UNIVERSITÀ DEGLI STUDI DI TRIESTE

XXVII CICLO DEL DOTTORATO DI RICERCA IN

Neuroscienze e Scienze Cognitive

DEVELOPMENT AND TESTING OF APPLICATIONS AND ALGORITHMS TO IMPROVE BCI SYSTEMS PERFORMANCE

Settore scientifico-disciplinare: BIO/09

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1. Introduction

During my PhD work I had the unique opportunity to face fascinating, current neuroscience challenges, that need the collaboration of different expertise, within a multidisciplinary team, to be fully understood and solved. Basically this happend because I chosed to focus my attention on pioneeristic devices that several research group worlwide had developed in order to overcome what we usually perceive as mind/body borders [the mind is not different from the brain: it is a product of it]: the brain computer interfaces (BCIs), or brain machine interfaces (BMIs).

A BCI is a system that allows to interact with the external world using only brain signal (Wolpaw et al., 2002). To do so , a BCI needs several elements that act in series (see Fig. 1a): the first, crucial, element is a signal acquisition device; then brain signal is processed, background noise is removed and some signal features are extracted. In this way it is possible to operate a classification of different brain states, and translate them into different commands: the last element, in fact, is represented by applications (in form of softwares and/or electronic devices) that operate thanks to commands coming from the voluntary modulation of user's brain states. Importantly, a BCI is a closed loop: users receive a real-time feedback (with sensorial modalities that can change among different BCI systems) about the quality of the performed mental task.

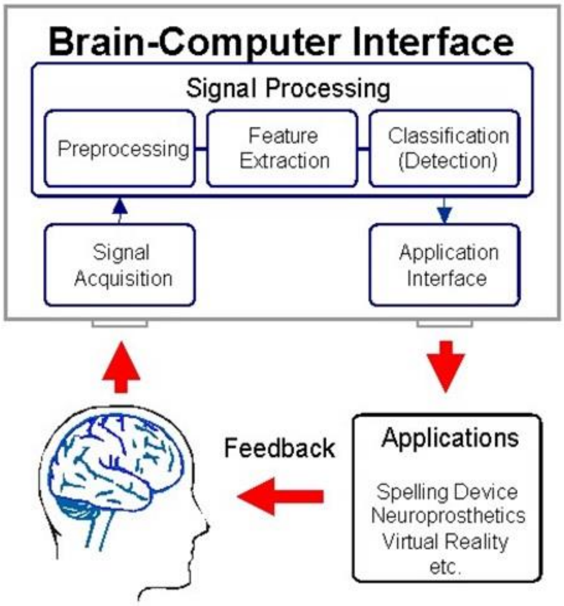

Fig. 1a: structure of a typical BCI: a signal recording device sends information to a software to identify, classify and translate brain signal changes into commands which are then used to produce applications that give to the BCI user information about his/her performance.

This kind of systems was firstly disegned to help people that have severe motor deficits, in which normal output pathways (i.e. muscles and nerves) are impaired. This condition could be due to several reasons: first of all people could be affected by neurodegenerative pathologies that lead to a slow but indeed progressive motor disability. In the most severe cases, as it happens in the last stages of Amyotrophic Lateral Sclerosis (ALS), people are stucked in a locked-in condition, in which they have intact cognitive functions but they are unable to move any muscle (Geronimo et al., 2014). Another category of potential BCI users is that of people who suffered from a traumatic event that caused spinal cord injury (Müller-Putz et al., 2014). Finally, there are patients who underwent limb amputation. Far from the pioneeristic prosthetic structures of decades ago, during the last years innovative assistive BCI devices were developed based on prosthetic limbs connected to the rest of the body. They can give the patient both a motor control and a somatosensorial feedback (White et al., 2010). In all these cases an alternative channel (for communication, interaction with the external environment, software and hardware control, entartainment) is needed, and it is the reason why BCI systems were first developed.

Successful result of a BCI implies that the system encodes commands from brain signals and, at the same time, that users learn to increase specific signal sources (Wolpaw et al., 2002), in a double-way learning process.

There are several kinds of BCI systems, according to the different device used to record signals, the mental task used to elicit signal changes and the desired application. Some of them are used only in a clinical/basic research context, other (after having passed a validation protocol) are already available for patients, and some other are only at the very first stages of experimentation in order to give patients a new level of control, sensibility and reliability.

1.1 Different BCI systems

BCI systems can be classified according to the invasiveness of their signal recording device or, in other terms, to how close sensors used to extract information are to the signal sources, that are pyramidal neuron cells in the cerebral cortex.

In fact, far to be a unique structure, the outer part of our head is composed by several overlapping layers (see Fig. 1b): over the cortex it is possible to find three meninges, membranes that, together with the cerebrospinal fluid (CSF), protect the central nervous system.

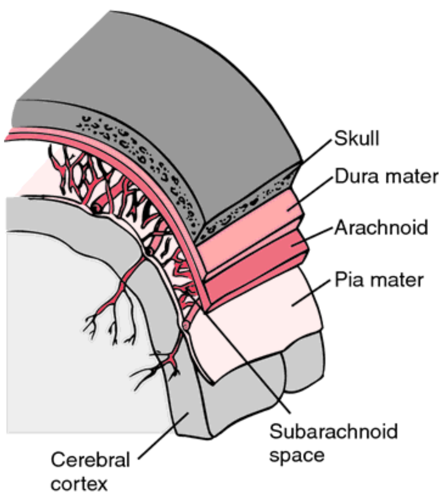

Fig 1b: outer layers of the head: the cortex, the meninges (the pia mater, the arachnoid mater, and the dura mater) and the skull.

They are, from inside to outside: the pia mater, the arachnoid and the dura mater. Then there is the skull, a bone protection, and finally the skin of the scalp.
Basically it possible to put electrodes at each level of this structure: it is then possible to distinguish between invasive BCI, partially invasive ones and totally non-invasive devices.

1.1.1 Invasive BCIs

Invasive BCIs are systems where sensors are totally inserted in the cerebral cortex (Fig. 1c). Signal has a high amplitude and is less contamined by external noise, since sensors are close to its source (sometimes it is even possible to establish a single neuron recording). On the other hand, invasive systems typically show problems related to infection and to scar-tissue growth, causing the signal to become weaker or even lost, since the body reacts to a foreign object in the brain.

Important application of such invasive implants include treatment of acquired blindness (Lewis et al., 2015), simulation of movements on a pc screen (Kennedy and Bakay, 1998) and even control of prosthetic limbs (Lai et al., 2007).

Fig. 1c: Braingate, an example of invasive BCI based on intracortical recordings

Since these systems are perceived as too invasive and possibly dangerous for the patient's health, different devices have been developed, which still offer good signal quality, but reduce risk of infections and other clinical side effects: they have been named *partially-invasive BCIs*.

1.1.2 Partially invasive BCIs

Partially invasive devices are implanted inside the skull but remain outside the brain rather than entering the grey matter. They produce better signals than non-invasive BCIs, where the bone deflects and deforms signals and they have greater long-term stability and lower risk of forming scar-tissue in the brain compared to fully-invasive systems, since they do not require cortical penetration (Leuthardt et al., 2006).

One of the most used partially invasive technique is the Electrocorticography (ECoG), in which electrodes are placed under the dura mater, over the aracnoid (see Fig. 1d). To position them, a craniotomy is needed, so usually ECoG is used in BCI research only when it is needed for other clinical application (i.e. localization of epilepctic foci in case of drug resistency).

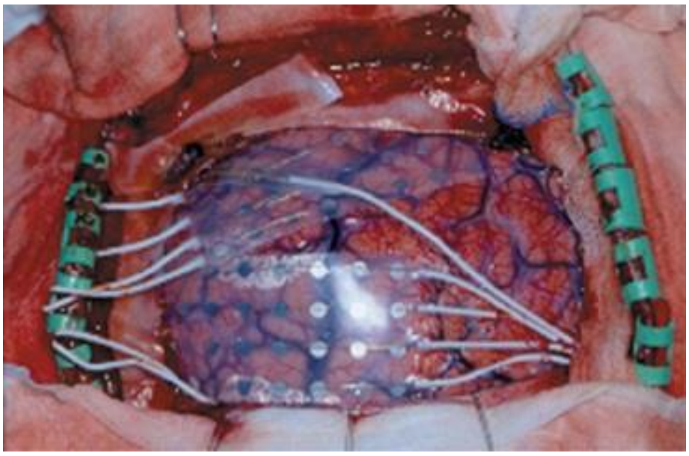

Fig. 1d: Electrocorticography performed with electrode grids placed on the cerebral cortex (rcsed.ac.uk)

ECoG records the postsynaptic potentials (local field potentials), directly from the exposed surface of the cortex. These potentials occur primarily in cortical pyramidal cells, and have to be conducted through several layers of the cerebral cortex, cerebrospinal fluid, the pia and the arachnoid before reaching sensors placed just below the dura mater. For this reason ECoG offers a temporal resolution of approximately 5 ms and a spatial resolution of 1 cm. ECoG technologies were first tried in humans in 2004 by Eric Leuthardt and Daniel Moran of the Washington University in St Louis. They found that BCI control by patients is rapid, requires minimal trainin, and may be an ideal tradeoff with regards to signal fidelity and level of invasiveness, indicating ECoG as a promising tool for patients affected by severe motor disabilities.

To overcome problems related to scar tissue and infections, some completely different neural interfaces have been very recently developed (Minev et al., 2015). They aim to cover the mechanical mismatch between soft neural tissues and artificial neural implants, to enhance long-term performance of implantable neuroprostheses. Such futuristic implants extract cortical states and, delivering electrochemical spinal neuromodulation, they should help to restore locomotion after paralyzing spinal cord injury.

However, for economic reason, but also to promote a soft, patient-indipendent approach to BCI application), researchers and clinicians often exploit totally non-invasive recoring techniques.

1.1.3 Non-invasive BCIs

Basically, any kind of signal recording technique can be used as a basis for a BCI system. During the past years several non-invasive BCIs have been developed, and each of them has the typical advantages/disadvantages of the recording technique they derive from.

For istance, a largely used BCI, especially in basic research studies, is the one based on functional resonance imaging (fMRI), which exploits BOLD response to derive commands (Weiskopf et al., 2003). In these systems the spatial resolution is very high, while the temporal one) is typically low, (due to the time needed to detect metabolic changes of neurons. This is an important limit for BCI application (as highlighted in recent works, see Cohen et al., 2014), in which real time commands are needed, confining the application of this method especially to basic research approach.

A second non invasive BCI approach is based on magnetoencephalography (MEG). This technique allows to map brain activity by recording magnetic fields produced by electrical currents that originate within the cortex. Neuronal currents induce magnetic fields, that are captured by very sensitive magnetometers. Also in this case, the pyramidal layer, in which cells are located perpendicular to the cortical surface, is crucial for signal production. MEG is expensive and the apparatus takes quite a lot of space but, compared to other recording tecnhiques, it may reduce training time and increase reliability of signal analysis (Mellinger et al., 2007). Due to these reasons MEG is used, within BCI studies, especially for source localization applications, because signal propagation of magnetic fields is less influenced by physical properties of the skull than is the case of other devices.

Another kind of BCI, the least expensive and cumbersome, but also the least precise, is based on Electoencephalography (EEG). Due to its importance in the BCI field, and specifically for my PhD work, this method is illustrated in detail in the below section .

1.2 The EEG

EEG represent one of the most used recording technique in the BCI field. This method, developed by Berger in 1929, found countless application in neuroscience studies, ranging from basic research to medical applications. EEG allows to record the simultaneous activation of thousands of cortical pyramidal cells, thanks to electrodes put on the scalp of the subject.

Electrodes are usually put on a tissue cap, and they are classified according to the so called 10-20 International System (Sharbrough et al., 1991). In this system sensors are put at 10 or 20% (according to the experimental design) of two main reference distances: the antero-posterial one and the right-left one. Antero-posterior distance is calculated between two bone references, the nasion (in the middle of the orbits) and the inion (in the occipital lobe); right-left distance is calculated between the centre of the pre-auricular lobes. Maintaining 10-20% of these distances assures that data taken from different subjects (with different head sizes) are still in proportion, and hence they can be compared within a study. In the 10-20 International System, sensors are named using a letter and a number (see Fig. 1e); the letter indicates the bone where the electrode is positioned: F for frontal, T for temporal, P for Parietal, O per occipital; C stays for Central, i.e. the midline. Positions across the borders of these regions are indicated with two letters (i.e. Fp, Cp, Po…). Then a number indicates if the sensor is in the right hemisphere (even) or in the left one (odd); moreover, higher is the number, farer the electrode is from the midline, where sensors are indicated with a “z” instead of a number.

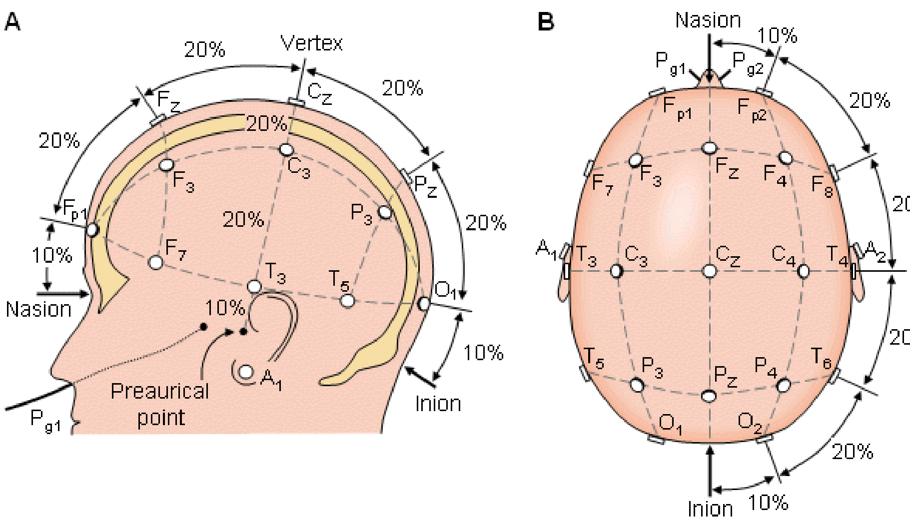

Fig 1e: the 10-20 International System: sensors follow a classification based on letters (indicating the lobe in which the electrode is put) and numbers (indicating its position in relation to the middle line).

The signal recorded by each electrode is calculated as the ratio between the voltage recorded by that sensor and the voltage recorded by a reference one. In this way it is possible to immediately understand if a recording problem is due to the specific sensor or to a more generalized interference. Moreover, a ground electrode is always present, both for users and device security. Once the signal is recorded, it is sent to an amplifier and then to a signal visualization software: thanks to this program, EEG can be visualized on paper or directly diplayed on a pc screen.

