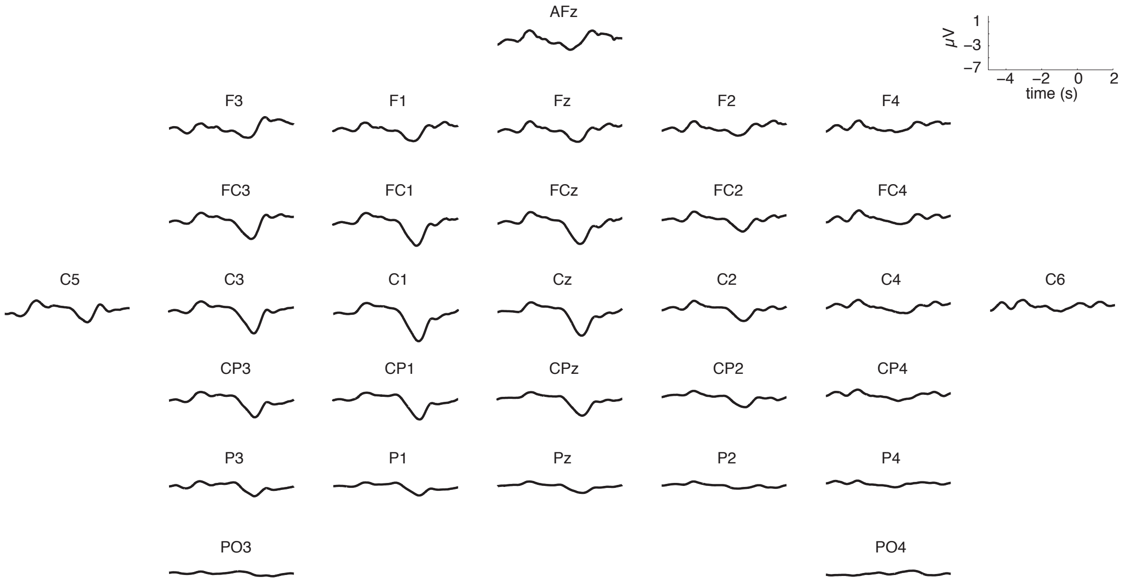


Figure 2.3: Distribution of BP slopes over the scalp with respect to right-arm movement onset (t = 0).

2.2.1.2 Sensorimotor Event Related Desynchronization and Synchronization

During resting conditions without movements, the neural networks of the sensorimotor cortex typically present firing patterns in the mu and lower-beta frequency bands, termed the sensorimotor rhythms. The event related desynchronization (ERD) over the sensorimotor cortex refers to the percentage of decrease of EEG signal power in the mu and lower-beta rhythms as a result of changes in the brain states associated to sensorimotor processing functions. During a voluntary unilateral hand movement, mu and beta ERD start contralateral to the side of the movement about 2 s before its onset, becoming bilateral at about the time the movement begins (see Fig. 2.4) [Pfurtscheller and da Silva, 1999; Bai et al., 2005]. This desynchronization pattern suggests a contralateral leading role in the preparation of voluntary movements. As an inverse effect, ERS is defined as the percentage of power increase (ERS), especially in the β band, after finishing a movement. These cortical patterns were first observed during the execution of overt hand or foot movements and they are also present during passive movements, somatosensory stimulation, and both observation and imagination of movements.

In order to characterize the cortical ERD/ERS patterns of a certain subject using a set of EEG segments (trials) time-locked to the movement event, time frequency de/synchronization maps are used. Standard ERD/ERS calculation is done by introducing the EEG signal of each trial into a bank of band-pass filters, computing the power of the filtered signals and averaging over trials. The ERD/ERS is then defined as the

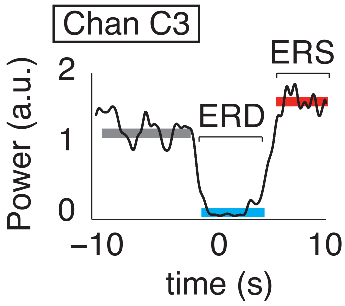


Figure 2.4: Average pattern of the ERD/ERS cortical process related to the movement execution onset

proportional power decrease/increase with respect to a certain reference interval typically picked from several seconds before the onset of the sensorimotor task analysed. The estimation of the ERD curve in each frequency band and channel analysed can be performed as follows:

$$Y_j = \frac{1}{N_{tr}} \times \sum_{i=1}^{N_{tr}} X_{ij}^2 \tag{2.1}$$

$$Ref = \frac{1}{k} \times \sum_{j=r_0}^{r_1} Y_j \tag{2.2}$$

$$ERD_j = \frac{Y_j - Ref}{Ref} \times 100 \tag{2.3}$$

where N_{tr} is the number of trials considered to estimate the ERD, X_{ij} is the j^{th} sample of the i^{th} trial. Ref is the average power of the band-pass filtered signal in the reference interval $r_0 : r_1$ [Pfurtscheller and da Silva, 1999].

An example of the ERD time/frequency maps obtained over a set of channels acquired from a subject performing self-paced reaching movements with the right arm is shown in Fig. 2.5. In this case, the ERD pattern (bright regions in the maps) starts around 1.5 s before the onset of the movements (t = 0 s), is most significant in the alpha and beta (below 25 Hz approximately) bands and over the contralateral hemisphere (in the C3 channel in this case, since movements with the right hand are performed), and it is maintained until the end of the movement (t > 2 s). The ERS phenomenon cannot be clearly observed in this case, since movements were synchronized with respect to their onsets and the lengths of the movements were variable (therefore, the average activity after the movements ended is blurred).

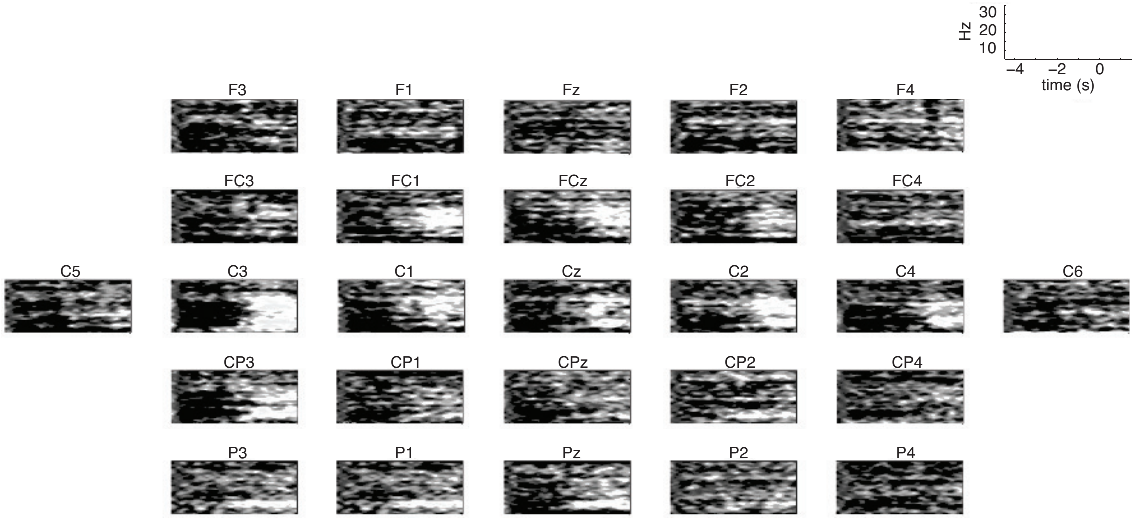


Figure 2.5: Distribution of average ERD time/frequency maps over the scalp from a subject performing self-paced reaching movements with the right arm. Bright areas represent power decay caused by ERD phenomenon around the movement onset.

2.2.1.3 Movement-related cortico-cortical and cortico-muscular interaction

Neural networks associate with each other by means of synchronized oscillations [Buzsáki and Draguhn, 2004]. This way, neural assemblies are built depending on the cognitive process that is being carried out. This synchronization may be present at a local level (within a certain neural region) or at a large-scale level (between distant neural populations). The former may be studied by analysing power changes in specific frequency bands using the information of single electrode positions (as the ERD and ERS patterns presented before), while the latter are typically studied by analysing the interaction between cortical regions. To carry out interaction studies between different neural populations, several mathematical approaches have been proposed up to date. In encephalographic recordings, synchronization is usually quantified with linear measures like coherence or with nonlinear measures like those based upon phase synchronization or generalized synchronization [Stam et al., 2007; Varela et al., 2001]. In addition, interaction between neural populations can be carried out between two different points on the scalp (cortico-cortical interaction) or between a point on the scalp and a point on a peripheral muscle (cortico-muscular interaction).

Regarding cortico-cortical interaction, a small number of studies have analysed it during movement tasks. The association between sensory inputs and motor responses [Classen et al., 1998; Hummel and Gerloff, 2005; Rilk et al., 2011] and the association between different sensorimotor regions [Gerloff et al., 1998; Sweeney-reed et al., 2009] have been subject of study in this area. Overall in this sort of studies two main problems of the

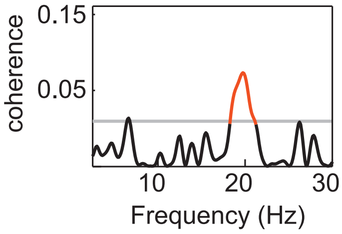


Figure 2.6: Corticomuscular coherence between EMG from the wrist extensors of the left hand and the FC2 channel (red part of the curve around 20 Hz).

EEG technology need to be solved in order to further advance in this regard: the volume conduction and the problem of the active reference [Tognoli and Kelso, 2009].

On the other hand, studies of cortico-muscular coherence have allowed to analyse how activity in the beta band in the motor cortex mediates cortico-muscular communication in different types of muscle contractions [Conway et al., 1995; Negro and Farina, 2011; Raethjen et al., 2008]. An example of such cortico-muscular coherence during the extension of the hand is shown in Fig. 2.6. According to these kind of analyses, where the existence of significant coupling at the beta band between the motor cortex and the population of motor units in voluntarily contracted muscles is observed, it is suggested that cortical commands are transmitted to the muscles at these frequencies through the descending pathways [Petersen et al., 2012; Kilner et al., 2000; Conway et al., 1995].

2.3 BCI systems for motor rehabilitation

EEG-based BCI systems are an emerging field aimed to provide a communication channel between the human and an external device using brain activity [Wolpaw et al., 2002]. This systems open a door for innovative applications in entertainment and gaming applications [Liao et al., 2012], and with higher relevance, in clinical and assistive applications. During the first years of BCI research, clinical applications were explored to provide alternative communication means to patients with lost ability to interact with the environment in any possible natural way [Birbaumer, 2006; Nijboer et al., 2008]. During the last decade, an important part of research efforts in BCI technologies have focused on rehabilitation applications, in which the main goal is to either restore or compensate the affected motor function of a patient's limb [Daly and Wolpaw, 2008]. In both scenarios (motor restoration and compensation), the EEG signal provides a relevant feature to the communication channel between the human and the device: having real-time access to movement-related cortical processes allows fast estimations regarding the user's intentions, which may in turn lead to achieving more natural interactions with the controlled device. Such natural interfaces are specially desired in man-machine interaction for rehabilitation purposes due to some relevant reasons:

- Biological reasons: human-robot interface systems seek to take advantage of the natural control mechanisms fully optimized in humans.

- Practical reasons: Delays are introduced when natural cognitive processes are encoded into an imposed sequence of tasks. In addition, a training phase is needed to teach the user to generate these non-natural commands or to map a cognitive process into a new set of outputs. Both factors, the delays and the mapping, can also induce fatigue in the user, both at a musculo-skeletal level and at a mental level. These limitations may be obviated if the natural outputs of a cognitive process are used instead.

- Rehabilitation: Interacting directly with the phenomena involved in the cognitive process is a means to excite them and assess the evolution of the rehabilitation therapy.

Two groups of BCI applications can be considered in the framework of motor rehabilitation: BCIs for motor compensation or assistance and BCIs for motor recovery.

On the one hand, BCI systems aimed to assist the movements have been proposed specially for upper-limbs and for different pathologies, mainly spinal cord injury [Müller-Putz et al., 2005; Onose et al., 2012] and stroke [Buch et al., 2008; Ang et al., 2011]. The major challenges here of the EEG-based movement detection algorithms are to achieve reliable estimations in realistic scenarios, to work asynchronously (that is, the user controls the timing of the movement events) [Mason and Birch, 2000; Borisoff et al., 2006; Delgado Saa and Cetin, 2013] and to reduce the impact of the wearable technology in the patient's daily living [Popescu et al., 2007]. Since alternative control mechanisms can be developed from non-cortical signals (muscular control, eyetracking devices etc.), the justified use of EEG-based interfaces in this field critically relies on the success of the decoding algorithms according to the aforementioned criteria.

On the other hand, EEG-based BCI systems focused on recovering the lost function of affected limbs of disabled patients have gained attention during the past few years, and there exists a large number of proposed interventions in which promoting motor neurorehabilitation is the main pursued goal [Daly and Wolpaw, 2008]. The most relevant BCI-based approaches for rehabilitation in the last ten years combine BCI training with physical therapy [Broetz et al., 2010] or with robotic-based therapy [Ang et al., 2010] showing motor function improvement in stroke patients. Two BCI-based strategies are distinguishable in this field. The first one is based on the neurofeedback approach, which hypothesizes that training the patients to produce more normal brain activation patterns will be accompanied by improved motor function. The second strategy focuses on using brain activity to drive a device providing proprioceptive feedback. This sensory feedback is expected to induce plasticity leading to restoration of the normal motor control. This second strategy relies on the idea that brain activity can guide activity-dependent central nervous system plasticity in the same way as the standard repetitive movement practice carried out by therapists or robots influences it [Várkuti et al., 2013].

The potential relevance of the second BCI-based strategy for changes in motor behaviour is exemplified particularly well in the context of stroke rehabilitation: assuming that the connection between peripheral muscles and the sensorimotor cortex has been disrupted due to a cortical or sub-cortical stroke, a concurrent activation of sensory feedback loops and primary motor cortex may reinforce previously silent cortical connections by Hebbian learning (repeatedly coincident activation of pre-synaptic and post-synaptic cells reinforces synaptic strength, tending to become associated) and thus support functional recovery [Mrachacz-Kersting et al., 2012; Niazi et al., 2012]. According to this arguments, as will be shown in subsequent studies, the fact that the EEG allows a precise location of the onsets of voluntary movements becomes a relevant aspect of this technology to be applied in neural rehabilitation interventions for stroke patients.

Chapter 3

EEG-based predictive classification of analytical upper-limb movements

3.1 Abstract

Chapter 2 has presented the most commonly used EEG patterns associated to motor processing functions (mainly the MRCPs and ERD/ERS patterns). Yet, the analysis of the characteristics and dynamics of the cortical rhythms originated from distributed points in the sensorimotor cortex and measured with EEG may allow an advanced characterization of how different motor-related cortical regions activate or deactivate when performing different kinds of motor actions. In this regard, one of the main limitations of EEG systems to characterize task-related cortical processes is their low spatial resolution. This limitation reduces the possibilities of distinguishing among mental states that present similar somatotopic representations. On the other hand, as has been commented before, EEG systems present a great potential to characterize relatively simple mental states preceding the onset of volitional movements. So far, the majority of BCI systems that have been proposed to classify different movement-related mental states have frequently presented paradigms in which movements of distant parts of the body (and therefore, with distant somatotopic representations) were to be distinguished (examples in this line are BCI systems distinguishing between movement imagery of the right hand, the left hand and the feet proposed by several BCI groups). In this chapter it is studied the possibility of classifying a number of simple movements, all of them performed with the same limb, based on premovement EEG signal segments. To do so, advanced data mining techniques are applied on a dataset with a large number of examples to find the optimal subset of features that allow a differentiation of classes over the chance level of the study. The scientific interest of experiments like this one in neurorehabilitation environments ranges from further understanding the cortical mechanisms underlying the generation of simple movements, to achieving new EEG processing techniques that can be integrated in rehabilitation BCI systems to test the pa-

tients' involvement in the rehabilitation process and to provide an adequate proprioceptive feedback associated to the movements they intend to do.

3.2 Introduction

The electroencephalographic (EEG) activity allows the description of cortical processes associated to volitional motor actions [Chatrian et al., 1959; Kornhuber and Deecke, 1965; Pfurtscheller and da Silva, 1999; Libet et al., 1982]. A number of studies with EEG have demonstrated its potential use to locate intervals of motor-related cortical activation and deactivation [Neuper et al., 2006; Pfurtscheller and Solis-Escalante, 2009], to anticipate the instants at which voluntary movements begin [Bai et al., 2011; Niazi et al., 2011; Ibáñez et al., 2013], to decode movement parameters such as velocity, strength, etc [Gu et al., 2009a], and to distinguish between different classes of movements [Morash et al., 2008; Pfurtscheller et al., 2006]. Yet, it remains unclear the extent to which the EEG activity allows the description of motor-related mental processes. Advances in this area will lead to further understanding the relevant parts of the brain taking part in the generation of volitional actions [Desmurget et al., 2009; Obhi et al., 2009], and to new ways of inducing neural rehabilitation by integrating EEG in novel clinical interventions [Buch et al., 2008; Daly and Wolpaw, 2008], either for passive monitoring the motor therapy, or for active mobilization with robotic devices. In this context, EEG technology is of great interest since it allows the real-time characterization of the motor-related cortical activity to obtain predictive information regarding intended actions. Such information has proven to be valuable to provide natural proprioceptive feedback inducing cortical plasticity [Mrachacz-Kersting et al., 2012; Niazi et al., 2012].

Recent studies have proposed methodologies to decode 3D kinematics of the upper-limb based on slow potentials measured with EEG [Bradberry et al., 2010]. Nonetheless, metrics applied to validate the results in these studies are subject of discussion [Antelis et al., 2013]. Previous studies using invasive recordings have pointed out that brain-machine interfaces (BMIs) based on the dynamics like those of muscles seem to be more robust and easier to learn than BMIs commanding forces or movements in external coordinates [Oby et al., 2013]. Several works have taken advantage of the changes of the cortical rhythms measured with EEG to estimate muscle activations and joint rotations [Morash et al., 2008; Pfurtscheller et al., 2006]. In[Deng et al., 2005] it was proposed a methodology to distinguish between movements performed with the shoulder and elbow of the dominant upper-limb. These two tasks present similar cortical representations, which makes them difficult to be distinguished from each other based on non-invasive recordings as the EEG activity. No previous works have tried to identify EEG-signal patterns classifying more than two different movements performed with the same arm.

In this chapter, results of a classifier of analytic movements performed with the upper-limb (7 different classes) based on pre-movement EEG activity are presented. The system is evaluated on 6 participants who performed 350 self-initiated movements during the experiments. To develop the classifier, data mining techniques extracting optimal features selected with a genetic algorithm were applied. The feature space considered were the power spectral values of the alpha and beta bands of the EEG signal (information of the activation or deactivation of cortical regions associated to movement tasks [Pfurtscheller and da Silva, 1999; Deng et al., 2005; Morash et al., 2008]). The average accuracy obtained with all subjects was above the chance accuracy level obtained by randomly labelling the acquired examples. Further analyses (discussed in the last part of the chapter) discard the hypothesis that other sources of information, different from the task-related cortical activity, were used to reach the classification results. The study supports the idea that EEG can supply with predictive information about upper-limb analytical movements.

3.3 Methods

3.3.1 Participants and experimental procedure

Six healthy male subjects, right-handed and with ages between 25 and 35 years-old were recruited for the experiments carried out in this study. They were seated in a comfortable chair and, during the exercises, they were asked to remain relaxed without performing any movements other than the tasks studied in the experiments. A screen was placed in front of the participants to guide them during the experiments.

Each subject performed seven analytic movement tasks with the dominant upper-limb: shoulder abduction (SA), shoulder extension (SE), shoulder rotation (SR), elbow extension (EE), forearm pronation (FP), wrist extension (WE) and wrist rotation (WR). For each one of these tasks, two runs of 25 trials each were executed, leading to 350 trials (7 tasks and 50 examples per task). Each trial was divided into two parts: during the first part of 12 s, the participants were asked to start a single movement when they wanted, trying to wait at least 2 s before performing it (during this part the word “Movement” was shown in the screen). The second part of the trial lasted 3 s and the participants relaxed and got prepared for the subsequent trial while the word “Rest” was shown in the screen. Each run lasted 6 minutes and 15 seconds in which the participants performed self-initiated movements (trials) of one of the seven tasks. The runs were interleaved as follows: the first type of analytical movement was performed in runs 1 and 8, the second type in runs 2 and 9, etc. (see Fig. 3.1). A session lasted around 2 hours.

Participants adopted three different starting positions of the arm to perform the move-

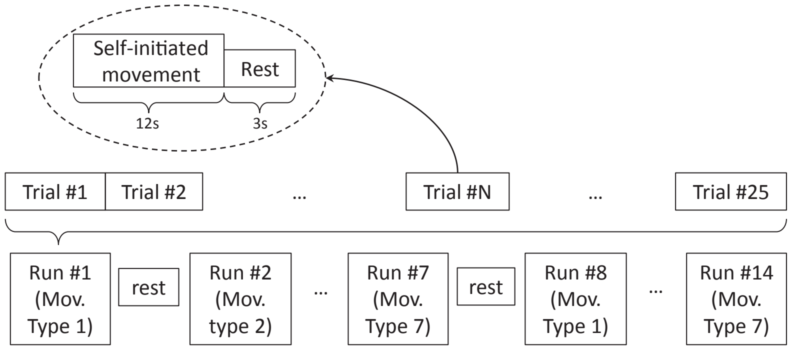


Figure 3.1: Scheme of the recording sessions. A trial (top), a run (middle) and the distribution of tasks along the session (down) are represented.

ments (see Fig. 3.3): A) the arm was left hanging and relaxed for tasks SA and SE, B) the arm was resting on the arm of the chair for tasks EE, FP and WE, and C) the arm was resting on an auxiliary desk for tasks SR and WR.

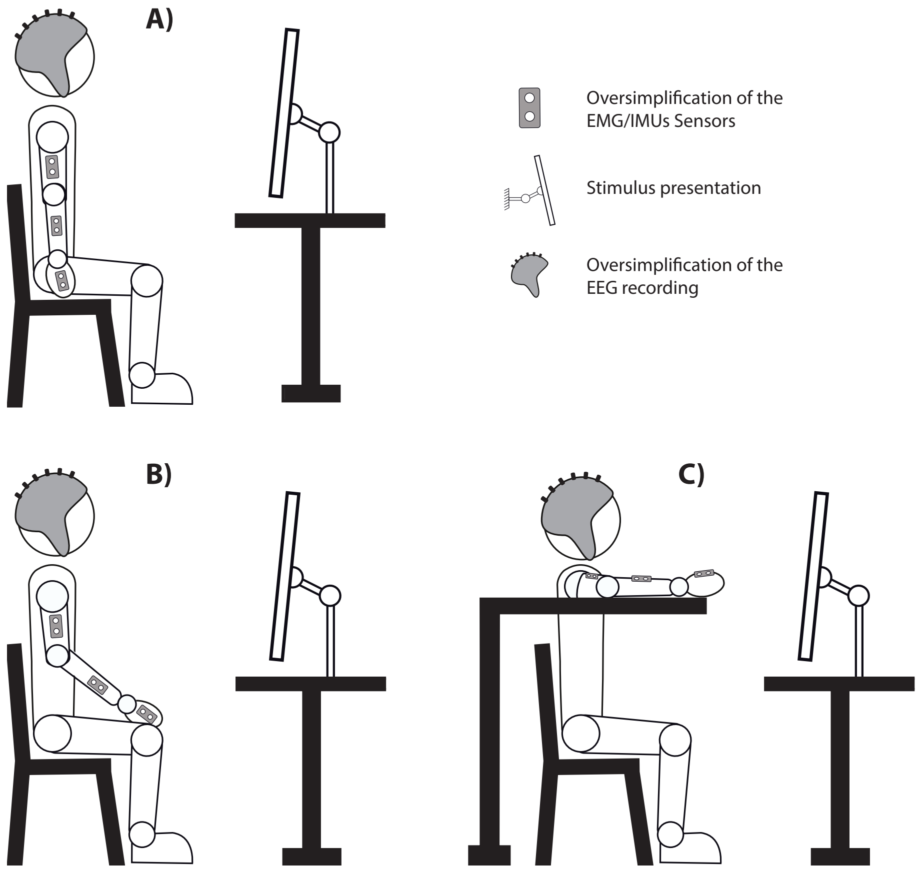


Figure 3.2: Schematic representation of the three positions adopted by the participants to perform the analytical movements.

3.3.2 Data Acquisition

Three synchronized gUSBamp amplifiers (g.Tec gmbh, Graz, Austria) were used to amplify and digitize the EEG and EMG data at a sampling frequency of 512 Hz. The EEG montage consisted of 32 electrode positions (see Fig. 3.4) and active Ag/AgCl scalp electrodes were used. The ground and reference electrodes were placed on FPz and on the left earlobe, respectively.

EMG activity was recorded with bipolar derivations on 8 muscular groups: extensor digitorum, extensor carpi ulnaris, palmaris longus, biceps brachii, triceps brachii, frontal part of the deltoid, lateral part of the deltoid and back part of the deltoid.

Gyroscopes were placed on the third metacarpal, the edge of the forearm (dorsal side), and above the olecranon process. The gyroscopic data were digitized at 50 Hz and synchronized with the EEG and EMG data by means of an external digital signal.

3.3.3 Data processing and classifier design

This section describes the methodology for building, for each participant, a classifier of the 7 possible analytical movements performed with the upper-limb during the measurements.

3.3.3.1 Detection of the movements' onsets

The onsets of the movements were obtained from the gyroscopes data as follows: the data were low-pass filtered (Butterworth, order 2, ≤ 6 Hz) and the rotation angle of each joint moved was obtained as the absolute value of the difference between the gyroscope measurements of the two adjacent sensors (the hand and forearm for wrist movements, the forearm and arm for elbow movements and the arm and trunk for shoulder movements). The threshold for the detection of the onset was set at 5 % of the maximum rotation speed of all movements of each type. The gyroscopes information was used to detect the onsets instead of the EMG because it was more robust for all movements with all the three possible initial positions. Notice that the latency between the EMG-based and the gyroscopes-based onset detections is expected to be small, given that the electromechanical delay for upper-limb tasks is in the order of tens of milliseconds [Norman and Komi, 1979]. EMG data served to assert that the onsets of the movements detected with the gyroscopes were correctly located, and that there was no muscular activity in the different initial positions during the resting intervals before the movements.

