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COGNITIVE ASSESSMENT AND REHABILITATION OF SUBJECTS WITH TRAUMATIC BRAIN INJURY

Anna Lisa Mangia

Supervisor

Prof. Angelo Cappello

Reviewer

Prof.ssa Serenella Salinari

Ph.D. Coodinator

Prof.ssa Elisa Magosso

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Summary

Overview

This thesis regards the study and the development of new cognitive assessment and rehabilitation techniques of subjects with traumatic brain injury (TBI).

Advances in emergency medicine have greatly increased survival rates of people sustaining TBI. However, these advances have come with the realization that many survivors are living with significant residual deficits in multiple areas of functioning, which make the resumption of a quality lifestyle that is extremely difficult. To this point, TBI has recently been characterized as a chronic disease. As well as other chronic diseases, TBI is often responsible for persistent disabling symptoms in multiple organ systems. Therefore, several researchers and clinicians have emerged to treat these symptoms in order to help these individuals regain function and live more productive and independent lives.

The use of technological innovations in assessment and neuropsychological rehabilitation has increased in research and clinical practice.

The literature shows that neuropsychological assessment benefits from the use of neuroimaging technique (i.e. qEEG) and computerized instruments. The use of these techniques in the assessment of a patient allows to have quantitative and objective parameters; moreover these techniques reduce the misdiagnosis rate. A correct assessment has deep implications in rehabilitation of the patients, than it is very important to search new technologies and methods of assessment.

In rehabilitation, the use of new technologies is more diversified, such as electronic devices and cell phones, quantitative EEG (qEEG), brain computer interface (BCI), virtual reality, robots, neurofeedback, transcranial direct current stimulation, among others.

In neuropsychological rehabilitation, the new technologies have facilitated the development of compensatory strategies and real-world simulations, but they have not yet been introduced in daily clinical practice.

For these reasons, we need new studies and investigations to understand the action mechanism of these new technologies and to validate their use on large scale.

This thesis i) provides an overview about the state of art of this new assessment and rehabilitation technologies, ii) suggests new methods for the assessment and

rehabilitation and iii) contributes to the explanation of the neurophysiological mechanism that is involved in a rehabilitation treatment.

This thesis is composed of 12 chapters. Some chapters provide useful information to contextualize TBI and its outcome; they describe the methods used for its assessment/rehabilitation. The other chapters illustrate a series of experimental studies conducted in healthy subjects and TBI patients that suggest new approaches to assessment and rehabilitation. The new proposed approaches have in common the use of electroencefalografy (EEG). EEG was used in all the experimental studies with a different porpouse, such as diagnostic tool, signal to command a BCI-system, outcome measure to evaluate the effects of a treatment, etc.

Chapter 1 gives an overview of TBI. It gives a definition of TBI, epidemiological information and the classification of TBI. In particular, TBI can be classified as mild, moderate and severe. This classification will be the guideline of all the paper. Infact, the thesis is divided into two main parts: the first part (cap4-cap7) is focused on the severe TBI. The second one is focused on mild and moderate TBI.

Chapter 2 resumes the basic information about the physiological origin, the properties and the application domains of the EEG signal and the most common analytical methods, involving methods for i) the analysis in the frequency and time-frequency domains, ii) the separation and the localization of EEG sources and iii) applications aimed to extract event-related modifications of some EEG properties.

Chapter 3 introduces the concept of BCI; it describes the EEG-based BCI typologies and their applications.

Chapter 4 defines severe-TBI that is classified in different levels of consciousness disorders (coma state, in the vegetative state, in the minimally conscious state, and affected by the so-called locked-in syndrome). The related issues have an enormous relevance due to ethical, clinical, and economical reasons. The focus in this review relies on i) the search for optimal (both in the neuroimaging and in the electrophysiological domains) methods to assess the functionality (and the degree of impairment) of the several functions of the central nervous system of the patients and ii) the possibility to communicate with these patients through properly developed BCI systems.

Chapter 5 describes the first experimental activity about the development of an improved procedure to detect brain response to imagery instruction in patients with disorders of consciousness. This work describes a procedure using EEG to detect

brain responses to imagery instruction in patients with disorders of consciousness. Five healthy subjects and five patients with different disorders of consciousness took part in the study. A support vector machine classifier applied to EEG data was used to distinguish two mental tasks (Imagery Trial) and to detect answers to simple yes or no questions (pre-Communication Trial). The proposed procedure uses feature selection based on a nested-leave-one-out algorithm to reduce the number of electrodes required. We obtained a main classification accuracy of 82.0% (SD 5.1%) for healthy subjects and 84.6% (SD 9.1%) for patients in the Imagery Trial, and a main classification accuracy of 80.7% (SD 11.5%) for healthy subjects and 91.7% (SD 7.4%) for patients in the pre-Communication Trial. The subset of electrodes selected was subject and session dependent.

After the development of the procedure for the discrimination of two imagery tasks, a BCI system for communication was proposed.

Chapter 6 describes a procedure to design a similitude-based brain computer interface system for communication. Five healthy subjects and two patients with disorders of consciousness took part in the study. A support vector machine classifier applied to EEG data was used to detect answers to simple yes/no questions, while reducing the number of required electrodes. Just using ten electrodes we obtained a main classification accuracy of 83.5% (SD 12%) for healthy subjects and 90% (SD 14.1%) for patients.

The two studies were conducted in collaboration with “Maggiore Hospital” of Bologna.

Chapter 7 describes a case of study conducted in collaboration with the Institute of Medical Psychology and Behavioral Neurobiology of Tübingen. The aim of the study was to develop an hybrid BCI system EEG-fNIRS based on the communication with amyotrophic lateral sclerosis (ASL) patients.

Four ASL patients took part in the study and after several online feedback sessions the achieved accuracy was higher than 65% for 90% of the sessions.

Chapter 8 defines moderate and mild TBI. The main cognitive impairment is listed and the EEG finding in TBI was analyzed. The chapter shows that the new techniques, developed in the last few years (computer assisted rehabilitation, neurofeedback, transcranial electrical modulation), can improve the rehabilitation of the subjects.

Chapter 9 describes a tele-rehabilitation system developed for the cognitive rehabilitation of people with brain injury using LabVIEW, a high-level graphical programming environment. The system offers several cognitive rehabilitation exercises and allows to patients' personal and clinical data and the results of the exercises performed by patients to be saved in an Access database. The system provides a remote connection between the database and the device suitable for rehabilitative training, allowing continuous monitoring of patients' performance.

In **Chapter 10**, transcranial electrical stimulation techniques were studied. In particular, the chapter was focused on the effects of these techniques on the EEG signal. The investigation of the modifications induced by transcranial electrical stimulation may support and detail the use of electrical stimulation as a therapeutic tool for several disorders characterized by abnormalities in electrophysiological and behavioral parameters.

Chapter 11 relates a case of study about the effect of transcranial direct current stimulation on EEG.

The study examine the effects of anodal tDCS on spontaneous cortical activity in a resting brain to disclose possible modulation of spontaneous oscillatory brain activity. EEG activity was measured in ten healthy subjects during and after a session of anodal stimulation of the postero-parietal cortex to detect the tDCS induced alterations. Changes in the theta, alpha, beta, and gamma power bands were investigated. Three main findings emerged: (1) an increase in theta band activity during the first minutes of stimulation; (2) an increase in alpha and beta power during and after stimulation; (3) a widespread activation in several brain regions.

Chapter 12 describes a study about i) the realization of a system able to generate and to record the steady-state visual evoked potential (SSVEP), and ii) the study of this potential before and after a session of tDCS. From the explorative analysis results that the SSVEP were well generated and recorded.

From the statistical analysis emerges that the tDCS induces changes in the oscillatory activity. The analysis shows that there is a significant difference before and after the stimulation, and in particular the anodal stimulation induces a decreasing of the power associated to the SSVEP.

Chapter 1

Traumatic brain injury (TBI)

1.1 Introduction

The term acquired brain injury enclose all types of neurological disorders that are not congenital or degenerative. There are two subsets of acquired brain injury. One type of acquired brain injury has an intrinsic derivation and does not involve an external mechanism. Such non-traumatic brain injuries may be caused by heart attacks, strokes, aneurisms, intracranial tumours, infectious diseases, venereal diseases, meningitis, hypo/hyperglycaemia, hypoxia and toxic exposure. The second type of acquired brain injury, known as traumatic brain injury, is caused by the impact of an external force. Traumatic brain injury is clearly defined in the following statement:

"Traumatic brain injury is an insult to the brain, not of a degenerative or congenital nature but caused by an external physical force, that may produce a diminished or altered state of consciousness, which results in impairment of cognitive abilities or physical functioning. It can also result in the disturbance of behavioral or emotional functioning. These impairments may be either temporary or permanent and cause partial or total disability or psychosocial maladjustment." (Brain Injury Association of America, 1986)

The rehabilitation needs of acquired brain injury survivors are likely to be similar, regardless of whether the injury was caused by trauma or not (Soryal et al. 1992).

Consequently, the sequelae of traumatic brain injury outlined in this literature review may be relevant to the non-traumatic brain injury population.

Traumatic brain injury is a significant cause of death and disability, particularly amongst people below the age of 35 years (Seel et al., 2003). The societal cost of traumatic brain injury is substantial (Ghajar, 2000). Survivors may require a multitude of services to aid their recovery. The process of rehabilitation may include acute care, rehabilitation nursing, physiotherapy, occupational therapy, social care work, counselling and home-based support services and, for younger survivors, specialist educational provision. The financial burden of providing neurorehabilitation care is amplified by the age distribution of head trauma injuries, given that a third of survivors are aged between ten and 19 years. The repercussion of acquiring brain injury at a young age is that individuals will spend considerably longer living with the consequences of their disability and, hence, society will spend longer providing rehabilitative care. The personal costs involved with poor outcome following traumatic brain injury are also extensive and pervasive. Empirical studies document adverse long term effects for brain injured individuals and their families in terms of emotional well being and social and occupational functioning.

1.2 Epidemiology

The overall incidence of TBI in the United States was estimated to be 538.2 per 100,000 population, or around 1.5 million new cases in 2003 (Rutland-Brown et al., 2003). Somewhat lower rates are reported in Europe (235 per 100,000) and Australia (322 per 100,000) (Tagliaferri et al., 2006; Hillier et al., 1997).

Rates of TBI are highest in the very young (age group zero to four years) and in adolescents and young adults (15 to 24 years); there is another peak in incidence in the elderly (age >65 years) (Rutland-Brown et al., 2003). Approximately 78 percent of TBI are treated in the emergency department only; 19 percent of patients require hospitalization, and 3 percent are fatal. Most cases treated in emergency departments occur in the very young (ages zero to four years), while hospitalization rates are highest in patients older than 65 years.

As with most traumatic injuries, the incidence of TBI is significantly higher in men compared to women, with ratios that vary between 2.0 to 1 and 2.8 to 1 (Langlois et al., 1997; Kraus et al.,1996; Feigin et al., 2013). For severe TBI, the gender ratio is

more pronounced, 3.5 to 1. Lower socioeconomic status, and underlying psychiatric and cognitive disorders are also risk factors for head injury (Liao et al., 2012).

Falls are the leading cause of TBI (particularly in older patients), followed by motor vehicle accidents (Feigin et al., 2013; Langlois et al., 2006; Jennett et al., 1990). The proportion of TBI secondary to violence has risen over the past decade and now accounts for 7 to 10 percent of cases (Butcher et al., 2007)). TBI related to military combat has received increased attention in the years from 2002 to 2009 (Summers et al., 2009). Mechanistic aspects of combat-related trauma may differ from TBI related to other causes, as the former usually involve blast explosives.

Moderate and severe TBIs are associated with neurologic and functional impairments. The prevalence of long-term disability related to TBI in the United States is variably estimated to be between 3.2 to 5.3 million, or approximately 1 to 2 percent of the population (Thurman et al., 1999; Zaloshnja et al., 2005).

1.3 Classification of TBI

The severity of brain injury relates to the amount of damage incurred through trauma. This can range from mild bruising to a prolonged coma, a persistent vegetative state or death. **Severity is inferred from the extent and duration of alterations in responsiveness**.

There are **three** generally accepted **assessment measures** to classify severity of the injury during the acute stage. The most common is the **Glasgow Coma Scale** (GCS) (Teasdale & Jennett, 1974; 1976). This quantitative assessment rates the depth and duration of altered consciousness, along three parameters; eye opening, verbal response and motor response. The second measure is an assessment of '**Post-Traumatic Amnesia' (PTA)**, which appraises the time taken to regain recall of continuous memories. It is considered a more sensitive gauge of mild and moderate brain injury compared to the GCS (Bay & McLean, 2007). As such, extended versions of the GCS have been devised to incorporate amnesia as an additional factor (Nell, et al., 2000; Batchelor & McGuiness, 2002). The third measure is the **Loss of Consciousness (LOC)**, which refers to the duration of unconsciousness. As there is no definitive measure of brain injury severity, a classification system may use any combination of these three measurements (Rao & Lyketsos, 2000). Moreover, the measures may be used in conjunction with diagnostic tools that draw on additional predictor variables of outcome (Brewer & Therrien, 2000; McNett, 2007).

Three broad grades of severity are used to categorize brain injury; mild, moderate and severe. However, universally accepted definitions for the severity of brain injury do not exist (Petchprapai & Winkelman, 2007). Consequently, different sources often use contrasting inclusion criteria to determine severity, especially when using combined measures. Even for single measures, the demarcations used for severity may sometimes overlap or be discontinuous. Also, some authors have proposed a fourth severity category to identify 'minor' brain injuries, as distinct from other mild and more serious forms of brain injury. Generally, a mild brain injury is generally defined by a GCS score of 13–15 (Jennett, 2002), LOC of less than 30 minutes (Rao *et al*., 2000) and/or PTA of less than an hour (Teasdale, 1995). A GCS score of 9–12 (Jennett, 2002), LOC of 30 minutes to 24 hours (Rao *et al*., 2000) and/or PTA of one to 24 hours (Teasdale, 1995) is classified as a moderate brain injury. Those with a severe brain injury have a GCS score less than 8 (Jennett, 2002), LOC of more than 24 hours (Rao *et al*., 2000) and/or PTA of more than 24 hours (Teasdale, 1995).

Mild and moderate brain injuries represent the majority of brain injury cases. Estimates for the proportion of brain injury diagnoses classed as mild have ranged from 75% to 95% [75%, (Bazarian *et al*., 2005); 79%, (Miller, 1993); 80% (Tiret *et al*., 1990), 83%, (Hawley *et al*., 2003); 95%, (Teasdale, 1995)]. The seriousness of mild brain injuries should not be underestimated. Such injuries can result in long-term problems that affect daily functioning. The neurobehavioural deficits of mild brain injury may include: headaches, dizziness, attention difficulties, memory, lapses, sleep disturbances, fatigue, irritability, depression, anxiety, low motivation, poor planning, visual problems and heightened sensitivity to stimuli (Alves et al., 1993; Youngjohn et al., 1995). This group of symptoms has been termed 'post-concussion syndrome'. However, the use of this term is controversial because of significant difficulties in establishing the aetiology of such symptoms and in making accurate diagnoses. The term 'syndrome' is a misnomer given that headaches and memory difficulties are the only typically reported symptoms. Also the subjective nature of the reported symptoms prevents any kind of accurate evaluation or assessment of change. Symptoms are particularly prevalent immediately after injury-onset but then tend to recede with time. Still, around half of mild brain injury survivors reported suffering one or more symptoms between six and twelve months post-injury. This persistence can be considered to arise from a delay in awareness or

onset of symptoms. However, the dominant view, originally proposed by Lishman (1988), is that the aetiology of such complaints is organic initially and then psychological thereafter. Indeed, continued reports of post-concussion symptoms may be motivated by litigation claims for compensation (Youngjohn *et al*., 1995). **Only a minority of traumatic brain injuries are severe.** According to a review of European epidemiology studies (Tagliaferri *et al*., 2006), severe injury types account for less than 10% of all traumatic brain injuries. The ratio of mild to moderate to severe traumatic brain injury is estimated to be 22:1.5:1. The fatality rate amongst those with severe brain injuries is 40% for coma admissions (Choi *et al*., 1994). **Of those that survive severe brain injuries, a small proportion (1%–3%) remain in a persistent vegetative state and some more (10%–20%) suffer severely disability for at least six months** (Teasdale, 1995). Some common consequences of severe brain injury may include significant physical disabilities, long-term cognitive deficits, gross changes in personality, behaviour problems and poor emotional well-being.

Chapter 2

EEG: Basics and Applications

Before describing the application of the EEG in the context of TBI assessment and rehabilitation is necessary to provide the basis of the EEG signal relating to the generation, processing and features that can be extracted and used in applications that will be described below.

2.1 EEG Basics

Electroencephalogram (EEG) is a record of the electric activity from the scalp, obtained with the aid of an array of electrodes. EEG signals have been studied extensively since Dr. Hans Berger, a German neuro-psychiatrist, published the earliest research on human EEG in 1929 (Berger, 1933). It has been used as a clinical diagnostic and research tool ever since. Since its early use by Dr. Berger, EEG has been motivated by the need to study the mental (psychiatric) state and disease diagnosis. Before brain-imaging techniques became available, EEG was the main tool in this area. The development of quantitative EEG (qEEG) was motivated by the need for objective measures as well as some degree of automation. qEEG may also prove to be useful in understanding electrical brain activity and brain function. EEG analysis started from the long EEG recordings available since the end of the 1930s. Subsequent use of computers and digitization led to the evolution of qEEG methods. Before the 1980s, qEEG mainly consisted of frequency related analysis (Hughes et al., 1999). Essentially, the signal was decomposed into its subband frequencies or the

power spectrum was obtained. Since the 1990s, more novel techniques have been applied to EEG signal processing, including nonlinear and information theory-based methods. In the following, the current methods in qEEG analysis and the research issues will be addressed.

2.1.1 Origin

EEG is the recording of the brain's electrical activity. Some of the activities recorded by scalp electrodes are generated by the action potentials of cortical neurons, but most are generated by excitatory postsynaptic potentials. Yet fine details about EEG generation are not fully understood. The EEG rhythms recorded on the scalp are the result of the summation effect of many excitatory and inhibitory postsynaptic potentials (EPSPs and IPSPs) produced in the pyramidal layer of the cerebral cortex. In humans, the thalamus is thought to be the main site of origin of EEG activities (Alpha and Beta bands) (Hughes et al., 1999). Thalamic oscillations activate the firing of cortical neurons. The depolarization (mainly in layer IV) creates a dipole with negativity at layer IV and positivity at more superficial layers. The scalp electrodes will detect a small but perceptible far-field potential that represents the summed potential fluctuations. In clinical and experimental conditions, EEG is the recording of the potential difference between two electrodes (bipolar EEG) or one scalp electrode and the ear as the reference (unipolar EEG). Scalp electrodes cannot detect charges outside 6 cm^2 of the cortical surface area, and the effective recording depth is several millimeters. The brain is an extremely complex system, constantly carrying out information transfer and processing. The neural system works through the interactions between large assemblies of neurons in the central nervous system (CNS) and the peripheral neural system. At the cellular level, neurons transfer and process the information via the action potentials and neural firing (also known as spikes). When this kind of electrical activity transfers to the surface of the cortex and to the surface of the scalp, we can record it as the EEG. One of the rationales for qEEG is that EEG signals originate in the brain and carry redundant physiological or pathological information inside the brain.

To perform qEEG analysis, sensors, also known as electrodes, are positioned at standardized locations on the scalp. During the data acquisition phase of brain mapping, each electrode collects electrical signals from the CNS. The EEG recording system includes the: (I) electrode and head stage, (II) preprocessing and quantitative EEG, and (III) data/results storage.

2.1.2 EEG Properties

The properties of the EEG signal can be described as complex. The EEG complexity originates in the intricate neural system. Traditionally, the spontaneous EEG is characterized as a linear stochastic process with great similarities to noise. From the signal processing view, EEG has the following properties:

- noisy and pseudo-stochastic: the EEG is often between 10-300 μV , which is easily affected by various physiological and electrical noises. Meanwhile, artifacts from electrocardiogram (ECG), electrooculogram (EOG), electromyogram (EMG), and recording systems can also contaminate the signals. Even the EEG shows a high degree of randomness and nonstationarity.
- time-varying and nonstationary: EEG is not a stationary process; it varies with the physiological states. The waveforms may include a complex of regular sinusoidal waves, irregular spikes/polyspikes, or spindles/polyspindles. In most pathological conditions, such as epileptic seizures, the EEG may show evident singularity or nonstationarity. In practice, we regard EEG as a stationary process over a relatively short period (inferior to 3.5 s for routine spontaneous EEG (Goel et al., 1996).
- High nonlinearity: Although the traditional linear models of EEG still play significant roles in EEG analysis and diagnosis, EEG is a nonlinear process (Palus, 1996). This kind of nonlinearity is also time-, state-, and site-dependent (Pijn et al., 1991).

2.1.3 Known Rhythm

The clinical technician interprets the EEG by the features or magnitudes of waves in each frequency band. Spectral analysis has been used for decades as the most important diagnostic tool. Even though the physicians do not calculate the spectrum, they usually focus on some specific wave rhythms (frequency components).

Delta rhythm

Delta is the frequency range up to 4 Hz. It tends to be the highest in amplitude and the slowest waves. It is seen normally in adults in slow wave sleep. It is also seen normally in babies. It may occur focally with subcortical lesions and in general distribution with diffuse lesions, metabolic encephalopathy hydrocephalus or deep midline lesions (Niedermeyer et al., 2005). It is usually most prominent frontally in adults and posteriorly in children.

Theta rhythm

Theta is the frequency range from 4 Hz to 7 Hz. Theta is seen normally in young children. It may be seen in drowsiness or arousal in older children and adults; it can also be seen in meditation (Bazhenov et al., 2001). Excess theta for age represents abnormal activity. It can be seen as a focal disturbance in focal subcortical lesions; it can be seen in generalized distribution in diffuse disorder or metabolic encephalopathy or deep midline disorders or some instances of hydrocephalus (Niedermeyer et al., 2005). On the contrary this range has been associated with reports of relaxed, meditative, and creative states.

Alpha rhythm

Alpha is the frequency range from 8 Hz to 12 Hz. Hans Berger named the first rhythmic EEG activity he saw, the alpha wave. This is activity in the 8-12 Hz range seen in the posterior regions of the head on both sides, being higher in amplitude on the dominant side. It is brought out by closing the eyes and by relaxation. It was noted to attenuate with eye opening or mental exertion. This activity is now referred to as posterior basic rhythm, the posterior dominant rhythm or the posterior alpha rhythm. The posterior basic rhythm is actually slower than 8 Hz in young children (therefore technically in the theta range). In addition to the posterior basic rhythm, there are two other normal alpha rhythms that are typically discussed: the mu rhythm and a temporal third rhythm. Alpha can be abnormal: an EEG that has diffuse alpha occurring in coma and is not responsive to external stimuli is referred to as alpha coma (Niedermeyer et al., 2005).

μ rhythm

Mu rhythm is alpha-range activity that is seen over the sensorimotor cortex. It characteristically attenuates with movement of the contralateral arm (or mental imagery of movement of the contralateral arm) (Pfurtscheller, 1992).

Beta rhythm

Beta is the frequency range from 12 Hz to about 30 Hz. It is seen usually on both sides in symmetrical distribution and is most evident frontally. Beta activity is closely linked to motor behavior and is generally attenuated during active movements (Benjamini et al., 2001). Low amplitude beta with multiple and varying frequencies is often associated with active, busy or anxious thinking and active concentration. Rhythmic beta with a dominant set of frequencies is associated with various pathologies and drug effects, especially benzodiazepines (Niedermeyer et al.,

2005). It may be absent or reduced in areas of cortical damage. It is the dominant rhythm in patients who are alert or anxious or who have their eyes open.

Gamma rhythm

Gamma is the frequency range approximately 30-100 Hz. Gamma rhythms are thought to represent binding of different populations of neurons together into a network for the purpose of carrying out a certain cognitive or motor function (Niedermeyer et al., 2005).

2.2 EEG Analysis technique

2.2.1 Frequency analysis technique

EEG frequency analysis usually means power spectral analysis. The spectra can be estimated by the following methods.

Periodogram

In general terms, one way of estimating the power spectral density (PSD) of a process is to simply find the discrete-time Fourier transform of the samples of the process (usually done on a grid with an FFT) and take the magnitude squared of the result. This estimate is called the periodogram. The periodogram estimate of the PSD of a length-L signal X_L[n] is:

$$\widehat{P_{xx}(f)} = \frac{\|X_L(f)\|^2}{f_s \cdot L} \tag{1}$$

where:

$$X_L = \frac{1}{N}\sum_{n=0}^{L-1} X_L[n] e^{-j2\pi\frac{f_n}{f_s}} \tag{2}$$

The actual computation of $X_L(f)$ can be performed only at a finite number of frequency points, N, and usually employs the FFT. In practice, most implementations of the periodogram method compute the N-point PSD estimate:

$$\widehat{P_{xx}(f)} = \frac{\|X_L[f_k]\|^2}{f_s \cdot L} \qquad f_k = \frac{k \cdot f_s}{N} \tag{3}$$

k=0, 1, 2, … , N-1

Modiefied Periodogram

FFT-based spectral estimation assumes that the signal is stationary and slowly varying. This kind of spectrum estimation has some drawbacks and limitations with respect to its resolution and leakage (or aliasing) effects (Muthuswamy et al., 1998). If the function to be transformed is not harmonically related to the sampling

frequency, the response of an FFT looks like a sinc function (although the integrated power is still correct). Spectral leakage can be reduced by using a tapering function (such as gabor, hanning window, and others). Nevertheless, reduction of spectral leakage is at the expense of broadening the spectral response.

The modified periodogram windows the time-domain signal prior to computing the FFT in order to smooth the edges of the signal. This has the effect of reducing the height of the side lobes or spectral leakage. This phenomenon gives rise to the interpretation of side lobes as spurious frequencies introduced into the signal by the abrupt truncation that occurs when a rectangular window is used. For nonrectangular windows, the end points of the truncated signal are attenuated smoothly, and hence the spurious frequencies introduced are much less severe. On the other hand, nonrectangular windows also broaden the main lobe, which results in a net reduction of resolution. Nonrectangular windowing affects the average power of a signal because some of the time samples are attenuated when multiplied by the window. To compensate for this, the presence of the window needs to be normalized to have a window average power of unity. This way the choice of window does not affect the average power of the signal.

The modified periodogram estimate of the PSD is:

$$\widehat{P_{xx}(f)} = \frac{\|X_L(f)\|^2}{f_s \cdot L \cdot U} \tag{4}$$

where U is the window normalization constant:

$$X_L = \frac{1}{L}\sum_{n=0}^{L-1} |w_n|^2 \tag{5}$$

which is independent of the choice of window. The addition of U as a normalization constant ensures that the modified periodogram is asymptotically unbiased.

Whelch's method

An improved estimator of the PSD is the one proposed by Welch (Welch, 1967). The method consists of dividing the time series data into (possibly overlapping) segments, computing a modified periodogram of each segment, and then averaging the PSD estimates. The result is Welch's PSD estimate. The averaging of modified periodograms tends to decrease the variance of the estimate relative to a single periodogram estimate of the entire data record. Although overlap between segments tends to introduce redundant information, this effect is diminished by the use of a nonrectangular window, which reduces the importance or weight given to the end

samples of segments (the samples that overlap). However, as mentioned above, the combined use of short data records and nonrectangular windows results in reduced resolution of the estimator. In summary, there is a trade-off between variance reduction and resolution. One can manipulate the parameters in Welch's method to obtain improved estimates relative to the periodogram.

2.3 Time - Frequency analysis technique

2.3.1 Short time Fourier Transform

Time-domain analysis does not provide any frequency information. When signals such as EEG are time varying, the spectral analysis can provide the frequency details, but unfortunately, we do not know at what times the frequency changes occur. As described above, the EEG signal is dynamic, time varying, sometimes transient (spikes/bursts), mostly nonstationary, and usually corrupted by noise. In practice, we not only need to know the frequency components but we also want to know the time relation. Time-frequency analysis is especially suitable for addressing such problems (Thakor et al., 1994). Time-frequency analysis has been successfully used to analyze the epileptic EEG (Blanco et al., 1998) and electrocorticograms (ECoG) to locate the seizure source. The simplest method uses a short time FT (STFT) to increase the time resolution:

$$\text{STFT}(\omega,t)=\int_{-\infty}^{+\infty} x(\tau)g(\tau-t)e^{-j\omega\tau}d\tau \qquad (6)$$

where g(t) is the window function. Equation 6 is also called Gabor transform. The FFT based time-dependent spectrum is also called a spectrogram. The spectrogram, however, has some pitfalls.

- STFT is based on FFT such that its time resolution cannot be high, and also there is bias at the boundaries. A high time and frequency resolution can be obtained through Wigner-Ville distribution (WVD):

$$Wx(\omega,t)=\int x\left(t+\frac{\tau}{2}\right)\,x^{*}\left(t-\frac{\tau}{2}\right)e^{-j\omega\tau}d\tau \qquad (7)$$

  $Wx(\omega,t)$ is the FT of the autocorrelation function of signal x(t) with respect to the delay variable. It can also be thought of as an STFT where the windowing function is a time-scaled, time-reversed copy of the original signal. In general, it has much better time and frequency resolution than does the STFT. Nevertheless, WVD has notable limitations: cross-term calculations may give rise to negative energy and the aliasing effect may distort the spectrum such

that a high-frequency component may be misidentified as a low-frequency component.

- the second pitfall of STFT is the fixed time and frequency resolutions. By the uncertainty principle, the product of the time uncertainty and frequency uncertainty is larger than a constant. In signal processing, we usually need more time accuracy in locating the transient waves (high frequency). For a slow waveform, we may be more interested in the frequency resolution. Such an analysis needs an adaptive time-frequency analysis method. The wavelet transform (WT) is such a tool.

2.3.2 Wavelet Transform

Two main formulation of the wavelet decomposition / representation exist: the Continuous Wavelet Transform (CWT) and the Discrete Wavelet Transform (DWT). Both of them are of interest in the field of EEG analysis, and their usage answer to different needs. To compute a continuous wavelet transform, the original signal time series, x(t), is convolved with a scaled and translated version of a mother wavelet function, Ψ(t). The convolution leads to a new signal of wavelet coefficients:

$$Wx^{\psi}(a,b) = A_{\psi} \cdot \int \psi^{*} \left(\frac{t-b}{a}\right) \cdot x(t)dt \qquad (8)$$

where ψ^{*} denotes the complex conjugation of the wavelet function, b is the translation parameter, a is the wavelet's scaling parameter, and A_{ψ} denotes a (wavelet specific) normalization parameter. The wavelet coefficients quantify the similarity between the originalsignal and the wavelet function at a specific scale a and target latency b. Hence, the wavelet coefficients depend on the choice of the mother wavelet function. The mother wavelet is constructed in such a way that it has zero mean and is localized in both time and frequency space. This is in contrast to the Fourier transform where the harmonic basis functions have a well determined frequency but extend over the whole time axis. Due to its localization properties the wavelet transform allows to follow the time-course of component structures in the signal. This feature is of crucial importance when analyzing non-stationary signals but has to be paid for with a reduced frequency resolution. Another important feature of the wavelet transform is its zooming property. When the scaling parameter, a, is varied from high to low values the wavelet function, Ψ([t-b]/a), will be compressed. The corresponding wavelet transform zooms from coarser (i.e. lowfrequency) to

finer (i.e. high-frequency) signal structures. In the case of Morlet's wavelets, also referred to as Gabor wavelets,

the mother wavelet function is given by the formula:

$$\psi(t) = e^{j\omega_0 t} \cdot e^{-t^2/2} \quad (10)$$

where j denotes the imaginary unit and !0 is 2_ times the frequency of the unshifted and uncompressed mother wavelet. Morlet wavelets are complex functions. Both their real and imaginary part consist of a harmonic oscillation windowed in time by a Gaussian envelope. Using sinusoidal wavelets like the Morlet wavelet is ideally suited for detecting sinusoidal EEG activity since the wavelet transform is similar to detecting whether the used wavelet is contained in the signal. Other wavelets which are more spiky can be used for detecting transient phenomena in EEG like epileptic spikes (Schiff et al., 1994). In the frequency domain, Morlet wavelets also have a Gaussian shape around their modulation frequency, i.e. the wavelet scale can be directly interpreted in terms of a well-defined center frequency (the terms scale and frequency will be used synonymously here). Hence, the scaled, unshifted wavelet can be written as a function of frequency, f:

$$\psi(t) = e^{j2\pi f t} \cdot e^{-t^2/2\sigma_t^2} \quad (11)$$

where the standard deviation _t of the Gaussian temporal envelope is reciprocally related to the frequency (σ_t~=f) in order to retain the wavelet scaling properties. If the number of significant cycles of the wavelet is kept constant it varies in temporal width as a function of frequency, since the same number of cycles spread over a longer time interval for lower frequencies. Therefore, at high frequencies the temporal resolution of a wavelet is better than at low frequencies; the inverse is true for the frequency resolution of the wavelet transform. Convolutions with Morlet wavelets can be computed for multiple frequencies in order to yield a time-frequency representation of the analyzed signal, x(t). Because the Morlet wavelet function is complex, the wavelet transform, $W_x(t, f)$, is also a complex function, which can be divided into its real part, $\Re W_x$ and its imaginary part, $\Im W_x$.

A wavelet function can be thought of as a finite impulse response filter. In this context, the real part, $\Re W_x$, of the Morlet wavelet transform represents a bandpass-filtered signal, $x_f(t)$, while the imaginary part, $\Im W_x$, yields a 90-degree phase shifted signal (Hilbert transform). In analogy to the Fourier power spectrum, the wavelet

power spectrum is defined as $\|W_x(t,f)\|^2$. It is a measure for the signal energy (signal variance) contained in the time-frequency bin covered by the transform, centered around time point t and frequency f. The Wavelet functions can be normalized prior to the convolution to have unit energy at all scales. What's continuous about the CWT, and what distinguishes it from the discrete wavelet transform, is the set of scales and positions at which it operates. Unlike the discrete wavelet transform, the CWT can operate at every scale, from that of the original signal up to some maximum scale that you determine by trading off your need for detailed analysis with available computational power. The CWT is also continuous in terms of shifting: during computation, the analyzing wavelet is shifted smoothly over the full domain of the analyzed function.

Calculating wavelet coefficients at every possible scale is a fair amount of work, and it generates an awful lot of data. What if we choose only a subset of scales and positions at which to make our calculations? It turns out, rather remarkably, that if we choose scales and positions based on powers of two - so-called dyadic scales and positions - then our analysis will be much more efficient and just as accurate. We obtain such an analysis from the discrete wavelet transform (DWT). An efficient way to implement this scheme using filters was developed in 1988 by Mallat (Mallat, 1989). The Mallat algorithm is in fact a classical scheme known in the signal processing community as a two-channel subband coder In wavelet analysis, we often speak of approximations and details. The approximations are the high-scale, low-frequency components of the signal. The details are the low-scale, high-frequency components.

2.4 Blind Source Separation Techniques

EEG signals are not produced in the scalp or the brain directly under the recording electrodes. Rather, they are generated by partial synchrony of local field potentials in many distinct cortical domains - each domain being, in the simplest case, a patch of cortex of unknown extent. The radial orientation of pyramidal cells relative to the cortical surface within such a domain allows summation of temporally synchronous extra-neuronal potentials whose summed far-field potentials project to the scalp electrodes near instantly through passive volume conduction. In the absence of such local area synchrony and near parallel orientations of neighboring pyramidal neurons, local field activities would partially or completely cancel each other out,

thus preventing far-field potentials of sufficient strength to be detected at scalp electrodes. By the basic laws of electrical conductance, far-field potentials generated within all cortical (and non-brain) domains project to and sum linearly at nearly every scalp electrode. Thus, EEG data recorded at a single electrode are a simple sum (or more technical, a weighted linear mixture) of underlying cortical source signals. The weights of each recorded mixture are determined by the distance of the cortical source domains or patches from the electrode pair (active and reference), the orientation of the cortical patch relative to the electrode pair locations, and the electrical properties of intervening tissues (cortex, cerebralspinal fluid, skull, and skin).

This spatial mixing of EEG source signals by volume conduction produces the strong correlations observed between EEG recordings at nearby electrodes and is the reason why EEG has long been denigrated as having poor spatial resolution. The term spatial resolution has several meanings, however, and the actual degree of spatial resolution of EEG depends on the intended sense of the term resolution. For any signal modality, three separable meanings of the term spatial resolution are the degree to which the exact location of a single source may be accurately determined; the spatial separation between two sources that is necessary to separate their signals; and the number of such sources that can be separated from the whole data. While the spatial resolution of EEG imaging has in the past been considered to be poor in all three of these aspects, we believe that new techniques for EEG analysis including those discussed in this review significantly improve its spatial resolution by all definitions of the term. The recovery of the exact cortical distribution of an EEG source region is limited by the under completeness of the inverse source localization problem. For example, far-field potentials from two synchronously active but physically opposing cortical source areas, e.g., source areas facing each other on opposite sides of a cortical sulcus may cancel, and their joint activity will have no effect on the scalp data. If a third area is coherently active, there will be no way to determine from scalp recordings whether the observed activity arises within the third area alone, within all three areas synchronously, or in any other combination of partially self-canceling source areas whose summed activity at the scalp also matches or closely resembles that of the third area alone. The inverse source localization problem may be greatly simplified by relying on the well-accepted assumptions that EEG signals arise from cortical pyramidal cells oriented perpendicular to the cortical

surface and (usually) located within a single contiguous and therefore highly interconnected cortical domain. It is not easy, however, to separately record an EEG scalp distribution generated in only one cortical domain, since many EEG source domains contribute to each recorded EEG signal at nearly all time points. An ideal goal for EEG analysis should be to detect and separate activities in multiple concurrently active EEG source areas, regardless of their relative strengths at different moments. Recently, a new approach to finding EEG source activities has been developed (Makedig et al., 1996) based on a simple physiological assumption that across sufficient time, the EEG signals arising in different cortical source domains are near temporally independent of each other.

This assumption is sufficient to separate signals from both physically distant and adjacent EEG source areas - if their contributions to the scalp EEG are largely independent over time. This insight and the resulting algorithms for signal separation that have emerged in the last decade have created a new field within signal processing in general known in particular as independent component analysis (ICA) or more generally as blind source separation. ICA methods can be used to decompose recorded EEG data into temporally, functionally, and spatially independent source signals.

2.4.1 EEG sources and source independence

The idea that EEG signals originate from temporally independent or near-independent brain processes is consistent with the long observed fact that cortex is organized into compact regions of specialized function. More particularly, connectivity among pyramidal cells is highly skewed toward short (intra-columnar) connections, principally between inhibitory cells that help sustain oscillatory field activity (Budd et al., 2001). In fact, inhibitory cells not only favor short-range synaptic contacts, but they also communicate via electrical gap junction connections (Gibson et al., 1999). These facts alone suggest that a partially synchronous local field activity pattern, once initiated, should spread through a compact cortical area (of unknown extent), much as observed by Freeman (2004) using small electrode grids placed on the cortex of animals.