One of the main problems intrinsecately related to EEG is the so called signal to noise ratio: signal has to cross several layers and loses, step by step, a part of its amplitude. The lowest is the signal that reaches the sensor, the highest is the risk of contamination due to *artefacts*: they are all the phenomena that cause interference with the EEG signal, masquering it and leading to a malfunctioning of the BCI system. They include the effect of displacements of sensors on the scalp, body movements (due to electrical activity generated by eyes, mouth, facial muscles or, sometimes, even limbs) and environmental events (that rise from electronic devices, such as PC, radio, cell phones). Luckily, artefacts have well defined temporal, spatial and frequency features: hence it is possible to use (in both on-line and off-line modality) spatial and temporal filters, to mitigate and even eliminate their negative effect.

1.3 EEG signals used in BCI research

Among the several brain signals that is possible to record thanks to the EEG, I will focus on the two that represent the most used brain features in BCI research and those I worked on during my PhD work: the P300 wave and the sensorimotor rhythms.

1.3.1 P300

The EEG is a valuable tool to evaluate brain signal changes. Among them, one of the most used in BCI research are the so called Event Related Potentials (ERPs). ERP occour in response to an external stimulus of different origin (i.e. visual, acoustic, somatosensory) and it represents the brain response to it. Hence, each kind of stimulus will produce a different ERP. In fact, each ERP is composed by a series of peaks, that follow a standard classification (Fig 1f): a letter (P for positive and N for negative) indicates their polarity, and the following number (i.e. 1, 2, 3 or 100, 200, 300) indicates, in milliseconds (or hundreds of milliseconds), the time occurring between the stimulus presentation and the peak itself.

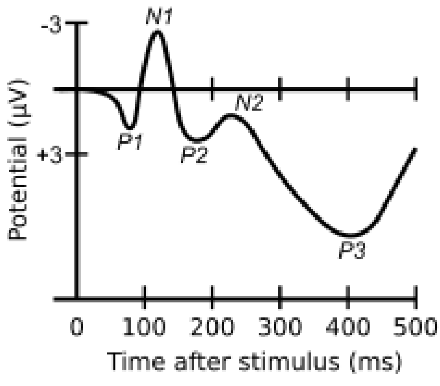

Fig 1f: a typical Event Related Potential

It is then possible to distinguish between early peaks, typically associated to sensory processes (that differentiate different ERPs) and peaks related to higher processing steps. In particular, a component often used in BCI is the P300: the electrical correlate of a cognitive response which appears as a positive wave at about 300 msec after the presentation of a rare but attended stimulus. Usually the chosen sensorial modality is the visual one, and P300 is elicited using the so called oddball paradigm: an expected, desired stimulus (target) is immersed into several unexpected stimuli (non-targets). In this way it is possible to recognize the presence of a certain stimulus on the basis of the appearance of the P300 wave. The most used application is the P300 speller, that allows a completely paralyzed person to communicate, simply focusing on the letter he/she decides to select (see Fig. 1g).

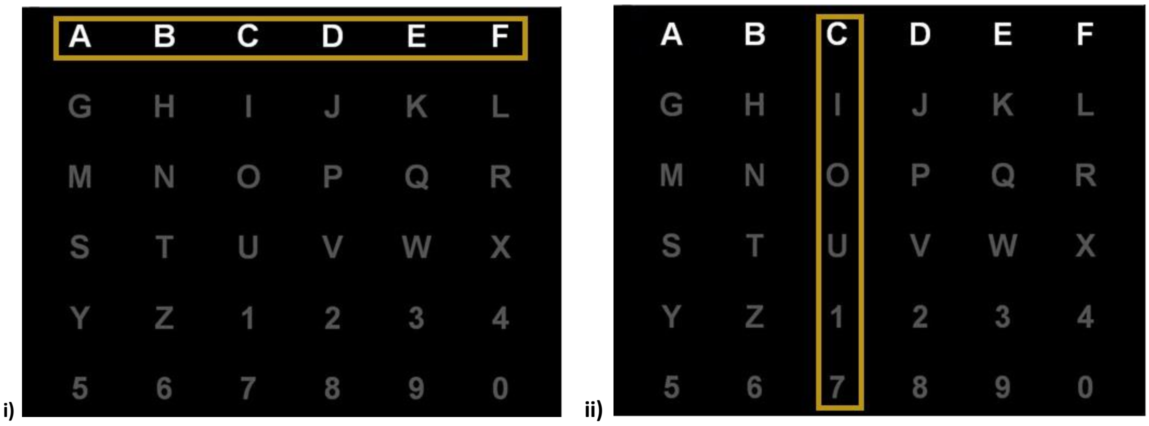

Fig 1g: structure of a classic P300 speller. Items are arranged in a virtual keyboard; rows and columns flash pseudorandomly, allowing to detect the P300. Let's say the user selects letter C: flashes of the the row (i) and column (ii) containing it will evoke a P300 response, while other rows and columns flashes will not. In this way, from the intersection between row and column that produced the P300, the BCI system is able to identify the user's target.

In a P3 speller, rows and columns of items contained in a matrix are highlighted in a pseudorandomized order (i.e. users and operators cannot predict flashing order, even if the BCI software exactly knows which element is highlighted at a certain time).

Unfortunately, since the EEG reflects a moltitude of simultaneously ongoing brain processes, the response to a single stimulus or event of interest is not usually visible in a single trial. The ERP of a certain stimulus is then built averaging records of several trials. This causes random responses to be reduced in amplitude while those which appear in the same time window are enanched. In this way, random brain activity and noise are excluded, while relevant features (i.e. P300 caused by target stimuli) remain. This implies that many rows and columns flashes are needed in order to detect a reliable P300 wave.

A typycal P300-based BCI protocol starts with a calibration session. This phase is crucial to train the linear classifier, an algorithm that distinguishes between trials that contain the desired response and trials that do not. Since P300 response is different in different users, and even within the same subject in different conditions (Sklare and Lynn, 1984), this first phase aims to optimally fit the BCI system to the user's neurophysiological features. Typically during the calibration session the user is asked to focus on a specific item, counting its flashes. In this way (knowing which element should elicit the P300), the system is able to derive the P300 features, giving this information to the classifier algorithm.

Once the classifier is trained in the calibration session, it can operate online discriminations between brain responses to target/non target stimuli, recognizing the wanted items.

There are several classifying methods that is possible to use in P300 research: one of the most used ones, that I exploited during my PhD work, is the Stepwise linear discriminant analysis (SWLDA), a linear classifer introducted in BCI resarch by Farwell and Donchin (Farwell and Donchin, 1988).

This method performs feature space reduction by selecting suitable features to be included in the discriminant function (Krusienski et. al., 2006) and provides, by sampling a 800 ms epoch for each stimulus, a spatiotemporal vector of coefficients (or weights) for each EEG channel.

In other terms, in a P300-based BCI the Linear Classifier's input is a sequence of averaged EEG time courses obtained in response to external stimuli, and its output is considered to represent the likelihood for each of these responses to be a P300. This likelihood is expressed as a weight, that in the Linear Classifier matrix is associated to each channel, for each temporal unit.

1.3.2 SMRs

With EEG it is also possible to record brain rhythms, oscillations of the brain signal that derive from the activity of thousands of piramidal cells. Brain rhythms, called also brain waves, have different frequencies and each frequency band is associated to a certain cognitive state (see Fig 1h). In general, the higher is the engagement of a person, the fastest his/her neurons will fire. In particular, when the brain is actively engaged in physical and/or mental activities, it generates gamma and beta waves. The frequency of these rhythms ranges from 13 to even 120 cycles per second (cps, or Hertz). Where beta represents arousal, alpha represents non-arousal states. Alpha brainwaves are slower and higher in amplitude. Their frequency ranges from 8 to 12 Hz and are typically expressed by a person in a rest state. Next brainwaves are theta, characterized by even greater amplitude and slower frequency (4-7 Hz); they are associated to lightest states of sleep and dream. Finally there are delta (0.5-3 Hz), associated to deep sleep periods.

To make a clear example, when we go to bed and read for a few minutes before attempting sleep, we are likely to be in low beta. When we put the book down, turn off the light and close our eyes, our brainwaves will descend from beta to alpha, to theta and finally, when we fall asleep, to delta.

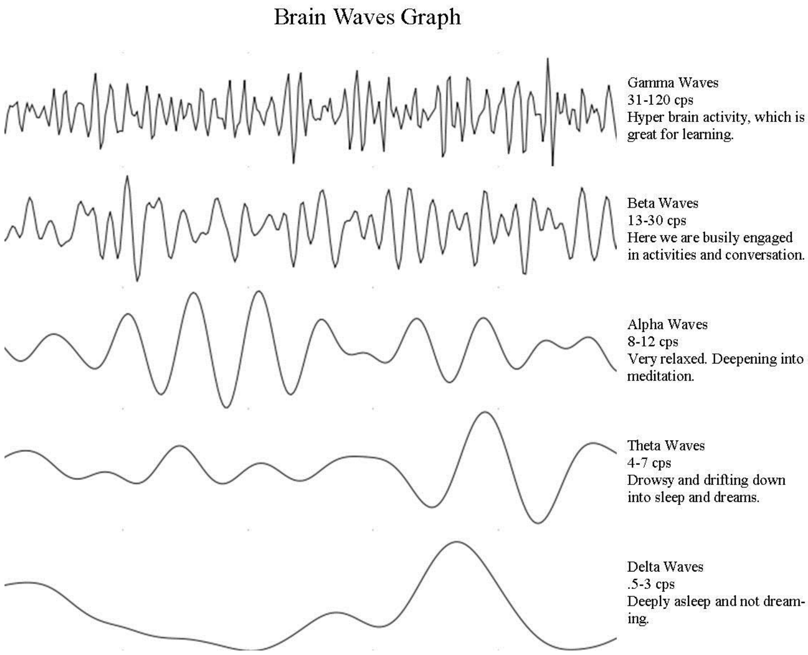

Fig 1h: main brain rhythms that is possible to record with EEG

One kind of brain waves often used in the BCI research are the so called sensorimotor rhythms: these brain patterns are specifically expressed in the motor and somatosensory primary cortices, and they show a desynchronization (called Event Related Desynchronization, ERD) when a person performs a movement (Fig. 1i). This happens because when a movement is performed, the involved neurons are more active, discharge at higher frequency than before and reduce the synchronization they typically have at rest. Interestingly, it is possible to observe an ERD even when the movement is simply imaged, and this desynchronization has the same neurophysiological feature of when a physical movement is actually performed (Pfurtscheller and Neuper, 1997). Usually this mental task, that requires finely regulated executive functions and involves the activation of frontal and prefrontal regions, is referred to as *motor imagery* (MI). Hence, it is possible to exploit these brain signal changes in order to control application and or electronic devices without the need to perform any movement, and this is exactly what happens during an ERD-based BCI session.

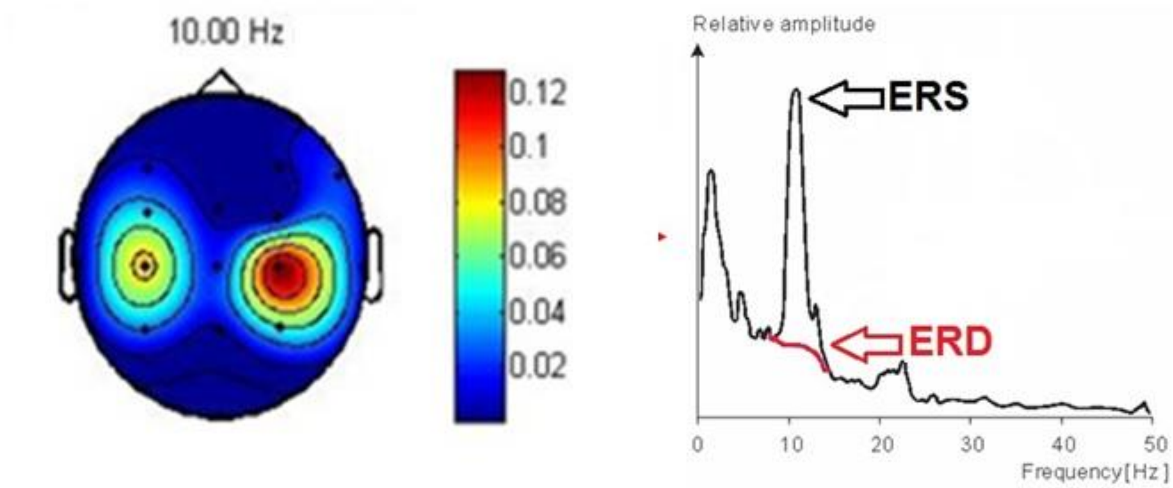

Fig 1i: the typical localization of a left hand movement ERD. On the left, the desynchronization on the scalp is highlighted in a red scale: the more an area is coloured in red, the bigger ERD is. On the right, the spectra (expressed as relative amplitude versus frequency) of the sensorimotor rhythms during (in red) and after (in black) motor imagery task

SMRs originate from the region of cortex where the motor and somatosensory homunculi are represented (Fig 1l). It is then possible to discriminate and anlayze ERD related to different body districts, particularly those that have a large representation (i.e. those that present a fine, regulated motor control and/or an high level of sensitivity) as it is the case of the hand.

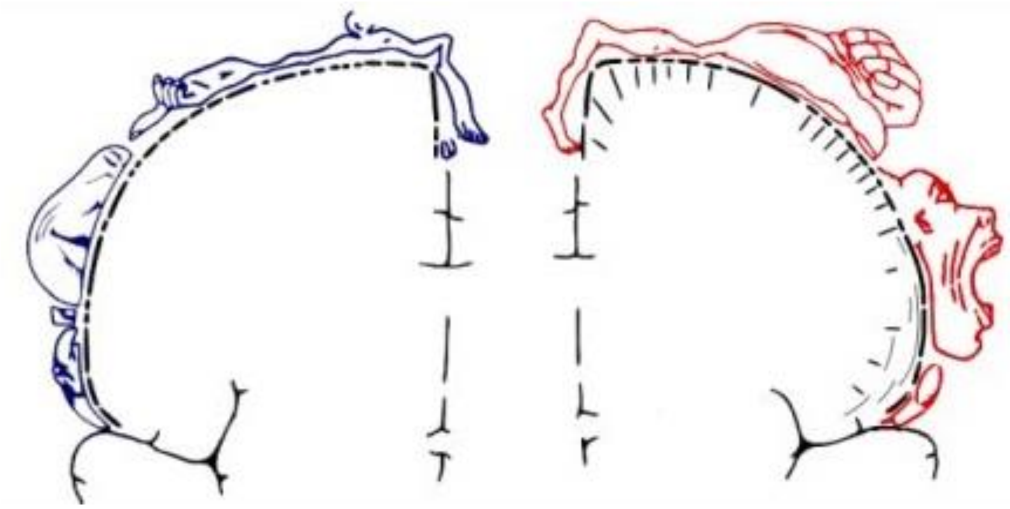

Fig 1l: representations of the somatosensory (left, in blue) and motor (right, in red) homunculi: biggest areas belong to body districts that have, rispectively, an high sensitivity and fine control.

In particular, in BCI research there are at least four main ERD signals that it is possible to exploit to obtain a real time command: mouth, right hand, left hand and feet (Pfurtscheller et al., 1999).

1.4 BCIs and neurofeedback

Brain signals can be exploited not only to obtain commands and controls: they can be used as basis to novel nerurorehabilitation treatments known as neurofeedback (NF) strategies.

