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COVERT ORIENTING OF VISUOSPATIAL ATTENTION IN A BRAIN-COMPUTER INTERFACE FOR COMMUNICATION

Direttore della Scuola: **Prof.ssa Clara Casco**

Coordinatore d'indirizzo: **Prof.ssa Francesca Peressotti**

Supervisore: **Prof. Konstantinos Priftis**

Dottorando: **Mauro Marchetti**

To my father,

in loving memory

CONTENTS

Preface

“What is it like to be conscious, but paralyzed and voiceless?” This is the partial title of a paper by Laureys et al. (2005), in which the locked-in state (LIS) is described. The LIS is a clinical condition with different etiologies. One of the causes of this clinical condition is a neurodegenerative pathology named amyotrophic lateral sclerosis (ALS). This pathology affects the motor neurons and it is characterized by muscular atrophy, spasticity, dysarthria, dysphagia, and impaired respiration. Those patients who survived the progress of the pathology, in the latest stages of the illness enter in the condition of the complete LIS (CLIS).

What can be the answer to the initial question? I think none. We can only try to imagine it. Or we can try to ask it directly to the CLIS patients. How? By translating their thoughts into commands! The brain-computer interfaces (BCIs) are systems that can directly translate the brain signals into commands, for an external device. By modulating their brain activity, patients may be able to control a software, which in turn, permits them to communicate.

Unfortunately, to date, no CLIS patient has been able to communicate through a BCI. Thus, “giving a voice” to an ALS-CLIS patient is still a challenging open question. It is easy to imagine the implications that an efficient BCI may have in the clinical practice, in the patients’ quality of life, and in the ethical-legal debate on the end-of-life question related to such clinical condition.

In the present dissertation is described the attempt to develop an efficient visual BCI for ALS patients, by implementing principles derived from cognitive psychology. The focus of the dissertation is on the development of visual interfaces for controlling a virtual cursor, which does not require muscles control, or eye movements. This is a crucial point in order to facilitate the communication, through visual interfaces, of paralyzed patients who cannot easily control the directional movements of their gaze. This is the case of the ALS patients in the latest stages of their illness.

Summary

English version

1. Introduction

The multidisciplinary approach of using brain signals for directly controlling external devices, like computers or prosthesis, is named brain-computer interface (BCI). Farwell and Donchin (1988) showed that it is possible for humans to communicate using a BCI, by means of their event-related potentials (ERPs; e.g., P300), without the involvement of their voluntary muscle activity. The use of brain-wave-guided BCIs offered new perspectives regarding communication and control of devices for patients suffering from severe motor impairment or for patients who completely paralyzed, such as the patients affected by amyotrophic lateral sclerosis (ALS), in the latest stages of the illness.

In the last two decades an important scientific and clinical challenge has been the development of efficient BCIs for ALS patients. Most of the progress in the field has been mainly concerned with algorithm improvement for better signal classification. In contrast, only few studies have addressed, to date, the role of cognitive mechanisms underlying the elicitation of brain-signals in BCIs.

In the present study we investigated the possibility to modulate the brain signal and, by doing so, the performance of an ERP-guided BCI system, by designing and implementing three new interfaces in which participants were required to perform covert visuospatial attention orienting (Posner, 1980), in order to control the movement of a cursor on a monitor.

2. Experiment 1

The effects of covert visuospatial attention orienting within an ERP-guided BCI were tested on healthy participants. We compared the effectiveness of three visual interfaces, each of whom elicited different modalities of covert visuospatial attention orienting (exogenous vs. endogenous). Twelve adult participants performed 20 sessions, using the abovementioned ERP-guided BCI interfaces to control the movement of a cursor. Brain waves were recorded on each trial and were subsequently classified online, by means of an ad-hoc algorithm. Each time the target ERPs were correctly classified, the cursor moved towards the target position. The “endogenous” interface was associated with significantly higher performance than the other two interfaces during the testing sessions, but not in the follow-up sessions. Endogenous visuospatial attention orienting can be effectively implemented to increase the performance of ERP-guided BCIs.

3. Experiment 2

To investigate whether the findings reported in Experiment 1 depended on the used classification system, we performed an offline reclassification of the data of Experiment 1. The online analysis of the epochs was made via Independent Component Analysis (ICA), which, in turn, was followed by fixed features extraction and support vector machine (SVM) classification. The offline epochs analysis was performed by means of a genetic algorithm (GA), which permitted us to retrieve the relevant features of the signal to be classified, and then to categorise them with a logistic classifier. The offline analysis confirmed the advantages derived from the use of the “endogenous” interface. The performance-related findings were in line with those obtained in the neurophysiological data analysis. Nonetheless, epoch categorization was performed better with the GA algorithm than with the ICA: the higher mean and the smaller standard deviation of the classification performed with the GA seem to promise a possible improvement of the ERP-guided BCI also on online tests.

4. Experiment 3

On the basis of the results of Experiments 1 and 2, we tested the efficacy of two visual interfaces, each of whom elicited different modalities of covert visuospatial attention orienting (exogenous vs. endogenous), in ALS patients. Ten ALS patients performed 16 online sessions with each interface. Although the ALS patients had a performance of about 70% with both the interfaces, the endogenous interface elicited a larger difference on ERP potentials between target and non-target trials. These results supported the hypothesis that the use of the endogenous interface may offer a more efficient channel of communication for ALS patients with respect to the use of the exogenous interface.

5. Conclusions

Neurological diseases that affect the motor system may impair communication abilities of patients, as in the case of amyotrophic lateral sclerosis. This pathology might evolve in the locked-in syndrome (LIS), a condition in which patients remain conscious but cannot move any of their muscles. For instance, they may become unable to express their opinions and decisions on important questions regarding their clinical treatment or their living and biological wills. The BCIs represent a potential solution to the communication problems of ALS-LIS patients. Despite the fact that more than 20 years have passed since the first published article on a P300-guided BCI, the effects of cognitive mechanisms (i.e., executive functions, attention, memory, etc.) involved in brain signal elicitation have not been investigated extensively.

In the abovementioned experiments, we tested the effect of covert visuospatial attention orienting on an ERP-guided BCI, by comparing a number of visual interfaces, each of whom elicited a different modality of covert visuospatial attention orienting. Taken together, the results supported our main hypothesis: It is possible to modulate the performance of an ERP-guided BCI, by using endogenous or exogenous visuospatial attention orienting. Of particular relevance is the fact that our ALS patients were able to use endogenous visuospatial attention orienting and, by doing so, they could increase their performance in an ERP-guided BCI. We suggest that the study of covert visuospatial attention orienting is essential for developing efficient visual BCIs for patients who cannot control their eye movements.

Implementing principles taken from cognitive psychology, may improve BCIs efficiency. This, in turn, can increase the benefits for patients with severe motor and communication disabilities. Finally, an efficient cognitive-based BCI may have the considerable ethical implication of "giving a voice" to CLIS-ALS patients.

Sommario

Versione in italiano

1. Introduzione

Farwell e Donchin (1988) per primi hanno dimostrato la possibilità che l'uomo ha di comunicare usando i potenziali evento correlati (ERP; e.g., P300), senza bisogno di usare alcun muscolo per tale fine. Questa scoperta ha offerto nuove prospettive per la comunicazione ed il controllo di periferiche in pazienti affetti da gravi disabilità motorie o completamente paralizzati, come nel caso dei pazienti affetti da sclerosi laterale amiotrofica (SLA), negli stadi più avanzati di malattia. L'approccio multidisciplinare che consente di tradurre segnali cerebrali direttamente in comandi per controllare computer o protesi meccaniche è chiamato *brain-computer interface* (BCI). Negli ultimi vent'anni un'importante sfida scientifica è stata quella di sviluppare una BCI efficace, affinché potesse essere usata nella pratica clinica con i pazienti. I progressi più rilevanti fatti finora riguardano principalmente la registrazione e l'elaborazione dei segnali cerebrali, grazie ad algoritmi sempre più potenti ed efficaci nella categorizzazione dei biosegnali.

Minore attenzione è stata posta, invece, nell'investigare il ruolo dei meccanismi cognitivi che sottendono l'uso di una BCI. Nel presente studio è stata indagata la potenzialità dei partecipanti di modulare specifiche onde cerebrali e, di conseguenza, l'efficacia di un sistema BCI guidato dagli ERP, attraverso l'uso di diversi processi di orientamento implicito dell'attenzione visuospaziale (Posner, 1980). A tale scopo sono state progettate e testate tre nuove interfacce visive per controllare il movimento di un cursore su un monitor.

2. Esperimento 1

Nel primo esperimento è stato testato l'effetto dell'orientamento implicito dell'attenzione visuospaziale in partecipanti sani, il cui scopo era di controllare il movimento di un cursore con una BCI guidata da ERP, per raggiungere specifici bersagli. È stato confrontato l'uso di tre interfacce, ciascuna delle quali prevedeva l'utilizzo di una specifica modalità dell'orientamento implicito dell'attenzione visuospaziale (esogeno vs. endogeno). Dodici partecipanti adulti hanno eseguito 20 sessioni, con ciascuna delle tre interfacce. Simultaneamente, gli ERP associati a ciascun trial di ogni interfaccia erano registrati e classificati da un algoritmo *ad hoc*. Ogni volta che gli ERP associati alla direzione della posizione bersaglio erano correttamente classificati, il cursore era mosso di un passo verso la posizione bersaglio. I partecipanti hanno ottenuto un'accuratezza migliore nel controllo del cursore con l'interfaccia che prevedeva l'orientamento endogeno dell'attenzione visuospaziale rispetto alle due interfacce che prevedevano l'orientamento esogeno.

3. Esperimento 2

Nel secondo studio è stata eseguita una classificazione *offline* degli ERP registrati nell'Esperimento 1, con lo scopo di verificare se gli effetti ottenuti nell'Esperimento 1 fossero indipendenti dal tipo di algoritmo di classificazione utilizzato. La classificazione *online* dei segnali cerebrali avveniva attraverso l'analisi delle componenti indipendenti (ICA), un'estrazione di 78 caratteristiche stabilite *a priori* del segnale, e la loro categorizzazione attraverso un algoritmo matematico di tipo lineare (support vector macchine: SVM). La riclassificazione *offline* è stata eseguita per mezzo di un algoritmo genetico (genetic algorithm: GA), che rilevava *ad personam* le caratteristiche significative del segnale, le quali, infine, venivano categorizzate attraverso un classificatore logistico. Il metodo di classificazione *offline* nell'Esperimento 2 ha confermato l'effetto ottenuto nell'Esperimento 1. Questi risultati sono stati confermati anche dalle analisi statistiche eseguite sui dati neurofisiologici. Inoltre, le medie di accuratezza più alte e la minore variabilità associate al sistema di classificazione *offline* sembrano offrire potenziali miglioramenti dell'efficacia dell'uso in tempo reale della nostra BCI.