Since the density of longer-range cortical connections is so low relative to the density of local connections, a neurobiologically plausible working hypothesis for EEG analysis is that over sufficient time, locally synchronous activities within roughly cm-scale patches of cortex are in fact nearly temporally independent of each other

and act as single, distinct, temporally independent sources of EEG activity. Alternatively, locally synchronized field activities in a pair of cortical source patches that are densely connected to each other, as for example via corpus callosum, may become synchronized, forming a single effective EEG source. In either case, EEG scalp signals may be modeled as the sum of distinct, phase-independent, and spatially stationary signals from cortical patches (or coupled patch pairs). A third major category of EEG signal sources are non-brain artifact sources including the eyes, scalp muscles, defective or poorly attached electrodes, and ambient line noise, whose volume-conducted activities are also summed in EEG recordings. While sufficiently dense multi-scale recordings of macroscopic field activity in cortex are still lacking, the physiological plausibility and heuristic accuracy, at least, of the above EEG source model allows the principled application of a new form of information-based signal processing.

2.4.2 Independent component analysis history

In the simplest terms, ICA algorithms are a family of related methods for unmixing linearly mixed signals using only recorded time course information, e.g., blind to detailed models of the signal sources as required by earlier signal processing approaches. Three early and relatively effective ICA algorithms were JADE (Cardoso et al., 1996), infomax ICA (Jung et al., 2001), and so-called FastICA (Hyvärinen et al., 2000). The original infomax ICA algorithm was soon enhanced by introducing natural gradient normalization and an extended mode capable of learning filters for sources such as sinusoids that have sub-Gaussian value distributions. Jung et al. (2001) reviewed how these and other methods may all be derived from a common information theoretic framework. The ICA algorithms above only consider the higher order statistics of the separate data maps recorded at different time points, with no regard for the time order in which the maps occur. The so-called second-order blind identification (SOBI) approach (Molgedey et al., 1994) considers relationships between multiple time points using an autoregressive model in which sources are assumed to have both differing spatial distributions and stable power spectra.

2.4.3 ICA model assumptions

Following the points discussed above, EEG may be plausibly modeled as a linear mixture of the activities of multiple brain and non-brain sources with (near) independent time courses. A further ICA assumption, that the cortical EEG source

domains remain spatially fixed for the duration of the input data, requires careful consideration.

2.4.4 The ICA model

The data submitted to ICA are simply the recorded EEG channel data arranged in a matrix of n channels (rows) by t time points (columns). ICA performs a blind separation of the data matrix (X) based only on the criterion that resulting source time courses (U) are maximally independent. Specifically, ICA finds a component unmixing matrix (W) that, when multiplied by the original data (X), yields the matrix (U) of independent component (IC) time courses:

$$U = W \cdot X \tag{12}$$

where X and U are n × t matrices, and W is n × n By simple matrix algebra, Eq. 12 implies that:

$$X = W^{-1} \cdot U \tag{13}$$

Here, W^{-1}, is the n × n component mixing matrix whose columns contain the relative weights with which the component projects to each of the scalp channels, i.e., the IC scalp map. The portion of the original data (X) that forms the i^{th} IC (X_i) is the (outer) product of two vectors, the i^{th} column of W and the i^{th} row of U,

$$X_i = W_i \cdot U_i \tag{14}$$

And the whole data (X) are the sum of the (back-projected) ICs (X_i):

$$X = \sum X_i \tag{15}$$

where i=1,2, … n.

Again, each column of the (W^{-1}) mixing matrix represents the relative projection weight at each electrode of a single component source. Mapping these weights to corresponding electrodes on a cartoon head model allows visualization of the scalp projection or scalp map of each source. The source locations of the components are presumed to be stationary for the duration of the training data. That is, the brain source location s and projection maps (W^{-1}) are assumed to be spatially fixed, while their activations (U) reveal their activity time courses throughout the input data. Thus, the IC activations (U), can be regarded as the EEG waveforms of single sources, although obtaining their actual amplitudes at the scalp channels requires multiplication by the inverse of the unmixing matrix (W^{-1}). The backprojected Ics (X_i) are in the same mV units as the recorded scalp data. However, neither the IC scalp maps nor the IC activations are themselves calibrated. Rather, the original activity units (mV) and polarities (+/−) are distributed between the two IC factors –

the IC scalp map and activation time series. For example, reversing the polarities of the activation and inverse weight matrices, then backprojecting the activations through the respective columns of (W^{-1}) recovers the original component activities in their native mV units. Thus, neither the sign of the scalp maps nor the sign of the activations are meaningful in themselves, but only their product, which determines the sign of the potential accounted for at each scalp channel. However, IC activation magnitudes may be normalized by multiplying each by the root-mean square (RMS) amplitude of the corresponding IC scalp map. The activation units are then RMS mV across the scalp array. The ICA decomposition considered here is termed complete, i.e., a decomposition in which the number of ICA components recovered is the same as the number of channel inputs. Thus, 30-channel data will be decomposed by ICA into 30 ICs, whereas 60-channel data will be decomposed into 60 ICs. Methods for overcomplete ICA decomposition also exist, though these require additional assumptions. An often-posed question is whether there are really 30 or 60 source components in the data, and if not, what are the effects of recording and decomposing different numbers of data channels? Anatomic considerations suggest the number of near independent sources in the brain may in general be nearly unlimited, although most of them may be very small and thus difficult to resolve from a limited amount of scalp data. Results of ICA decomposition of high-density (e.g., 128 or more channel) data acquired from normal subjects during performance of cognitive tasks show that some dozens of temporally and dynamically distinct EEG sources are large enough to be separated into components with physiologically interpretable scalp maps and activations. Applying ICA decomposition to fewer data channels must result in some or all of the extracted components summing activity from more than one underlying source. However, in this case, ICA should efficiently arrange for even these mixtures to have minimal common or mutual information.

2.5 Sensory Evoked potential

Evoked potentials (EPs) are time-locked responses of the nervous system to external stimuli. Sensory evoked potentials (SEPs) are one type of EP, which are generated by stimulation of afferent peripheral nerve fibers elicited by electrical, tactile, or other stimuli. Following either mixed nerve or sensory nerve stimulation, SEPs can be recorded over more proximal portions of the peripheral and central nervous system including peripheral nerves, spinal cord, and/or brain. SEP are recorded from the

central nervous system following stimulation of sense organs (for example, visual evoked potentials elicited by a flashing light or changing pattern on a monitor: auditory evoked potentials by a click or tone stimulus presented through earphones) or by tactile or somatosensory evoked potential elicited by tactile or electrical stimulation of a sensory or mixed nerve in the periphery. They have been widely used in clinical diagnostic medicine since the 1970s, and also in intraoperative neurophysiology monitoring , also known as surgical neurophysiology.

Several kinds of events, the most notably being sensory stimuli or cues for the onset of specific internal processings, can induce timelocked changes in the activity of neuronal populations that are generally called event-related potentials (ERPs).

On the other hand, rapid periodic stimulation produces a brain response characterized by a "quasi-sinusoidal" waveform whose frequency components are constant in amplitude and phase, the so-called steady-state response (SSR) (Celesia, 1982). The traditional motivation for dividing the electrophysiological literature into the ERP and the SSR fields is summarized in the following statement: "*If the brain responded in a linear fashion, steady-state responses would be completely predictable from the transient response. However, the brain is not linear, and steady-state and transient responses therefore provide independent views of its function*" (Capilla et al., 2011).

There are three kinds of evoked potentials in widespread clinical use: i) **auditory** evoked potentials, usually recorded from the scalp but originating at brainstem level; ii) **visual** evoked potentials, and iii) **somatosensory** evoked potentials, which are elicited by electrical stimulation of peripheral nerve.

2.5.1 Event-related potential

In order to detect such ERPs, averaging techniques are commonly used. Indeed, the basic assumption is that the evoked activity, has a more or less fixed time-delay to the stimulus or to the onset of the internal processing mechanism, while the ongoing EEG activity is considered as additive noise; although the ongoing EEG reflects a wide range of neural activity related to the various sensory and cognitive functions, it also reflects the myriad of self-regulation processes ongoing in the brain at the same time (e.g., maintaining body temperature, heart rate, breathing). This intermixing of signals makes it difficult to separate cognitive and physiological contributors to the observed EEG.

In contrast, the ERP approach permits investigators to link recorded signals with stimulus events more directly by focusing on the change in electrophysiological

signal that occurs immediately following the stimulus event. The smaller size of ERPs relative to other physiological events can make it difficult to discern the relevant signal. To accommodate these factors, researchers employ repeated presentations of the evoking stimulus to average out potentially unrelated events. ERPs have been successfully used to study both general and specific aspects of an individual's response to events in the external as well as internal environment. Additional advantages of the ERP technique over other procedures include (a) very fine temporal resolution (on the order of milliseconds) that reveals even momentary changes in patterns of brain activation, and (b) relatively gross-level spatial resolution capabilities that allow for theorizing about the distribution of brain mechanisms that subserve these cognitive functions.

ERP waveforms are typically described in terms of positive and negative peaks (i.e., the most positive and negative deflections in the waves). At a general level, the labeling refers to the sequence in which the peak occurs and to its polarity. The naming scheme for ERP components can also identify the positive and negative peaks by their latency (usually defined as the time from stimulus onset). N100 in this example refers to the negative peak that occurs 100 msec following stimulus onset. P300 would identify the positive peak that occurred 300 msec poststimulus onset.

In addition to the latency measures and functional interpretations, ERP descriptors often include topographical scalp distributions or identify electrodes where maximum amplitudes are typically observed.

Such information can be useful for interpreting ERP peaks that may occur at the same time but over different scalp areas reflecting different cognitive processes. In the following, the most important ERP waveform are listed:

P100

This peak is not always easily identified, but when present it occurs approximately 50 msec after an auditory stimulus onset (also known as P50) or about 100 msec after the onset of a visual stimulus.

Functionally, this component is usually interpreted as a neurophysiological indicator of preferential attention to sensory inputs (suppression of unattended information) and is thought to reflect the general level of arousal.

N100

Generally, N100 is assumed to reflect selective attention to basic stimulus characteristics, initial selection for later pattern recognition, and intentional

discrimination processing (Luck et al., 2000). Latency and amplitude of the peak depend on the stimulus modality. Auditory stimuli elicit a larger N100 with shorter latency than visual stimuli.

P200

The P200, like the N100 and P100, has long been considered to be an obligatory cortical potential because it has low interindividual variability and high replicability (Sandman et al., 2000).

N200

The N200 component is characterized by higher interindividual variation and has multiple psychological interpretations, including orienting response , stimulus discrimination (Ritter t al., 1983), possibly reflecting task demands.

N170

The N170 peak is another member of the N2 family and ranges in latency between 156 msec and 189 msec. It is associated primarily with visual processing of human faces. The topographic distribution of the N170 component or both familiar and unfamiliar faces is largest over the occipitotemporal regions (Jemel et al., 2003).

MMN

The MMN is a negative deflection that has a typical latency of 100 ms to 250 ms. The amplitude is largest at frontal and central electrode sites (Liebenthal et al., 2003) and has been replicable with different reference points, including the tip of the nose, the earlobe, and noncephalic locations. MMN is elicited using an oddball paradigm where an occasional deviant stimulus is presented in a stream of more frequent standard stimuli. MMN paradigms typically do not require attention to the stimuli.

P300

The P300 is the most extensively researched ERP component. It was first identified by Sutton, Tueting, Zubin, and John (1965) (Sutton et al., 1967) in a cuing paradigm as a pronounced positivity over parietal areas that occurred in response to an unexpected stimulus type approximately 300 ms after stimulus onset. This effect was present for auditory (clicks) and visual (light flashes) stimuli. Unlike the MMN paradigms, for a P300 to be elicited, the participant must pay attention and respond (overtly orcovertly) to the stimuli. In addition, the ratio of target to distracter stimuli must be low (the fewer targets, the larger the peak). P300 amplitude is affected by attention, stimulus probability, stimulus relevance, and the amount of processing resources available, such as in single versus dual tasks, the quality of selection, and

attention allocation. The P300 component has also attracted attention in clinical studies. Because P300 amplitude varies with the amount of attention paid to the stimuli, this component is widely studied in populations with attention deficits (e.g., ADHD) where it is interpreted to reflect information regarding various attentional functions.

Sources of the P300 are not clearly identified, but intracranial recordings indicate that at least some are expected to be in the medial temporal lobe, including the hippocampal region, parahippocampal gyrus, amygdala, or thalamus.

N400

This negative component occurs approximately 400 msec after stimulus onset and is usually associated with visual and auditory sentence comprehension tasks in paradigms where words of a sentence are visually presented one after another at fixed intervals (Klumpp et al., 2010).

The last word of the sentence is syntactically appropriate and either congruous or incongruous with the rest of the sentence. The incongruous words elicits a larger amplitude N400 response than the congruous words. Further, the amplitude of the N400 is correlated with the degree of incongruency of the sentence and the final word.

It has been reported (Kutas et al., 1983) that the N400 effect is elicited for semantic, but not syntactic, deviations from expected endings. The N400 is also elicited in semantic word pairs , semantic priming tasks , and matching semantic material to visual displays (Klumpp et al., 2010).

For both visual and auditory stimuli, the N400 is larger over the parietal and temporal regions in the right hemisphere. N400 latency varies with the modality of the task, with visual stimuli resulting in an earlier peak relative to the auditory presentation (475 msec vs. 525 msec), but only over the temporal, anterior temporal, and frontal sites. The N400 is likely to arise from multiple generators that are segregated both functionally. Results of intracortical recordings point to the parahippocampal anterior fusiform gyrus or medial temporal structures near the hippocampus and amygdala, whereas others suggest locations in the lateral temporal region.

P600

This component has two functionally different interpretations, one associated with memory processes and another related to language.

Although both peaks have roughly similar topographies, they appear to have different brain sources. Some researchers proposed that the P600 component, especially the one associated with language, is a delayed variant of the P3 because both peaks have relatively similar scalp distributions and are both sensitive to probability manipulations.

The P600 phenomena due to memory processes is typically observed in recognition-recall memory paradigms and is often referred to as an old-new effect. Typically, the peak onsets at 400 msec and continues for approximately 400 msec to 600 msec.

Maximum amplitudes are noted over the left temporo-parietal regions. The P600 old-new effect often co-occurs in time with a frontal N400 effect present over the left fronto-central areas, starting at 300 msec to 500 msec post-stimulus and continuing to 1,200 msec and beyond (Rugg et al., 2000).

2.5.2 Steady State Evoked Potential

An evoked potential is the electrical response of the brain to a sensory stimulus. Regan constructed an analogue Fourier series analyzer to record harmonics of the evoked potential to flickering (sinusoidally modulated) light but, rather than integrating the sine and cosine products, fed them to a two-pen recorder via lowpass filters (Regan et al., 1966). This allowed him to demonstrate that the brain attained a steady-state regime in which the amplitude and phase of the harmonics (frequency components) of the response were approximately constant over time. By analogy with the steady-state response of a resonant circuit that follows the initial transient response he defined an idealized steady-state evoked potential (SSEP) as a form of response to repetitive sensory stimulation in which the constituent frequency components of the response remain constant with time in both amplitude and phase (Regan et al., 1966; Regan et al., 1979). Although this definition implies a series of identical temporal waveforms, it is more helpful to define the SSEP in terms of the frequency components that are an alternative description of the time-domain waveform, because different frequency components can have quite different properties (Regan et al., 1979). For example, the properties of the high-frequency flicker SSEP (whose peak amplitude is near 40–50 Hz) correspond to the properties of the subsequently discovered magnocellular neurons in the retina of the macaque monkey, while the properties of the medium-frequency flicker SSEP (whose amplitude peak is near 15–20 Hz) correspond to the properties of parvocellular neurons. Since a SSEP can be completely described in terms of the amplitude and

phase of each frequency component it can be quantified more unequivocally than an averaged transient evoked potential.

It is sometimes said that SSEPs are elicited only by stimuli of high repetition frequency, but this is not generally correct. In principle, a sinusoidally modulated stimulus can elicit a SSEP even when its repetition frequency is low. Because of the high-frequency rolloff of the SSEP, high frequency stimulation can produce a near-sinusoidal SSEP waveform, but this is not germane to the definition of a SSEP. By using zoom-FFT to record SSEPs at the theoretical limit of spectral resolution ΔF (where ΔF in Hz is the reciprocal of the recording duration in seconds) Regan and Regan discovered that the amplitude and phase variability of the SSEP can be sufficiently small that the bandwidth of the SSEP's constituent frequency components can be at the theoretical limit of spectral resolution up to at least a 500-second recording duration (0.002 Hz in this case). Repetitive sensory stimulation elicits a steady-state magnetic brain response that can be analysed in the same way as the SSEP.

SSVEP

Steady-state visually evoked potentials (SSVEP) are the oscillatory electrical responses of neurons in the visual cortex to stimuli that are repeatedly presented (or flashed) at frequencies above 6 Hz. For many years, it has been known that such rapid stimulus sequences set up stable and synchronized neural oscillations in the occipital cortex, at frequencies corresponding to that of the stimulus (Vialette et al., 2010). SSVEPs are easy to detect, as their frequency content is completely determined by the visual stimuli used to elicit them. These stimuli typically also elicit oscillations at harmonics of the stimulating frequency (Vialette et al., 2010).

SSSEP

Analogous to visually evoked SSVEPs, steady-state somatosensory evoked potentials (SSSEPs) are elicited by a continuous vibrotactile stimulus of a constant carrier frequency and a modulation frequency applied to the skin (Zhang et al., 2010). Using this technique, early research reported that when the palm (Muller er al., 2001) or the palm and sole (Snyder et al., 1992) were stimulated, corresponding steady-state responses were recorded at the scalp.

ASSEP

Actually, Cortically recorded steady-state acustic response (ASSEP) are generated presenting amplitude-modulated tones to the ear (Pastor et al., 2002).

Chapter 3

EEG and BCI application

3.1 Introduction

In the 7 decades since Hans Berger's original paper (Berger, 1929), the EEG has been used mainly to evaluate neurological disorders in the clinic and to investigate brain function in the laboratory; and a few studies have explored its therapeutic possibilities (e.g. Kuhlman, 1978; Rice et al., 1993; Sterman, 2000). Over this time, people have also speculated that the EEG could have a fourth application, that it could be used to decipher thoughts, or intent, so that a person could communicate with others or control devices directly by means of brain activity, without using the normal channels of peripheral nerves and muscles. However, EEGbased communication attracted little serious scientific attention until recently, for at least 3 reasons.

First, while the EEG reflects brain activity, so that a person's intent could in theory be detected in it, the resolution and reliability of the information detectable in the spontaneous EEG is limited by the vast number of electrically active neuronal elements, the complex electrical and spatial geometry of the brain and head, and the disconcerting trialto- trial variability of brain function. The possibility of recognizing a single message or command amidst this complexity, distortion, and variability appeared to be extremely remote. Second, EEG-based communication requires the capacity to analyze the EEG in real-time, and until recently the requisite technology

either did not exist or was extremely expensive. Third, there was in the past little interest in the limited communication capacity that a first generation EEG-based BCI was likely to offer. Recent scientific, technological, and societal events have changed this situation. First, basic and clinical research has yielded detailed knowledge of the signals that comprise the EEG. For the major EEG rhythms and for a variety of evoked potentials, their sites and mechanisms of origin and their relationships with specific aspects of brain function, are no longer wholly obscure. Numerous studies have demonstrated correlations between EEG signals and actual or imagined movements and between EEG signals and mental tasks (e.g. Keirn and Aunon, 1990; Lang et al., 1996; Anderson et al., 1998; McFarland et al., 2000). Thus, researchers are in a much better position to consider which EEG signals might be used for communication and control, and how they might best be used. Second, the extremely rapid and continuing development of inexpensive computer hardware and software supports sophisticated online analyses of multichannel EEG. This digital revolution has also led to appreciation of the fact that simple communication capacities (e.g. 'Yes' or 'No', 'On' or 'Off') can be configured to serve complex functions (e.g. word processing, prosthesis control). Third, greatly increased societal recognition of the needs and potential of people with severe neuromuscular disorders like spinal cord injury or cerebral palsy has generated clinical, scientific, and commercial interest in better augmentative communication and control technology. Development of such technology is both the impetus and the justification for current BCI research. BCI technology might serve people who cannot use conventional augmentative technologies; and these people could find even the limited capacities of first-generation BCI systems valuable.

In addition, advances in the development and use of electrophysiological recording methods employing epidural, subdural, or intracortical electrodes offer further options. Epidural and subdural electrodes can provide EEG with high topographical resolution, and intracortical electrodes can follow the activity of individual neurons (Schmidt, 1980; Ikeda and Shibbasaki, 1992; Levine et al., 1999). Furthermore, recent studies show that the firing rates of an appropriate selection of cortical neurons can give a detailed picture of concurrent voluntary movement (e.g. Georgopoulos et al., 1986; Schwartz, 1993; Wessberg et al., 2000). Because these methods are invasive, the threshold for their clinical use would presumably be higher than for methods based on scalp-recorded EEG activity, and they would probably be

used mainly by those with extremely severe disabilities. At the same time, they might support more rapid and precise communication and control than the scalp-recorded EEG.

Like any communication or control system, a BCI has input (e.g. electrophysiological activity from the user), output (i.e. device commands), components that translate input into output, and a protocol that determines the onset, offset, and timing of operation. Figure 1 shows these elements and their principal interactions.

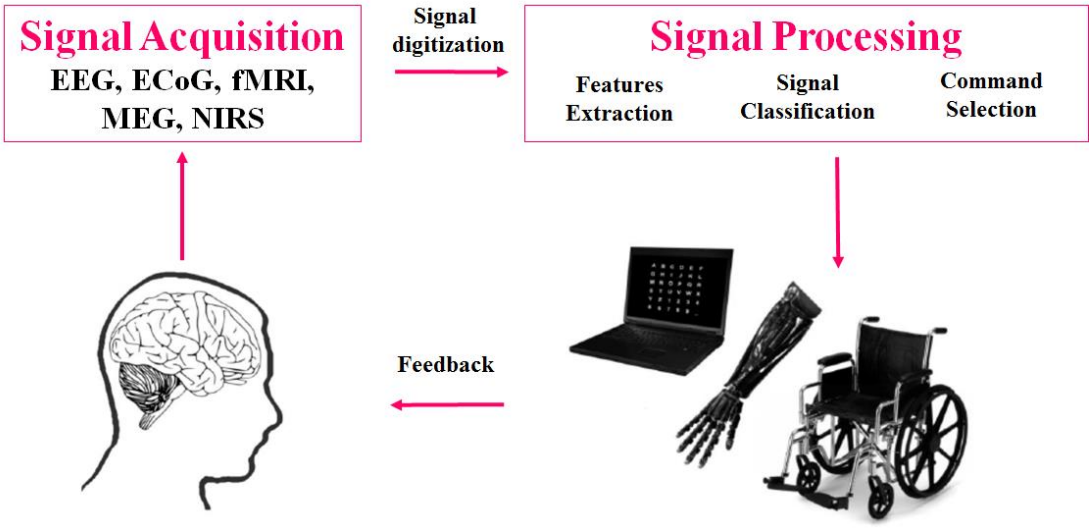

Figure 1: Basic designed and operation of any BCI system. Signals from the brain are acquired and processed to extract specific signal features that reflect the user's intent. These features are translate into commands that operate a device (e. g. a simple word processing program, a wheelchair or neuroprosthesis).

3.2 Dependent and independent BCI

A BCI is a communication system in which messages or commands that an individual sends to the external world do not pass through the brain's normal output pathways of peripheral nerves and muscles. For example, in an EEG-based BCI the messages are encoded in EEG activity. A BCI provides its user with an alternative method for acting on the world. BCIs fall into two classes: dependent and independent.

A dependent BCI does not use the brain's normal output pathways to carry the message, but activity in these pathways is needed to generate the brain activity (e.g. EEG) that does carry it. For example, one dependent BCI presents the user with a matrix of letters that flash one at a time, and the user selects a specific letter by looking directly at it so that the visual evoked potential (VEP) recorded from the scalp over visual cortex when that letter flashes is much larger that the VEPs

produced when other letters flash (Sutter, 1992). In this case, the brain's output channel is EEG, but the generation of the EEG signal depends on gaze direction, and therefore on extraocular muscles and the cranial nerves that activate them. A dependent BCI is essentially an alternative method for detecting messages carried in the brain's normal output pathways: in the present example, gaze direction is detected by monitoring EEG rather than by monitoring eye position directly. While a dependent BCI does not give the brain a new communication channel that is independent of conventional channels, it can still be useful (e.g. Sutter, 1992). In contrast, an independent BCI does not depend in any way on the brain's normal output pathways. The message is not carried by peripheral nerves and muscles, and, furthermore, activity in these pathways is not needed to generate the brain activity (e.g. EEG) that does carry the message. For example, one independent BCI presents the user with a matrix of letters that flash one at a time, and the user selects a specific letter by producing a P300 evoked potential when that letter flashes (Donchin et al., 2000). In this case, the brain's output channel is EEG, and the generation of the EEG signal depends mainly on the user's intent, not on the precise orientation of the eyes (Sutton et al., 1965; Donchin, 1981). The normal output pathways of peripheral nerves and muscles do not have an essential role in the operation of an independent BCI. Because independent BCIs provide the brain with wholly new output pathways, they are of greater theoretical interest than dependent BCIs. Furthermore, for people with the most severe neuromuscular disabilities, who may lack all normal output channels (including extraocular muscle control), independent BCIs are likely to be more useful.

Present-day BCIs fall into 6 groups based on the electrophysiological signals they use. The first and the second groups, those using **VEP**s and **SSEP**, are dependent BCIs, i.e. they depend on muscular control of gaze direction. The other 4 groups, those using **slow cortical potentials**, **P300** evoked potentials, **mu and beta rhythms**, and **cortical neuronal action potentials**, are believed to be independent BCIs, though this belief remains to some extent an assumption still in need of complete confirmation.

3.2.1 Steady State Evoked Potential (Chatelle)

Several BCI approaches are based on the volitional modulation of steady-state electrical responses set up in the brain by the presentation of oscillatory stimulus

sequences. Such BCI designs are distinguished based on the sensory modality used to present these stimuli, considered here in turn.

SSVEP-based BCIs.

SSVEPs are easy to detect, as their frequency content is completely determined by the visual stimuli used to elicit them. These stimuli typically also elicit oscillations at harmonics of the stimulating frequency.

For the purposes of BCI design, the finding that the strength of the SSVEP is modulated by endogenous attention is crucial. Specifically, it has been found that, when the visual system is presented with multiple stimuli flashing at different frequencies, the frequency of the stimulus being attended to generates the largest oscillatory response in the brain.

Tapping into this knowledge, researchers have built BCIs that use stimuli at different frequencies to represent a set of responses from which the user selects one by paying attention to it. Such BCIs are particularly attractive because occipital SSVEPs have high signal-to-noise ratios and are nearly completely free of eye movement (Perlstein et al., 2003) and electromyographic artifacts (Regan, 1966; Gray et al., 2003). Moreover, SSVEP-based BCIs allow the user to select from a relatively large number (up to 64 of different choices) without adversely affecting classification accuracy, which tends to range between 64–96.5% (Vialatte et al., 2010). Stimulation for modern SSVEP-based BCIs is delivered either on a computer screen or using lightemitting diodes flickering at different frequencies (Wang et al., 2006; Cheng et al., 2002). The power at the stimulation frequencies over occipital electrodes is fed to a classifier, which is trained a priori to identify the stimulus frequency most likely to be focused on by the user. It has been found that the first three harmonics of the stimulus frequencies carry additional information, providing for a significant increase in classification accuracy (Müller-Putz et al., 2005). Progressive improvements in the design have produced systems that allow for an impressive rate of communication. Parini et al. (2009) showed performance results from an SSVEP-based BCI that employed four cubic LED stimuli mounted at each side of a display. Seven healthy participants and four patients affected by muscular dystrophy at different stages were able to successfully use this system. In particular, the study reported the robustness of the system and the rapidity of user performance.

SSSEP-based BCIs.

Several SSSEPs BCI system were developed. The first study showing attentional modulation of SSSEP amplitude in humans was done by Giabbiconi et al. (2004), using tactile stimuli with different frequencies applied simultaneously to the left and right index finger. Following this, the usability of SSSEPs in BCI design was evaluated by Muller-Putz et al. (2006). They stimulated both index fingers using tactile stimulation in the resonance frequency range of the somatosensory system. Four healthy subjects participated in the experiments and were trained to modulate the induced SSSEPs by focusing their attention on either their left or their right index fingers. Two of them learned to modulate their SSSEPs with accuracies between 70–80%, demonstrating the initial possibilities of this approach. Researchers have also attempted to combine multiple modalities to improve the classification accuracy of steady-state BCIs. Such BCIs, based on multi-modal attention, have been proposed by Zhang et al. (2007). They combined tactile and visual stimuli to realize a 3-class BCI based on SSSEPs and SSVEPs. The combination of the two modalities resulted in improved classification accuracies when compared to either modality alone. Further, they showed that steady-state evoked potential amplitudes were modulated not only by switching spatial attention within one sensory modality, but also by switching across different modalities.

ASSR-based BCIs.

There have been a few relatively recent attempts to use steady-state responses produced by auditory stimulation, i.e. ASSRs (Auditory steady-state responses (Roß et al., 2000; Roß et al., 2003; Pastor et al., 2002)) to drive BCIs. Cortically recorded ASSRs are generated presenting amplitude-modulated tones to the ear. Ross et al. (2003) showed that the amplitude of the prominent ASSR generated by 40 Hz stimulation is modulated by selective attention. However, as of yet, there has been no demonstration of a BCI driven by such attentional modulation of ASSRs. The BCI design challenge yet to be overcome here is the relatively small size of this modulation effect, making it difficult to detect in real-time. BCIs employing ASSRs would come with the important advantage of not requiring the visual modality.

3.2.2 Visual evoked potentials

In the 1970s, Jacques Vidal used the term ‘brain–computer interface’ to describe any computer-based system that produced detailed information on brain function. This early usage was broader than current usage, which applies the term BCI only to those

systems that support communication and control by the user. Nevertheless, in the course of his work, Vidal developed a system that satisfied the current definition of a dependent BCI (Vidal, 1973, 1977). This system used the VEP recorded from the scalp over visual cortex to determine the direction of eye gaze (i.e. the visual fixation point), and thus to determine the direction in which the user wished to move a cursor. Sutter (1992) described a similar BCI system called the brain response interface (BRI). It uses the VEPs produced by brief visual stimuli and recorded from the scalp over visual cortex. The user faces a video screen displaying 64 symbols (e.g. letters) in an 8 × 8 grid and looks at the symbol he or she wants to select. Subgroups of these 64 symbols undergo an equiluminant red/green alternation or a fine red/green check pattern alternation 40–70 times/s.

Each symbol is included in several subgroups, and the entire set of subgroups is presented several times. Each subgroup's VEP amplitude about 100 ms after the stimulus is computed and compared to a VEP template already established for the user. From these comparisons, the system determines with high accuracy the symbol that the user is looking at. A keyboard interface gives access to output devices. Normal volunteers can use it to operate a word processing program at 10–12 words/min. In users whose disabilities cause uncontrollable head and neck muscle activity, scalp EMG can impede reliable VEP measurement and reduce performance. For one such user, a man with ALS, this problem was solved by placing a strip of 4 epidural electrodes over visual cortex. With this implant, he could communicate 10–12 words/min (Sutter, 1992). Middendorf et al. (2000) reported another method for using VEPs to determine gaze direction. Several virtual buttons appear on a screen and flash at different rates. The user looks at a button and the system determines the frequency of the photic driving response over visual cortex. When this frequency matches that of a button, the system concludes that the user wants to select it. These VEP-based communication systems depend on the user's ability to control gaze direction. Thus, they perform the same function as systems that determine gaze direction from the eyes themselves, and can be categorized as dependent BCI systems. They show that the EEG can yield precise information about concurrent motor output, and might prove superior to other methods for assessing gaze direction. It is possible that VEP amplitude in these systems reflects attention as well as gaze direction, and thus that they may be to some extent independent of neuromuscular function.

3.2.3 Slow cortical potentials

Among the lowest frequency features of the scalp-recorded EEG are slow voltage changes generated in cortex.

These potential shifts occur over 0.5–10.0 s and are called slow cortical potentials (SCPs). Negative SCPs are typically associated with movement and other functions involving cortical activation, while positive SCPs are usually associated with reduced cortical activation (Rockstroh et al., 1989; Birbaumer, 1997). In studies over more than 30 years, Birbaumer and his colleagues have shown that people can learn to control SCPs and thereby control movement of an object on a computer screen. This demonstration is the basis for a BCI referred to as a 'thought translation device' (TTD). The principal emphasis has been on developing clinical application of this BCI system. It has been tested extensively in people with late-stage ALS and has proved able to supply basic communication capability (Kubler, 2000). In the standard format EEG is recorded from electrodes at the vertex referred to linked mastoids. SCPs are extracted by appropriate filtering, corrected for EOG activity, and fed back to the user via visual feedback from a computer screen that shows one choice at the top and one at the bottom. Selection takes 4 s. During a 2 s baseline period, the system measures the user's initial voltage level. In the next 2 s, the user selects the top or bottom choice by decreasing or increasing the voltage level by a criterion amount. The voltage is displayed as vertical movement of a cursor and final selection is indicated in a variety of ways. The BCI can also operate in a mode that gives auditory or tactile feedback (Birbaumer et al., 2003). Users train in several 1–2 h sessions/week over weeks or months. When they consistently achieve accuracies ≥75%, they are switched to a language support program (LSP). The LSP (Birbaumer, 2003) enables the user to choose a letter or letter combination by a series of two-choice selections. In each selection, the choice is between selecting or not selecting a set of one or more letters. The first two selections choose between the two halves of the alphabet, the next two between the two quarters of the selected half, and so on until a single letter is chosen. A backup or erase option is provided. With this program, users who have two-choice accuracies of 65–90% can write 0.15–3.0 letters/min, or 2– 36 words/h. While these rates are low, the LSP has proved useful to and highly valued by people who cannot use conventional augmentative communication technologies. Furthermore, a predictive algorithm that uses the first two letters of a word to select the word from a lexicon that encompasses the user's

vocabulary can markedly increase the communication rate. A new protocol provides Internet access to one disabled user (Birbaumer et al., 2003). A stand-by mode allows users wearing collodium-fixed electrodes to access the system 24 h/day by producing a specific sequence of positive and negative SCPs (Kaiser et al., 2001). This sequence is essentially a key for turning the BCI on and off.

3.2.4 P300 evoked potentials

Infrequent or particularly significant auditory, visual, or somatosensory stimuli, when interspersed with frequent or routine stimuli, typically evoke in the EEG over parietal cortex a positive peak at about 300 ms (Walter et al., 1964; Sutton et al., 1967; Donchin and Smith, 1970). Donchin and his colleagues have used this 'P300', or 'oddball' response in a BCI (Donchin et al., 2000).

The user faces a 6 × 6 matrix of letters, numbers, and/or other symbols or commands. Every 125 ms, a single row or column flashes; and, in a complete trial of 12 flashes, each row or column flashes twice. The user makes a selection by counting how many times the row or column containing the desired choice flashes. EEG over parietal cortex is digitized, the average response to each row and column is computed, and P300 amplitude for each possible choice is computed. P300 is prominent only in the responses elicited by the desired choice, and the BCI uses this effect to determine the user's intent. In online experiments and offline simulations, a variety of different algorithms (e.g. stepwise discriminant analysis, discrete wavelet transform) for recognizing the desired choice have been evaluated, and the relationship between the number of trials per selection and BCI accuracy has been described. These analyses suggest that the current P300-based BCI could yield a communication rate of one word (i.e. 5 letters) per minute and also suggest that considerable further improvement in speed should be possible. In people with visual impairments, auditory or tactile stimuli might be used (Glover et al., 1986; Roder et al., 1996). In related work, Bayliss and Ballard (2000) recorded P300s in a virtual environment. Offline analyses suggested that single-trial P300 amplitudes might be used for environmental control.

A P300-based BCI has an apparent advantage in that it requires no initial user training: P300 is a typical, or naive, response to a desired choice. At the same time, P300 and related potentials change in response to conditioning protocols (Glover et al., 1986; Roder et al., 1996). A P300 used in a BCI is also likely to change over time. Studies up to the present have been short-term. In the long term, P300 might

habituate (Ravden and Polich, 1999) so that BCI performance deteriorates, or it might get larger so that performance improves. Thus, appropriate adaptation by the translation algorithm is likely to be important for this BCI, as it is for others.

3.2.5 Mu and beta rhythms and other activity from sensorimotor cortex

In awake people, primary sensory or motor cortical areas often display 8–12 Hz EEG activity when they are not engaged in processing sensory input or producing motor output (Neidermeyer, 2005). This idling activity, called mu rhythm when focused over somatosensory or motor cortex and visual alpha rhythm when focused over visual cortex, is thought to be produced by thalamocortical circuits (Lopes da Silva, 1991; Neidermeyer, 2005). Unlike the visual alpha rhythm, which is obvious in most normal people, the mu rhythm was until quite recently found only in a minority. However, computer-based analyses reveal the mu rhythm in most adults. Such analyses also show that mu-rhythm activity comprises a variety of different 8–12 Hz rhythms, distinguished from each other by location, frequency, and/or relationship to concurrent sensory input or motor output. These mu rhythms are usually associated with 18–26 Hz beta rhythms. While some beta rhythms are harmonics of mu rhythms, some are separable from them by topography and/or timing, and thus are independent EEG features (McFarland et al., 2000). Several factors suggest that mu and/or beta rhythms could be good signal features for EEG-based communication. They are associated with those cortical areas most directly connected to the brain's normal motor output channels. Movement or preparation for movement is typically accompanied by a decrease in mu and beta rhythms, particularly contralateral to the movement. This decrease has been labeled 'event-related desynchronization' or ERD. Its opposite, rhythm increase, or 'event-related synchronization' (ERS) occurs after movement and with relaxation (Pfurtscheller, 1999). Furthermore, and most relevant for BCI use, ERD and ERS do not require actual movement, they occur also with motor imagery (i.e. imagined movement) (McFarland et al., 2000). Thus, they might support an independent BCI. Since the mid-1980s, several mu/beta rhythm based BCIs have been developed.

3.2.6 Cortical Neurons

Since the 1960s, metal microelectrodes have been used to record action potentials of single neurons in the cerebral cortices of awake animals during movements. While most studies focused on the relationships between this neuronal activity and simple or complex sensorimotor performances, a few have explored the capacity of animals

to learn to control neuronal firing rates. With operant conditioning methods, several studies showed that monkeys could learn to control the discharge of single neurons in motor cortex (Fetz and Finocchio, 1975; Schmidt, 1980). From such work came the expectation that humans, including many with motor disabilities, could develop similar control and use it to communicate or to operate neuroprostheses.