3.3.3.2 EEG signal processing and feature extraction

Small Laplacian filtering [Hjorth, 1975] was applied to the EEG channels that were surrounded by 4 neighbouring positions and a Common Average de-referentiation was applied to the boundary positions of the used electrodes set-up.

The EEG data were band-pass filtered (Butterworth, order 2, passed band 5 - 45 Hz). Each trial was segmented in the following time intervals: i) a 2-seconds segment starting 2 s before the movement onset (referred to as "Whole"), ii) a 1-second window starting 2 s before the movement onset ("Early"), and iii) a 1-second window starting 1 s before the movement onset ("Late"). The features from these three windows were used in combination by the classifier. The "Whole" window was expected to supply the classifier with global and low-variance information of the cortical activity related to the voluntary movement, while the "Early" and "Late" windows were expected to provide information regarding transitory mental processes before the voluntary movement initiation.

For each of these segments, the Power Spectral Density (PSD) values of the EEG signal of each channel were obtained in the frequency range from 7 - 30 Hz (alpha and beta bands), with a frequency resolution of 1 Hz (Welch's method with Hamming windowing, 75 % overlap, no zero-padding). Therefore, 23 power values were extracted per window, channel and trial, leading to 2208 features extracted per trial.

The logarithms of the PSD values extracted were computed as the features fed to the data mining process, aimed to construct the EEG-based classifier of analytic movements performed. The logarithmic power values were used to convert the extracted features into normal distributions.

3.3.3.3 Classifier implementation

Firstly, the feature space was reduced eliminating features correlated ≥ 0.75 in the training dataset.

Feature selection was performed using a genetic algorithm that maximized the accuracy of a Bayesian classifier of independent features (the scheme is presented in Fig. 3.3). The algorithm was programmed to run 1000 generations, with 500 new individuals generated in each generation. The number of features of each the individual was set to be between 50 and 100. A 4-fold cross-validation was used to evaluate the classifier's performance for each individual in each generation, avoiding singular solutions of the classification problem.

In the classification stage, a Bayesian Classifier of independent features with Gaussian modelling was also selected to classify the examples because it showed better performance than neural networks and support vector machines with the data of these experiments. Moreover, similar studies have also obtained optimal results with Bayesian classification methods [Bai et al., 2007]. A 4-fold cross-validation was used to obtain the classification results.

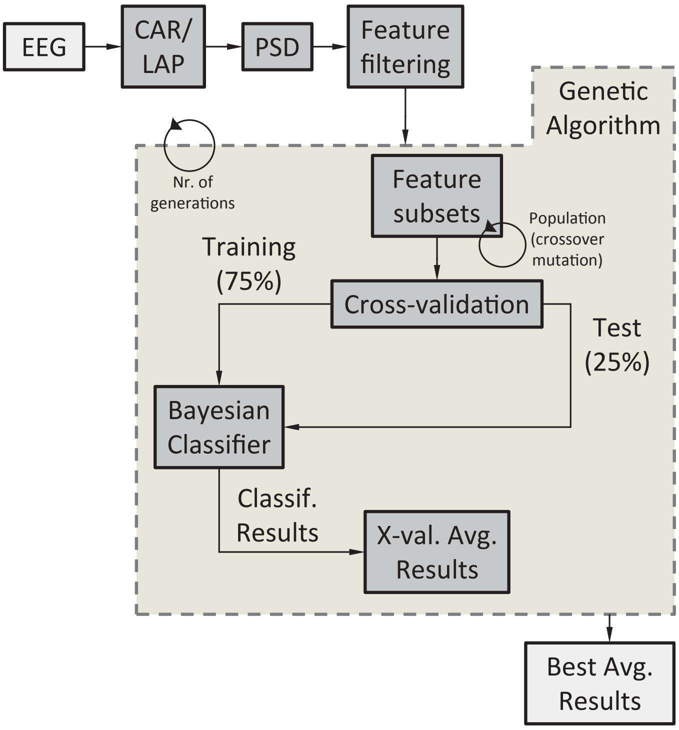


Figure 3.3: Schematic representation of the three positions adopted by the participants to perform the analytical movements.

3.3.4 Additional experiments to prove the validity of the classification results

Three additional experiments aimed to further validate the classification results were performed and are described here.

3.3.4.1 Validation experiment 1: Estimation of the significance of the obtained class description

The experiment was performed to obtain a referential chance level, in order to compare it with the accuracy results obtained with the classifier of analytical tasks. To get the chance level, the following process was repeated 10 times for each subject: firstly, the labels of the examples in the dataset were reorganized randomly, and secondly, the new dataset was applied the classification procedure detailed in 3.3.3.3. Mean ± SD of the accuracy results over the 10 repetitions was computed for each participant and compared to the classification results with the correctly labelled examples.

3.3.4.2 Validation experiment 2: Analysis of the influence of the time segments location

A second experiment was run to test whether varying the location of the time segments used for the feature extraction process had any influence in the accuracy of the classifier. Average accuracy results were obtained with the tasks' classifier using three different conditions, with the signal segments used for the features extraction ("Whole", "Early" and "Late" as defined before) located: i) from -3s to -1 s (0 s is the movement onset); ii) from -2 s to 0 s (note that this condition is the same as the one presented in Section 3.3.3); and iii) from -1.5 s to +0.5 s.

3.3.4.3 Validation experiment 3: Extraction of other tentative sources of information

Three different initial positions were adopted by the participants. This may influence the results obtained with the tasks' classifier. Therefore, an additional classifier was developed to classify among the three different initial positions adopted. The selected features for this classifier were compared with the ones selected for the classification of analytic movement tasks. The purpose was to evaluate how similar the classifiers of tasks and initial positions were. The percentage of shared features obtained from this comparison represents an index of the influence of the initial positions on the tasks' classification results.

3.3.5 Statistical analysis of the features selected

Three one-way ANOVAs ($P < 0.05$) were performed to test whether there were spatial or frequency preferences in the feature selection process of the tasks' classifier. Multiple comparison tests were performed using Bonferroni post-hoc analysis.

To evaluate the spatial distribution of the selected features, the measured scalp positions were divided into 9 areas (see Fig. 3.4). In order to look for statistical differences in the spatial distribution of the selected features along the Caudal-to-Rostral direction, features from sectors 1, 2 and 3 were labelled as "Frontal Features", features from sectors 4, 5 and 6 were labelled as "Rolandic Features" and features from sectors 7, 8 and 9 were labelled as "Parietal Features". For the analysis of the statistical differences in the spatial distribution of the selected features along the central sulcus direction, features from sectors 1, 4 and 7 were labelled as “Left Features”, features from sectors 2, 5 and 8 were labelled as “Central Features” and features from sectors 3, 6 and 9 were labelled as “Right Features”. The number of features in each region was normalized to the number of positions in that region, so that the statistical analysis was unbiased.

To study statistical differences in the frequency distribution of the selected features, they were divided into three groups: alpha band (7-12 Hz), lower-beta band (13-19 Hz), and upper-beta band (20-29 Hz). Normalization was also performed in this case.

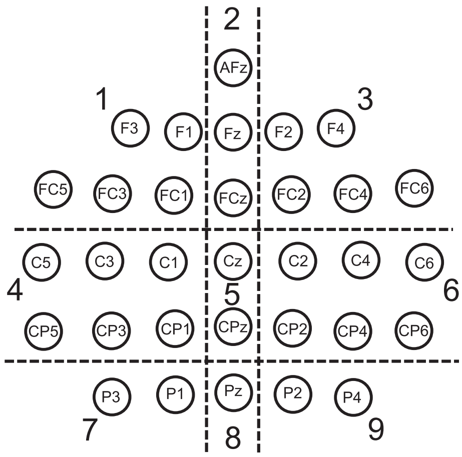


Figure 3.4: Scalp division into 9 regions to perform the statistical analysis of the locations of the selected features.

3.4 Results

3.4.1 Classification results of 7 analytical movements

The genetic algorithm selected on average 86 $\pm$ 4 features (out of the initial set of 2208 features) to classify the 7 movement tasks. The plots of Fig. 3.5 represent the spatial distribution of features selected for each subject. In 4 cases (subjects 01, 02, 03 and 06), contralateral features of the central regions of the scalp were preferentially selected by the classifier. According to the statistical analysis of the features selected with all subjects, significantly more features were selected from the upper-beta band than from the alpha band ($P < 0.0001$), and the number of features located around the central sulcus (“Rolandic Features”) was significantly higher ($P = 0.017$) than the number of “Parietal Features”. No further statistically significant results were found in this regard.

The precision and recall results obtained are shown in Table 3.1. Results are presented for the classification of each one of the 7 tasks. The last row and column present average results across subjects and tasks respectively. On average, 62.6 % of the trials were

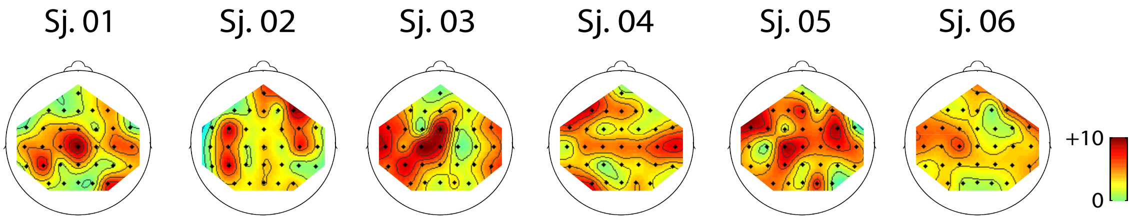


Figure 3.5: Scalp maps of all subjects representing the number of features selected from each electrode position.

correctly classified with a precision of 63.7 %. Subjects 03 and 06 presented the best classification results (accuracies of 76.6 ± 4.5 % and 64.2 ± 0.7 % respectively), while the system showed the worst performance with subject 04 (54.2 ± 6.8 %).

Code	SA		SE		SR		EE		FP		WE		WR		Avg. Subj.	
	R(%)	P(%)	R(%)	P(%)	R(%)	P(%)	R(%)	P(%)	R(%)	P(%)	R(%)	P(%)	R(%)	P(%)	R(%)	P(%)
01	84.0	80.8	46.9	52.3	67.3	57.9	64.0	60.4	52.0	63.4	44.0	46.8	68.0	63.0	60.9	60.6
02	67.3	70.2	50.0	59.5	66.0	56.9	36.2	56.7	54.2	55.3	72.0	59.0	72.9	61.4	59.8	59.9
03	70.0	79.5	89.6	89.6	78.0	73.6	68.0	82.9	62.5	65.2	82.6	67.9	86.0	79.6	76.7	76.9
04	54.0	52.9	56.0	54.9	51.1	47.1	55.1	57.4	46.0	46.0	66.0	66.0	51.0	55.6	54.2	54.3
05	64.0	76.2	57.1	62.2	80.0	69.0	66.0	63.5	51.0	55.6	70.8	65.4	44.0	42.3	61.9	62.0
06	74.0	54.4	80.0	75.5	60.0	75.0	45.8	91.7	46.0	53.5	61.7	64.4	70.0	63.6	62.5	68.3
Avg.	68.9	69.0	63.3	65.7	67.1	63.2	55.8	68.8	51.9	56.5	66.2	61.6	65.3	60.9	62.6	63.7

Table 3.1: Tasks classification results. The Recall (R) and Precision (P) results are presented for each subject and task. The last row shows the average results across subjects. The last column shows the average results across joints moved.

The confusion matrix obtained by adding up all single-subject confusion matrices is presented in Fig. 3.6. The performance of the tasks classifier is represented by the increase of darkness in bins on the main diagonal. According to this figure, the tasks involving the elbow joint were the ones that returned the worst classification results (see matrix columns "True EE" and "True EP" in Fig. 3.6).

3.4.2 Results of validation experiment 1: Estimation of the significance of the obtained class description

Fig. 3.7 compares between the accuracy results obtained for each subject using the correctly labelled trials (Section 3.4.1) and the randomized ones (chance level). The average chance level of the accuracy is 30.2 ± 4.3 %. The results obtained with the correctly labelled examples are higher than the results with the classifier of randomly labelled trials for all participants.

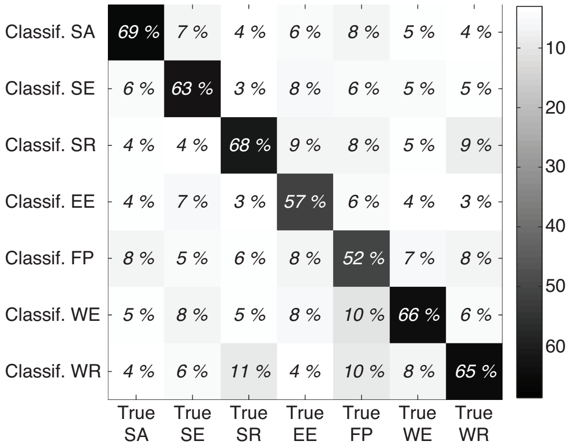


Figure 3.6: Confusion matrix of the tasks' classification results. Each column of the matrix shows the distribution of the classifications of all the examples of each analytical movement. A linear grey scale is used to represent the number of cases in each bin (also indicated numerically).

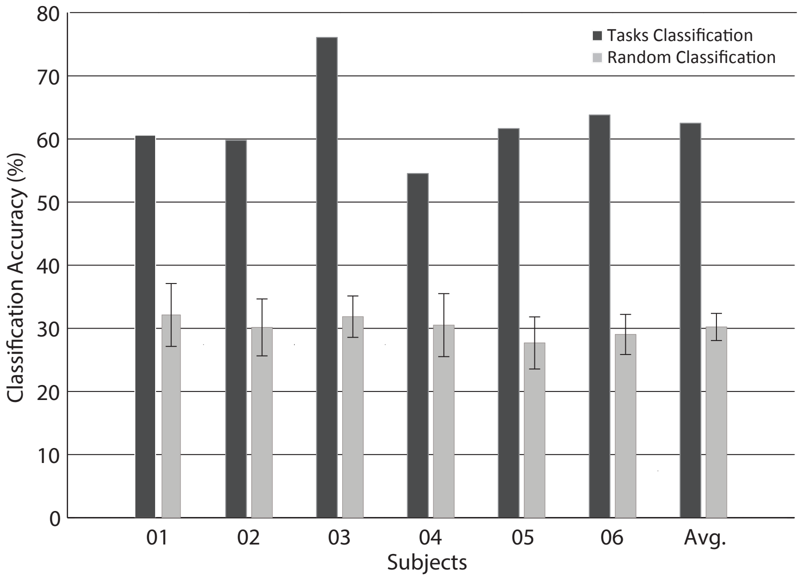


Figure 3.7: Comparison between the tasks' classification results and the classification results with the randomly generated dataset of examples. Standard deviation is included in the second case as these are average results from 10 different random datasets.

3.4.3 Results of validation experiment 2: Analysis of the influence of the time segments location

Fig. 3.8 shows three box-plots with the average accuracy results obtained with the classifier of tasks under three different conditions in terms of time segments locations for the feature extraction. The segment starting -1.5 s before the onset of the movement and finishing

0.5 s after it returned the best classification results for all subjects (65.3 ± 7.4 %), and the segment starting at -3 s with respect to the onset of the movements and finishing at -1 s returned worse accuracies than the other two conditions (60.7 ± 7.8 %). Notably, the same positive trend was also observed for each participant separately.

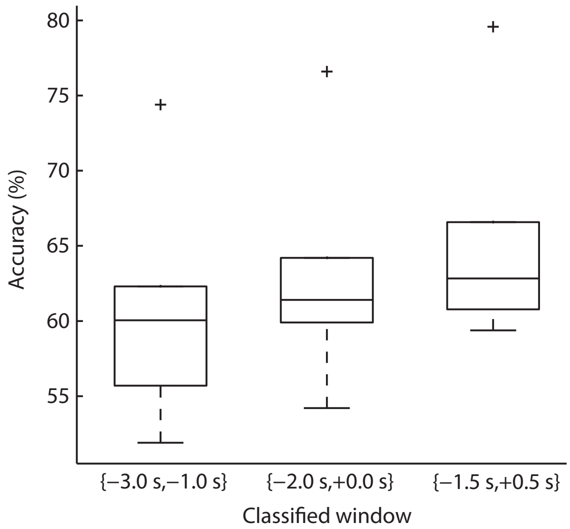


Figure 3.8: Average classification accuracy obtained using three different time intervals to extract the features.

3.4.4 Results of validation experiment 3: Extraction of other tentative sources of information

On average, 78.3 ± 11.0 features were selected by the classifier of initial positions, from which 18.7 ± 3.4 % were shared by this classifier and the classifier of analytic movements.

3.5 Discussion

This chapter described and validated an experimental methodology to identify the type of unilateral and self-initiated upper-limb analytical movements based on the EEG information extracted from the initial stages of their executions. The decoding system achieved an average classification accuracy (62.9 ± 7.5 %) significantly above the chance level for the proposed methodology (30.2 ± 4.3 %), thus providing evidence that movement-related neural information associated to different tasks performed with a single limb can be extracted from the premovement EEG activity. It is expected that this information will be valuable in neurorehabilitation environments.

Classification problems of tasks with close spatial representations in the cortical areas (as the movements of a single arm) and based on the EEG activity are challenging, due to its low spatial resolution. To our knowledge, no previous studies have tried to decode more than two different analytical movements with a same limb. Therefore it becomes difficult to compare the methodology used here with similar works. A set of studies in the past have used the EEG to decode two kinds of analytical movements performed with a same limb [Deng et al., 2005; Zhou et al., 2005; Zhou and Yedida, 2007]. In these works, positive results were obtained in the classification of torques performed with either the elbow or the shoulder using EEG data preceding the onsets of the movements. Two classes were thus distinguished and the obtained accuracies were higher than the ones presented in this document. This was expected given that in the case of the tasks' classifier, seven classes were to be distinguished. Besides, no further testing of the obtained results was accomplished in these previous studies, so direct comparisons cannot be performed with the present results. In a study by Hammon et al., results of classification of reaching movements to predefined targets were presented [Hammon et al., 2008]. In that case cued movements were performed and premovement EEG information was used to predict the planned target. Classification rates above chance level were obtained in the four-targets classification problem, therefore suggesting a potential presence of relevant movement planning information in the EEG activity.

The additional experiments performed with the acquired data in this study are useful to assert that the cortical activity is the main information responsible for the classifier performance, and no other non-cortical signal sources are biasing the results. In this regard, four factors that could have biased the classification results may be considered, given the design of the experiments and the characteristics of the EEG signal described in the literature.

Firstly, as described in the Methods section, three different initial positions were adopted to start the movements in the experimental sessions. These three initial positions differed only in the arm position that was used to perform the movements, and they could have altered the EEG signal properties due to differences in the muscles' resting activity. In order to reject the hypothesis that the initial arm position biases the tasks classification results, two arguments are used. On one hand, the data of the confusion matrix (Fig. 3.6) shows that tasks starting from same positions (SA and SE; EE, FP and WE; SR and WR) are distinguished from each other with accuracies similar to the ones obtained with the rest of the tasks. This suggests that the information used to classify tasks is independent of the initial positions in these specific cases. In order to reinforce this argument, it was also run a new feature selection and classification process in which the trials were labelled according to the initial positions adopted for each task tasks (Section 3.3.4.3). The percentage of selected features that were shared by the classifiers of tasks and initial positions was less than 20 %. This suggests that a large portion of different information is used by the classifiers. Notice that although this could also be due to the fact that similar but not equal features are being selected, the feature space reduction performed before the feature selection process discarded features with high correlations. Therefore it is hypothesized that the first alternative (the classifiers of tasks and initial positions are different) is more likely.

Secondly, the EEG signal cannot be considered stationary along long measurement intervals due to the changes in the system's set-up (as for example changes in the electrodes impedances due to deterioration of the conductive gel) [Shenoy et al., 2006] or to fluctuations in the patients' vigilance or involvement [Blankertz, 2008]. Therefore, variations in the features extracted from the EEG signal during the measurement sessions are expected. Nevertheless, in these experiments it is unlikely that this phenomenon is introducing any bias in the classification results, since the experimental design alternated the types of movements performed in consecutive runs (the two runs of the same movement were separated by one run of each of the rest of the movements). In addition, a 4-fold cross-validation was used, which separated the data in 4 randomly generated testing groups. It is therefore expected that, in general terms, training and validation subsets were randomly collected from session intervals all along the whole experiment, and the effects of the EEG non-stationarities were marginal.

Thirdly, it cannot be asserted that the developed classifier of tasks is using cortical activity directly involved in the motor actions. However, it can be analysed whether certain characteristics of the classifier's design and of its behavior fit what may be expected from a neurophysiological point of view. On the one hand, a higher number of features were selected from EEG channels around the contralateral rolandic fissure (i.e. from the motor and somatosensory areas of the cortex) in four out of the six subjects. This was specially observed with participants 03 and 06, who also returned the best classification results, whereas with participant 04 the classification results were poorer and the selected featuers presented a different distribution over the scalp. This is in line with previous studies regarding the spatial distribution of the cortical rhythms associated with voluntary motor activities [Bai et al., 2005; Desmurget et al., 2009; Pfurtscheller and da Silva, 1999; Pfurtscheller et al., 2003; Urbano et al., 1996]. In addition to this, the number of features in the upper-beta bands was higher than in other bands, which is in line with studies showing that these rhythms are involved in the preparation of voluntary movements [Salmelin et al., 1995; Morash et al., 2008; Engel and Fries, 2010]. Besides, given that they present higher frequencies than the mu rhythm, they are associated with smaller neural associations [Buzsáki and Draguhn, 2004], therefore allowing for a finer description of the cortical representation associated with the performed task. This is in turn desired in the present study of classifying among tasks with similar cortical representations. Moreover, a temporal dependency of the classification results on the location of the time segments for feature extraction was observed (see Section 3.4.3). The segment starting -1.5 s before the onset of the movement returned the best classification results for all subjects and the segment starting at -3 s with respect to the onset returned worse accuracies than the other two conditions. This is in line with what is documented about EEG activity associated to voluntary actions: the first changes in the signal start around 2 s before the movement becomes apparent and the significance of these changes is greatest with the beginning of the movement [Pfurtscheller and da Silva, 1999; Bai et al., 2005; Pfurtscheller et al., 2003].

Finally, it may be argued that the dataset of examples is so small (50 trials per class in the case of classifying analytic movements) that suboptimal solutions are obtained with the genetic algorithm, and that these solutions only adapt the measured examples of the dataset, but would fail generalizing to new unseen data (i.e. overfitting). Nevertheless, given that a Bayesian Classifier has been used in combination with a cross-validation methodology, suboptimal classification solutions are highly unlikely. Furthermore, the results obtained with the original dataset outperform the classification results with the randomly labelled dataset.

In summary, the posterior analysis of the methods used and results obtained here demonstrates that the motor-related cortical activity associated to the execution of voluntary movements performed with a single limb can be characterized to a certain degree. Nevertheless, since these results have been obtained with an offline analysis of the data acquired in a single session with each participant, it still needs to be studied whether the performance of the developed classifiers remain stable along different sessions. Furthermore, variations of the classifier's performance were observed when features were extracted from time segments at different locations with respect to the actual movements. Higher accuracies were obtained when the initial part of the apparent movements (the first 500 ms) were considered, probably suggesting either an influence of the somatosensory information in the classification results, or an increased activation of the primary motor cortex and other cortical areas related to movement execution, once the movement starts. Future experiments also including motor imagery tasks of the analytical movements may help to gain knowledge in this regard.

Finally, a system capable of decoding the cortical activity related to the kind of upper-limb movements can be of interest for neural rehabilitation protocols [Daly and Wolpaw, 2008]. The system proposed could serve as a monitoring tool of the patient's involvement in the rehabilitation task or it could also be included as an additional input to a controller of assistive robotic devices. Therefore, analogous studies need also to be performed with patients presenting altered cortical activity due to lesions in the nervous systems [Wiese et al., 2004; Stepien et al., 2010; Serrien et al., 2004], to test the reliability of the classifier in such conditions.

3.6 Chapter conclusions

It has been proposed a classifier of self-paced analytical movements performed with the upper-limb and based on premovement EEG information. An average accuracy of 62.9 $\pm$ 7.5 % has been reached in the classification of the seven analytical movements performed with the dominant arm, which was above the chance level (30.2 $\pm$ 4.3 %). Several tests have been performed to discard the hypothesis that the information used by the classifiers could come from different sources than the cortical activity.

This chapter has described an innovative experimental procedure regarding the decoding of mental states related to 7 different movement actions performed with a single limb. It is therefore a step forward in the use of EEG signals to model cortical patterns related to planning and execution of movements and it is expected to improve future BCI systems aimed to respond in close association with users' intentions to move.

Chapter 4

Study of alprazolam-induced changes in cortical oscillations and tremors of patients with ET

4.1 Abstract

In the first chapters of this thesis it was emphasised the potential capacity of EEG systems to acquire, with high temporal resolution, cortical processes associated with sensorimotor states, and it was also indicated that current electrophysiological systems (such as EEG and EMG devices) allow the concurrent measurement of neuronal information from different body regions and with negligible synchronization errors. These advances open a door to studies of interaction between central (cortical) and peripheral (muscular) neural activity. While in Chapter 3 the distribution of cortical rhythms associated to the execution of different voluntary movements was characterized , in this chapter it is presented a study of the effects of a clinically used drug (alprazolam) on pathological (involuntary) tremors and cortical oscillations of patients with ET. The study analyses tremor changes after alprazolam intake and how they are related to other changes in the cortical activity. This chapter is therefore aimed to provide new insights about the mechanisms of tremor generation in ET and to propose a novel application of EEG systems to analyze the effects induced by a drug in patients with tremor.

4.2 Introduction

ET is a neurological disease characterized by postural and action tremor of the arms with a frequency of 4-12 Hz [Benito-León and Louis, 2006]. Although it is the most prevalent movement disorder [Louis et al., 1998; Thanvi et al., 2006; Benito-León et al., 2003], and constitutes one of the most common neurological disorders among adults [Benito-León et al., 2003, 2005], the exact mechanisms of tremor generation in ET are still unknown [Elble and Deuschl, 2009; Louis et al., 2013].

A number of studies using different brain imaging techniques point to a neuronal loop involving cerebello-thalamocortical pathways as the structures involved in the generation of the pathological tremor-related neural activity [Benito-León et al., 2009; Hua et al., 1998; Hellwig et al., 2001; Raethjen et al., 2007; Raethjen and Deuschl, 2012; Schnitzler et al., 2009]. In particular, studies of coherence between the cortical activity, measured with electroencephalography (EEG), and muscle activation, measured with electromyography (EMG), have demonstrated the implication of cortical structures in the pathological neural network [Hellwig et al., 2001], and have even allowed to postulate how such interaction may change over time [Raethjen et al., 2007].