4. Esperimento 3

Alla luce dei risultati riportati negli Esperimenti 1 e 2, è stata testata l'efficacia di un'interfaccia che prevedeva l'uso dell'orientamento esogeno dell'attenzione visuospaziale e di un'altra che prevedeva l'uso dell'orientamento endogeno, con pazienti affetti da SLA. Dieci pazienti con SLA hanno eseguito 16 sessioni con ciascuna delle due interfacce. Anche se i pazienti hanno ottenuto un'accuratezza di circa 70% con entrambe le interfacce, è stata registrata una maggior differenza tra gli ERP target e quelli non-target con l'uso dell'interfaccia "endogena". Questi risultati supportano l'ipotesi che l'interfaccia che usa l'orientamento endogeno dell'attenzione visuospaziale consenta un miglior controllo del sistema BCI, con conseguenti vantaggi comunicativi per i pazienti affetti da SLA.

5. Conclusioni

Le patologie neurologiche che colpiscono il sistema motorio possono intaccare i normali canali di comunicazione, come nel caso di pazienti affetti dal SLA. Questa malattia può sfociare nello stato denominato sindrome *locked-in* (LIS), una condizione clinica in cui i pazienti sono completamente paralizzati ma mantengono intatta la loro consapevolezza. Nella condizione di LIS, un paziente non può comunicare, non potendo così esprimere la propria opinione riguardo alle scelte etico-giuridiche legate alla sua condizione clinica. Le BCI rappresentano una potenziale soluzione ai problemi comunicativi dei pazienti nella LIS. Negli ultimi vent'anni di ricerca scientifica sulle BCI è stata rivolta grande attenzione alle componenti tecnologiche implicate nella registrazione del segnale cerebrale e nella sua classificazione in comandi per controllare specifiche periferiche. Viceversa, minor attenzione è stata posta alle caratteristiche dell'utente nell'utilizzo delle BCI, in particolar modo riguardo alle componenti cognitive coinvolte.

Negli esperimenti riportati nella presente tesi, abbiamo testato l'efficacia di diverse interfacce, ciascuna delle quali utilizzava una specifica modalità dell'orientamento implicito dell'attenzione visuospaziale (endogena o esogena). I risultati di questi esperimenti supportano l'ipotesi che è possibile modulare l'efficacia di una BCI guidata da ERP attraverso l'implementazione di interfacce visive che utilizzano diversi principi dell'orientamento implicito dell'attenzione visuospaziale. Tale risultato è di particolare rilevanza dal punto di vista clinico per i pazienti affetti da SLA, negli stadi terminali di malattia, cioè quando entrano nella condizione clinica di LIS. In particolare nell'Esperimento 3 è riportato come l'ampiezza degli ERP sia diversamente modulata nelle due interfacce testate e questo fatto può giocare un ruolo rilevante nello sviluppo di un efficace sistema BCI che permetta la comunicazione a pazienti affetti da SLA nella condizione di completa LIS.

I nostri risultati portano evidenze di come l'implementazione dei principi della psicologia cognitiva nello sviluppo di una BCI ne possano modulare l'efficacia, e questo a vantaggio dei pazienti affetti da gravi disabilità motorie. In conclusione, un'efficace applicazione dei principi cognitivi nello sviluppo delle BCI può avere l'effetto rilevante di "dare una voce" a pazienti in stato di completa LIS.

List of Abbreviations and Acronyms

ALS	Amyotrophic Lateral Sclerosis
ALSFRS-R	ALS Functional Rating Score - Revised
ANOVA	Analysis of Variance
BCI	Brain-Computer Interface
BMI	Brain-Machine Interface
BOLD	Blood Oxygenation Level-Dependent
CLIS	Completely Locked-In State
CNS	Central Nervous System
ECoG	Electrocorticogram, Electrocorticography
EEG	Electroencephalogram, Electroencephalography
EOG	Electrooculogram
ERD	Event-Related Desynchronization
ERN	Error-Related Negativity
ERP	Event-Related Potentials
ErrP	Error-Related Potentials
ERS	Event-Related Synchronization
fMRI	Functional Magnetic Resonance Imaging
FU	Follow-Up
GA	Genetic Algorithm
HCI	Human-Computer Interaction
ICA	Independent Component Analysis
ITI	Inter Trial Interval

LIS	Locked-In State
LNC	Late Negative Component
LS	Learning Session
MEG	Magnetoencephalography
NIRS	Near Infrared Spectroscopy
PNS	Peripheral Nervous System
P300	ERP of positive amplitude with a latency of about 300-500 ms
Pr	Precision
QoL	Quality of Life
Re	Recall
SCP	Slow Cortical Potential
SMR	Sensorimotor Rhythm
SNR	Signal to Noise Ratio
SSVEP	Steady State Visual Evoked Potential
SVM	Support Vector Machine
TS	Testing Session
TTD	Thought Translation Device
VR	Virtual Reality

1. INTRODUCTION

In everyday life, we interact with other people in order to communicate, or we interact with our environment by means of tools use in order to reach our goals. All these forms of communication and of device control require the involvement and the complex interaction among our central nervous system (CNS), our peripheral nervous system (PNS), and our muscles' activity. This happens all the times (e.g., when we want to speak with someone or when we want to write an e-mail). The process starts with the formulation of our intents. Underlying our intents, several nervous activities occur in the CNS. Those nervous activities are associated with the mental representations of our goals (i.e., to type an e-mail on the computer), to the processing of proprioceptive stimuli (e.g., the position of my arms, etc.), and to the processing of environmental stimuli (e.g., the positions of the keyboard, of the monitor, etc.). On the basis of the processing of such events, we perform the act. The activation of specific brain areas in the CNS triggers a signal to the PNS for eliciting specific muscle movements. All that happens in order to type our e-mail. Moreover, while we are typing, the letters are displayed on the monitor. The letters' onset works as both the final output and the feedback of our performance. On the basis of these feedbacks we could correct our errors or continue to write the text. In summary, we modulate our brain activity for controlling the PNS and, by doing so, our muscles, in order to obtain the desired output. This is schematically how works such a human-computer interaction (HCI; Figure 1).

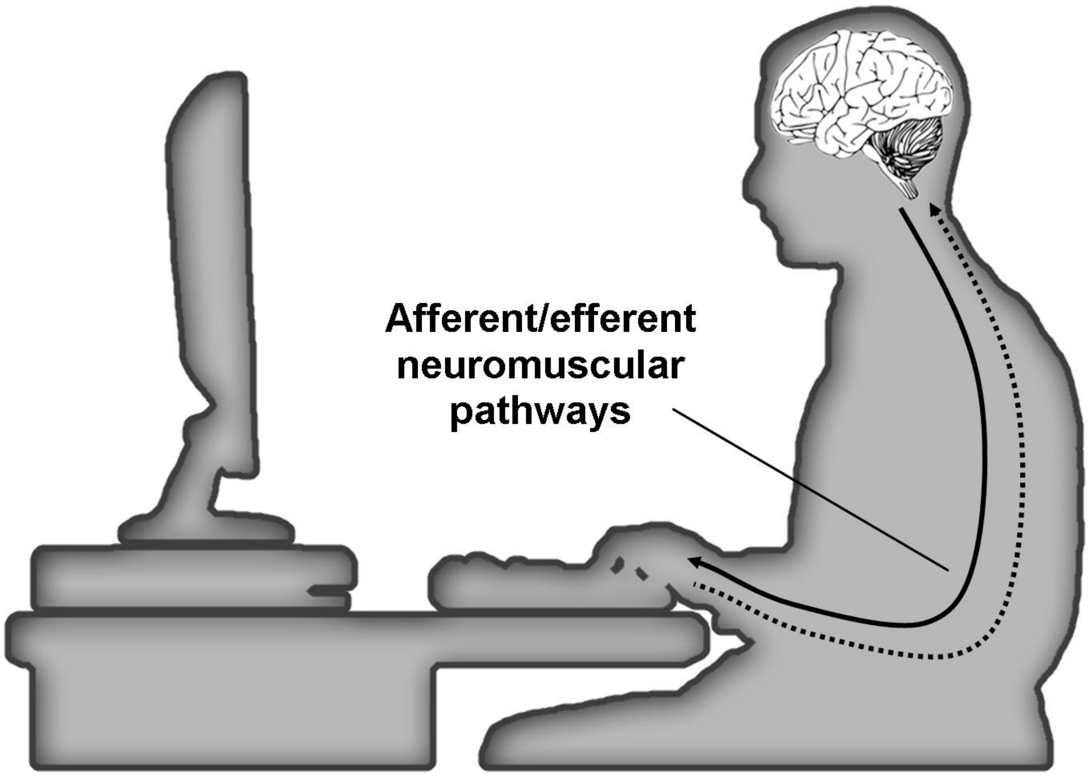

Figure 1.1 Normal human-computer interaction.

One of the most ambitious human dreams regards the possibility to directly control external devices just by means of our thought, without the aid of the PNS and the muscles. Scientists and clinicians, but also writers and movie directors, suddenly realized the key role that the brain had in making this dream real. Hans Berger (1924), who first discovered the electroencephalography (EEG) for recording the brain electrical activity, had already speculated about the possibility of investigating human thoughts through sophisticated algorithms. His aim was not forgotten: some decades after Berger's discovery, Grey Walter (1964) developed the first automatic analyzer of EEG frequency. His intention was to discriminate specific signs of the human language and thought. Moreover, Walter first implemented a system for controlling the advancement of a slide projector. He recorded the electrocorticogram (ECoG) from electrodes directly placed on the motor area of a patient who was undertaking a neurosurgical operation. Unfortunately, Walter did not publish his groundbreaking findings, but he only presented them at the Ostler Society in London (Dennet, 1992).

In the last twenty years many scientific and clinical programs were born, which aimed to make people use brain signals to directly control devices. This has been possible thanks to the increasing theoretic knowledge about brain activity, to the technological improvements in brain signal detection and processing, and to the cheaper costs of the equipments for brain signal recording. This multidisciplinary approach is named brain-computer interface (BCI) or brain-machine interface (BMI).