Historically, biofeedback has been used in order to improve physical therapy efficacy. From this experience the idea arose of the coupled application of a neurorehabilitation protocol and a brain-derived feedback (neurofeedback). Here patients learn to voluntary modulate, through specific mental task, certain brain patterns. They receive a real time feedback (that can be chosen among several sensorial ways, but that always relies on neural activation) of this modulation, allowing them to be constantly informed about their performance. In this way, BCI users are able to reinforce it (if the NF is positive) or to adjust it (if the NF is negative).

Different brain patterns are associated to different brain functions which can, in turn, be affected by the voluntary modulation of the related brain waves. On these bases, NF has been proposed as a promising treatment for different pathologies: depression, anxiety, cronic fatigue (Choobforoushzadeh et al., 2014), hyperactivity and attention problems, especially in scholastic population (for a review see Gevensleben et al., 2014) and drug resistent epilepsy (Strehl et al., 2014).

These treatments promise to succed because NF training helps patients to maintain high level of attention and increased concentration. Importantly, this can be achieved even with relatively cheap devices and game-based software (to facilitate infant use, Fig. 1m).

Fig. 1m: a young user experiencing a BCI-mediated NF treatment based on the voluntary modulation of attention-related brainwaves (neurogadget.com)

Another important application of NF is the reinforcement of motor re-learning. In a variety of clinical situations with motor deficits, new noninvasive therapeutic approaches are needed, specifically intended for the patient's neurophysiological conditions. They must be adaptive, able to provide real-time adjustment, with as less adverse side effects as possible (Broccard et al., 2014). A reserach and clinical field that largely exploit the possibility of MI-based BCI for motor rehabilitation is the one related to stroke. In fact, about 30% of all stroke patients have poor motor recovery, that results in constant need of assistance to manage their daily life (Langhorne et al., 2009). As a matter of fact, BCI systems which are based on planning or intended execution of limb movements (MI), to control external devices (such as orthosis driving movements, Birbaumer and Cohen, 2007) or virtual reality movements and environments (Ortner et al., 2012, Fig. 1n) have beneficial effects on motor recovery (Daly and Wolpaw, 2008).

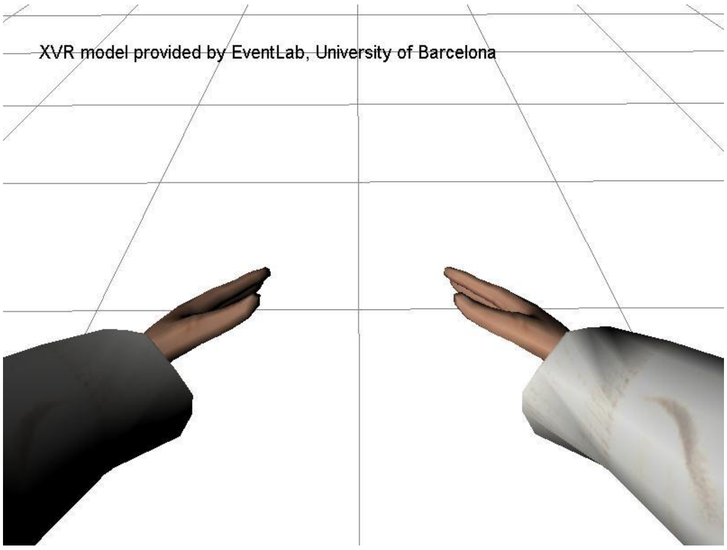

Fig. 1n: example of a 3D virtual environment for MI-based stroke rehabilitation (getc.at)

2. P300-based applications

As described above, one of the most exploited application in BCI research are communication systems based on the cognitive response known as P300. Within the first years of my PhD program I have then largely explored this research field, and the multidisciplinary group I had the pleasure to work with developed two novel communication systems: the Multimenu (Jarmolowska et al., 2013) and the Polymorph (Casagrande et al., 2013).

2.1 Multimenu

2.1.1 Aims and study design

Until a few years ago, P300 speller required a relatively long time for the selection of a single item. It has been reported that the P300-based EEG BCI can usually provide between 3 and 8 selections per min (Ryan et al., 2011), considering as communication system the classical Farwell and Donchin's speller (Farwell and Donchin,1988). Since a less time-consuming procedure is obviously desirable, in recent years these systems of communication have been improved: P300 speller has been modified, for example, by filling the matrix with figures and other elements (instead of single alphanumeric characters) to best fit it with the task that the user had to perform. This method was then used for painting (Münssinger et al., 2010), surfing the web (Mugler et al., 2010), or even remotely control an external device in a pure domotic context (Wang et al., 2005), simply using the P300 response. In all these cases, it has been shown that there is essentially no difference between the response evoked by icons and that evoked by letters, numbers or words.

In this regard, we propose the Multimenu as a tool to increase communication speed, allowing patients to select several deliverable messages in a few steps. The cue is to use words that represent wishes and needs, but also general topics that could be hardly represented by figures. The first goal of the present study was to demonstrate that the Multimenu is a valid and easy-to-learn BCI communication tool, that could be used in a real life context. The second goal was to assess the performance of the Multimenu BCI system by comparing it with a classical P300 Speller in terms of classifier accuracy, bit rate and signal (i.e. P300 response) amplitude.

2.1.2 Participants, materials and methods

Seven healthy adults (2 males, 5 females, age 23.9 ± 3.2 years) were recruited to test the Multimenu. All subjects were naive to BCI use and had full comprehension and use of the Italian language. Each subject signed informed written consent before the experiment (according to the Helsinky Declaration), and the study was pre-approved by the local ethical committee.

EEG was recorded with a standard cap (Electro-Cap International, Inc.) with sensors placed following an adapted version of the EEG 10–20 International system. In particular, signals were recorded from eight channels, that covered parieto-occipital zones (Fz, Cz, P3, Pz, P4, O1, Oz, O2). Each electrode was referenced to Afz and grounded to Poz. Impedance was always maintained below 5 kOhm for each sensor. Signal was then amplified and digitalized with a Micromed amplifier (SAM 32FO fc1; Micromed S.p.A., Italy), high-pass filtered at 0.1 Hz and sampled at 128 Hz. A general-purpose and free BCI software platform, BCI2000 (Schalk et al., 2004; http://www.bci2000.org/), controlled stimulus presentation, data collection and online processing.

During the calibration phase, an alphanumeric string was displayed at the top of the monitor with the next item-to-spell indicated in brackets at the end of the string itself. A pause of 2 seconds was present between one item and the next one. Subjects performed the initial session with a flash duration and an inter stimulus interval (ISI) between two consecutive flashes of 125 ms. Flashes were organized into 20 sequences (a sequence is a single intensification of each row and of each column in the matrix).

Data coming from the calibration session were then used to determine the presence of the P300 component and to train the feature weight classifier of the BCI2000 software: from each channel, a 800 ms data segment, related to each row/column flashing was considered, and a StepWise Linear Dyscriminant Analys (SWLDA) classifier checked for the P300 response. Once the user's P300 features were classified, online testings were conducted.

The Multimenu is a communication tool based on concatenated matrices, each one containing nine Italian words arranged into rows and columns (so, since the system is based on 3 × 3 matrices containing words, it can also be referred to as 3W).
Words allow the BCI user to navigate into a tree-shaped series of submenus, where the first selection does not usually lead to a direct output sentence, but rather is a link for a second level of the Multimenu (Figure 2.1a).

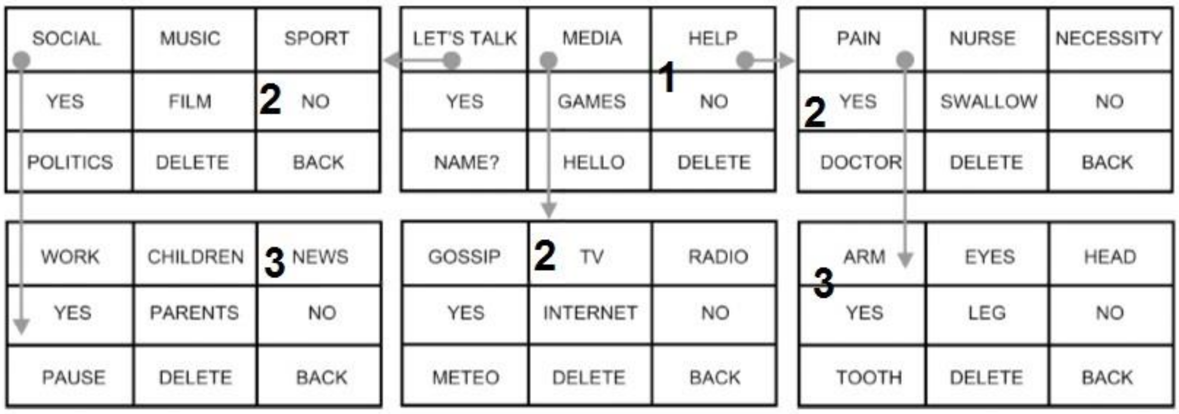

Fig. 2.1a: Multimenu structure (modified version of an original figure contained in Jarmolowska et al., 2013). The main menu (1) allows to communicate direct, fast sentence or to enter into submenus (2). Then, it is possible to enter to a beneath menu (3) or to select an output.

This level contains words that can be used to compose a sentence and that may give access to further levels. In each level, there is the possibility to delete a wrong selection and to return to the previous level using dedicated commands. Let's say, for instance, that user would like to say he/she is experiencing pain at one arm. The selection needed in the first menu would be "Help", allowing to then select "pain" and, with the third selection, the interested body part (i.e. "arm"). In this way, with only 3 selections operated in a 3x3 matrix environment, a BCI user is able to communicate "I have pain at the arm".
To speed up communication even more, "direct-output" words were also included in each menu (especially in the first), allowing, for instance, to write "hello," the user's name or to produce quick answers such as "yes" or "no," by performing a single selection.

In a first experiment, carried out to demonstrate the robustness of the Multimenu, the target phrases or words to be completed were dictated by the experimenter (i.e. externally imposed, or “EI mode”), or freely chosen by the participants themselves (i.e. free choice, or “FC mode”). Each participant completed a total of 60 selections, equally randomized between FC and EI modes. In both modalities, accuracy was calculated as the number of correct selections made by the participant divided by the total number of selections: in particular, in the FC condition, user was asked to report, in the pauses between one selection and the next, the item he/she would like to select in the next trial. In this way, it was possible to have online, continuous monitoring of the progress of the experiment and of the reached level of accuracy.

In a second experiment, carried out to compare Multimenu with the classical P3 speller, participants had to complete four different calibration sessions. The experiment was conducted using a copy mode of BCI2000 (in which user has to spell a predefined text displayed on the screen): hence, for each condition subjects were requested to select the same amount of items (i.e. 20 target items per condition) in order to maintain a reliable comparison among conditions. Four kinds of matrices were used: 3 x 3 and 6 x 6 words grids (called 3W and 6W, respectively), and 3 x 3 and 6 x 6 letters grids (3L and 6L). In the word matrices, items were composed of different numbers of letters (in particular, for 3W there were from 2 to 9 letters, average word length of 5; in 6W from 2 to 7 letters, average word length 4). Different word lengths were used to account for the different size of matrices. Selections covered all the rows and columns contained in the matrices to reduce the influence of target position. In this second experiment, a total of 15 flash sequences for each item was applied.

The first element we compared was the evoked P300 amplitude. Further measures were the classification accuracy (calculated referring to the classifier percentage gained with the four conditions), bit rate and the amount of transferred bits during one selection.

The amplitude of P300 was defined as the highest peak present in the target stimuli ERP mean amplitude, considering an interval between 200 and 500 ms post stimulus presentation.

Classifier accuracy was computed for each condition using the BCI2000 toolbox “P300 classifier”. Once the classifier accuracy was checked, the amount of bit transferred in one selection was calculated following the definition proposed by Wolpaw and colleagues (Wolpaw et al.,1998) for noisy channels (Shannon and Weaver, 1949) using the formula:

$$\text{Bit trans} = \log 2\ N + P \times \log 2\ P + (1 - P) \times \log 2\ (1 - P)/N - 1$$

where “N” is the number of the possible choices present in the matrix, “P” is the classifier accuracy and, consequently, “1-P” is the classification error. Once this value was found, bit rate, which corresponds to the amount of transferred bits in 1 min (Wolpaw et al., 1998), was calculated by relating it to V (where V is the application speed in trials/second, i.e., how many items are recognized per second) according to the formula:

$$\text{Bit rate} = V \times \text{Bit trans}$$

Statistical analysis were conducted on both experiments. More specifically, for the first experiment the user’s performance in the FC selection method was compared to the EI one. Analysis was carried out using a non-parametric statistic (Wilcoxon test), considering that, in this case, data were not normally distributed. It was also accounted for the presence of many observations that were numerically similar. As a consequence, an “exact” Wilcoxon test was used.

Data obtained in the second experiment were analysed to evaluate the existence of significant differences between the amplitude of the P300 component when different matrix sizes and types of stimuli were presented. In this case, data were normally distributed and a repeated measures ANOVA was conducted considering the size of the matrix (i.e. 3×3 or 6×6) and type of stimuli (i.e. letters or words) as main factors. When an effect representing a main factor or an interaction resulted significant, simplification of the model was conducted using a Student’s t-test. Moreover, we compared the bit rate obtained for each of the four conditions indicated above. In this case, data were not normally distributed and an "exact" Wilcoxon test was applied, also accounting for the presence of observations with the same result. Statistical tests were always two-tailed. Normality of data was verified using the Shapiro–Wilk test, and a $p < 0.05$ was considered statistically significant.

2.1.3 Results and discussion

The Multimenu accuracy was analyzed over 30 EI and 30 FC selections, in order to assess its robustness and availability, both in a research environment and in a real life condition (i.e. with maximal rate of freedom for each selection). The chosen number of selections (n = 30) is, in fact, adequate to communicate basic information and express feelings, desires and needs that the user is experiencing. Mean accuracy in all subjects was 87.6% (± 6.6%) and 86.7% (± 8.2) for EI and FC conditions, respectively; no significant differences were found between them (Wilcoxon test: = 0.72). In Fig. 2.1b results obtained by each subject are shown.

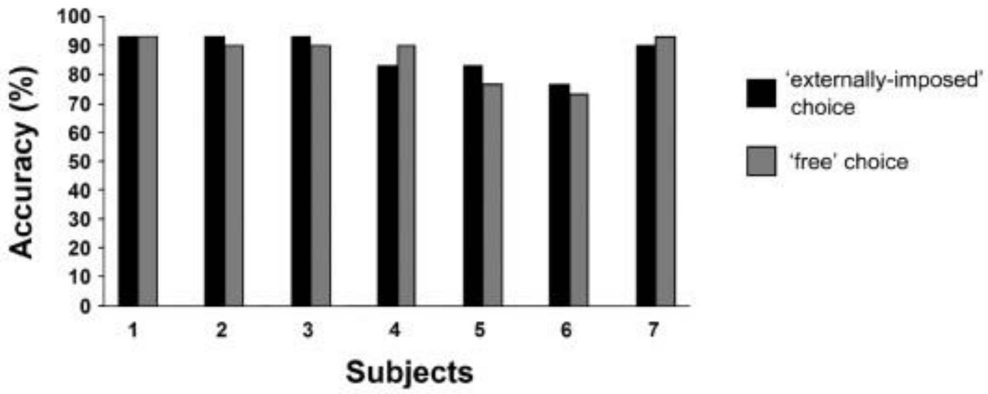

Fig. 2.1b: on line accuracy obtained by each subject under two experimental conditions: EI selections (Externally Imposed) and FC (Free Choice) ones.