Evaluation of this possibility was delayed by lack of intracortical electrodes suitable for human use and capable of stable long-term recording from single neurons. Conventional implanted electrodes induce scar tissue and/or move in relation to individual neurons, so that over time recording deteriorates or neurons come and go. In 1989, Kennedy described an intracortical electrode consisting of a hollow glass cone containing recording wires (Kennedy, 1989). Neural tissue or neurotrophic factors placed inside the cone induced cortical neurons to send processes into the cone so that their action potentials could be recorded. These electrodes, implanted in motor cortices of monkeys and several humans nearly locked-in by ALS or brainstem stroke, have provided stable neuronal recordings for more than a year (Kennedy et al., 2000). Up to now, one user has learned to control neuronal firing rates and uses this control to move a cursor to select icons or letters on a computer screen. By using neuronal activity to control one dimension of cursor movement and residual EMG control to control the other dimension and final selection, communication rates up to about 3 letters/min (i.e. about 15 bits/min) have been achieved. While training has been limited by recurring illness and medication effects, the results have been encouraging and suggest that more rapid and accurate control should be possible in the future. Furthermore, by demonstrating this control in people who are almost totally paralyzed, these initial data suggest that cortical neurons can support an independent BCI system.

Several laboratories have used multielectrode arrays to record from single neurons in motor cortex of monkeys or rats during learned movements (Georgopoulos et al., 1986; Schmidt et al., 1988). The results show that the firing rates of a set of cortical neurons can reveal the direction and nature of movement. At the same time, almost all of this work has studied neuronal activity associated with actual movement. It is not clear whether the same patterns of neuronal activity, or other stable patterns, will be present when the movements are not made, and, most important, when the animal is no longer capable of making the movements (due, for example, to a spinal cord

injury). Limited data suggest that the patterns persist for at least a time in the absence of movement (Craggs, 1975; Chapin et al.).

Chapter 4

Severe TBI and Disorder of consciousness

4.1 Doc classification

Disorder of consciousness (DOC) can result from focal brain injuries that induce widespread functional changes, or from more-global injuries. DOC are categorized largely on the basis of observable behavioral features and their inferred relationship to level of consciousness diagnostic taxonomies based on pathophysiological mechanisms have not yet been developed. DOC exist on a continuum, and patients may or may not transition sequentially through each state of consciousness.

Accurate differential diagnosis is essential to the clinical management of patients with DOC. Diagnosis drives the approach to treatment, and is strongly associated with functional outcome (Giacino et al., 1997; Nakase-Richardson et al., 2012). Augmentative communication training, for example, should be deferred until the patient transitions to MCS and demonstrates evidence of language comprehension. The clinical examination should be designed to identify the key distinguishing features (Table 1), so that the prognosis can be established and appropriate therapeutic interventions initiated as early as possible (Giacino et al., 2014).

Table 1: Caracteristic clinical features of disorders of consciousness.

Disorder	Arousal and attention	Cognition	Receptive language	Expressive language	Visuoperception	Motor function
Coma	No sleep-wake cycles	None	None	None	None	Primitive reflexes only
Vegetative state	Intermittent periods of wakefulness	None	None	None	Inconsistent visual startle	Involuntary movement only
Minimally conscious state	Intermittent periods of wakefulness	Inconsistent but clear-cut behavioural sign of self-awareness or environmental awareness	Inconsistent one-step command-following	Aspontaneous and limited to single words or short phrases	Visual pursuit Object recognition	Localization to noxious stimuli Object manipulation Automatic movement sequences
Locked-in syndrome	Normal sleep-wake cycles	Normal to near-normal	Normal	Aphonic	Normal	Tetraplegia

4.1.1 Two components of consciousness

Clinically defined, consciousness encompasses two main components: arousal and awareness (Zeman, 2001). At the bedside, arousal (also called vigilance or alertness) is observed by looking at the presence of eye opening. At a neuroanatomical level, the level of arousal (and in particular of sleep-wake cycles) is mainly supported by the brainstem (which is the region between the brain and the spinal cord), and the thalami (which are the nuclei in the center of the brain) (Schiff, 2008; Lin, 2000). Awareness, the second component of consciousness, refers to conscious perception which includes cognition, experiences from the past and the present, and intentions. At a clinical level, awareness is mostly inferred by command following (e.g. “squeeze my hand”, “close your eyes”). At a neuroanatomical level, awareness is underpinned by the cerebral cortex, which is a thin mantle of gray matter covering the surface of each cerebral hemisphere, and mainly through a wide frontoparietal network. Awareness can be further divided into awareness of the environment and awareness of self. Awareness of the environment can be defined as the conscious perception of one’s environment through the sensory modalities (e.g. visual, auditory, somesthetic or olfactory perception) whereas awareness of self is a mental

process that does not require the mediation of the senses and is not related to external stimuli for its presence (as shown by mind wandering, daydreaming, inner speech, mental imagery, etc.). Awareness of self also refers to the knowledge of our own social and cultural history as well as our family membership. To be aware, we need to be awake but when awake, we are not necessarily aware. Consciousness depends on the interaction between the activity of the cerebral cortex, the brainstem and thalamus. When one of these systems is disrupted, consciousness gets impaired. Thus, consciousness is not an all-or-nothing phenomenon but lies on a continuum of states (Wade, 1996). The various states of consciousness include wakefulness, deep sleep and paradoxical sleep (dreaming sleep, i.e. rapid eye movement sleep, REM sleep), anesthesia, coma, vegetative state and the minimally conscious state (Figure 2). The boundaries between these different states are not always sharp but often are progressive transitions (Figure 3).

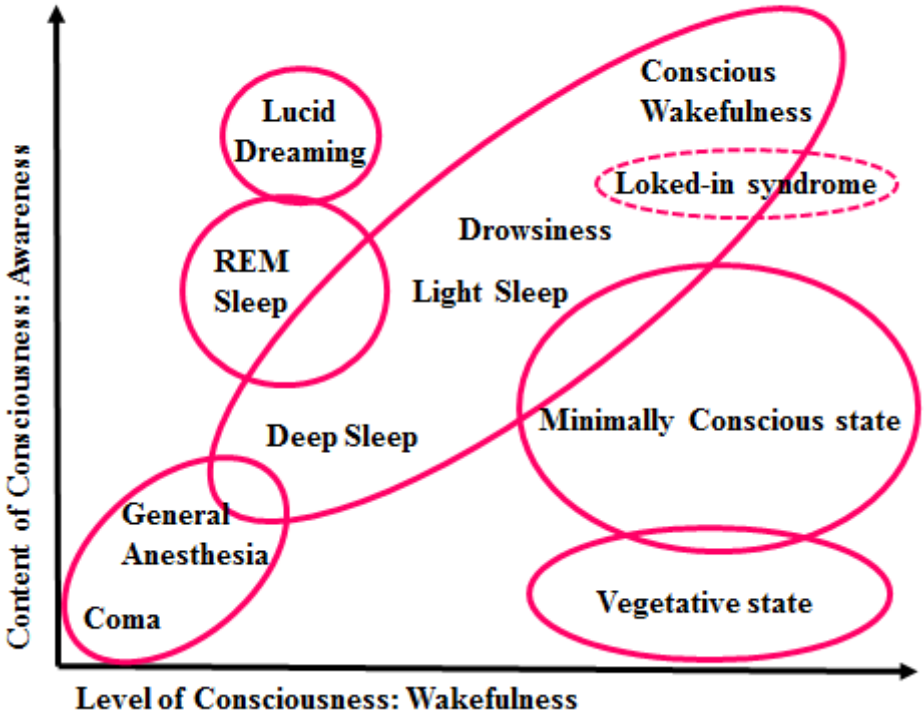

Figure 2: Illustration of the two major components of consciousness: the level of consciousness (arosal or wakefulness) and the content of consciousness (awareness) in normal physiological states and in pathological states or pharmacological coma.

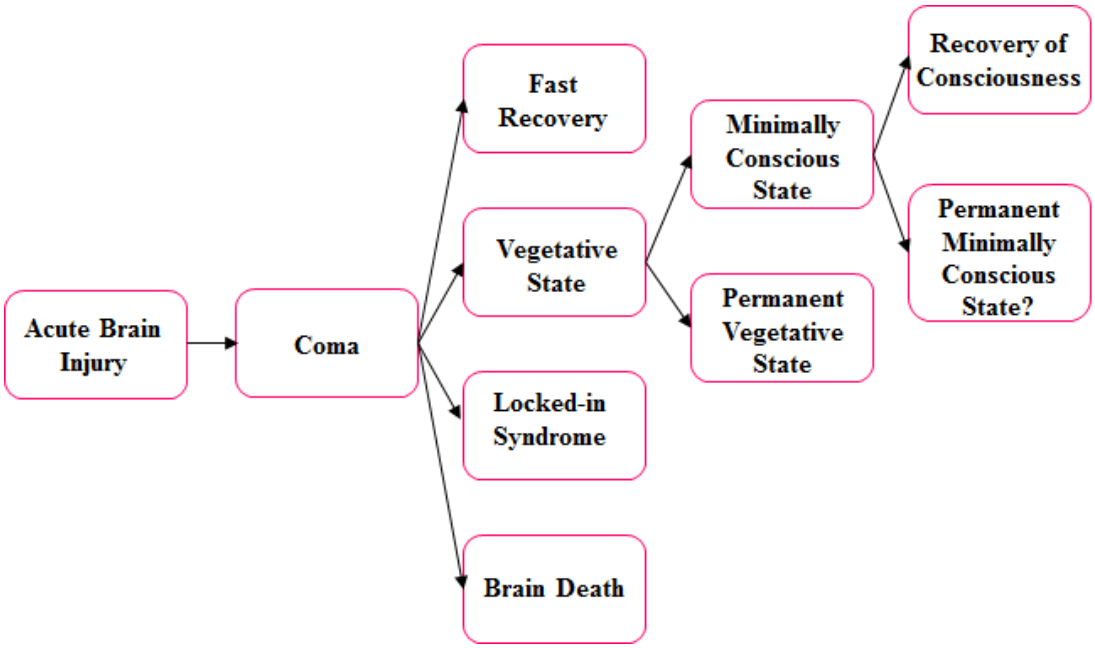

Figure 3: Different conditions may follow acute brain injury. Classically, coma lasts for a couple of days, and once the patients open their eyes they evolve into a vegetative state. Then they may enter a minimally conscious state after showing some signs of consciousness, and eventually they recover full consciousness. In rare case, a person may develop locked-in syndrome, a nearly complete paralysis of the body's volontary motor responses.

4.1.2 Coma

Coma is a state of unarousable unresponsiveness in which the patient lies with the eye closed and has no awareness of self and surroundings (Posner et al., 2007). These patients will never open their eyes even when intensively stimulated. To be clearly distinguished from syncope, concussion, or other states of transient unconsciousness, coma must persist for at least one hour. In general, comatose patients who survive begin to awaken and recover within 2 to 4 weeks. This recovery may sometimes go no further than the vegetative state or the minimally conscious state. There are two main causes for coma: (1) bihemispheric diffuse cortical or white matter damage or (2) brainstem lesions bilaterally affecting the subcortical reticular arousing systems (Laureys et al., 2004). Many factors such as etiology, the patient's general medical condition, age, clinical signs and complimentary examinations influence the management and prognosis of coma. After 3 days of observation, absence of pupillary or corneal reflexes, stereotyped or absent motor response to noxious stimulation, iso-electrical or burst suppression pattern EEG, bilateral absent cortical responses on somatosensory evoked potentials, and (for anoxic coma) biochemical markers such as high levels of serum neuron-specific enolase are known to herald bad outcome. Prognosis in traumatic coma survivors is known to be better than in

anoxic cases (Posner et al., 2007). An important general slowing characterizes the EEG in patients who are in coma. In addition, functional neuroimaging showed a global decrease of 50-70% in cerebral metabolism in coma patients, similar to values observed in general anesthesia.

4.1.3 Vegetative State

After some days to weeks comatose patients will eventually open their eyes. When this return of wakefulness without awareness of self and environment is accompanied by reflexive motor activity only, devoid of any voluntary interaction with the environment, the condition is called a vegetative state, VS. The VS may be a transition to further recovery, or not. It can be diagnosed soon after a brain injury and can be partially or totally reversible or it may progress to a permanent VS or death. Many people in VS regain consciousness in the first month after brain injury. However, after a month, the patient is said to be in a persistent VS and the probability of recovery diminishes as more time passes. If patients show no sign of awareness one year after a traumatic brain injury or three months after brain damage from lack of oxygen, the chances of recovery are considered close to zero, and the patient is considered in a permanent VS. However, rare cases of patients who recover after this interval have been reported (Childs et al., 1996). It is very important to stress the difference between persistent and permanent VS (Laureys et al. , 2000). It is now recommended to omit persistent and to describe a patient as having been vegetative for a certain time. When there is no recovery after a specified period (depending on etiology three to twelve months) the state can be declared permanent and withholding and withdrawal of treatment can be discussed (Coleman et al., 2005; Laureys et al. , 2000). No validated diagnostic nor prognostic markers for patients in a VS exist at present. The chances of recovery depend on patient's age, etiology (worse for anoxic causes), and time spent in the VS. Recent data indicate that damage to the corpus callosum and brainstem indicate bad outcome in traumatic VS (Kampfl et al., 1998). Importantly, VS is not brain death: the VS can be partially or completely reversible. Unlike VS patients who have their eyes spontaneously open, patients in brain death never show eye opening. Moreover, contrary to brain death, VS patients can breathe spontaneously without assistance and have preserved brainstem reflexes and hypothalamic functioning. Additionally, positron emission tomography (PET) studies have showed clear differences between brain metabolism of VS and brain death patients. EEG shows an important general slowing of the

electrical brain activity of VS patients. Somatosensory evoked potentials may show pre served primary somatosensory cortical potentials and brainstem auditory evoked potentials often show preserved brainstem potentials. Endogenous evoked potentials measuring for example the brain's response to complex auditory stimuli such as the patient's own name (as compared to other names) permits to record a so-called P300 response. Recent data show that the P300 is not a reliable marker of awareness but rather signs automatic processing, as it could be recorded in well-documented VS patients who never recovered (Perrin et al., 2005). VS patients show substantially reduced (40-50% of normal values) but not absent overall cortical metabolism. In some VS patients who subsequently recovered, global metabolic rates for glucose metabolism did not show substantial changes In addition, PET studies on pain perception have showed that healthy control subjects and VS patients didn't demonstrate the same brain activity when they received a painful stimulation. In VS patients, the activity of primary somatosensory cortex was isolated and disconnected from the rest of the brain, in particular from the frontoparietal network believed to be critical for conscious perception (Laureys et al., 2002).

4.1.4 Minimally Conscious State

The criteria for the MCS were recently proposed in 2002 (Giacino et al., 2002). The MCS describes patients who are unable to communicate their thoughts and feelings, but who demonstrate inconsistent but reproducible behavioral evidence of awareness of self or environment. Patients in a MCS have to show at least one of the following behaviors: oriented response to noxious stimuli, sustained visual pursuit, command following, intelligible verbalization or emotional or motor behaviors that are contingent upon the presence of specific eliciting stimuli such as episodes of crying that are precipitated by family voices only. Like the vegetative state, the MCS may be chronic and sometimes permanent. At present, no time intervals for permanent MCS have been agreed upon. Some patients who have remained in the MCS for years were shown to slow recover to meaningful lives (Voss et al., 2006). The emergence from the MCS is defined by the ability to use functional interactive communication or functional use of objects [59]. Given that the criteria for the MCS have only recently been introduced, there are few clinical studies of patients in this condition. Similar as for the VS, traumatic etiology has a better prognosis than non-traumatic (anoxic) MCS. Preliminary data show that overall outcome is better than for the VS (Giacino et al., 2002). The EEG shows a general slowing of the electrical

brain activity in MCS patients. Neuroimaging has shows that minimally conscious patients differ from VS patients in their metabolic activity in the precuneus and posterior cingulate cortex (Laureys et al., 2004).. In addition, in patients in a MCS, auditory stimuli trigger higher-order cortical activity normally not observed in the VS (Boly et al., 2005). In the same line, auditory stimuli with emotional valence (such as infant cries or the patient's own name (Laureys et al., 2004). or a narrative told by the patients mother) induce a much more widespread activation in patients in MCS than meaningless stimuli do. This indicates that content does matter when talking to a patient in MCS. A recent fMRI study reported a young women considered as being in a VS while she showed indistinguishable brain activity from these observed in healthy people when we asked her to imaging playing tennis and visiting her house (Owen et al., 2006). Despite the clinical diagnosis that the patient was in a VS, she understood the tasks and repeatedly performed them and hence must have been conscious. A few months after the study, the patient evolved towards a MCS. The results of this study should not be misinterpreted as evidence that all patients in a VS may actually be conscious. The most likely explanation of these results is that the patient was already beginning the transition to the MCS at the time of the experiment. A study conducted by Di et al. (2007) also indicated that the activation of higher-level brain regions during functional MRI seems to predict recovery to the MCS. In addition, MRI studies permit to visualize the extent of brain damage, and new advances in MRI scanning, such as diffusion tensor imaging and spectroscopy, can also offering prognostic information (Galanaud et al., 2007). This technique can also shed light on mechanisms of recovery from the MCS: an MRI diffusion tensor imaging study identified axonal regrowth in the brain of a patient who emerged from a MCS after 19 years of silence (Voss et al., 2006).

4.1.5 Locked-in Syndrome

The locked-in syndrome describes patients who are awake and conscious but have no means of producing speech, limb, or facial movements. Brainstem lesions are its most common cause. People with such lesions often remain comatose for some days or weeks, needing artificial respiration and then gradually wake up, albeit remaining paralyzed and voiceless, superficially resembling VS patients. Locked-in patients can be divided into three categories (Bauer et al., 1979): (a) classical locked-in syndrome is characterized by quadriplegia and anarthria with eye coded communication; (b) incomplete locked-in syndrome permits remnants of voluntary responsiveness other

than eye movement; and (c) total locked-in syndrome consists of complete immobility including all eye movements, combined with preserved consciousness. Once a locked-in syndrome patient becomes medically stable, and given appropriate medical care, life expectancy now is several decades. Even if the chances of good motor recovery are very limited, existing eye-controlled computer-based communication technology currently allows these patient to control their environment, use a word processor coupled to a speech synthesizer and access the world wide net. Neuropsychological testing batteries adapted and validated for eyeresponse communication, have shown preserved intellectual capacities in locked-in syndrome patients (Schnakers et al., 2008). Recent surveys show that chronic locked-in syndrome patients self-report meaningful quality of life and the demand for euthanasia, albeit existing, is infrequent (Laureys et al., 2004). According to some studies, the EEG does not consistently distinguishes the locked-in syndrome from the VS. PET scanning has shown preserved metabolic cerebral functioning in a locked-in syndrome when compared to those in a VS or MCS.

4.2 The issue of misdiagnosis between VS and MCS

Diagnostic accuracy is critical to designing an appropriate plan of care, establishing an accurate prognosis, and providing appropriate information to caregivers (Giacino et al., 2009, Giacino et al., 2007). Unfortunately, diagnostic error is common among patients with VS and MCS. Reports consistently find that approximately 30–40% of people diagnosed with VS actually retain conscious awareness. Misdiagnosis may contribute to premature withdrawal of life-sustaining care and lead to inappropriate medical management (for example, neglect of pain treatment). The risks associated with early misdiagnosis are highlighted by a Canadian study, which found that 70% of the deaths reported in six level I trauma centres were attributable to withdrawal of life-sustaining therapy, with half occurring within the first 72 h of injury (Turgeon et al., 2011). The failure to detect conscious awareness may also limit access to specialized neurorehabilitative services, as many insurance policies will not authorize admission to a rehabilitation programme for individuals believed to be unconscious.

The lack of a ‘gold standard’ for detection of conscious awareness is the most prominent confounding factor for diagnostic assessment. In the absence of an objective test of consciousness, diagnostic impressions are based on behavioural

observations at the bedside. Behaviour is, however, an unreliable proxy for consciousness (Giacino et al., 2009). Interpretation of the significance of a specific behaviour reflects the subjective bias of the observer and is a byproduct of the range of behaviours sampled (narrow versus broad), the frequency of assessments performed (one-off versus serial), and the parameters established for response interpretation (qualitative versus operationally defined).

A second source of diagnostic error arises from patient-specific characteristics. Underlying peripheral and cortical sensory deficits, neuromuscular impairments, fluctuations in arousal level, cognitive dysfunction, subclinical seizure activity, and occult illness may all mask conscious awareness (Giacino et al., 2009). Environmental factors that constrain the patient's behavioural response repertoire — for example, use of restraints or sedating medications—may also bias the diagnostic impression.

Various approaches have been employed to discern levels of consciousness in behaviourally non-responsive and non-communicative patients. Neurobehavioural assessment methods are most commonly employed in clinical practice, in view of their availability, low cost and ease of use. Structural and functional neuroimaging strategies and electrophysiological techniques have garnered scientific and clinical attention in light of increasing evidence that they can detect active cognitive processing in the absence of behavioural signs of consciousness (Goldfine et al., 2011).

4.3 Behavioural assessment

4.3.1 Neurobehavioural rating scales

Neurobehavioural rating scales rely on standardized administration and scoring procedures to detect subtle but important behavioural signs of consciousness. Scales designed for this purpose have generally been shown to have good reliability and validity, although other important psychometric properties such as sensitivity and specificity, and positive versus negative predictive value, have not been adequately investigated. An evidence-based review of neurobehavioural rating scales designed specifically for patients with DOC was recently completed by a task force of the American Congress of Rehabilitation Medicine. The task force identified six scales that seem to be sensitive for detecting conscious awareness (Seel et al., 2010). The Coma Recovery Scale-Revised (CRS-R) (Giacino et al., 2004) received the strongest

recommendation ("minor reservations") of those reviewed, on the basis of psychometric properties deemed important for clinical assessment.

4.3.2 IQBA

Individualized quantitative behavioural assessment (IQBA) employs single-subject experimental design to address case-specific questions, and is intended to complement comprehensive neurobehavioural assessment. This method of assessment is particularly useful when behavioural responses are ambiguous or infrequent (Giacino et al., 2005).

In IQBA, behaviours of interest are operationally defined and tested under varying conditions constructed to address a specific question. For example, one can ask whether movement of the thumb is volitional by testing the frequency of thumb movement following a command to move the thumb (volitional condition) or another part of the body (noise condition), and in the absence of any command (rest condition). Differences in the frequency of the target behaviour can then be tested statistically to determine whether the rate of occurrence is significantly greater in one condition relative to the others. If the analysis indicates that the frequency of movement is significantly higher in the volitional condition relative to the noise and rest conditions, the behaviour is very likely to be under volitional control (Giacino et al., 2005). IQBA can be adapted to address a broad range of questions and has been shown to be useful for detection of command-following, visual field deficits, hemispatial neglect, and medication effects (Whyte et al., 1999; Di Pasquale et al., 1996).

4.4 Neuroimaging strategies

While behavioural assessment of DOC remains the gold standard, neuroimaging permits objective documentation of CNS damage after acquired brain injury. From a scientific standpoint, neuroimaging studies aid our understanding of the neural correlates of human consciousness. From a clinical perspective, they provide additional information concerning diagnosis, prognosis and the course of recovery of consciousness, and can serve as surrogate markers for novel therapeutic interventions.

4.4.1 Stuctural imaging

MRI is the method of choice to visualize the location and extent of brain damage in chronic DOC. In the acute setting, however, CT scanning may be preferred, owing to

its accessibility, speed of acquisition, and sensitivity to acute haemorrhage or lesions that require immediate surgery. Standard T1-weighted structural MRI assessments cannot reliably differentiate VS from MCS, but voxel-based morphometry analyses may allow this distinction in the near future. Older studies have shown the possible **prognostic** value of 'classic' structural MRI sequences to predict DOC outcome; for example, the presence of corpus callosum and dorsolateral brainstem lesions correlates with lack of recovery at the group level (Kampfl et al., 1998). However, recently developed quantitative diffusion tensor imaging (DTI) techniques, which permit assessment of structural white matter damage, have been shown to outperform clinical markers in predicting 1-year functional outcome at the individual-patient level in patients with traumatic or anoxic brain injury. In our view, DTI-MRI techniques offer a unique opportunity to quantify the structural integrity of the white matter, and can also quantify the primary and secondary axonal damage encountered in DOC (Voss et al., 2006).

4.4.2 Functional Neuroimaging

Key advances in our understanding of DOC have come from the use of functional imaging. Depending on the technique employed, functional neuroimaging can measure the brain's metabolic activity (for example, by use of 18F-fluorodeoxyglucose PET, [FDG-PET] or MRI spectroscopy), haemodynamic activity (for example, by use of H215O-PET or functional MRI [fMRI]) or electrical activity (for example, EEG, evoked potentials or magnetoencephalography). Depending on the acquisition conditions, these approaches can measure resting or active brain function, the latter through either passive external stimulation or active cognitive paradigms.

PET imaging

FDG-PET studies in 'resting state' conditions were the first to demonstrate massive decreases in brain metabolism in DOC. In VS, FDG-PET classically shows a reduction of brain function to 40–50% of normal values (Laureys et al., 2012). Voxel-based studies indicated that the lateral and medial frontoparietal associative cortices are the most hypometabolic areas, and recovery of consciousness seems to be characterized by recovery of activity in this frontoparietal 'awareness network'. More-recent studies have used automated classifiers for the analysis of FDG-PET data, permitting calculation of the probability that individual patients are conscious ('locked in') or unconscious (VS) (Phillips et al., 2011). At the single-patient level,

FDG-PET cannot disentangle VS from MCS, but group studies have shown that CRS-R total scores correlate with metabolic activity in the awareness network. Within this network, fronto-parietal midline structures are thought to be important for internal, stimulus-independent or 'self' consciousness, whereas lateral fronto-parietal cortices seem to be critical for external or sensory awareness. The latter network seems to be relatively preserved in MCS (compared with VS), possibly reflecting recovery of voluntary interaction with the environment. Patients who are considered to be in MCS because they display nonreflexive behaviour but fail to follow commands (a condition newly termed MCS-MINUS) have been shown to have metabolic dysfunction in the dominant left-hemispheric language network, possibly related to the presence of aphasia (Giacino et al., 2014).

H2 15O-PET studies suggest that VS represents a global disconnection syndrome in which the awareness networks are functionally disconnected from primary cortical areas. By contrast, patterns of activation observed in patients in MCS indicate preservation of large-scale cortical networks associated with auditory and pain processing (Giacino et al., 2014).

fMRI imaging

In recent years, PET activation studies have been largely superseded by non-ionizing fMRI techniques. Activation fMRI studies using auditory, tactile or visual stimuli have shown near-normal high-level cortical activation in MCS and low-level activation in VS (Laureys et al., 2012). The minority of patients in VS who exhibited high-level activation often showed clinical signs of recovery at long-term follow-up (Di et al., 2008). Despite their potential value as prognostic markers, the diagnostic value and interpretation of activation fMRI studies in DOC in terms of the presence or absence of residual consciousness have remained controversial. Indeed, in the absence of a full understanding of the neural correlates of consciousness, deficient cortical activation to external stimuli does not necessarily prove the absence of consciousness.

'Active' fMRI paradigms have been developed to probe for possible motor-independent signs of command-following (Boly et al., 2007). Patients with DOC are asked to perform cognitive tasks in motor (for example, "imagine playing tennis"), visuospatial (for example, "imagine walking around in your house") or visual (for example, "look at the face") domains. This approach provided an opportunity to ask yes–no questions to a patient with an initial clinical diagnosis of VS (but later shown

to be in MCS) (Monti et al., 2010). It should be stressed, however, that many of the tested patients in MCS who showed behavioural signs of command-following failed to show a response to these active fMRI tests, leading to false-negative findings. Because this approach depends on adequate processing and performance of the cognitive task, these paradigms cannot document residual consciousness in patients with severe sensory, cognitive or language impairment.

Task-free 'resting-state' blood oxygen level-dependent (BOLD) fMRI measurements have also been performed in DOC (Heine et al., 2012). Recording of spontaneous fluctuations in BOLD fMRI activity under unstimulated conditions has identified various functional networks, some of which are thought to represent conscious cognitive activity. The best-studied network is the default mode network (DMN) encompassing the posterior and anterior cortical midline structures, which are considered to be involved in stimulus-independent thought, mind-wandering and self-consciousness (Demertzi et al., 2013). The DMN was shown to be absent in brain death, but still partially preserved in VS, probably reflecting residual structural connectivity. At the group level, resting-state network activity revealed reduced interhemispheric connectivity and correlated with levels of consciousness in patients with DOC (Vanhaudenhuyse et al., 2009). At the single-patient level, however, it fails to reliably distinguish VS from MCS, and contamination by motion or other artefacts can impede the identification of true neuronal activity.

The arterial spin labelling (ASL) technique allows noninvasive measurement of resting-state cerebral blood flow. A recent ASL-MRI study in patients in MCS showed a profound decrease in blood flow in anterior cortical midline structures (Liu et al., 2011). Finally, MRI spectroscopy, a measure of biochemical changes in the brain, has uncovered severe metabolic cortical and thalamic neuronal dysfunction in DOC, with probable prognostic value (Carpentier et al., 2006).

Despite the very promising results obtained by these studies, fMRI-based applications remain challenging for many reasons: 1) high costs; 2) limited scanner availability; 3) the inactive state of these patients; 4) the frequent uncontrolled, involuntary movements inside the scanner; 5) the substantial physical stress to patients on transfer to the fMRI facility. Furthermore, metal implants, including plates and pins, which are common in most traumatically injured populations, rule out the use of fMRI.

A variety of other diagnostic tools is currently in development and is being tested on DOC patients. Amongst the most promising are electromyography, "sniffing"-tests, and functional near-infrared spectroscopy (fNIRS). Electromyography has been used to study the occurrence of subthreshold muscle activity in response to verbal command. In a study by Bekinschtein and colleagues (2010), one VS/UWS and two MCS patients showed increases in the electromyography signal related to the command "move your hand." Willful modulation of nasal pressure ("sniffing") can also be used for communication, writing texts and driving a wheelchair (Plotkin et al., 2010). Sniffing can provide a control interface that is fast, accurate, robust and highly conserved following severe injury. It is therefore possible that this can be used as a diagnostic tool in DOC, although more research is needed. When studying the brain, fMRI has the advantage of showing with high precision the brain areas that are involved in cognition and consciousness. As mentioned before, this information can be used to communicate via brain modulation by the patient. However, although attempts for such fMRI-based communication have been successful in a number of cases, it has the disadvantage of being dependent on expensive and immobile fMRI scanning equipment. fNIRS might offer a solution to this problem in the near future (Sorger et al., 2009), as it is a portable, silent, low-cost alternative to fMRI. The technique capitalizes on the changing optical characteristics of blood in the visible and near-infrared light range, when oxygenated hemoglobin in the blood becomes deoxygenated due to oxygen extraction by brain tissues. Although initial fNIRS studies have been performed in several neurological and psychiatric disorders (Irani et al., 2007), validation of the technique in DOC is still awaited. A limitation of fNIRS is the fact that it cannot measure activity in deep brain structures. However, the technique offers the possibility of continuous scanning for longer periods of time than would be possible with fMRI and can include patients that have physiological limitations that make fMRI scanning impossible.

4.5 The use of EEG in context of research

The majority of electrophysiological studies on VS/MCS focused on the search for the presence of specific event-related potentials that would sustain the integrity of some superior functions of the central nervous system of the patients. Among the whole set of ERP, two of them have been demonstrated to be the best predictor of a good outcome; the P300 and the Mismatch negativity. They are included in protocols

testing particularly the integrity of sensory processing pathways in the acoustic channel.

- Mismatch negativity (MMN) is a mid-latency ERP (peaking after 100-150 ms from the stimuli) that reflects the automatic detection of rare stimuli in a sequence, and, for the acoustic channel, it is believed to be a product of processing in the associative acoustic areas in the temporal lobes.
- P300 is a long-latency ERP components that reflect attentional processing in responses to rare, deviant and or meaningful stimuli to the subject. It is a product of attentional processes mainly located in the parietal areas and can be divided in two subcomponents: P300a, produced by attentive mechanisms evoked by just the rarity of a given stimulus in a sequence (latency: 200- 300 ms) and P300b, elicitable when some executive processes are requested to the subject when faced to a given stimulus (latency: 300-400 ms).

Aside from studies involving ERP methodologies, other studies involved spectral and coherence analyses of EEG in SV/MCS patients. Such studies have shown a general slowing of EEG in SV/MCS, with a general increase of power in lower bands (range delta, theta) over the whole scalp, and a generalized decrease of spectral coherence for every band and over the whole scalp. Authors suggested that the latter could be probably an index of functional disconnection between the different cortical regions. Up to now, these research studies have not conduced to the definition of new diagnostic and/or prognostic methodologies: such studies rely on relatively small groups of subjects, and results are difficultly interpretable and integrable with results from ERP-based assessments.

Systematic studies involving EEG spectral parameters of SV/SMC patients were published only recently (Babiloni et al., 2009; Keller et al., 2007, Sharova et al., 2007]). Babiloni et al. (2009) showed that power in the alpha band in the parieto-occipital areas positively correlates with recovery degree after 3 months from injury (assessed through the Level of Cognitive Functions scale, LCF) in a study involving 50 VS patients. Keller et al. (2007) studied the modifications induced by different sensory stimulations on the spectral baricentric frequency in 18 VS patients, showing that tactile stimulation induces higher increases compared to auditory stimulation.

Several studies used **EEG-based** systems to validate the scientific reliability of EEG-related procedures in discriminating mental imagery tasks in DoC patients (Lemm et al., 2011). These studies demonstrated that EEG-signals could be produced and

controlled by thinking about specific imagery tasks, thereby confirming that this activity could also serve as a new form of communication in patients with disorders of consciousness. With a paradigm similar to that of Monti et al., Cruse and colleagues used EEG to detect command-following in vegetative state patients undertaking two motor imagery tasks (image moving hand and toe). They used EEG-signals recorded by 25 electrodes located over the motor area and a support vector machine (SVM) to classify the two tasks, obtaining a classification accuracy of 61–78% (Cruse et al., 2012). In a second study, Cruse and colleagues optimized their technique using only four fixed electrodes and confirmed the classification accuracy of their previous study (Cruse et al., 2012). Cruse et al.'s results were discussed by Goldfine et al. because of the difficulty of the tasks and the critical reliance on certain statistical assumptions. They reanalyzed the data with a method independent of such assumptions and reported no evidence for covert consciousness (Goldfine et al., 2013). Using Fisher's linear discriminant approach and two different tasks with respect to those used by Cruse et al. (image swimming and image walking in one's own home). Goldfine and colleagues were the first to translate to the EEG motor imagery tasks (imagine swimming/ stop imagining) and spatial navigation tasks (imagine walking around your home/stop imagining) similar to those used with fMRI. They tested 5 healthy controls and 3 DOC patients, 2 MCS and 1 LIS. The authors reported variability in the patients' responses, which allowed only limited conclusions to be drawn about the applicability of these paradigms to patients with disorders of consciousness. In the first patient, the authors observed that the task-related signals were different from those observed in the healthy controls. In the second patient, the authors observed variability between the task-related signals produced during 2 different visits. The signal from the first visit was consistent across runs, but the signal from the second visit was inconsistent across runs, and was classified as indeterminate. The third patient showed a similarly indeterminate pattern during both visits. The authors concluded that assessment of larger sample sizes of both healthy controls and patients groups would be needed before this task could be used as a clinically diagnostic tool. However, as the first study to translate to EEG the motor imagery paradigms that have been used successfully in fMRI, this work is an important proof of principle (Goldfine et al., 2011). John and colleagues established the reproducibility of differential EEG source localization during requested imagery tasks in vegetative state patients (Jhon et al., 2011), as had been

established for fMRI. Kotchoubey and colleagues described a CLIS patient whose slow EEG activity significantly differed between trials when he was asked to try to move the left compared to the right hand (Kotchoubey et al., 2003). In healthy participants, motor imagery also produces clearly distinguishable modulation of EEG sensorimotor rhythms (SMRs), similar to those seen during motor execution. Kubler and colleagues showed that LIS patients with ALS could learn to modulate their SMRs with . 70% accuracy, but did not test VS patients with this paradigm (Kubler et al., 2005). Results obtained in the above studies are often discrepant but confirm the usefulness of EEG to reliably detect awareness in patients with a clinical diagnosis of VS. Therefore, EEG may serve as an important tool for the assessment of awareness components in patients with disorders of consciousness in the clinical setting.

4.6 BCI in DOC

Typically, BCI applications with (behaviorally) responsive participants involve analysis and classification of brain responses, produced either voluntarily, or in response to sensory stimulation, to infer a desired command that reflects the user's intention. The executed command brings about a state change of the BCI system that is communicated to the BCI user, for example, through a visual display (Kübler et al., 2007). This cycle can be repeated iteratively until there is bidirectional feedback, or online communication between the user and the operator. Such an advanced BCI system involves reading and interpreting the user's intention in real time to produce physical outcomes/changes in the system, which can inform the user's subsequent response. For conscious participants, the BCI user's intent is clear—for example, to regulate one's own brain activity, such as that which produces the sensation of chronic pain, via neurofeedback. A major hurdle in communicating with behaviorally nonresponsive patients is the lack of a priori knowledge about their level of conscious awareness, cognitive capacities, and even their communicative intent. Moreover, the level of arousal, awareness, and more generally, cognition varies dramatically between patients who are truly in a VS and those who are (minimally) aware, but have been misdiagnosed as VS. Thus, to maximize the chances that any given patient will be able to respond, a BCI system for DOC patients must be as robust to this variation, and as straightforward to use, as possible. Another significant challenge in the development of BCIs for DOC patients is the limited sensory

processing that these patients are likely to have (Andrews et al., 1996). The majority of BCI techniques, which have been developed for conscious participants, rely on visual stimulation and feedback. However, vision is among the most affected senses in DOC patients (Andrews et al., 1996; Gill-Thwaites et al., 2004). By definition, VS patients lack the ability to fixate on or pursue objects in their visual field,12 which results in highly impaired visual processing. This precludes the use of visually based BCI systems in this group, and moreover the modification of such systems for use in other modalities (eg, auditory) is not trivial.