The BCIs are man-machine systems that are able to establish a direct communication route between the brain and the external world. Without the aid of peripheral nerves and muscles, a BCI allows users to control external devices such as computers (Figure 2), prosthetic limbs, wheelchairs, and so on. After the first attempts to develop an efficient BCI system that could work in real time, it became clear the potential clinical application that BCIs could have for patients with devastating motor impairments. Since then, the development of an efficient BCI for patients' communication and motor control has still been an open challenge in scientific research, with fascinating implications for future everyday life applications also for healthy people.

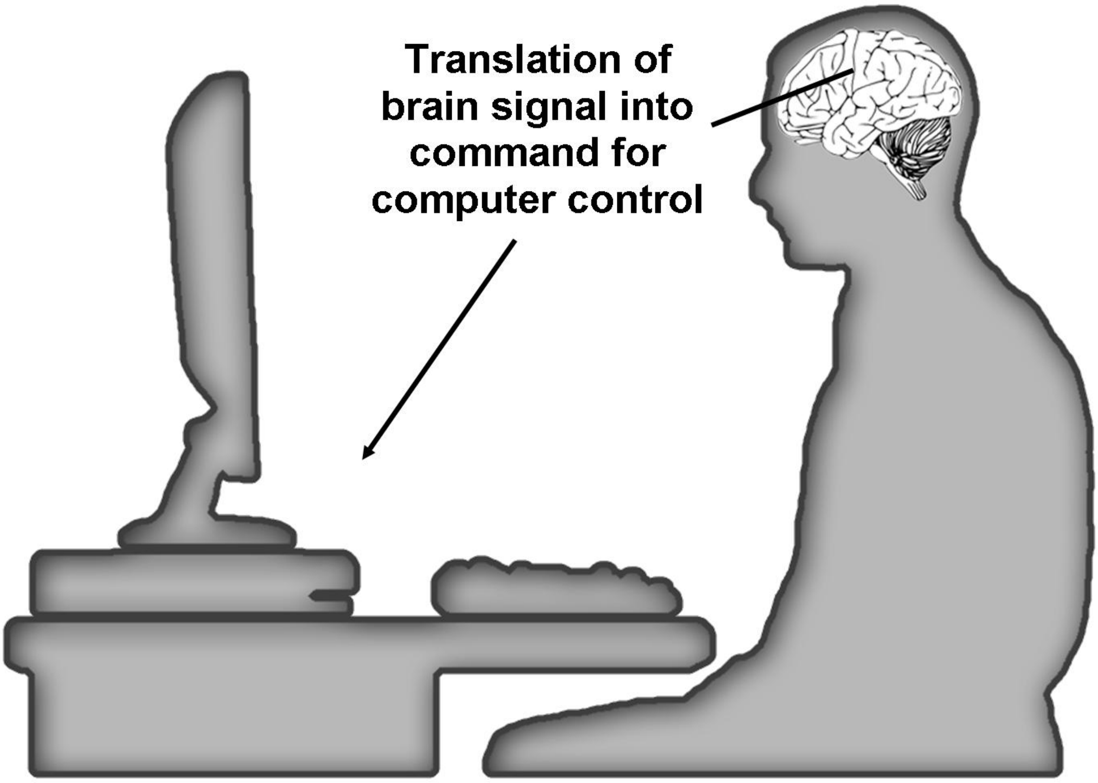

Figure 1.2 Brain-computer interface.

1.1. DEFINITION AND TYPOLOGIES OF BRAIN-COMPUTER INTERFACES

Several definitions of brain-computer interface can be found in the scientific literature. Here are listed some of them:

1. Wolpaw et al. (2002): "*A direct brain-computer interface is a device that provides the brain a new, non-muscular communication and control channel*".

2. Donoghue et al. (2002): "*A major goal of a BMI (brain-machine interface) is to provide a command signal from the cortex. This command serves as a new functional output to control disabled body parts or physical devices, such as computers or robotic limbs*".

3. Birbaumer et al. (2008): "*A brain-computer interface (BCI) or brain-machine interface (BMI) activates electronic or mechanic devices with brain activity alone*".

As it was clearly stated in all the above mentioned definitions, for having a BCI, are required a recordable brain signal, that could be modulated at least into two different states, and a device, to be controlled by the brain signal. More in detail, every BCI system (Figure 3) is composed by:

a. the user, who has to modulate his brain activity in order to obtain the desired output on the device;
b. the recording system for acquiring the brain signals;
c. one or more computational algorithms for processing the brain signal and for translating it into a command;
d. the device that executes the classified command, giving a feedback to the user about his performance on brain activity modulation.

The recording system is used in order to acquire the brain signal, that must be classified in, at least, two states or levels. Indeed, having at least two levels is the minimum requirement for having a binary code (e.g., I/O; on/off; yes/no). Once

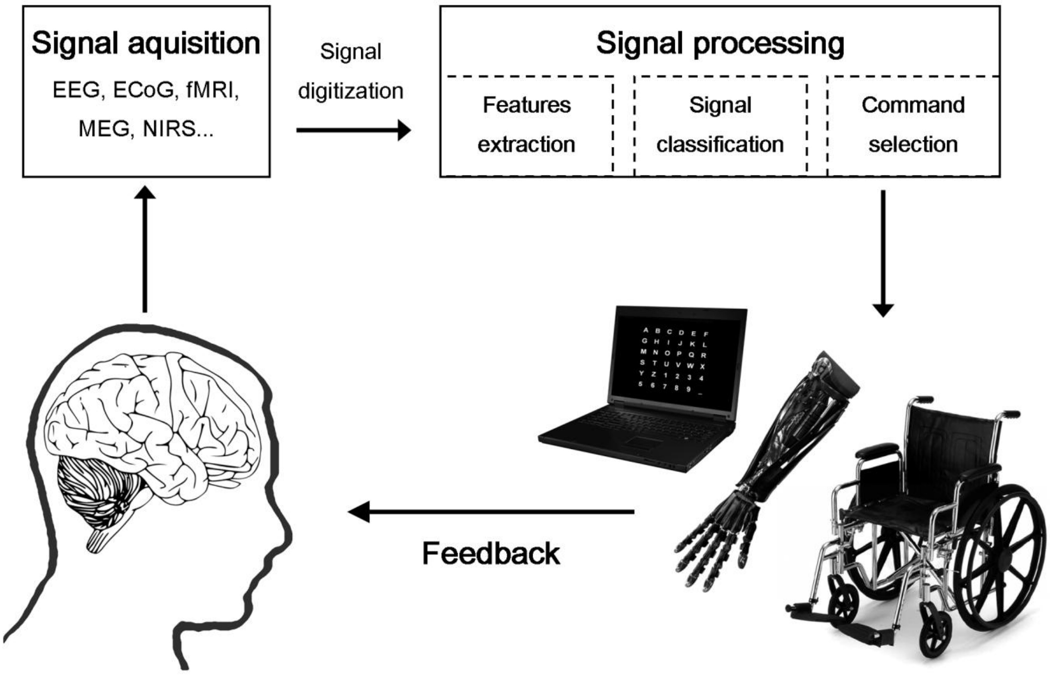

Figure 1.3 Schematic representation of a brain-computer interface.

acquired, the brain signal is digitized, in order to be further processed by the classification algorithms. The classification algorithms are a class of informatics techniques that permit us to categorize the signal into the different levels or states. This phase comprises two main steps: the extraction of the features that best define the acquired signal, and a classification procedure in order to categorize the signal features. Once categorized, the brain signal is translated into a command for the device. The execution of the command on the device works as both the last step of the BCI system and the feedback for the user, who has to modulate his mental activity in order to obtain the desired effect on the device.

There are several characteristics that allow us to distinguish between different BCI systems. According to the recording technique used, BCIs are divided into *invasive* or *non-invasive*. BCIs can be categorized also according to the mode of operation, which could be *synchronous* (cue-paced: in order to elicit the brain signal for BCI control the presentation of stimuli-cues is needed; e.g., P300-based BCI) or *asynchronous* (self-paced: in order to elicit the brain signal for BCI control the presentation of stimuli-cues is not needed, but the user has to perform specific brain task; e.g., BCI based on motor imagery tasks). Furthermore, the mode of operation with a BCI system is strictly related to user's cognitive processes for modulating the brain signal (e.g., selective attention, operant conditioning, motor imagery, etc.). A detailed description of the abovementioned classifications (i.e., invasive/non-invasive BCIs, synchronous/asynchronous BCIs, and mode of operation for controlling the BCI) will be given in the following paragraphs.

It has to be mentioned here that a further principle, for listing the BCI systems, relies on the classification procedure used. Below, in the present dissertation (paragraphs 3.2.3.1. and 3.2.3.2.), two classification methods for signal categorization, that were used in our experiments, will be described in detail. No more hints will be given on this topic, because the goal of the present dissertation is to focus more on interfaces' and users' aspects involved in BCI's use. For an overview about classification methods, we suggest the following reviews and original articles: Sitaram et al. (2011, 2007a) about the fMRI technique; Zhang et al. (2011) about the MEG technique; Bauernfeind et al. (2011) and Sitaram et al. (2007b) about the NIRS technique; Kleih et al. (2011), Lotte et al. (2007) and Rezaei et al. (2006) about the EEG technique.

1.1.1. Invasive BCI

Invasive methods require surgery (i.e., craniotomy) to implant the necessary sensors for signal recording. This is the case of the ECoG-based and intracortical recording-based BCIs (Figure 4, b and c).