The Multimenu turned out to be robust and easy to use, allowing users to communicate fast, with an high level of freedom and with an accuracy the exceeds the level considered as adequate for a BCI-based communication (Kübler et al., 2001; Serby et al., 2005).

Moreover, in the second set of experiments, some objective factors have been examined in order to compare Multimenu to already existing BCI systems. In particular, classifier accuracy, bit rate and P300 peak amplitude were assessed.

Classifier accuracy was very high with all matrices, assesting at 97.14% (± 0.03) for 3L, 97.86% (± 0.04) for 3W, 98.57% for 6L and 6W (± 0.02 and ± 0.04, respectively). It has been theorized that classifier performance (that directly reflects on user's performance) should be related to the degree of user's attention. Fazel- Rezai highlighted that habituation can affect the P300 detection for real-time applications. In particular, the level of attention can decrease with repeated presentation of the same type of stimulus (Fazel-Rezai, 2009). The author suggested that habituation in the speller system can be reduced by altering the region of stimulus location on the screen, its background, and other visual effects that create a change in the paradigm. This is exactly what happens in the Multimenu, where level of attention might have been facilitated by the use of words, which change according to the intended meaning, and by the immediate feedback given by the system. Moreover changes of matrices from one submenu to another might allow to maintain an high level of attention, avoiding a habituation process that can affect the P300 detection in experiments where the same matrix is always displayed (e.g., Fazel-Rezai, 2009). For the same reasons, the Multimenu system might reduce fatigue, which is one of the main causes of error in classical BCI speller programms (Fazel-Rezai and Ahmad, 2007).

The average bit rate recorded among partecipants was 7.56 (± 0.6) for 3L, 7.79 (± 0.8) for 3W , 6.63 (± 0.3) for 6L and and 6.63 (± 0.4) for 6W. Significant differences were found between bit rates obtained in the 3L vs. 6L conditions (Wilcoxon test: $p = 0.016$: due to its reduced selection time, the Multimenu allows a higher bit rate than a conventional speller system, since it is possible to make more selections in 1 min (see Tab. 2.2a). This happens even if, always for a matrix size reason, the number of transferred bits for each selection was higher in the 6 × 6 matrices compared to the 3 ×3 ones, both when using letters and words, as shown in Tab 2.2b. The higher bit rate in the Multimenu allowed for faster transfer of information in a defined time range using 3 × 3 matrices compared to the 6 × 6 ones with the classical P300 Speller, allowing at the same time a meaningful communication.

Tab 2.2a: accuracy levels and bit rates reached by each partecipant, for the four conditions

Subjects	3 x 3 letters		3 x 3 words		6 x 6 letters		6 x 6 words	
	Accuracy	Bit rate	Accuracy	Bit rate	Accuracy	Bit rate	Accuracy	Bit rate
1	95%	7.09	100%	8.24	95%	6.06	100%	6.72
2	95%	7.09	100%	8.24	100%	6.72	100%	6.72
3	100%	8.24	95%	7.09	95%	6.06	100%	6.72
4	95%	7.09	100%	8.24	100%	6.72	100%	6.72
5	100%	8.24	100%	8.24	100%	6.72	100%	6.72
6	100%	8.24	90%	6.24	100%	6.72	90%	5.59
7	95%	7.09	100%	8.24	100%	6.72	100%	6.72
Mean	97.14%	7.56	97.86%	7.79	98.57%	6.53	98.57%	6.56
SD	(0.03)	(0.6)	(0.04)	(0.8)	(0.02)	(0.3)	(0.04)	(0.4)

Tab 2.2b: Number of transmitted bits per trial in the different matrix sizes and different levels of probability (P), intended as accuracy reached by the classifier

3 x 3 $P = 1$	6 x 6 $P = 1$	3 x 3 $P = 0.95$	6 x 6 $P = 0.95$	3 x 3 $P = 0.9$	6 x 6 $P = 0.9$
3.2	5.2	2.7	4.6	2.4	4.2

In the past, other BCI studies showed improvements in terms of accuracy and/or bit rate with respect to classic P300 speller, often exceeding the bit rate obtained in the present study (see, for example, Diez et al., 2011; Ryan et al., 2011; Kaufmann et al., 2012). Kaufmann et al. (2012) effectively demonstrated that the integration of predictive text directly into the matrix may result in higher benefits in terms of speed of spelling without loss of accuracy. Despite the lower levels of bit rate obtained in the present study with respect to the evidence in the literature, the strength of Multimenu is that it allows to save time with respect to a classical P300 Speller condition. In fact, the selection of a target can provide the immediate expression of a message or, in the case of two/three selections, it can lead to the expression of a whole sentence or concept. In fact in the Multimenu system, thanks to the dimensions of the matrices, the user obtains an online, direct feedback in half the time required by the classic P300 Speller.

Concerning the P300 morphology, effects related to the matrix size computed with ANOVA resulted significant [$F (1, 6) = 49.04$, $p < 0.0009$]: for all items, the amplitude was clearly lower in the 3 × 3 matrices compared to the 6 × 6 ones. No significant effect was evident when considering the use of letters or words [$F(1, 6) = 3.7$, $p = 0.1$]. Analyses conducted with Student's t-tests confirmed that the P300 amplitude obtained in the 3×3 conditions (independently of the type of stimulus used, i.e., letters or words) was significantly smaller in comparison to that obtained in the 6 × 6 condition [$t(6) = 6.94$, $p < 0.0009$]. The observed differences were probably due to the higher ratio between expected and unexpected items (see, for a discussion, Duncan-Johnson and Donchin, 1977; Allison and Pineda, 2003; Sellers et al., 2006). Since Multimenu is composed by a series of 3 × 3 matrices, it evoked lower P300 amplitudes compared to the classical speller system (based on a 6 x 6 matrix). On the other hand, relevant variations in the type of stimuli (letters or words) were not observed, suggesting that this parameter does not affect the identification of the response.

Thus, even if lower P300 amplitudes were obtained with Multimenu, the online accuracy remained considerably high compared to the recommended threshold for reliable BCI (Kübler et al., 2001; Serby et al., 2005), and good performance was maintained in selections with this system.

An objection that could be moved against Multimenu is that the choice of messages is limited to the words that appear in the matrix: this, in fact, implies that users cannot write everything they want, while this is possible using the classic P300 Speller. In fact, Multimenu should not be considered for the creation of complex and articulated text messages, but as an easy way to give a simple and efficient communication and/or assistance tool. As a consequence, it should be modified with respect to the specific user's needs so that it becomes a semantic and significant communicative tool which will best fit the patient's requirements (see Huggins et al., 2011 for discussion). However, precautions were taken to avoid the risk of a system that is too rigid. If the patient would like to express something that is not in the Multimenu scheme, the system is sufficiently flexible to give access to the classic P300 Speller from a dedicated submenu.

Results obtained in these two sets of experiments suggest that Multimenu can provide a substantial advantage to an individual communicating via the P300 component in an online environment, especially for expression of simple messages.

Experiments with the Multimenu system have, in fact, already been carried out with two severely motor impaired patients, representative of the final users of such a system. Patient MB is a 24 years old male affected by ALS, clinically evident since 5 years. He talks and moves on an electronic wheelchair through joystick control. Patient GG is a 55 years old male, who entered a locked-in condition 5 years ago as a consequence of a traumatic injury. He shows preserved cognitive abilities carried out with a simple communication aid which exploits his residual eye movements.

During an experimental session composed by 20 EI vs. 20 FC selections with Multimenu, patient MB reached a communication accuracy of 75%, while GG got an accuracy of 95%. These preliminary observations confirm that online accuracy is in the order of those observed in healthy subjects, indicating that the Multimenu may be an efficient communication tool for patients. However, the reduced dimension of the sample make these last observations non-statistically significative, and more experiments are needed to validate the use of Multimenu with patients.

2.2 Polymorph

2.2.1 Aims and study design

As mentioned above, one of the main problems related to the Multimenu system is that, with it, a BCI user is able to select only pre set-up messages. In this way we have an improved communication speed, compared to the classical P300, but a reduced level of communication freedom. So, it was almost natural to move towards a system that could mitigate this disadvantage, allowing the BCI user to write in an efficient way whatever he/she would like to communicate. The idea was, then, to develop a system that, thanks to a predictive algorithm, could reduce the number of selections (i.e time) needed to write structured phrases, allowing, at the same time, a total communication freedom.

In the past, several research groups suggested methods to reduce, in a P300-based BCI, selections needed to communicate. Blankertz et al., for example, proposed a two steps character selection on a tree whose nodes are visually-presented as hexagons (Blankertz et al., 2006): the first selection allows to select between six groups (each one composed by six symbols), while the second selection identifies the desired symbol in the selected group. Pires and collaborators presented a similar strategy, but they also noted that the group transition rate depends on the organization of groups, and suggested a way to improve it (Pires et al., 2011). Ryan and collegues integrated suggestions, based on prefix of the already written characters string, in the classical row-column matrix (Ryan et al., 2011). Importantly, in this system suggestions are not presented inside the selection matrix, but in an additional window. This system overcame the non-predictive system in terms of both average time needed to complete a sentence (12 min 43 sec vs 20 min 20 sec, respectively) and average output characters per minute (OCM) ($\mu = 5.28$, $\sigma = 1.67$ vs $\mu = 3.76$, $\sigma = 0.75$) Ryan et al. (2011). However, the average accuracy of the predictive system was lower than the non-predictive system (84.88% vs 89.80%, respectively), while there were no significant differences in either bit rates (19.39 vs 17.71, respectively) or selections per minute (3.71 vs 3.76, respectively). Kaufmann and collegues proposed a different approach, which preserved the level of accuracy achieved by the non-predictive speller (Kaufmann et al., 2012). In this case, predicted words and alphabetic characters were presented in the selection matrix at the same time. As result, the bit rate (in terms of selections per minute) was high for both the predictive and non-predictive systems (15.7 vs 15.1, respectively). Yet, the predictive system exhibited a higher true bit rate (in terms of characters per minute) with respect to the non-predictive speller (20.6 vs 12, respectively), it required less time to write an entire sentence, and it enhanced the OCM ($\mu = 3.83$, $\sigma = 0.88$ for the predictive speller vs $\mu = 2.12$, $\sigma = 0.52$ for the non-predictive one). Finally, D'Albis et al. described a predictive speller whose symbols are dynamically organized (D'Albis et al., 2012).

We decided to create a human-oriented system, that reduced the number of selections needed to spell a sentence in a natural language and, at the same time, minimized the needed cognitive workload.

In this regard, we firstly considered that, in some situations, natural languages have an alphabet that is overabundant with respect to the message to be communicated: this could lead to a waste of time and, in a BCI context, in a waste of trasferred information and bits. For instance, none of the English words whose first character is “k” have as second one either “t” or “z”. Similarly, in Italian the letter “q” would be followed only by the letter “u”. Thus, if we are writing in English, once we know that the first character is “k”, the symbols “t” and “z” are unnecessary and they can be transitorily removed from the selection matrix. Or, if we are writing in Italian, we would have a double character output with a single selection: “q” and “u”.

In this context, thanks to the priceless collaboration of Dr Alberto Casagrande (Department of Mathematics and Geosciences of the University of Trieste), we developed and tested a modified version of the classical row-column P300 speller, called PolyMorph. Our system, suggests how to complete current word based on what has already been written by the BCI user. Suggestions are inferred from a knowledge base and take into account the spelled prefixes of both words and sentences, exploting both a lexicographic and a semantic level. PolyMorph is able to understand the number of selectable symbols (according to the past selections) and, as a consequence, to dynamically resize the selection matrix; this sort of polymorphism, that reflects into continuous matrices size and content, is in fact the reason for its name.

In order to validate PolyMorph, we performed two kinds of tests: an in-vivo set of tests, which was conducted to test PolyMorph efficacy on real users, and an in-silico set of tests, which statistically strengthened the performance analysis. In both cases, we also used the classical P3 Speller to compare the efficiency of the proposed system to the one obtained by a valid, largely used communication tool.

2.2.2 Participants, materials and methods

For the in-vivo experiments, that were designed in accordance to the Declaration of Helsinki and pre-approved by the local ethics committee, we tested 10 healthy subjects (6 males and 4 females, mean age 24.9 ± 1.9 years): partecipants gave signed informed consent, and all of them were Italian native speakers: because of this, we built the PolyMorph's knowledge base by using an Italian phrasebook. We collected 111.176 Italian sentences, containing 51.590 distinct words, using as primary sources books, newspaper and the web. In particular, the 200 most commonly used Italian nouns, adjectives, verbs and generic locutions were considered. Then we collected all the 107.075 most common sentences containing these words from the '*Corpus dell'italiano*' of the *Istituto di Linguistica Computazionale* (http://www.ge.ilc.cnr.it/) and we inserted them into the system. Moreover, we added 4101 sentences by randomly selecting them from the web. The average sentence length in the so created database is 37.2 characters; the average word lenght is, instead, 5.3 character.

It is possible to identify, within the Polymorph structure, two distinct levels of the database: a lexicographic level (which stores all the known words and all the admissible character combinations), and a syntactic level, which memorizes all the sentences that either are contained into the phrasebook or have already been selected by the user.

The lexicographic level allows to present only those symbols that, taking into account the given dictionary, are compatible with the already spelled string. The variability in the set of the proposed symbols leads to a polymorphic selector which tries to minimize the size of the selection matrix at each selection.

This has two main effects: it decreases the number of the flashes required for the selection of each symbol (i.e. reducing the total selection time), and it enables to increase the size of the fonts used in the symbol presentation. This modification has an important effect on the system accuracy, since the amplitude of the evoked P300 component is related with the strength of the stimulus that elicits it (Chapman et al., 1958); by increasing the font size, we should obtain a more evident P300 in target stimuli, decreasing the probability of an error in the identification of the aimed symbol.

The lexicographic level can then identify words that complete the already chosen character string and either have been selected more times so far or are the most used in the original dataset.
These are then suggested to the user who can spell them with a single selection (see Fig. 2.2a for an example).