Below, we review BCI research in 3 noninvasive neuroimaging technologies, fMRI, EEG, and functional near-infrared spectroscopy (fNIRS), all of which may be applicable to varying degrees in nonresponsive patients. Invasive technologies, such as electrocorticography, single microelectrodes, or microelectrode arrays involve implantation of electrodes in the cortex, and therefore provide superior signal-to-noise ratio and better detection of high-frequency oscillatory activity than noninvasive technologies. A proof of principle study used invasive electrodes in a BCI application for patients with limited behavioral response (eg, locked-in) (Guenther et al., 2009). However, invasive technologies are of limited relevance to patients who are the main focus of this article for several reasons. Electrode implantation is often a corollary of a surgical procedure in the course of a patient's treatment, and rarely an option with stable and/or chronic DOC patients. The DOC patients we consider here (VS and MCS) are not able to provide informed consent. For any research, legal approval is required from the patient's family or other legal representative. This is far less likely to be granted for invasive BCI applications, especially when they are not part of treatment protocols, as they may adversely influence the patient's health. For similar reasons, with the exception of rare cases, where the patient requires surgical intervention and the appropriate legal and ethical permissions are already in place, such research is prevented by rulings of ethics boards and other regulatory organizations. Finally, issues of financing and access to medical resources available only to acute patients with specific conditions further prohibit invasive BCI applications in DOC patients (Naci et al., 2012).

4.6.1 fMRI BCIs

fMRI has several strengths for BCI applications, including its noninvasive nature, global brain coverage of the cortex and deep subcortical structures, and excellent spatial resolution (in the millimeter range). As introduced above, Monti and

colleagues (2010) employed an fMRI-based mental imagery paradigm to assess command following in a patient who had been clinically diagnosed as VS and had been unresponsive for 5 months. The patient was asked to imagine playing tennis (for 30 seconds) when she heard the word tennis, and to relax (for 30 seconds) when she heard the word relax. In a separate spatial imagery task, she was asked to imagine moving around the rooms of her home (for 30 seconds) when she heard the word house, and to relax (for 30 seconds), when she heard the word relax. The patient showed task-specific fMRI activation in the appropriate regions of the supplementary motor area following the instruction to imagine playing tennis, and in the parahippocampal gyrus, the posterior parietal lobe, and the lateral premotor cortex following the instruction to imagine moving from room to room in her house. Moreover, this activity was indistinguishable from that of healthy participants performing the same tasks (Owen et al., 2006; Bol et aò., 2007). The patient's fMRI activation was statistically robust, reproducible, task appropriate, and sustained over long time intervals (30 seconds), allowing Owen and colleagues (2006) to conclude that she was responding to the commands by performing the imagery tasks in the absence of any overt action. Monti et al (2010) extended this approach to demonstrate that fMRI could also be used to communicate with a nonresponsive patient who was assumed to be in a VS. One type of imagery (tennis or spatial navigation) was mapped to a yes response, and the other to a no response. A single neutral word, answer, was used to cue each response to a question. To decode the answers, each communication scan was compared to 2 localizer scans, during which the patient was asked to simply imagine playing tennis, or imagine moving around his house (see Owen et al 2006). Following 6 autobiographical questions (eg, ''Is your father's name Thomas?''), the answers that were decoded from the brain activity matched the factually correct answers (in 5 of the 6 questions), which were unknown to the experimenters at the time. This study demonstrated that the presence of voluntary, reliable, and sustained brain activity in response to command could be used as a proxy for physical behavior, such as movement or speech, to facilitate communication with nonresponsive participants. In the study described above, (Monti et al., 2013) VS and MCS patients were tested and, of those, only 5 (4 VS) showed significant changes in fMRI activation during the basic imagery tasks. One interpretation of this finding is that the diagnosis was accurate in the vast majority of cases, and the negative results reflect a genuine lack of awareness in those patients.

Several other factors, however, may also explain these findings. First, it is possible that this technique lacks sensitivity, and thus failed to show activation in patients who might have been engaged in the task. Indeed, it is known that in brain-damaged patients, the coupling of hemodynamics and neuronal firing, which lies at the basis of the fMRI signal, may be very different from that in healthy volunteers. Alternatively, it is possible that in some patients, deficits in language comprehension, decision making, working memory, or executive function may have hampered their efforts to express themselves through the imagery task, yielding brain activity too weak to be interpreted. Consistent with this possibility, a recent report found an MCS patient who showed no distinguishable activation in the mental imagery task, but nonetheless was able to voluntarily modulate his brain activity by allocating visual attention in response to verbal commands. Finally, in some patients, functional reorganization of the brain following the injury may have produced highly atypical, and therefore uninterpretable, patterns of fMRI activation. Communication via fMRI BCIs has been attempted in 6 other DOC patients, 5 MCS and 1 LIS. Bardin et al. (2011) used binary paradigms involving motor imagery, similar to those used by Monti and colleagues, and a multiple-choice paradigm, adapted from Sorger et al. (2009). In a novel application of this 4-choice paradigm, the experimenters presented each patient, at their bedside, with 1 playing card, which could be 1 of 4, differing in 2 dimensions (suit and face). Subsequently, while inside the fMRI scanner, each patient was aurally provided with the 4 options for the suit and face of the card, and was asked to perform a mental imagery task (swimming or tennis) to indicate the correct card, for each of the 2 dimensions. The authors reported a communication signal in 1 of the 6 patients. Although the patient showed significant brain activity to the task, this activity conveyed incorrect responses to the 2 questions asked, with respect to the face and the suit of the card. However, the patient was able to correctly show command following behaviorally at the bedside, and by modulating her brain activity in the scanner, according to the instructions of the binary mental imagery task. The authors suggested that a delay in the timing of the hemodynamic signal to the patient's response might explain why the neural responses to 2 stimuli proximal in time could not be disambiguated with traditional fMRI analyses (Bardin et al., 2011)). This study highlighted the issue of unknown delay range of the neural signal in this patient group, which could be driven by an unusual coupling of hemodynamics and neuronal firing, as compared to healthy individuals (Gsell et al.,

2000). Although the optimal interval for a reliable measurement of the neural response is not known, the 30-second intervals reported by Owen, Monti, and colleagues have so far yielded unequivocal results of successful communication in 1 patient, and command following in 6 patients, documented in published reports. A systematic study of the delay range would be necessary to determine the optimal response interval, and furthermore this parameter might differ across neuroimaging methodologies (fMRI, fNIRS, EEG). A second patient reported by Bardin et al. (2011) raised a different issue relevant to communicating with DOC patients through neuroimaging BCIs. This patient could show command following by using motor imagery (swimming) in 2 different visits, but could not use the motor imagery task to produce robust brain activity that could be used for binary (yes/no) communication. Several factors could be behind this patient's failure to communicate. The patient's profile of cognitive deficit, in particular her short-term memory reserve, may underlie her inability to communicate. Beyond command following, where the patient has to perform a task in response to a specific command such as tennis or swim to communicate, the patient must be able to perform at least 2 additional processes. First, the patient must be able to find the answer to the question that is being asked. In addition, the patient must also be able to abstract the demand characteristic of the task (ie, imagine playing tennis/swimming), to a particular answer word (yes or no), which applies in some situations (ie, questions whose answer is that word) but not in others. A patient with a pronounced memory deficit may not be able either to think of the answer and/or to maintain in short term memory the abstract link between the arbitrary response function (ie, a specific form of motor imagery) and the answer word to a question (yes or no). This patient highlights the need for new paradigms that rely on more intuitive response modes, to maximize the chance that patients with very limited cognitive reserves will be reached.

At least the issue of delayed response might be resolved with more sophisticated neuroimaging analysis methods, (Bardin et al., 2012) such as multivoxel pattern analysis (MVPA). MVPA is an fMRI analysis technique that is highly sensitive to the information content in the neural signal. Traditional univariate fMRI analyses average across activations in a brain region, and compare overall changes in signal strength between different types of conditions. MVPA, conversely, does not discard the information relating to the patterns of activity within that brain region. As such, it

is capable of dissociating overlapping neural patterns to different stimuli or mental states, which could not be disentangled with univariate methods (Christopher deCharms et al., 2008). By dissociating several mental states/responses elicited by a single command, MVPA also has the potential to expand communication from binary responses to multiple-choice answers. For example, although this is still in the future, with MVPA it may eventually be possible to ask a patient to express how much pain he/she feels on a sliding scale from 1 to 10, by imagining the appropriate number. In a follow-up study, Bardin et al. (2012) provided the first proof of principle that MVPA can decode a patient's answers elicited from a multiple-choice response paradigm. In the case described above, (Bardin et al., 2011) conventional fMRI analysis could not distinguish which was the patient's response between 2 choices in each question relating to the 2 card features (suit or face). For each question, 2 options, temporally proximal in the 4-choice stimuli presentation, produced statistically significant responses that were undistinguishable with univariate analysis. By contrast, an MVPA classifier was able to disambiguate the response patterns for each question, by classifying the response to the correct option (selected prior to the scanning session) above chance, and the response to the incorrect option at chance, with a significant difference between the 2 classifications.

MVPA methods can also be applied in real time, (Caria et al., 2012; Sitaram et al., 2011) and present exciting possibilities for communication without perceptible delay between the question and the interpretation of the response. With these methods, however, classification accuracy is strongly dependent on the amount of available fMRI data. This may be a problem for VS patients, where the scanning time is often limited for physical reasons, for example, the patient experiences difficulty lying supine for long periods of time. Moreover, one has to consider that VS patients may become exhausted easily. Other approaches have also been used to explore the potential uses of fMRI for BCI-related applications.

In a study with healthy participants, Sorger and colleagues (2009) were able to generate the differential blood oxygenation level-dependent (BOLD) responses necessary to answer a 4-choice question within the length of a single, 1-minute trial. To express their choice, participants had the option of 1 of 2 tasks, performed at 1 of 4 moments in time, which were indicated by a highlighted letter on the screen and offset by 5 seconds one from the other. Thus, the BOLD responses could be differentiated with respect to at least 2 of 3 features of the BOLD signal: its source

location, onset, and offset. An automated decoding procedure deciphered the answer by analyzing the generated single-trial BOLD responses online. Participants' answers were decoded correctly with a mean accuracy of 94.9%, ranging from 75% to 100%. This study made an important contribution by demonstrating that single-trial (ie, brief, or, 1 minute long) fMRI time courses can be used as a robust source of information for decoding responses. Furthermore, it showed that fMRI can be used to communicate multiple-choice answers online/in real time, and within a reasonable response time scale (eg, 1 minute). This length of time does not introduce excessive time pressures, and may prove patient-friendly. However, the applicability of this design for communication with nonresponsive patients would be limited by its reliance on visual processing. Although, as we have discussed, fMRI has great strengths for BCI applications, including its noninvasive nature, global brain coverage, and excellent spatial resolution of specific brains structures, it also comes with significant limitations, which restrict its widespread use in DOC patients. In particular, its high cost, lack of portability, and physical impositions on some patients (eg, patients must not wear paramagnetic equipment, must refrain from any minor movement, and must be able to cope with the loud noise of the fMRI scanner) make it unlikely that fMRI will provide the ultimate communicative solution that DOC patients require in real life situations. fNIRS and EEG, however, are not susceptible to these same problems, and provide exciting opportunities to extend these fMRI developments.

4.6.2 fNIRS BCIs

fNIRS exploits the penetrability of biological tissue by light in the near-infrared spectrum (700–1,000nm) to infer neural activity. The amount of near-infrared light at specific wavelengths that is absorbed by blood vessels varies depending on the concentration of oxygenated and deoxygenated hemoglobin. Using head-mounted near-infrared emitters and sensors, fNIRS provides a noninvasive hemodynamic measure of cortical activity. The main advantage of fNIRS over fMRI is that it is portable. Furthermore, in contrast to fMRI, fNIRS is also a relatively comfortable method. It is nearly noiseless, does not expose patients to a high magnetic field, thus avoiding the restrictions imposed by paramagnetic medical equipment, and is less sensitive to movement artifacts. Moreover, fNIRS is relatively affordable, less technically demanding, and easier to operate than fMRI.

These qualities make fNIRS a viable technology for use at the patients' bedside. Although it is in its infancy, some early applications have demonstrated the potential of fNIRS as a BCI method. Naito and colleagues (2007) mapped 2 mental imagery tasks, calculation and singing, to yes/no responses, and were able to detect responses with fNIRS in 40% of 17 CLIS patients. The brain response for these patients could be decoded with 74% accuracy. As the first BCI method successfully applied in CLIS patients, this study highlighted the future potential of fNIRS in this field. Although fNIRS has certain benefits over fMRI, it also suffers from technological challenges that limit its application for BCI systems, at least in its current state. In particular, fNIRS only allows reliable measurement of hemodynamic responses in cortical tissue that is close to the head surface, up to approximately 3cm in depth. Thus, brain activation in deeper subcortical structures, accessible with fMRI, cannot be targeted. Moreover, the spatial resolution of fNIRS, in the range of a few cubic centimeters, is considerably lower than the resolution that can be obtained with fMRI. Thus, BCI paradigms that employ fNIRS must be based upon neural responses that are relatively broad. Future improvements in the development of multichannel fNIRS systems promise to address this issue (Joseph et al., 2006). Another area that will benefit greatly from further research and development is that of analyses methods, which are still relatively rudimentary in fNIRS, as compared to those used for fMRI. For example, the limited spatial resolution may be overcome by employing more sensitive data analysis techniques such as MVPA that maximize the likelihood of decoding different mental states from widely distributed brain activation patterns.

4.6.3 EEG BCIs

EEG is another noninvasive, portable, and relatively inexpensive neuroimaging method that has been used extensively in BCI applications. The experience gained with its use in many populations, from healthy participants to severely paralyzed and LIS patients, lends itself to application in nonresponsive DOC patients. The EEG signal that is measured on the scalp results from neural activity originating in the cortex, which can be captured with high temporal resolution, in the millisecond range. However, in contrast to fMRI, EEG provides limited spatial resolution (centimeter range) that strongly decreases with the depth of the source. Similar to fNIRS, EEG is silent, less physically demanding for the patient (for example, it can be applied in the seated and supine positions, or even when the patient is asleep), and easier to operate than fMRI. EEG is susceptible to artifacts from electromyographic

activity from cranial muscles, and electrooculographic activity from eye movements, but sophisticated analysis methods can eliminate these artifacts. Below, we review the EEG markers that hold promise for BCI systems in nonresponsive DOC patients, as well as a number of challenges that thus far have limited the application of this technology in this patient group.

P300 evoked potential

One prominent component of event-related potentials (ERPs; electrical potentials related to events/stimuli) that has been widely used for EEG BCI applications in responsive patients is the P300. The active/willful modulation of the P300 may be employed to establish an EEG BCI method, where the patient's response is expressed through attention to specific (eg, auditory) stimuli, according to the operator's commands. Schnakers presented a CLIS patient with her own and other people's names, and asked her to count specific names (Schnakers et al., 2009). Although the patient's own name elicited a P300 in all conditions, the P300 elicited when the patient was specifically asked to count her own name was significantly larger in amplitude than that elicited by her own name when she was asked to count other names. This suggested that the patient was able to follow instructions, and consciously processed the meaning of the words she had heard. In another study, Schnakers and colleagues (2008) tested 14 DOC (MCS and VS) patients with a similar technique, and showed that the MCS patients exhibited a P300 to their own names, in both active (counting) and passive (listening) conditions. Like controls, this P300 was larger in the active condition than in the passive condition, suggesting voluntary compliance with task instructions. By contrast, the VS patients did not show any P300 differences between the active and passive conditions, suggesting that they were unable to comply with task instructions in the active condition.

Similar to the study by Monti et al, (2010) at least 2 alternative interpretations may explain the negative result observed in the VS patients. One interpretation is that the diagnosis for these patients was accurate; they were not aware of the task they were being asked to perform and therefore did not produce any responses. An alternative explanation is that the task lacked sensitivity and thus failed to detect VS patients who retained some level of consciousness, but were perhaps unable to understand the instructions and/or to sustain attention for a sufficient period to perform the task. This paradigm may permit the detection of voluntary brain function in patients who show very limited signs of awareness and thus has potential to be used as a BCI

communication paradigm. However, further work is needed to establish its suitability for detecting awareness in VS patients, whose attention and cognitive faculties are subject to drastic fluctuations over time, and may therefore be detected only by methods robust to noise and sensitive to weak responses.

A completely different approach for using the P300 modulation as a BCI method was originally proposed by Farwell and Donchin (1988). In this paradigm, participants were presented with a screen displaying a matrix of letters A to Z and asked to choose a letter they wished to write on the screen. Columns and rows of the matrix flashed in a pseudorandomized order. By identifying which column and row flashed immediately prior to an evoked P300 component, it was possible to deduce that the letter at their intersection was the attended one and therefore the one the participant wished to write. At least, also Lule´ et al. proposed an auditory P3-based BCI to detect command-following in patients with disorders of consciousness (Lulè et al., 2013).

Although this BCI technique proved very efficient for severely paralyzed and locked-in patients, its reliance on visual presentation limits its applicability to VS patients.

Efforts to translate this paradigm to the auditory modality (Furdea et al., 2009) have met with a number of problems, even in healthy controls. For instance, visual information can be presented in parallel, that is, an entire matrix of 26 letters can be presented at once, whereas equivalent auditory stimuli must be presented sequentially. Even if the many items of the matrix could be coded by fewer auditory stimuli, compared to the visual paradigm, remembering the coding system requires focusing of attention for a longer period, while keeping much of the information in short-term memory. Such cognitive demands would very likely hamper the performance of brain-damaged patients, especially those assumed to be in the VS. Sellers and Donchin84 introduced a simpler version of this paradigm. They developed the so-called 4-choice speller, in which participants were presented with only 4 visual or auditory stimuli, namely, yes, no, pass, and end.

This paradigm has been tested with LIS (ALS) patients, (Kübler et al., 2009) all of whom exhibited a P300 effect to the stimulation, but classification accuracies were lower in the auditory than in the visual version of the task. For reasons similar to those discussed above, DOC patients are likely to find this task more difficult than LIS patients. Other studies with late stage ALS patients have used the self-regulation of slow-cortical potentials to assess and train conditional learning (Iversen et al.,

2008) and cognitive function, including the ability to perform simple computations in these patients. However, the translation of such paradigms, developed for patients who are known to be conscious and have preserved cognitive responsivity, to patients whose clinical diagnosis precludes the presence of conscious awareness (ie, VS patients), faces several major challenges. In particular, they rely on training, which is not generally an option with VS/MCS patients. These challenges point to the need for continued development of EEG auditory BCI paradigms that are amenable to the limitations of nonresponsive (DOC) and especially VS patients.

Mu and Beta rhytms

Another type of active EEG paradigm has utilized attempted, or imagined, motor actions, which produce neural activity that can be measured with EEG, as it can with fMRI. Kotchoubey and colleagues (2003) described a CLIS patient whose slow EEG activity significantly differed between trials when he was asked to try to move the left as compared to the right hand. In healthy participants, motor imagery also produces clearly distinguishable modulation of EEG sensorimotor rhythms (SMRs) (Cincotti et al., 2003), similar to those seen during motor execution. Kubler and colleagues showed that LIS patients with ALS could learn to modulate their SMRs with >70% accuracy, but did not test VS patients with this paradigm (Kubler et al., 2005).

Cruse et al. (2012) have shown the most promising application of EEG as a BCI technology for VS patients to date. They instructed a group of 16 VS patients to perform 2 motor imagery tasks, imagining moving their right hand and imagining moving their toes. By submitting the EEG data associated with each task command to a cross-validated support vector machine classifier, Cruse et al. were able to demonstrate that 3 of the 16 VS patients were able to reliably and consistently modulate their SMR, with classifier outputs of up to 78% accuracy. Such a result provides the necessary proof of concept for the use of motor imagery as a BCI method and with the future application of real time data analyses may allow for bedside communication with VS patients.

Alternative forms of imagery

Despite its popularity in BCI research, motor imagery is not the only task that can be used for volitional modulation of oscillatory rhythms in the brain. Mental arithmetic (Sakurai et al., 1996), mental task rotation (Rappelsberger et al., 1988) and many others have been shown to lead to differentially specific patterns of spatially-specific

cortical activation and deactivation (Curran et al., 2003). Given that some patients with DoC were able to follow command imagine playing tennis and spatial navigation with fMRI, it might be fruitful to draw upon this previous work to explore novel imagery tasks that are well suited for use with EEG. The most suitable sorts of tasks in this context are likely to be based on well-established, long-term mental capabilities that might be preserved in DoC. Looking ahead, tapping into these capabilities might allow BCI design to move beyond the two-choice design, into the realm of complex and nuanced communication.

Steady-state evoked potential

Visual - The ability to focus gaze and attention is an obvious requirement for using SSVEP BCIs. Hence, their use by a majority of patients with DoC, who often have little or no control of their eye movements, would seem infeasible. There has been some progress in addressing this limitation; paradigms based on covert spatial attention (Kelly et al., 2005), selective attention to spatially overlapping stimuli (Allison et al., 2008) and superimposed illusory surfaces (Zhang et al., 2010) have also been found to evoke changes in SSVEP activity. However, preliminary tests with healthy controls have found significant increases in the variability of performance, making it difficult for a patient to reliably control the BCI. BCI based on auditory and tactile information presentation may provide a solution to this problem.

Somatosensory - A BCI-based on steady state evoked potential independent of vision was entroduced by Muller-Putz and collegues (2006). The authors used vibratory stimulation of left and right hand finger tips to elicit SSSEP. Online accuracy of four participant varied between 53% (chance level) and 83%.)

Auditory - Hence, as with SSSEP-based BCIs, they could find applications for patients with DoC. However, a potential drawback, the seriousness of which is yet to be properly studied, might be related to sensory stress and irritation brought on by continual steady-state stimulation. The problem of cognitive fatigue and short attention spans, common in patients with DoC, might be exacerbated with steady-state stimulation, limiting the viability of steady-state BCI applications in this context.

Slow Cortical Potential

Over the last few decades, Birbaumer and colleagues (1999; 2003) have worked on the development of SCPs-based BCIs. Crucially, they have shown that people can

learn to modulate their SCPs and use them to control the movement of an object on a computer screen. Further, this system has been tested in people with late-stage ALS and has proved capable of providing basic communication capacities (Kubler et al., 1999). Often, these BCIs are based on visual feedback from a computer screen that shows one choice at the top and one at the bottom. Two seconds of baseline are necessary to provide the system the user's initial voltage level. In the next 2 seconds, the user selects either the top or bottom choice by attempting to decrease or increase their SCP voltage level by a criterion amount, leading to a vertical movement of a cursor in the chosen direction. In addition to the commonly used visual feedback mode, SCP BCIs have also been set up to provide auditory or tactile feedback (Birbaumer et al., 2000). However, a study by Pham et al. (2005) in healthy participants showed that auditory feedback resulted in a relative increase in the variability of performance. SCP-based BCIs come with the advantage of being the most stable over longer periods of usage and do not require the use of any specific sensorimotor functions. This is a potential advantage for patients with DoC. On the other hand, the speed of choice selection is low, owing to the slow rates at which SCPs manifest. More importantly, these BCIs require relatively long periods of user training, sometimes in the order of months for some LIS patients. It will probably be a minority of patients with DoC, showing consistent signs of awareness, who will be able to exercise the cognitive control required to train their SCPs over extended periods of time.

Semantic classical conditioning

The latest study by De Massari et al. demonstrated the possibility of yes-no communication with an amyotrophic lateral sclerosis (ALS) subject using an EEG signal (De Massari et al., 2012). This study included 15 healthy control subjects. De Massari et al. developed a semantic classical conditioning paradigm able to discriminate between conditioned yes or no responses in the cortex, and thus enable basic affirmative and negative communication in all subjects. Classification accuracy in the discrimination of answers was 64% in healthy subjects and 62% in the ALS patient. Another study by De Massari et al. found no reliable communication in a completely locked-in state (CLIS) patient, but satisfactory BCI performance in a locked-in state (LIS) patient obtaining an accuracy up to 70% (De Massari et al., 2013).

Chapter 5

Case of study

A Feasibility Study of an improved procedure for using EEG to detect brain responses to imagery instruction in patients with disorders of consciousness

5.1 Introduction

One of the major concerns of recent studies is the correct discrimination between vegetative and minimally conscious state as the distinction between these two conditions has major implications for subsequent patient rehabilitation. In particular, it would be advantageous to establish communication with these patients. This work describes a procedure using EEG to detect brain responses to imagery instruction in patients with disorders of consciousness.

Results obtained in the above studies are often discrepant but confirm the usefulness of EEG to reliably detect awareness in patients with a clinical diagnosis of VS. Therefore, EEG may serve as an important tool for the assessment of awareness components in patients with disorders of consciousness in the clinical setting. In the

light of these findings, we set out to improve classification accuracy in yes-no communication with subjects, while reducing the number of electrodes required. We report here the results of a feasibility study conducted on a group of five healthy subjects and five patients with different levels of disorders of consciousness who underwent EEG recording during the execution of two mental imagery tasks. Without any assumption about the positioning of electrodes, the main aim of the study was to see whether some mental activation patterns could be discriminated using only EEG data and simple power parameters extracted from the EEG. A preliminary investigation was conducted on healthy subjects. Results obtained were used to design the experiments with patients. With a view to clinical application, the first step of the study was to simplify the set-up for the acquisition of EEG data by reducing the number of electrodes. The second aim of the study was to evaluate the reliability of a classification procedure to distinguish between the electrode activation patterns of the two mental states evoked by the two imagery tasks. The third was to evaluate the reliability (and hence practical feasibility) of the classification results during communication with the subjects, using the EEG signal to detect answers to simple yes or no questions.

5.2 Methods

5.2.1 Subjects

Five control subjects and five patients with different levels of consciousness disorders took part in the study. The five control subjects (age 26 to 37) were healthy and free of medication and any central nervous system disorder.

Table 2 lists the demographic and clinical information of the five patients (Gouvier et al., 1987; Giacino et al., 2004). In addition, Figure 4 shows the power spectra of patients in resting condition as extracted from 120s signal recording.

5.2.2 Protocol

Healthy subjects and imagery tasks

The experiment comprised two sessions repeated on two consecutive days at the same time of day. Each session included two trials: an Imagery Trial and a pre-Communication Trial. The Imagery Trial consisted of ten one minute repetitions of two tasks: one imagining a movement of the right hand and the other imagining a movement of the right foot. The subjects were instructed to mentally simulate the movements (kinaesthetic motor imagery). We chose this internal imagery because several studies demonstrated that good recognition rates are only achieved when the

'imaginer' uses the strategy of kinaesthetic motor imagery (first-person process), whereas recognition is almost impossible when the subject forms a visual image of another's action (third-person process) (Neuper et al., 2005).

The sequence of hand and foot imagery was randomized. In the pre-Communication Trial the

subjects were asked simple yes or no personal questions. Subjects were instructed to imagine for 30 seconds a movement of the right hand for an affirmative answer and a movement of the right foot for a negative answer. The pre-Communication Trial comprised six questions repeated five times. The entire experiment was performed with closed eyes. The subjects' answers were collected after the experiment.

Patients

The experiment consisted of one session comprising the same two trials used for the healthy

subjects: the Imagery Trial and the pre-Communication Trial. The Imagery Trial consisted of seven 30 second repetitions of the two imagery tasks. In the pre-Communication Trial the patients were asked the same simple yes or no questions used for healthy subjects. The six questions were repeated twice. The patients' answers were collected after the experiment through their relatives.

Fewer repetitions were made in patients because of their limited attention span. The healthy participants and the families of the patients included in the study provided their written informed consent to participate in the study. The Ethical Committee of the Maggiore Hospital and Bologna Health Trust approved the study and consent procedure.

Table 2: Demographic and clinical information of the five patients with disorders of consciousness (DoC).

Patient no.	Age at assessment (years)	Sex	Interval post trauma (months)	Aetiology	CRS-R	LCF	DoC classification
1	**22**	**F**	**10**	**TBI**	**-**	**7**	**CS**
2	**29**	**F**	**22**	**TBI**	**2/1/2/2/1/2**	**3**	**MCS**
3	**36**	**M**	**5**	**TBI/Anoxia**	**1/0/2/2/0/2**	**3**	**VS/MCS**
4	**63**	**M**	**4**	**TBI**	**2/1/5/1/0/2**	**3**	**MCS**
5	**60**	**M**	**17**	**TBI**	**3/4/5/2/1/2**	**4**	**MCS**

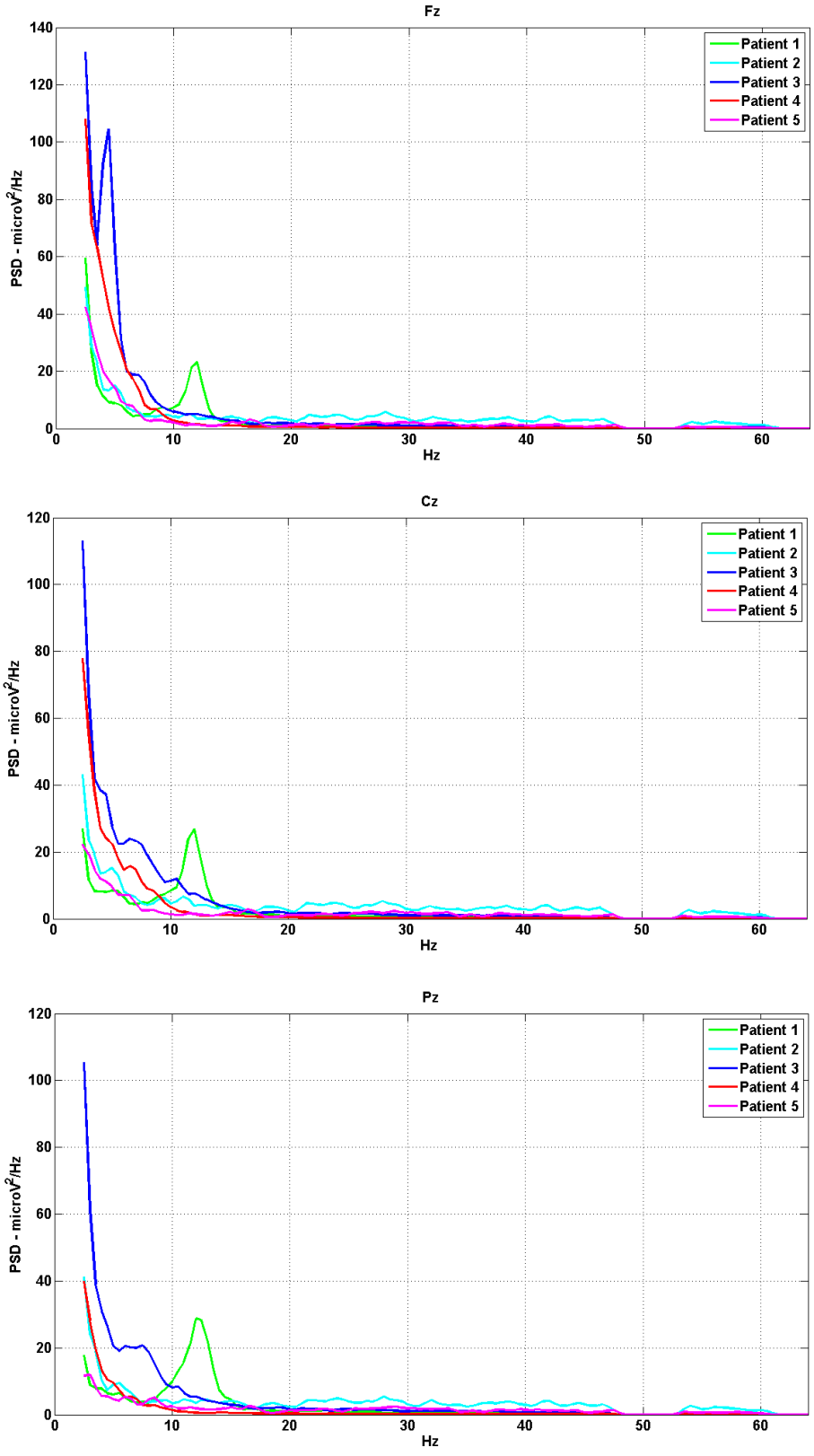

Figure 4: The figure shows the PSD spectrum in the frontal (Fz), central (Cz) and parietal (Pz) regions. The alpha peak is visible only in spectra of patient 1, i.e. the only patient in conscious state. All other spectra are characterized by an attenuation of the alpha rhythm. In these spectra there was relatively greater power at lower frequencies and diminished power at higher frequencies. The predominant rhythms are delta and theta, which represent the most prominent abnormality in awake EEGs on VS-MCS patients.

5.2.3 Recordings and signal preprocessing

EEG was recorded from 31 electrodes (Fp1, Fp2, AF3, AF4, F3, F4, F7, F8, Fc1, Fc2, Fc5, Fc6, Fz, C3, C4, Cp1, Cp2, Cp5, Cp6, Cz, P3, C4, PO3, PO4, Pz, T3, T4, T5, T6, O1, and O2) positioned according to the international 10-20 layout using a Neurowave System (Khymeia, Italy). EEG signals, referenced to linked ear lobes, were sampled at 256 samples/s, and preliminarily band-pass filtered between 3 Hz and 60 Hz. Trial datasets underwent i) manual identification and rejection of artefactual segments, and ii) data cleaning with independent component analysis (Congedo et al., 2008).

For each section, the epochs after the fifth second were eligible for the classification process. Power spectral density (PSD) was extracted from two second epochs without overlap.

A modified periodogram method, based on FFT-algorithm and Blackman Harris window, was used.

Subsequently, we averaged eight values of the extracted PSD with a six second overlap, thus obtaining one PSD for every 16 seconds. A 16-second epoch length PSD represents a good compromise between reliability and sensitivity with respect to EEG signal variations (Gudmundsson et al., 2007). The power in four frequency bands was extracted from the calculated PSD value: theta (4-8 Hz), alpha (8-13 Hz), beta (13-25 Hz), and gamma (25-40 Hz). We restricted the analysis to these four bands because these are supposed to be the most active during the performed tasks (Yuan et al., 2010; Li et al., 2009). *Parameter* was defined as the group of the powers in theta, alpha, beta and gamma bands extracted for each 16- second epoch and each electrode.

For each subject and each session, there are 31 sets of parameters, one for each electrode. Ten parameters were included in each set for the Imagery Trial and five for the pre-Communication Trial. Each value of the variable described above was labelled with the corresponding imagery task.

5.2.4 Search for the best site

The first aim of the study was to simplify the set-up for the acquisition of EEG data with a view to clinical use of the proposed method. To reduce the number of electrodes, a one-way analysis of variance (ANOVA) on two levels (hand and foot) was performed with a significance level $p<0.05$. ANOVA analysis was carried out for each subject, each session and each electrode-band combination of the Imagery

task. The total number of ANOVAs executed was 1240 (5 subjects x 2 sessions x 31 electrodes x 4 bands). We then selected the electrodes showing a significant difference between hand and foot imagination in at least one frequency band for each subject and each session assigning a unit score to the selected electrodes. Finally, we ordered the electrodes on the basis of the total maximum score of 10 (5 subjects and 2 sessions). Best electrodes (BE) for successive analyses were selected as the eight electrodes with the highest score. After selection of the BE an ANOVA analysis was carried out on two levels (hand and foot) with a significance level $p<0.05$. The ANOVA was performed for each patient and each BE-band combination of the pre-Communication Trial. The total number of ANOVAs executed was 160 (5 patients x 8 electrodes x 4 bands). This analysis aimed to evaluate if the BE selected on the healthy subject also provided a significantly different activation in the two imagery tasks in the patients.

5.2.5 Classification performance

The second and third aims of the study were 1) to evaluate the possibility of classifying the two mental states corresponding to the two imagery tasks, through an analysis of the Imagery Trial, and 2) to establish a means of communicating with the subject by detecting his/her answer to simple yes or no questions, by analysing the pre-Communication Trial. We thought that the two trials involve different cognitive processes. During the Imagery Trial the subject imagines a definite behaviour, without other contingent activities. During the pre-Communication Trial the subjects are involved in additional mental processes, i.e., initiating and sustaining the will to answer through the imagery activities. Moreover, content-dependent additional emotions and memory-related activations could not be excluded *a priori*. For these reasons we considered the two trials separately.

Imagery Trial

A linear SVM classifier (SVMc) was used to find the best hyperplane capable of discriminating between the two classes with the maximum possible margin (Burges et al., 1998), since this is known to increase the generalization capability (Kurita, 2004). The parameters used for the SVM classifier were a soft margin equal to 1, a linear kernel function and a least-square method to find the separating hyperplane. To obtain an unbiased estimation with small sample sizes, nested leave-one-out cross validation was employed to determine the classifier's generalization error across the entire dataset (Kohavi et al., 1997). The external leave-one-out cross validation

(LOO CV) was used to evaluate the final discriminant ability of the classifier through the classification accuracy. This external LOO CV splits the dataset into N different combinations of training and testing sets (TRi, TSi), where N is the size of the dataset. An internal LOO CV was performed on each resulting TRi to find the best subset related to that specific training set. The aim of this work was to select the best group of electrodes to maximize the classification accuracy. For this reason, all possible combinations of these electrodes were considered after preliminary selection of the eight BE. These combinations are all single BE (8), all BE couples (28), all BE triples (56), all the groups of four BE (70), all groups of five BE (56), all groups of six BE (28), all groups of seven BE (8), and all BE considered together. The number of electrodes included in each group was defined as "cardinality" (1, 2, 3, 4, 5, 6, 7, 8).

An exhaustive search was performed in each internal LOO CV (all subsets of all cardinalities among the BE) to find the subset optimizing the classification performance (see Figure 5). We defined the features of the classification process as the powers of the 32 electrode-band couples (4 bands x 8 electrodes). To make an exhaustive analysis for each subject and patient, and each session of the Imagery Trials, we trained and tested the classifiers using 4-8-12-16-20-24-28-32 features (4 bands x 1-8 electrodes) using all the BE combinations. In each internal loop we trained and tested 8-28-56-70-56-28-8-1 SVMc respectively. The output of the classifiers trained with the Imagery Trial data defined the imagery classification accuracy (ICA). The ICA is the rate of correctly classified parameters (each parameter is the group of the four powers in theta, alpha, beta and gamma bands) in the Imagery Trial using the features selected by the internal loop of the nested LOO. We compared the ICA for both healthy subjects and patients with the random classification level computed with the theoretical method proposed by Müller-Putz et al. (2008), with a significance level of 0.05.

Pre-Communication Trial

As for the Imagery Trial, we used a linear SVM classifier and a nested cross validation. In this Trial the N different combinations of datasets in which we split the data are the questions and not the single parameters; for the healthy subject N=30, for the patients N=12. For each question there are five parameters, so we define the cross validation procedure as Leave-Five-Out Cross Validation (LFO CV). The external LFO CV splits the dataset into N different combinations of training and testing sets

(TRi, TSi), where N is the number of questions. An internal LFO CV was performed on each resulting TRi to find the best subset related to that specific training set. An exhaustive search was performed in each internal LFO CV (all subsets of all cardinalities among the BE) to find the subset optimizing the classification performance (see Figure 5). As for the imagery trial, we defined the features of the classification process as the powers of the 32 electrode-band couples (4 bands x 8 electrodes). To make an exhaustive analysis for each subject and patient, we trained and tested the classifiers with 4-8-12-16-20-24-28-32 features (4 bands x 1-8 electrodes) using all the BE combinations. In each internal loop we trained and tested 8-28-56-70-56-28-8-1 SVMc respectively.