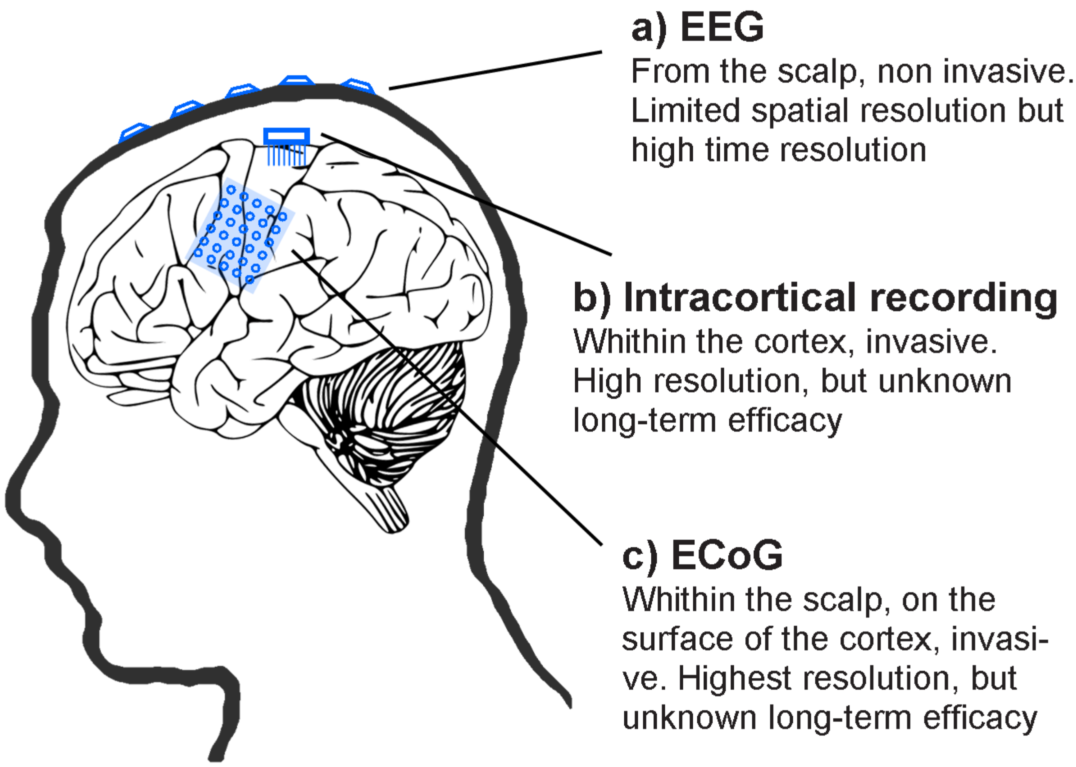

Figure 1.4 Three methods for recording brain's electrical activity.

These techniques are used for recording the EEG from the surface of the brain (i.e., ECoG), or directly from specific areas within the brain (i.e., intracortical recording). The ECoG does not cause any neuronal damage, because the sensors are leaned in specific positions on the cortical surface. Modulation of the brain signals in time, in frequency, or in both, could be used in order to control a BCI (Krusienski & Shih, 2011; Brunner et. al 2011; Blakely et al., 2009; Schalk et al., 2008; Hill et al., 2006; Leuthardt et al., 2004). The intracortical recording-based BCI (Nicolelis, 2001), instead, requires electrodes that penetrate the brain tissue, with consequent risk of neuronal damage. Kennedy and colleagues (2000) described a LIS patient, who was able to control the movement of a cursor on a display by means of electrodes implanted in the outer layer of his cortex. Compared to scalp-recorded EEG, both the ECoG and the intracortical recording present several advantages. The higher spatial and time resolution, the larger amplitude, and the higher signal-to-noise ratio are all good reasons for investing on invasive BCIs research. These advantages, however, have the serious drawback of requiring neurosurgery. Ethical, financial, and other considerations make neurosurgery impractical, except for those users who have no other way than these BCIs for communicating. Moreover, the long-term stability of these techniques might be problematic, because of signal deterioration.

1.1.2. Non-invasive BCI

Non-invasive BCIs are systems that do not require neurosurgery. The brain processes produce electrical and magnetic activity that can be recorded without the need of intracranial sensors. For instance, the functional magnetic resonance imaging (fMRI) measures changes in the blood oxygenation level-dependent (BOLD) signal associated with brain activity (Logothetis & Pfeuffer, 2004). The fMRI technique has been used for BCI purposes (Weiskopf, In press), by exploiting the specific activations of several brain areas, generally following mental imagery tasks. Also the magnetoencephalography (MEG), that records the magnetic fields associated with brain activity, has been used for developing a BCI.

Several paradigms, which allow the modulation of the brain signal at least into a binary level, can be used with fMRI and MEG for controlling a BCI (Mellinger et al., 2007). The fMRI has a high spatial but a low time resolution. This means that the distinction of different brain signal levels, on the basis of spatial features can be performed well by means of fMRI, but the communication speed will be quite low because of the slowness of the BOLD signal. On the contrary, the MEG has higher time resolution but lower spatial resolution, with respect to the fMRI. Both, however, are very large devices and prohibitively expensive, rendering, thus, very impractical the development of applicative BCIs for everyday use, outside the laboratory. Like fMRI, but with cheaper costs, also near infrared spectroscopy (NIRS) is a recent technique for assessing hemodynamic activity in the human cortex. Different blood oxygen levels result in different optical properties, which can be measured by NIRS, and used as brain signals for controlling a BCI (Sitaram et al., 2009). The NIRS has low time but quite good spatial resolution, with the advantage of being portable. Nevertheless the NIRS technique is still in an early stage of development.

1.1.2.1. EEG-based BCI

The cheapest and the most used technique in the BCIs is the EEG. The EEG is a well established technique, used for recording brain electrical activity from the scalp (Figure 4a), by mean of sensors (electrodes) placed over the head in specific positions (i.e., International 10-20 system). With respect to the above described techniques, the EEG equipment is lightweight, inexpensive, and easy to apply. The temporal resolution of the EEG is very good, whereas its spatial resolution is quite low and dependent on the number of electrodes placed on the scalp. For these reasons, the 80% of the BCI systems described in the literature rely on EEG-based techniques.

There are several types of EEG signals implemented for BCI control. Slow cortical potentials (SCP) are negative or positive polarizations of the EEG, which last from 300 ms to several seconds. They originate from depolarizations of the apical dendritic tree of the neurons in the upper cortical layers. These depolarizations are caused by synchronous firing, mainly from thalamocortical afferents. Birbaumer et al. (1999) first reported the successful modulation of SCP by two locked-in patients, for communication through a BCI. By producing voluntary changes in SCPs, the patients were able to select letters displayed on a monitor. This communication system was later called "thought translation device" (TTD; Kübler et al., 1999; Birbaumer et al., 2000; Hinterberger et al., 2003a, 2003b, 2004, 2005a). Nevertheless, the efficient control of an SCP-based BCI requires long periods of training, and the selection speed of the commands is quite slow (Birbaumer, 2006b).

The sensorimotor rhythm (SMR) or μ rhythm is an oscillatory rhythm of synchronized EEG activity, which has its maximal expression over the sensorimotor cortex (Figure 5, a and b). For most individuals, the frequency of the SMR is in the frequency range from 8 to 12 Hz. The SMR has been used by four paralyzed patients for controlling the movement of a cursor on a monitor, through EEG modulation in frequency and space, (Wolpaw and McFarland, 2004). Event-related desynchronization (ERD) and event-related synchronization (ERS) of SMRs have also been used for word spelling with patients (Neuper et al., 2003; Pfurtscheller & Neuper, 2006), and for developing a four-level brain signal for BCI's control (Pfurtscheller et al., 2006).

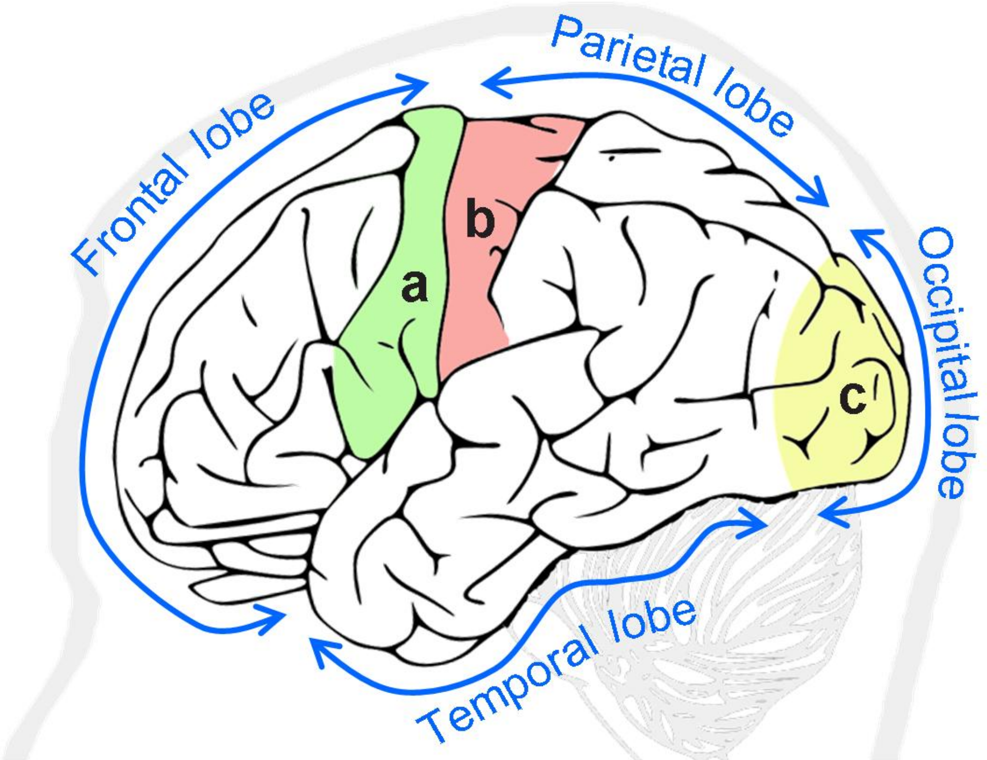

Figure 1.5 Classical lobe division of the brain. Brain areas of particular relevance for BCI systems are colored: a) motor cortex; b) somatosensory cortex; c) visual cortex.

The steady state visual evoked potential (SSVEP) is a brain signal recorded in response to specific visual stimulation frequencies. It is most prominent in occipital areas, because of the visual nature of the stimulation required. In a SSVEP-based BCI, the commands are associated with specific visual stimulation, which consists in a continuous flickering with different frequencies in the range from 5 to 35 Hz. Each visual stimulation has a specific flickering frequency. The user has to focus his attention on the stimulus associated to the to-be-selected command. As a result, in the visual cortex (Figure 5, c) SSVEPs will be elicited, which have the same frequency of the flickering stimulus. These potentials are recognized by the classifier and then the associated command is executed (Zhu et al., 2010). The SSVEP approach currently provides the fastest and most reliable communication paradigm for the implementation of a non-invasive BCI (Volosyak, 2011).

The event-related potentials (ERPs) are averaged brain waves in response to internal or external stimuli. They are also called evoked potentials because they are usually elicited by repetitive stimulation, while the EEG is recorded. The main point is that ERPs could be actively modulated by having the user performing specific cognitive tasks (e.g., focusing his attention on the occurrence of one out of several stimuli/events during their serial presentation). With respect to SCP- and SMR-based BCIs, ERP-based BCIs do not require a long training period, and, thanks to the stimulation characteristics of the interface used, it permits users to select among several symbols/commands. For example, Townsend et al. (2010) have proposed a visual interface for communication that permits users to select one among 72 symbols displayed in a 9 x 8 matrix. For these reasons, ERPs are to date the most used brain signals for controlling a BCI system.