ET is commonly treated either with neurosurgery or with drugs. However 50 % of the ET population does not benefit from any of the available alternatives [Deuschl et al., 2011]. All the pharmacological treatments for ET were discovered by chance [Deuschl et al., 2011] and are still limited and only partly effective [Benito-León and Louis, 2006, 2011]. The action mechanisms of these drugs are barely understood, although it is assumed that they attenuate tremor by interfering with the widespread pathological oscillations occurring throughout the motor system [Deuschl et al., 2011]. Among the pharmacological alternatives to treat ET, alprazolam is a short-acting benzodiazepine accepted by the Quality Standards Subcommittee of the American Academy of Neurology as a probably efficacious (level B) agent [Zesiewicz et al., 2011]. Two studies using clinical rating scales found that alprazolam reduced the limb tremor in a 2-4 week monotherapy trial [Gunal et al., 2000; Huber and Paulson, 1988]. Nevertheless, its use is recommended in patients who require only intermittent therapy, due to its abuse potential, and to the risks of developing tolerance [Huber and Paulson, 1988]. As in the case of other pharmacological treatments for ET, the way in which alprazolam alleviates tremor is unknown.

Previous studies with healthy subjects have observed an increased activity in the cortical beta rhythms (around 13-30 Hz) after benzodiazepine intake [Baker and Baker, 2002; Hall et al., 2010; Jensen et al., 2005; Lindhardt et al., 2001]. It is known that benzodiazepines increase the affinity of the λ–aminobutyric acid (GABA)-A receptor toward its neurotransmitter, increasing the size of the inhibitory postsynaptic potentials that it generates [Connors et al., 1988]. However, it is not intuitive how enhancing inhibition increases the power of the beta and gamma rhythms, and why such increase is observed in the somatosensory cortex [Minc et al., 2010; Hall et al., 2010]. In this regard, it has been proposed that mutual inhibition between interneurons, and the reciprocal loop between excitatory and inhibitory cells provide two general mechanisms for rhythmogenesis, especially for fast cortical oscillations [Wang, 2010].

Whether the expected changes in the cortical beta activity of ET patients after alprazolam intake are part of the neural process that alleviates tremor or they rather represent a side effect in the ET treatment with alprazolam is an open question. Since voluntary motor commands are projected to the targeted motor unit populations at the beta band [Conway et al., 1995; Kilner et al., 2000; Petersen et al., 2012], it is hypothesized that the increase in the cortical beta activity due to benzodiazepines alters the transmission of descending motor commands. It is further expected that such an increase of oscillatory beta activity in turn impedes the appearance of pathological tremor-related cortical activity. Therefore, this study analyses the interplay between the cortical activity in the beta band and in the tremor frequency after alprazolam intake, and how this interaction is associated with the drug effects on the tremor and the cortico-muscular coupling at the tremor frequency.

4.3 Methods

4.3.1 Patients, data acquisition and experimental procedure

Eight patients (two female, age 64.1 $\pm$ 13.2 years; mean $\pm$ SD) were included from a general neurology outpatient clinic (details in Table 4.1). All of them had been diagnosed as ET according to the Movement Disorders Society Diagnostic Criteria [Deuschl et al., 1998]. Patients with severe tremor at the hands or the head were excluded from the study to avoid interferences with the recordings. None of the patients had any other neurological condition apart from ET, or suffered from psychiatric disorders. None of them was taking medication to treat their tremor, or any other drugs that could alter it.

Wrist tremor at the most affected side was measured with solid-state gyroscopes and surface EMG. Two gyroscopes, placed on the hand dorsum and the distal third of the forearm, measured wrist tremor by computing the difference between them [Gallego et al., 2010]. The data were sampled at 50 Hz.

Surface EMG was recorded using a grid of 13 X 5 electrodes (1 missing electrode),

Patient	01	02	03	04	05	06	07	08	09
Gender	Male	Female	Male	Female	Male	Male	Male	Male	Male
Age (years)	76	80	44	63	45	65	77	69	58
ET family history	Y	Y	Y	Y	Y	Y	Y	N	N
Disease duration (y)	5	32	15	7	4	10	2	3	4
Dominant side of tremor	L	R	R	L	R	L	L	L	R
EMG tremor freq. (Hz)	6.2	5.2	7.0	6.2	-	6.2	7.0	6.2	8.2
Leg tremor	N	Y	N	Y	N	N	N	N	N
Head tremor	N	N	N	Y	Y	Y	N	N	N
ETRS	45	32	17	38	18	15	14	16	22

Table 4.1: Main baseline demographic and clinical variables. Fahn, Tolosa, Marin Essential Tremor Rating Scale (ETRS).

with 8 mm inter-electrode distance. The electrode grid was placed on the wrist extensors, centred on the muscle exhibiting the clearest tremorogenic activity; the common reference was set to the wrist using a humidified bracelet. The data were amplified, band-pass filtered (10-750 Hz), and sampled at 2.048 Hz.

EEG signals were recorded from 16 positions (F2, F4, FCz, FC2, FC4, FC6, Cz, C2, C4, C6, T8, CP2, CP4, CP6, Pz, and P4, according to the International 10-20 system, when the left arm was recorded; the symmetric positions were employed when the right arm was recorded) using passive Au electrodes. The cortical activity at the contralateral hemisphere was recorded because it is where significant cortico-muscular coherence at the tremor frequency [Hellwig et al., 2001, 2003; Raethjen et al., 2007; Timmermann et al., 2002], and the beta band [Conway et al., 1995; Negro and Farina, 2011], is best observed. The reference was set to the common voltage of the two earlobes. AFz was used as ground. The signal was amplified, band-pass (0.5-60 Hz) and notch filtered (50 Hz), and sampled at 256 Hz.

The recording systems were synchronized with a common digital signal.

The study was performed in a sound and light-attenuated room. Patients sat in a comfortable chair with the arms supported. During the measurements, they were asked to remain relaxed, keeping their eyes open and fixing their gaze on a point in the wall. Patients were instructed not to eat or drink anything (water was allowed) from 2 h before the recordings. In order to evaluate the effects of alprazolam, patients were measured during four 4-min runs, as follows: before the administration of alprazolam (Run0), immediately after it (Run1), 40 min after it (Run2), and 80 min after it (Run3). Postural tremor was elicited by asking patients to hold the measured hand outstretched, with palms down, and parallel to the ground. In patients who exhibited a very mild tremor before the experiments (patients 02 and 04), weight loads of 0.5 Kg were attached to the hand to enhance it [Hellwig et al., 2001; Raethjen et al., 2007].

A single dose of 0.50 mg of alprazolam was administered to patients who weighed less than 75 kg; the rest (5 patients) received a single dose of 0.75 mg. No patient reported adverse effects. Two patients were discarded due to technical problems with EEG acquisition (patient 03) and to the absence of tremor during the measurement session (patient 05), respectively.

4.3.2 Data processing and analysis

The EEG signals were spatially filtered using Hjorth transform [Hjorth, 1975]. The resultant channels (FC2, FC4, C2, C4, C6, CP2 and CP4) were used in the subsequent analyses. Artefacts were removed based on visual inspection.

After examination of the amplitude spectra of the gyroscope and EMG data, the defined tremor frequency range for the group of patients was 4-9 Hz (see Fig. 4.1). This range was used to estimate both the tremor power (measured with gyroscopes and EMG), and the power of the tremor-related cortical activity.

To select the surface EMG channel that best characterized the tremor, the criterion of maximizing the signal-to-noise ratio (SNR) of the tremor component of the EMG signal was used.

To select the surface EMG channel that best characterized the tremor, the criterion of maximizing the signal-to-noise ratio (SNR) of the tremor component of the EMG signal was used. This value was defined as the ratio of the integral of the power spectral density (PSD) within the tremor frequency range, to the integral of the PSD of the rest of the signal, similarly to [Hellwig et al., 2001]. This channel was used throughout the whole analysis.

The percentage of tremor reduction between the first and last runs (Run0 and Run3) was computed by analyzing the gyroscope data. Tremor severity was defined as the integral of the PSD of the signal in the tremor frequency range. Before, the data were band-pass filtered (2-15 Hz) to extract the tremor [Gallego et al., 2010]. It was also calculated how the neural drive to the muscles related to tremor was reduced after alprazolam intake by computing, with the EMG data, the percentage of tremor power decrease in Run1, Run2 and Run3 with respect to Run0.

Cortico-muscular coherence was computed to assess how the tremor-related cortical drive to the muscle varied due to the effect of alprazolam. The coherence between all the processed EEG channels and the rectified EMG at the electrode previously selected was calculated [Farina et al., 2013], and the EEG channel exhibiting the largest coherence peak at the tremor frequency was chosen for subsequent calculations. It was used the method for coherence estimation proposed in [Halliday et al., 1995]: the signals were divided into epochs of 1 s, and their individual spectra and cross-spectra were computed (Hanning window of 1 s and 0.125 Hz resolution, achieved with zero-padding). The coherence $|R_{xy}(\lambda)|^2$ was estimated as

$$|R_{xy}(\lambda)|^2 = \frac{|C_{xy}(\lambda)|^2}{C_{xx}(\lambda)C_{yy}(\lambda)}$$

with $|C_{xy}(\lambda)|^2$ being the magnitude squared cross-spectrum, and $C_{xx}(\lambda)$ and $C_{yy}(\lambda)$ the individual power spectra [Halliday et al., 1995; Hellwig et al., 2001]. The confidence limit was obtained as:

$$1 - (1 - \frac{\alpha}{100})^{\frac{1}{N-1}}$$

where N is the number of epochs used to calculate the coherence and α is the significance level [Rosenberg et al., 1989].

To study how alprazolam affected the tremor-related cortical activity and the cortical activity in the beta band, the changes in the EEG spectra were assessed by calculating the integral of the PSD at the selected channel in the tremor frequency range (4-9 Hz, see above) and in the beta band (13-30 Hz).

4.3.3 Statistical analysis

The Wilcoxon rank sum test was used to compare the tremor severity measured by the gyroscopes before (Run0) and 75 min after the administration of alprazolam (Run3).

The Kruskal-Wallis test was used to compare the tremor-related neural drive to the muscle in Run3, Run2 and Run1 with respect to Run0. Significant differences between pairs of data were assessed with the Games-Howell test assuming non-equal variances. The same test was used to compare the changes of the power of the cortical activity in the beta band and in the tremor-frequency range, and to compare the changes of the ratio between the activity in these two bands; in all cases changes in Run3, Run2 and Run1 were obtained with respect to Run0.

Finally the Spearman's rank correlation was calculated between the decrease in tremor severity (in terms of neural drive to the muscle, i.e. EMG) and the changes of the ratio between the EEG activity in the beta band and in the tremor frequency range, using the data of Run3, Run2 and Run1 with respect to Run0, to investigate whether both phenomena were related.

Results are reported as mean ± SD, and considered significant if $P < 0.05$.

4.4 Results

The amplitude of the tremor measured with gyroscopes showed a significant ($P = 0.029$) reduction 75 min after the administration of alprazolam (mean 74.3 ± 30.2 %). The mean tremor amplitude during Run0 and Run3 was 0.31 ± 0.34 $rad^2 s^{-2}$ and 0.043 ± 0.049 $rad^2 s^{-2}$, respectively.

Fig. 4.1 illustrates the changes of the tremorogenic muscle activity along the different runs. There was a significant difference in the tremor power reductions observed in Run3, Run2 and Run1, all compared to Run0 ($P = 0.002$). Post hoc analysis showed that the decrease in the tremor power observed in Run3 (mean 75.0 ± 17.6 %) and in Run2 (mean 69.3 ± 17.9 %) were not statistically different from each other ($P = 0.82$), but both were significantly larger than that observed in Run1 (mean 4.6 ± 23.6 %), always with respect to Run0 ($P < 0.001$ and $P < 0.001$, respectively).

There were no significant differences ($P = 0.917$, Wilcoxon rank sum test) between the tremor frequency measured with gyroscopes (6.22 ± 0.53 Hz) and EMG (6.20 ± 0.56 Hz). The tremor frequency did not change during the recordings, although no statistics were extracted since the tremor was no clearly identifiable in some patients after alprazolam intake (see panel C in Fig. 4.1).

Fig. 4.2 shows the coherence between the EEG (channel providing the largest coherence at the tremor frequency) and the selected EMG channel. The coherence at the tremor frequency in Run0 was significant (P < 0.05) for all patients. In Run3, the coherence at the tremor frequency decreased in all cases and fell below the significance threshold in 5 out of 7 patients. In the case of patient 07, the significant coherence in Run3 was accompanied with the observed rebound of EMG tremor power in Run3 with respect to Run2 (see Fig. 4.1).

Fig. 4.3 shows the time course of the EEG power spectrum along the runs. There was a significant difference in the increase of the ratio between the beta and tremor-related cortical activities for Run3, Run2 and Run1, all with respect to Run0 ($P = 0.003$). Post hoc analysis showed no statistical difference between Run3 (mean 129.2 ± 96.7 %) and Run2 (mean 94.0 ± 48.5 %) data groups ($P = 0.68$), but both were significantly larger than that observed in Run1 (mean 9.81 ± 17.6 %) ($P = 0.039$ and $P = 0.007$, respectively).

As a graphical representation of the increase in beta power observed in one patient, Fig. 4.4 shows in a spectrogram the increased beta activity since 40 minutes after alprazolam intake for patient 7 in the analysed EEG channel.

Taken separately, the changes in the cortical beta activity and in the cortical activity within the tremor frequency range, the results were similar. The beta power increases in Run1, Run2 and Run3 with respect to Run0 (5.7 ± 3.6 %, 54.4 ± 26.8 % and 64.8 ±

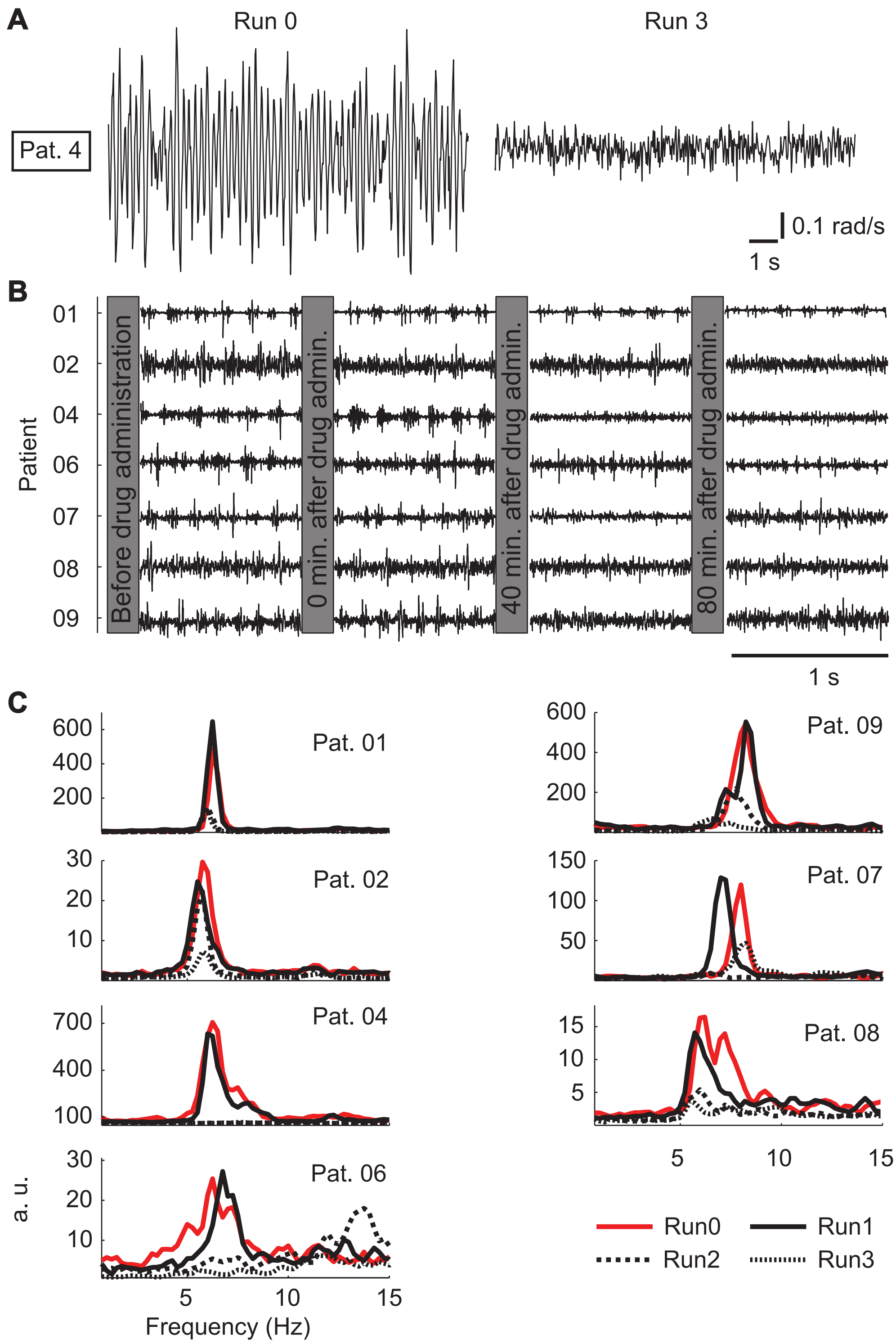


Figure 4.1: Changes in tremor along the recording runs. (A) Example of tremor reduction between Run 0 and Run3 according to gyroscopic data. (B) Time course of the raw EMG (same amplitude scale for all subjects); (C) PSD of the EMG signals (one panel per patient).

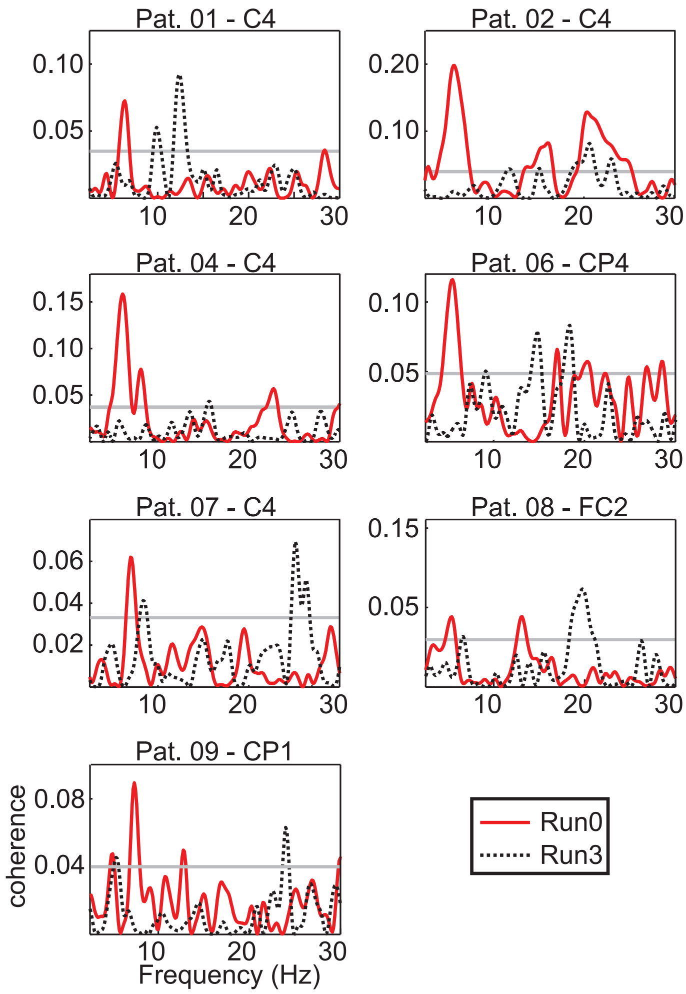


Figure 4.2: Cortico-muscular coherence. Obtained from Run0 and Run3 (Run2 is also included for patient 07 only). Each panel represents a different patient. The significance level (P < 0.05) is also displayed (solid gray line).

29.2 % respectively) were significantly different ($P = 0.002$). Post-hoc analysis showed that statistical significance was observed only in the comparison between Run1 and Run2 ($P = 0.007$), and between Run1 and Run3 ($P = 0.004$), while between Run2 and Run3 no significant differences were found ($P = 0.77$). The decreases of the cortical activity in the tremor frequency range in Run1 (1.7 ± 15.4 %), Run2 (18.1 ± 16.2 %) and Run3 (23.1 ± 16.1 %) with respect to Run0 were significantly different ($P = 0.035$). In this case, post hoc analysis did not show significant differences between groups. A graphical representation of these results is shown in Fig. 4.5, where it is shown that the decrease in the cortical activity within the tremor frequency range and the increase of the cortical beta activity increase along the time and are positive 75 min after alprazolam intake for

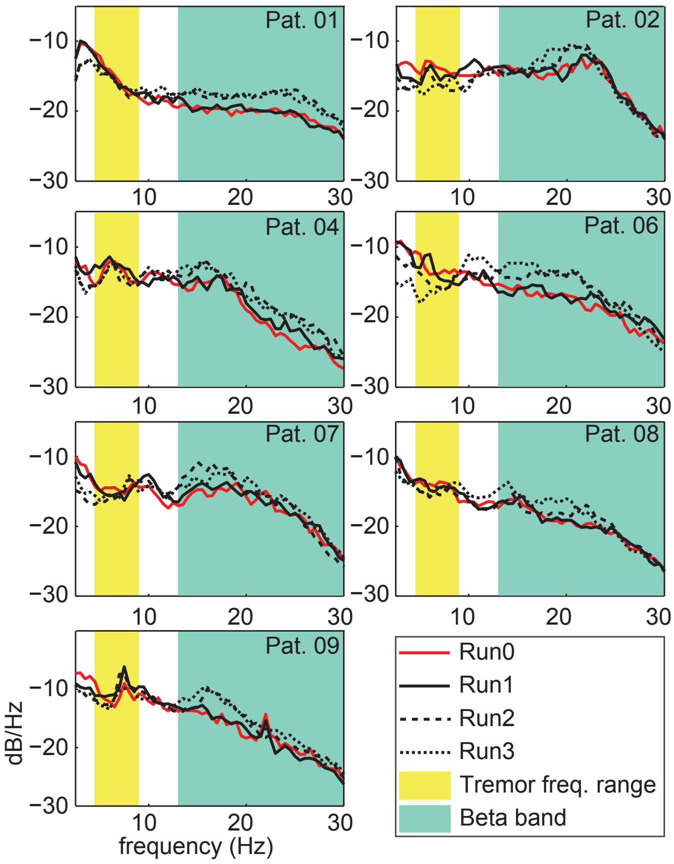


Figure 4.3: PSDs of the EEG data in the optimal channel for each patient. The shaded areas represent the tremor frequency range (yellow) and the beta band (green), as used to evaluate changes in the cortical activity. Each panel represents a different patient.

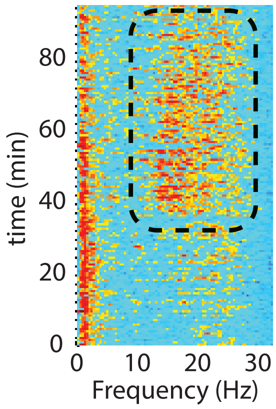
all patients.

There was a significant correlation (r = 0.757, $P < 0.001$) between the tremor power decrease (as measured with EMG) and the increase of the ratio between the beta and tremor-related activity in the cortical areas contralateral to the measured hand (in the EEG channel where significant cortico-muscular coupling was best observed, see Fig. 4.6). This relation also held when analysing the results of the patients separately, *i.e.* all of the patients presented a positive relationship between both variables, as shown in Fig. 4.6.

4.5 Discussion

This study characterizes the dynamics of the tremor and the cortical activity in ET patients after alprazolam intake. Significant changes in the measured tremor as well as in the cortical activity both in the beta band and in the tremor frequency range due to the

Figure 4.4: Spectrogram along the whole recording session with patient 7. The area of increased beta activity is emphasized with a discontinuous black line.



effects of the drug were found. These changes led to a significant correlation between the reduction of the tremor and the relative change in the cortical activity in the beta and tremor-related bands.

This study also provides the first quantitative evidence of tremor changes after a single dose intake of alprazolam. Two previous studies showed a significant improvement in tremor rating scales after treating ET patients with alprazolam. They reported a 30 % reduction in a double-blind placebo-controlled trial [Huber and Paulson, 1988], and a 25 % decrease in tremor intensity rated by functional scores and a 46 % improvement in the global improvement scale by self-evaluation of the patients [Gunal et al., 2000] respectively. Here these results are confirmed quantitatively, by showing a significant tremor reduction of 69.4 % and 75.8 % according to the EMG data (i.e. the neural input to the muscle related to tremor) acquired 40 and 80 min after a single dose intake of alprazolam. The timing of the observed effects is also in line with the time peak of concentration of alprazolam

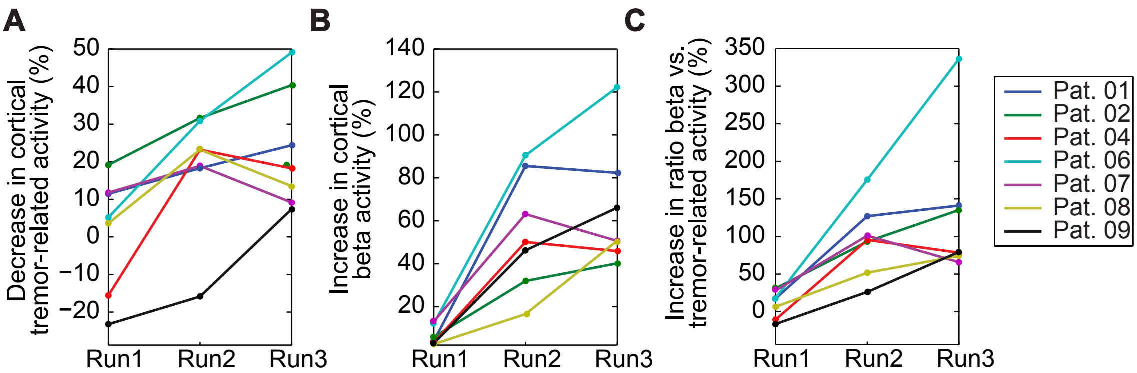


Figure 4.5: Changes (in %) of the cortical beta and tremor related activities in Run1, Run2, and Run3 with respect to Run0. (A) Decrease of the power of the cortical activity within the tremor frequency range. (B) Increase of the power in the beta band. (C) Increase of the ratio between the power in the beta band and in the tremor frequency range.