The external LFO CV was used to evaluate the final discriminant ability of the classifier through the classification error rate.

The output of the classifiers trained with the pre-Communication Trial data defined the communication classification accuracy (CCA). The CCA was computed not in terms of correctly classified parameters, as for the Imagery Trial, but in terms of correctly classified answers. Each answer comprised five parameters, then the class to which answers are attributed is decided by counting the assignment of the parameters in the two classes (yes/no) according to a majority criteria. CCA computation was used to estimate how accurately the classifier will perform with respect to future questions. As for the Imagery Trial, we compared the CCA for both healthy subjects and patients with the random classification level computed with the theoretical method proposed by Müller-Putz et al. (2008), with a significance level of 0.05.

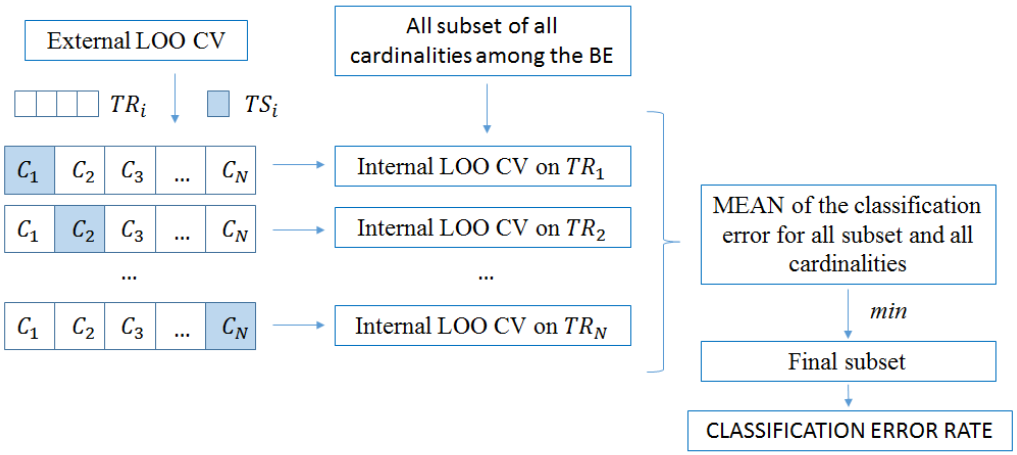

Figure 5: Explanation of the features selection procedure; $TR_i = i^{th}$ training set, $TS_i = i^{th}$ testing set.

5.2.6 Software tools

MATLAB language and toolboxes were used for data processing and analysis. In particular, we used the Signal Processing Toolbox to preprocess the recorded data, and the Bioinformatics Toolbox for the SVMc classification.

5.3 Results

5.3.1 Search for the best site

Table 1s (Supplementary File) lists the significant electrodes in at least one band for each subject and each session. As shown in Figure 6, the eight BE selected were: C4, C3, PO4, O2, T4, O1, Fc6 and Cp1. These electrodes will be used in the following analyses. Table 2s (Supplementary File) shows the couple BE-band with a significantly different activation in the two imagery tasks for the patients in the pre-Communication Trial.

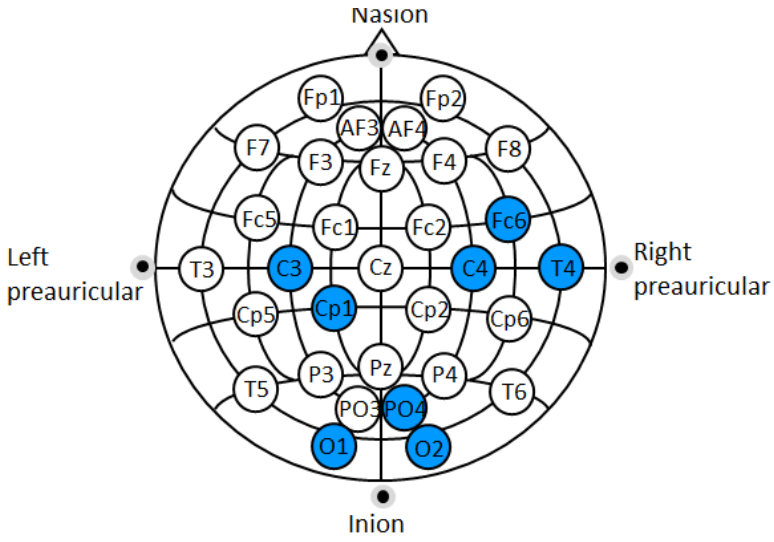

Figure 6: Best electrodes (BE) selected by the ANOVA analysis. All marked electrodes registered a significantly different activation during the two tasks for each healthy subject and each session in at least one frequency band.

5.3.2 Classification performance

For each subject and each patient, each session and each trial, we extracted the mean power in theta, alpha, beta and gamma bands for the BE and we trained and tested the classifiers using these features. Figure 7 shows an example of the features used for the classification process for one healthy subject and one patient.

Table 3 shows the mean and standard deviation of the best classification accuracy obtained for the healthy subjects and the patients for each cardinality in the Imagery Trial and in the pre-Communication Trial. Tables 3s and 4s (Supplementary File)

show the complete results on the best classification accuracies obtained for each subject, each patient, each session and each cardinality for the Imagery Trial and pre-Communication Trial, respectively. Considering the best configuration for each subject and each patient, we computed the mean ICA and the mean CCA.

Table 3: Mean and standard deviation (SD) of the best classification accuracy obtained for the healthy subjects and the patients for each cardinality in the Imagery Trial and in the pre-Communication Trial.

CLASSIFICATION ACCURACY % (Mean±SD)								
Electrodes	**one**	**two**	**three**	**four**	**five**	**six**	**seven**	**eight**
IMAGERY TRIAL								
Subjects	67.2±5.1	74.1±6.0	77.1±6.3	79.2±5.4	**81.7±5.1**	79.8±5.3	79.6±5.0	76.8±5.1
Patients	63.4±8.8	76.1±8.4	78.9±9.3	81.9±8.8	83.3±7.8	**83.6±8.5**	**83.6±10.3**	82.4±9.6
PRE-COMMUNICATION TRIAL								
Subjects	66.4±17.2	**73.7±14.5**	71.1±15.8	66.4±14	68.1±12.9	66.4±12.1	65.4±16	68.3±8.6
Patients	66.7±20.4	**80.1±17.2**	66.7±15.6	65.1±3.7	63.4±9.5	68.4±10.8	70.1±12.6	66.8±11.7

The mean ICA of the best configurations for each session was 82.0% (SD 5.1%) for healthy subjects and 84.6% (SD 9.1%) for patients. The mean CCA of the best configurations for each session was 80.7% (SD 11.2%) for healthy subjects and 91.7% (SD 7.4%) for patients (see Figure 8). In each case the ICA and CCA were greater than the random classification level with a significant level of 0.05. Table 5s (Supplementary File) lists the electrode configurations maximising the classification accuracy for each subject, each session and each trial.

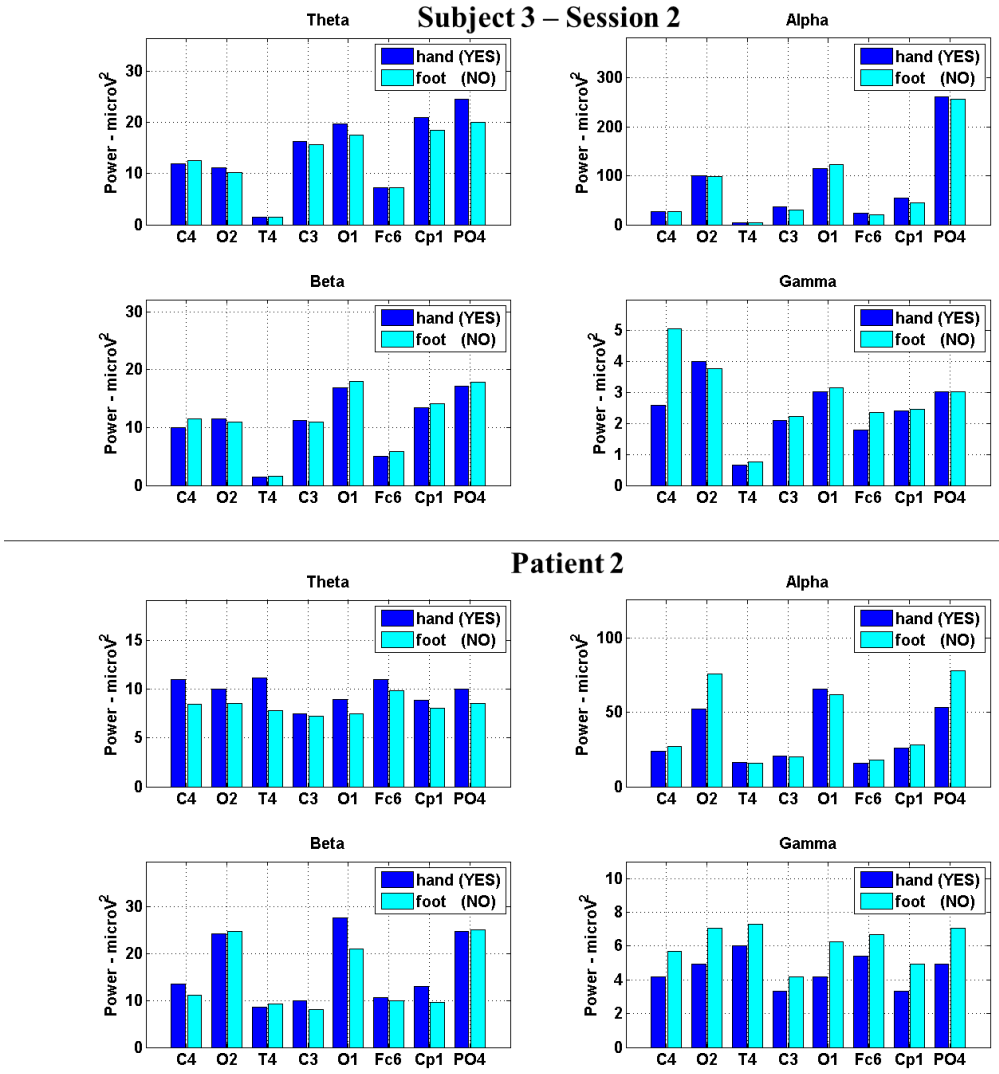

Figure 7: Example of the features used in the classification process for subject 3 in session 2 and patient 2. The features are the powers in theta, alpha, beta and gamma bands extracted by the BE for the two motor imagery tasks.

5.4 Discussion

5.4.1 Search for the best site

Neuroanatomical correlation

We did not use a specific algorithm for source localization, so only a qualitative analysis of the detected electrode sites can be made. We found that the BE are mainly located in the centro-parietal and parieto-occipital cortex. This confirms the results of a previous study demonstrating activation of motor cortex, temporo-occipital, parieto-occipital areas and occipital lobe during the execution of motor imagery tasks. Solodkin et al. used fMRI and structural equation modelling to study the activation pattern during motor execution and motor imagery (Solodkin et al., 2004). They demonstrated a predominant activation of the motor and premotor

cortex but also an activation of the occipital cortex during the imagery task. Ishizu et al. (2009) demonstrated that the act of imaging hand movement activates the extrastriate body area in the lateral occipital cortex. Lebon et al. (2012) studied the role of the inferior parietal cortex in the motor circuits, explaining that the inferior parietal lobe is part of an inhibitory network that may prevent unwanted movement during imagery tasks. Szameitat and colleagues (2007) investigated the functional neuroanatomical correlates of motor imagery. The participant imagined motor tasks involving the whole body, e.g. swimming: activation was apparent in Brodmann areas 4 and 6, corresponding to the motor cortex. Munzert and colleagues (2008) demonstrated activation of the motor area during imagery of dance and gymnastic movements.

The pre-motor cortex plays important roles in the planning paradigm, programming and execution of motor acts. Imagined and executed movements often require the same activation to be performed (Guillot et al., 2005), suggesting they are generated through analogous computational steps in the brain. This implies that imagined movements also include a planning/preparation phase before the imagination.

The parietal cortex is an important sensory integration hub and its different sub-regions, projecting to various brain areas including the premotor and motor cortex, play important roles during motor execution. In particular the postero-parietal cortex is involved in the visuo-motor transformation process.

Clinical relevance

Although EEG has many practical advantages over fMRI, correct positioning of the electrodes is time-consuming and requires skilled personnel. Several studies (Ishai et al., 200; Popescu et al., 2007; Lal et al., 2004; Kamrunnahar et al., 2009; Arvaneh et al., 2011; Chungki et al., 2012; Wing-Kin et al., 2011) investigating selection of the minimum number of channels for classification purposes in BCI systems were able to reduce the number of electrodes required to between 4 and 12. All studies with motor imagery tasks used a pre-fixed set of electrodes positioned over the motor cortex. We did not make any *a priori* assumptions on the positioning of the electrodes, so the electrodes selected were not localized in a single area on the scalp. Nevertheless, the use of fewer electrodes simplifies preparation by unskilled personnel. The preliminary choice of the eight electrodes in healthy subjects,

selecting the optimum subject-specific subset also proved suitable for patients and guaranteed a higher

classification accuracy of their answers.

5.4.2 Classification performance

We initially analysed the Imagery Trial finding a mean ICA of 82.0% (SD 5.1%) for healthy

subjects and 84.6% (SD 9.1%) for patients considering the BE configuration for each subject and each session. A high ICA in the classification of the two tasks demonstrates that both healthy subjects and patients were able to perform the tasks. Since the two tasks can be reliably differentiated, we think that the patients' (and subjects') level of cognitive activity is sufficient to allow attempts to communicate.

The pre-Communication Trial analysis evaluated the possibility of detecting answers to simple yes or no questions. The search for the best configuration specific for each subject and each session from the BE allowed us to distinguish between the two answers with a mean CCA of 80.7% (SD 11.2%) for healthy subjects and 91.7% (SD 7.4%) for patients.

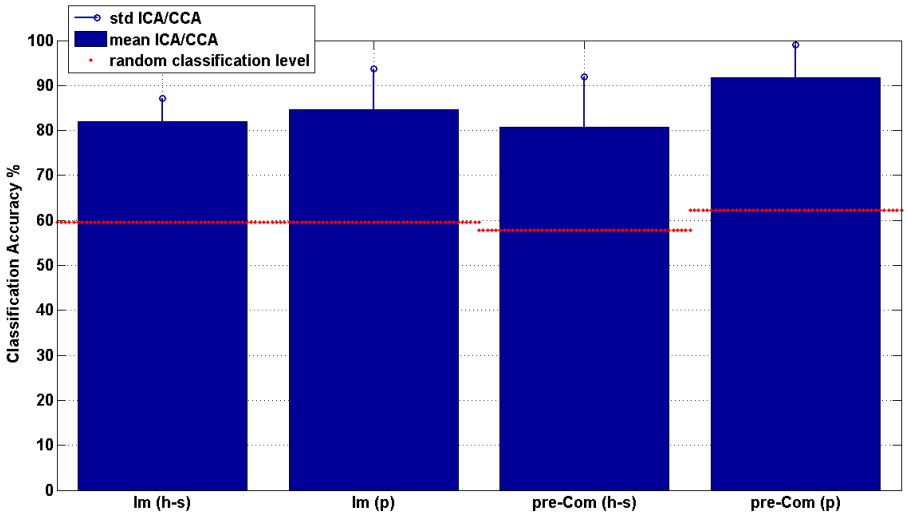

Figure 8: Mean and SD of the classification accuracy of the best configurations for the healthy subjects (h-s) and patients (p) in the Imagery (Im) and pre-Communication (Com) Trials. The classification accuracy was the mean of the accuracy obtained using the best configuration (in terms of electrodes selected by the nested CV procedure) for each subject and each patient. The figure also shows the random classification level computed for healthy subjects and patients and each trial.

The search for the optimum subset from the eight BE shows that the best ICA and the best CCA were obtained with different electrode configurations. This variability was found in all subjects and all sessions. In the Imagery Trial, the classification performance for both healthy subjects and patients improved using more than four

electrodes, while the use of five electrodes yielded the highest mean accuracy. In the pre-Communication Trial, the classification performance for both healthy subjects and patients improved using two electrodes. The proposed procedure allowed us to fix a robust and statistically significant common subset for all subjects (BE), but we also considered the inter and intra-subject variability by selecting a subject and session specific subset. In a future practical application of our protocol, each communication session will be preceded by a configuration session in which the classification algorithm selects the optimum electrode subset from the fixed BE. Comparing the performance of the healthy subjects with that of the patients we found a higher classification accuracy in the patients. This finding could depend on the simplified brain activity of the patients that allows a simpler representation during the two imagery tasks. The healthy subjects could be thinking about many things besides the imagery task, whereas the patients perhaps could only perform the task by concentrating on it, thus decreasing spurious variability that would lead to decreased ICA and CCA. Lastly, the patients could be more motivated in conducting the experiment.

5.5 Conclusions

This study evaluated the possibility to classify two mental states corresponding to two imagery tasks, using non-event-related EEG techniques, and to use them for communication purposes.

Firstly, we outlined a general, automated procedure to identify the BE sites in terms of statistical significance of the PSD features in the two tasks. We paid particular attention to issues related to discrimination between and communication with patients affected by different levels of consciousness disorders. This preliminary study involved just five healthy subjects and five patients and hence did not aim to define a standard protocol for clinical assessment. The proposed automated procedure provided good classification accuracy for the two investigated imagery tasks, while identifying suitable and clearly defined sites for EEG spectral parameters classification.

These promising results suggest further studies and investigations, namely: 1) increasing the

number of patients who are vegetative or minimally conscious; 2) developing an online procedure to establish communication with the patients.

Chapter 6:
Case of Study
A similitude-based BCI system for Communication

6.1 Introduction

This work describes a procedure to investigate a subject's pattern of activation during mental imagery tasks. It aims to design a brain computer interface system for communication. Five healthy subjects and two patients with different levels of disorders of consciousness underwent EEG recording during yes/no personal questions. They were instructed to execute two imagery tasks to answer to the questions. The first aim of the study was to develop a procedure of features selection in order to reduce the number of electrodes required. The second aim of the study was to realize an adaptive classifier that, after the training with two questions with known answers, is able to forecast the third unknown answer.

6.2 Methods

6.2.1 Subjects

Five control subjects and two patients with different levels of consciousness disorders took part in the study. The five control subjects (age 26 to 37) were healthy

and free of medication and any central nervous system disorder. The first patient was a 21-year-old female car crash victim who received traumatic brain injury with diffuse axonal damage and subarachnoid hemorrhage. At the time of the study, ten months after the injury, the patient's level of cognitive functioning (LCF) was 7, corresponding to automatic and appropriate cognitive behavior. The second patient was a 28-year-old female car crash victim with a contusion focus in the left temporal-occipital-parietal cortex and an axonal hemorrhage lesion in the right frontal area. At the time of the study, 22 months after the injury, the patient's LCF was 3, corresponding to localized response.

6.2.2 Protocol

The experiment consisted of a Communication Trial. Simple yes/no personal questions were asked to the subjects (e.g. "Are you married?"). Subjects were instructed to imagine for 30 seconds a movement of the right hand for an affirmative answer and a movement of the right foot for a negative answer. The Trial comprised six questions which were repeated six times for the healthy subjects and twice for patients. The experiment was repeated on two consecutive days only for the healthy subjects. The answer were collected after the experiment from subjects and relatives of patients.

6.2.3 EEG recording and signal processing

The EEG was recorded from 31 electrodes (Fp1, Fp2, AF3, AF4, F3, F4, F7, F8, Fc1, Fc2, Fc5, Fc6, Fz, C3, C4, Cp1, Cp2, Cp5, Cp6, Cz, P3, C4, PO3, PO4, Pz, T3, T4, T5, T6, O1, and O2) positioned according to the international 10-20 layout using a Neurowave System (Khymeia, Italy). EEG signals, referenced to linked ear lobes, were sampled at 256 samples/s, and preliminarily band-pass filtered between 3 Hz and 60 Hz. Trial datasets underwent i) manual identification and rejection of artefactual segments, and ii) data cleaning with independent component analysis (Congedo et al., 2008). For each section, the epochs after the fifth second were eligible for the classification process. Power spectral density (PSD) was extracted from two seconds epochs without overlap. A modified periodogram method, based on FFT-algorithm and Blackman Harris window, was used. Subsequently, we averaged 5 values of the extracted PSD with a four seconds overlap, then obtaining one PSD for every 10 seconds. The power in four frequency bands was extracted from the calculated PSD value: theta (4-8 Hz), alpha (8-13 Hz), beta (13-25 Hz) and gamma (25-40 Hz). For each subject and each session and each answer, there were

31 (electrodes) × 4 (bands) × *n* (repetition) subsets. The number *n* of repetitions included in each set depended on the EEG signal length after rejection of the artefactual segments. Each value of the variable described above was labelled with the corresponding imagery task.

The first aim of the study was to choose the Best 10 common Electrodes (BE) for all the healthy subjects using a similitude criteria between equal answers. After the BE selection procedure we listed the subject-specific most significant features, in terms of Band-Electrodes Couples (BEC) for each subject and each patient. The feature selection procedure used the same criteria of similitude of the BE research. A certain number of BEC will be used in the classification process. For each healthy subject, each patient and each session we divided the dataset into two parts. The first one includes the 31 (electrodes) × 4 (bands) × *n* (repetition) subsets of the first half of the Communication Trial and it was used to select the BE and the BEC. The second includes the 10 (BE) × 4 (bands) × *n* (repetition) sets of the remaining half of the Communication Trial and it was used to classify the answers of the subjects and the patients.

6.2.3 Search of the BE and BEC

For each subject, on the basis of the given answers, all the sequences of three answers, with the first and the second one different (one hands and one foot movement imagery), were identified in the first part of the dataset. Considering the data of each healthy subject, each session, each triple we computed a similitude index $s_{i,j,k}$:

$$s_{i,j,k} = \frac{\sum_k \frac{P3_{i,j,k} - P1_{i,j,k}}{P2_{i,j,k} - P1_{i,j,k}}}{n} \tag{16}$$

where *i* is the electrode index, *j* the band index, *k* is the repetition index, *n* the number of repetitions and *P1*, *P2* and *P3* are the power of the first, of the second and of the third answer of the triple, respectively. If the third answer is the same of the first one, *s* tends to zero, while if the third one is equal to the second, *s* tends to 1. Using *s* we calculated the similitude between equal answers and we selected the 10 BE that optimize *s* for all the healthy subjects. After this preliminary selection, we applied again the same criterion for each healthy subject and each patient separately, with the aim to find a list of the BEC according to the similitude criterion.

6.2.4 Classification Performance

The second aim of the study was to establish a mean of communicating with the subject by detecting his/her answer to simple yes/no questions. We designed an adaptive classifier trained with two questions with known answers that was able to forecast the third unknown answer.

After each sub-session of three questions, the classifier will be retrained with new data. As first we used the first part of the dataset to select the number of BEC to be considered. For each subject, each patient and each session, a linear SVM classifier (SVMc) was used to train and to test all the triples of the first half of the dataset using a variable number, from 1 to 10, of BEC from the ordered list. The classification error rate was computed and the number of BEC with the smaller error was selected.

Subsequently we considered the second half of the dataset. For each subject, each patient and each session we trained and test all the triples using the number of BEC previously selected. The first and the second answers were used to train the SVMc and the third one was used to test it. Each answer have different repetition, than the class of attribution is decided by counting yes/no responses.

6.3 Results and Discussion

6.3.1 Search of the BE and BEC

Considering all the healthy subjects and all the sessions, the ordered list of the ten BE was: PO3, Fc2, C3, O1, Fc1, Cz, Fz, P3, PO4 and T6 (Figure 9). We did not use a specific algorithm for source localization, so only a qualitative analysis of the detected electrode sites can be made. We found that the BE are mainly located in the fronto-central and parieto-occipital cortex. This confirms the results of the previous studies demonstrating activation of motor cortex and parietal cortex during the execution of motor imagery task (Ishizu et al., 2009; Lebon et al., 2012). Using the BE we searched for the healthy subject and patient a subset of subject-specific and session specific BEC optimizing the similitude index *s*. Table 4 lists the BECs selected for the classification process for each subject, each patient and each session.

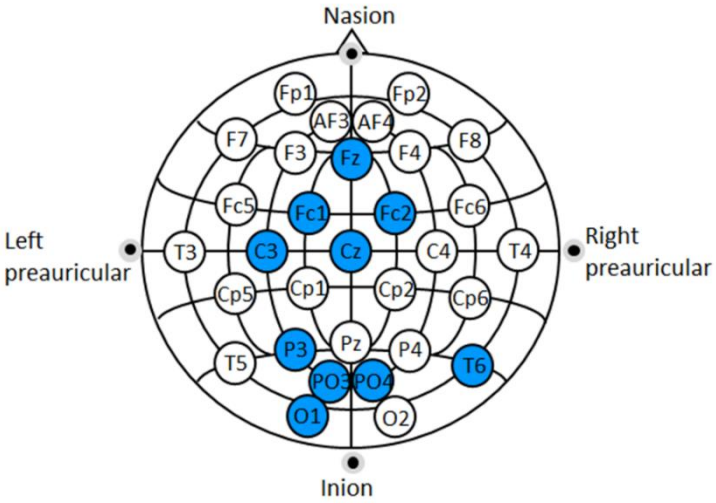

Figure 9: The figure shows the ten BE selected through the similitude criteria considering the data of all subjects and all patients. These electrodes are: PO3, Fc2, C3, O1, Fc1, Cz, Fz, P3, PO4 and T6.

6.3.2 Classification Performance

The mean of the classification error was 16.5% (SD 12%) for healthy subjects and 10% (SD 14.1%) for the patients. Table 4 shows the results for each subject and each session.

The preliminary choice of the ten electrodes in healthy subjects, selecting the optimum subject-specific subset, also proved suitable for patients and guaranteed a low error rate in the classification of their answers. The proposed procedure allowed us to fix a robust common subset for all subjects (BE), but we also considered the inter and intra-subject variability by selecting a subject and session specific subset. In a future practical application of our protocol, each communication session will be preceded by a brief configuration session in which the classification algorithm selects the optimum electrode subset from the fixed BE. Furthermore it will be necessary to train the classifier with two known questions. Even if the procedure is long and repetitive, guarantee a very low classification error for the patients.

Table 4: The table shows for each healthy subject, each patient and each session the best couples electrodes-band selected using the similitude index *s* and the related classification errors.

Subjects	**Sessions**	**Band-Electrode Couples selected**				**Classification Error**
		θ	**α**	**β**	**γ**	
1	1	O1	Cz-PO4	C3-Cz-PO4		10 %
	2			P3-Fc1-T6	PO3-O1-T6	10 %
2	1	C3- T6-PO3	O1-PO3-P3		O1-PO4	20 %
	2	P3-PO4		C3	Fz-T6-Fc1-P3-O1-PO3	20 %

3	1				Fz-C3	0 %
	2	Fc1-Fc2	PO4		C3	25 %
4	1	Fc2		C3	Fc2-PO3	20 %
	2	Cz			O1-PO3	40 %
5	1		C3	Fz		0 %
	2	Fc2-Fz	O1-Cz-PO3-P3-PO4		O1	20%
Mean±SD						**16.5±12%**
Patients						
1	1	PO3-C3	Fc1-P3	Fc2	PO4	20%
2	1	PO3-C3	C3-P3			0%
Mean±SD						**10±14.1%**

6.4 Conclusion

This study evaluated the possibility to classify two mental states corresponding to two imagery tasks, using non-event-related EEG techniques, and to use them for communication purposes. The proposed automated procedure provided good classification accuracy for the two investigated imagery tasks, while identifying suitable and clearly defined sites for EEG spectral parameters classification.

Chapter 7

Case of study

Brain computer interface fNIRS-EEG based for communication in completely locked-in patients

The study that will be introduced in this chapter was conducted at the **Institute of Medical Psychology and Behavioral Neurobiology of Tübingen.**

The study was conducted in collaboration with **Dott. U. Chaudary** and **Prof. N. Birbaumer.**

7.1 Introduction

An increasing number of research activities and different types of studies in brain-computer interface (BCI) systems show potential in this young research area. Research teams have studied features of different data acquisition techniques, brain activity patterns, feature extraction techniques, methods of classifications, and many other aspects of a BCI system. However, conventional BCIs have not become totally applicable, due to the lack of high accuracy, reliability, low information transfer rate, and user acceptability.

A new approach to create a more reliable BCI that takes advantage of each system is to combine two or more BCI systems with different brain activity patterns or different input signal sources. This type of BCI, called hybrid BCI, may reduce disadvantages of each conventional BCI system. In addition, hybrid BCIs may create more applications and possibly increase the accuracy and the information transfer rate.

In general, in a hybrid BCI, two systems can be combined sequentially or simultaneously (Pfurtscheller et al., 2010). In a simultaneous hybrid BCI, both systems are processed in parallel. Input signals used in simultaneous hybrid BCIs can be two different brain signals, one brain signal, or one brain signal and another input. In sequential hybrid BCIs, the output of one system is used as the input of the other system. This approach is mostly used when the first system task is to indicate that the user does not intend to communicate or as a "brain switch".

Several combinations of signal were used to realize hybrid BCI: i) SSVEP-Motor Imagery (Allison et al., 2008), ii) P300-Motor imagery (Rebsament et al. 2008), iii) P300-SSVEP (Panicker et al., 2011), EEG-EMG (Leeb et al., 2011), iv) EEG-EOG (Punsawad et al., 2010), v) SSVEP-NIRS (Pfurtscheller et al., 2010) and vi) EEG-NIRS (Fazli et al., 2012; Khan et al., 2014; Ma et al., 2012).

The Hibryd systems based on EEG and NIRS are really interesting for this work because the study that will be described uses this technology.

A type of hybrid BCI that uses EEG and NIRS was introduced by Fazli et al (2012). In this study, EEG and NIRS measurements were used simultaneously for ERD-based BCIs. The experiment made up of 2 blocks of motor execution and 2 blocks of motor imagery. For all blocks, both EEG and NIRS were measured simultaneously. The increase in concentration of oxygenated hemoglobins (HbO) and decrease in concentration of deoxygenated hemoglobins (HbR) were measured using NIRS. The global peak cross-validation accuracy for each subject was considered for evaluation of the hybrid BCI. The main classification accuracies of HbO, HbR, and EEG for executed movement tasks were 71.1%, 73.3%, and 90.8%. For motor imagery tasks they were 71.7%, 65.0%, and 78.2%. The main classification accuracies of EEG/HbO, EEG/HbR, and EEG/HbO/HbR for executed movement tasks were 92.6%, 93.2%, and 87.4%, and for motor imagery tasks were 83.2%, 80.6%, and 83.1%, respectively. It was shown that the combination of EEG and NIRS improved

the classification accuracy in both MI and executed movement tasks. However, the information transfer rate may decrease.

Khan et al. (2014) used an experimental hybrid near-infrared spectroscopy-electroencephalography technique to extract and decode four different types of brain signals. The NIRS setup was positioned over the prefrontal brain region, and the EEG over the left and right motor cortex regions. Twelve subjects participating in the experiment were shown four direction symbols, namely, "forward," "backward," "left," and "right." The control commands for forward and backward movement were estimated by performing arithmetic mental tasks related to oxy-hemoglobin (HbO) changes. The left and right directions commands were associated with right and left hand tapping, respectively.

They obtained an accuracy of 94.7% for the left and right task, 80.2 % for the Forward task and 83.6 % for the back task.

Ma et al., (2012) proposed a hybrid BCI system based on the combination of the EEG signal and the cerebral blood oxygen changes measured by NIRS to detect the state of motor imagery. Six healthy subjects took part in the experiment. The result shows that the average recognition rate can achieve above 75.04%, which is higher than when only using EEG or NIRS.

The described studies, carried out on healthy subjects, suggested that the proposed hybrid BCI systems have a good performance in the combination of these two different signals and motivate the interest in the following study.

The aim of the study was to apply an hybrid BCI system EEG-fNIRS based on the communication with amyotrophic lateral sclerosis (ASL) patients.

ALS is a progressive motor disease of unknown etiology resulting eventually in a complete destruction of the peripheral and central motor system but only affecting sensory or cognitive functions to a minor degree. Almost all the people with ALS experienced a motor speech disorder as the disease progresses. At some point in the disease progression, 80 to 95% of patients with ALS are unable to meet their daily communication needs using natural speech. Later, most patients become unable to speak at all. Brain computer-interface (BCI) technology has generated considerable research interest for the "locked-in" patients such as those in the late stages of ALS. Several EEG-based BCI are currently in use namely slow cortical potential (SCP)-BCI, sensorimotor rhythm (SMR)-BCI and P300-BCI but none of them have been successful for communication in ALS patients in completely locked in state (CLIS).

Hence there is a need to find an alternative neuroimaging technique to design a more effective BCI to help ALS patient in CLIS with communication. Near infrared spectroscopy (NIRS) is an emerging neuro-imaging modality which employs near-infrared light to non-invasively or invasively investigate cerebral oxygenation changes in healthy and neurologically challenged adults and children. Previous researches have shown that NIRS can be successfully used to design BCI; hence NIRS was used to design BCI to help ALS patient in CLIS with communication.

The use of both EEG and NIRS signal could improve the accuracy of classification and than the communication with these patients.

7.2 Materials and Methods

7.2.1 Subject

Two ASL patients take part in the study.

7.2.2 Protocol

The experiment consists in the repetition of a certain number of blocks. One block consists in the presentation of 20 sentences, 10 true and 10 false sentences (ie. “Rome is the capital of Russia” or “Rome is the capital of Italy”). The blocks are repeated for consecutive days and the number of blocks is different for each day, according to the fatigue of the subject.

If the sentence that was correct, the subject was instruct to think YES, in the sentence that was incorrect, the subject was instruct to think NO.

The EEG signal was recorded from two channels, P3 and P4. The NIRS signal was recorder from 20 channels. All the channels were positioned according to the 10-20 internationl system. Figure 10 show the experimental protocol.

The data were recorded in the patient’s home.

7.2.3 Signal Preprocessing end features extraction

EEG

EEG signals, referenced to linked ear lobes, were sampled at 500 samples/s, and preliminarily band-pass filtered between 3 Hz and 35 Hz.

Power spectral density (PSD) was extracted from five second epochs without overlap. A modified periodogram method, based on FFT-algorithm and Blackman Harris window, was used. Subsequently, we averaged four values of the extracted PSD, thus obtaining one PSD for each sentence. The power in four frequency bands

was extracted from the calculated PSD value: delta (1-4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta1 (13–20 Hz), and beta2 (20–30 Hz).

NIRS

NIRS signals were sampled at 6.25 samples/s, and preliminarily low-pass filtered at 0.2 Hz. HbR, the main value between 3 s and 8 s was extracted.

Then, the extracted features are the 2(channels) ×20(sentences) ×5(bands) for EEG and 20(channels) ×20 (sentences) ×2 (HbO/HbR) for NIRS.

All the features were labeled with the correspondent imagery task (YES/NO).

7.2.4 Statistical Analysis and Classification

The data of the first patient were processed and classified offline and they were used to choose the best features to use for the next patients. The selected features were used for the online classification of the patients answers. The output of the classifier was used to give an auditory feedback to the patient, reporting him/her if the classifier classified his answer as YES or as NO.

EEG and NIRS signal were compared to obtain the best features in term of statistical analysis and classification performance. For this porpoise the following steps were executed:

- EEG: statistical analysis and classification
- NIRS: classification
- EEG and NIRS: classification

Statistical analysis

One-way ANOVA analysis on two level (YES and NO) was performed to compare the statistical significance of the different activation during the two imagery tasks ($p<0.05$). The analysis was performed for each block and each frequency band.

Classification

A linear SVM classifier (SVMc) was used to find the best hyperplane capable of discriminating between the two classes with the maximum possible margin, since this is known to increase the generalization capability. The parameters used for the SVM classifier were a soft margin equal to 1, a linear kernel function and a least-square method to find the separating hyperplane.

For the offline analysis, 5-fold cross validation was employed to determine the classifier's generalization error across the entire dataset.

The results will be reported in term of number of blocks in which the classification accuracy is higher than the random level of classification (65%).

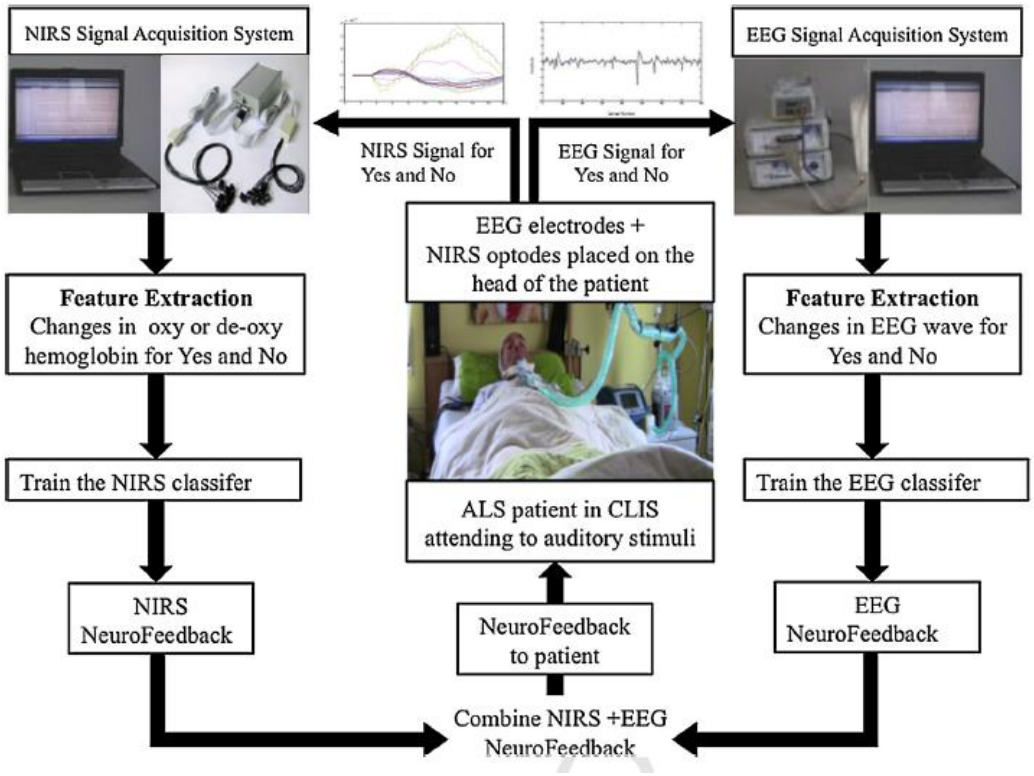

Figure 10: Experimental setup of fNIRS-EEG-based BMI system developed for communication in CLIS patients by researchers from the Institute of Medical Psychology and Behavioral Neurobiology, University of Tubingen. The fNIRS-EEG-based BMI consists of fNIRS system, EEG system, computers and an audio system. The fNIRS and EEG signals are combined to provide neurofeedback to the CLIS patient, when they attend to the auditory stimuli, as ‘‘your answer was classified as (in) correct’’.