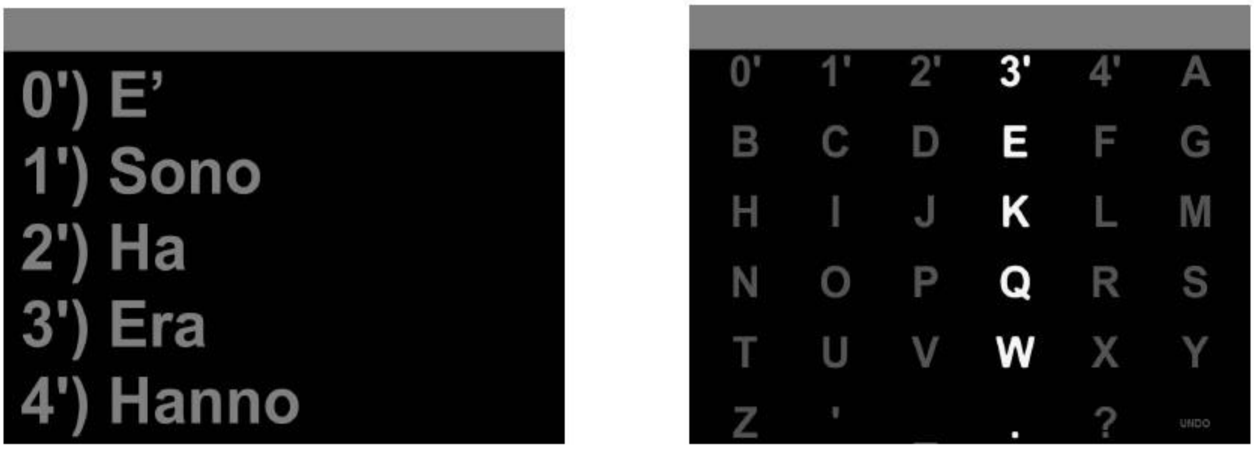

Fig. 2.2a: an example of selection operated with the Polymorph system On the left, suggestion that user can examine before starting character selection. On the right, the panel for item selection: in ther first row symbols 0',1', 2', 3' and 4' allow to directly write words suggested in the previous phase

As the lexicographic level, the syntactic level is used to identify words that are more likely to be suggested: however, this level takes into account the entire spelled string in place of the word prefix that user has spelled. In particular, it can furnish the list of words that follow a prefix p and together with p either have already been selected at least once or are present in the initial phrasebook. However, the main conceptual difference existing between the lexicographic level and the semantic one is that within the lexical one user can combine words to obtain sentences that are not present in the original phrasebook. Beyond the grammatical aspect, this level contains, in some sense, semantic information about sentences: if a phrase is a non-sense, then it will never be selected by the user and will not be stored in the knowledge base.

Since both the selectable characters and the most likely words completing the current prefix depend on the current prefix itself, we decided to use radix trees labelled with statistical information to store the knowledge base. PolyMorph maintains two statistical radix trees: one for the lexicographic and one of the syntactic level. The former stores all the words that may occurs in a sentence. The latter contains all the sentences that either are in the original dataset or have been selected by the user. The statistical information stored in the two trees is updated at each sentence selection and, whenever a new sentence is selected, the sentence itself is memorized into the tree of the syntactic level. For details about Polymorph structure and its implementation please consider the work by Casagrande (Casagrande et al., 2013).

The EEG for the in-vivo tests was registered using a standard cap (Electro-Cap International, Inc.), with electode positions that followed the 10-20 International System. The electrodes used to record P300 response were located in the centro-parietal-occipital cortex (in particular, the following electrodes were used: Fz, Cz, P3, Pz, P4, O1, Po7, Oz, and Po8). The right mastoid was used as a reference for these electrodes, and the left mastoid was used as ground. Impedance was maintained below 5.0 k. The signal was amplified and digitized with a Micromed amplifier (SAM 32FO fc1; Micromed S.p.A., Italy; analog high-pass filter 0.1 Hz; sampling frequency 256 Hz). The signal registered in each channel was processed with a CAR spatial filter. From each EEG channel a data epoch of 800 ms was extracted after presentation of the stimulus. BCI2000 software was used to manage the experiment (i.e., for presentation of stimuli, collection and off-line elaboration of EEG data and management of the spelling session).

Speller parameters were chosen to maximize selection time, allowing to carefully read, understand and choose suggestions. In particular, inter-stimuli interval (ISI) duration and stimulus duration were set to 125 ms; pre-sequence duration (i.e. time before starting of the rows and columns flashing) was set to 3 s for both P300 Speller and PolyMorph, while the post-sequence duration for P300 Speller and the suggestion phase duration for PolyMorph were set to 3 s and 10 s, respectively. For each user, we determined the needed number of flashes sequences (given that a sequence, as in the case of Multimenu and, in general, of any P300-based communication tool, is the flash of each row and each column contained into the speller matrix) according to the accuracy results obtained in the calibration phase (in particular 6, 14, 12, 20, 13, 6, 9, 11, 14, and 11 sequences were used for each participant, respectively).

We then asked participants to spell two sentences: sentence A was “Piace tanto alla gente." (i.e. “People like it so much.”, while sentence B was “Sono andato sulla luna.” (i.e.“I went to the moon.”). The words present in both sentences are included in the phrasebook, but only the sentence A is contained in it. In this way it was possible to study the performance of Polymorph when a BCI user wanted to communicate a totally new concept, that is not present in the used database. Since the suggestions proposed by PolyMorph depend on both the occurrence of a certain locution in the phrasebook and on the number of times a word/sentence is spelled (i.e. PolyMorph is able to *learn* a user-oriented vocabulary, adapting suggestions to it), we asked participants to spell each sentence twice: we should observe an improvement bewteen the first and the second Polymorph spelling, due to the online learning algorithm that automatically updates database and, consequently, words/sentences occurrence. We also asked the subjects to use P300Speller and spell sentence A character by character, in order to compare Polymorph performance to the one obtained by a traditional P300-based communication system. Since P300-speller performance does not depend on the kind of sentence (i.e. present or not in the phrasebook) or on the number of times a sentence is spelled, we asked participants to spell only sentence A once. Moreover, to avoid any bias, the order of tests fed to each user was randomly selected.

Concerning the in-silico tests, Casagrande wrote a program that is able to automatically spell sentences with PolyMorph; to perform these additional tests, two sets of 500 phrases each one were built: set A, which contains 20137 characters, is a subset of the original phrasebook, while none of the sentences present in set B, counting 13200 symbols, were initially included into the knowledge base. Nevertheless, all their words were present in the phrasebook. As done for the in-vivo experiments, the spells were repeated twice and the sentence order was randomly chosen.

The used phrasebook database was identic to the one used during in-vivo analysis, while the flashing sequences parameter was set to 12 (the average of sequences used by participants during the in-vivo tests).

2.2.3 Results and discussion

Conceirning in-vivo experiments, PolyMorph outperforms the classical P300 Speller in writing both sentences. Performance was evaluated as the amount of characters spelled by the two systems in one minute (OCM). Inter-individual differences were due to different amount of flashes sequences used (see Fig.2.2b and Tab. 2.2a for users' details).

In sentence A and B, we observed larger OCM in both turn 1 and 2 of PolyMorph session with respect to that obtained by using P300 Speller (Wilcoxon test: $p\text{-value} = 0.00195$ in both cases): this means that, apart from the fact that a sentence is present or not into the database, PolyMorph represents (flashes sequences given equal) an improved communication tool compared to the P300 traditional speller.

Within the same sentence, OCM obtained during turn 2 is larger than that of turn 1 for both sentence A and B ($t(9) = 4.2$; $p\text{-value} < 0.002$ and $t(9) = 9.88$; $p\text{-value} < 0.0009$, respectively): this additional data confirms that PolyMorph is able to learn by previous use, improving user communication speed and giving him/her a better BCI experience.

We found a substantially increased OCM in turn 1 of sentence A compared with the OCM of the same turn of sentence B ($t(9) = 6.69$; $p\text{-value} < 0.0009$): the first time a sentence is written, it is important that the database is well structured, and as much bigger as possible. However, this difference disappears for the second spelling of the sentences, confirming the quality of the PolyMorph learning algorhitm.

The differences between P3 Speller and PolyMorph on the first spelling of sentence B are due to the lexicographic level. On the other hand, the increased efficiency of the second spelling with respect to the first spelling of the same sentence is due to the syntactic level and so it is for the differences between the first spelling of sentence A, which is initially included into the knowledge base, and the first spelling of sentence B, which is a new sentence.

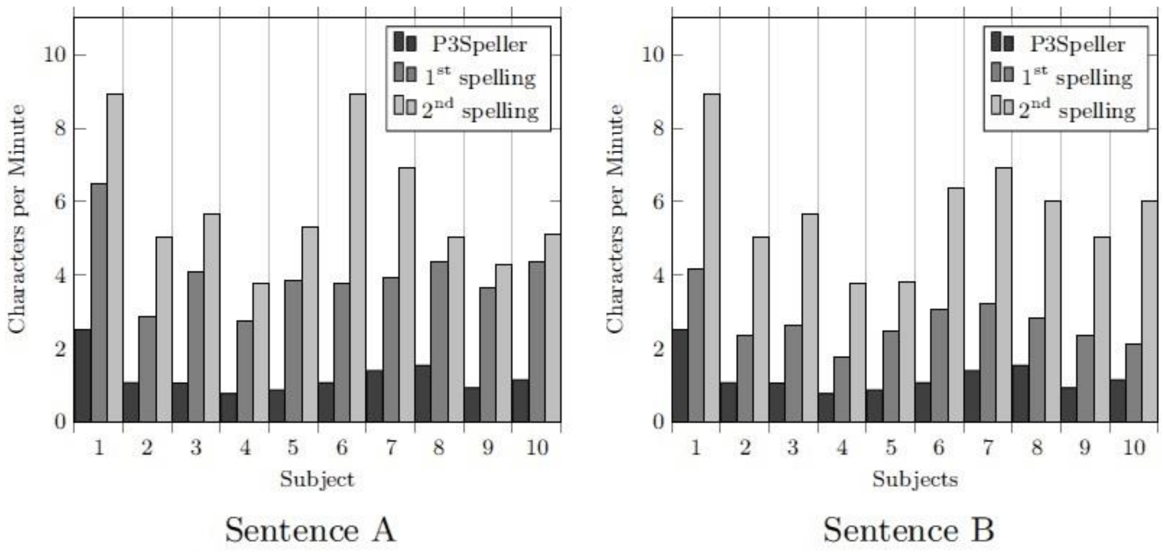

Fig. 2.2b: characters per minute spelled by P3 speller and Polymorph (two times), for sentence A (left) and sentence B (right).

Table 6: Online session output characters per minute (OCM) for the PolyMorph for the first time (1^{st} PM), PolyMorph for the second time (2^{nd} PM) and P3Speller (P3S).

	Sentence A			Sentence B	
Subject	1^{st} PM OCM	2^{nd} PM OCM	P3S OCM	1^{st} PM OCM	2^{nd} PM OCM
1	6.47	8.94	2.51	4.15	8.94
2	2.85	5.03	1.07	2.35	5.03
3	4.11	5.65	1.06	2.64	5.65
4	2.76	3.79	0.78	1.78	3.79
5	3.87	5.32	0.88	2.49	3.80
6	3.76	8.94	1.07	3.06	6.39
7	3.94	6.92	1.40	3.23	6.92
8	4.37	5.01	1.54	2.81	6.02
9	3.66	4.28	0.93	2.35	5.03
10	4.37	5.12	1.15	2.12	6.02
Mean	4.02	5.9	1.24	2.70	5.76
StDev	1.03	1.8	0.50	0.67	1.52

PolyMorph also decreases the error-rate with respect to both spelled characters and selections (see Fig. 2.2c), increasing communication accuracy. Data were calculated as the ratio between errors and the total amount of selections performed by subjects. Errors per each character selected were assessed. Test indicates that the distribution of results significantly differ within subjects (df = 2; $\chi 2$ = 14.89, p-value = 0.00058). Post-hoc analysis exhibits a significant reduction of errors per each character in both PolyMorph turn 1 and 2 of sentence A and B with respect to errors per each character obtained in P300 classical Speller (Wilcoxon test: p-value is 0.0078 in both cases).

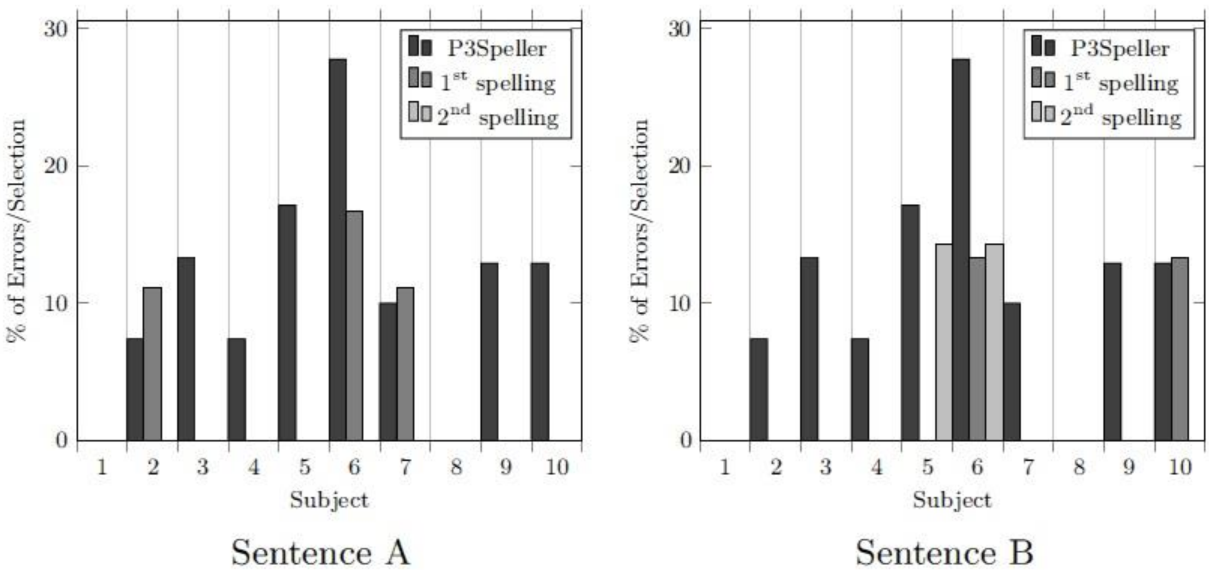

Fig. 2.2c: error rates for each subect obtained with the classical P3 speller and with Polymorph, for sentence A (left) and B (right). Where bar is not present, subject reached an accuracy of 100%.

This may be due to four reasons, or a combination of them: first, it reduces the number of selections required to spell a sentence and, as a consequence, the probability of wrong selections. Second, due to the polymorphism, the selection matrix sometimes contains a low number of symbols. In such cases, the font size is increased and the P300 signal is more detectable. Third, since the suggested words appear always on the first two rows of the selection matrix, the users tend to focus their attention there and, probably, they filter the noisy stimulus coming from the remaining part of the matrix. As soon as the aimed word is suggested, the error-rate decreases. Finally, PolyMorph reduces the number of stimuli required to spell a sentence: this increases the user comfort and, thus, his ability of focusing on a single event.

With respect to the spelling time, the in-silico experiments confirm the results obtained in-vivo (see Fig. 2.2d).