1.1.3. Synchronous and asynchronous BCI

The core of a BCI is the detection and the classification of a brain pattern. Specific brain patterns are elicited in the user's brain. The user has to modulate his mental state in order to elicit the brain signal associated to desired command. Detection and classification efficiency can be simplified by defining specific time windows in which the user modulates his brain signals. To this aim, a stimulus is usually presented (e.g., a sound or a visual event). This stimulus indicates to the participant when to execute the mental task for obtaining the desired effect on the to-be-controlled device. This mode of operation is called synchronous or cue-paced. All ERP-based BCIs belong to this category, because for eliciting the ERPs it is necessary to present the user with a sequence of stimuli. Usually, the stimuli are designed both for triggering the brain signal and for selecting the command. The participant has to focus his attention on the stimulus/cue associated with the command he wants to select, and to avoid paying attention to the other stimuli/cues. The advantage of this category of BCIs is the reduced computational cost (the classifier “knows” when to process the brain signal) and the possibility of the user to choose among a large number of possible commands, according to the numerosity of the cues presented (each different cue is associated with one different command). The most well-known example of BCI belonging to this class of BCIs is the P300-speller (Farwell & Donchin, 1988), which is also the most studied paradigm in BCI research. A detailed description of this BCI is given in paragraph 1.2.

On the contrary, the asynchronous BCIs do not require the presence of a cue. These BCI are self-paced, because the user can perform the mental task just when he wants to execute a command on a device, without waiting for a cue. In this case, the BCI system has to process and analyze the brain signal continuously. Examples of asynchronous BCIs are those, which are based on motor imagery (e.g., the movement of the right arm vs. the movement of the left arm). Specific brain activation patterns are associated with different imagined movements. These activation patterns can be detected and translated into commands for BCI applications. The advantage of asynchronous BCI is that the users can send the command whenever they want. Nevertheless, this mode of operation is technically more demanding. Moreover, it permits the execution of a number of commands, which is equal to the levels of brain activation that the user is able to modulate, and the classifier can detect. Unfortunately, to date, the number of these levels is very limited.

1.1.4. Strategies for brain patterns modulation

BCI does not read mind. A BCI translates a specific brain pattern into an associated command, which will be executed on or by a device. So it is not sufficient to record a brain signal and to have a classifier for distinguishing among different brain patterns. It is necessary, instead, that the user learns to modulate his mental states in order to obtain the desired brain pattern that is associated with a specific command. There are several cognitive processes used in order to do that. The most common are: selective attention, motor imagery, and operant conditioning.

The BCIs which are based on selective attention require external stimuli provided by the interface. To this category belong the ERP- and the SSVEP-based BCIs. Different stimuli, each one associated with a specific command, are presented to the user. The user's task is to focus his attention on the stimulus that is associated with the target command. By performing this cognitive process (i.e. focusing his attention on a specific stimulus), a different brain pattern will be elicited by the target stimulus with respect to all the other stimuli (Farwell & Donchin, 1988; Zhu et al., 2010; Kleih et al. 2011).

The other highly used cognitive process for BCI control is mental imagery. Users are trained to imagine specific movements that elicit different brain patterns; then specific commands are associated to those brain patterns and executed via BCI. Mental imagery permits to use the spatial position of the brain activity elicited in the brain as feature for signal classification. For example, imaging to move the left hand will produce specific brain activation in the right motor cortex, whereas imagining moving the right hand will produce specific brain activation in the left motor cortex. Such signals, for example, are sufficient for developing a two-level control BCI (Sitaram et al., 2007b). Systems which are based on fMRI, NIRS, or EEG technique could use the spatially different brain activations for BCI's control. The EEG technique can be use also with other features associated to motor imagery tasks. Imaging to perform a movement produce the modulation of specific electrical frequencies in the brain (i.e., the SMR), that could be used in order to control a BCI. For examples, ERD/ERS patterns (see paragraph 1.1.2.1.) can be volitionally produced by users who are imagining to perform a movement (e.g., arms, hands, feet, and tongue movements). Such brain activity is used to develop SMR- (Pfurtscheller et al., 2006) or MEG- (Battapady et al., 2009) based BCIs.

BCIs that operate without prior conditioning of a specific EEG response do not require that the users undergo long or complex training procedures (i.e., ERP- and SSVEP- based BCIs). It seems reasonable, however, to think that the long-term use of any BCI would cause changes in the user for reaching the best adaptation on the to-be-controlled BCI (Kübler et al., 2001). Some BCI systems, instead, require operant learning in order to control successfully brain signals. It is the case of BCIs, which are based on neurofeedback principles for modulating specific EEG signals, such as the SCP (Birbaumer et al., 1999) or SMR (Wolpaw & McFarland, 1994; Wolpaw et al., 1991).

1.2. ERP GUIDED BCIs FOR COMMUNICATION

To date, the ERPs are the most studied and used technique for BCI control. The first example dates back to 1988, when Farwell and Donchin developed a mental prosthesis for “talking off the top of the head”. They presented to their participants a 6 x 6 matrix of letters and symbols. The rows and the columns of the matrix were randomly flashed, and the participants were required to focus their attention on a specific target letter. They found that a rather distinct P300 (i.e., larger amplitude) was elicited by the flash occurring in the combination of columns and rows, where the attended letter was positioned. Moreover, they investigated the possibility to detect the P300 associated with the target letter, by processing offline the ERPs through different algorithms for signal detection. The first ERP-based BCI was born. Farwell and Donchin used a variation of the oddball paradigm for eliciting the ERPs. The oddball is the classic procedure in order to elicit the P300 (Sutton et al., 1965). Usually, in the oddball task, two stimuli that differed for one feature (e.g., the frequency of acoustic stimuli, or the color of visual stimuli) are presented to the participants. One stimulus (e.g., standard or non-target) has a high probability of occurrence, whereas the other (e.g., deviant or target) has a low probability of occurrence. This simple experimental paradigm is sufficient for eliciting the P300 in response to the target stimulus. In the “mental prosthesis”, designed by Farwell and Donchin, all the columns and rows of the matrix where flashed the same number of times. The fact that the attended letter was present only in one out of six columns or rows was sufficient for creating an oddball-like paradigm, and, thus, for eliciting a larger P300 associated with the attended letter, with respect to all the non-attended letters. The crucial point is that the user can decide by himself which letter to select. Then the classification algorithms can detect the P300 associated with the flash of the column and the flash of the row containing that letter, and can display it on the monitor.

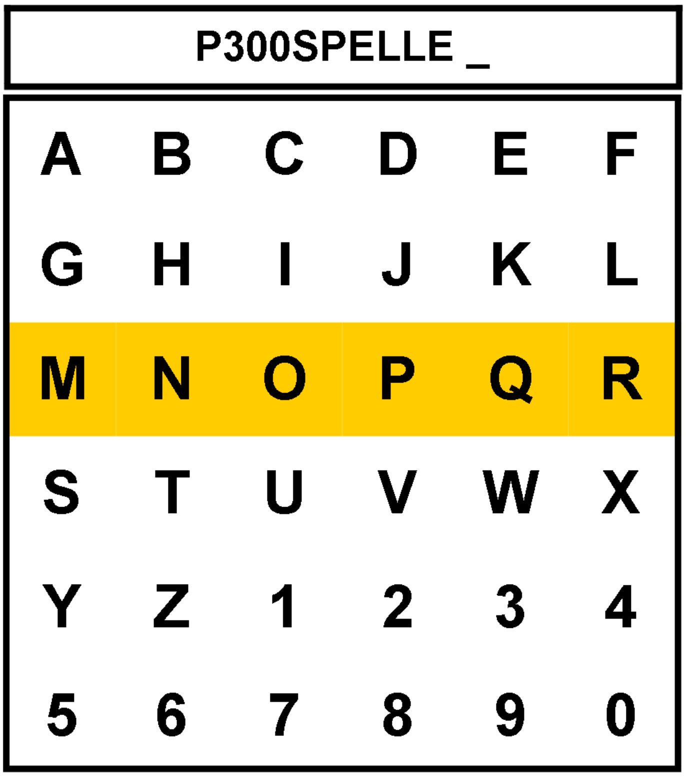

Figure 1.6 Schematic example of a P300-speller. Letters and numbers are displayed in a 6 x 6 matrix. Columns and rows are randomly flashed (i.e., the third row from the top in this matrix). Users have to focus their attention on the symbol they want to select. By doing so, a larger P300 is elicited when the column and the row containing the to-be-selected symbols are flashed. On the top box, the selected symbols are displayed.

For this reason the Farwell and Donchin "mental prosthesis" was lately called the "P300-speller" (Figure 6). The term "P300-speller" may induce the error of thinking that the P300 is the only ERP that could be used for guiding a BCI. Indeed, the classification systems in Farwell and Donchin experiment processed a whole epoch of EEG related to the event, and they evaluated all the features related to that epoch, not only the P300 component. It is true that the oddball-like task is the paradigm used with most ERP-based BCIs, and that the most prominent potential elicited is the P300. This is the reason why the term “P300-based BCI” is usually employed in the place of the more correct term “ERP-based BCI”.

To our knowledge, the only other ERP used for controlling a BCI or for improving the efficacy of a P300-based BCI is the error related negativity (ERN; also called error-related potential, ErrP). The ERN is a negative deflection in the EEG associated with incorrect motor responses. It has been recorded also in association with erroneous command selection in ERP-based BCIs. Some authors have successfully investigated the possibility of using the ERN for correcting the wrong command selections, in order to improve the efficacy of ERP-based BCIs (Jrad et al., 2011; Dal Seno et al., 2010; Parra et al., 2003). Compared to other signals, such as the SCP and the SMR, the P300 has the advantage of being independent from training. The P300 is quickly and robustly classifiable, even in patients with neurodegenerative diseases and in ecological settings (Silvoni et al., 2009; Nijober et al., 2008), when the signal-to-noise ratio (SNR) is quite low. Furthermore, the ERP does not require expensive equipment and high skilled personnel. Finally P300-based BCIs could be used at the patients’ bedside. For all these reasons, the P300-based BCI has been the most studied for clinical purposes with patients affected by severe motor disease, such as the ALS patients.

1.2.1. Clinical applications

The potential applications of BCI in clinical settings are many. The main point is that the use of brain signals could permit patients affected by severe motor impairments to communicate and to control devices. This technology would allow patients, who are completely dependent on clinical personnel and caregivers, to reach a basic level of autonomy in everyday life. ERP-based BCI could be used as an assistive tool able to restore patients' autonomy and independence (Mìllan et al., 2010).