7.3 Results

7.3.1 Statistical Analysis

The ANOVA analysis showed that only in Delta band there was a significant difference in the activation during the two imagery tasks (p=0.0055).

7.3.2 Classification

The results were showed in Table 5.

Table 5: Numbers of blocks in which the classification accuracy is higher than the random level of classification (65%) using EEG features, NIRS features and the combination of all the features (EEG and NIRS) in the first patient.

	NIRS				
EEG		HbO	HbR	HbO-HbR	/
	Delta	**25/45**	24/45	21/45	22/45
	Theta	22/45	20/45	21/45	14/45
	Alpha	19/45	21/45	20/45	22/45
	Beta1	18/45	17/45	19/45	17/45
	Beta2	18/45	21/45	19/45	21/45
	/	19/45	17/45	17/45	

7.3.3 Online analysis

Comparing the results obtained with statistical analysis and with the classification with SVM we found that using both EEG and NIRS give better results than using only EEG or only NIRS.

In particular, the couple EEG-delta band and NIRS-HbO give the best performance.

For this reason we chose the couple delta-HbO to give the feedback in the online classification on the second patient.

After the online sperimental session, the data were reanalyzed offline and the obtained results were reported in Table 6.

Table 6: Numbers of blocks in which the classification accuracy is greater that the random level of classification (65 all the features (EEG and NIRS) in the second patient.

HbO d	HbR d	HbO t	HbR t	HbO a	HbR a	HbO b1	HbR b1	HbO b2	HbR b2
14/25	13/25	12/25	9/25	9/25	12/25	11/25	8/25	9/25	11/25

The offline analysis confirm that the chosen features give the best classification accuracy.

7.4 Discussion and Conclusion

After this preliminary investigation, the study was extended to 4 ASL patient and after several online feedback sessions the achieved accuracy was higher than 65% for 90% of the sessions.

It suggests that the proposed hybrid BCI system has a good performance in the combination of these two different signals. Further investigation may help develop better BCIs with high accuracy and significant efficiency.

Chapter 8

Mild and moderate TBI

Cognitive impairments are a common consequence of traumatic brain injury.

Cognitive deficits can be grouped into the following broad categories: perception, learning and memory, attention and communication (Stratton *et al*., 1994). These categories are outlined below. However, it should be made clear that all cognitive processes are integrated and any deficits in one category invariably impact upon others.

The extent and duration of the cognitive deficits experienced by brain injury survivors have been found to be related to the severity of injury.

8.1 Cognitive Function

8.1.1 Perception

Neurological damage in areas that govern sensory and attentional processes impinge upon the ability to discriminate, organize and interpret information, relating to the self and the external environment. A variety of perceptual impairments can result.

These include neglect disorders (inattention to particular aspects of the environment), various types of agnosia (inability to recognize percepts), body scheme disorders (inability to identify body parts or their spatial relations), visuospatial deficits and sensory losses. Such impairments in perception often underlie many physical difficulties. Apraxia can cause difficulties in performing purposeful actions, maintaining postures, moving on command, coordinating precise movements,

engaging in rapid movements or learning new motor skills. Perseveration may also occur, which manifests in the continuous repetition of behaviours. Some perceptual deficits may resolve over time. Thomsen (1991) observed visual recovery particularly with minor visual problems. However, severe visual impairments remained in over a tenth (13%) of the sample twenty years after injury onset. Other reports have suggested that even minor difficulties with vision may not resolve over time. Brooks and colleagues (1986) discovered that over 40% of survivors were reported to have subtle visual difficulties one and five years following the injury.

8.1.2 Learning and Memory

The most common cognitive impairment following traumatic brain injury is impaired memory (Gloag, 1985). Regions of the brain implicated in memory processes include the medial temporal lobe, which incorporates the hippocampus, and the basal forebrain. Brain structures governing memory systems can be affected from direct or diffuse damage. Memory deficits are the most enduring cognitive impairment and are particularly difficult to treat (Gloag, 1985). An extensive study of long-term outcomes found that over half the sample (54%) presented significant memory problems (Colantonio *et al*., 2004). It has been reported that the extent of memory deficits is associated with brain injury severity

Memory deficits may arise from impaired arousal, attention, retrieval and/or encoding processes. Two types of memory impairment are often observed. Retrograde amnesia, where memory for events occurring prior to the injury is disturbed, is an impairment of long term episodic memory. Anterograde amnesia, where memory for events occurring after the injury is disturbed, is an impairment of consolidating new information in long term memory. Both retrograde and anterograde amnesia can occur together. Difficulties in short term and working memory are also usual. Impairments in categorical knowledge have been documented. Severe amnesia may lead to confabulations, which relates to false, grandiose and absurd memories. In amnesic syndrome, the most severe form of memory impairment, memories cannot be retained long enough to carry out even simple behavioural sequences. This inability to attend, encode or recall information causes incapacity to plan and execute actions and learn information. Slower rates of learning and difficulties in generalizing and initiating learned behaviours are typical consequences of memory problems.

This poses a challenge to rehabilitative efforts, which typically require a mastery of new skills and the relearning of adaptive behaviours.

8.1.3 Attention

Attention can be conceptualised as "the capacity to focus on particular stimuli over time and to manipulate flexibly the information" (Sohlberg & Mateer, 1987).

Numerous attention deficits may follow brain trauma (Mathias & Wheaton, 2007). Survivors may exhibit deficits in orient attention, selective attention, divided attention and sustained attention. Such deficits may lead to impairments in both automatic and controlled attention processing. Survivors may require conscious attention to engage in previously automatic activities and controlled attention processing may also be impaired. However, it is not clear whether such cognitive impairments reflect specific deficits.

It has been argued that such impairments may be due to a more general disruption in information processing (Brouwer et al., 2002; Felmingham et al., 2004). Experimental data have shown that traumatic brain injury survivors, irrespective of the severity of their injury, produce slower response rates and more errors in various tests of attention compared to controls (Ziino *et al*., 2006). These deficits in attention, and/or information processing speed, also impact on memory, fatigue, task performance and skill acquisition.

8.1.4 Communication

Due to impairments in information processing and attention, language difficulties are common in the brain injury population. Long-term difficulties with reading, writing and word finding are reported frequently by survivors and their relatives (Masson *et al*., 1997). The gravity of the language deficits experienced varies.

Neurological assessments have shown that the degree of language impairment shown by survivors with severe head injury was greater than those with only moderate injuries (Hellawell *et al*., 1999). However, communication difficulties are not limited to those with only moderate and severe head injuries. Significantly impaired verbal fluency was observed in individuals with mild brain injury, compared to healthy controls and patients with Parkinson's

Disease (Raskin & Rearick, 1996). These differences were attributed to attention deficits and slower retrieval processes. The findings suggest that communication impairments may arise from memory deficits, attention disorders and perceptual problems.

Communication impairments can also be caused by direct damage to brain regions that govern language. However specific disorders of language function following brain trauma are rare (Richardson, 2013). Aphasia is a loss of the ability to produce or comprehend language that arises from damage to Broca's and Wernicke's area. Different classifications exist and the extent of the inability can vary. However, aphasia is a rare clinical disorder. The brain injury population is far more likely to experience dysphasia. Dysphasia relates to a group of subclinical disorders of comprehension and speech production. It is associated with generic left hemisphere damage, executive dysfunction and short term memory deficits (Stratton *et al*., 1994). Receptive dysphasia relates to difficulties in understanding written and spoken words. Rehabilitation can be severely hindered by survivors' incomprehension of simple instructions and sentences. Although the impairment concerns the input of language, there can also be associated problems related to output. For instance, even though fluent speech is enjoyed by those with receptive dysphasia, the speech may distorted or even unintelligible. The spoken words may contain irrelevant, illogical and digressive themes. Perseveration (repeating words and phrases) and echolalia (copying another's words) may also occur. Expressive dysphasia relates to difficulties in articulating speech, due to either the inability to form or pronounce words. The articulated speech is slow, monotonous and seemingly effortful. It is often characterised by word finding difficulties, word and syllable substitutions, new words and non-content words.

Expressive language problems are much more common, especially amongst those with severe brain injury (Richardson, 2000). Schalen and colleagues (1994) conducted various outcome tests, five to eight years post-injury, and found a prevalence rate of 22% for expressive dysphasia and only 3% for receptive dysphasia. However, the rate of articulation problems may be higher as mild language impairments may not be perceptible in a neuropsychological assessment but may be manifested during normal communication efforts.

8.2 EEG Findings in Traumatic Brain Injury

This paragraph will discuss the various EEG findings seen in head injury when it results in a brain injury, though any given head injury may or may not result in traumatic brain injury. When an injury is incurred by the brain there are a few varieties of findings seen in the EEG, ranging from spectral changes associated with

either white or gray matter damage, to the changes in “connectivity”, seen as changes in coherence or correlation measured across the cortex, or between more distant functionally related areas.

Damage is seldom restricted to merely being exclusively either white or gray matter, and mixed findings are seen commonly. There are studies showing the correlation of quantitative EEG findings with quantitative MRI findings that are instructive in identifying the nature of the effect on the EEG of the different types of damage.

The EEG changes following brain injury are spectrally different between white and gray matter damage, which helps when evaluating the nature of the damage with the EEG. The white matter is a high speed relay system that innervates the cortex, both with primary sensory input relayed from the thalamus, and with cortical-cortical input via various fasciculi.

When the cortex has decreased innervation, delta content emerges, according to the IFCN’s position paper on the basic mechanisms of cerebral rhythmic EEG. Thus, traumatic brain injury resulting in white matter damage is associated with slower spectral increases in the areas cortically where decreased innervation is present. These slow spectral increases are seen primarily as delta, and may also be seen as a slower band including theta, especially with larger increases in the slow spectra.

White matter also carries signals across the cortex, and from the cortex through subcortical structures to other cortical locations, resulting in the neural network’s “connectivity”. There has been a small case series showing that in some direct frontal injuries, there is a decrease in correlation from the left to the right frontal lobe, seen as decreased spectral correlation, also referred to as co-modulation. This is identical to the changes seen with damage to the anterior portions of the corpus callosum following surgery.

Coherence changes may also be seen with head injury, with both hypercoherence and hypocoherence reported, depending on the nature of the specific case’s damage. Isolated areas may become hypercoherent due to the lack of input, though separated areas will be hypocoherent due to the damage to their connective network.

Damage may be seen in gray matter, which is highly “plastic”, unlike white matter, where damage persists. The neural plasticity allows for regeneration of the cortical gray matter following injury, so the spectral changes associated with gray matter damage may change over time, from the more acute stages, through a transition

phase into a static phase, which may allow for re-integration into functional relationships with neural network activity.

The immediate changes seen spectrally with gray matter injury is a decrease in the function of the thalmo-cortical neural network activity, seen spectrally as decreased alpha and beta, as well as decreased gamma in the affected gray matter. These changes last for the period of the healing, commonly seen across a period from 6 months to a year.

As the gray matter heals, but is not integrated into the neural network function, the idling rhythm in alpha may return and even be seen as an excessive value in database comparisons, since the cortical area is not "working". The beta and gamma remain low during this phase, since they are not seen at normal levels in the idled cortical areas. Beta is generated in local gray matter network activity, and gamma is seen in functionally bound and active networks only.

Once the neural network of the local gray matter is re-integrated into the functional processing, the alpha will then be reduced, and the faster activity seen associated with local function will also be seen as returning to more normal levels. This may not happen spontaneously, and may require specific interventions, such as neurofeedback, physical therapy, and/or various cognitive-behavioral interventions (Thatcher et al., 1999).

The work of Kirtley Thornton showed that the gamma and beta remain low, even when the alpha return has occurred. These faster patterns returned following successful clinical therapy to re-integrate the neural tissue into the functional neural network of the cortical gray matter and white matter.

8.3 Cognitive rehabilitation

Cognitive rehabilitation is a systematic, functionally oriented program of interventions designed to improve neuropsychologic performance. Following a thorough neuropsychologic assessment of a patient's cognitive strengths and deficits, interventions are designed to reestablish or reinforce previously learned skills, develop compensatory strategies for cognitive deficits, or facilitate adaptation to irremediable cognitive impairments.

Regardless of the specific type of intervention, cognitive rehabilitation is intended to promote functional improvement, and limit the impact of permanent cognitive disabilities on everyday functioning and quality of life.

Cognitive rehabilitation is often multimodal, but each component is directed towards the improvement of a specific cognitive domain or ability. Programs targeting impairments in attention, language and communication, memory, visuospatial function, and executive function have been studied in TBI patients. The literature regarding cognitive rehabilitation is complex, and interpretation of treatment studies is challenging.

The goal of cognitive rehabilitation therapy is to help an individual with a brain injury enhance his or her ability to move through daily life by recovering or compensating for damaged cognitive functions. A restorative approach helps the patient reestablish cognitive function, while compensatory approaches help the individual to adapt to an ongoing impairment.

Cognitive rehabilitation therapy interventions are nearly as unique and varied as the individuals they are used to treat. A comprehensive rehabilitation program may be used for individuals with multiple impairments, for example memory loss combined with difficulties in problem-solving, while approaches focused on a single cognitive function attempt to work on each impairment in isolation. In addition to the variation in treatment, an individual's response to any one treatment may vary as well, depending on the injury, the individual's prior state of health, and the individual's social context. Treatment strategies evolve, as different treatments become necessary at different points in time

8.4 New Technologies in Neuropsychological Rehabilitation

There is increasing use of technological innovations in neuropsychological rehabilitation in research and clinical practice. For example, Cochlear implants have restored hearing to thousands of people, while devices to restore sight and movement are progressing rapidly. Sensory devices inject signals into the nervous system, while motor prosthetics extract signals from the nervous system and send them to control devices such as robotic arms or stimulators to re-activate paralyzed muscles (Serruya et al., 2004). Other types of neurotechnology devices improve health by modulating pre-existing systems: deep brain stimulators, for example, deliver targeted electrical stimulation to the basal ganglia to relieve the symptoms of Parkinson's disease. Non-invasive techniques under development include transcranial magnetic or direct current stimulation, and biofeedback delivered from quantitative electroencephalography (EEG) or functional magnetic resonance imaging (fMRI).

Several behavioral and external modulatory techniques will be described in the following.

8.4.1 Behavioral techniques

Assistive devices

Simple, low-cost interventions such as a memory book or wallet, containing pictures of familiar places or people, can help patients with impaired episodic memory better navigate conversations and daily activities. Mobile phones and pagers can be set up to actively remind patients of tasks.

Cognitive orthotic software can facilitate skill acquisition and self-sufficient management of daily tasks. These systems can be highly customized to take into account the deficits and rehabilitation goals of a particular patient. Expert systems comprising mobile phones and palm-top computers linked by radio to web-based central workstations have been found to help remind patients with brain injury, stroke and dementia that certain tasks must be performed such as taking a medication or calling a relative. A palmtop computer can literally step a patient through a task: it might alert them that it is time to call a sister, and then either to provide the phone number and await confirmation the task was completed, or give the patient the option to defer the task and follow-up later. Patients with brain injuries may benefit from both wearable computers that facilitate interaction with the environment, and computer-based diaries, with auditory alarms and linked entries (Serruya et al., 2008).

Virtual reality (VR)

VR has been shown to promote learning in people with memory impairments; furthermore, this learning appears to transfer to improved real-world performance (Zhang et al., 2003). Virtual worlds based on a patient's own home enable safe practice of daily activities and memorization of the location of items. Just as VR tools can be used for data management by scientific teams to capture and manage complex data, so too the annotated display might be adapted to help individuals with memory impairment. Given that enriched environments increase new neuron production in rodents, elaboration of gray matter and remyelination in white matter (Mahncke et al., 2006), the mere act of having patients navigate through complex VR worlds may yield clinical benefits.

Computerized Cognitive Training

Cognitive treatments using computers, which began with memory training, are being widely used these days. Computer-assisted cognitive rehabilitation has advantages, in that it provides personalized treatment based on a subject's neuropsychological pattern to stimulate impaired areas (Talassi et al., 2007). A computer-assisted cognitive rehabilitation training program consists of exercises focused on visual reaction, visual scanning, attention, information processing speed, memory, and problem solving. These exercises can not only provide flexibility and adjustment within a treatment regimen, but may also shorten treatment time. They also provide a means for objectively measuring subject's performance as well as providing instant feedback. The causes of decreasing cognitive information processing speeds among the elderly include the decrease in the number of brain cells, the weakening of motor nerve cells, and a decrease in general activity. Cognitive dysfunction begins with memory decline and is accompanied by miscalculation, disorientation, misjudgment, and comprehension disability, all of which greatly affect daily life (Rhee et al., 1993; Lee et al., 2013).

8.4.2 Noninvasive modulation (paper TBI e brain stimulation)

Neurofeedback

Neurofeedback is biofeedback, or operant conditioning, of any measure of brain functioning. The term *neurofeedback is used* to refer to the use of the electroencephalogram (EEG) to produce biofeedback, although the use of other measurements, such as cerebral blood oxygenation, are also possible (Zotev et al., 2011). In the practice of neurofeedback, an auditory or visual cue is used to guide the patient toward a "healthy" EEG signal as defined by a sample of healthy subjects. This behavior has not been found to correlate with any type of subjective thought process on the part of the patient, although understanding of the paradigm and attention to the task are typically presumed prerequisites. Treatment usually is broken into 5 to 60 sessions, each lasting 30 to 60 minutes, depending on the patient's condition and response to treatment. Double-blind, placebo-controlled studies have shown that neurofeedback can be effective for the treatment of refractory epilepsy, attention-deficit/hyperactivity disorder, and obsessive-compulsive disorder.

Neurofeedback often is guided by the patient's quantitative electroencephalogram (QEEG), typically a Fourier transform of EEG data. This provides power spectral density measurements at each EEG channel, and measures of "coherence," or power

density that correlates between 2 channels. Power and coherence measurements at each of 64 frequencies for 19 channels provide thousands of measurements that can be the target of biofeedback (Nuwer et al., 2005). Targets often are chosen with the help of a normative database, built from the QEEGs of healthy subjects.

Neurofeedback has led to symptom improvement for patients with a history of mTBI. A number of damage experienced in a stroke or TBI can be helped with neurofeedback. Neurofeedback helps connectivity and timing in the brain, and specific areas of the brain can be targeted to have the most impact. Some common repercussions of stroke and TBI that can be helped are: Speech, Movement, Mood regulation, Better behavior control, Headache reduction. Neurofeedback works extremely well for these because the brain regulates each of those issues. For people recovering from stroke and TBI, neurofeedback training can be particularly helpful in improving speech. During brain training, the specific areas of the brain associated with speech can be targeted, strengthened, and improved (May et al., 2013).

Transcranial magnetic stimulation (TMS)

TMS is based on Faraday's principle of electromagnetic induction and features the application of rapidly changing magnetic fields to the scalp via a copper wire coil connected to a magnetic stimulator (Kobayashi et al., 2003). These brief pulsed magnetic fields of 1-4 Tesla pass through the skull and create electric currents in discrete brain regions. Applied in single pulses (singlepulse TMS) appropriately delivered in time and space, the currents induced in the brain can be of sufficient magnitude to depolarize a population of neurons and evoke a certain phenomenon. Paired-pulse application of TMS can be used to evaluate intracortical inhibitory/excitatory circuits and cortico-cortical connectivity. These TMS measures have proved valuable in understanding the neurophysiologic basis of various neuropsychiatric diseases and can provide useful diagnostic information in conditions with intra- or intercortical excitability abnormalities (Hallet et al., 2007). Repetitive trains of TMS (rTMS) applied to targeted brain regions can suppress or facilitate cortical processes, depending upon stimulation parameters (Kobayashi et al., 2003). In most instances, continuous low frequency (≤1Hz) rTMS decreases the excitability of the underlying cortex while bursts of intermittent high frequency (≥5Hz) rTMS enhance it. Also, a subtype of rTMS, known as Theta Burst Stimulation (TBS), incorporates very short, high frequency (50Hz) trains of stimuli delivered intermittently or continuously at 5Hz (Di Lazzaro et al., 2005). TBS can

induce or decrease excitability when applied in an intermittent (iTBS) or continuous (cTBS) paradigm, respectively. The fact that the modulatory effects of rTMS can outlast the duration of its application has led to the exploration of the technique as a potential treatment modality with promising results in various neuropsychiatric disorders. The rTMS after-effects are influenced by the magnitude and duration of stimulation, the level of cortical excitability and the state of activity in the targeted brain region (Silvanto et al., 2008). Extensive neurophysiologic and neuroimaging studies in human and animal models are starting to illuminate the neurophysiology underlying rTMS effects. Overall, rTMS of a targeted brain region has been demonstrated to induce modulation distributed across corticosubcortical and corticocortical networks by means of transsynaptic spread, resulting in distant but specific changes in brain activity along functional networks. Modeling studies can provide essential information on the induced current and field distributions generated in biological tissue during TMS. Short-term effects of TMS on brain activity appear to result from changes in neural excitability caused by shifts in the ionic equilibrium surrounding cortical neurons, reafferent feedback from targeted structures, or the storage of charge induced by stimulation. The prolonged after-effects are considered to result from modulation of long-term depression (LTD) and long-term potentiation (LTP) between

synaptic connections, modifying neuronal plasticity. Increased expression of immediate early genes and neurotrophic effects have also been discussed as possible mechanisms.

Following diffuse damage after TBI, the induction of LTP and LTD may be abnormal due to cellular injury and altered connectivity, which may ultimately account for lasting deficits.

Importantly, this plastic potential might be guided using neuromodulatory strategies to improve clinical outcomes of TBI.

TMS-induced side effects primarily include transient headache, local pain, neck pain, toothache, paresthesias, transient hearing changes, transient changes in cognitive/ neuropsychological functions and syncope (possible as an epiphenomenon). 52-54 The most serious adverse event related to TMS is induction of a seizure but this is a rare complication if the stimulation is applied according to the safety guidelines. While not yet widely popular in TBI research, TMS appears to be well suited to serve as a diagnostic and prognostic factor in the case of TBI.

Importantly, the focality of TMS might be disadvantageous in the acute stage as diffuse damage is frequently a key component of the insult. In the subacute stage, TMS may affect potentially salvageable lesioned circuits dependent on maintaining adequate levels of arousal and avoiding activation of competitor circuits. In order to optimize the therapeutic potential of neuromodulation in promoting functional recovery in the chronic stage, extensions of insights gained from other patient populations can be translated to TBI patients with carefully characterized deficits (Demirtas-Tatlidede et al., 2012).

Transcranial direct current stimulation (tDCS)

tDCS is a noninvasive technique of neuromodulation, which uses low amplitude direct current to alter neuronal firing. While the use of anodal or cathodal direct current polarization to induce changes in the firing rates of neurons was demonstrated in the 1960's, the technique has received renewed interest in recent years. Nitsche and colleagues investigated the modulatory effects of tDCS on motor cortical excitability and reported that anodal tDCS elicits prolonged increases in the cortical excitability and facilitates underlying regional activity, while cathodal stimulation shows the opposite effects. The duration of aftereffects outlasts the period of stimulation and largely depends on the duration of tDCS (Nitsche et al., 2000).

Furthermore, several consecutive sessions of stimulation result in behavioral effects lasting several weeks, a particularly important feature with respect to cortical plasticity (Boggio et al., 2007).

The short-term effects of tDCS are likely elicited by a non-synaptic mechanism and result from depolarization of neuronal resting membrane, presumably caused by alterations in transmembrane proteins and electrolysis-related changes in hydrogen ions.58,62-64 Longterm effects are believed to depend on changes in NMDA (N-Methyl-Daspartate,) receptor activation as well as neuronal hyper- and depolarization, and thus, may share similarities with LTP and LTD.65

Indeed, we have directly relevant pilot data demonstrating modulation of synaptic LTP by tDCS in a murine model. In addition, a functional neuroimaging study investigating the effects of tDCS, demonstrated persistent metabolic changes in oxygen metabolism consistent with electrode location and neural network modulation. Therefore, tDCS has the potential to modify spontaneous activity and

synaptic strengthening, and to modulate neurotransmitter-dependent plasticity on the network level (Lang et al.,2005).

The procedure consists of a 1-2mA current applied through 35 cm2 pad electrodes placed on the scalp (George et al., 2009). The low-level current flows from the positive electrode, anode, to the negative electrode, cathode, and increases the regional activity by the anode while decreasing the activity underneath the cathode. The process may be referred to as cathodal or anodal tDCS depending on the electrode placed over the region being modulated. Large electrode size limits the focality of stimulation, but is preferential to avoid high current densities at the skin which may cause local irritation or even burning.64 It is also possible to apply the second electrode to an extracranial position (e.g. shoulder) instead of the scalp.

While providing greater specificity of stimulation effects on the brain, this application may lead to quite different effects at the primary site; modeling should be considered for such novel electrode arrangements to better predict and understand the current distribution (Wagner et al., 2007).

Future developments (e.g. employing carrier frequencies) may help to bridge the scalp and skull and deliver the stimulating current to the brain more reliably. Even in its present form, the density of stimulation is low enough that subjects only perceive the stimulus during the rapid change in current at the onset and offset of the stimulation. Thus, from a practical point of view, it is easy to sham stimulate subjects by slowly ramping down the intensity after switch on, and ramping up before switch off. This method of sham stimulation has tDCS has been shown to enhance motor learning in healthy subjects and stroke patients, language in normal subjects and patients with aphasia, and verbal fluency and verbal working memory in healthy subjects and patients with early Alzheimer's disease. Furthermore, modulation on the network level allows for modulation of behaviors such as decision-making or social interactions, and has been shown to have translational clinical applications in cases of impulsive behavior, addiction and depression (Demirtas-Tatlidede et al., 2012).

Therefore, tDCS has the potential to improve learning by modification of spontaneous activity and synaptic strengthening, and to modulate neurotransmitter-dependent plasticity on the network level.

Several studies of the safety of tDCS have concluded that it is a painless technique for electrically stimulating the brain with almost no risk of harm. The most frequent adverse effects include moderate fatigue (35%), mild headache (11.8%), nausea

(2.9%) and temporary mild tingling sensation, itchiness and/or redness in the area of stimulation. While the risks are rather minimal, tDCS may also result in temporary side effects such as dizziness, disorientation, or confusion.

Overall, tDCS features a highly portable, safe, noninvasive means to modulate cortical excitability with reasonable topographic resolution and reliable experimental blinding. It can focally suppress or enhance neuronal firing following TBI, depending on the size and location of the applied electrodes, and thus may offer a promising method to minimize the damage and promote functional recovery. Cathodal tDCS may be employed to suppress the acute glutamatergic hyperexcitability following TBI. In the subacute stage, when GABAergic activity is excessive and conditions neurologic, cognitive and functional disability, anodal tDCS may increase excitability to counter these aberrant GABAergic effects. In the chronic stage, brain stimulation coupled to rehabilitation may enhance behavioral recovery, learning of new skills and cortical plasticity. In this stage, the relative ease of use and portability of tDCS may enable modulation of plasticity via concomitant behavioral interventions such as cognitive behavioral, occupational and physical therapy.

Online or offline combinations of tDCS, EEG and fMRI may assist in understanding the extent of injury and the mechanisms of plasticity underlying functional recovery in TBI. Its neuromodulatory potential in rehabilitation of patients with TBI also remains to be investigated.

In a recent study, Ulam et al. recorded serial EEGs, along with serial neuropsychological tests, among a sample of 12 patients as they progressed through inpatient neurorehabilitation for TBI. The same measures were obtained from a group of 13 closely matched healthy controls. This sample of patients was completely separate from the sample recruited for the present study. Patients with TBI differed significantly from controls due to excesses of power in the delta and theta frequency bands, as well as in the mean peak frequency of alpha, which was slower than for controls. Using linear regression, we found EEG spectral power measures to be significantly related to neuropsychological tests such that as power in delta and theta decreased, performance on measures of attention and working memory increased, and as power in the alpha frequency increased, performance on the measures of attention and working memory increased. It was concluded that EEG spectral power measures tracked recovery from TBI in a meaningful way, providing

a useful neurobiological marker that could be used to quantify response to rehabilitative interventions, and could potentially become an important predictor of treatment response (Ulam et al., 2014).

Chapter 9

Case of study

A Tele-Cognitive Rehabilitation System Using LabVIEW

9.1 Introduction

Brain injury can produce a variety of cognitive disturbances depending on the location of the lesion (Gurd et al., 2010). Current methods for cognitive rehabilitation are based on traditional paper-and-pencil tests. However, significant difficulties are encountered when these conventional methods are applied to cognitively impaired patients. First, many patients with both cognitive and physical impairment, cannot reach the hospital alone, and most families cannot afford the high cost of accompanying patients to the rehabilitation hospital several times a week for training or even stay in the hospital. Second, traditional paper-and-pencil tests are usually carried out in one-to-one mode, meaning one doctor can only coach one patient at a time to do the cognitive training. For a large number of patients, this method of cognitive rehabilitation is ineffective. Since cognitive rehabilitation is a far-flung process, computer-based technologies show outstanding advantages in assisting therapy, evaluating residual function quantitatively, storing rehabilitation results, and so on. In addition, doctors can assist patients to perform the computer-based rehabilitation training through an internet connection and check the training results,

thus overcoming the problems arising with traditional therapy. The tele-therapy technology for cognitive disturbances offers good opportunities to satisfy the needs of an increasing number of patients (Bai et al., 2005; Dwolatzky et al., 2004; Tam et al., 2003). For this reason, we developed software for tele-cognitive rehabilitation using LabVIEW, a high-level graphical programming environment. This paper outlines the rehabilitation tests, the structure of the database connected to the application, and the LabVIEW-based remote connection between the database and the patient's training workstation.

9.2 Description of the Tele-Rehabilitation System

9.2.1 Cognitive Rehabilitation System

The tele-rehabilitation software contains several cognitive training programmes for the patients. The application for cognitive rehabilitation training is organized into four parts: (1) memory training, (2) visuo-spatial cognition training, (3) selection and classification training, and (4) cognitive phonology training. Rehabilitation exercises are characterized by adaptation of training difficulty to the performance of the patient, effective feedback and userfriendliness.

Rendering scales and scores are also provided to improve the patients' motivation. Furthermore, exercises are characterized by a random presentation of stimuli to avoid learning effects (Sohlberg et al.,1979).

9.2.2 Database Architecture

The software allows the personal and clinical data of the patients to be inserted and stored in a database along with the exercise settings and patients' scores. The relational database is based on Access. A relational database is a collection of data item tables formally described and organized according to a relational model. Data in a single table represent a relation and, in typical solutions, tables may have additionally defined relationships with each other (Ramakrishnan et al.,2000). Our database tables are: (1) Patient, containing patients' personal data, (2) Medical Case, containing patients' clinical data, (3) Training Exercise, containing the list of exercises executed by the patients with the setting parameters for each one, (4) Results and Score, containing the patients' results for each exercise. A block diagram of the database relations is shown in Figure 11. Different medical cases can be associated with each patient, different training exercises with each medical case, and

different results and scores with each training exercise. This allows the patient's performance to be monitored in real time and the follow-up phases easily executed.

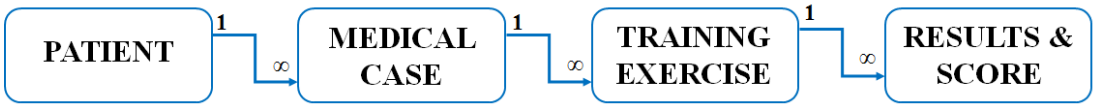

Figure 11: Database block diagram

We used the Access Database because it allows a simple consultation independently of LabVIEW. We used the Database Connectivity Toolkit (DCT) to connect the Database with LabVIEW. The DCT is a LabVIEW toolkit providing optimized Virtual Instruments (VI) for database access using ActiveX Data Objects (ADO) technology. The system allows a remote connection between the database and the patient's workstation executing the training.

9.2.2 Database Remote Connection

The database remote control uses the Client-Server model and the TPC/IP protocol. The server is the machine hosting the database at the rehabilitation centre, while the clients are the devices running the cognitive rehabilitation training software. To achieve remote connection, we used the LabVIEW VI Server functions. A VI Server is a set of functions that dynamically controls front panel objects, VIs, and the LabVIEW environment. With a VI Server, VIs and LabVIEW can also be loaded and run either on the same machine or across a network (Elliott et al., 2007). Our idea to achieve database remote control was to execute in the server machine all the VIs involved in database management, as shown in Figure 12. That occurs whenever information needs to be inserted in or retrieved from the database by the client device. We call the VI of the server involved in database management VIDM (VI Database Management).

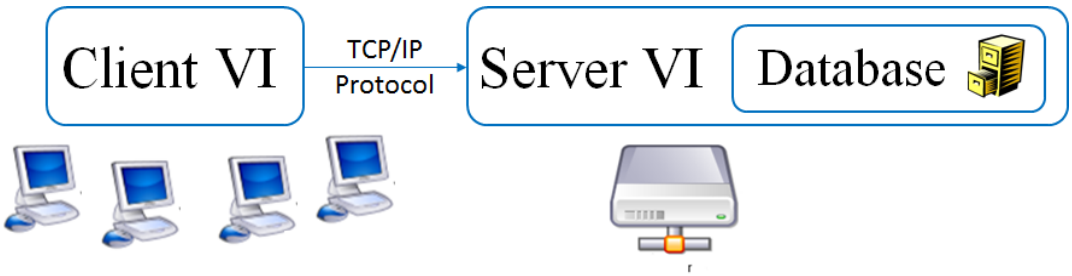

Figure 12: Schematization of the remore connection model

In order to build the VI server application, both the TCP/IP protocol in LabVIEW and the client access to the server had to be enabled, setting the client's IP. The

following steps were completed to allow the database to communicate with the VI running on the client device for the insertion of personal data and test results in the database. The client VIs: (1) open a reference to the server instance through the function *Open Application Reference*, (2) open a reference to the VIDM through the function *Open VI Reference*, (3) call the VIDM through the function *Invoke by Reference Node*, specifying the information inserted in the client device we want to store in the database, (4) close the VIDM reference and the server reference through the function *Close Reference.*

9.3 Experiment and Results

To demonstrate the concept introduced in this paper, the system is organized into two main parts: (1) the cognitive rehabilitation training battery, and (2) the database storing patients' personal and clinical data and the setting and results of the rehabilitation exercises performed by the patients. The exercise interfaces are interactive, motivating and easily adapted to individual patients' performance. Some exercise interfaces are shown in Figure 13. The system allows a remote connection with the database. Figure 14 shows the software interface for the insertion of the Client and Server IPs.

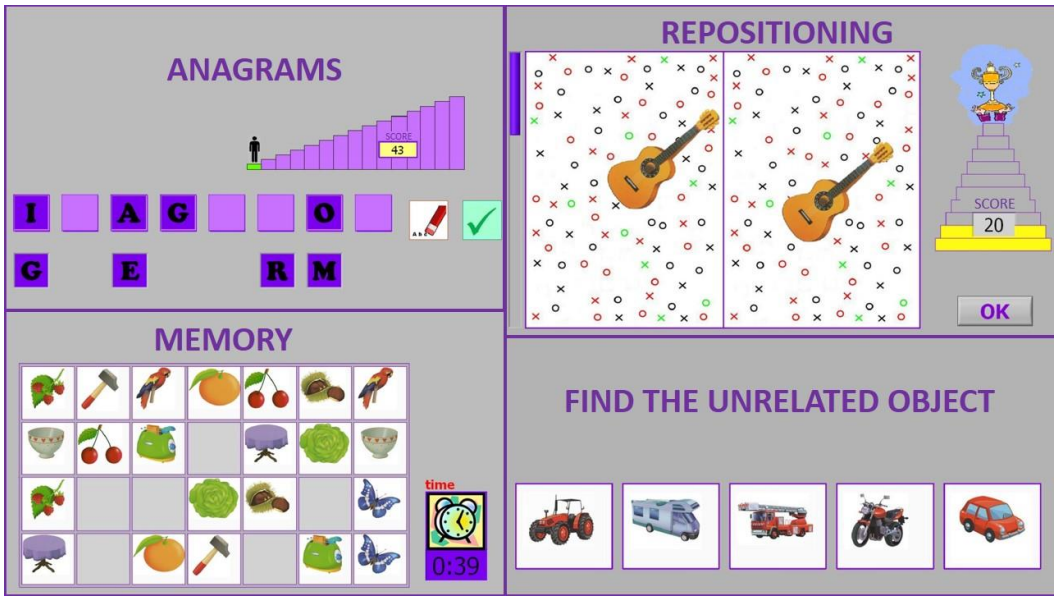

Figura 13: Some example of testing interfaces

The remote control of the application has many advantages. First of all, it uses a single database accessible from every outstation, in order to insert and retrieve patients' data. This makes the application lighter and suitable for portable devices like smartphones or tablet pc. The remote control opens the possibility of "shared

therapy" because the therapist monitors the training of different patients at the same time, increasing the total capability of the rehabilitation team. Our tele-cognitive rehabilitation model is home-based and tailor-made. As previously stated, people with brain injuries do not just have cognitive problems, but they may also suffer from physical impairment.

Tele-cognitive rehabilitation methods provide greater flexibility during service delivery. The system allows users to stay at home and avoid spending a long time travelling to receive tailor-made face-to-face treatments.

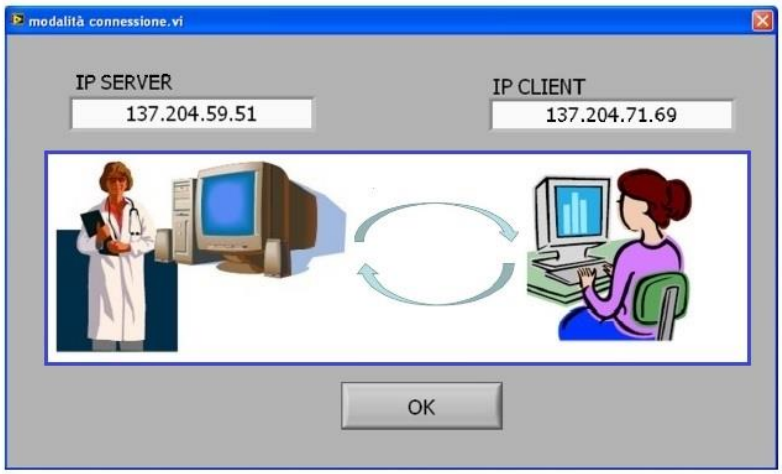

Figure 13: Software Interface for the configuration of Server and Client IP addresses.

9.4 Conclusion

This paper outlined a tele-therapy system for cognitive disturbances. The results obtained are promising since our system is safe and stable. However there are many ways to improve and integrate the system. Thanks to the modularity of the application, it will be simple and fast to complete the platform with new rehabilitation exercises. An application for portable devices like tablets or smartphones is also planned.