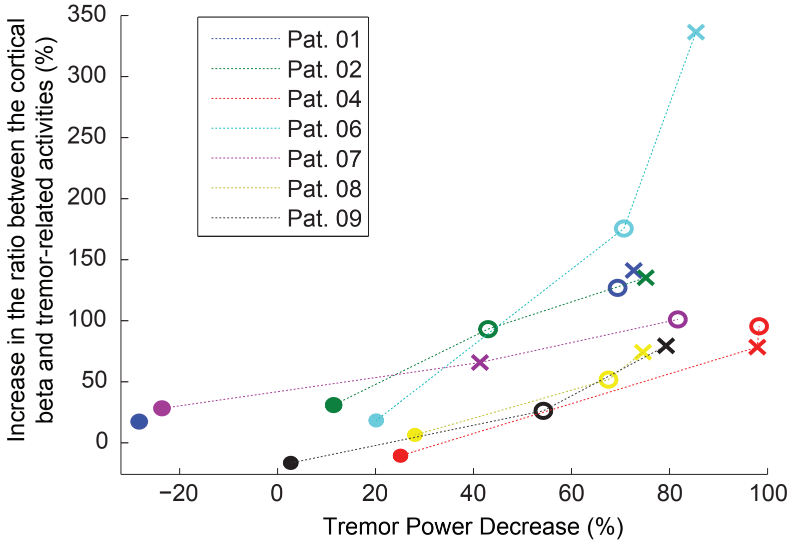


Figure 4.6: Relationship between changes in tremor power and the ratio between the beta and the tremor-related cortical activities for all patients and runs. Run1, Run2 and Run3 (all with respect to Run0) are represented with the symbols •, ∘ and × respectively.

reported for healthy elderly subjects (48 ± 18 min) [Kaplan et al., 1998]. The use of lower, single doses of alprazolam here was aimed to avoid drowsiness that could induce EEG changes consistent with sedation and not related to any supposed anti-tremorogenic effect. In fact, the observed increase of EEG activity in the beta band argues against a sedative effect of alprazolam, since the beta activity is considered as an index of cortical arousal [Niedermeyer, 2005].

The changes in the strength of cortico-muscular coupling due to the effect of alprazolam were assessed. As expected [Hellwig et al., 2001, 2003; Muthuraman et al., 2012; Raethjen et al., 2007], before intake, the coherence values at the tremor frequency were significant in all patients. The coherence decreased 75 min after alprazolam intake and it was below the significance threshold in all patients except for patients 07 and 08. Interestingly, patient 07 also presented a rebound of the tremor severity in Run3 compared to Run2 (according to the EMG data) and highest levels of the cortical beta activity 35 min after the drug administration. This pointed to an earlier beginning and termination of the effects of alprazolam in this patient. Additionally, it was observed a decrease in the power of the cortical activity in the tremor frequency range in the EEG channel showing the largest coherence at the tremor frequency. Taken together, these results suggest a decreased pathological oscillatory activity at the cortex when the drug starts to take effect. Regarding the coherence in the beta band, no consistent results were observed in the beginning of the session or during the subsequent runs. Unlike in other studies presenting robust coherence at the beta band, here the patients performed very mild contractions to hold their hands extended, which explains the lack of meaningful results in this regard [Baker and Baker, 2012; Chakarov et al., 2009].

It was observed that, during a period after alprazolam intake, there was a significant increase in cortical beta activity in all ET patients, similarly to what was previously reported in studies addressing the effects of other benzodiazepines in healthy subjects [Baker and Baker, 2002; Jensen et al., 2005]. Interestingly, the power of the EEG activity at the beta band is also enhanced in alcoholics [Rangaswamy et al., 2002] or after a small single dose of alcohol [Ilan and Gevins, 2001], and in 50-90 % of ET patients alcohol acts by reducing tremor amplitude [Growdon et al., 1975; Zesiewicz et al., 2011]. While the precise mode of action of ethanol in ET has not been established [Boecker et al., 1996], its principal effect is likely produced via the potentiation of GABA-A receptors [Wallner et al., 2003]. Although the effect of these substances increasing the beta power measured with EEG could not be related to its antitremorogenic effects, a significant relationship between the increase of the ratio between the beta and tremor-related cortical activity and the reduction of the contralateral postural tremor has been observed. Indeed, this dependency was seen for each patient individually (see Fig. 4.5). It is acknowledged that this finding could be an epiphenomenon or the consequence, albeit not necessarily direct, of the biochemical effect of alprazolam upon the brain. Nevertheless, considering that during maintained motor contraction the cortical motor areas and the muscles are synchronized in beta-range [Baker, 2007; Brown, 2000; Conway et al., 1995; Halliday et al., 1998; Kilner et al., 2000], it is hypothesized that the increased physiological beta activity at the primary motor cortex may be partially interfering the coupling of pathological oscillatory networks involved in the generation of tremor in ET.

The main structures in the central nervous system believed to be involved in the generation of the tremor in ET [Boecker et al., 1996; Jenkins et al., 1993; Park et al., 2010; Wilms et al., 1999] are controlled by GABAergic connections. Due to this reason, it is noted that the GABAergic effect of alprazolam would be not only limited to the sensorimotor cortex, but could be spread through other subcortical structures. Indeed, localized microinjections of the GABA-A agonist muscimol into the ventral intermediate nucleus (in areas where tremor-synchronous cells were identified electrophysiologically) of ET patients undergoing stereotaxy, were effective in reducing tremor [Pahapill et al., 1999].

This study presents some limitations, but their impact on the conclusions is expected to be minor. Firstly, a small group of patients was recruited for the experiments, and thus the obtained results might not be generalized to population dwelling ET cases. However, the homogeneity of the results obtained in all the patients (see Fig. 4.6), reinforce the hypothesis proposed in this study. Second, no placebo group was measured. However, the obtained data does not indicate that any of the patients experimented placebo effects, given that the observed reduction of tremor severity 4 min after alprazolam intake was negligible compared to subsequent runs (see Fig. 4.1). It is considered that the results were not influenced by expectancy bias since patients had never been previously treated with alprazolam, and did not know how and when the drug could improve the tremor.

4.6 Chapter conclusions

It has been shown that alprazolam attenuates tremor in ET at the same time that it increases the ratio between the beta and the tremor-related cortical activity, and decreases the strength of cortico-muscular coupling at the tremor frequency. It is hypothesized that the increase in the cortical beta activity due to the effects of alprazolam acts as a blocking mechanism of the pathological neural networks, which in turn helps reducing the tremor in ET.

This is the first study of the neurophysiological changes occurring in ET patients after the intake of a drug used to alleviate the tremor, and it is expected that further experiments with other drugs reducing the tremor in ET will help understanding the pathophysiology of this disease and its response to the different treatments. The study represents an example of possible clinical applications of EEG technology to characterize and/or monitorize the effects of certain pharmacological treatments in patients with neurological disorders affecting their motor capacity.

Chapter 5

Prediction of voluntary movements using the EEG signal and its application in BCI systems assisting patients with tremor

5.1 Abstract

It has been previously shown that cortical changes can be observed in the EEG activity when movement tasks are performed, and that these changes may appear up to 1.5-2 s before voluntary movements are initiated. Chapter 4 also showed that patients with tremor may present altered cortical activity at certain frequency bands as a result of the existing tremor. In this chapter, an EEG-based design predicting voluntary movements and integrated with other sources of information also related to the execution of motor tasks is presented. The ultimate goal is to build up a multimodal BCI system managing pathological tremors. In this multimodal interface, anticipated information regarding intended motor actions is extracted from the EEG signals and supplied to other subsystems (based on EMG and gyroscopic signals) to finely track and cancel the tremor superimposed on the voluntary movement. Results of two experiments are presented in the chapter. The first experiment is aimed to validate the EEG system anticipating voluntary movements with healthy subjects and patients with essential tremor, and to compare an adaptive and a fixed design of the system. The second experiment in the chapter is aimed to validate the idea of a multimodal interface integrating EEG data with other sources of movement information. In this second case, results are given for a group of patients and the main objective is to study the advantages of a multimodal system integrating EEG information with EMG and gyroscopic data. The proposed system represents the first approach to EEG-based systems anticipating voluntary movements under a fully asynchronous and continuously evaluated paradigm, and it also represents the first BCI application for patients with tremors and the

first time that EEG and EMG signals are fused to improve the performance of a system tracking motor tasks.

5.2 Introduction

Multimodal Human-Robot Interfaces (mHRI) for motor compensation take advantage of complementary sources of information to drive external devices. In such applications, a major goal is to provide the patient with a communication channel that behaves in a natural way. A natural human-robot interface controlling movement compensation devices aims at reducing the impact of the technology on the user, and to do so it must meet three objectives: 1) the system must reliably distinguish the user's intentions to move from the periods of non-intended activity (when the controlled device is in an idle state), 2) it must react with minimum latency with respect to the user's intentions to move, and 3) the assistive technology must rely on the biosignals that appear when the user performs an action in a normal way, *i.e.* the user does not need to learn artificial strategies to control the device. To achieve these goals, the multimodal interface needs to make use of as many movement-related sources of information as possible, with these sources reflecting complementary aspects regarding movement generation.

As it was presented in previous chapters, EEG activity acquired from regions around the central sulcus reflects cortical activity related to movement intentions and motor awareness [Desmurget et al., 2009]. Therefore, its integration with other noninvasive sensor modalities that track actual human movements, like EMG (analysing musle activation) and gyroscopic information (analysing rotations of body parts), makes it possible to characterise a voluntary movement during the planning and execution stages.

In this chapter it is presented an Online EEG-based Detector of the Intention to Move (ODIM) and its integration (with EMG and gyrosopic technology) in a mHRI aimed to cancel pathological tremors by means of electrical stimulation. In such integrated platform, the proposed ODIM distinguishes resting states from intervals preceding the execution of upper-limb movements, and therefore it is aimed to provide the EMG/gyroscopes-based systems with predictions of voluntary movements. Having anticipated information about intended actions, the pathological tremor can be characterized and tracked from right before intended actions begin, giving rise to a successful detection of the voluntary movement onset and to a precise tremor tracking and cancellation from the exact moment at which the movement begins. The proposed platform helps to meet the aforementioned requirements of a natural interface. First, given that EEG holds information on the patient's intentions to move, it enables the gyroscopes/EMG-based movement tracking systems to detect voluntary actions. Besides, providing the EMG and gyroscopic systems with predictive information on voluntary actions is useful to detect movement onsets with short delays (this can be complicated if tremor is present before the movements begin). Finally, the ODIM proposed here is based only on the EEG patterns present before a subject self-initiates a movement with the upper-limb. Therefore, learning artificial mental strategies to command the interface is not required. The integration of EEG technology in such a mHRI is hence justified. Nevertheless, the EEG-based system must demonstrate a proper function providing cortical information that allows anticipation of intended actions and being robust against false activations during long periods of non-activity. Additionally, the system must demonstrate its suitability for tremor patients, given that EEG movement-related patterns in the most typical tremor-related pathologies may be somewhat different to those observed in healthy subjects [Tamás et al., 2006; Lu et al., 2010; Magnani et al., 1998, 2002].

As it was described in Chapter 2, two EEG patterns are suitable for movement intention detection: the BP and the ERD. Although both cortical processes appear approximately 2 s before the onset of voluntary movements, to detect the intention to move using the BP presents an important drawback: the "early-BP" presents small amplitudes (2-3 μV) [Bai et al., 2011], which are barely detectable in a single-trial analysis. For that reason, the robust online single-trial detection of the BP relies on "late-BP" detection. This makes it difficult to anticipate the onset of the movements using this cortical pattern. ERD, on the other hand, overcomes this problem since the switch between the synchronised and the desynchronised states is faster and more pronounced [Bai et al., 2011; Morash et al., 2008]. Several previous works have dealt with the problem of detecting the intention to move [Niazi et al., 2011; Bai et al., 2011; Lew et al., 2012]. On the one hand, [Niazi et al., 2011] and [Lew et al., 2012] used the BP to locate the onsets of voluntary movements performed with the ankle and the arm, respectively. A high percentage of movements was detected, although no anticipation was achieved due to the aforementioned characteristics of the BP. On the other hand, Bai et al. [Bai et al., 2011] used subject-specific ERD-patterns to detect the intention to move in healthy subjects. High prediction periods (0.62$\pm$0.25 s) were obtained with an average precision of 75$\pm$10 %, but a small number of movements was detected with most subjects analyzed (less than 50 % of the movements were detected with the best subject). Importantly, most of these studies provide results of paradigms in which rest intervals preceding voluntary actions last on average $\tilde{5}$ s, thus reducing the chances of the systems to generate false detections.

ODIM uses the ERD pattern to anticipate movements and it is validated with an asynchronous paradigm (no external cues are used to indicate when to move) on 6 healthy subjects and 4 patients with ET, which consitutes the most common tremor-related neurological disease, typically implicating postural and action tremor of the arms [Louis et al., 1998; Benito-León and Louis, 2006]. Besides, the results of the integrated function of a mHRI taking advantage of the EEG information are provided in an additional experiment with 5 patients with ET.

5.3 Methods

5.3.1 Experimental protocols

5.3.1.1 Experiment 1

Six healthy subjects (one female), all right-handed and between 27 and 36 years old, and four ET patients, males, right-handed and between 75 and 85 years old were recruited. The patients and 2 control subjects were measured in a single session, while the rest of the control subjects participated in two measurement sessions performed over different days. Patients were diagnosed as ET according to the Movement Disorders Society Diagnostic Criteria [Deuschl et al., 1998]. They presented bilateral postural and action tremor of mild and moderate severity. Patients P01 and P02 presented also mild rest tremor. None of them had other neurological symptoms. The patients were asked not to take antitremorogenic drugs within the 24 hours before the experiments.

During the experiments, subjects were seated in a comfortable chair and with the arms supported. One measurement session of one subject was divided into 3-minute-long runs. In each run, the subject was asked to stay steady and to repeat a motor task consisting of focusing on the dominant hand and performing a single wrist extension followed by a return to the resting position (with the arm and hand relaxed on the armrest of the chair). The subjects were asked to stare at a fixation cross presented on a wall in front of them to avoid ocular artifacts. An acoustic signal sounded 10 s after each movement onset to indicate that a new trial was starting. The subjects were asked to wait more than 3 s between the acoustic signal and the execution of the movement. A valid trial contained an initial acoustic signal followed by a period of no motor activity (before the subjects decided to start the movement), an execution of the motor task and an additional 10 s time period without motor activity (see Fig. 5.1). All patients and two control subjects (C05 and C06) completed six to eight 3-minute runs in a single session. The rest of the measured subjects completed two sessions on two different days. For those participating in a single session, the runs performed during this session were divided into runs for training (first 2 runs) and for classification (remaining runs in the session). As for the rest of the control subjects, the first session was used as the training dataset and the whole second session was used for validation. On average, 35±19 trials were used to calibrate the ODIM and 56±11 trials were used to validate it. In each trial, 87.4±2.8 % of the time corresponded to intervals with the subjects presenting a resting state, and these resting periods of time between movements lasted more than 15 s. This is a relevant information in order to objectively validate the precision of the EEG system in asynchronous paradigms; the longer the idle states, the more likely it is that the system generates false activations.

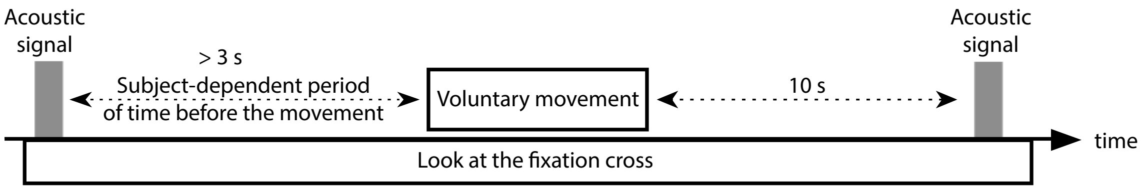


Figure 5.1: Graphical representation of one trial.

5.3.1.2 Experiment 2

This experiment was aimed to validate the combined function of the EEG and EMG and gyrscopic systems in the mHRI. Five essential tremor patients (2 female and 3 male) between 47 to 79 years old were recruited. All patients presented postural and kinetic tremor of mild or moderate severity. Medications were continued at the time of the recordings.

Similar conditions to the first experiment were given. Subjects were asked to perform a series of exercises that are commonly employed in the clinic to assess tremor: finger to finger and finger to nose tests, and elevating both arms and keeping them outstretched against gravity. Each patient performed 6 repetitions of each exercise. In this case, the trials were separately recorded. The execution of all the trials followed the same scheme: patients were asked to stay relaxed avoiding eye movements, and self-initiate the exercise after allowing for a sufficient repose time after the trial started. In this case, the resting intervals preceding the self-initiated movements were significantly shorter than in Experiment 1.

The system validation was performed offline using a leave-one-out procedure (to test the system on each trial, the rest of the trials were used to calibrate the ODIM). To evaluate the multimodal platform, only those classified trials with visible tremor were used to present the results of this experiment. On average, results of 10.0 $\pm$ 5.6 trials per patient are presented.

5.3.2 Data acquisition

EEG signals were recorded with passive Au electrodes from positions FC3, FCz, FC4, C5, C3, C1, Cz, C2, C4, C6, CP3, CPz and CP4 according to the extended international 10/20 system. Impedances were kept below 7 KOhm. The reference was set to the common potential of the two earlobes and Fz was used as ground. The amplifier filtered the signal between 0.1 and 60 Hz, and an additional 50 Hz notch filter was used. The sampling frequency was 256 Hz. Reference-free estimations of the EEG signals were obtained by spatially filtering the 13 channels acquired. A Laplacian filter was applied to the C3, C1, Cz, C2, and C4 positions [Hjorth, 1975], *i.e.* for each electrode position the average voltage of the four equally close neighbours was subtracted. For boundary channels, a common average reference was used (the average voltage of all channels was subtracted).

Wrist extension/flexion was monitored by means of two gyroscopic sensors placed on the hand and forearm. Wrist rotation was obtained by computing the difference between both gyroscopes [Gallego et al., 2010]. Both measuring systems were acquired in two different computers and they were synchronised by means of a pulse signal that was generated by the computer storing the gyroscopes data and sent through a DAQ to the EEG (two pulses at the start and the end of the recordings and one pulse each time the IMUs detected a wrist extension).

In addition to EEG and gyroscopic data, in Experiment 2 tremor was recorded from the most affected side (with which tasks were performed) using surface EMG. EMG signals were recorded over the wrist extensors and flexors with a 128-channel amplifier in differential configuration. A 64-channel array electrode was placed on the muscle belly, and a humidified wrist bracelet served as common reference. The signal was amplified, band-pass filtered (10-500 Hz), and sampled at 2048 Hz by a 12 bit A/D converter. Synchronization of the different systems was controlled by a digital clock signal. Only results from those trials with visible tremor are presented here.

5.3.3 Detection of the movement onset with the gyroscopes

In order to detect the time at which each movement started in the training data (the recorded data used to calibrate the EEG system), wrist movement in the resting condition was characterised at the beginning of each session, and the threshold amplitude was set as two times the maximum amplitude value in this interval. The data from the gyroscopes were low-pass filtered (Butterworth, order 2, ≤ 6 Hz). Movements incorrectly detected by the online gyroscopes-based algorithm were either corrected or discarded manually after the sessions, to ensure a rigorous evaluation of the ODIM.

5.3.4 Description of the ODIM architecture

The core of the ODIM consisted of a Bayesian Classifier (BC) fed by the logarithmic Power Spectral Density (PSD) values. Previous results presented in [Bai et al., 2007] showed that these techniques (the BC and PSD estimations) provide the best classification performances in similar experiments. The BC also presents the advantage of requiring low computational load during its online function and also during its training process.

During the function of the ODIM (see Fig. 5.2), the logarithmic power values of three selected channel/frequency pairs (see 5.3.4.1) were extracted from the EEG signal every 125 ms using 2-s windows.The power estimations were performed using Welch's method (Hamming windows, 128 samples, 75 % overlap). A single class Bayesian Classifier (BC) was fed with these values and the three output probabilities were combined to generate the final output probability. An optimized threshold (see 5.3.4.3) was then used to convert this probability into a binary signal, and a Refractory Period (RP) was applied in order to maintain each positive output interval of the ODIM active for at least 2.5 s, thus generating a stable output of movement predictions [Townsend et al., 2004].

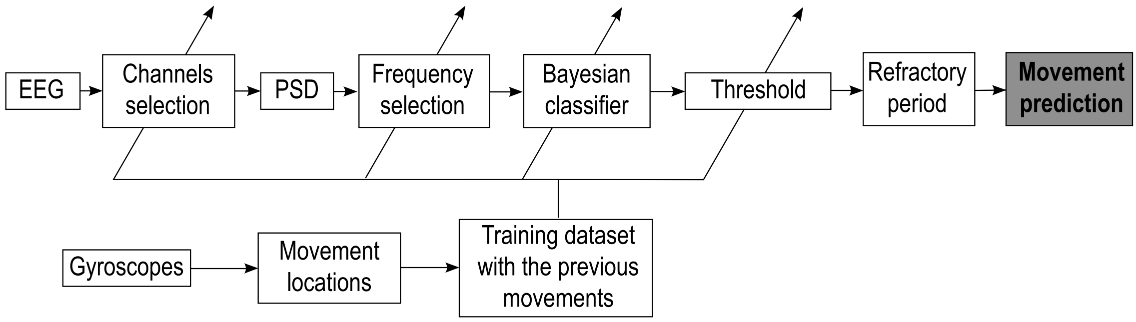


Figure 5.2: Flowchart of the ODIM. The arrows crossing the blocks represent the adaptive design of the parameters in these blocks.

5.3.4.1 Selection of subject-specific optimal channels and frequencies for the ERD characterization based on the training data

The process was aimed to search for the channel/frequency pairs with largest and most anticipative ERD. The process was divided in two steps. First, the system looked for the frequency at which the largest ERD was observed in each channel. This frequency was the one that maximized the ratio between the average frequency spectra of the basal and movement states. In previous tests with the training data of the control subjects, using this criterion provided better results in the selection of optimal frequency components than the Bhattacharyya index, the two-sample t-test and the Kullback-Leibler distance. The frequency spectrum of the movement state was characterised by averaging the PSDs of all the movement intervals included in the training dataset. The movement intervals were taken from 2 s before the onsets of the movements (when the average ERD is expected to begin in most subjects [Pfurtscheller and da Silva, 1999]) until they ended. Similarly, the frequency spectrum of the basal state was characterised by averaging the PSDs of all

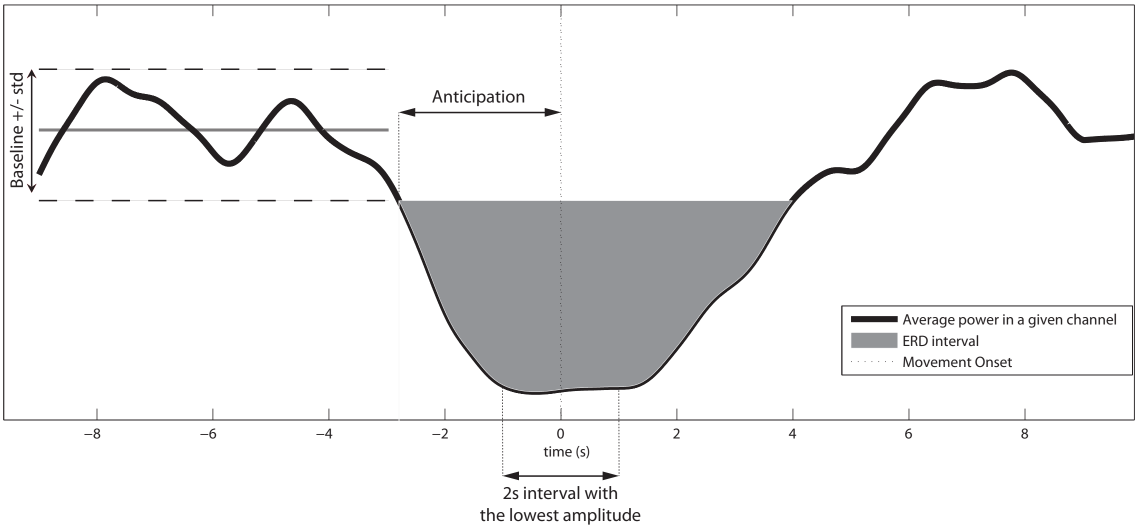


Figure 5.3: Smoothed ERD of one channel at the optimum frequency. The amount of prediction is the gray area under the ERD curve from its begining (at around time = -2.5 s in this case) until the movement onset (time = 0 s).

the basal intervals. The basal intervals were taken from the end of the movements until 3 s before the subsequent movements. Welch's method was used to estimate the spectra. At the end of this first step, it was obtained the frequency at which the ERD was most prominent in each channel.

Second, in each channel, the average ERD was obtained at the selected frequency by filtering the training trials (Butterworth, order 4, band-pass, 2 Hz resolution) and averaging over the trials. The resulting 13 curves were used to estimate ERD prediction with respect to the real movement in each channel. The amount of prediction of ERD in each channel was obtained as the integration of ERD from the time at which the average ERD fell below the baseline level until the movement onset detected by the IMUs (see Fig. 5.3).

The three most perdictive channels at the best pre-determined frequencies were selected to model and classify pre-movement states.

5.3.4.2 Initial training of the BC and online recalibration

The BC was trained with the logarithmic power values of the movements from the training dataset for the three features (channel/frequency pairs) selected as in 5.3.4.1. The power estimation method used to extract the features training the BC was the same as the one used to classify the trials.

Every time a movement was detected during the classification in Experiment 1, the BC was retrained using the updated training dataset containing the most recent movements acquired (including the one just detected). The number of past movements taken into account for online retraining of the system was configurable and for this study, the 30 most recent trials were used. This amount of past movements is expected to be large enough to correctly characterise the ERD phenomenon [Graimann et al., 2002]. In Experiment 2, given that a leave-one-out validation procedure was carried out, no classifier update was performed.

5.3.4.3 Classifier performance and threshold selection

In order to select the optimum threshold applied to the output probability of the BC, its performance was evaluated with the training dataset. The selected threshold was the one that maximised the percentage of predicted movements (recall) while keeping the false positives per minute rate (FPMR) below a maximum level of 1.5 false activations per minute for the training data. The recall and FPMR were defined as:

$$Recall = TP \cdot (NumberOfTrials)^{-1} \tag{5.1}$$

$$FPMR = FP \cdot (1 \quad minute)^{-1} \tag{5.2}$$

where TP (True Positives) was the number of time intervals during which the output of the ODIM was true and the movement onset (reported by the IMUs) was inside it. FP (False Positives) was the number of time intervals during which the output of the ODIM was true and they were located in the resting intervals, when the subjects were not performing any kind of movement. Similar metrics have been used in previous studies dealing with asynchronous BCIs [Townsend et al., 2004; Mason and Birch, 2000; Mason et al., 2006; Niazi et al., 2011].