Since the pioneering work of Farwell and Donchin (1988), the P300-speller has been the most studied BCI for word spelling. Several physical characteristics of that interface have been manipulated in order to find out the best combination of parameters, for reaching the highest accuracy in letter selection (for a more detailed description of these studies, see paragraph 2.1.). By using this interface, healthy participants were able to reach spelling accuracy up to 100% offline (Donchin et al., 2000; Guger et al., 2009) and online (Kleih et al., 2010). Also four ALS patients obtained good accuracy in letter selection with the P300 speller (78.8%, Nijboer et al., 2008). Unfortunately, it has been demonstrated that the efficacy of the P300-speller depends on the possibility of the patients to move their gaze on the to-be-selected letter (Brunner et al., 2010; Treder & Blankertz., 2010). This is a very relevant problem for those ALS patients who have impaired eye-muscle control, or who are in the completely locked in state (CLIS). For ALS patients who have impaired eye-muscle control, a possible solution has been recently reported by Liu et al. (2011). These authors described a visual interface for communication in which groups of letters were sequentially presented on a monitor within a visual angle of 3.28°. Their healthy participants were able to select letters with an accuracy that was higher than 93%. For the CLIS patients, the visual modality is not suitable because of lack of adequate eye movement, lubrication, and moisture (Murguialday et al., 2011). The BCI systems, which are based on the acoustic modality should offer a more realistic channel of communication, but their efficiency with patients, in real time sessions, has not been proved yet (Sellers & Donchin, 2006; Furdea et al., 2009; Schreuder et al., 2010).

Other approaches which use ERPs for developing communicative BCI have been proposed. Silvoni et al. (2009) used four directional flashing arrows in order for ALS patients to control the movement of a cursor on a monitor. On each side of the monitor an icon was displayed, depicting everyday life needs that the patients could select by reaching the icons with the cursor. With this interface, participants had to focus their attention on the flashing arrows indicating the direction of the icon that they want to select (i.e., the target icon). On the one hand, it is true that with this interface communication is limited to the number of icons implemented, of which only four could be displayed at the same time on the monitor. On the other hand, the same protocol can be used for several other goals, such as for controlling the movement of a wheelchair or for interacting with the surrounding environment by means of a robot (Piccione et al., 2008). The control of a robot and the interaction with the surrounding environment represent a non-extensively explored field of applications for ERP-based BCIs. Nonetheless, there are some notable exceptions which show the potential use of BCI within this area. Bayliss (2003) first demonstrated the possibility of environmental control with P300-based BCI, by means of virtual reality (VR). Another efficient method, tested with both healthy participants and patients with severe motor impairments, was proposed by Hoffman et al. (2008). These authors used a serial presentation of object images, which could be selected by the patients (e.g., TV, phone, radio, etc.). By using this interface, the patients reached very good performance. Other BCI approaches have been proposed for improving the quality of life (QoL) of paralyzed people. Adapting the command selection of a given software, it is possible to develop interfaces, which permit users to exploit the potentialities of a personal computer. That is the case of ERP-based BCI for internet browsing (Mugler et al., 2010) or for virtual brain-painting (Münßinger et al., 2010). The use of robots, instead, permits users to explore and interact with their environment, by means of the telepresence principle. An ERP-based BCI system for telepresence, which makes possible navigation, exploration and bidirectional communication, has been proposed by Escolano et al. (2010, 2011). These authors have successfully tested the telepresence through BCI with healthy participants. Nevertheless, tests on patients are required in order to evaluate the possibility of using the telepresence in everyday life.

The abovementioned examples give us the idea that the possible applications for ERP-based BCIs can be many.. The crucial point regards the interfaces' design. The possibility of transforming an interface into a stimulation paradigm that allows to elicit and to modulate ERPs is the only real limit for new applications with the ERP-based BCIs.

1.2.2. Amyotrophic lateral sclerosis

The amyotrophic later sclerosis is a progressive neurodegenerative disease that affects neurons in the brain and in the spinal cord. The first motor neuron neurons reaches the spinal cord, and from the spinal cord, the second motor neuron reaches the muscles throughout the body. The progressive degeneration of the motor neurons in ALS eventually leads to their death. When the motor neurons dies, the ability of the brain to initiate and control muscle movement is lost. Because voluntary muscle action is progressively affected, patients in the later stages of the disease may become totally paralyzed. This pathology evolves toward the completely locked-in syndrome (LIS), a condition in which patients remain conscious but cannot move any of their muscles. For instance, they may become unable to express their opinions and decisions on important questions regarding their clinical treatment, or their living and biological wills. Because of their peculiar pathology's characteristics, ALS patients are the clinical population that has been most involved in BCI studies (Birbaumer et al., 2008).

Despite the promising results in BCI's use obtained by non CLIS-ALS patients (Birbaumer et al., 1999; Piccione et al., 2006; Sellers & Donchin, 2006), no case of successful communication with CLIS-ALS patients has been reported to date (Kübler & Birbaumer, 2008). In a meta-analysis on the use of BCI by 29 ALS patients, Kübler and Birbaumer speculated about the fact that brain signal regulation is possible in all the stages of ALS pathology, but not in the CLIS condition. On the basis of their meta-analysis, the authors hypothesized that it could be the complete lack of the motor control and of the respective feedback, which might be responsible for the cessation of voluntary cognitive activity, goal directed thinking, and imagery. On the basis of this hypothesis, it seems that is impossible to learn how to control a BCI system in the CLIS condition. Moreover, the authors suggest that a possible solution of this problem could be to teach the patients to use a BCI before they enter in the CLIS. The possibility of using a BCI may prevent the ALS patients from the "extinction of goal directed thinking", and, by doing so, it may permits the patients to control a BCI in the CLIS condition.

There are a few worth noting studies that have adopted the longitudinal perspective suggested by Kübler and Birbaumer with ALS patients. In these studies it has been reported that ALS patients are able to control a P300-based BCI for communication in follow-up sessions occurred few months (i.e., 6 ALS patients; Nijoboer et al., 2008) or one year (i.e., 5 ALS patients; Silvoni et al., 2009) after the initial tests took place. Furthermore, Sellers et al. (2010) described the long-term use of a P300-speller system by a LIS-ALS patient. With that ERP-based BCI, this patient was able to maintain a sufficient level of autonomy, enough for communicating with his family and for continuing his job. The main limit of these studies is that the BCIs used are based on the visual modality. In a recent physiological single-case study of an ALS patient who passed from the LIS to the CLIS condition (Murguialday et al., 2011), it has been proposed that auditory and proprioceptive BCIs are the only remaining communication channels for CLIS patients.

1.3. AIM OF THE PRESENT STUDY

After more than twenty years from the Farwell and Donchin "mental prosthesis", satisfactory results have been reached with healthy participants using BCIs. The main goal of developing an efficient BCI for clinical purposes and everyday use with paralyzed patients, instead, is still a challenging question. This is maybe due to a lack of studies testing the BCI efficacy directly on clinical populations (Birbaumer, 2006b). Generally, the BCI research is done in laboratory settings, most by technicians and with minor intervention of clinical personnel. Most of the BCI-related literature is focused on the development of efficient mathematical algorithms, in order to perform effective online classification (Birbaumer & Sauseng, 2010). This fact could be a partial reason why much more attention has been paid to the technical improvements for the BCI systems, than to the users' aspects involved in BCI control. There are few examples of experimental studies investigating the psychological factors that could modulate participants' performances with BCIs. The psychological factors that have been experimentally related to BCI use were mood, motivation, and the QoL (Kübler et al., 2001; Nijboer et al., 2010; Kleih et al., 2010), but only Kleih et al. have studied these factors with ALS patients.

A missing point, to our view, is the investigation of cognitive factors which could have an effect on BCIs performance. On the one hand, implementing and testing principles deriving from cognitive psychology may bring considerable advantages in BCI usability. Moreover, this "ergonomic advantage" would be inexpensive, because no addictive costs will be required for the system's implementation, but only a different design of the interfaces, according to specific "cognitive hints". On the other side, the possibility of having several interfaces, each one exploiting a particular cognitive process, may be useful for patients with neuropsychological deficits. There are several studies describing the presence of cognitive deficits in ALS patients (Abrahams et al., 2005; Phukan et al., 2007; Lakerveld et al., 2008). This fact suggests that patients may need different BCIs according to their cognitive abilities. An additional point that could justify the interest in implementing cognitive principle on BCI is that no one has empirically reported whether, in the CLIS condition, cognitive functions are spared or not.

The central point investigated in this dissertation is the possibility of modulating performance in a visual ERP-based BCI for controlling the movement of a virtual cursor (Piccione et al., 2006), by implementing different principles of covert visuospatial attention orienting described by Posner (1980). It has to be mentioned that some authors have tried to manipulate the visual interface of the P300-speller, without an overt intention of investigating cognitive effects on BCI. In fact, that was done for testing the possibility to have faster communication speed and the possibility to choose among few or several symbols displayed in the matrix (Allison & Pineda, 2003, 2006; Sellers et al., 2006). Only more recent studies have investigated the ergonomic aspects of the P300-speller: both Brunner et al. (2010) and Treder and Blankertz (2010) have compared healthy users' performance with the P300-speller in overt vs. covert visuospatial attention orienting. The two independent studies reached the same conclusion: the use of the P300-speller is not possible in a condition of covert visuospatial attention. In other words, it is not possible for the participants to perform word spelling through a visual P300-speller without moving their gaze. This is a crucial result regarding BCI usability in ALS patients, because in the latest stages of the illness also eye-muscle control is impaired.

In the following three experiments we tested whether it is possible to develop a visual ERP-based BCI which does not require overt orienting of visuospatial attention. Moreover, we investigated the effects of different modalities of covert visuospatial attention, by designing new interfaces, in each of whom a different principle of covert orienting of visuospatial attention was implemented (i.e., exogenous vs. endogenous; Posner, 1980). Our hypotheses were tested with both healthy participants and ALS patients.