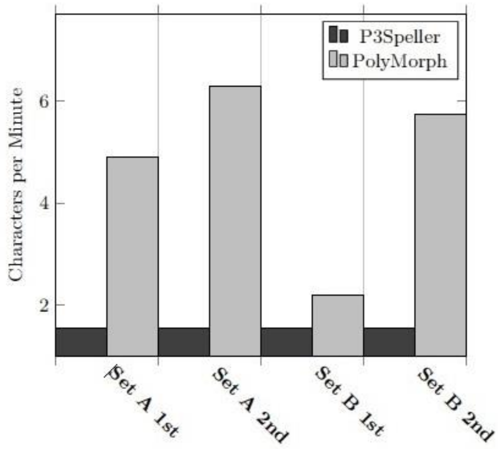

Fig. 2.2c: characters per minute obtained by in-silico testingP3 speller and Polymorph (double spelling of each sentence) on two different sentences sets

They also underline that PolyMorph presents a much smaller number of visual stimuli compared to the classical P3 Speller (see Fig. 2.2e).

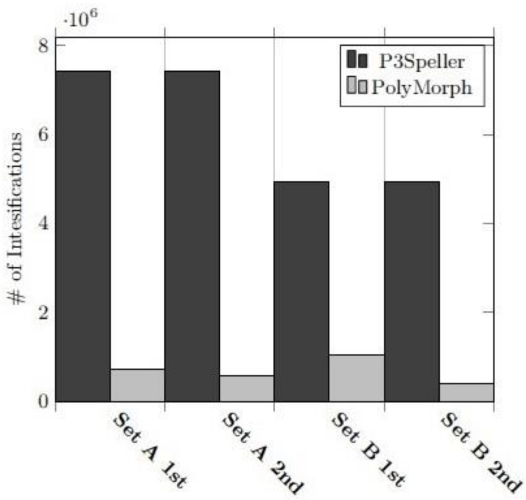

Fig. 2.2e: number of total intensifications (i.e. flashes of rows/columns) needed for P3 speller and Polymorph

Despite the in-silico experiments do not provide any relevant information about selection errors and accuracy, these data suggest an improved user experience and we are confident that this will reflect into a reduced error-rate, as preliminarly underlined during in-vivo experiments.

With the coupled testing on real BCI users and in-silico software we then demonstrated that PolyMorph is an, efficient communication system. Its lexicographic and semantic levels allow users to spell articulated sentences at a faster way, compared to traditional P300 spellers. Moreover, its learning algorhitms continuosly improves PolyMorph's and user's performance, adapting words and sentences suggestion to the user's vocabulary and spelling habits.

Further studies about this system will include some experimentation on severly motor impaired patients, and its use with different natural languages (both in vivo and in silico).

3. More suitable assistive BCIs: Hybrid systems

Each EEG signal used in BCI research has advantages and disadvantages when facing users' needs. P300, for example, is a relatively stable feature, and it is innate in most subjects; however, several flashes are needed in order to identify the brain response to a certain stimulus. This makes it a time consuming application. On the other hand, SMRs and their desynchronization are immediate responses, allowing rapid control, but they are not present in all persons and they need more training in order to have an optimal control. Hence, there is an emerging need of a system that is able to profit from the advantages of different techniques, allowing the user to switch between several control types for an improved BCI performance.

In the last years several ways to improve BCI performances have been proposed, including hybrid BCIs (hBCI) (Allison et al., 2012; Pfurtscheller et al., 2010). Their main purpose is to allow users to have a better BCI control, combining different control channels (see Fig. 3a); in these communication systems, a classical BCI application is combined with other physiological signals (Müller-Putz et al., 2012) like electromyography (EMG) or heart rate or even a joystick. When it is not possible to use muscles, different cerebral signals (elicited by different mental tasks) are used to drive the application: this is the case of the so called pure hBCI, in which different mental tasks are used sequentially or in parallel.

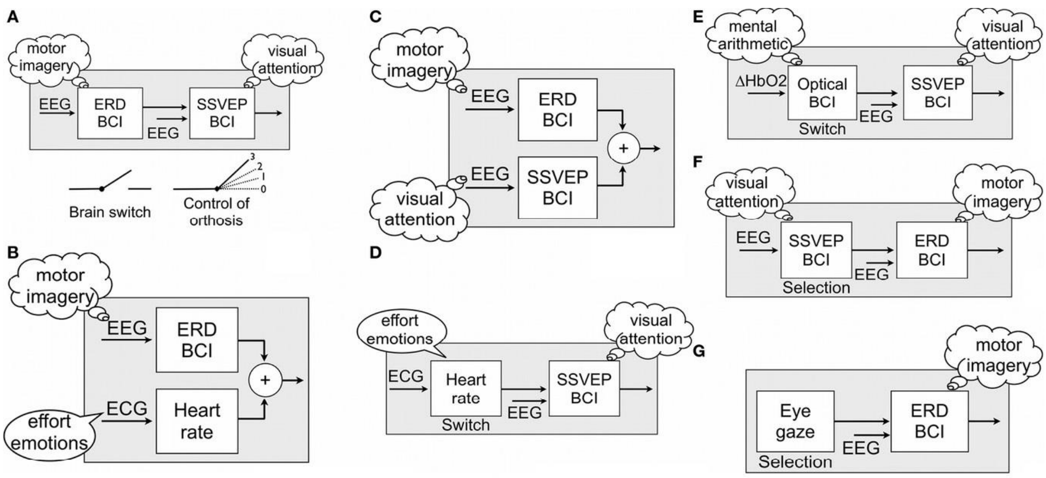

Fig. 3a: different kind of hybrid BCIs with sequential (A, D–G) and simultaneous processing (B,C).

3.1 Aims and study design

In this context, during the second year of my PhD (that I fully spent in the BCI laboratories of the Technical University, in Graz) I participated to the validation on healthy users of a P300-ERD based hybrid interface.

Hybrid BCI combines two different systems: the first one is a novel, user friendly and very efficient P300 communication system, developed in the BCI laboratory of the TU Graz by Dr Pinegger and colleagues. The system is based on three operative modules, that work strictly in conjunction: the first one is a universal data acquisition module, that allows to connect the BCI to several EEG recording devices. The second module is a prototyping platform based on Matlab/Simulink and used for data processing, while the third module is a graphical user interface, which also acts as main controller (for details about this system please refere to Pinegger et al., 2013).

The second component of the hBCI is an adaptive BCI framework that exploits sensorimotor rhythms desynchronization (obtained by feet movement imagery) to obtain control; this system, developed at Graz by Dr Faller and collaborators, gives user a feedback after only a few minutes of autocalibration, in a two-class BCI setup: also in this case the system is very user friendly, allowing to be used also by patients, relatives and care giver (without the need of any competence, excluding the montage and starting procedure (for details about how the system was implemented and tested, see Faller et al., 2012).

The experiment in which I was involved had, then, the principal goal of testing and validating this novel hBCI approach. In particular, I focused on the effect that a sequential use of P300 and motor imagery driven-ERDs could have on hBCI users' performance.

In fact, using consecutively several mental tasks can induce mental workload (and, consequently, fatigue). Actually, one of the main factor to keep in mind when a new BCI paradigm is developed is the mental fatigue and high cognitive workload that the application can induce in the user, and that can affect his/her performance (Tran et al., 2007): indeed, mental fatigue is one of the main causes of error in BCI applications, especially in P300-based ones (Fazel-Rezai and Ahmad, 2007).

It has been shown (Cheng and Hsu, 2011; Hohnsbein et al., 1995) that fatigue and workload can affect the shape of the P300 wave, leading to decreasing accuracy in mental tasks performances. Hohnsbein and colleagues (1995) showed that performing mental tasks for a sustained period that involve attention and time-pressure leads to a relevant shift in latency of the P300 and consequently to an increased error rate. P300 amplitude decrease (Ullsperger et al., 1988) and latency increase (Murata, 2005) could be seen as a neurophysiological index of mental fatigue, since P300 is a neurophysiological marker of the attentional level (Cheng and Hsu, 2011). Hence it is important, when a new hybrid BCI application is developed, to consider mental workload as a crucial index, and to be sure that other used mental tasks, even when sequentially applied in a complex protocol, will not influence the P300 response.

More concretely, the level of attention can decrease with repeated presentation of the same type of stimulus (Lakey et al., 2011). Other factors, such as subjects' motivation, involvement and psychological state have been found to be crucial in determining the performance of a P300-based BCI, both in healthy volunteers (Leeb et al., 2007) and patients (Nijboer et al., 2007): thus, it is fundamental also that the proposed system maintains users' involvement and motivation at a sufficient level for the whole time it is on use.

This is true especially if the final aim is to use these systems outside the lab or the hospital, in a home context where, to have a certain degree of independence, the user will use them for a sustained time. In this context, the aim of the present study is pointing out if, during an experimental session conducted with a pure hybrid BCI, in which the P300 spelling procedure is alternated with different mental tasks (i.e. MI, watching a video, fixing the screen), P300 response varies, hence affecting classifier's accuracy and system performance.

3.2 Participants, materials and methods

Fifteen able-bodied, BCI-novice volunteers (eleven male, four female, mean age 26.8 ± 3.6 years old) took part in the study. Each subject received information about the potential risks related to the experiment, given informed consent and detailed instructions (in English or in German) about the following tasks. Moreover, to keep them motivated, they were paid 7.5 € per hour.

The EEG was recorded from 37 active, unipolar electrodes (see Fig. 3b), with positions according to a modified version of the International 10–20 System. In addition, the electrooculogram (EOG) was recorded from three sensors, and the electromyogram (EMG) was recorded from two electrodes (tibilias anterior muscle of both legs). Finally, one bipolar electrocardiogram (ECG) sensor was used.

The acquisition hardware was a g.GAMMAsys active electrode system along with a g.USBamp amplifier (g.tec, Guger Technologies OEG, Graz, Austria). The system sampled at 512 Hz, with a bandpass filter between 0.5 and 100 Hz and a notch filter at 50 Hz. The BCI application was driven by a software based on Matlab Simulink and developed by the Graz BCI lab (Pinegger et al., 2013).

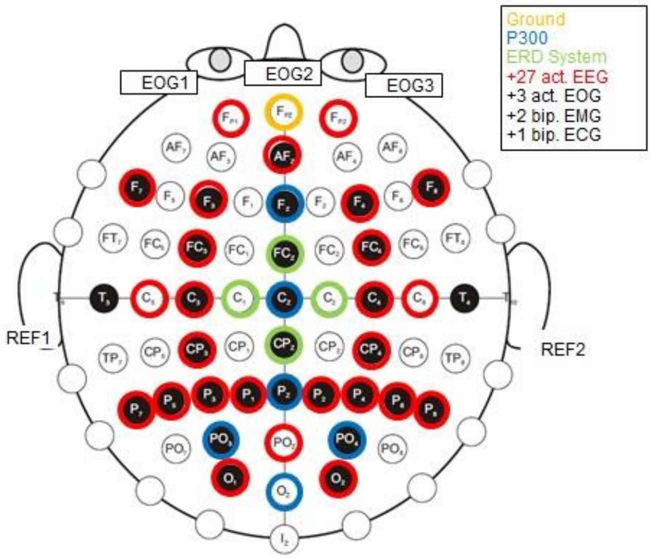

Fig. 3b: electrodes montage used in the hybrid BCI testing

In the present study the P300 and the SMR components of the EEG were used sequentially for BCI control. First, subjects underwent two calibration sessions both for P300 and for SMRs. These sessions were conducted in order to train the BCI classifier on the subject´s electrophysiological signals.

The P300 part consisted of a copy spelling mode of 10 letters (“v0qatod7h3”) using a 6x6 matrix speller. Each flash of row/column lasted 50 ms, with an inter stimulus interval (ISI) of

125 ms. For each letter to be selected, 15 sequences of flashing (i.e. of all rows and all columns) were used. Data were then used to train a Stepwise Linear Discriminant Analysis (SWLDA) classifier.

The calibration for SMRs consisted in a brisk movement imagery (MI) of both feet, evaluated versus a relaxed state, and it was actually split in two parts (see fig. 3c): offline and online training.

In the offline training the user had to do the MI and the relax tasks without receiving any feedback from the system. After two artefact free trials per class (giving that, in this case, the two classes were MI and relax) available, the system performed an autocalibration and it was possible to start the online training (for more details see Faller et al., 2012).
During the online training the user received feedback in form of a bar: the bar increased if the MI task was correctly performed and furthermore an additional compensation, a smiling face at the end of the trial, was shown. This second part lasted 54 trials per class and was split into three runs.

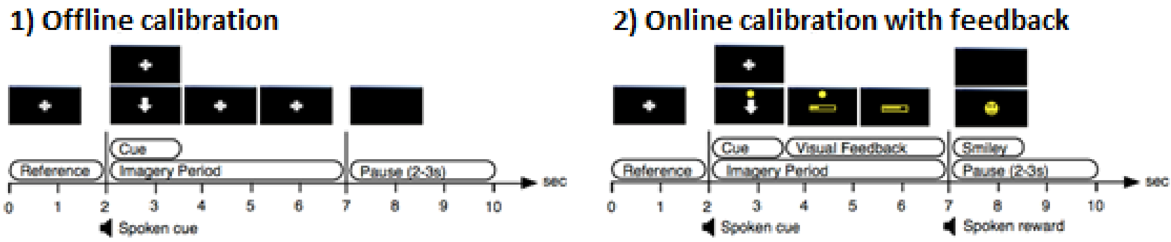

Fig.3c.: Design of the SMR calibration. In the first part the user did not receive any feedback about his/her motor imagery; then, in the second part, a bar indicated the level reached in each trial. If the trial was good, a smiling face gived an additional positive feedback.

The order in which the user underwent the calibration phases for the two cerebral signals (i.e. SMRs/P300 or P300/SMRs) was pseudo-randomized within the subject population, to compensate contingent effects of the calibration order: every subject underwent the same calibration, but 8 of them performed SMRs training and then the P300 one, the other 7 followed the opposite order.

After both calibrations, subjects performed the online hBCI phase: the aim of this phase was to mimic a real, ecologic hybrid BCI performance in which different tasks were sequentially performed. In the main control panel there were (see fig. 3d) the 6x6 speller matrix and, on the bottom, a series of 6 squares containing devices that could possibly be activated/deactivated using SMRs (from left to right TV, Video, Light, E-mail, Internet and Alarm). There was a vertical line going from left to right (taking 36 seconds to make the whole tour), and if the user would like to select a specific output, he/she had to perform MI while the line was in the desired square.