Similarly to the BC calibration update described in the previous section, the threshold was also updated each time a movement was performed in Experiment 1.

5.3.5 Design of the mHRI with the ODIM system

This section presents a general view of the ODIM integration in a mHRI combining the EEG information with EMG data and gyroscopes to drive a electrical stimuli aimed to cancel the tremors during voluntary movements. The way the mHRI used the information gathered from the different sensors was based on the main characteristics of each technology regarding movement characterization (see Table 5.2). According to this table, EEG was conceived to provide the other sensors with anticipated information of voluntary movements, the EMG data was aimed to monitor the onset of tremor in the presence of voluntary muscle activation, and gyroscopes were used to drive the electrical stimulation

	Advantages	Drawbacks
EEG	- Predictive - Distinction of voluntary movement and tremor	- Low reliability - Variable anticipation time ([$\tilde{2}$ - 0] s) - Some subjects do not have ERD - Electrical stimulation may affect the EEG signal
EMG	- Robust detection of voluntary and tremulous activity - Fast and accurate detection of tremor - Direct identification of tremulous muscles (preferred stimulation sites)	- Incompatibility with electrical stimulation - Nonlinear complex relationship between muscle activation and joint kinematics - Limited maximum movement anticipation
Gyros.	- Usable with FES - Reliable and accurate parameterization of tremor	- Delayed detection of voluntary movements and tremors - Impossibility to identify the source (muscle) that causes the tremor - Convergence time of tremor tracking algorithms

Table 5.1: Advantages and disadvantages of EEG, EMG and gyroscopes to detect and track tremors and voluntary movements.

once it was triggered.

In order to analyze the influence of the EEG system in the mHRI architecture, two conditions were compared:

- An mHRI platform, without EEG data, in which the EMG-based system detected the tremor and voluntary movement onsets in windows with 50 % overlap.
- An mHRI platform integrating EEG information to alert the EMG-based system when movement intentions were detected. In case a movement intention was detected by the EEG system, the EMG increased the overlap between consecutive windows to 75 %.

The latency in movement and tremor onset detections for both cases were compared to analyze possible benefits of using EEG combined with EMG data. The Wilcoxon signed rank test (with $p < 0.05$ for significant results) was used.

5.3.6 Results in Experiment 1

The ODIM results obtained with all subjects who took part in Experiment 1 are presented in the following lines along with the comparison of an adaptive and fixed design.

5.3.6.1 Results obtained with the adaptive design

The plots in Fig. 5.4 show 140 s of continuous function of the ODIM with subject C02. Four movements are performed along this period of time. Three movements are predicted, no false detections are generated and a late detection is achieved in the second trial. The ODIM outputs higher probabilities when more significant ERD is found in the selected channels. The anticipation is achieved through an optimized selection of the most anticipative channels and of the threshold.

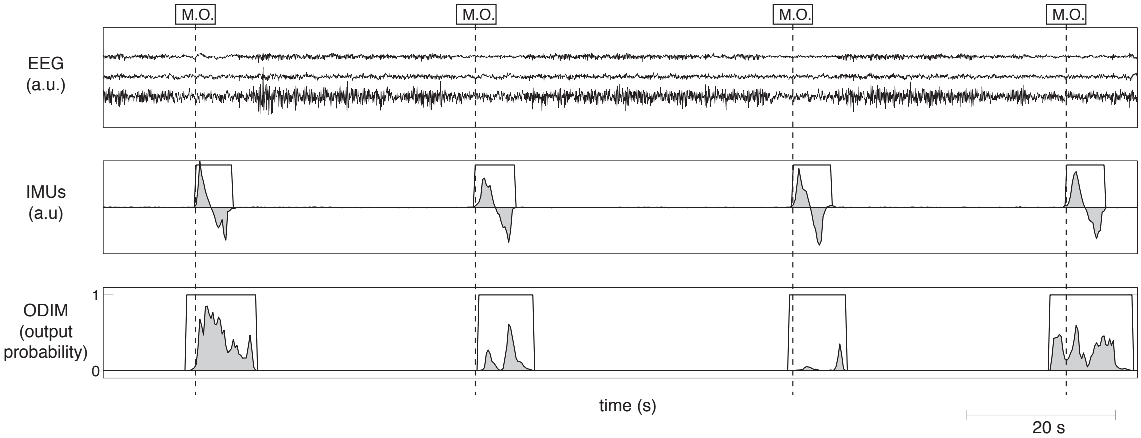


Figure 5.4: Example of ODIM performance during 140 s of continuous function with subject C02. The plots show from top to down: 1) the spatially filtered EEG data of the three channels selected by the ODIM, 2) the raw wrist flexion/extension recorded with inertial sensors (gray areas) and the movement intervals obtained with this information (solid black line), 3) the ODIM output probability (gray area) and the system's binary output after applying the threshold (solid black line). The vertical dashed black lines indicate the onsets of the movements (M.O.).

Table 5.2 shows the channel/frequency pairs selected as features by the ODIM for each of the measured subjects. Channels of the contralateral hemisphere are selected more frequently. In some cases, ipsilateral positions are also selected, implying an anticipated activation of this cortical region, also observed in other studies involving the upper-limb [Bai et al., 2011; Pfurtscheller and Berghold, 1989]. The frequencies chosen with the control subjects are mostly from the upper-alpha band (between 10 Hz and 13 Hz), while in the case of the patients' group, the frequencies where the ERD phenomenon is more predictive correspond either to the lower-beta band (P02 and P03) or to the lower-alpha band (P01 and P04).

Subject	Ch.1	Fr.1(Hz)	Ch.2	Fr.2(Hz)	Ch.3	Fr.3(Hz)
C01	C5	10.5	C3	10.5	CP4	10.5
C02	C3	11.5	C1	11.5	CP3	11.5
C03	FC3	12.5	C5	12.5	C3	12.5
C04	FC3	12.5	C3	12.5	CP3	12.5
C05	C3	12.5	Cz	9.0	C6	9.0
C06	FC4	11.5	C3	11 .0	C1	11.5
P01	FC4	8.5	C5	8.0	CP3	8.5
P02	C1	15.5	C2	15.0	CP3	11.0
P03	FCz	16.5	FC4	17.5	C5	17.5
P04	C3	8.5	Cz	8.0	CP3	8.5

Table 5.2: Selected features (Channel-Frequency pairs) by the ODIM.

The results obtained with the ODIM are summarised in Table 5.3. The prediction period column refers to the average distance between the times at which the EEG-based movement detections start and the onset of the movement. 'RecallLate' refers to all the movements performed by a subject and detected by the ODIM, regardless of whether the detection anticipates or not the onset of the movement (the ODIM activations after the actual onset of the movement and considered false negatives for the estimation of the Recall ratio are considered true positives in this case). Finally, the continuous specificity (last column in the table) is calculated by dividing the length of all false activations (activations during resting intervals) by the total length of the resting intervals.

On average, 60±11 % of the movements performed by the control subjects were correctly predicted. Two patients presented Recall ratios equal to or above 50 %. The ODIM generated on average 1.5±0.1 false activations per minute with the controls and 1.4±0.5 with the patients. Given that in the experimental protocol used, resting intervals represented more than 80 % of the total length of the measuring sessions, 2.25 false activations would be given in a minute of permanent resting state in the worst case (with P04). The Wilcoxon rank sum test showed no significant difference in Recall ($P = 0.26$) and FPRM ($P = 0.90$) between results obtained with patients and controls. Subjects C03, P01 and P03 presented Recall ratios under 50 %, while in these cases, the RecallLate results substantially increased, suggesting a late initiation of the ERD in most trials.

Subject	Recall (%)	FPMR	Prediction period (s)	RecallLate (%)	Continuous specificity (%)
C01	65	1.5	0.77±0.96	100	97
C02	77	1.3	0.80±0.90	100	93
C03	44	1.6	1.27±1.02	84	92
C04	55	1.6	0.99±0.87	98	92
C05	57	1.3	1.17±1.17	89	92
C06	60	1.5	0.83±1.02	100	92
Controls Average	60±11	1.5±0.1	0.97±0.99	95±7	±
P01	14	1.7	0.98±1.24	74	91
P02	76	0.7	0.90±0.95	100	97
P03	28	1.3	0.81±0.67	91	93
P04	50	1.9	1.36±1.11	100	88
Patients Average	42±27	1.4±0.5	1.01±0.99	91±12	92±4

Table 5.3: Classification results of the ODIM.

The mean prediction latency achieved with all the subjects was longer than 700 ms. Fig. 5.5 shows the histogram of distances between the movement predictions with the ODIM and the onsets of the actual movements observed in all the classified runs of all subjects. Most detections were achieved with prediction periods between -1 s and 0 s.

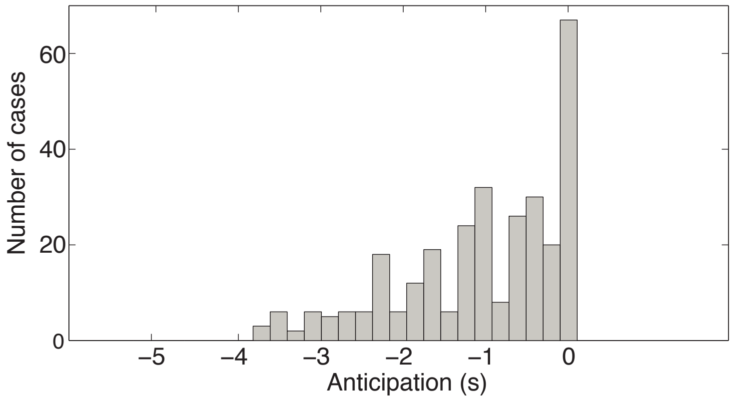


Figure 5.5: Histogram of the distances between the movement intention detections and the onset of the actual movements detected by the IMUs.

5.3.6.2 Comparison of the results using adaptive and nonadaptive ERD detection designs

To check whether the online adaptations of the model used by the BC and the threshold were appropriate for the detection of the intention to move, Fig. 5.6 compares the Recall and the FPMR for three cases: 1) the ODIM adapts both the threshold and the model of the BC, 2) only the threshold is adapted, and 3) only the model of the ODIM is adapted. When no adaptation was used for the threshold or the model, fixed values were assigned to these parameters and only the initial training dataset was taken into account.

Differences in four subjects were found between the cases where the threshold was adapted and not. For P03 and P04, the recall results were maintained and the FPMR significantly increased when no threshold adaptation was carried out. The recall results with C01 and C04 fell sharply when the fixed threshold was used and ODIM performance clearly deteriorated for both cases.

Slight differences in the results were observed between an adaptive model for the BC and a fixed model, although in most cases Recall and FPMR were higher with the adaptive version.

Only in the case of P01 the results obtained using the ODIM with the adaptive threshold and model were worse than using the other two cases (the FPMR increased while the Recall virtually did not change). In the previous section, the ODIM was unable to robustly detect intentions to move in this patient, and hence the differences in this case may not be representative of the suitability of the adaptive ODIM design for the objectives defined.

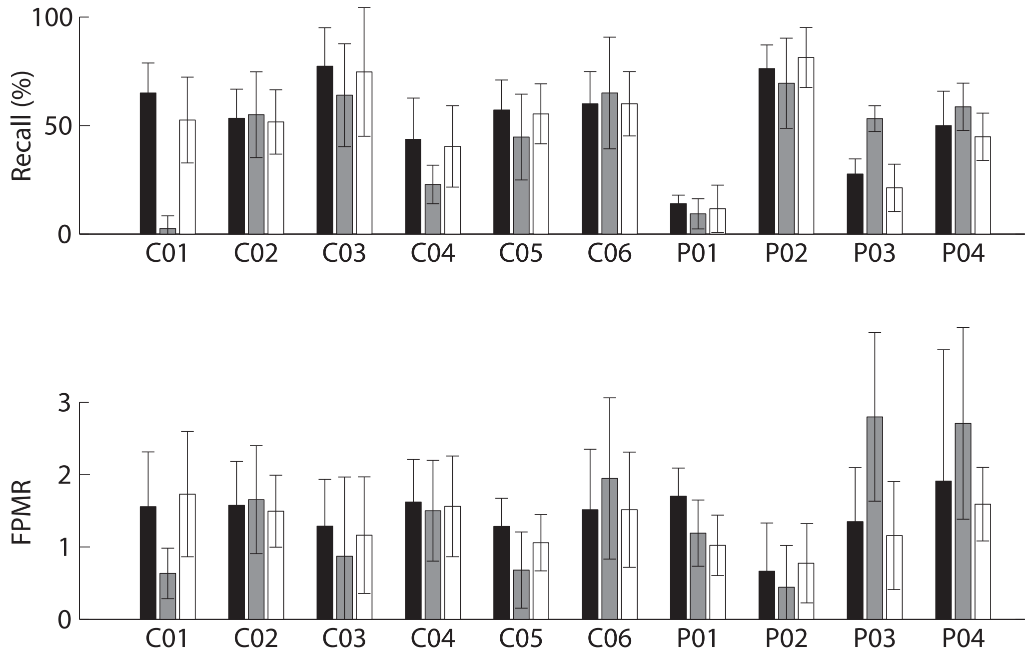


Figure 5.6: Comparison of the Recall and FPMR results for three conditions: 1) Both the model of the BC and the threshold are adapted (black), 2) only the model is adapted (grey), 3) only the threshold is adapted (white). Mean and standard deviations across runs are presented.

5.3.7 Results in Experiment 2

Table 5.4 shows the detection results of the ODIM with the valid trials in Experiment 2 (those in which tremor was visible). Results for patient 02 are not supplied since he did not exhibit a visible ERD. In general terms, although in this case a significantly lower number of examples was used to validate the system than in Experiment 1, higher recalls are obtained with equivalent number of false activations and similar amounts of anticipation. This was in part due to the fact that here, the resting periods of time preceding the movements were shorter. In summary, the results indicate that the mHRI was capable of consistently anticipating the intention to move (in those patients that exhibited ERD). Moreover, the delay in the detection of both voluntary movement and tremor was considerably increased in the patient 02, who did not present a detectable EEG-based movement anticipation (average delay 1.83±1.77 s and 1.79±0.91 s for the voluntary activity and the tremor, respectively) when compared to the other patients (average delay in all trials 0.88±0.45 s and 0.77±0.45 s for the voluntary activity and the tremor respectively). The outcome of increasing the overlapping of the windows that the EMG algorithm used from the 50 % to the 75 % was also evaluated. When the ODIM was used, a statistically lower ($P < 0.05$) delay in the detection of both the voluntary

Patient	Recall (%)	Prediction period (s)	Continuous Specificity (%)
01	88	0.75±0.98	96
02	-	-	-
03	92	1.84±1.52	95
04	67	0.41±0.37	96
05	80	1.43±1.39	86
Average	82 ± 11	1.11 ± 0.52	93 ± 5

Table 5.4: Classification results of the ODIM in Experiment 2.

movements and the tremor was observed, which highlights the benefit extracted from using the prediction of movements derived from EEG to drive the system.

5.4 Discussion

This chapter presented and EEG-based system to predict online voluntary movements with the arm. The robustness of the system against false detections was demonstrated validating its continuous function with a protocol with non-action intervals between movements lasting over 15 s on average (1.4±0.3 false activations per minute were generated in Experiment 1). With most subjects, more than 50 % of the movements could be anticipated by the system. With two patients small recall results were obtained, although the late detection of the movements was achieved, suggesting a delayed appearence of the ERD pattern. In addition, it has been proposed for the first time a design of a multimodal interface taking advantage of the EEG information regarding motor intentions. The EEG system was aimed to give anticipatory information to other systems tracking voluntary movements and tremors and doing so, detection latencies of voluntary and tremulous movement onsets were significantly lower than in the case where no EEG technology was used.

The ODIM represents a step forward in the development and validation of BCI technology for patients with tremor. The proposed interaction between EEG and other sensor modalities is also original. The ODIM is conceived to give advanced information on voluntary movements to other sensors, such as EMG and gyroscopes. Information from these sensors are in turn expected to trigger the electrical stimulation that assists tremor patients. As was shown in the comparative Table 5.2, EMG- and gyroscopes-based systems require muscle contraction or actual movements to assess that an action is being performed, increasing the latency of the response of a system aimed to assist or compensate the voluntary movement. This is critical with tremor patients, since the tremors are superimposed to the voluntary movement and the precise detection of the movement onset becomes more complicated. In this terms, the EEG activity becomes a valuable source of information to improve the response time of neurorobotic or neuroprosthetic devices. In fact, a synchronised operation of an active device and the user's commands governing it is desired to improve the interface between man and machine [Gomez-Rodriguez et al., 2010]. This depends on how accurately the user's intentions are estimated. Moreover, after anticipating information on future volitional movements it is then also interesting to start characterizing the patient's tremor before each movement starts. In such case, the tremor cancellation can be tackled already before the start of the voluntary movement [Kinoshita et al., 2010].

ODIM performance has been tested with ET patients. As it was described in Chapter 4, ET seems to be due to abnormal oscillations within the thalamocortical and olivocerebelar pathways [Elble, 2006], and this may cause variations in the characteristics of the ERD patterns in patients with tremor as observed in previous studies [Tamás et al., 2006; Lu et al., 2010]. Besides, the proprioception of hand movements while the tremor is present can also influence the ERD patterns during the intervals of intended basal (resting) activity in patients with rest tremor. The ERD single trial detection system must hence be tested with these kind of patients. Here, several differences were observed in Experiment 1 in the results with the ET group compared to the ones obtained with the control group. The feature selection showed that the frequencies at which the tremor patients exhibited ERD corresponded to the lower alpha- and beta-bands (7-10 Hz and 13-19 Hz), while with the controls, most features were at frequencies in the 10-13 Hz range. The channels selected in both groups differed slightly, and the C3 position (covering the right hand cortical area) was more frequently selected in the control group than in the patients' group. Pathological oscillations of cerebellothalamocortical pathways causing ET [Benito-León and Louis, 2006] could be causative of such differences in the spatial and frequencial distribution of the ERD, although other factors, mainly the age of the patients, are also likely to play a role in this regard, in agreement with previous studies [Derambure et al., 1993]. No statistically significant differences were found in the Recall and FPMR results obtained here in Experiment 1, although two patients (P01 and P03) showed the worst performances. These results could be caused by the pathology of these patients, although it may also be due to differences in the task involvement (fatigue, concentration, motivation) of these patients as compared to the rest of the subjects measured. As no studies of ERD in ET patients have been documented to date, further research may be done in this area. Nevertheless, the performance of the ODIM with P02 and P04 is encouraging to consider the ODIM as a valid interface for patients with tremor.

Also in Experiment 1, an adaptive design for the ODIM was proposed to face the expected inter-subject variability caused by changes in the subjects' fatigue, concentration and degree of involvement, among others [Blankertz et al., 2006; Shenoy et al., 2006]. Previous studies have demonstrated the benefits of adaptive BCIs based on sensorimotor rhythms [McFarland et al., 2011]. In the present study, no feedback was given, so no learning was expected. The ODIM worked using a training dataset acquired on a different day (in 4 control subjects) or with a small amount of training examples (all patients and 2 control subjects). In both cases the ODIM can benefit online from synchronised movement tracking with the gyroscopes, by enriching the training dataset each time new examples are accomplished. The results obtained with the adaptive design have been compared with non-adaptive alternatives. Using a fixed threshold worked worse with 4 subjects because it was too restrictive (C01 and C02) or too tolerant (P03 and P04). These differences were probably due to aforementioned changes in the subjects' brain processes, which made the training dataset unrepresentative to choose a threshold for the validation dataset. Comparing the adaptive design with a design only adapting the threshold showed similar results. A higher number of movements predicted and of false detections was obtained in 9 out of 10 subjects with the adaptive alternative. For the here proposed application, the minimization of false detections was not so critical as the maximization of true positives, because the final decision for triggering an active strategy with electrical stimulation would rely on the EMG/gyroscopes-based system. Therefore, the results obtained with the adaptive model are more suitable in this case.

Comparing the results obtained here in Experiment 1 with other works is difficult, since the experimental protocols used, the subjects measured and the goals addressed vary significantly. Several studies have presented results of EEG-based movement onset detection systems using the BP pattern and showing similar specificity results and significantly higher recall ratios without anticipation of voluntary movements (see [Niazi et al., 2011; Lew et al., 2012; Xu et al., 2014] and Chapter 6 in this thesis). The fact that, in those studies, movements were detected and not anticipated is a crucial aspect of the significant difference in this regard. The important increase in the number of late detections (Recall-Late) achieved in our study supports this idea. The characteristics of the experimental protocol used are also an important factor, since using longer non-action intervals has a direct influence on the specificity of the system (the longer the basal intervals, the more likely it will be that the system generates false activations). On the other hand, Bai et al. in [Bai et al., 2011] presented results of an EEG-based system predicting voluntary movements, but only 50 % of the movements were detected in the best case. In their study the length of the rest intervals preceding the movements was similar to that in [Niazi et al., 2011] and thus shorter than here.

Results obtained in Experiment 2 provided a proof of concept (with a reduced number of trials and patients) on how an mHRI may benefit from the anticipated information regarding motor tasks provided by the ODIM to detect and parameterize the concomitant tremor, in order to drive electrical stimulation to compensate it. The integration of the ODIM in the mHRI shortened the reaction time of the system: significantly ($P < 0.05$) lower delays in movement and tremor onset detections were obtained when the ODIM was integrated in the mHRI. This aspect has obvious implications for tremor compensation, since a response of the interface matched in time with the intended actions of the patients becomes possible, giving rise to a more natural interaction. There are, nevertheless, two scenarios in which the mHRI needs to overcome the absence of ERD information. The first of them is those patients that present not classifiable ERD, where the EMG detection algorithms will have to assume larger detection delays (as for Patient 02 in Experiment 2). The second scenario corresponds to the generation of false positives by the EEG classifier, which unnecessarily increases the overlapping of windows of the EMG subsystem, but these misdetections do not propagate to the patient (electrical stimuli are only triggered by the EMG and gyroscopic systems). As a matter of fact, the idea of enhancing the reliability of the neuroprosthesis control by combining recorded data with redundant information (as in the case of EEG, EMG and gyroscopic signals) constitutes the rationale for always running the EMG classifier in parallel. It is worth noting, however, that the number of false negatives of the EEG classifier throughout the experiments here is remarkably low. It is also worth mentioning that the overlapping of the EMG windows could be increased more, which would yield a faster detection of both voluntary muscle activity and tremor. The value selected here was chosen to analyse the interest of the approach, while ensuring low computational burden.

5.5 Chapter conclusions

Experiments with 6 healthy subjects and 4 ET patients were conducted to assert the ability of the proposed EEG-based system to anticipate voluntary movements while reducing the number of false activations during long ($>$ 15 s) periods of resting activity. On average, 60 ± 10 % and 42 ± 27 % of the movements were anticipated with the control subjects and the patients respectively. The number of false activations generated per minute was kept low in both groups (1.5 ± 0.1 and 1.4 ± 0.5) despite using an experimental protocol in which long non-action intervals were given. Further experiments with 5 additional ET patients were run to validate the interaction between EEG- and EMG-based systems in a proposed mHRI for patients with tremors. The movement predictions provided by the EEG system allowed a significant improvement in the detection of movement and tremor onsets when the patients started new tasks.

In summary, this chapter has proposed an asynchronous EEG application in which anticipated detections of motor intentions are performed. To rigorously validate the online function of the system, already proposed metrics by other studies and *ad hoc* metrics defined here have been used. An adaptive configuration of the detector has been proposed, which allows an optimized robustness of the system when dealing with the non-stationarities of the EEG signals recorded along different measurement days. These are the first results of a BCI system in patients with tremors and the first time that a multimodal platform integrating EEG sensors with other movement-related sources of information is proposed and justified.

Chapter 6

Detection of the onsets of upper-limb reaching movements using ERD and BP patterns to elicit associative facilitation

6.1 Abstract

As it was presented in the first chapters of this thesis, the EEG signal allows the characterization of movement-related cortical processes with high temporal accuracy. Chapter 5 demonstrated the potential use of the EEG signal to anticipate voluntary movements performed with the arm. In this chapter the goal is slightly modified: it is studied how accurately is it possible to decode the onset of voluntary movements with temporal resolution using the EEG signal. Developing online systems able to decode motor intentions at the exact time they occur is of special interest for the neurorehabilitation of stroke patients, since it then becomes possible to develop conditioning paradigms associating cortical and peripheral neural processes with temporal accuracy (in the range of hundreds of milliseconds). This chapter proposes for the first time an EEG-based detector of the onsets of voluntary upper-limb functional movements using information extracted from cortical rhythms and slow cortical potentials. The system is evaluated with data from healthy subjects and chronic stroke patients and a rationale for the combination of oscillatory and slow cortical informations is provided. Additionally, results of a feasibility study using the developed EEG system in a one-month BCI intervention with chronic stroke patients is presented.

6.2 Introduction

During the past few years, the development of brain-computer interfaces (BCIs) for the functional rehabilitation of patients with motor disabilities has gained special interest [Daly and Wolpaw, 2008; Buch et al., 2008]. The main purpose of BCIs in such scenarios is to provide a way to promote the neural rehabilitation of the patients. EEG-based systems allow the real-time characterization of the cortical activity over the motor cortex while the subject is performing motor tasks. This way, it becomes possible to detect online when a person is attempting or imaging a movement [Pfurtscheller and Solis-Escalante, 2009; Bai et al., 2011; Niazi et al., 2011], and to predict certain properties of the movement to be performed [Pfurtscheller et al., 2006; Morash et al., 2008; Gu et al., 2009b; Jochumsen et al., 2013]. Such information may in turn be used to close the loop with neuroprosthetic or neurorobotic devices. In this regard, recent studies have proven the importance of the proprioceptive feedback timing to achieve long-term associative neural facilitation effects [Mrachacz-Kersting et al., 2012; Niazi et al., 2012].

In a series of previous studies, it has been proposed the use of the BP (described in Chapter 2) to detect the movement intention [Niazi et al., 2011; Garipelli et al., 2013; Lew et al., 2012; Jochumsen et al., 2013; Xu et al., 2014]. Since the BP presents an identifiable pattern that is decaying until the movement starts, it is suitable to achieve temporal precision in the detection of the onsets of voluntary movements. In fact, previous studies showing results of online systems based on this pattern indicate that average detection latencies of 315 $\pm$ 165 ms can be obtained [Xu et al., 2014]. Nevertheless, the BP is not detectable in all cases, since some subjects do not present a significant pattern during self-paced movements. In addition, results obtained in previous studies using the BP have not fully validated the use of this cortical pattern alone to detect movement intentions in stroke patients [Niazi et al., 2011]. In fact, altered BP patterns have been observed in previous studies with this type of patients [Daly et al., 2006; Fang et al., 2007].