2. EXPERIMENT 1

2.1. INTRODUCTION

Brain-computer interfaces (BCIs) are systems that enable direct communication and interaction between the brain and the external world. Participants can guide and use these systems, such as computers or prostheses, by means of their brain signals and without the aid of the somatic division of the peripheral nervous system. The development of efficient BCIs represents a potential solution for the communication problems of patients with locked-in syndrome (LIS). LIS is a condition in which most but not all of the voluntary muscles are paralyzed. Thus, LIS patients have severe difficulties in communicating (verbally or non-verbally), even though their cognitive abilities might be spared. When communication becomes impossible, patient enter in the completely LIS condition. In the late 80s, it was demonstrated that it could be possible for people to communicate through a computer by using the P300 event-related potential (ERP) component, a positive brain wave that appears about 300 ms following target presentation (Farwell and Donchin, 1988). With respect to other EEG signals used to develop BCIs (e.g., sensorimotor rhythm [SMR] or slow cortical potentials [SCP]), the P300 does not need a long training period. This fact is in accordance with Birbaumer's (2006) proposal that "non-invasive EEG-driven BCIs offer a realistic perspective for communication in paralyzed patients".

After the “P300-speller” of Farwell and Donchin (1988; i.e., a 6 x 6 letter-and-number matrix, where either rows or columns were randomly flashed and participants had to focus their attention to a specific row or column; the target letter or number consisted in the intersection between each row and column) many studies have tested P300-guided BCIs in order to improve both accuracy and communication speed of these systems. Many of these studies were based on the P300 speller paradigm in order to assess the effects of matrix dimension and inter-stimulus interval (Allison and Pineda, 2003; Sellers et al., 2006a), the effects of sensory modality (Furdea et al., 2009; Klobassa et al., 2009; Halder et al., 2010), and the effects of different algorithms on the detection of the P300 component (e.g., Donchin et al., 2000; Serby et al., 2005). Other studies have been concerned with the development of efficient algorithms for detecting the P300 (e.g., Beverina et al., 2003; Xu et al., 2004; Kaper et al., 2004; Thulasidas et al., 2006; Rakotomamonjy and Guigue, 2008). Finally, in recent studies the efficacy of different interfaces has been assessed (Bayliss, 2003; Piccione et al., 2006; Sellers and Donchin, 2006b; Citi et al., 2008; Hoffman et al., 2008). Only few studies, however, have reported data from P300-guided BCIs in clinical populations (Piccione et al., 2006, Sellers and Donchin, 2006; Citi et al., 2008; Hoffman et al., 2008; Nijboer et al., 2008; Silvoni et al., 2009) and, to date, there is only a single case study which reports the successful everyday use of a P300-BCI by a LIS patient (Sellers et al., 2010).

Although progresses have been made with regard to signal recording and classification algorithms for improving BCI’s performance, the effects of cognitive processes on BCI efficiency are less investigated (see Halder et al., 2011, for a more recent explicit investigation of some cognitive mechanisms for a BCI). One of these cognitive processes is visuospatial attention. For instance, in all the aforementioned studies that have tested the efficacy of different interfaces, complex odd-ball-like paradigms are used. In these paradigms, participants are required to pay attention to relevant and rare targets and to ignore frequent distracters, in order to elicit the P300. But what is exactly meant by the term "attention"? Attention is a complex neurocognitive function that enables us to select information for further processing (Umiltà, 2001). Attention, however, is not a unitary function. It can be rather considered as a set of specialized cognitive processes, which are involved in different tasks (visuospatial attention, divided attention, sustained attention, etc.). These cognitive processes work together in order for the organism to produce coherent and adaptive behavior. When the to-be-selected information is a stimulus in space, then the focus of visuospatial attention is oriented in the environment. Visuospatial attention orienting occurs by means of three distinct neurocognitive operations (Posner, 1980; Posner and Petersen, 1990): "disengagement" (i.e., the focus of visuospatial attention is disengaged from its spatial location, because of posterior parietal activation), "movement" (i.e., the focus moves to the new spatial location, because of superior colliculi activation), and "engagement" (i.e., the focus is engaged at the new spatial location, because of pulvinar activation).

Two modalities of visuospatial attention orienting have been described (Posner, 1980): the exogenous (bottom-up, automatic) and the endogenous (top-down, voluntary). Exogenous orienting of the focus can be elicited by abrupt sensory changes (e.g., a change in brightness, color, etc.) in the periphery of the visual field. Endogenous orienting of the focus, instead, is driven by voluntary cognitive interpretation of signals presented in the center of the screen (e.g., a directional word, such as “left”, indicating a spatial location to which the focus of visuospatial attention must be oriented). Exogenous orienting is subserved by a distributed cortical network which comprises the temporo-parietal junction and the ventral premotor cortex, whereas endogenous orienting is subserved by a distributed cortical network which comprises the intraparietal sulcus and the frontal eyefields (Corbetta and Shulman, 2002). It is worth noting that visuospatial attention orienting can occur with (overt) or without (covert) head and eye movements (Posner and Petersen, 1990).

LIS patients might orient the focus of visuospatial attention even when they are unable to execute overt eye and head movements, although this remains a working hypothesis. Recently, some studies have investigated whether participants could control a P300-speller BCI without using their eye movements (Trader and Blankertz, 2010; Brunner et al., 2010). Note, that by asking participants not to perform eye movements, one might simulate one of the most disabling conditions of the completely-LIS patients, namely their inability to execute any voluntary movements, including eye movements. Both Trader and Blankertz and Brunner et al., compared the performance of a P300-speller in two conditions: Overt visuospatial attention orienting (i.e., participants had to move to and fixate their gaze on the to-be-selected letter in the periphery) and covert visuospatial attention orienting (i.e., participants had to fixate their gaze in the center of the screen and to orient their visuospatial attention to the to-be-selected letter in the periphery). They found that participants were better at using the P300-speller in the overt visuospatial attention condition than in the covert one, suggesting that the use of the latter by patients with impaired eye movements may be limited. Trader and Blankertz implemented also an alternative visual interface for word spelling, the “Hex-o-Spell”. Using covert orienting of visuospatial attention, the performance of the participants was better in the Hex-o-Spell interface than it was in the P300-speller. Nevertheless, the overall performance of the participants was quite low (< 40-60% correct) for both interfaces. Trader and Blankertz have suggested, however, that taking into account the peculiarities of peripheral vision, for designing a visual BCI interface, could improve substantially the BCI’s performance.

An alternative approach, that could be useful also for patients who cannot execute eye movements, could be that of using the acoustic modality for eliciting the P300 (Sellers and Donchin, 2006; Furdea et al., 2009; Klobassa et al., 2009; Hadler et al., 2010; Schreuder et al., 2010). Liu et al. (2011), however, have described an efficient gaze-independent BCI, in which for stimuli presented within a visual angle of about 3.28°, healthy participants are highly accurate (i.e., > 93% correct in selecting target letters).

The present pilot study aimed to investigate further the effects of different modalities of visuospatial attention orienting (exogenous vs. endogenous), by means of covert visuospatial orienting, on the online performance of a P300-guided BCI with healthy participants. We compared the efficiency of three interfaces in directing a cursor towards targets in the periphery of the visual field. The first interface (Figure 2.1), named “Arrows”, was similar to that of Piccione et al. (2006), in which four peripheral flashing arrows were used in order to control the movement of a cursor, from the center of the screen towards one of the arrows. We designed the “Arrows” interface by implementing a few changes to the original one of Piccione et al. The “Arrows” interface was based on the principles of exogenous visuospatial attention orienting. Also the second interface

(Figure 2.2), named “Auto”, was based on the principles of exogenous attention orienting. Four images, which disappeared briefly and reappeared in their original position, were used in the place of the arrows. The third interface (Figure 2.3), named “Vol”, was based on the principles of endogenous attention orienting. Four letters, each indicating a different spatial position (above, below, left, right), were presented one at a time in the center of the screen.

Many studies in the last four decades (for a comprehensive, recent review, see Wright and Ward, 2008) have suggested that visuospatial attention can be oriented by two types of signals (i.e., cues): peripheral cues (i.e, presented in the periphery of the visual field), which elicit exogenous orienting (i.e., stimulus-driven, automatic, involuntary) and central cues (i.e., displayed in the center of the screen), which activate endogenous orienting (i.e., goal-driven, non-automatic, voluntary). Peripheral cues consist in abrupt changes of the sensory flow in the periphery of the visual field and are characterized by physical proximity to the target position. Thus, an abrupt sensory change (i.e., “Arrows” interface: brief change of the color ink of an arrow; “Auto” interface: brief offset-onset of an icon), at the same spatial position as that of the targets or the non-targets in the periphery of the visual field, orients visuospatial attention exogenously. In contrast, central cues are symbols which are not physically proximal to the targets. Central cues carry spatial information that must be cognitively derived. Thus, a letter which stands for a word that must be cognitively interpreted in order to understand the meaning of the conveyed spatial position (i.e., “Vol” interface: above, below, right, left), and which is presented in the center of the screen (i.e., a position that is not physically proximal to that of the targets), orients visuospatial attention endogenously. One might argue that the mere presentation of letters in the center of a screen might elicit exogenous (i.e., automatic) shifts of visuospatial attention. This hypothesis has been tested by Dodd et al. (2008), who showed that visuospatial attention is not oriented automatically following the presentation of letters in the center of the screen.

We assumed that visuospatial attention orienting would be necessary for the participants in order to process effectively a target (arrow or icon) at a specific location in the periphery of the visual field, while they maintained their gaze at a fixation point presented in the center of the screen (i.e., covert spatial attention orienting). We aimed to investigate the effects of different modalities of visuospatial attention orienting (i.e., endogenous vs. exogenous) on BCI's performance.

2.2. METHODS

2.2.1. Participants

Twelve naïve healthy participants with normal or corrected-to-normal vision took part in the study (mean age: 37 years; range: 20-61 years; 5 males). All participants gave their informed consent to participate in the study, in accordance with the Declaration of Helsinki.

2.2.2. Apparatus, stimuli, and procedure

The experiment took place in a sound-attenuated chamber. Participants sat in an adjustable chair in front of a computer screen (HP L1906T Flat Panel LCD Screen; dimension: 38 x 30.5 cm; refresh frequency: 60 Hz; resolution: 1024x768), with their head positioned on a chinrest, that was fixed on the table.

The distance between the center of screen and the chinrest was 57 cm. Three interfaces were presented to all participants. All interfaces were based on the Piccione et al. (2006) paradigm, where participants had to control the movement of a cursor to reach a target by paying attention to peripheral stimuli.