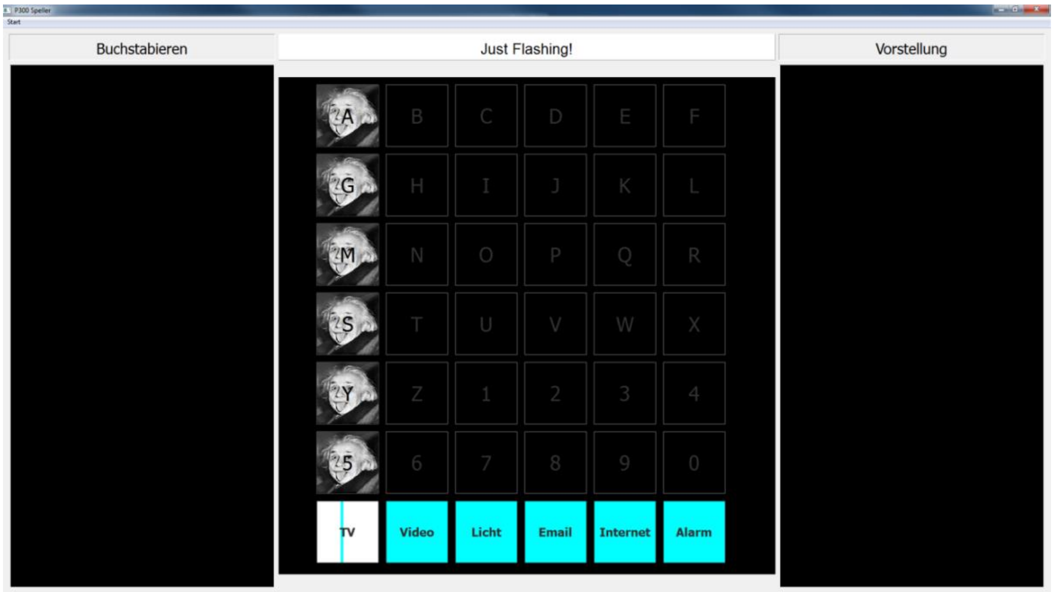

Fig. 3d: structure of the system interface used during the online phase; in the P300 speller matrix rows and columns were flashed using superimposing of famous faces; on the bottom, six squares allowed to select, using SMR, different devices; on the top commands are shown, on the left and on the right there are respectively P300 and SMR outputs.

Since it was the first time this system was tested, and we would like to keep conditions as much controlled as possible, subjects were not free to select or write whatever they wanted, but instructions were given automatically during the experimental session. These instructions appeared within the window above the speller, while on its left and right sides appeared, respectively, P300 and SMRs output selections.

During the online phase different paradigms were alternate: first of all, writing of a four letters word realized by the P300 (15 sequences of rows/columns flashes for each letter, 5 words within the whole hBCI phase), and 40 selections, divided into 20 (2x, i.e. Video and Alarm) trials for the SMRs task.

During both calibration tasks and the on-line session, the P300 selections were highlighted transparently superimposing Einstein´s face on characters, following the protocol suggested by Kaufmann and colleagues (Kaufmann et al., 2011).

Moreover, to make the BCI experience more complex and realistic, we added two further conditions: in one condition the subject had to look at the frozen screen (without any particular instruction about the screen area he/she had to look at) for one minute and in the other condition the task was to watch a movie (showing a marathon or a waterfall scenario, and running on a second screen), lasting 1 minute as well. In both cases an instruction ("look at the frozen screen 1" or "look the marathon/waterfall on screen 2") was displayed on the top of the main screen.

Different tasks were divided by a 5-seconds resting period, in which subjects were able to relax, blink, swallow without create muscular artefacts, before focusing on the next task. The order in which instructions were given and also the kind of video (i.e. marathon or waterfall) were pseudo-randomized between subjects.

We collected P300 data during both calibration phase (T0, for a total of 300 trials) and online phase (T1, for a total of 600 trials), in order to compare them and find any significant difference.

Only P300 data were then analysed in order to find differences, in shape and/or in latency, between T0 and T1: we considered as P300 the moment for each subject, between 250 and 500 ms, in which the difference between target stimuli and non-target stimuli event related potentials was maximized.

Before comparing P300 values, raw data underwent an offline processing realized with EEGLAB analysis tool (Schwartz Center for Computational Neuroscience, University of California, San Diego- USA). First, a manual rejection of artefacts on continuous data was performed, to delete data segments that were particularly corrupted by user´s involuntary movements; then, data were divided into 0.5 sec epochs, on which automatic online rejection was applied through an EEGLAB dedicated tool, which rejects epochs containing extreme values (limits: -75-+75 µV), abnormal trends (> 40 µV per epoch) and improbable data (>5 std). Then Independent Component Analysis (ICA) procedure was applied to get Weight Transposition Matrix (M), that was used in backprojection on raw data to exclude EOG and muscular artefacts. Data were then filtered (bidirectional FIR low pass, cut off at 15 Hz) and target stimuli related epochs (-0.5 sec- +1 sec) containing the P300 response were extracted. For that purpose an automatic online rejection was applied (with same criteria as before) that allowed us to remove P300 epochs corrupted by artefacts (their number changed within subjects, from a minimum of 24 rejected epochs to a maximum of 76); finally we selected the first (for calibration) and last (for online phase) 100 artefacts clear available epochs. In this way it was possible to have a number of stimuli responses sufficient to extract a proper P300, while on the other hand the time window between T0 and T1 was maximized (around two hours).

To analyze the morphology of the ERP, a grand average of subjects´ERPs for the two conditions (T0 and T1) was generated. P300 peaks were found searching for the highest values, for each subject, between 250 and 500 ms: to check that the found peak was the P300 response we compared also epochs containing target stimuli and epochs not containing them (where P300 was not present).

Values of classification accuracies were given by the SWLDA classifier itself, in terms of accuracy percentage reached after each flash sequence, and also in this case data of all users were merged to get their pre and post-protocol average.

3.3 Results and discussion

We analysed latency and amplitude values of P300 peaks on the central electrode line (Cz, Pz, Poz and Oz), to verify contingent shape changes. Furthermore, a comparison between accuracy levels reached by the classifier at T0 and T1 was performed.

Peak amplitudes and latencies

In order to analyse possible changes in P300 peak amplitude and latency over time we performed two 4 x 2 repeated measures analyses of variance (ANOVA). The ANOVAs included the factors ELECTRODE (Cz, Pz, POz, Oz) and TIME (T0 = calibration phase; T1 = online phase) as within-subject variables for amplitude and latency separated. Normal distribution of the data was tested and confirmed with a Kolmogorov–Smirnov test for normal distribution and whenever the sphericity assumption was violated Greenhouse-Geisser corrected values were used for further analysis. The probability of a type I error was maintained at 0.05.

The results of both 4 x 2 ANOVA revealed a significant main effect of ELECTRODE for P300 peak amplitude ($F(3.42) = 4.495$; $p = 0.024$) and latency ($F(3.42) = 3.714$; $p = 0.27$).

For posthoc comparisons a paired-samples t-test was conducted to compare the peak amplitudes in two time intervals (T0 and T1) for 4 electrode positions (Cz, Pz, POz, Oz). The results, reported in Tab. 2, showed no significant difference between the peak amplitudes in the calibration condition (T0) and the online condition (T1) for all four electrode positions.

A further paired-samples t-test was performed to compare the latencies of the P300 in the two time intervals (T0 and T1) for the 4 electrode positions. Again, no significant differences were found (see Tab. 3).

Table 2 *:* Descriptive Statistics and t-test Results for P300 peak amplitudes

	Before		After		95% CI for mean difference	T value	df	P value
	M	SD	M	SD				
Cz	3.016	1.881	2.188	2.013	-0.152; 1.807	1.812	14	0.092
Pz	3.033	2.023	2.418	1.521	-0.204; 1.434	1.610	14	0.130
POz	2.826	2.092	2.301	2.131	-0.304; 1.354	1.358	14	0.196
Oz	1.569	1.018	1.362	1.372	-0.495; 0.910	0.633	14	0.537

Table 3 *: Descriptive Statistics and t-test Results for P300 latencies*

	Before		After		95% CI for mean difference	T value	df	P value
	M	SD	M	SD				
Cz	0.455	0.049	0.471	0.078	-0.058; 0.026	-0.787	14	0.444
Pz	0.457	0.064	0.456	0.084	-0.027; 0.031	0.133	14	0.898
POz	0.454	0.066	0.446	0.085	-0.016; 0.032	0.726	14	0.480
Oz	0.435	0.063	0.432	0.071	-0.024; 0.029	0.228	14	0.823

Post hoc comparisons have been tested with a Bonferroni correction. However, also applying this adjustment P300 shape and amplitude remained not statistically different.

These results suggest that the P300 is not affected neither in amplitude nor in latency by further distracting tasks (performing motor imagery or watching a video) within the hybrid BCI system.

The fact that no significant differences were observed (neither in the amplitude or latency evaluation, even if a decreasing tendency was observed in the peak amplitude of the four electrodes) could be seen as a first cue that mental fatigue does not occur in the proposed BCI system.

In fact, in the proposed hBCI, SMRs modulation and P300 were used sequentially, concurring to select different commands, in a protocol that seems not to create mental fatigue in users.

Classifier accuracy

To see the effects of a prolonged hBCI protocol on the system performance, also the classifier accuracy was evaluated at T0 and T1. Accuracy was calculated by the SWLDA classifier using recordings of the whole montage, and results are given as accuracy curves (i.e. relationship between number of flashing sequences and percentage of accuracy). Then, for each subject the area under the curve was evaluated, and subjects means before and after the protocol were compared (Fig.3e) using a t-student test. Again, no significant result was obtained by the accuracy curves comparison between T0 and T1 ($p = 0.7464$), showing that the system performance was not affected by sustained use.

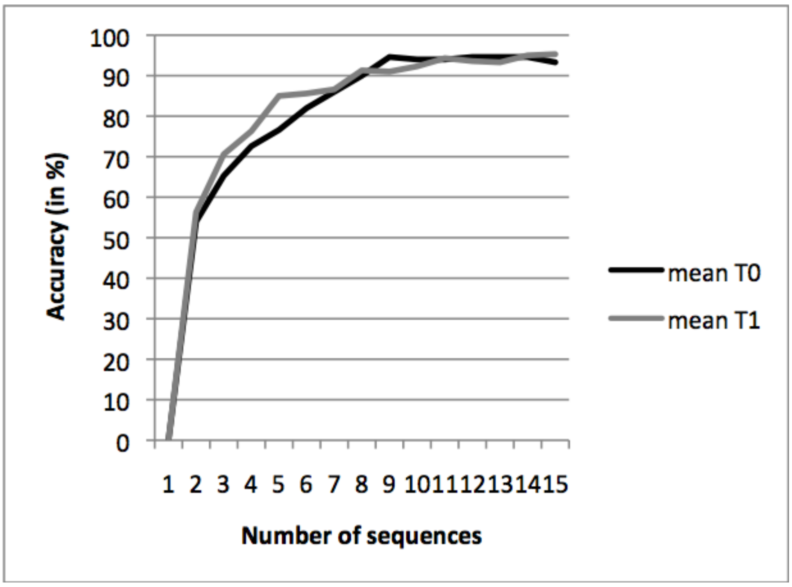

Fig. 3e: Grand average among all the subjects of the accuracy curve at T0 (before BCI protocol) and T1 (after protocol)

Actually, this continuous alternation between different tasks seems to maintain user´s attentional level and engagement very high, a crucial point to maintain an optimal accuracy level.

To verify this hypothesis, also classifier accuracy levels were evaluated. It has been pointed out from other authors (Riccio et al., 2011), in fact, that the accuracy measurement, together with workload assessment, are promising instruments for the evaluation of novel BCI systems.

Even after the prolonged application of the hBCI protocol, these accuracy values did not change in the proposed system, and they remained comparable to the one reported in P300 speller literature (i.e. Kaufmann et al., 2011).

This effect is very important when thinking to BCI end users, like patients with severe motor impairments. In this kind of patients an high accuracy maintained for a sustained period is crucial to use BCI systems even outside a laboratory/clinical environment (Fezal-Rezai, 2009). Indeed, it has been shown (Faller et al., 2014) that this kind of patients could benefit, in terms of performance and usability, of a system in which non-motor tasks are alternated to motor ones, as in the proposed hBCI.

With the present study, supported by the European Union research project BACKHOME, we have shown that a complex hBCI protocol, based on the alternated presentation of different tasks (i.e. spelling, brisk feet motor imagery, watching a movie and fixing the screen), does not affect the P300 response. The proposed application appears in fact not tiring and capable of engaging users´ attention, and appears therefore suitable for sustained use in a real-world scenario: actually, in further studies the proposed hBCI will be tested on a population of severely paralyzed patients, final users of such a system, in even longer sessions and with an higher degree of freedom (concerning commands selection order).

4. A Neurorehabilitation BCI: Parkinson's Disease study

4.1 Aims and study design

Parkinson's Disease (PD) is a neurodegenerative disease that affects, worldwide, more than 250 patients per 100.000 individuals (Abruzzese et al., 2009). Due to increasing life exptectance, especially in Western countries, this ratio is believed to become higher and higher in the next years. Moreover, due to the social and economical costs that this disease leads to, fighting it became one of the crucial challenge of the modern neuroscience.

PD is carachterized by a slow but indeed progressive loss of dopaminergic neurons from the *pars compacta* of the substantia nigra (Fig. 4a). This loss dramatically affects important motor circuits, such as the direct and indirect pathways, mediated by basal ganglia (DeLong and Wichmann, 2007).

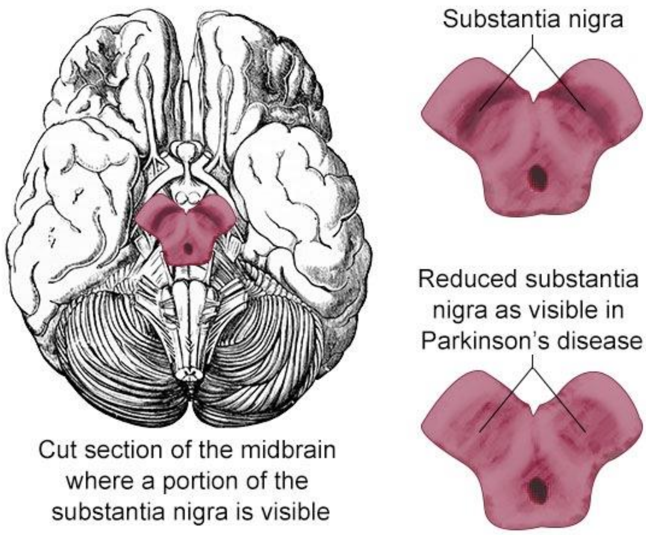

Fig. 4a: Anatomy of PD. On the left, anatomical localization of the substantia nigra; on the right, the neruodegeneration of its pars compacta, a process typically associated to Parkinson's Disease

In a small percentage of patients, the cause of Parkinson's disease is genetic; in this context, mutations in specific genetic loci have been associated to a dramatically increased risk of developing PD. These genes are involved in the production of alpha-synuclein (SNCA), parkin (PRKN) and leucine-rich repeat kinase 2 (LRRK2 or dardarin) (Klein and Westenberger, 2012). However, in the majority of cases the causes that lead to dopaminergic neurons degeneration are unknown, leading to a diagnosis of idiopathic PD. A number of environmental factors have been associated with an increased risk of PD onset, including pesticide exposure, head injuries, and living in the country or farming.

The neural degeneration of dopaminergic neurons leads, in the majority of PD patients, to severe motor deficits that include tremor at rest, bradikynesia, akynesia and gait disturbances (Xia and Mao, 2012). Gait symptoms are one of the most severe, since they affect patients' indipendence and quality of life, and they cohomprende freezing of gait and festination.