A possible way of boosting EEG-based systems aimed to detect the onsets of voluntary movements is to combine the BP with other EEG movement-related patterns providing complementary information [Fatourechi et al., 2008]. The ERD (described in Chapter 2) is a well-known cortical pattern related to the execution of voluntary movements. Although a variable anticipation may be observed in the ERD of a specific channel and frequency in a subject during consecutive movements, the spatio-tempo-frequential distribution of the ERD observed when averaging a number of EEG segments preceding voluntary movements shows a desynchronization pattern attached to the movement event [Bai et al., 2005].

Therefore, the analysis of the ERD also provides certain degree of information regarding the timing of volitional motor actions. Indeed, previous studies have used the ERD pattern to anticipate movement events [Bai et al., 2011; Ibáñez et al., 2013]. As in the analysis of the BP, the ERD pattern of stroke patients presents variations with respect to healthy subjects [Stepien et al., 2010]. Therefore, it is of special relevance to study how stroke-related cortical changes may affect a BCI driven by these cortical patterns.

This chapter presents results from two experiments. In the first experiment, an EEG-based system combining the information extracted from the analysis of the BP and ERD cortical processes is proposed to estimate the onsets of voluntary upper-limb reaching movements. The comparison between the proposed classifier and equivalent classifiers using either the BP or the ERD patterns is also performed to justify the fusion of these two sources of information. The second experiment presents preliminary results of a BCI intervention for stroke patients using functional electrical stimulation (FES) and the developed EEG system. The intervention is tested with four chronic stroke patients in eight sessions along one month. Changes in two functional scales are studied to analyze the effects of the BCI intervention on the patients.

6.3 Methods

6.3.1 Participants

Healthy subjects and chronic stroke patients were recruited for the two experiments described in this chapter (referred to as Exp1 and Exp2 from nowon here). Six healthy subjects (all males, right-handed and under 35 years old) were measured and considered the control group in Exp1. Nine patients were recruited (three females, age 62 ± 14 years, mean ± SD; details are provided in Table 6.1). Patients P1-P6, P8 and P9 were recruited for Exp1. Patients P8 and P9 were discarded for further analysis because they could not comply with the demands of the task performed during the experimental protocol. Patients P2, P3, P5 and P7 participated in Exp2. None of the subjects measured had prior experience with BCI paradigms.

6.3.2 Data Acquisition

The movements of the arm were measured with solid-state gyroscopes and EMG electrodes. Two gyroscopes, placed on the distal third of the forearm, and the middle of the arm measured the limb kinematics. The data were sampled at 100 Hz.

Surface EMG was recorded using bipolar derivations on the main muscle groups involved in the execution of the reaching task (pectoralis major, anterior deltoids, medium

Pat. code	Age	Gender	Stroke type	Affected hemisphere	Years since stroke	Fügl-Meyer	Minimental	Ashworth	Rh sessions a week
P1	52	F	Isquemic	L	4	126	30	0	1
P2	54	M	Isquemic	R	4	69	30	2	2
P3	54	M	Isquemic	L	3	68	30	3	2
P4	75	M	Hemorrg	L	1	60	30	3	2
P5	69	M	Hemorrg	R	4	64	29	3	-
P6	57	F	Isquemic	L	1	93	26	1	Discont
P7	40	M	Hemorrg	R	13	81	30	3	2
P8	83	F	Isquemic	L	5	112	23	1	2
P9	75	M	Isquemic	L	3	- (mixed aphasia)	-	2	2

Table 6.1: Demographic table of the patients participating in the present study.

deltoids, biceps, triceps and wrist extensors). The data were amplified and sampled at 2,000 Hz.

EEG signals were recorded from 31 positions (AFz, F3, F1, Fz, F2, F4, FC3, FC1, FCz, FC2, FC4, C5, C3, C1, Cz, C2, C4, C6, CP3, CP1, CPz, CP2, CP4, P3, P1, Pz, P2, P4, PO3, PO4 and Oz) using active Ag/AgCl electrodes. The reference was set to the voltage of the earlobe contralateral to the arm moved. AFz was used as ground. The signal was amplified and sampled at 256 Hz.

All recorded data were synchronised with a common digital signal.

Additionally, Functional Electrical Stimulation (FES) was used in Exp2 to provide proprioceptive feedback to the patients. Stimuli were delivered at the anterior deltoid, triceps and wrist extensors with a multichannel monopolar neurostimulator with charge compensated pulses. The common electrode was located at the oleocranon. A stimulation sequence was applied each time the FES system was triggered: first the anterior deltoid was stimulated during 500 ms alone, then the stimulation of triceps and extensors was also activated. The three muscles were then stimulated during 1 s and after this period of time the stimulation sequence was finished. The currents of the stimuli at each muscle were adjusted in each session to optimise the elicited movements in each patient. Pulse width and frequency were set to 250 μs and 30 pps, respectively. The stimulator was controlled by a stand alone computer (with a real-time operating system) that received activation commands from the computer recording the EEG activity via a digital signal.

6.3.3 Aims and description of the experimental protocol in Exp1

The first one of the two experiments presented in this chapter was intended to validate the EEG-based detector of movement intention. Each participant was measured during one single session. The study was performed in a sound- and light-attenuated room. Participants sat in a comfortable chair with their arms supported on a table. During the measurement phase, participants were instructed to remain relaxed with their eyes open and their gaze fixated on a point on the wall. They were asked to perform self-initiated reaching movements with the affected arm (the dominant arm in the case of the control subjects). The point to be reached was in the midline of the body and at around 75 % of the maximum distance achievable by each subject. The average distance between consecutive movements was around 8-15 s. During the resting state between movements, participants were asked to remain as relaxed and quite as possible, whereas they were asked to start a movement as soon as they felt the urge to do it. Runs of 30 movements were performed.

The intervals containing at least 5 s of resting activity followed by a self-initiated reaching movement and free of EEG artefacts were considered trials and were used in the subsequent steps of the data analysis to validate the EEG detector. On average, 53 $\pm$ 8 and 55 $\pm$ 12 trials were collected with the healthy subjects and the patients, respectively. A leave-one-out validation methodology was used, *i.e.* to validate the detector function on each trial, the rest of the trials performed by the same patient were used for training.

6.3.4 Aims and description of the experimental protocol in Exp2

In the second experiment presented in this chapter, four patients participated in a feasibility study of a BCI intervention for the upper-limb. The intervention consisted of eight sessions along a month (2 sessions/week). In each session, patients were first asked to perform the same task as in Exp1 until 30 trials were acquired. These trials were used to calibrate the EEG-based detector of movement onsets. After this process, patients were asked to perform 80 more trials in a single run. In this case, the EEG system detected online intervals of motor intention and triggered the FES assisting the patients' reaching movements. The patients were asked to concentrate in the task and to perform the movements when they decided to. They were also asked to block the arm in case the electrical stimulation arrived at time intervals in which they were not planning a movement.

The performance of the proposed EEG-based system along the intervention sessions was analysed to test whether a reliable interface was feasible and stable. To evaluate the effects of the proposed intervention on the patients, two functional scales, namely the Stroke Impact Scale (SIS) and the Fügl-Meyer index (FMI), were measured at the beginning (pre-intervention) and in the end (post-intervention) of the month during which the intervention was carried out. The SIS assesses the health status of the stroke patient according to his/her self-reported outcome. The FMI, on the other hand, is one of the most widely used stroke-specific quantitative measures of motor impairment and it evaluates and measures recovery in post-stroke hemiplegic patients by assessing patients' performance of activities of daily living, functional mobility and pain.

Additionally, patients were asked to perform self-initiated imagined (instead of real) reaching movements in a single run (30 trials) during the last experimental session. The purpose of this additional measurement was to ascertain that the proposed BCI intervention would also present a reliable performance in the case of patients with no residual voluntary muscle activity. Patients were asked to say "YES" if the electrical stimuli arrived when they were imaging a movement and to say "NO" in case the stimuli arrived without movement imagination or in case no stimulus was perceived when they were imaging a movement.

6.3.5 Estimation of the real onsets of the movements for training and validation purposes

To detect the real onsets of the movements, the kinematic information (gyroscopes) was used instead of the muscle activation data (EMG). This decision was made to solve the difficulties in detecting onsets of muscle activation in spastic muscles as the ones likely found in the affected limbs of stroke patients. The real onsets served both to calibrate the EEG-based proposed detector with the training data and to test its performance with the validation data.

The gyroscopic sensor that first detected that a movement was starting was used to locate the onsets of the reaching movements. This sensor selection was performed for each participant. Data were low-pass filtered (Butterworth, 2nd order, fc = 6 Hz), and the peak amplitude was estimated for each subject performing the reaching movement. The threshold amplitude for the detection of the onsets of the movements was set to 5-7 % (patient dependent) of this peak amplitude.

The EMG data was used to ascertain that no sudden muscle activations were present in any of the muscles of the measured arm during the resting intervals between consecutive movements. Sudden muscle contractions (which were only observed in the patients in few moments along the recordings, such as when they readjusted their position on the chair to be comfortable) were marked as artefacts and were not considered in subsequent analyses.

6.3.6 Description of the EEG-based detector architecture and validation

The following lines describe the structure of the proposed EEG-based detector of movement intention based on the combination of ERD and BP patterns. Fig. 6.1 shows the general overview of the system structure, identifying 1) the block characterising the ERD pattern preceding the onsets of the movements, 2) the block characterising the BP pattern, 3) the block combining both outputs to generate a binary estimation of motor intention, 4) the blocks converting the binary signal into a more stable estimation triggering the electrical stimulation and 5) the FES block closing the BCI loop.

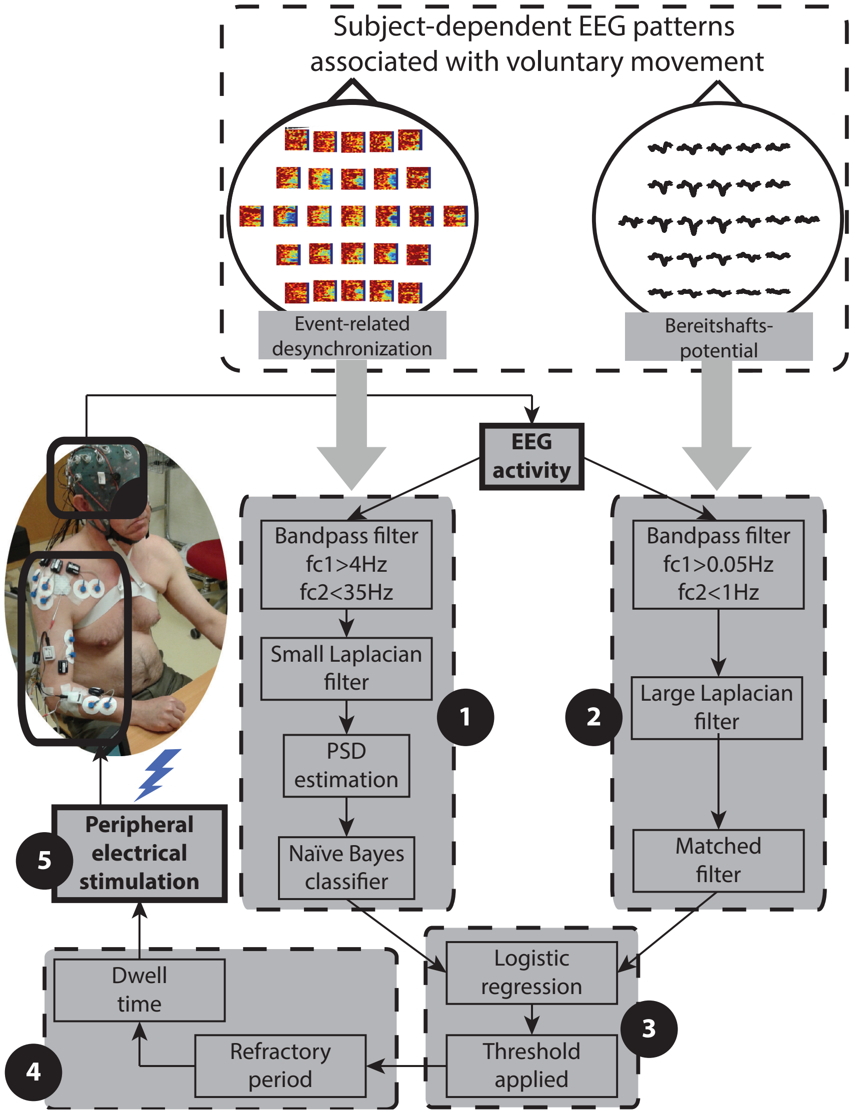


Figure 6.1: Structure of the EEG-based system detecting the onsets of voluntary upper-limb movements.

6.3.6.1 ERD-based detector of the onset of the movement

A Naïve Bayes classifier was used to detect the ERD pattern preceding the movements. Previous studies have demonstrated the suitability of this type of classifiers for ERD detection [Bai et al., 2007; Ibáñez et al., 2013]. Band-pass filtering was first applied to the EEG signals (Butterworth IIR filter, 3th order, 6 Hz $<$ f1, 35 Hz $>$ f2) and then a small laplacian filter (for each electrode position the average voltage of the closest neighbours is subtracted) was used [Hjorth, 1975]. Frontal, fronto-central, central, centro-parietal and parietal channels were kept. The power values were estimated in segments of 1.5 s and for frequencies between 7-30 Hz in steps of 1 Hz. Welch's method was used to this end (Hamming windows of 1 s, 50 % overlapping). Estimations were generated every 125 ms.

The power estimations obtained in all training trials from -3 s to -0.5 s (with respect to the movement onsets) were labelled as examples of the resting state, whereas the estimations generated at t = 0 s where labelled as movement onset examples. The Bhattacharyya distance was used to select the 10 best features (channel/frequency pairs) to build the classifier. This number of features was chosen on the one hand to correctly characterize the ERD pattern in several channels and frequencies and, on the other hand, to achieve a real-time function without requiring an excessively high computational load.

The trained classifier was applied to the test data generating estimations of movement intention every 125 ms.

6.3.6.2 BP-based detector of the onset of the movement

A similar procedure to the one proposed in [Niazi et al., 2011; Jochumsen et al., 2013] was used to detect the BP. Nevertheless, unlike in those two previous studies, we used a finite impulse response band-pass filter with linear phase (FIR filter, 15th order, 0.05 Hz $<$ f1, 1 Hz $>$ f2) using the fir1 routine of Matlab software. This solution was adopted since linear preservation is crucial to extract the entire BP pattern, and using non linear phase filters (as for example the Butterworth filter) does not allow to decode this pattern unless zero-phase filtering (filtering in the forward and reverse direction) combined with framing of the EEG signal is performed, which leads to a delayed (few hundreds of milliseconds) detection of the BP in the online function, due to filtering edge effects.

After the temporal filters were applied, spatial filtering and channel selection were performed. Three virtual channels were computed from the original 31 set of channels in the experimental set-up. These channels were obtained by subtracting the average potential of channels F3, Fz, F4, C3, C4, P3, Pz and P4 to channels C1, Cz and C2 (similarly to [Jochumsen et al., 2013]). The average BP was computed for the three resulting channels using the training data. The channel showing the highest absolute peak at the movement onset was selected for the BP-based detection of movement onsets. The selection of one of these channels instead of directly choosing Cz (as in [Jochumsen et al., 2013]) was conducted because, in healthy subjects, upper limb movements typically present a maximal late BP over the contralateral central areas of the cortex [Shibasaki and Hallett, 2006].

A matched filter was designed using the previously selected channel. To this end, the average BP was obtained using the time intervals from -1.5 s to 0 s of the trials in the training dataset. The matched filter was applied to the virtual channel in the validation dataset. As with the ERD-based detector, estimations were also made every 125 ms.

6.3.6.3 Detector of the movement onsets based on the combination of the ERD- and BP-based systems

Outputs from ERD-based and BP-based detectors were combined using a logistic regression classifier. Training examples of the resting condition were taken from estimations of the two detectors between -3 s and -0.5 s with respect to the movement onset (in steps of 125 ms). The output estimations of the ERD and the BP classifiers at the movement onset with the training dataset were used to model the movement state. The classifier generated estimations of the intention to move every 125 ms.

6.3.7 Threshold selection

A threshold was applied to the output of the detector to decide at each moment whether movement intention was detected. The threshold was optimally obtained from the training dataset, following the criterion of maximizing the percentage of good trials (GT), *i.e.* trials with a true positive (TP) and with no false positives (FP) (these and other performance metrics are defined in 6.3.8). In Exp2, the threshold was further adjusted (manually and around the optimal value) before initiating the intervention sessions.

6.3.8 Metrics of the detector performance and threshold selection

As the present study uses asynchronous paradigms in both experiments, conventional metrics used in traditional BCI paradigms could not be used [Townsend et al., 2004; Mason et al., 2006]. Three metrics were used to evaluate the ability of the EEG-based system to reliably locate movement onsets. The TP rate was defined as the percentage of trials with a movement detection contained in the time interval from -0.75 s to +0.75 s with respect to the real onset estimated by the gyroscopes. The precision of the detector was characterized as the number of FP per minute (FP/min), *i.e.* rate of detections during the resting intervals. The percentage of GT was obtained by counting the amount of trials in which no FP were generated and a TP was achieved. Finally, the latencies of the TP with respect to the real onsets of movements were also computed to analyse the temporal accuracy of the system.

6.3.8.1 Application of a refractory period and a dwell time

In order to generate stable estimations that could be used to trigger the FES, a minimum time period between the onsets of two consecutive FES activations (refractory period) and a fixed duration of FES stimuli (dwell time) were used [Townsend et al., 2004]. The thresholded output of the logistic regression classifier was applied a refractory period of

6 s. The dwell time was set between 1.5-2 s (subject dependent) after analysing the time spent by the patients to reach the target point on the table.

6.3.9 Statistical analysis

In Exp1, a comparison between the performance of the proposed detector combining the ERD and the BP information and the performances of detectors based only on each one of the two patterns was carried out to validate the proposed methodology. Given that the performances of the three detectors depend on each subject, a Friedman's test was used. In order to gain statistical power and to reduce the size of the statistical results, samples from healthy subjects and patients were used together to test the hypothesis that the three proposed detectors supplied significantly different results. Bonferroni post-hoc correction was used to analyse significant differences between pairs. The statistical analysis was performed on the dependent variables GT, TP and FP/min. Results were considered significant for values of $P < 0.05$. All presented results are reported as the mean $\pm$ SD.

6.4 Results

6.4.1 Results of Exp1

Results of Exp1 are presented in this section. First, the average ERD and BP patterns of the measured subjects are shown in order to look for differences in the spatio-temporal distribution of the cortical activation patterns in healthy subjects and patients. Then, results of the EEG-based detector of movement intention are presented and the comparison between the proposed EEG system and two alternatives relying either on the ERD or the BP patterns (based on the corresponding algorithms described before) is performed.

6.4.2 Summary of observed cortical patterns in patients and healthy subjects

A summary of the average BP and ERD patterns observed in all patients and healthy subjects is shown in Figs. 6.2 and 6.3. Overall, the ERD and BP could be observed in most subjects analysed, although differences in spatial distribution and in strength of these patterns were found. The average BP peak across healthy subjects was found at -19.8 $\pm$ 57.6 ms with respect to the movement onsets. In the case of the patients, this peak was observed at 97.5 $\pm$ 47.3 ms. A more homogeneous BP pattern could be observed in the group of healthy subjects than with the patients according to both, the temporal BP pattern and its spatial distribution. The ERD spatial distribution presented a predominant contralateral activation both in the alpha and beta bands in the group of healthy subjects, whereas activation patterns presented a central (P1, P2 and P5 in the alpha band and P2, P3 and P5 in the beta band) or bilateral distribution (P3 in the alpha band and P1 in the beta band) in the patients group.

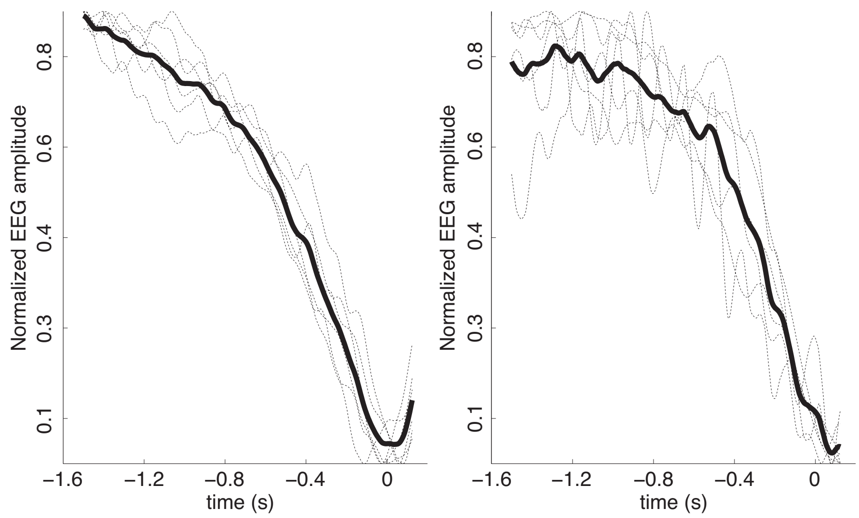


Figure 6.2: Average BP of all subjects (discontinuous lines), and average BP across subjects (solid line). Averages from healthy subjects and patients are presented in the left and right panels, respectively.

6.4.3 Results of the EEG-based detection of the onsets of movements

Fig. 6.4 shows a representative example of the detector function on a single trial performed by participant C2. The different stages in the EEG signal processing to extract information regarding movement intention are represented. The three last curves show the estimations of the onset of the movement based either on the BP pattern, on the ERD pattern or on the combination of both, respectively. In this example, the EEG-based detection is achieved with few hundreds of milliseconds of anticipation.

Table 6.2 summarizes the results obtained by the detector based on the ERD and BP patterns. On average 63.3 ± 13.8 % and 66.4 ± 18.8 % of GT are obtained with the healthy subjects and the patients, respectively. The percentage of true positives achieved with patients is smaller than with healthy subjects, but also the FP/min generated with the patients is higher. These results lead to a similar average performance of the system in terms of detections and false activations in both groups. Nevertheless, more delayed detections are obtained with patients (35.9 ± 352.3 ms) than with healthy subjects (-89.9 ± 349.2 ms).

The features selected by the ERD-based detector of movement onsets in the healthy subjects and patients are summarized in Table 6.3 and Table 6.4, respectively. According

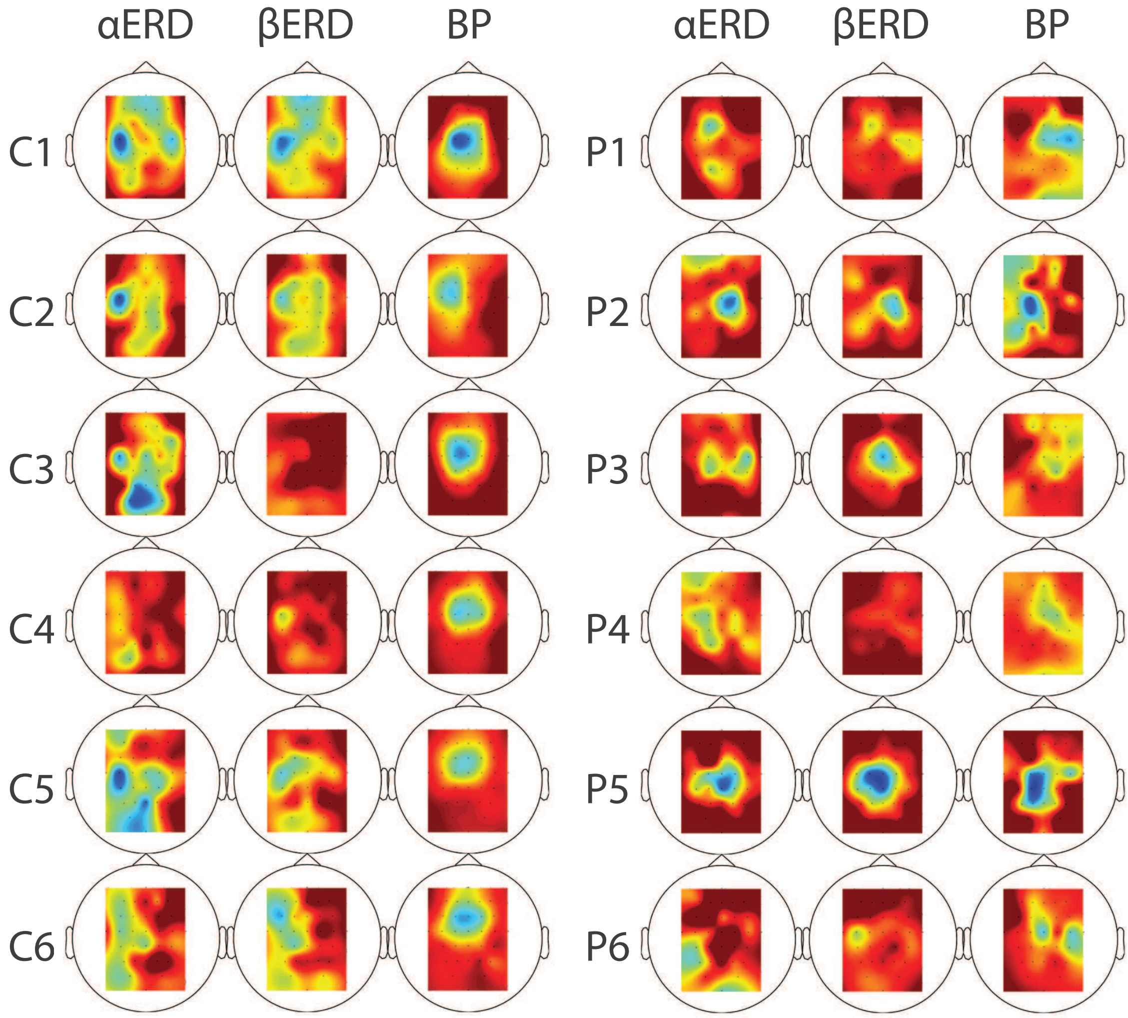


Figure 6.3: ERD and BP spatial maps with healthy subjects (left) and patients (right). Left and central columns show the spatial distribution of the α-ERD and β-ERD (normalized power changes) obtained by comparing a window of 1.5 s ending at the movement onset with an equivalent window 4 s before the onset. The third column shows the spatial distribution of the BP peak amplitude. For each column, the same colour scales are used with all subjects. Colour scale normalization is performed representing the lowest value in each column with dark blue and calibrating the level of dark red in order to optimize the patterns representation.

to the average ERD patterns observed in section 6.4.2 a predominance of contralateral central features is observed in the first case (healthy subjects), therefore most features correspond to channel C3 and the surrounding positions. In the case of the patients, a more spatially spread distribution of selected features is obtained. Features from the midline (around Cz) become more relevant in this case. The selection of features from the alpha or beta band varies for each subject, although predominance of beta band features

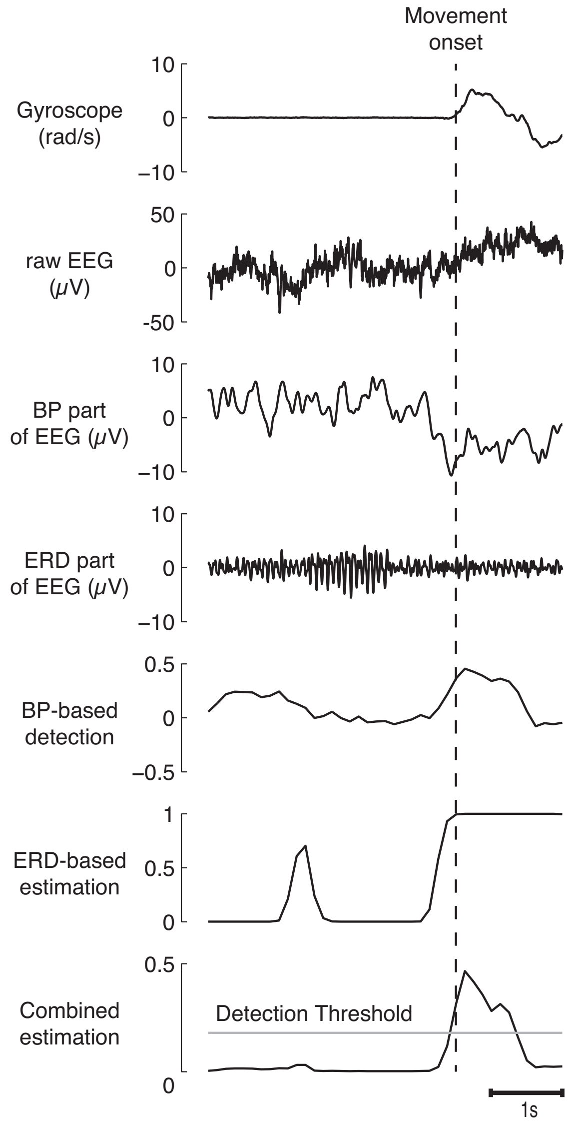


Figure 6.4: Simulated online function of the single-trial EEG-based detector of onsets of voluntary movements. The plots show from top to bottom: 1) the gyroscopic data used to locate the actual onset of the movement, 2) the raw EEG signal of a single channel, 3) the virtual channel obtained after spatial and temporal filtering the EEG signal to detect the BP pattern, 4) the EEG signal in one channel after applying a small laplacian filter and a band-pass filter (between 6 Hz and 35 Hz) for the ERD-based detection, 5) the output of the matched filter applied by the BP-based detector, 6) the output of the bayesian classifier applied by the ERD-based detector, and 7) the final estimation of the intention to move and the optimal threshold level used to convert the estimation to a boolean signal.

is observed. Finally, the tables show that selected features relative to the alpha-band in the case of the patients present lower frequencies than the ones in the group of healthy subjects.