Chapter 10

Transcranial Stimulation e EEG

10.1 Introduction

The recent emergence of new, noninvasive brain stimulation (NIBS) techniques for inducing reversible changes in brain activity has allowed the temporary modulation of a wide range of functions (Wassermann et al., 2008). The development of NIBS techniques for the study of mechanisms underlying perceptual, motor, and cognitive functions, as well as the ability to modulate these functions in the human brain, has constituted a significant advance in basic neuroscience. The combination of NIBS with neuroimaging techniques has gained popularity in recent years, due to its potential to investigate the state of targeted brain areas and the roles of these areas in specific functions. The NIBS techniques used to modulate cortical activity include transcranial magnetic stimulation (TMS) and transcranial electrical stimulation (tES). The tES technique (Priori et al., 2003) involves the application of weak electrical currents directly to the head for several minutes. These currents generate an electrical field that modulates neuronal activity according to the duration, intensity, and modality of the application, which can be direct (transcranial direct current stimulation [tDCS]), alternating (transcranial alternating current stimulation [tACS]), or random noise (transcranial random noise stimulation [tRNS]) (Pausul et al.,2011).
Several studies using animal models have suggested that neurons respond to membrane polarization changes induced by tDCS, thereby leading to a reduction in

spontaneous neuronal firing rates after cathodal tDCS and an opposite effect after anodal stimulation. Firing increases when the positive pole (anode) is located near the cell body or dendrites and decreases when the field is reversed.

Accordingly, the first studies performed on the motor cortex showed that cathodal polarization induced robust inhibition of motor cortex excitability, whereas anodal polarization increased motor cortex excitability (Nitsche et al. 2000).

Similar results have been observed using tRNS (Terney et al.,2008), although the mechanisms for tRNS-induced alterations have been assumed to be the result of repeated subthreshold stimulations.

Therefore, in the same manner as tDCS, tRNS can change the cortical excitability by means of mechanisms of membrane polarization. In addition, the advantage of using tRNS over tDCS is that tRNS is not constrained by the sensitivity of the current flow direction. Instead, random frequencies are typically presented, and all coefficients have a similar size (i.e., white noise).

To date, few studies have evaluated the modulation effects induced by tRNS, which have been shown to induce substantial behavioral modifications. The use of an approach, such as EEG, could allow for a more detailed understanding of the neural mechanisms involved in these observed changes.

The few studies published to date on cortical measures have indicated that the alternating stimulation used as tACS is a powerful tool for investigating human brain oscillations. Using tACS, it is possible to deliver an oscillatory current to the cortex in a frequency-specific manner to induce a particular oscillatory entrainment (Kanai et al., 2008). In this respect, tACS may serve as an instrument to interact with ongoing cortical oscillations and induce entrainment, thereby contributing to a better understanding of cortical binding through frequencies during different functions.

10.2 tDCS e EEG

Investigating the effects of a low electric current passing through the human scalp is now common (Paulus 2011). So far, researchers have investigated the modifications induced by tDCS given that advances in this field may further support and detail the use of tDCS as a therapeutic tool for several disorders characterized by abnormalities in electrophysiological and behavioral parameters. Electroencephalogram (EEG) constitutes a simple and cost–effective methodology to measure modifications of brain activity during and after tDCS delivery. Indeed, the EEG: i) reflects the

fluctuation of the local field potentials resulting from the postsynaptic potentials of the cortical neurons, then the changes of the neuronal resting membrane potential due to the tDCS; ii) offers the possibility to identify responses to tDCS within an area or across circuits, thereby helping to determine *in vivo* the brain areas that are directly or indirectly affected by the stimulation.

Two combined EEG-tDCS methodologies can be identified: i) the "offline" method, with the EEG recording performed after the tES stimulation, in order to evaluate the short- and long-term aftereffects induced by tES, and ii) the "online" method, with the EEG recording performed during the tES stimulation, in order to evaluate the ongoing changes that occur during tES delivery.

10.2.1 Offline approach

Several electrophysiological changes in EEG oscillations following tDCS have been previously observed using offline methods in experiments involving a task for the subject or with the subject at rest. Ardolino et al. (2005) reported that cathodal stimulation of the motor cortex (1.5 mA, 35 cm^2 electrode, 10 minutes) increased the power on delta and theta rhythms. Matsumoto et al. (2010) evaluated how tDCS applied over the left primary motor area (1mA, 35 cm^2 electrode, 10 minutes) influenced event-related desynchronization (ERD) of the mu rhythm recorded during the imaging of right hand grasping. An increase and decrease in mu ERD after anodal and cathodal stimulation, respectively, were observed. These results are in partial disagreement with the afore-mentioned report by Ardolino et al.. Nevertheless this apparent discrepancy may be explained by the different state of the subject (rest state vs active state) (Miniussi et al. 2012). Polania et al. (2012) reported that, following anodal stimulation over the primary motor cortex, functional connectivity patterns significantly increased within the premotor, motor, and sensory motor areas of the stimulated hemisphere during motor activity. Notturno et al. (2013) investigated the effects of cathodal and anodal tDCS on the electric activity of primary motor cortex during a finger-tapping task. They found an increment of low alpha ERD in bilateral central, frontal areas and in the left inferior parietal region, as well as an increment of beta ERD in fronto-central and parieto-occipital regions, after anodal stimulation compared to sham and cathodal stimulations. Finally, beta band coherence among signals from left sensorimotor cortex and activity of bilateral parietal, occipital and right frontal regions was higher after anodal stimulation compared with sham condition. Similarly, theta coherence with parietal and frontal

regions was enhanced after anodal stimulation. Electrophysiological changes were also observed following stimulation over non motor area. Antal et al. (2004) applied anodal and cathodal tDCS (1mA, 35 cm^2 electrode, 10 minutes) over Oz. They recorded the EEG activity during the presentation of visual stimuli and found a decrease of the power in the beta and gamma frequency bands after cathodal stimulation, whereas no changes were observed after anodal stimulation. In a second study, Antal et al. (2004b) studied if tDCS applied over the occipital cortex, is also able to affect visual-evoked potentials (VEPs). They found reversible excitability changes on the amplitude of the N70 and P100 component in a polarity-specific and time-specific way. On a working memory task, Keeser et al. (2011b) showed that 20 minutes of anodal stimulation (2 mA) over the left dorsolateral prefrontal cortex significantly reduced left frontal delta activity. Further, Zaehle et al. (2011) stimulated the left dorsolateral prefrontal cortex during a working memory task and reported a significant reduction of power in the delta band after anodal stimulation. At least Zaehle et al. (2011b) applied tDCS over the left temporal as well as the left temporo-parietal cortex and investigated tDCS-induced effects on auditory evoked potentials after anodal, cathodal, and sham stimulation. They found that anodal tDCS over the temporal cortex increased auditory P50 amplitudes, cathodal tDCS over the temporo-parietal cortex induced larger N1 amplitudes.

Changes on ongoing oscillatory brain activity subsequent to tDCS have been investigated also during rest in few studies (Ardolino et al. 2005; Spitoni et al. 2013; Zaehle et al. 2011b). Brain activity at rest constitutes an index of the internal state of the brain in the absence of an external input or motor output. Spitoni et al. studied the effect of tDCS on postero-parietal cortex in the resting state, finding that anodal stimulation alters ongoing brain activity, specifically in the alpha band rhythm.

Ulam et al. (2014) investigated in a randomized, double-blind design, cumulative effects of anodal tDCS on EEG oscillations and neuropsychological tests among patients with (TBI) undergoing subacute neurorehabilitation. Twenty-six patients were randomly assigned to active (n = 13) or sham (n = 13) tDCS groups. EEGs were recorded at 6 different time points, assessing both immediate and cumulative effects of tDCS on EEG oscillations. Twenty minute sessions of 1 mA anodal stimulation to the left dorsolateral prefrontal cortex (F3, cathode placed at right supraorbital site, Fp2), were provided on 10 consecutive days. Neuropsychological tests were administered before and after the series of tDCS sessions.

The results showed that theta was significantly reduced for active tDCS patients following the first tDCS session. Delta decreased and alpha increased, both significantly, for the active tDCS group after 10 consecutive tDCS sessions. No significant changes were seen for sham group. Decreases in delta were significantly correlated with improved performance on neuropsychological tests for the active tDCS group to far greater degree than for the sham group. Participants in the active tDCS group who had excess slow EEG activity in their

initial recordings showed greater improvement on neuropsychological tests than other groups.

Results suggest that 10 anodal tDCS sessions may beneficially modulate regulation of cortical

excitability for patients with TBI. EEG-guided tDCS warrants further investigation as a potential intervention for TBI during subacute neurorehabilitation.

10.2.2 Online approach

The aforementioned studies mostly focused on the "offline" method for studying the effects of tDCS on EEG, while we think that the "online" approach should be the optimal candidate for combined tDCS-EEG investigations. Indeed, i) online approaches can yield information regarding the effects that are directly induced by tDCS, thus providing valuable information on the mechanisms of action of tDCS (this is particularly important in order to fully understand and exploit the potential of tDCS when used as a modulatory tool together with concomitant behavioral conditioning strategies (i.e. biofeedback) (Bolognini et al 2011; Wirth et al 2011); ii) EEG findings during tDCS can be interpreted as surrogate marker for the effects of tDCS and thus can be used to optimize the tDCS parameters in the context of a given application; iii) online approaches could also be envisioned to be used for preventive treatment of neurological conditions characterized by abnormal peaks of cortical excitability, such as seizures (Faria et al. 2012; Schestatsky et al. 2013). The study of Soekadar et al. (2014) used the online approach to understand if learned EEG-based brain-machine interface control during tDCS is feasible. They recorded the learned desynchronization of mu-rhythms (8–15Hz) associated with motor imagery over C4 during the application of anodal stimulation in a site of stimulation placed 1 cm anterior to C4. They found a significant power increase in the lower frequencies mostly evident in the signal spectrum of the EEG channel closest to the stimulation electrode.

Accornero et al. (2007) assessed VEP-P100 latencies and amplitudes in response to pattern-reversal checkerboard stimuli before, during, and after polarization. Anodal polarization reduced VEP-P100 amplitude whereas cathodal polarization significantly increased amplitude but both polarities left latency statistically unchanged. These changes persisted for some minutes after polarization ended depending on the duration of tDCS and on the contrast level of visual stimuli. tDCS-induced changes in VEPs seem to depend on the duration of polarization and type of visual stimuli used. The effects induced on visual cortical neurons during polarization are more consistent than the after effects. In a further study, Accornero et al. (2014) evaluated EEG mean frequency changes induced by prefrontal transcranial direct current stimulation (tDCS) and investigated whether they depended on tDCS electrode montage. Eight healthy subjects underwent tDCS for 15 minutes during EEG recording. They completed six tDCS sessions, one week apart, testing left and right direct current (DC) dipole directions with six different montages: four unipolar montages (one electrode on a prefrontal area, the other on the opposite wrist) and two bipolar montages (both electrodes on prefrontal areas), and a single sham session. EEG power spectra were assessed from four one-minute EEG epochs, before, during and after tDCS. During tDCS the outcome variable, the EEG mean frequency, changed significantly, and the changes persisted for minutes after tDCS ended. With the DC dipole directed to the left (anode on the left prefrontal area or wrist) increased, with the DC dipole directed to the right (anode on the right prefrontal area or wrist) the mean frequency decreased, suggesting asymmetric prefrontal cortex functional organization in the normal human brain. Anodal and cathodal effects were opposite but equally large.

Song et al. (2014))performed simultaneous electroencephalogram (EEG) monitoring during tDCS on 10 healthy individuals. They recorded EEGs with direct current stimulation, as well as during a 5-min resting state before and after the stimulation. All participants kept their eyes closed during the experiment. Anode and cathode patches of tDCS were placed on the left and the right dorsolateral prefrontal cortex, respectively. In addition, an EEG electrode was placed on the medial prefrontal cortex. The beta frequency power increased promptly after starting the stimulation. The significant beta-power increase was maintained during the stimulation. Other frequency bands did not show any significant changes. The results indicate that tDCS

of the left dorsolateral prefrontal cortex changed the brain to a ready state for efficient cognitive functioning by increasing the beta-frequency power.

Roy et al. used a combination of Transcranial Magnetic Stimulation (TMS) and Electroencephalography (EEG) in order to explore local and global cortical excitability modulation during and after active and sham tDCS. Single pulse TMS was delivered over the left posterior parietal cortex (PPC), before, during, and after 15 min of tDCS over the right PPC, while EEG was recorded from 60 channels.

For each session, indexes of global and local cerebral excitability were obtained, computed as global and local mean field power (Global Mean Field Power, GMFP and Local Mean Field Power, LMFP) on mean TMS-evoked potentials (TEPs) for three temporal windows: 0e50, 50e100, and 100e150 msec. The global index was computed on all 60 channels. The local indexes were computed in six clusters of electrodes: left and right in frontal, parietal and temporal regions. GMFP increased, compared to baseline, both during and after active tDCS in the 0 e100 msec temporal window. LMFP increased after the end of stimulation in parietal and frontal clusters bilaterally, while no difference was found in the temporal clusters.

In sum, a diffuse rise of cortical excitability occurred, both during and after active tDCS.

This evidence highlights the spreading of the effects of anodal tDCS over remote cortical regions of stimulated and contralateral hemispheres.

This evidence foster the application of this technique in rehabilitation settings (e.g., Brunoni et al., 2011), based on results showing that tDCS may induce not only on-line effects on spontaneous neuronal activity, but also long-lasting after-effects likely mediated by mechanisms of synaptic long-term potentiation and depression (i.e., LTP and Long-term Depression, LTD, respectively), which affect neuroplasticity (Liebetanz, Nitsche, Tergau, & Paulus, 2002; Nitsche, Fricke et al., 2003, 2008; Stagg et al., 2009).

Chapter 11

Case of study

Transcranial Direct Current Stimulation and Power Spectral Parameters: a tDCS/EEG co-registration study

11.1 Intoduction

We present here a preliminary study aiming i) to investigate the effects of tDCS on spontaneous cortical activity at rest and ii) to differentiate between ongoing modifications and aftereffect modifications. To this end, we measured the modulation of spontaneous EEG during and after a session of anodal tDCS stimulation of the postero-parietal cortex. We decided to focus the study solely on the anodal stimulation (and sham control), excluding the cathodal stimulation, since Spitoni et al. (2013) did not found significant EEG modifications after cathodal tDCS. Moreover, we decided to focus on the tDCS over posterior parietal cortex since several studies demonstrated the utility of tDCS in the rehabilitation of the visual functions in both healthy subjects and patients with lesions on the parietal cortex, while a few studies (Spitoni et al. 2013) investigated the ongoing electrophysiological effects of the stimulation.

We also aimed to determine the beginning and the duration of the alterations induced by the stimulation. Several studies demonstrated that the effects of tDCS were stronger in the first 5 minutes after the stimulation and persisted for about 20 minutes (Keeser et al. 2011b; Antal et al. 2010). Therefore, we studied the effects of the stimulation over EEG power spectral parameters, specifically in theta, alpha, beta and gamma bands, through a statistical analysis of variance, with the aim to determine: 1) the bands showing a change in their power, 2) the duration of the effects, and 3) their localization.

11.2 Materials and Methods

11.2.1 Subjects

Ten healthy subjects (seven male) participated in the study. They ranged in age from 23 to 51 years. The inclusion criteria were (1) no history of neurological or psychiatric disorder, (2) no history of substance abuse or dependence, and (3) no use of medication affecting the central nervous system. All participants provided written consent for the experiment participation. The study conformed to the Declaration of Helsinki and was approved by the local ethics committee.

11.2.2 tDCS Stimulation

We used the same protocol of Brunoni at al. (2012) and Spitoni et al. (2013). The Spitoni protocol aimed to investigate the electrophysiological changes that are induced through anodal and cathodal tDCS over posterior parietal areas during the resting state. A direct of 1.5 mA (during the stimulation the impedance value was maintained in a range of 4-6 kOhm), induced through two saline-soaked surface sponge electrodes (7 x 4.5 cm), was delivered using a battery driven, constant-current stimulator (neuroConn GmbH, Ehrenbergstr, Ilmenau, Germany). To avoid confounding biases that could have arisen from two electrodes with opposite polarities over the scalp, we used an extra-cephalic reference electrode for tDCS. The active electrode, the anode, was placed over the right posterior parietal cortex and the reference electrode, the cathode, was placed over the ipsilateral deltoid muscle. The location of the active electrode was determined according to the 10-20 EEG standard montage, placing the electrode over P4, as suggested in previous studies (Spitoni et al 2013). In the stimulation session, the current was ramped up from 0 to 1.5 mA in 30 s. Fifteen minutes after onset, the current was ramped down back to 0 in 30 s. Sham stimulation was used as control in the experiment, in order to isolate the effects

solely due to the current stimulation and not due to the placebo and somatosensory effects that could arise from tDCS application. During the sham condition the electrodes were located in the same positions as in the anodal stimulation, but the current was supplied only for the first 43 s (8 s ramp up, 30 s of DC stimulation and 5 s ramp down). This procedure ensured that the subjects felt the tingling sensation at the beginning of the stimulation.

11.2.3 Protocol

The subjects seated in a quiet room and were asked verbally every 2 minutes to open or close their eyes, thus allowing us to conduct the subsequent analyses for two different behavioral conditions, the Eyes Open condition (EO) and the Eyes Closed condition (EC). During EO intervals, the subjects were instructed to fix a point in front of them and not to move their eyes. The participants did not know whether anodal tDCS or sham stimulation was delivered.

The protocol consists in a Baseline session (B), a Sham session (SS) and an Anodal session (AS) executed in sequence, as shown in Figure 15. The Sham session and the Anodal session consisted each in a Stimulation and Recording Session (SS and AS, respectively) and in a Post recording session (PSS and PAS, respectively). It was decided to have the Sham session always preceding the Anodal session~~,~~ in order to avoid the possible effects of the Anodal stimulation on the Sham session recordings. Indeed, given a choice to be made, we *a priori* hypothesized the effects due to ~~the~~ Anodal stimulation being equally or more relevant than the effects induced by Sham stimulation.

In order to further control for the placebo/somatosensory effects due to the stimulation, we administered a side effects questionnaire to the subjects to investigate if they perceived differently during the Anodal and the Sham stimulations.

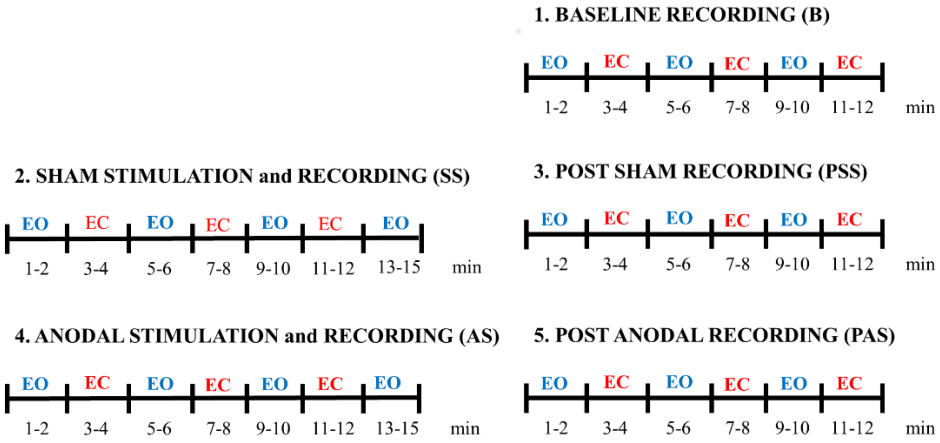

Figure 14: Experimental protocol. The protocol consists in a Baseline session (B),a Sham session (SS) and an Anodal session (AS) executed in sequence.

11.2.4 EEG recording and preprocessing

EEG was recorded from 18 electrodes (Fp1, Fp2, F3, F4, F7, F8, Fz, C3, C4, Cz, P3, Pz, T3, T4, T5, T6, O1, and O2) positioned according to the international 10-20 layout using a Neurowave System (Khymeia, Italy). The EEG electrode over the stimulated area (P4) was removed from the registration cap to allow for the positioning of the stimulation electrode. EEG signals, referenced to linked ear lobes, were sampled at 512 samples/s, preliminarily band-pass filtered between 3 Hz and 60 Hz (through an high pass IIR filter (2^{nd} order) and a low pass IIR filter (7^{th} order) filters. An additional stopband IIR filter at 50 Hz (7^{th} order) was applied. Trial datasets underwent 1) manual identification and rejection of artefactual segments; 2) decomposition in 2–seconds long segments; 3) detrend of the signal of the segments by removing the mean and the linear trends in each 2-second segment (Muthuswamy et al 1998); 4) Power spectral density (PSD) estimation for each 2-seconds segment (without overlap) through a modified periodogram method based on FFT-algorithm and Blackman Harris window. PSDs for each interval of interest (e.g. experimental sessions) were obtained by averaging the PSDs of the related 2-seconds segments. Power values were extracted from the calculated PSDs in four frequency bands: theta (4-8 Hz), alpha (8-13 Hz), beta (13-25 Hz) and gamma (25-40 Hz).

In order to compare the data of all subjects, we performed an intra-subject normalization, by dividing the powers of each band, each electrode and each session (B, SS, PSS, AS and PAS) by the correspondent power during the B session.

11.2.5 Statistical Analysis

Effects of Stimulation

We preliminarily tested for the normality of the power data distribution through a Kolmogorov–Smirnov test (Massey et al. 1951). We found a normal distribution of the data, justifying the subsequent use of ANOVA analyses.

A one-way ANOVA analysis on five levels (B, SS, PSS, AS, and PAS) was performed for each band and for each electrode, using the data of all subjects, separately for the EO and the EC conditions. This analysis allowed us to test the hypothesis stating that there is a significant effect due to the stimulation conditions, against the general alternative that there is no significant effect. Since we were also interested in which pairs of conditions were significantly different, multiple comparison *post-hoc* tests were also conducted, in cases where the ANOVA found a significant effect. We choose a significance level p=0.01 % and we used the Bonferroni correction for multiple comparisons (Benjamini et al. 2001).

The correction factor was computed considering each electrode independent from the other. Then this factor is given by the number of levels in the ANOVA analysis and repetitionsIn fact, for each electrode, we carried out the ANOVA test four times, one for each power band that we considered (theta, alpha, beta and gamma). Then, the correction factor is 20 (5 levels × 4 bands). In order to further reorganize and interpret the results, we considered: i) the effects of tDCS during the SS and PSS sessions (SHAM effects) as being significant only if SS and PSS power values were significantly different from B and ii) the effects of tDCS during the AS and PAS sessions (STIMULATION effects) as being significant only if AS and PAS power values were significantly different from B, SS, and PSS simultaneously.

Effects Over Time

In order to investigate the effects over time of tDCS, the AS and PAS periods were divided into 2 minutes segments. For the EO condition we obtained four segments for AS (AS1 (1-2 min), AS2 (5-6 min), AS3 (9-10 min) and AS4 (13-14 min)), and three segments for PAS (PAS1 (1-2 min), PAS2 (5-6 min), PAS3 (9-10 min)). For the EC condition we obtained three segments for AS (AS1 (3-4 min), AS2 (7-8 min), AS3 (11-12 min)), and three segments for PAS (PAS1 (3-4 min), PAS2 (7-8 min), PAS3 (11-12 min)).

Moreover, the effects of tDCS over time were analyzed by one way ANOVA analysis with ten levels for the EO condition and one way ANOVA analysis with

nine levels for the EC condition, with subsequent multiple comparison tests. For the EO condition, the levels of the analysis were: B, SS, PSS, AS1, AS2, AS3, AS4, PAS1, PAS2 and PAS3. For the EC condition, the levels of the analysis were: B, SS, PSS, AS1, AS2, AS3, PAS1, PAS2 and PAS3. As for the analysis conducted to evaluate the stimulation effects, we choose a significance level p=0.01 % and we used the Bonferroni corrections for the multiple comparison tests (Benjamini et al. 2001). In this case, the correction factor is 40 (10 levels × 4 bands) in eyes open condition and 36 (9 levels × 4 bands) in eyes open condition.

11.2.6 Side Effects Questionnaire

After the experiment, we administered a side effects questionnaire to each subject to evaluate if there were differences in their physical perception of the tDCS. If there were no differences between these two conditions of stimulation we could exclude that the tDCS effects over the EEG rhythm were due to the marked physical sensations associated with the anodal stimulation. The questionnaire consists in eleven questions about: tingling, itching sensation, burning sensation, pain, headache, fatigue, difficulty in concentrating, nervousness, visual perceptual changes, discomforting sensations, visual sensation associated with the start/end of the stimulation (Poreisz et al. 2007). The severities of the side effects were rated in a numerical discrete scale from one to five, one being very mild and five being extremely strong intensity of any given side-effect. To determine the statistical significance of each effect, these were analyzed with an independent samples Mann-Whitney U test between the anodal and the sham conditions. We used the Mann–Whitney U test because the data distribution is not Gaussian. For each side effect, we computed the p-value and used a significance level p=0.01.

11.2.7 Software Tools

MATLAB language and toolboxes were used for data processing and analysis (The Mathworks, US). In particular, we used the Signal Processing Toolbox to preprocess the recorded data and the Statistics Toolbox for statistical analysis.

11.3 Results

11.3.1 Statistical Analysis

Effects Of Stimulation

We analyzed the significance of each electrode-band couple for the different stimulation conditions as detailed in the Methods.

We did not found any significant SHAM effect. The results reported below and in the next sessions refer only to the STIMULATION effects.

Considering the EO condition, we did not found any significant effect. Considering the EC condition, we found: i) a significant effect in theta band during AS for the electrodes F4, C4, O2, T4, T6, Cz and Pz; ii) a significant effect in alpha band during AS for the electrodes C4, T6, Cz and Pz; iii) a significant effect in alpha band during PAS for the electrodes Fp2, O2, F8, T4, T6, Fp1, F3, C3, P3, O1, T5 and Fz; iiii) a significant effect in beta band during AS for the electrodes P3, O1, T3, T5, Cz and Pz; iiiii) a significant effect in beta band during PAS for the electrodes C3, P3, O1, T3, T5 and Fz.

Figure 16 and Figure 17 show an example of the Power Spectral Density for the electrode O2 in the five experimental conditions (B, SS, PSS, AS, PAS), respectively for the EO and EC conditions.

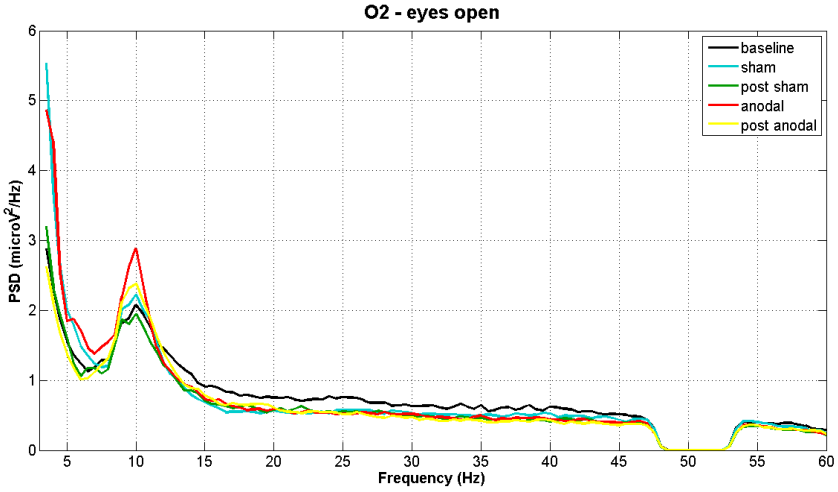

Figure 15: EEG power spectral density of B, SS, PSS, AS, and PAS (EO condition) for electrode O2 (mean of all subjects). Even if there are no significant effects considering the whole session duration, there is a significant peak increment in theta and alpha bands during stimulation. These effects are significant in the analysis of time effects.

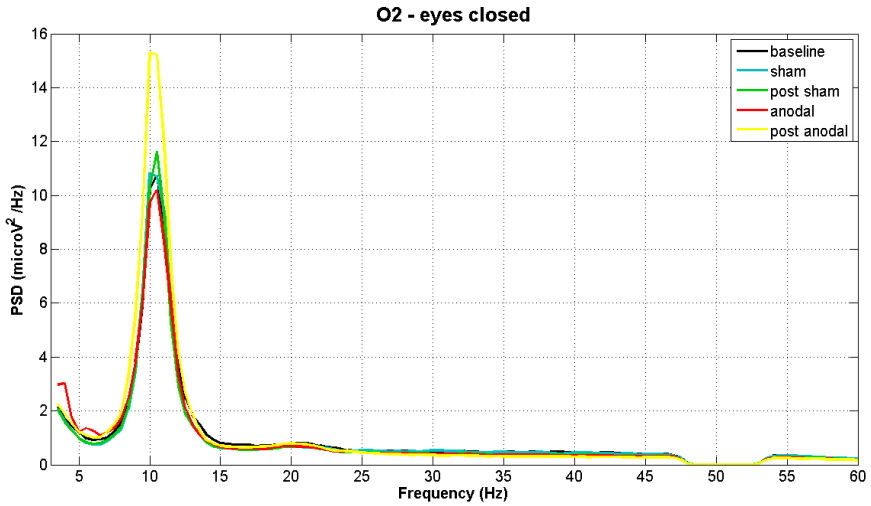

Figure 16: EEG power spectral density of B, SS, PSS, AS, and PAS (EC condition) for electrode O2 (mean of all subjects). The figure shows the increase in alpha band after stimulation**.**

Effects Over Time

As previously described, we examined the effects of tDCS during 15 minutes of stimulation and for additional 12 minutes after the stimulation. In order to monitor the effects of stimulation in detail, the AS and PAS were divided into a certain number of epochs, of two minutes each. In Table 7 and Table 8 we report the electrode-band couples with a significant activation during and after the stimulation, respectively in the EO and EC conditions. In Figure 18 we show the trend of the power in the four analyzed bands for the electrode O1 in the EC condition.

Table 7: Electrode-band couples with a significant activation during and after anodal tDCS. The table reports the activation pattern in the EO condition.

EYES OPEN							
	AS1	**AS2**	**AS3**	**AS4**	**PAS1**	**PAS2**	**PAS3**
Theta	/	Fp2 Fp1 C4 O2 F8 F3 F7 Fz Cz Pz	/	/	/	Fp2 Fp1	Fp2 Fp1
Alpha	/	F4 C4 O2 Pz	C3 P3	/	/	/	/
Beta	/	/	/	/	/	/	/
Gamma	/	/	/	/	/	/	/

Table 8: Electrode-band couples with a significant activation during and after anodal tDCS. The table reports the activation pattern in the EC condition.

EYES CLOSED						
	AS1	**AS2**	**AS3**	**PAS1**	**PAS2**	**PAS3**
Theta	T4 Cz	C4	F4 C4 Fz Pz	T4	Fp2 T4 Fp1 Fz	Fp1 F3 Fz
Alpha	O2 C3 P3 O1 T5 Cz	C4 O2 P3 O1 Cz Pz	C4 O2 C3 P3 O1 Pz	O2 Fp1 F3 C3 P3 O1 T5 Fz Pz	O2 Fp1 F3 C3 P3 O1 T5 Fz Pz	O2 F3 C3 P3 O1 T5 Fz
Beta	O1 P3 Cz	O1 P3 C3 Cz	O1 P3 C3 Pz	O1 P3 C3	O1 P3 C3	C3 P3
Gamma	/	/	/	/	/	/

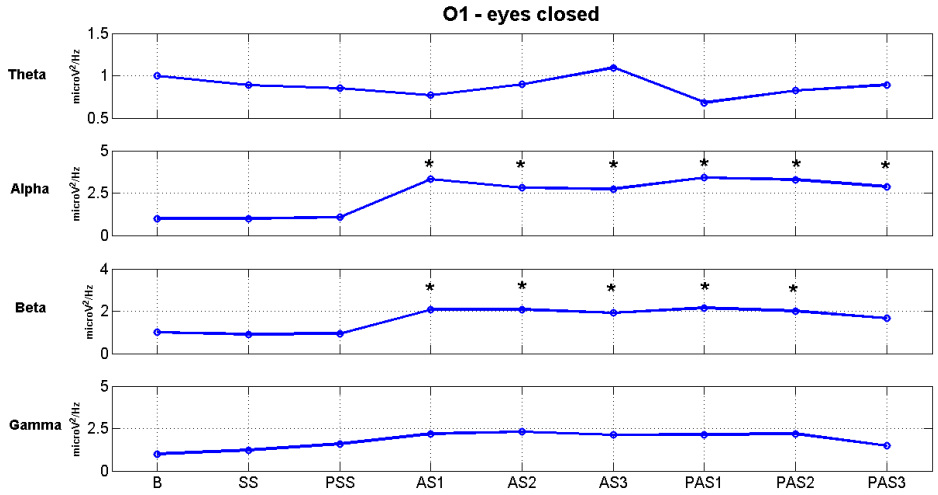

Figure 17: The effectsofstimulationovertimeforelectrodeO1inthe EC condition. Alpha and beta powers increase significantly (*$p < 0.01$) during the first minutes of stimulation and the effects persist for at least 12 min after the end of stimulation in the alpha band and for 6 min in the beta band.

The Tables S6, S7, S8 and S9 (Supplementary file) show the p-value, the F-value and the significance of each couple band-electrode in EO and EC for stimulation-effects and the time-effects respectively.

11.3.2 Side Effects Questionnaire

The results of the Mann-Whitney *U* test showed that none of the eleven considered side effects shows a significant difference between the two conditions of sham and anodal stimulation. Therefore, we can exclude that the effects over the EEG rhythm are due to the physical perception of the stimulation.

11.4 Discussion

11.4.1 Statistical Analysis

Effects of Stimulation

The mechanism underlying the neuromodulatory effects induced by tDCS is a very hot topic and numerous studies are trying to better understand this phenomenon. Several studies, using animal models, have suggested that neurons respond to membrane polarization changes induced by tDCS (Liebetanz et al. 2002), thereby leading to a reduction in spontaneous neuronal firing rates after cathodal tDCS and an opposite effect after anodal stimulation. Accordingly, the first study performed on the motor cortex showed that cathodal polarization induced robust inhibition of motor cortex excitability, whereas anodal polarization increased motor cortex excitability (Nitsche et al. 2000). In the light of these findings, we expected in our

study a decrease of theta and alpha powers associated with cortical deactivation, and an increase of beta and gamma powers associated with cortical activation. On the contrary, the main findings are the increase of theta power during the stimulation and the increase of alpha and beta powers during and after the stimulation in the EC condition. In the EO condition we did not found any effect. This finding can be explained because the tDCS perturbs the equilibrium on both excitatory and inhibitory neurons inducing an increase of the activity in theta band in the first minutes of the stimulation and in alpha and beta bands during and after the stimulation. The increase in alpha band after the anodal stimulation confirms the results of Spitoni et al. (2013).

Effects Over Time

The effect of tDCS over time is a critical issue, because the aftereffect of the stimulation might last minutes to hours, depending on the intensity and the duration of the stimulation. Antal et al. (2010) found that, at equal intensity and duration, the effects of stimulation lasted longer on motor cortex than posterior cortex. We observed significant effects both during and after the stimulation. In particular, in the EO condition the effect is predominant during AS2 in theta and alpha bands, while in the EC condition it is present during the whole stimulation and the whole interval after the stimulation. In particular, theta power had a significant activation in the centro-parietal regions during the stimulation and a propagation in the frontal region after the stimulation. In the EO condition, a significant activation was found mainly in the frontal region. These results are consistent with the spontaneous flow of information between sources of brain activity of the theta band. Indeed, Michels et al. (2013) found that, in resting state condition, there is an information flow involving both parietal and frontal region in EC condition, and only frontal region in the EO condition.

Alpha power increases significantly during and after the stimulation. The effects persist for all the 12 minutes after the stimulation and we did not observe a decline of these effects. Alpha amplitude modulation is not observed only in posterior areas but also in frontal regions. Several studies demonstrated that tDCS increases the coherence of the cerebral rhythm and the interaction between inter and intra cerebral cortexes (Keeser et al. 2011a, Hampstead et al. 2013). Polania et al. (2012) demonstrated that tDCS applied over the primary motor cortex produces modifications in the EEG synchronization and in the functional organization in

healthy subjects. Furthermore, they demonstrated the presence of coherence modification in all frequency bands (theta, alpha, beta and gamma).

We found an increase of beta band during and after the stimulation for three electrodes positioned in the contro-lateral site with respect to the site of stimulation.

We did not found significant effects in the gamma band.

Comparison between the EC and the EO responsiveness to tDCS Stimulation

We found evident differences between the EO and the EC conditions (EOC, ECC) in terms of responsiveness to tDCS, with the EEG power parameters much more sensitive to the tDCS stimulation in the ECC than in the EOC. Several studies investigated the difference of the EEG signal properties between the ECC and the EOC in resting state: in particular, the study of Barry et al. (2007) showed that: i) the signal power in the EOC is lower than in the ECC for the delta, theta, alpha; ii) a reduction of lateral frontal delta, a reduction of posterior theta, a reduction of right-posterior beta, and an increment of the left-frontal beta are present in the EOC compared to the ECC; iii) no significant topographic differences were evident for the power in the alpha band between the two conditions. The results cited above allow us to interpret our results in terms of different processing capability of the brain in the two conditions. In particular, the brain is much more stimulated in the EOC than in the ECC: the lower powers in delta, theta and alpha bands in the EOC reported by Barry et Al. are clearly related to a lower involvement of cortico-thalamic (idling) dynamics, and (possibly) to a higher involvement of intra-cortical (processing) dynamics; the higher value of frontal beta power in the EOC further confirms such interpretation key. Given the premises above, the higher responsiveness to tDCS in the ECC could be interpreted, in general terms, as the consequence of a higher processing capability to the external tDCS stimuli available in the ECC than in the EOC.

Comparing the results of the studies interested in EEG modifications induced by tDCS in resting state conditions, we found that the stimulation of the posterior cortex generates, as its most clear results, modifications of the alpha power (our results and Spitoni et al. 2013). Such result is not surprising since it is well known from the literature that the alpha rhythm is mainly generated in the posterior cortex and that posterior cortexes resonate to external stimulations in the alpha band. (Omata et al. 2013, Sadato et al. 1998, Laufs et al. 2003, Tyvaert et al. 2008). Several other studies showed that stimulating other areas would produce power changes in

different bands, e.g., the stimulation of the prefrontal cortex induced a significant decrease in frontal delta power (Ardolino et al. 2005, Keeser et al. 2011b) and a significant increase in frontal beta power (Keeser et al. 2011b) in resting state condition.