Freezing of gait (FOG) has been described as a walking deficit in which patients feel as their feet are glued to the floor; it is especially common during gait initiation or when facing an obstacle, and it happens because, due to degeneration that affects motor pathways mediated by basal ganglia, walking is an action less automatic in PD compared to healthy people.

However, far to be a merely motor pathology, PD is also carachterized (especially in the later stages of the disease) by a cognitive decline, often referred to as as 'PD Mild Cognitive Impairment (PD-MCI)' or as 'PD dementia' (PD-D), which main feature is a decline in executive functions, visuospatial abilities and memory maintanance (Lewis et al, 2005).

It has been shown (Cools et al., 2002) that the ability to plan, initiate and conclude goal directed tasks, as well as working memory and problem solving capacities, are impaired in PD patients due to a degeneration of fronto-striatal pathways.

Construction and praxis abilities are severely impaired, and the same is valid for visuospatial functions and attention (Ballard et al, 2002). Another important and frequent cognitive symptom in PD patients (around 67% of patients diagnosed with PD-D, see Meireles and Massano, 2012) is memory deficit. In these patients, short-term memory could be impaired, both for initial learning and for recall. These non-motor features obviously cause a reduction of patients' quality of life and indipendence, and they are usually unresponsive to classical therapeutic strategies.

Finally, it is possible to observe (Soikkeli et al., 1991) a change in brain activity patterns, especially in terms of brain oscillations frequency: in PD patients brain rhythms (i.e. simultaneous neural population firing) at rest are slowed down, with an increased power of certain rhythms typically related to resting states (i.e. delta and theta ones) coupled with a decresed amplitude of alpha and beta, commonly associated to brain-engaging activities.

Commonly used ways to tackle the disease are the pharmacological one, the deep brain stimulation (DBS) and motor rehabilitation. Drug assumption mainly concernes dopamine agonists, such as L-DOPA, a dopamine precursor that is able to cross the blood-brain barrier allowing to re-establish the normal dopamine concentration in PD patients. However, in a large part of patients treated with L-DOPA, hyperdopaminergia can occour, causing many of adverse side effects: physical ones may include hypotension, especially in case of drug over assumption, arhythmias, nausea, gastrointestinal complications, breath problems and hair loss. Chronic L-DOPA administration cal lead to end-of-dose deterioration of function and dose failure (drug resistance), and to an increase of normally observed motor symptoms (i.e. freezing during movements and dyskinesia, see Warren et al., 2013). Moreover, neuropsychological side effects cohomprend a large range of disturbs, such as disorientation and confusion, extreme emotional states (i.e. anxiety, extreme libido and gamble addiction), sleep disturbances and insomnia, auditory or visual hallucinations and effects on learning (Rascol et al., 2000).

A more invasive method to tackle PD symptoms is represented by the insertion of a deep brain stimulation (DBS) device into the patient's brain: this kind of system allows to mitigate symptoms, executing functions originally done by the deteriorated motor pathways.

However, only 5-10% of PD patients are considered suitable for DBS implantation: inclusion criteria include the pathology course, symptomatic picture, age and general life style.

Commonly, PD patients undergo a series of motor physiotherapic terapies, which include treadmill walking and specific physical excercise that aim to restore motor functions (or at least slow down motor decay).

All these treatments, however, typically have an impact only on motor symptoms; moreover, they have side effects (as in the case of drug assumptions) or they are tiring and not easy to follow (as for the physical rehabilitation). The emerging need of a novel therapeutic strategies pushed research toward neurorehabilitation field, that allows to correlate neurophysiological understanding of healthy people's and patients' brain circuits to motor and cognitive enhancement. In this optic, one of the tools that is possible to use within a neurorehabilitation approach are BCIs.

We then started a pilot study aimed to developed and tested a novel neurorehabilitation tool for PD, based on the coupled application of BCI technology and MI, to tackle the disease in three different aspects: motor, neurpsychological and neurophysiological.
To do so we took advantage of the collaboration of Dr Paolo Scoppola (www.paoloscoppola.com) that developed a customization of the 'Cursor task' module of BCI2000. In particular, his software translates the intensity of the recorded ERDs into the speed of a minimovie in which a walking person is shown (see Fig. 4b).

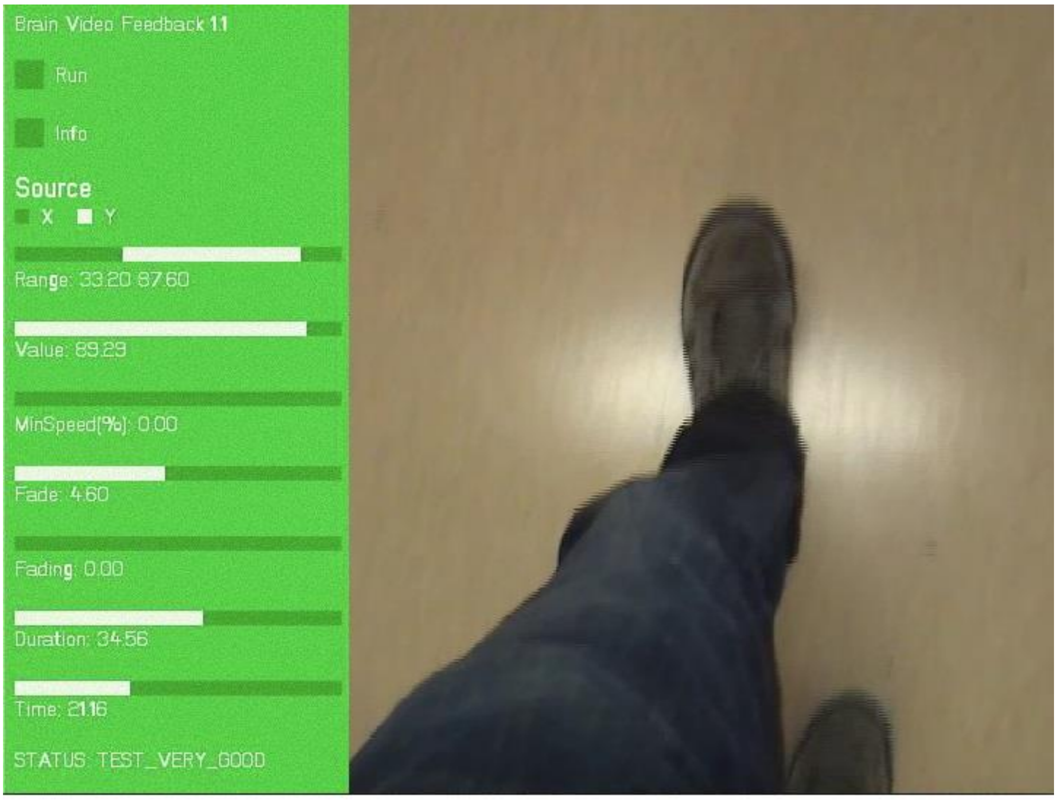

Fig. 4b: screenshot from the Neurofeedback application. From the menu on the left it is possible to regulate the signal range used to get feedback, the minimum speed of the movie, and the fading time (i.e. period without perfect signal in which movie continues slowly in order to motivate users)

The study design included a baseline valutation (a battery of neuropsychological tests, a motor and clinical analysis and a quantitative EEG). Neuropsychological tests were done in collaboration with Dr Pierpaolo Busan, while clinical analysis were performed in the

Physioterapic Unit of the University of Trieste, under the guidance of Dr Susanna Mezzarobba. Then 15 experimental sessions followed with a frequency of 2-3 times per week. The study ended with a post-treatment evaluation which was performed within 10 days from the end of the treatment. Each experimental session was composed by a calibration phase, needed to adapt the BCI system to the user's brain signal features, an offline analys of data and an online application phase, in which parameters obtained during calibration were used to drive the neurofeedback software.

In our idea the equipment needed to repeat this treatment outside the lab, once it would be validated, should not be too much expensive, allowing patients to continue the training at home, with a very little degree of needed assistance .

4.2 Participants, materials and methods

Four patients with conclamated PD and gait disturbances (2 males, 2 females, 72,5±5 years old) were recruited for the present study. Patients followed a standard pharmacological therapy for PD, and both evaluations and experimental sessions were conducted in "on" state. All subjects gave signed consense, and the study was pre-approved by the University Ethical committee, according to Helsinki regulation. One of the four subjects did not conclude the treatment protocol, due to an occurred comorbility.

Recordings were acquired with a standard EEG cap in which electrodes positions followed the International 10-20 coordinate system: signal was recorded from 11 positions (F3, Fz, F4, T3, C3, Cz, C4, T4, P3, Pz and P4) which are supposed to cover sensorimotor areas. For the baseline and post-treatment EEG evaluation other 10 electrodes (Fp1, Fpz, Fp2, F7, F8, Po5, Po6, O1, Oz and O2) were added, in order to cover the whole scalp. All electrodes were referenced to Afz and grounded to Poz. To detect muscular artifact also electroculography (EOG) and electromyiographic (EMG) electrodes were added. Impedances were always maintained below 5.0 kΩ. Signals were amplified and digitalized with a Micromed amplifier, high-pass analogical filtered at 0.1 Hz and sampled at 256 Hz.

Participants underwent a preliminary assessment of motor functions, a battery of neuropsychological tests for cognitive evaluation and a recording of spontaneous EEG activity. Then they underwent the BCI protocol, which consisted in 15 neuro-feedback (NF) sessions (1.5 – 2 hours, 2-3 times per week). A post-treatment evaluation was then executed, at the end of the cycle of experimental sessions, in the same way as the preliminary one in order to find contingent differences caused by NF training.

Each experimental session started with a calibration phase, in order to understand the neurophysiological features related to the patient's ERD. To do so we asked them to watch a PC screen. On it, a word ("cammina", i.e. "walk" in Italian) appeared for 7 seconds, followed by 7 seconds of blank screen. This turnover continued for a total of 20 sequences switches. We asked partipants to perform feet MI (walking) while the word "cammina" was on the screen; on the other hand, when the screen was blank, they should be as relaxed as possible, avoiding to think about motor tasks. At the end of the trial partipants could relax for a while, then we asked them to repeat this phase. For each participant we collected a total of 40 "feet MI periods" and 40 "relax periods", allowing BCI2000 classifier to understand which brain regions showed an ERD and at which frequency this phenomenon was maximed.

We then performed the on line NF training, in which patients' feet MI was translated into the movement of a movie. Gait in the movie is shown in first person (see Fig. 4c) in order to create the most ecological and immersive feedback for users.

a)

b)

Fig 4c: screenshots of the minimovie used for male (a) and female (b) patients.

Timing of this phase followed the parameters used in the calibration sessions, to obtain comparable (and so recognizable by the classifier) ERDs: 7 seconds of MI followed by 7 seconds of relax. The amount of NF trials varied (minimum of 32, maximum of 48) from participant to participant, and from one experimental session to another, in order to avoid patients' fatigue.

4.3 Results and discussion

Data from motor evaluation (see Table 4.1) indicated a reduction of the severity of FOG (FOG Q) and an improvement in mobility, as assessed by a dual task condition (MPAS). Postural stability was enhanced in two patients out of three (Berg Balance). These results are very interesting and promising, since patients achieved significant motor improvements without undergoing to stressing motor rehabilitation sessions.

Neuropsychological evaluation showed more variable results: subjects had a general cognitive improvement (MMSE) and performed better on some attention and executive tasks (interference task of the Stroop's Test; part B of the Trail Making test; phonemic fluency task), but they were worst on a series of other tests such as attention matrices. They also showed variable performance on a series of different tests, such as those evaluating mnemonic capacities.

Table 4.1: Significant results obtained by the three patients in the clinical and neuropsychological evaluation: baseline values (T0) are compared to post treatment (T1) ones. In particular, results of the Timed Up and Go test (TUG) are given in seconds, and those of the phonemic fluency test are given as amount of given words.

	Patient 1		*Patient 2*		*Patient 3*	
Clinical	*T0*	*T1*	*T0*	*T1*	*T0*	*T1*
BERG	51	53	54	52	51	54
MPAS	60	64	62	64	60	64
FOGQ	10	8	11	8	8	6
TUG (sec)	9.91	7.94	8.45	7.53	11.18	10.08
Neuropsych.						
MMSE	24.86	25.86	24.85	26.85	30	30
Stroop	15.4	20.4	14.3	19.3	20.8	22.8
Phonemic Fluency	38	42	13	18	44	56

Analysis of the spontaneous EEG mainly showed a higher power in beta and alpha bands, especially in frontal positions (see Table 4.2), as well as a higher power of slower brain rhythms (e.g. theta rhythms). These neurophysiological findings, which point to a possible normalization of alpha and beta activity, suggest a biological evidence of the efficacy of the BCI-based neurofeedback to restore a more normal brain activity.

The possibility exists, however, that EEG changed during the evolution of the disease, as a degenerative and/or compensatory mechanisms (Helmich et al., 2007). Positive results might also have been due to a synergic or aspecific effect of the different treatments (Mulder, 2007).

Table 4.2: most significant EEG results for the three patients; data are given as ratio between bands power (respectively α and β), recorded at baseline and post treatment, in two conditions (*op* = open eyes and *cl* = closed eyes), in resting state.

	Patient 1				*Patient 2*				*Patient 3*			
chann	**α op**	**α cl**	**β op**	**β cl**	**α op**	**α cl**	**β op**	**β cl**	**α op**	**α cl**	**β op**	**β cl**
Fp1	1,1	0,6	1,3	1,8	1,4	2,1	2,9	5,4	6,2	1,8	22,3	3,6
Fp2	1,7	0,7	2,2	1,3	1,8	1,6	3,5	1,9	3,7	2,4	15,5	2,6
F7	0,8	0,9	1,0	1,7	0,5	1,5	1,0	4,0	3,0	0,9	4,6	1,1
F3	1,4	1,5	1,5	1,7	1,3	0,5	6,4	1,1	2,3	1,2	3,1	1,5
Fz	0,9	1,3	0,9	1,5	1,7	0,6	2,0	0,6	1,2	1,8	1,2	2,2
F4	1,2	0,6	1,6	1,1	0,8	1,0	0,9	0,6	42,8	1,5	54,2	1,3
F8	0,9	1,2	0,6	3,0	0,5	1,6	1,3	1,5	3,8	2,6	4,6	1,5

Qualitatively, all patients reported that they were able to better face FOG episodes thanks to the mental task they were trained to, which they used as an internal cue to overcome gait blocks. However, these preliminary success are far to be considered as a proof of the validity of the present NF method, especially compared to more classical tecnhiques. The protocol will be tested on a larger population, and coupled with appropriate control groups (e.g., MI without NF) to disentangle these ambiguities and obtain an adequate statistical support. Thanks to the encouraging results obtained in these first trials, however, we are confident that the MI, used to drive a neurofeedback procedure through a BCI system, can reliably become a rehabilitation strategy in PD, complementary to the more traditional ones (which require active motor behavior). Its main limitation lies in the need of some assistance for the placement of the EEG cap, nevertheless it remains that single patient can use it with relatively little help, while a single care giver can follow several patients in the same session.

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