Code	GoodTr (%)	TP (%)	FP/min	Latency (ms)
C1	81.3	82.8	0.47	-48±351
C2	63.8	81.0	1.34	-24±278
C3	39.0	56.1	2.63	-180±476
C4	64.6	70.8	0.38	-198±322
C5	69.8	84.9	1.13	-3±388
C6	61.5	71.2	1.96	-164±290
Average	63.3 ± 13.8	74.5 ± 10.8	1.32 ± 0.87	-89.9 ± 349.2
P1	56.5	84.8	1.83	-58±368
P2	75.0	83.3	0.92	123±290
P3	60.3	80.9	1.94	98±386
P4	60.0	70.0	1.08	83±449
P5	100.0	100.0	0.00	-89±147
P6	46.5	74.4	3.21	50±520
Average	66.4 ± 18.8	82.2 ± 10.4	1.50 ± 1.09	35.9 ± 352.3

Table 6.2: Detection results obtained with control subjects and patients.

C1	C2	C3	C4	C5	C6
C3/21Hz	C3/12Hz	Pz/12Hz	F1/7Hz	C3/12Hz	FC3/19Hz
CP3/21Hz	C3/11Hz	C3/12Hz	F1/8Hz	C3/19Hz	CP1/19Hz
C3/20Hz	C3/23Hz	C3/13Hz	C6/29Hz	C3/11Hz	FC3/20Hz
CP3/20Hz	FC1/18Hz	FC4/9Hz	C3/27Hz	CP3/10Hz	FC3/18Hz
C3/10Hz	FC1/17Hz	P1/12Hz	FC1/23Hz	CP3/11Hz	F3/19Hz
C3/19Hz	C3/22Hz	P1/11Hz	C3/26Hz	C3/22Hz	CPz/20Hz
C3/22Hz	C2/17Hz	CP1/8Hz	C3/24Hz	CP3/12Hz	C1/19Hz
CP3/19Hz	FC1/19Hz	Pz/10Hz	C3/28Hz	Pz/11Hz	F3/18Hz
C3/9Hz	FC1/14Hz	P1/9Hz	FC2/18Hz	C3/18Hz	CP3/18Hz
CP3/22Hz	C3/13Hz	FC4/10Hz	C3/29Hz	CP3/13Hz	FC3/17Hz

Table 6.3: Features selected by the ERD-based detector for the control group.

Fig. 6.7 compares the detection results obtained with the combined detector (ERD and BP) with the results obtained by detectors based only on the BP or the ERD. Statistically significant differences between the three detectors are found in GT, TP and FP/min (p = 0.002, p = 0.010 and p = 0.008, respectively). Pos-hoc multiple comparisons show significant differences between the ERD-based detector and the combined detector in GT (p = 0.007) and FP/min (p = 0.015), but not in TP (p = 0.192). In the comparison between the BP-based detector and the combined detector, significant differences are found in GT (p = 0.003) and TP (p = 0.003), but not in FP/min (p = 0.0.059). Finally, no significant differences are found in GT (p = 0.611), TP (p = 1) and FP/min (p = 0.305) between the detector based on the ERD and the one based on the BP.

P1	P2	P3	P4	P5	P6
C1/9Hz	C2/9Hz	Cz/20Hz	F3/8Hz	CP2/13Hz	C3/14Hz
Cz/13Hz	C2/8Hz	Cz/21Hz	C1/10Hz	C2/13Hz	P2/18Hz
FC1/10Hz	C2/10Hz	Cz/13Hz	F3/9Hz	C1/22Hz	C3/19Hz
FC1/13Hz	CP2/18Hz	Cz/22Hz	C2/11Hz	C1/21Hz	C2/23Hz
C1/10Hz	C2/7Hz	Cz/14Hz	F1/8Hz	Cz/21Hz	CP3/14Hz
CP4/18Hz	Cz/9Hz	Cz/16Hz	P1/10Hz	C1/20Hz	CP1/15Hz
FC1/9Hz	Cz/10Hz	Cz/15Hz	C1/9Hz	CPz/22Hz	FC2/19Hz
FC1/11Hz	CP2/19Hz	Cz/17Hz	P3/8Hz	CPz/16Hz	Pz/22Hz
C1/12Hz	CP2/17Hz	CP1/11Hz	F4/20Hz	CPz/12Hz	CP4/21Hz
C1/13Hz	Cz/8Hz	Cz/19Hz	FC3/8Hz	C1/23Hz	CP3/11Hz

Table 6.4: Features selected by the ERD-based detector for the patients.

For healthy subjects, the detector combining ERD and BP information achieves 6.5 ± 5.2 % more GT than the BP-based detector and 22.4 ± 10.0 % more GT than the ERD-based detector (see Table 6.5). For patients, the percentage of GT also increases when using the combined detector (13.3 ± 10.9 % and 12.6 ± 16.3 % increase as compared to the BP- and ERD-based detectors, respectively).

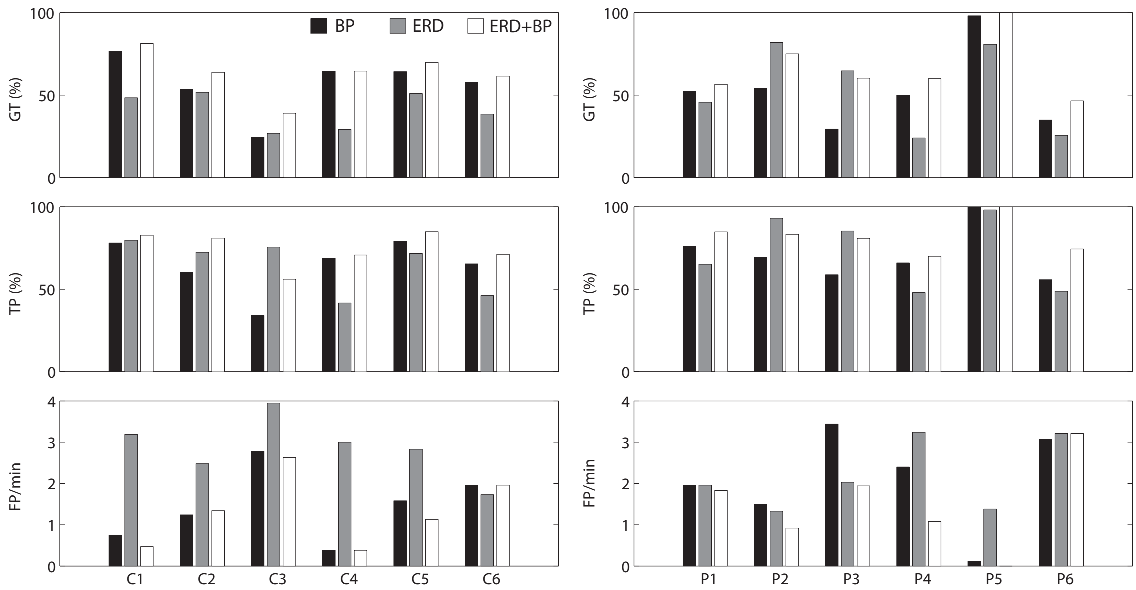


Figure 6.5: Performances of the three compared detectors (BP-based, ERD-based and combined detector) in the healthy subjects group (left) and in the patients (right) in terms of GT, TP and FP/min

Finally, the latencies in the detections of the movement onsets are represented by means of histograms in Fig. 6.6. The latencies obtained when using the detectors based only on the BP or the ERD information are superimposed in the figure. The histograms

Code	Combined vs BP	Combined vs ERD
C1	4.7	32.8
C2	10.3	12.1
C3	14.6	12.2
C4	0.0	35.4
C5	5.7	18.9
C6	3.8	23.1
Average	6.5 ± 5.2	22.4 ± 10.0
P1	4.3	10.9
P2	20.8	-6.9
P3	30.9	-4.4
P4	10.0	36.0
P5	1.9	19.2
P6	11.6	20.9
Average	13.3 ± 10.9	12.6 ± 16.3

Table 6.5: Gain in the performance of the detector (GT in %) when using the combined information of the ERD and BP compared to the use of either of these patterns alone.

shown depend on how much the ERD and BP patterns vary across trials with respect to the onsets of the movements, and also on the detection threshold applied to each one of the three detectors. The figure shows a more delayed distribution of the detections with the group of patients. Nonetheless, around 85 % of these BP detections are located earlier than +375 ms. Given that the window used for the BP detector are 1.5 s long, this result supports the absence of movement artefacts in the activity analysed. The ERD-based detector appears to be the less precise in terms of latencies of the detections, while the BP-based detector presents distributions clearly centred at t = 0 s. Also noticeably, the ERD-based detector shows a certain degree of anticipation in the detections of movement onsets in the group of healthy subjects, although it generates delayed detections in the case of the patients.

6.4.4 Results of Exp2

Overall, patients could reliably control the EEG-based interface by performing the self-paced movements and low detection latencies were obtained in most cases. Fig. 6.7 shows, for each intervention session and patient, the percentages of GT obtained and the latencies for the correct detections of the movements. The GT percentages increased across sessions in P2, P3 and P7, suggesting learning mechanisms in the interaction with the BCI platform. The best GT results were 80.9 %, 64.4 %, 91.7 % and 81.2 % for patients P2, P3, P5 and P7, respectively (green bars in the left panels of Fig. 6.7). Results were similar to those obtained in Exp1. The detection latencies were stable across sessions and in some

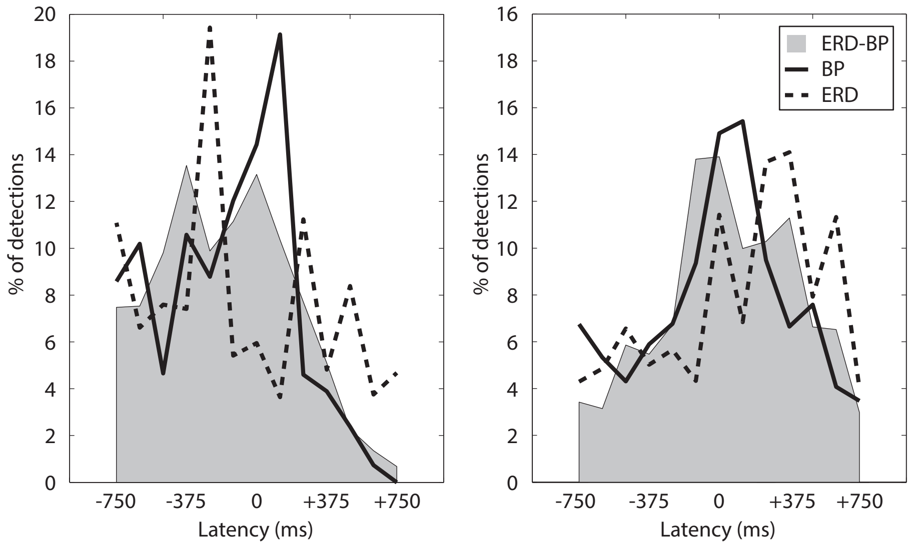


Figure 6.6: Histograms of the distances between the movement detections and the actual movement onsets for healthy subjects (left panel) and stroke patients (right panel). The histograms of the detectors based only on the ERD or the BP are superimposed in the graphs.

cases (P3 and P7) they slightly improved as the intervention evolved. Average detection latencies (considering all sessions) for P2, P3, P5 and P7 were 202 ± 266 ms, 130 ± 316ms, 3 ± 190 ms and 103 ± 254 ms, respectively. Unsuccessful results of the BCI system were only observed in one session (sixth session with patient P3). In this case the BCI-based intervention was cancelled since the patient reported an uncomfortable interaction with the FES system.

As for the EEG-based system performance with motor imagery (blue bars in the left panels of Fig. 6.7), results varied among patients and they provided in all cases reliable estimations. GT results over 50 % were obtained in three out of four patients, which means that in more than 50 % of the trials the BCI system was able to successfully detect the onset of the movement imagination without generating any false activation in the resting period preceding it. Bad trials, on the other hand, were those presenting a false activation in the resting period preceding the movement, or those in which movement imagery was not detected or it was detected too late according to the patients' reports.

Table 6.6 shows the changes obtained in the two evaluated functional scales. Average increases of 10.5 ± 8.7 and 15.7 ± 11.9 points in the SIS and the FMI were obtained with the intervention. Patients P2, P5 and P7 showed changes in the quantified FMI over the minimal detectable change (which is 5.2 points for upper-extremity assessments). Changes of FMI in P3 were slightly below this threshold, despite the positive results observed in the self-report test. Interestingly, P3 was also the patient showing the worst detection results

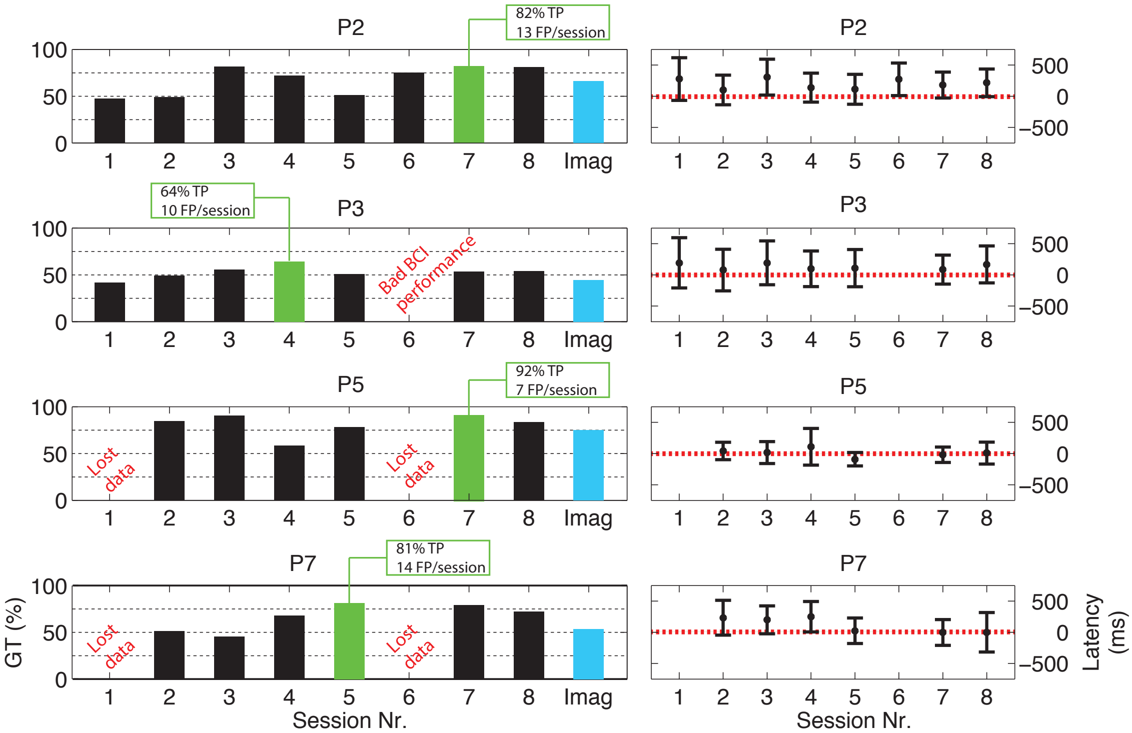


Figure 6.7: Summary of the EEG-based detector performance during the intervention with the patients. Left panels: GT (%) results along sessions for each patient. The best session in each patient is represented with a green bar and for this session the percentage of TP and the number of FP is shown. The GT results for the imagined movements performed by the patients is represented with blue bars. Right panels: Detection latencies (Mean ± SD) along the sessions for each patient. The real onsets of the movements are represented with dashed red lines.

of the EEG-based system, both in terms of GT and detection latencies across intervention sessions.

Code	SIS-pre	SIS-post	FMI-pre	FMI-post
P2	64	74	61	93
P3	66	79	83	88
P5	44	64	65	82
P7	73	72	81	90

Table 6.6: ISI and FMI scales of the patients before and after the BCI intervention.

6.5 Discussion

The accuracy with which movements can be detected online using EEG activity (both in terms of temporal precision and ratio between true and false activations) represents an important criterion to decide whether BCI technology can be brought to clinical practice in neurorehabilitation environments. This study shows the results of an EEG-based detector of voluntary movement onsets combining information extracted from the processing of cortical rhythms and slow cortical potentials. This is the first time that both sources of information are combined to this end. It is also the first time in which the benefits of a detector combining information from the ERD and BP patterns in patients with stroke are demonstrated. Moreover, the EEG system has been tested in a BCI intervention lasting one month with chronic stroke patients. The observed changes in the FMI of three out of four patients were over the minimal detectable change in Fügl-Meyer assessments of the upper-extremity function. This is, to the author's knowledge, the first study of a BCI intervention for upper-limb movements focusing on the idea of inducing associative cortico-muscular facilitation by means of an accurate (in terms of temporal precision) characterization of motor intentions.

Previous studies have described several aspects on the characterization of the BP to locate onsets of voluntary movements. On the one hand, Garipelli et al. studied the relevance of choosing appropriate spatial and temporal filters to extract the BP pattern [Garipelli et al., 2013], without showing results regarding temporal precision in the detections. In a study by Lew et al., average results of BP detection were presented for healthy subjects and stroke patients, although no single trial validation was carried out [Lew et al., 2012]. Up to date there are, to the authors' knowledge, no studies regarding the detection of upper-limb voluntary movements based on the detection of the BP and using an online feasible design. In a recent study, Xu et al. presented a system using a manifold method (Locality Preserving Projection) with a LDA classifier to optimize the classification of the BP. The algorithm was tested on healthy subjects performing ankle dorsiflexions. The TP and FP/min results obtained in that study (79 ± 12 % and 1.04 $\pm$ 0.8, respectively) were similar to the ones obtained here with the healthy subjects and upper-limb movements. Nevertheless, the average latencies presented in their study (315 $\pm$ 165 ms) were higher than the ones obtained here. This differences could be due to variations in the way subjects performed the task in each experiment (differences between upper- and lower limb cortical patterns, length of the resting intervals between movements and speed of movements among others). The observed differences could also be due to the combined use of the ERD and BP features proposed here, which allows to reduce the rate of FP and, as a consequence, allows the selection of less restrictive (more anticipative) detection thresholds.

While several previous studies have made use of the cortical rhythms to either detect movement events [Townsend et al., 2004; Müller-Putz et al., 2005] or to anticipate movement intentions (see [Bai et al., 2011] and Chapter 5 in this thesis), no studies so far have tried to use ERD information to locate onsets of voluntary movement with time precision. In a previous study by Fatourechi et al., the combined use of cortical rhythms and slow cortical potentials was proposed for an asynchronous BCI, although in that case the device was not intended to detect the onset of voluntary movements [Fatourechi et al., 2008]. The Naïve Bayes classifier described here has demonstrated that the ERD supplies valuable information in this sense. Indeed, it has been shown here the benefits of the combined use of the information about the ERD and BP as compared to detectors relying solely on either the BP or the ERD. Significantly better performances could be achieved with the combined detector in all metrics analysed: a higher number of GT and TP was achieved with lower rates of false activations during the resting intervals. Previous studies have demonstrated that different neural mechanisms are involved in the generation of the ERD and the BP, and therefore may justify their complementarity. On the one hand, the BP is assumed to originate in the presupplementary and supplementary motor areas [Babiloni et al., 1999; Shibasaki and Hallett, 2006], which are associated with the movement planning and with the process of focusing on the intention to move [Lau et al., 2004]. On the other hand, the ERD is first visible over the contralateral motor cortex [Pfurtscheller and da Silva, 1999], and it is associated with the formation of more specific neural assemblies synchronized at higher frequencies in order to generate the desired descending motor commands [Pfurtscheller and da Silva, 1999; Buzsáki and Draguhn, 2004]. The spatial distribution of both phenomena in the here presented data also points to different cortical sources. Given these evidences, it seems reasonable to point to an improved outcome in the combination of both sources of information to estimate certain aspects regarding the motor planning.

Differences in the average ERD and BP patterns between patients and healthy subjects were found in Exp1. On the one hand, a delayed peak of the BP was observed in the patients group, likely associated with the higher cognitive motor planning time and the slower speed with which stroke patients perform voluntary movements [Daly et al., 2006; Jochumsen et al., 2013]. On the other hand, differences in the spatial distribution of both ERD and BP patterns were also observed (see Fig. 6.3), reflecting altered cortical activation patterns in stroke patients, also described in previous studies [Wiese et al., 2004; Daly et al., 2006; Platz, 2000; Stepien et al., 2010]. Regarding the single-trial detection results, previous offline studies [Niazi et al., 2011] showed differences in the BP-based detection performance with healthy subjects and stroke patients (significantly worse

TP results were obtained with the patients). In contrast, the detection results obtained here in Exp1 (in terms of GT, TP and FP/min) were similar for patients and healthy subjects. Apart from the differences in the recruited subjects and paradigms used in both experiments, these better results with patients were likely due to the improvement of the detector performance when the ERD information was used, which provided a 13.3 ± 10.9 % increase in the number of GT as compared to the BP-based detector alone (see Table 6.5). On the other hand, differences were observed in the detection latencies: detections in patients were achieved later than with the healthy subjects. According to Fig. 6.6, this is especially evident in the ERD-based detection (while ERD-based detections in healthy subjects tend to anticipate the actual movement onsets, the reverse effect is observed in the group of patients). Such difference may be the combined result of the altered ERD in stroke patients [Platz, 2000; Stepien et al., 2010] and an aging factor [Derambure et al., 1993].

Given the detector design proposed here, the influence of movement artefacts in the detections achieved after the onset of the movements are considered negligible. First, regarding the ERD-based system, the combined use of a small laplacian filter and a band-pass filter discarded the presence of movement-related common low-frequency components in the analysed EEG. In addition, the use of premovement signals in the training stage ensured that the Bayesian classifier focused specifically on the ERD phenomenon, as it may be attested by analysing the features selected in Exp1 by the Bayesian classifier (see Tables 6.3 and 6.4). In the case of the BP-based detection, the use of spatial filtering together with the spatial distribution of this pattern (see Fig. 6.3) reduces the chance that artifactual sources are having any influence. Indeed, around 95 % of the detections in the case of the healthy subjects in Exp1 (around 85 % with the patients) were obtained with latencies under +375 ms (see Fig. 6.6). Since a matched filter of 1.5 s was used, it is highly unlikely that any of these detections were caused by the effect of movement artefacts. In fact, BP-based detections later than +375 ms in the stroke patients are likely related to the intrinsic difficulties in the detection of the real onsets of the movements, and to the delayed BP observed in these patients due to slower movement velocities with the affected limb [Jochumsen et al., 2013] and to an increased cognitive motor planning time [Daly et al., 2006]. Results with imagined movements in Exp2 reinforce the idea that the EEG-based detector proposed here did not rely on muscular artefacts. Despite the fact that movement imagery is associated with weaker cortical changes over the sensorimotor cortex [Neuper et al., 2006; Nascimento, 2008], results here with the imagined movements were similar (although worse) to the ones with the actual movements, and in all cases, they were clearly above chance levels.