It is evident that the significant effects found are not easy to interpret. Even taking into account the simplest interpretation of EEG rhythms, stating that power in delta, theta and alpha bands are positively correlated with cortical idling and power in beta and gamma bands are positively correlated with cortical processing (Barry et al. 2007, Basar et al. 2001), the effects found need to be further investigated with more complex interpretative tools. Future investigations on the results of combined tDCS–EEG experiments could benefit from the interpretative power of neural mass models. Neural mass models have been so far successfully used in order to interpret EEG power modifications as dynamic modifications of functional connectivity of cortical networks during sleep rhythms (Cona et al., 2014), due to cognitive and motor tasks (Cona et al. 2009), and, intriguingly, due to dynamic perturbation of brain networks with TMS (Transcranic Magnetic Stimulation) (Cona et al. 2011), the latter being a companion technology of tDCS.

11.5 Conclusions

In this study, we investigated the ongoing and aftereffects of anodal tDCS applied over postero-parietal cortex, in a resting brain. We compared the power spectral parameters obtained from a sham condition (during and post) and a real condition (during and post) of stimulation. We found that the main effect regards the theta, alpha and beta bands. This effect begins with the start of the stimulation and lasts at least for 12 minutes after the end of the stimulation. We confirmed the results of the study by Spitoni, the only one that studied the effects of tDCS over parietal cortex in resting state, and, in addition, we investigated the effects during the stimulation. Possible future developments, aimed to reach a wider interpretation of the results found, were suggested.

Chapter 12

Case of study

Transcranial direct current stimulation and Steady state visual evoked potential

12.1 Introduction

The aim of this study was to evaluate if tDCS-elicited visual cortical excitability shifts are accompanied by a similar change of oscillatory activity. In particular, they are interested in the effects of tDCS on the SSVEP.

The first aim of the study was to realize a system able to generate and to record the SSVEP; the second one was to study this potential before and after the electrical simulation.

The study of the effects of the tDCS on the SSVEP allows:

- to understand better the neuro-physiological mechanism and its modification due to the stimulation
- to search the best stimulation parameters to obtain SSVEPs as much as possible discriminable and to improve the performance of a BCI system SSVEP-based.

12.2 Methods

12.2.1 Subjects

Six healthy subjects took part in the study (age between 21 and 51; 4 men).

12.2.2 Visual Stimuli

The experiment consists in the visualization of three squares (three red squares or three yellow squares) in a black screen. The three squares flicker simultaneously at three different frequencies: 12 Hz, 15 Hz and 20 Hz. The software allows to configure the following parameters:

- Target indication: Time (in seconds) between the appearance of the arrow marking the square to stimulate and the beginning of the flickering:1
- Visual Stimulation: Duration (in seconds) of the stimulation period: 7
- Rest: Duration (in seconds) of the break period:4

We defined trial the repetition of 15 sequences (5 repetition x 3 frequencies) of these three operations. In each session, one trial was repeated 4 times alternating the colour of the visual stimuli (Red-Yellow-RedYellow).

12.2.3 tDCS

A direct of 1.5 mA (during the stimulation the impedance value was maintained in a range of 4-6 kOhm), induced through two saline-soaked surface sponge electrodes (7 x 4.5 cm), was delivered using a battery driven, constant-current stimulator (neuroConn GmbH, Ehrenbergstr, Ilmenau, Germany)., we used an extra-cephalic reference electrode for tDCS to avoid confounding biases that could have arisen from two electrodes with opposite polarities over the scalp. The active electrode, the anode, was placed over the occipital cortex and the reference electrode, the cathode, was placed over the ipsilateral deltoid muscle. The location of the active electrode was determined according to the 10-20 EEG standard montage, placing the electrode over Oz, as suggested in previous studies (Antal et al 2004, Accornero et al. 2007). In the stimulation session, the current was ramped up from 0 to 1.5 mA in 30 s. Fifteen minutes after onset, the current was ramped down back to 0 in 30 s. Sham stimulation was used to control in the experiment, in order to isolate the effects solely due to the current stimulation and not due to the placebo and somatosensory effects that could arise from tDCS application. During the sham condition the electrodes were located in the same position as they were in the anodal stimulation, but the current was supplied only for the first 43 s (8 s ramp up, 30 s of DC

stimulation and 5 s ramp down). This procedure ensured that the subjects felt the tingling sensation at the beginning of the stimulation.

12.2.4 SSVEP recording

Electroencephalography was recorded from 2 bipolar channels (O1-PO7 and O2-PO8) positioned according to the international 10–20 layout using a Neurowave System (Khymeia, Italy). EEG signals were sampled at 128 samples/s.

PROTOCOL

The protocol consists of the following sessions (Figure 19):

1. SSVEP recording (4 trail repetition) baseline
2. Sham stimulation
3. SSVEP recording (4 trail repetition) post Sham
4. Anodal stimulation
5. SSVEP recording (4 trail repetition) post Anodal

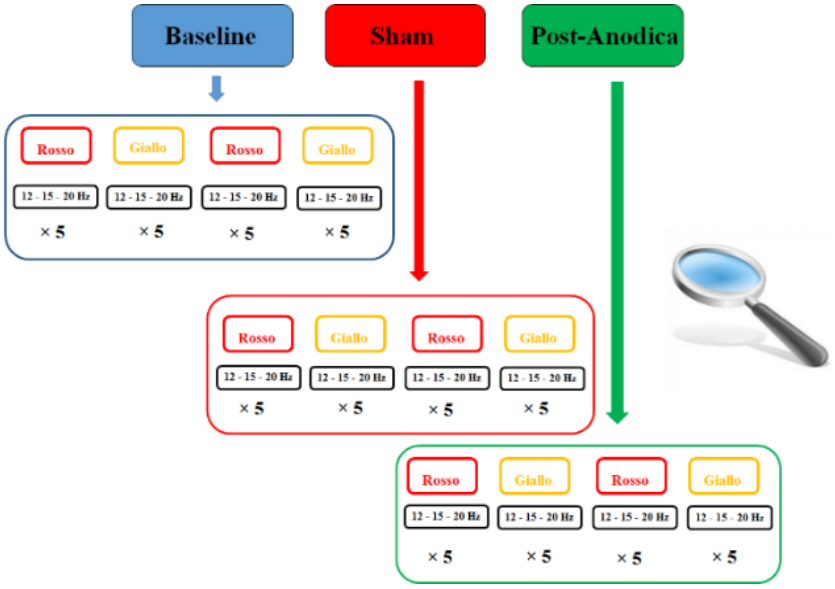

Figure 19: Experimental Protocol

12.2.5 Signal Processing

EEG signals were preliminary band-pass filtered between 3 and 60 Hz. An additional stop-band filter at 50 Hz was applied. The signal epochs corresponding to the effective 7 seconds of stimulation were extracted. At least, the signal was divided into 4 classes:

- stimulation at 12 Hz
- stimulation at 15 Hz
- stimulation at 20 Hz
- rest

For each class (12 Hz-15Hz-20Hz-rest), each color (red-yellow) and each session (baseline-sham-anodal), there are 10 EEG segments. The segments belonging from the three stimulation classes was 7-s long, the segments belonging from the rest class was 4-s long.

Power spectral density (PSD) was estimated for each 7-s or 4-s segment through a modified periodogram method based on FFT-algorithm and Blackman Harris window.

In order to compare the results of all the subjects, for each subject, all the stimulation PSD were normalized compared to the Rest PSD of the own baseline session.

The powers in the range of the interesting frequency, the frequency of stimulation, were extracted. In particular, the powers were extracted in the ranges 12Hz, 15 Hz and 20 Hz ± 0,5714. These powers are the features that we will use in the statistical analysis.

12.2.7 Statistical Analysis

The powers in the range of the frequency of interest will be used in the statistical analysis. Three effects will be studied: stimulation effect, frequency effect and color effect.

Stimulation Effects

A one-way ANOVA analysis on three levels (Baseline, Sham and Anodal) was performed for each frequency and for each color, using the data of all subjects. This analysis allowed us to test the hypothesis stating that there is a significant effect due to the stimulation conditions, against the general alternative where there is no significant effect. Since we were also interested in which pairs of conditions were significantly different, multiple comparison post-hoc tests were also conducted, in cases where the ANOVA found a significant effect. We choose a significance level p=0.05 %.

Frequency Effects

A one-way ANOVA analysis on three levels (12 Hz, 15 Hz and 20 Hz) was performed for each color and for each stimulation condition, using the data of all subjects. This analysis allowed us to test the hypothesis stating that there is a significant effect due to the frequency, against the general alternative where there is no significant effect. Since we were also interested in which pairs of conditions were significantly different, multiple comparison post-hoc tests were also conducted, in

cases where the ANOVA found a significant effect. We choose a significance level p=0.05 %.

Color Effects

A one-way ANOVA analysis on two levels (red and yellow) was performed for each frequency and for each stimulation condition, using the data of all subjects. This analysis allowed us to test the hypothesis stating that there is a significant effect due to the color, against the general alternative that there is no significant effect.

12.3 Results

12.3.1 Explorative Analysis

The explorative analysis of the frequency-domain signal shows the presence of the peak corresponding to the stimulation frequency (i.e. 15 Hz in the example of Figure 20). The second and third harmonics (30 Hz and 45 Hz) are also visible in the figure.

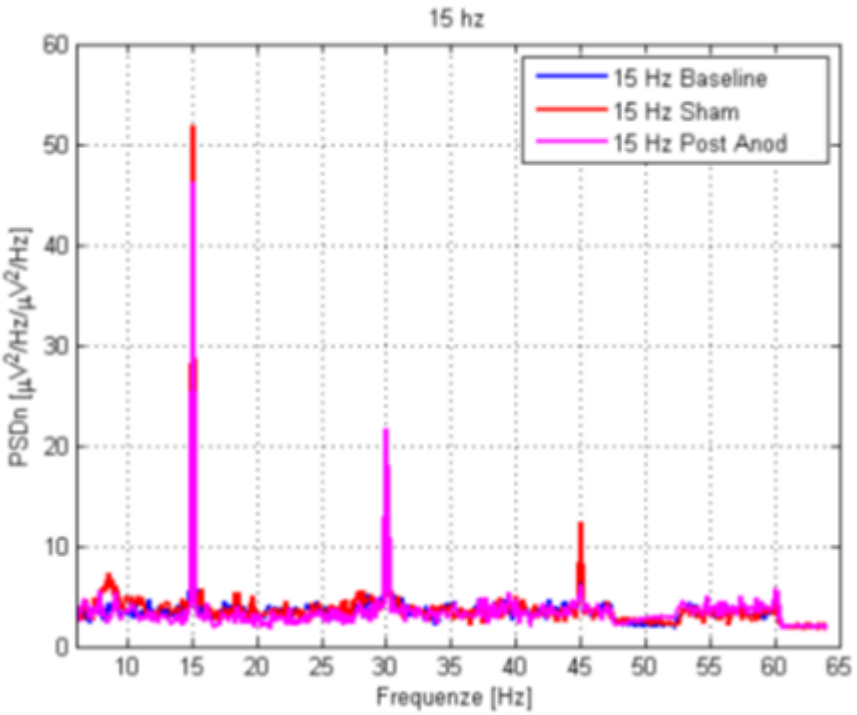

Figure 20: Example of the PSD in the three condition, Baseline, Sham and Anodal stimulation (15 Hz stimulation).

12.3.2 Statistical Analysis

Stimulation Effects

We analyzed the significance of each frequency and each color for the different stimulation conditions as detailed in the "Materials and Methods" (see Table 9).

We found the following results:

- Hz-red: no significance was found;

- 15 Hz-red: no significance was found between the two baseline conditions and sham, significant difference was found between baseline and anodal and baseline and sham. In power decreased in anodal condition.
- 20 Hz –red: no significance was found between baseline and sham condition and sham and anodal condition. The anodal condition was significantly different from the baseline condition. In power decreased in anodal condition.
- Hz-yellow: no significance was found between the two baseline conditions and sham, significant difference was found between baseline and anodal and baseline and sham. In power decreased in anodal condition. In power decreased in anodal condition.
- Hz-yellow: no significance was found between the two baseline conditions and sham, significant difference was found between baseline and anodal and baseline and sham. In power decreased in anodal condition. In power decreased in anodal condition.
- 20 Hz-yellow: no significance was found between the two baseline conditions and sham, significant difference was found between baseline and anodal and baseline and sham. In power decreased in anodal condition. In power decreased in anodal condition.

Table 9: Statistical Analysis results; Stimulation Effects.

Color	**Frequancy**		
	12 Hz	15 Hz	20 Hz
Red	/	Post Anodal * (<)	/
Yellow	Post Anodal * (<)	Post Anodal * (<)	Post Anodal * (<)

Frequency Effects

No significant difference was found with respect the effect frequency.

Color Effects

A significant different was found according to the color condition. In particular, the power corresponding to the yellow stimulation was greater than the red stimulation.

12.4 Discussion and Conclusion

The aims of this work were to realize a system able to generate and record the SSVEP, and to study this potential before and after the tDCS.

From the explorative analysis results that the SSVEP were well generated and recorded.

From the statistical analysis emerge that the tDCS induces changes in the oscillatory activity. The analysis shows that there is no difference between the sham condition and the baseline condition, instead a significant difference was found between the two baseline conditions and anodal and baseline and sham. It is possible to conclude that the anodal stimulation induces a decreasing of the power associated to the SSVEP. This result is in contrast with the results of Antal et al. 2004. They found a decrease statistically significant of the VEP after the cathodal stimulation and an increase statistically not significant o the VEP after the anodal stimulation. This difference could be explained with the different montage used in our study and antal study. Infact, he used a bipolar montage whit the two electrodes of stimulation positioned in Oz and Cz, than the provenience of the effects is not well defined. On the contrary, our results confim the results obtained by Accornero et al. (2007). They assessed VEP-P100 latencies and amplitudes in response to pattern-reversal checkerboard stimuli before, during, and after polarization. Anodal polarization reduced VEP-P100 amplitude whereas cathodal polarization significantly increased amplitude.

The results related to the color effect confirm the results of Duszyk et al. (2014). They found a significantly stronger SSVEP response during yellow visual stimulation than red stimulation.

There is growing evidence that tDCS allows the manipulation of cortical network activity in the human and can cause perceptual changes. This work shows that tDCS can change SSVEP response.

We need further studies to study the effects of cathodal stimulation and to study if the performance of a BCI system SSVEP-based can change during or after tDCS.

Conclusions

The presented thesis regards the study and the development of new assessment and rehabilitation techniques of subject with TBI.

At the beginning of the Ph.D. course, the hypothesized ensemble of aims to be pursued mainly involved the development of smart system able to integrate many quantitative informations, becoming from EEG signal and computerized neuropsychological tests, and able to make a complete diagnosis of a patients with TBI and to plan a rehabilitation process.

These goals were achieved partially because the carried out activity allowed to study and to develop separately methods and devices for assessment and rehabilitation purpose but not to integrate these systems.

The main achieved results are about:

- the study and the development of a system for the communication with patients with disorders of consciousness. It was possible to identify a paradigm of reliable activation during two imagery task using EEG signal or EEG and NIRS signal.
- the study of the effects of a neuromodulation technique (tDCS) on EEG pattern. This topic is of great importance and interest. The emerged founding showed that the tDCS can manipulate the cortical network activity and through the research of optimal stimulation parameters, it is possible move the working point of a neural network and bring it in a condition of maximum learning. In this way could be possible improved the performance of a BCI system or to improve the efficacy of a rehabilitation treatment, like neurofeedback.

Next steps along the present research pathway will be taken in order to continue investigating the spectral reactivity to tDCS stimulation (by extending the preliminary group of subjects involved up to now), and to develop and design (in collaboration with clinical centers) experimental setups and protocols aimed to investigate the effects of tDCS on patients EEG, in resting state and during cognitive tasks (i.e. imagery task for BCI application, neurofeedback, ets.).

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Supplemetary file

Table S1: Electrodes with significant level of ANOVA ($p<0.05$) in at least one band for each subject and each session.

	Session 1	**Session 2**
Subject 1	F4 – C4 – O2 – F8 – T4 – T6 - C3 – O1 – T3 – Cz – Pz – Fc2 – Fc6 – Cp1 - Cp2 - Cp6 – PO4	F4 – C4 – P4 – O2 – T4 – T6 – Fp1 – F3 – C3 - P3 – O1 – F7- T3 – T5 – Fz – Cz – Pz – AF3 – AF4 – Fc5 – Fc1 – Fc2 – Fc6 – Cp5 – Cp1 – Cp2 – Cp6 – PO3 – PO4
Subject 2	Fp2 – C4 – P4 – O2 – F8 – T4 – T6 – Fp1 – C3 – P3 – O1 – F7 – T5 – Fz – Cz – Pz – AF3 – AF4 – Fc1 – Fc2 – Fc6 - Cp5 – Cp1 – Cp2 – Cp6 – PO3 – PO4	C4 – O2 – T4 – T6 – Fp1 –F3 – C3 – P3 - F7- T3 – Fz – AF3 – Fc5 – Fc1 –Fc6 – Cp6 – PO4
Subject 3	Fp2 – F4 – C4 – O2 – F – T4 – Fp1 F3 – C3 – O1 – F7 – T3 – AF3 – AF4 – Fc5 – Fc1 – Fc6 –Cp1 – PO3 – PO4	Fp2 - C4 – P4 – O2 – F8 – T4 – Fp1 –F3 – C3 – O1 - F7- T3 – T5 – Fz – Cz – Pz – AF3 – AF4 – Fc5 – Fc1 – Fc2 – Fc6 – Cp5 – Cp1 – Cp2 – Cp6 – PO4
Subject 4	Fp2 – F4 – C4 - O2 – F8 – T4 – T6 – Fp1 – F3 – C3 - P3 – O1 – F7- T3 – T5 – Fz – Cz – Pz – AF3 – AF4 – Fc5 – Fc1 – Fc2 – Fc6 – Cp5 – Cp1 – PO3 – PO4	C4 – P4 –O2 – F8 - T4 – T6 – Fp1 - C3 - P3 – O1 – F7 - T3 – T5 - Pz – AF3 – Fc5 – Cp5 - Cp1 – Cp2 – Cp6 – PO3 – PO4
Subject 5	Fp2 – C4 – P4 – Fp1 – C3 – P3 – O1 – T3 – T5 – Cz – Pz – AF3 - Cp5 - Cp1 – Cp2 – Cp6 – PO3 – PO4	Fp2 – F4 – C4 – P4 - O2 – F8 – T4 - C3 - P3 – O1 – T5 – Cz – Pz – AF4 - Fc2 – Fc6 – Cp5 – Cp1 – Cp6 – PO3 – PO4

Table S2: The Table shows the results of ANOVA analysis performed for each patient (P) and each BE-band (C4 O2 T4 C3 O1 Fc6 Cp1 PO4 – Theta Alpha Beta Gamma) combination of the pre-Communication Trial ($p<0.05$). The ANOVA analysis allowed to find the BE-band couples with a significantly different activation during the two imagery tasks, then during the two answers "yes" (y) and "no" (n). The table reports also if the power increases or decreases depending on the answers. It is possible to observe that Theta, Alpha and Gamma bands contribute likewise in the discrimination of the two answers. The Table shows also that "yes" answer, that corresponds to the hand movement imagery, increases the power in the low frequency bands, while "no" answer, that corresponds to the foot movement imagery, increases the power in the high frequency bands.

p<0.05(*)	C4	O2	T4	C3	O1	Fc6	Cp1	PO4
Theta	**P3 (y>n)** **P4 (y>n)** **P5 (y>n)**	**P4 (y>n)**	**P3 (y>n)** **P4 (y>n)** **P5 (y>n)**	**P5 (y>n)**	**P5 (y>n)**	**P3 (y>n)** **P4 (y>n)** **P5 (y>n)**		**P3 (y>n)** **P4 (y>n)**
Alpha	**P1 (n>y)** **P4 (y>n)**	**P2 (n>y)** **P4 (y>n)**	**P1 (n>y)** **P3 (n>y)** **P4 (y>n)**	**P4 (y>n)**		**P1 (n>y)** **P4 (y>n)**	**P4 (y>n)**	**P2 (n>y)** **P4 (y>n)**
Beta			**P1 (n>y)**	**P2 (y>n)**	**P5 (n>y)**		**P2 (y>n)**	**P3 (n>y)**
Gamma	**P1 (n>y)** **P2 (n>y)** **P5 (n>y)**	**P1 (n>y)** **P2 (n>y)**	**P1 (n>y)** **P3 (n>y)**	**P1 (n>y)** **P2 (n>y)** **P5 (n>y)**	**P1 (n>y)** **P2 (n>y)**	**P1 (n>y)** **P3 (n>y)**	**P1 (n>y)** **P2 (n>y)** **P5 (n>y)**	**P1 (n>y)** **P2 (n>y)**

Table S3: Best classification accuracy obtained for each subject, each patient, each session and each cardinality for the Imagery Trial.

IMAGERY TRIAL (classification accuracy %)									
Subjects	**Sessions**	**Electrodes**							
		one	**two**	**three**	**four**	**five**	**six**	**seven**	**eight**
Subject 1	Session 1	69.2	79.2	82.5	84.2	**84.9**	82.5	82.5	83.4
	Session 2	66.7	74.2	80	79.2	**82.4**	80.9	79.2	75
Subject 2	Session 1	75.9	78.4	84.2	85	**85.8**	83.4	83.4	79.2
	Session 2	66.7	75.9	76.7	81.7	**84.9**	83.4	81.7	73.4
Subject 3	Session 1	66.7	72.5	77.5	**84.2**	84.1	83.4	83.4	80.9
	Session 2	66.7	70.9	74.2	77.5	81.6	80	**82.5**	78.4
Subject 4	Session 1	70	82.5	83.4	84.2	**87.4**	84.2	84.2	82.5
	Session 2	71.7	78.4	79.2	**81.7**	79.9	79.2	76.7	75.9
Subject 5	Session 1	59.2	63.4	65.9	69.2	**70.6**	67.5	69.2	66.7
	Session 2	59.2	65.9	67.5	72.5	**75.7**	73.5	73.4	72.5
Mean±SD		67.2±5.1	74.1±6.0	77.1±6.3	79.2±5.4	**81.7±5.1**	79.8±5.3	79.6±5.0	76.8±5.1
Patient 1	Session 1	75	84.2	84.2	85.9	89.2	89.2	**90**	**90**
Patient 2	Session 1	70	81.7	87.5	**89.2**	88.4	**89.2**	88.4	**89.2**
Patient 3	Session 1	55.9	69.2	66.7	68.4	**71.7**	70.9	68.4	69.2
Patient 4	Session 1	60.9	65	70.9	77.5	**78.4**	**78.4**	77.5	75
Patient 5	Session 1	55	80	85	88.4	88.4	90	**93.4**	88.4
Mean±SD		63.4±8.8	76.1±8.4	78.9±9.3	81.9±8.8	83.3±7.8	**83.6±8.5**	**83.6±10.3**	82.4± 9.6

Table S4: Best classification accuracy obtained for each subject, each patient, each session and each cardinality for the pre-Communication Trial.

PRE-COMMUNICATION TRIAL (classification accuracy %)									
Subjects	**Sessions**	**Electrodes**							
		one	**two**	**three**	**four**	**five**	**six**	**seven**	**eight**
Subject 1	Session 1	83.4	**97.7**	93.4	86.7	83.4	76.7	73.4	66.7
	Session 2	**93.4**	83.4	86.7	86.7	86.7	83.4	83.4	76.7
Subject 2	Session 1	56.7	**70**	**70**	66.7	43.3	63.4	46.7	60
	Session 2	56.7	**80**	76.7	60	76.7	60	43.4	60
Subject 3	Session 1	50	**76.7**	73.4	70	66.7	66.7	66.7	66.7
	Session 2	**90**	76.7	73.4	70	63.4	46.7	53.4	60
Subject 4	Session 1	**60**	56.7	**60**	53.4	50	50	**60**	**60**
	Session 2	53.4	50	43.4	46.7	73.4	**76.7**	**76.7**	73.4
Subject5	Session 1	73.4	**86.7**	83.4	73.4	73.4	76.7	83.4	83.4
	Session 2	46.6	60	50	50	50	63.4	**76.7**	**76.7**
Mean±SD		66.4±17.2	**73.7±14.5**	71.1±15.8	66.4±14	68.1±12.9	66.4±12.1	65.4±16	68.3±8.6
Patient 1	Session 1	66.7	66.7	66.7	66.7	75	75	**83.4**	**83.4**
Patient 2	Session 1	50	58.4	50	66.7	58.4	**83.4**	**83.4**	58.4
Patient 3	Session 1	50	**91.7**	**91.7**	66.7	66.7	58.4	58.4	58.4
Patient 4	Session 1	66.7	**100**	66.7	66.7	66.7	58.4	58.4	58.4
Patient 5	Session 1	**100**	83.4	58.4	58.4	50	66.7	66.7	75
Mean±SD		66.7±20.4	**80.1±17.2**	66.7±15.6	65.1±3.7	63.4±9.5	68.4±10.8	70.1±12.6	66.8±11.7

Table S5*:* Electrode configurations maximizing classification accuracy for each subject, each patient, each session and each trial**.**

Subject	**Session**	**Electrodes**	
		IMAGERY TRIAL	**PRE-COMMUNICATION TRIAL**
Subject 1	Session 1	O2, T4, O1, Fc6, PO4	T4, O1
	Session 2	C4, T4, C3, O1, Fc6, Cp1	O1
Subject 2	Session 1	C4, O2, C3, Cp1, PO4	C4, O1 C4, O1, Fc6
	Session 2	C4, O2, C3, O1, PO4	C4, Fc6
Subject 3	Session 1	O2, T4, O1, Fc6	O2, PO4
	Session 2	C4, O2, T4, C3, Fc6, Cp1, PO4	C4
Subject 4	Session 1	C4, T4, O1, Fc6, Cp1	O1 C4, O1, PO4 C4, O2, T4, C3, O1, Cp1, PO4 C4, O2, T4, C3, O1, Fc6, Cp1, PO4
	Session 2	C4, O2, O1, Fc6	C4, O2, C3, Fc6, Cp1, PO4 C4, O2, T4, C3, Fc6, Cp1, PO4
Subject 5	Session 1	C4, T4, O1, Fc6, PO4	C4, Cp1
	Session 2	C4, O2, C3, O1, Fc6	C4, O2, T4, C3, Fc6, Cp1, PO4 C4, O2, T4, C3, O1, Fc6, Cp1, PO4
Patient 1	Session 1	C4, T4, C3, O1, Fc6, Cp1, PO4 C4, O2, T4, C3, O1, Fc6, Cp1, PO4	C4, O2, T4, O1, Fc6, Cp1, PO4 C4, O2, T4, C3, O1, Fc6, Cp1, PO4
Patient 2	Session 1	O2, T4, Fc6, Cp1 C4, O2, T4, C3, Cp1, PO4 C4, O2, T4, C3, O1, Fc6, Cp1, PO4	C4, O2, T4, C3, O1, Fc6 C4, O2, T4, C3, O1, Fc6, PO4
Patient 3	Session 1	T4, O1, Fc6, Cp1, PO4	O1, Cp1 C3, O1, Cp1
Patient 4	Session 1	T4, O1, Fc6, Cp1, PO4 O2, T4, O1, Fc6, Cp1, PO4	O2, PO4
Patient 5	Session 1	C4, O2, T4, C3, Fc6, Cp1, PO4	C4

Table S6: The table shows the p-value, the F-value and the significance of each couple band-electrode in EO condition in the comparison between B, SS, PSS, AS and PAS1 (stimulation-effects). The significance (s) is reported in three conditiosn: (*) indicates the significance without Bonferroni correction ($p<0.01$), (**) indicates the significance after the Bonferroni correction ($p<0.01/20$), (***) indicate the significance, after the Bonferroni correction, of the AS and PAS condition with respect the B, SS and PSS ($p<0.01/20$).

EYES OPEN												
	theta			alpha			beta			gamma		
	p-value	F-value	sign	p-value	F-value	sign	p-value	F-value	sign	p-value	F-value	sign
Fp2	0,00000	9,91648	(**)	0,06547	2,23549		0,20967	1,47599		0,01011	3,38170	
F4	0,49692	0,84623		0,49743	0,84540		0,29622	1,23512		0,32997	1,15743	
C4	0,47077	0,88926		0,41338	0,98999		0,39195	1,03028		0,31262	1,19649	
O2	0,36931	1,07473		0,22725	1,42076		0,11593	1,86989		0,07149	2,17992	
F8	0,46539	0,89833		0,15974	1,65920		0,00133	4,58968	(*)	0,01458	3,16095	
T4	0,05183	2,38228		0,00001	7,57855	(**)	0,00404	3,93071	(*)	0,70567	0,54110	
T6	0,65399	0,61247		0,57252	0,72942		0,54438	0,77175		0,00013	5,95445	(**)
Fp1	0,00000	10,59812	(**)	0,01190	3,28382		0,03912	2,55724		0,00231	4,26260	(*)
F3	0,90956	0,24993		0,10577	1,92934		0,18059	1,57711		0,24802	1,36022	
C3	0,07695	2,13322		0,00019	5,74426	(**)	0,00195	4,36276	(*)	0,15093	1,69685	
P3	0,00718	3,58712		0,00000	8,28532	(**)	0,00385	3,95915	(*)	0,01824	3,02507	
O1	0,00186	4,39057		0,00028	5,49984	(**)	0,00171	4,44294	(*)	0,00235	4,25310	(*)
F7	0,72168	0,51922		0,19875	1,51239		0,04132	2,52337		0,12265	1,83319	
T3	0,00058	5,08478		0,07316	2,16528		0,00741	3,56888	(*)	0,13449	1,77290	
T5	0,00031	5,44081	(**)	0,00046	5,21460	(**)	0,00577	3,71806	(*)	0,08864	2,04300	
Fz	0,15287	1,68840		0,07816	2,12327		0,15069	1,69791		0,01141	3,30910	
Cz	0,11430	1,87912		0,00932	3,43073	(*)	0,11629	1,86791		0,07366	2,16098	
Pz	0,08403	2,07717		0,00012	6,02821	(**)	0,00001	7,24642	(**)	0,00028	5,50814	(**)

Table S7: The table shows the p-value, the F-value and the significance of each couple band-electrode in EC condition in the comparison between B, SS, PSS, AS and PAS1 (stimulation-effects). The significance (s) is reported in three conditiosn: (*) indicates the significance without Bonferroni correction ($p<0.01$), (**) indicates the significance after the Bonferroni correction ($p<0.01/20$), (***) indicate the significance, after the Bonferroni correction, of the AS and PAS condition with respect the B, SS and PSS ($p<0.01/20$).

EYES CLOSE												
	theta			alpha			beta			gamma		
	p-value	F-value	s	p-value	F-value	sign	p-value	F-value	sign	p-value	F-value	s
Fp2	0,00003	6,87943	(**)	0,00003	6,83202	(***)	0,59849	0,69150		0,47445	0,88351	
F4	0,00007	5,03744	(***)	0,01315	3,23384		0,00823	3,51769	(*)	0,00022	5,69386	(**)
C4	0,00000	13,66868	(***)	0,00000	9,77080	(***)	0,00000	10,23386	(**)	0,00002	7,22553	(**)
O2	0,00400	3,95220	(***)	0,00000	27,65414	(***)	0,00000	12,29829	(**)	0,00513	3,80309	
F8	0,26820	1,30674		0,00000	11,81246	(***)	0,00001	7,43366	(**)	0,35595	1,10276	
T4	0,00000	27,06526	(***)	0,00000	15,29106	(***)	0,00493	3,82670	(*)	0,77630	0,44457	
T6	0,00009	6,22067	(***)	0,00003	6,20693	(***)	0,00090	4,84810	(*)	0,00312	4,10123	
Fp1	0,00000	10,13106	(**)	0,00000	9,84762	(***)	0,50029	0,84113		0,59534	0,69609	
F3	0,00001	7,45191	(**)	0,00000	14,41640	(***)	0,00001	7,38426		0,31154	1,19996	
C3	0,01735	3,06451		0,00000	23,50859	(***)	0,00000	18,68782	(***)	0,31329	1,19593	
P3	0,50498	0,83359		0,00000	38,97035	(***)	0,00000	26,02585	(***)	0,35938	1,09567	
O1	0,17278	1,60887		0,00000	29,18315	(***)	0,00000	18,95819	(***)	0,00125	4,64681	
F7	0,40799	1,00057		0,02781	2,77501		0,16136	1,65470		0,30924	1,20530	
T3	0,00034	5,42699	(**)	0,26539	1,31416		0,00043	5,27972	(***)	0,01482	3,16084	
T5	0,15177	1,69555		0,00000	18,15574	(***)	0,00000	13,36395	(***)	0,08062	2,10750	
Fz	0,00000	14,30752	(**)	0,00000	21,15472	(***)	0,00007	6,39110	(***)	0,50943	0,82649	
Cz	0,00003	6,82041	(***)	0,00000	10,93108	(***)	0,00000	10,48662	(***)	0,00246	4,24379	
Pz	0,00035	5,41567	(***)	0,00000	17,24579	(***)	0,00000	8,96042	(***)	0,00186	4,41008	

Table S8: The table shows the p-value, the F-value and the significance of each couple band-electrode in EO condition in the comparison between B, SS, PSS, AS1, AS2, AS3, AS4, PAS1, PAS2 and PA3 (time-effects). The significance (s) is reported in three conditiosn: (*) indicates the significance without Bonferroni correction ($p<0.01$), (**) indicates the significance after the Bonferroni correction ($p<0.01/40$), (***) indicate the significance, after the Bonferroni correction, of the AS and PAS condition with respect the B, SS and PSS ($p<0.01/40$).

EYES OPEN												
	theta			alpha			beta			gamma		
	p-value	F-value	s	p-value	F-value	s	p-value	F-value	s	p-value	F-value	s
Fp2	0,00000	13,48195	(***)	0,12543	1,56595		0,57698	0,84312		0,06257	1,83256	
F4	0,04720	1,93586		0,00006	5,85947	(***)	0,04782	1,93114		0,04687	1,93839	
C4	0,00004	4,97342	(***)	0,00004	4,95482	(***)	0,04814	1,92865		0,04973	1,91691	
O2	0,00005	4,91615	(***)	0,00005	6,89704	(***)	0,06398	1,82432		0,07185	1,78100	
F8	0,00000	7,51130	(***)	0,06191	1,83648		0,02900	2,10952		0,18027	1,41766	
T4	0,00565	2,66329	(*)	0,00042	3,49031	(*)	0,00398	2,77786	(*)	0,02142	2,21505	
T6	0,17366	1,43332		0,08192	1,73150		0,09437	1,67741		0,00339	2,83001	(*)
Fp1	0,00000	15,03025	(***)	0,03714	2,02203		0,24799	1,27941		0,03455	2,04775	
F3	0,00000	5,19098	(***)	0,27635	1,23028		0,52939	0,89590		0,57824	0,84174	
C3	0,00041	3,49846	(*)	0,00024	3,66250	(***)	0,02294	2,19134		0,50776	0,92041	
P3	0,00003	4,30247	(*)	0,00000	5,31510	(***)	0,03621	2,03107		0,14040	1,52070	
O1	0,00010	3,92985	(**)	0,00074	3,31479	(*)	0,01095	2,44353		0,02586	2,14971	
F7	0,00001	4,68154	(***)	0,56226	0,85930		0,30173	1,18942		0,49930	0,93012	
T3	0,00056	3,40535	(*)	0,23141	1,31017		0,04512	1,95212		0,17465	1,43094	
T5	0,00003	4,35848	(**)	0,00055	3,40845	(*)	0,04797	1,92994		0,18777	1,40044	
Fz	0,00000	7,56427	(***)	0,15531	1,47957		0,52196	0,90427		0,11537	1,59911	
Cz	0,00004	4,18541	(***)	0,02884	2,11146		0,37477	1,08394		0,33442	1,14028	
Pz	0,00003	4,32360	(***)	0,00000	5,78812	(***)	0,00000	4,89278	(**)	0,00060	3,37961	(*)

Table S9: The table shows the p-value, the F-value and the significance of each couple band-electrode in EC condition in the comparison between B, SS, PSS, AS1, AS2, AS3, AS4, PAS1, PAS2 and PAS3 (time-effects). The significance (s) is reported in three conditions: (*) indicates the significance without Bonferroni correction (p<0.01), (**) indicates the significance after the Bonferroni correction (p<0.01/36), (**) indicate the significance, after the Bonferroni correction, of the AS and PAS condition with respect the B, SS and PSS (p<0.01/36).

EYES CLOSE												
	theta			alpha			beta			gamma		
	p-value	F-value	sign	p-value	F-value	sign	p-value	F-value	sign	p-value	F-value	sign
Fp2	0,00017	4,02145	(***)	0,00070	3,53366	(*)	0,74541	0,63794		0,78021	0,59667	
F4	0,00003	4,03875	(***)	0,12223	1,61191		0,06726	1,86008		0,00459	2,87190	(*)
C4	0,00000	8,70197	(***)	0,00001	5,09023	(***)	0,00000	6,13439	(**)	0,00002	4,76163	(**)
O2	0,00469	2,86389	(*)	0,00000	14,15470	(***)	0,00000	6,33374	(**)	0,04323	2,03594	
F8	0,43362	1,00414		0,00000	5,86189	(**)	0,00015	4,07554	(**)	0,37155	1,08907	
T4	0,00000	13,51774	(***)	0,00000	7,60158	(**)	0,00114	3,36601	(*)	0,02506	2,24630	
T6	0,00120	3,34641	(*)	0,51521	0,90236		0,00695	2,72185	(*)	0,02054	2,32152	
Fp1	0,00000	5,57060	(***)	0,00001	4,97888	(***)	0,67057	0,72363		0,78040	0,59644	
F3	0,00001	5,23098	(***)	0,00000	7,25957	(***)	0,00014	4,08870	(**)	0,51608	0,90131	
C3	0,00294	3,03057	(*)	0,00000	11,80555	(***)	0,00000	9,68550	(***)	0,56631	0,84226	
P3	0,09267	1,72873		0,00000	19,69973	(***)	0,00000	13,29208	(***)	0,61844	0,78261	
O1	0,09207	1,73145		0,00000	14,81725	(***)	0,00000	9,78090	(***)	0,01060	2,56754	
F7	0,20910	1,37327		0,17228	1,46157		0,28883	1,21858		0,44058	0,99508	
T3	0,00052	3,64162	(*)	0,66536	0,72952		0,00136	3,30217	(*)	0,01768	2,37775	
T5	0,08900	1,74553		0,00000	9,17247	(***)	0,00000	6,98598	(**)	0,30541	1,19066	
Fz	0,00000	9,28820	(***)	0,00000	10,51237	(***)	0,00056	3,61232	(*)	0,75177	0,63050	
Cz	0,00009	4,44606	(***)	0,00000	5,66459	(***)	0,00000	5,50613	(***)	0,02023	2,32719	
Pz	0,00000	6,24298	(***)	0,00000	11,57693	(***)	0,00000	6,93207	(***)	0,00042	3,71499	(*)