A number of studies have been proposed during the last years in the field of EEG-based BCI systems for functional rehabilitation of stroke patents [Grosse-Wentrup et al., 2011; Silvoni et al., 2011; Ang and Guan, 2013]. To the author's knowledge, the most relevant studies up to date are the ones by research groups from Tübingen [Buch et al., 2008; Ramos-Murguialday et al., 2012, 2013], Rome [Pichiorri et al., 2011], Aalborg and Göttingen [Niazi et al., 2012; Mrachacz-Kersting et al., 2013; Xu et al., 2014]. On the one hand, BCI experiments proposed by the groups from Tübingen and Rome focused on paradigms promoting the patient's self-modulation of sensorimotor rhythms. Results from these experiments showed improvements in upper limb FMI motor scores in stroke patients with no active finger extension [Ramos-Murguialday et al., 2013] and significant increase in motor cortical excitability, as revealed by post-training TMS mapping of the hand muscle's cortical representation [Pichiorri et al., 2011]. On the other hand, studies performed in Göttingen and Aalborg have focused their attention in the temporal benefits of using EEG systems to decode motor intentions, which provides a faster way to induce long-term associative facilitation by increasing the excitability in cortical areas representing the part of the body to be moved [Mrachacz-Kersting et al., 2012]. In this regard, it has been exposed that any feedback that does not fulfill the requirement of coincident activation of the targeted brain regions is unlikely to result in long-term behavioural changes [Grosse-Wentrup et al., 2011]. Results of BCI interventions with EEG systems optimized for the detection of the onsets of the movements have demonstrated plastic changes in the supraspinal level when using proprioceptive electrical [Niazi et al., 2012] or mechanical [Xu et al., 2014] feedback, and have also provided preliminary results of a BCI intervention on stroke patients, leading to improvements in their gait [Mrachacz-Kersting et al., 2013]. The BCI intervention proposed in this chapter is therefore similar to the second group of BCI interventions. While this latter group of studies have mainly focused on the rehabilitation of lower-limbs through analytical dorsiflexions of the ankle, the BCI intervention here has been proposed for upper-limb reaching movements. Moreover, the EEG based system uses both cortical rhythms and slow cortical potentials to supply patients with an appropriate afferent volley, and therefore, it may be expectable that benefits related to mechanisms associated to the modulation of sensorimotor rhythms are also summed to the expected associative facilitation effects in the here proposed scenario. Future studies in this regard will look for larger experimental groups and more adequate clinical validation studies will be pursued, using double-blind placebo-controlled techniques.

Developing EEG-based systems that can be trained in a short period of time is a critical aspect in order to bring this technology into the clinical practice. The training procedure proposed here in Exp2 contemplates that a number of self-initiated movements are performed in the beginning of each session and are used to train the detector (this process takes around 5 min in case 30 movements are used to train the system). In this regard, several studies have proposed ways to use training data from different sessions to calibrate the BCI system [Shenoy et al., 2006; Niazi et al., 2013], and they may be considered in future studies.

Finally, gyroscopic data were used to locate the movement events in order to extract and characterize the subject-specific ERD and BP patterns. Similar previous studies have frequently used muscle activation data (from EMG) for such purposes. In this case, because functional upper limb movements were measured on stroke patients, detecting the onsets of the movements from muscle activation became difficult, particularly in the patients with muscle spasticity. On the contrary, by using kinematic data of the upper-limb segments, it becomes possible to finely detect when a functional movement starts without significant latencies, considering that the electromechanical delay for upper-limb movements is relatively small (in the order of tens of milliseconds [Norman and Komi, 1979]). In agreement with this, results presented here of average BP patterns in healthy subjects and patients -obtained with movement references based on the gyroscopic data- show peaks of the BP with similar latencies than those observed in other studies using EMG data and healthy subjects [Mrachacz-Kersting et al., 2012].

6.6 Chapter conclusions

A system using the EEG activity to detect online the onset of voluntary upper-limb reaching movements based on the combined charaterization of the ERD and BP patterns has been tested here with healthy subjects and chronic stroke patients. The results obtained with the proposed detector point to an improvement in the temporal accuracy of the estimations, as compared to other similar online-feasible techniques. Remarkably, the obtained results offline with patients (TP = 82.2 $\pm$ 10.4 %, FP/min = 1.32 $\pm$ 0.87 and average latencies of -89.9 $\pm$ 349.2 ms) were close to the ones obtained with the healthy subjects (TP = 74.5 $\pm$ 13.8 %, FP/min = 1.50 $\pm$ 1.09 and average latencies of 35.9 $\pm$ 352.3 ms), and therefore suitable for online BCI applications. Moreover, a BCI intervention using the developed EEG-based detector of the movement intention has been proposed and tested with four chronic stroke patients in eight sessions along one month. The online function of the EEG-based detector was equivalent to results obtained offline, and the preliminary results obtained point to a functional improvement of the patients as a result of the proposed therapy (average increases of 10.5 $\pm$ 8.7 and 15.7 $\pm$ 11.9 points in the SIS and the FMI were obtained).

This study has tested for the first time the EEG-based detection of the onsets of voluntary upper-limb movements based on the combination of information from cortical rhythms and slow cortical potentials. The successful results obtained with stroke patients and the applied asynchronous paradigm demonstrate that the proposed system is suitable for rehabilitation applications in which the patient performs the self-paced tasks and receives assistance or simple proprioceptive feedback from a neuroprosthetic device. Indeed, the presented preliminary results of an upper-limb intervention are the first demonstration of an improved functional upper-limb capacity in stroke patients undergoing an EEG-based associative facilitation paradigm based on the characterization of the mental states related to motor intention.

Chapter 7

Conclusions and future work

This chapter puts together the main results and conclusions reached in this present thesis, enumerates the main contributions associated with the presented studies and discusses the main achievements and limitations found during the experimental sessions. A list of future research lines resulting from the here presented work in each of the studies and the scientific publications related to the work performed for this thesis are included as well.

7.1 General overview of the work presented in this thesis

The range of applications of EEG systems in the study and treatment of neurological diseases related to motor disabilities has exponentially grown during the last decades. This is mainly a result of the development of new EEG technologies integrated in computer-based platforms, which allows a fast and accurate characterization of different cortical states. As a consequence, relevant advances have been achieved with these technologies. Physical interfaces for the signal acquisition (active electrodes, impedance optimization, dry electrode technologies etc.) have been improved, the integration (with negligible temporal synchronization errors) of electrophysiological signals from different parts of the human body has become possible and much more versatile systems have been developed to record the EEG activity (with a wide variety of electrode montages, highly dense EEG measurements, portable systems robust against electromagnetic interferences etc.). In this present thesis, these technological advances have been used to propose a set of studies with a common link: exploring the possibilities of using techniques for the measurement, analysis and conditioning of the cortical activity to study and treat neurological disorders affecting the motor function. In addition, these studies represent different application examples of the EEG systems in patients. Given the current high prevalence of neurological disorders affecting the motor function in the adult population, advances in the proposed research lines for the diagnosis and treatment of these patients becomes a critical aspect to work on. In fact, the main strategic research lines funded by the European Commission in forthcoming years (in the framework of the HORIZON 2020) and in the clinical field will look for technologies improving diagnosis and prognosis of pathologies so that the patients' treatments become optimized, as well as innovative treatments and technologies that empower active and healthy ageing and allow patients to bring part of their treatments to their homes while maintaining the treatment-related benefits.

The first study presented an application of data mining techniques to explore the information hidden in EEG data and discriminating a number of movements performed with a single arm, and therefore sharing similar somatotopic representations. The obtained results were clearly above the chance level. In order to achieve these results, the developed classifiers looked for cortical sources of information distributed along different scalp regions (not only from the *a priori* expected contralateral central positions where the cortical representation of the moved arm is found). The obtained results may be a combined consequence of, among others, the differences in higher-order mental functions associated with the planning and execution of the different tasks (some of them were more natural than others) and the more separated cortical representation of the different joints of a single-limb. In order to fully validate the hypothesis that EEG carries information that allows the classification of the proposed tasks, a set of tests was carried out, all of them aimed at proving that other explanations for the obtained results (*e.g.* the fact that different initial positions affect the classification) could be discarded. The obtained results open a door to integrating advanced EEG classification techniques in BCI interventions for rehabilitation, enriching the capacities of the BCI systems.

The second study in the thesis has presented a neurophysiological characterization of the effects of a clinically used drug (alprazolam) in the tremors and the cortical activity of patients with ET, which has its origin in the pathological behaviour of the central nervous system. The presented study shows the temporal dynamics (due to the drug effects) of neurophysiological variables related to tremor manifestation in ET. This study is in line with other previous works, by a number of research groups, in which the main purpose is to characterize the mechanisms through which tremor is generated and altered in patients with ET, a neurological disease whose origin and action mechanisms are nowadays still not well understood. In this kind of studies, electrophysiological techniques such as the EEG and the EMG are of great interest, since they allow the characterization of electrical processes with high temporal resolutions (in the order of $\tilde{1}$ ms), which is a critical factor to detect the changes in the neurophysiological function intended to be characterized. Additionally, studies of connectivity between distant neural networks provides highly informative data regarding interacting structures and the way in which this interaction changes along time. In the concrete case of the study included in this thesis, the main contribution resides in the characterization of the interplay between the beta and tremor-related oscillations at the cortical level, a phenomenon expected to be shared by other subcortical structures. The interaction between these brain oscillations results in changes of the apparent tremor, and therefore, further understanding them will improve tremor management in patients with ET. Finally, the presented results constitute the first objective quantification of tremor reduction in ET as a result of the administration of a drug. Such numerical description of the effect of a drug in a given pathology are currently demanded by clinical environments, so that a precise and objective characterization of the patients status and the outcomes of applied treatments can be obtained.

In the third of the four studies included in this thesis, the design of an EEG-based system to anticipate voluntary movements and its integration in a BNCI to compensate pathological tremors have been presented. The proposed system is conceived as a proof of concept of multimodal systems to be used on patients with pathological tremors. The experimental sessions carried out allowed the evaluation of the EEG-based system as well as the whole acquisition system on patients with ET. The experimental paradigms used represented a simplified scenario of the real one in which the patient would be using the platform: long periods of inactivity followed by self-initiated simple movements were used in order to test the ability of the system to provide reliable and anticipated estimations about motor planning when the subjects were about to move. Results achieved demonstrate the potential of the EEG signal to be used to describe periods of movement preparation and they also show that, under optimal conditions (subjects concentrated in the task and reduced electromagnetic interferences), estimations on movement intentions may be achieved reliably (with high percentages of true positives and reduced number of false activations). Nevertheless, the proposed study presents a set of technological and methodological limitations that reduce the impact of these results in daily living conditions: wearable technologies working reliably at home are nowadays not available and the analysis of the EEG signal with currently available techniques is still not able to avoid its contamination (reducing the signal-to-noise ratio), produced while users perform daily living tasks. A major prerequisite of BCI systems for motor compensation is that the benefits provided by the technology outbalance the disadvantages of using it. These disadvantages may be caused, among others, by aesthetic or ergonomic factors regarding the use of the wearable technologies, economic costs associated with the development of the used technology or the cognitive requirements that the use of human-machine interfaces demand from the potential users. From the author's point of view, there are currently no commercial BCI devices for motor compensation that meet the aforementioned requisites. There are, nevertheless, cases in which the application of the BCI systems results in a clear improvement of the patients' capabilities, such as spelling interfaces for complete locked-in patients, giving them the only possible way of communication with the outside world. In these cases, the benefits provided by the BCI systems will more likely justify the efforts of using the available technology. The system proposed in this thesis must be considered a proof of concept of the advantages that can be derived from the use of multimodal systems for the precise neurophysiological characterization of the movement generation chain originated in the brain and manifested in the peripheral limbs. While the here proposed mHRI system integrating EEG technology aims at meeting some of the aforementioned requirements for motor compensation technologies (a small number of electrodes is used, adaptive algorithms reduce training demands of the system, the processing techniques described require a relatively small computational load and the system is focused on ecologically characterizing the natural cortical activity observed when a subject performs a voluntary movement), future works in this line will need to focus on ways to solve the mentioned limitations of the technology.

Finally, the fourth proposed study has presented an EEG-based technique to detect mental states associated with the initiation of voluntary functional movements. Inspired by some previous works regarding the online single-trial decoding of the BP [Niazi et al., 2011; Jochumsen et al., 2013], this study has proposed a way to optimize the detection of the movement onset-related mental states in patients with stroke, and this has been carried out by combining two different types of information: oscillatory changes (related to the ERD) and low-frequency cortical components (giving rise to the BP). The obtained results have demonstrated that it is possible to generate a reliable control signal about the onset of voluntary actions with temporal precision, high recall ratios and almost no false detections in experimental paradigms that could be easily transferable to clinical environments in case minor adjustments were performed (optimize the number of channels used for the detection, reduce training periods of time, increase the detector efficacy with subjects not showing identifiable ERD/BP patterns, etcetera). Importantly, results obtained with chronic stroke patients were similar than those with the control subjects despite the patients' altered cortical activity [Daly et al., 2006; Stepien et al., 2010]. Consequently, these patients are suitable for BCI systems using electrical stimulation aimed to provide associative facilitation between the cortex and the muscles of affected limbs. In addition, a BCI intervention for patients with a stroke has also been proposed and preliminary results of a clinical validation with four chronic stroke patients have been presented. Although further research must be carried out to fully understand the effects of EEG-based conditioning paradigms in the motor function of stroke patients, results here provide evidences of a possible improvement in the motor condition of the patients after a whole month intervention.

In summary, this thesis has proposed a set of novel scientific studies framed in the main research lines that are being currently explored with EEG technology. According to the results and conclusions reached in the proposed studies, it is considered that EEG systems represent a powerful way to characterise the neurophysiological mechanisms of neurologic diseases, and that the acquired information from this sort of studies represents a non-invasive and efficient opportunity to look for the cerebral regions originating certain motor-related pathologies. On the other hand, experiments carried out here with BCI systems using the EEG signal have demonstrated to be reliable and of special interest for rehabilitation scenarios, while the BCI application in daily-living conditions represents a challenging objective that still need to be further explored and requires dramatic technological improvements in order to find more robust and wearable technologies that can lead to an actual benefit of patients using the BCI systems for assistive/compensatory purposes. In conclusion, despite the several and well known limitations of EEG technologies for the analysis of the brain activity, it can be established that these systems allow the acquisition of highly relevant cortical information regarding motor-related mental processes, which makes this kind of technology a valuable tool for the research and conditioning of the human neurological system.

7.2 Contributions

This thesis has yielded advances from both the technological and the scientific points of view in all studies proposed.

The main contributions from the technological point of view are:

- The design of an integrated upper-limb platform working in real-time. The platform was designed to acquire information from different types of noninvasive sensors (EEG, EMG and gyroscopic sensors) characterising the planning and execution of voluntary movements. The platform was also capable of processing online the acquired data and generating an adequate feedback.

- The development of signal processing and classifying techniques adapted to the kind of signal recorded in the two kinds of patients considered in this thesis and to the requirements of online processing and real-time single-trial function desired for BCI applications. Especially in this regard, an original methodology to detect onsets of voluntary movements using slow cortical potentials and cortical rhythms has been presented.

- The design and validation in real-time of asynchronous BCI systems using motor planning EEG segments to anticipate or detect when patients begin a voluntary movement with the upper-limb.

- The proof of concept of the use of the EEG activity in a mHRI architecture that constitutes the first multimodal interface taking advantage of the combined acquisition of EEG, EMG and gyroscopic data, which allows the concurrent characterization of different parts of the body associated with the execution of a movement.

The main scientific contributions of this thesis are:

- It has been proposed for the first time an experiment to inspect whether the EEG signal carries enough information to classify up to seven different tasks performed with a single limb. Both the methodology applied and the validation procedure are also innovative in this sort of studies.

- It has been presented the first neurophysiological study using EEG and EMG data to analyse the effects of a drug on cortical activity and tremors of patients with ET.

In addition, the obtained results have shown for the first time that a significant correlation exists between the dynamics of specific cortical oscillations and pathological tremor manifestation as a consequence of the drug effects.

- The study of the EEG-based anticipation of voluntary movements presented in Chapter 5 was the first demonstration (to the author's knowledge) of the capacity of the EEG signal to provide reliable movement predictions based on single-trial classification of online data of healthy subjects and ET patients. This study also provides, for the first time, the results of a BCI system tested in ET patients and it represents an original approach to BCI applications for this group of patients.
- It has been demonstrated for the first time the relevance of combining different cortical sources of information (such as BP and ERD) to estimate the initiation of voluntary movements with the upper-limb. In this line, special relevance may be given to the positive results achieved with stroke patients, improving the results presented by similar previous EEG-based studies by other research groups. It has also been proposed for the first time an upper-limb intervention protocol for stroke patients using BP and ERD patterns to provide proprioceptive feedback tightly associated with the patients' expectations of movement. The effects of the proposed intervention have been studied with a small group of patients.

7.3 Scientific dissemination

The work performed to carry out this thesis has given rise to a number of contributions in scientific journals, conferences and book chapters in the neurorehabilitation framework. The following lines summarize these contributions:

Publications in journals:

- J.A. Gallego, J.L. Dideriksen, A. Holobar, J. Ibáñez, J.P. Romero, J.L. Pons, E. Rocon, D. Farina. Properties and determinants of the relative phase between neural drives to antagonist muscles in essential tremor. *Brain.* To be submitted.
- E. Monge, F. Molina, F.M. Rivas, J. Ibáñez, J.I. Serrano, I. Alguacil, J.C. Miangolarra. Electroencefalografía como método de evaluación tras un ictus. Una revisión actualizada. *Neurología.* In Press.
- J. Ibáñez, J.I. Serrano, M.D. del Castillo, J. Mínguez, J.L. Pons. Predictive classification of self-paced upper-limb analytical movements with EEG. *Medical & Biological Engineering & Computing.* (second revision).

- J.A. Gallego, J.L. Dideriksen, A. Holobar, J. Ibáñez, E. Rocon, J.L. Pons, D. Farina. Neural drive to muscle and common synaptic inputs to the motor neuron pool in essential tremor. *Journal of Neurophysiology.* Submitted.

- J. Ibáñez, J.I. Serrano, M.D. del Castillo, E. Monge, F. Molina, I. Alguacil, J.L. Pons. Detection of the onset of upper-limb movements based on the combined analysis of changes in the sensorimotor rhythms and slow cortical potentials. *Journal of Neural Engineering*, 11(5):056009, 2014.

- J. Ibáñez, J. González de la Aleja, J.A. Gallego, J.P. Romero, R.A. Saíz-Díaz, J. Benito-León, E. Rocon. Effects of Alprazolam on Cortical Activity and Tremors in Patients with Essential Tremor. *PLoS ONE.* 9(3): e93159, 2014

- J. Ibáñez, J.I. Serrano, M.D. del Castillo, J.A. Gallego, E. Rocon. Online detector of movement intention based on EEG – Application in tremor patients. *Biomedical Signal Processing and Control*, 8(6):822-9, 2013.

- J.A. Gallego, J. Ibáñez, J.L. Dideriksen, J.I. Serrano, M.D. del Castillo, D. Farina, E. Rocon. A multimodal human-robot interface to drive a neuroprosthesis for tremor management. *IEEE Transactions on Systems, Man and Cybernetics, Part C: Applications and Reviews*, 42(6):1159-68, 2012.

- M.D. del Castillo, J.I. Serrano, J. Ibáñez. Metodología para la creación de una interfaz cerebro-computador aplicada a la identificación de la intención de movimiento. *Revista Iberoamericana de Automática e Informática Industrial (RIAI).* 8(2):93-102. 2011.

Book chapters:

- S. Cremoux, J. Ibáñez, S. Ates, A. Dessí. *Neuromodulation on Cerebral Activities* in *Emerging therapies in neurorehabilitation*, J.L. Pons and D. Torricelli (Eds.), Springer Verlag, 2014.

Selected publications in conference proceedings:

- J. Ibáñez, J.I. Serrano, M.D. del Castillo, E. Monge, F. Molina, F.M. Rivas, I. Alguacil, J.C. Miangolarra, J.L. Pons. Upper-Limb Muscular Electrical Stimulation Driven by EEG-Based Detections of the Intentions to Move: A Proposed Intervention for Patients with Stroke. *2014 Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, accepted.

- J. Ibáñez, F. Molina, J.I. Serrano, M.D. del Castillo, E. Monge, F.M. Rivas, M. Carratalá, J. Iglesias, I. Alguacil, A. Cuesta, R.Cano, J.C. Miangolarra, J.L. Pons. A BCI intervention for upper-limb functional movements of chronic stroke patients. *2014 Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, accepted abstract.

- J. Ibáñez, J.I. Serrano, M.D. del Castillo, E. Monge, F. Molina, F.M. Rivas, I. Alguacil, J.C. Miangolarra, J.L. Pons. Detection of the Onset of Voluntary Movements Based on the Combination of ERD and BP Cortical Patterns. *Replace, Repair, Restore, RelieveBridging Clinical and Engineering Solutions in Neurorehabilitation. Springer International Publishing*, 437-46; 2014.

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- I. Alguacil, E. Monge, A. Cuesta, J. Ibáñez, F. Molina, M. Pérez de Heredia. Detección de la intención de movimiento mediante Brain-Computer Interface en el ictus. *51 Congreso Nacional de la Sociedad Española de Rehabilitación y Medicina Física SERMEF 2013*, accepted presentation.

- J. Ibáñez, J.I. Serrano, M.D. del Castillo, L. Barrios, J.A. Gallego, E. Rocon. An EEG-based design for the online detection of movement intention. *Advances in Computational Intelligence. Lecture Notes in Computer Science.* 6691, 370-377, 2011.

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- E. Rocon, J.A. Gallego, L. Barrios, A.R. Victoria, J. Ibáñez, D. Farina, F. Negro, J.L. Dideriksen, S. Conforto, T. DAlessio, G. Severini, G. Grimaldi, M. Manto, J.L. Pons. Multimodal BCI-mediated FES suppression of tremor. *Proceedings of 2010 Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, 3337-40, 2010.

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7.4 Future work

The applied methods in this thesis and the achieved results are expected to serve as a starting point for future projects and research lines. Some of the topics considered for future research are the consequence of the results and conclusions reached in the here presented work, while others constitute a planned continuation in the framework of the addressed research line. Future studies identified here are organized in two groups associated with the two considered pathologies considered in this thesis. According to this division, future studies in line with the EEG classifier presented in Chapter 3 (EEG-based classification of upper-limb analytical movements) are integrated in the block of studies related to stroke, since such an application is expected to be of interest both to characterize the cortical status of patients with cortical reorganization and to develop advanced BCI systems capable of predicting the kind of movements that the patients are planning to perform during the rehabilitation sessions.

Regarding the use of EEG and BCI technologies in the study and treatment of ET, the following future goals are identified, some of which have already been started at the time this document has been written:

- Study the possible benefits of EEG-based neuromodulation systems in pathological tremors. In this line, previous experiments have been carried out by other research groups showing promising results when patients with tremor are able to modulate movement-related cortical activity [Fumuro et al., 2013].

- Develop new signal processing techniques for electrophysiological signals to improve the findings achieved with EEG and EMG technologies and with ET patients so far. Of special interest in this regard are the improvement of techniques studying interaction between neural populations and the development of new means of extracting the directionality of this interaction and the estimated delays.

- Explore new technologies for the BNCI platform that allow bringing the proposed system into real-life conditions. This involves testing new acquisition technologies (modern dry electrodes, active electrodes with high signal-to-noise ratio...) and developing new signal processing techniques that allow filtering external sources of signal contamination that are present during daily living conditions.

- Design new experimental protocols to increase our knowledge regarding tremor generation mechanisms in ET. In this line, studies using vibrotactile stimulation will be carried out in the near future in order to analyze the effects of periodic sensory afferences in tremor manifestation. Combination of EEG measurements with other technologies such as functional magnetic resonance imaging and magnetoencephalography systems are also expected to provide a more detailed description of tremor-related neural structures, by analysing the pathological tremor from different perspectives.

- Look for more complex ways of combining the EMG and EEG information to improve the performance of the proposed mHRI.

- Increase the number of recruited patients for the validation of the mHRI system and include patients with pathological tremor caused by other tremor-related diseases, such as Parkinson's disease, or cerebellar tremor, so that the proposed platform can be robustly validated.

As for possible future research lines derived from the here presented studies with stroke patients, some of them are listed in the next lines:

- To test online the EEG classifier of analytical upper-limb movements (presented in Chapter 3) on a large number of patients with stroke. This will allow the analysis of the extent to which the proposed system is able to describe altered cortical activation patterns and of the possibility of integrating the system in a BCI with other classification modules, leading to an improved characterization of the patients' motor intentions while they perform rehabilitation tasks.

- To advance in the development of the EEG-based BCI intervention for stroke patients, including robotic technologies able to cooperate with the neuroprosthetic device to produce a more natural movements during the rehabilitation. Besides, the adaptive control of the assistive forces delivered to the patients' arms will be addressed in the future, so that an optimal movement generation is achieved.

- To improve certain aspects of the EEG signal processing techniques used in order to make the BCI-based intervention suitable for clinical scenarios. In this line, it is identified as a relevant goal to look for ways to make the training data from a patients valid along different intervention sessions, which requires overcoming the inter-sessions variability of the EEG signal properties (due to changes in the electrode impedances, specific electrode locations on the scalp or patients' vigilance). It is an additional goal to look for variations in the proposed system so that a reduced number of electrodes can still allow a robust detection of movement intentions. Future experiments will also seek to develop online artefact filtering techniques, so that patients can make use of this technology in a less restrictive way. All these advances will have as a final goal to adapt EEG-based BCI technology to the clinical scenario by reducing the time required for the interventions, allowing cost-effective EEG systems and allowing a proper function of the proposed system in electrically contaminated rooms (typically found in clinical environments).

- To explore EEG sources of information that allow a fine characterization of the status of a patient with stroke and an accurate prognosis about the patient's evolution both in terms of functional motor capacity and cortical activation patterns. It is expected that gaining knowledge in this regard will serve to develop interventions tailored to patients' needs and to evaluate the efficacy of current interventions using longitudinal studies.

- To explore the benefits that the BCI intervention presented here may provide to stroke patients in acute or subacute states. This kind of studies are of great interest, since stroke patients in early stages present high plastic changes during the first weeks and months after the brain injury, and therefore, conditioning paradigms may provide more significant changes in these patients. In this regard, it should also be further analysed what sorts of cortical changes can lead to maladaptive rehabilitation (inducing cortical changes that are suboptimal for the treated patient).

- To carry out a clinical validation procedure in which a larger sample of patients can be considered, so that more reliable results are reachable by increasing the number of subjects in each of the experimental groups and also by increasing the number of control groups to discard all possible non EEG-based effects leading to patients' improvement.

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