The first interface named “Arrows” (Figure 2.1), was similar to that of Piccione et al. (2006), and used a stimulation paradigm that elicited exogenous visuospatial attention orienting. This interface was composed of a fixation point (i.e., a cross presented in the center of the screen), a cursor placed in the center of the screen (i.e., a blue circle measuring 1° in diameter) and four arrows (i.e., a triangle with base measuring 2.5° and height measuring 2.5°) presented in the periphery. All stimuli were displayed against a black background. The distance between the center of the fixation point and the center of each arrow was 7°. Two of the arrows were positioned along the vertical midline of the screen (i.e., one above the fixation point, and the other below). The remaining two arrows were positioned along the horizontal midline (i.e., one to the left of the fixation point, the other to the right). Each arrow indicated one out of four possible directions: above, right, below and left. On each trial, a red cross indicating the target position was displayed close to a specific arrow. Participants had to maintain their gaze on the fixation point and to avoid head and eye movements. For eliciting brain potentials, we used a fast change of the color of each arrow from green to yellow and then back to green (color change duration: 150 ms; overall event probability for each arrow: 25%). A trial was defined as the time elapsed between the color changes of two arrows. The order in which the arrows changed color was semi-random. That is, within each block of four consecutive trials, each arrow changed color once randomly. The first trial of the next block of four trials, however, could have been either the same or different from that of the last trial of the preceding block. Participants were required to pay attention to the arrow next to the red cross (target) and to ignore the other three arrows (non targets), in order to control the movement of the cursor for reaching the red cross.

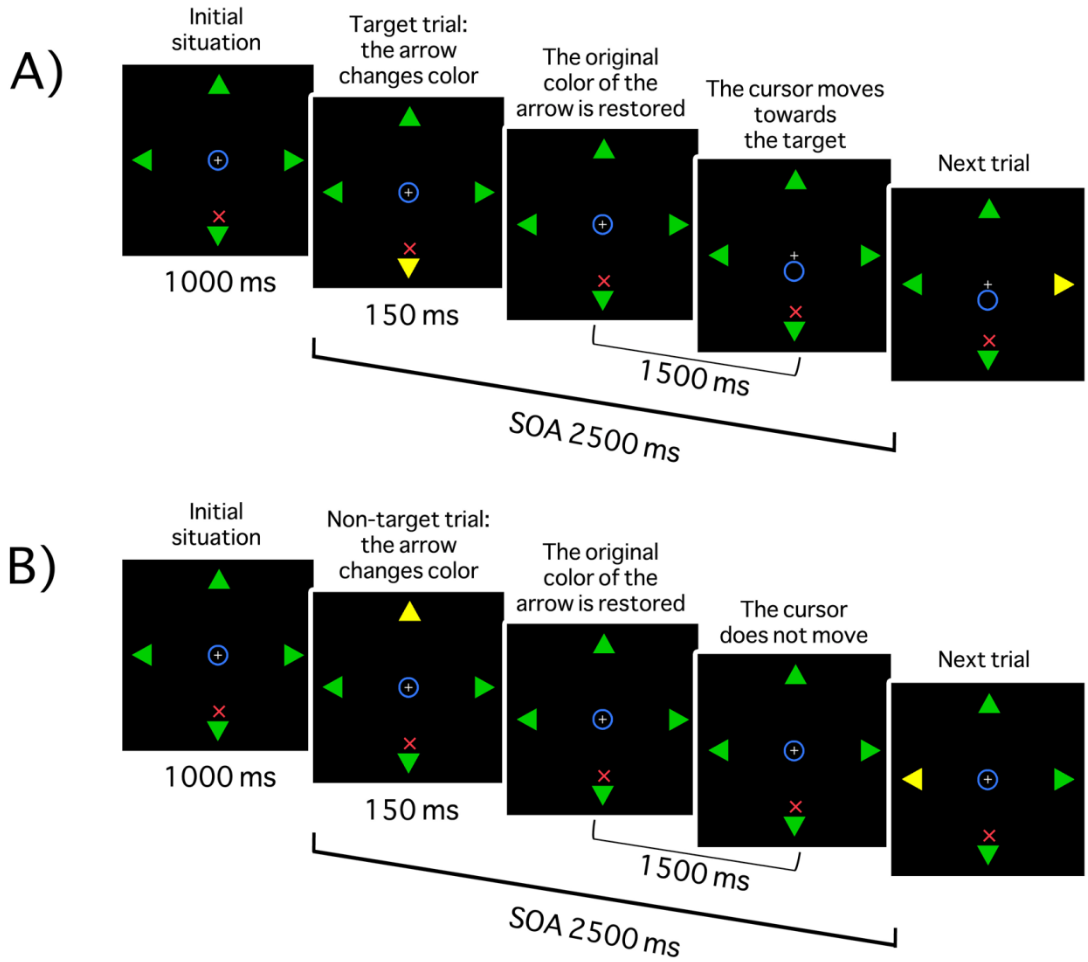

Figure 2.1 The "Arrows" interface. A: Example of a target trial (i.e., a trial in which a target spatial position is cued; in this example the cued target spatial position is that below the fixation point). B: Example of a non-target trial (i.e., a trial in which a non-target spatial position is cued; in this example the cued non-target spatial position is that above the fixation point).

The second interface, named "Auto" (Figure 2.2), used a stimulation paradigm that elicited exogenous attention orienting. This interface was composed of a fixation point (i.e., a cross presented in the center of the screen), a cursor initially placed in the center of the screen (i.e., a blue circle measuring 1° in diameter) and four icons presented in the periphery (instead of the arrows used by Piccione et al. 2006). The distance between the center of the fixation point and the center of each icon was 7°. Two of the icons were positioned along the vertical midline of the screen (i.e., one above the fixation point, and the other below). The remaining two icons were positioned along the horizontal midline (i.e., one to the left of the fixation point, the other to the right). The icons were four black and white drawings. They were shown within a square (side: 3.5°) and were selected among a set of eight drawings depicting everyday life activities (eating, drinking, etc.) that had been adapted from a battery for the assessment of aphasic disorders (Miceli et al., 1994*)*. All stimuli were displayed against a black background. Participants had to maintain their gaze on the fixation point and to avoid head and eye movements. For eliciting brain potentials, we used a brief offset of one icon (duration: 75 ms; overall event probability for each icon: 25%) and its onset in the same position. A trial was defined as the time elapsed from the offset of an icon to the offset of the next icon. The order in which the icons in the different spatial positions disappeared and re-appeared was semi-random, as it was for the “Arrows” interface. Participants were required to pay attention to a target icon (e.g., eating), previously indicated by the examiner, and to ignore the remaining three non-target icons, in order to control the movement of the cursor for reaching the target. We assumed that the focus of visuospatial attention was exogenously oriented, given that each icon offset/onset resulted in an abrupt sensory change in the periphery that should capture automatically the visuospatial attention focus.

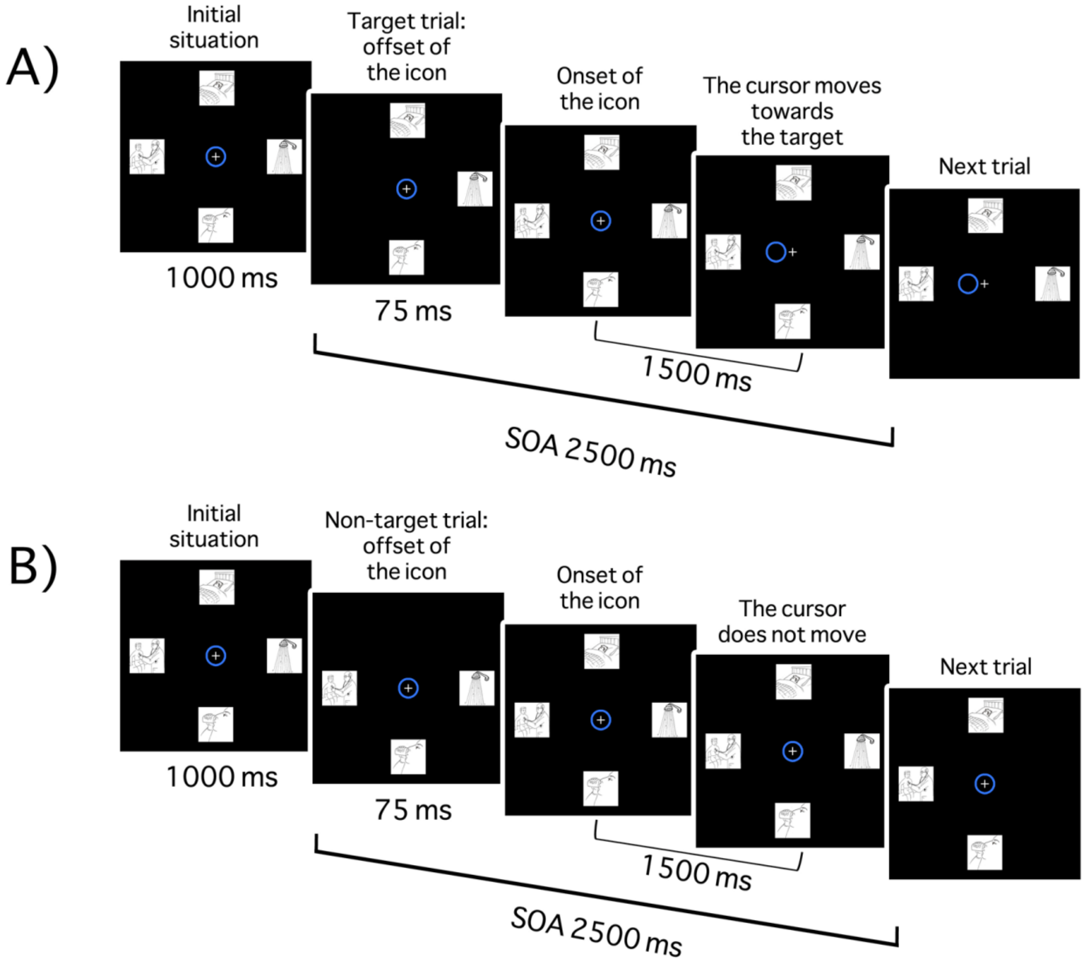

Figure 2.2 The "Auto" interface. A: Example of a target trial (i.e., a trial in which a target spatial position is cued; in this example the cued target spatial position is that to the left of the fixation point). B: Example of a non-target trial (i.e., a trial in which a non-target spatial position is cued; in this example the cued non-target spatial position is that above the fixation point). The icons in the periphery of the visual field represented various activities of everyday life (e.g., eating, drinking, taking a shower, asking for a doctor, sleeping, listening to the radio).

In the third interface, named "Vol" (Figure 2.3), we used a stimulation paradigm that elicited an endogenous orienting of attention. The fixation point, the cursor, and the four icons were the same as those used in the "Auto" interface but all the four icons were always displayed on the screen. Participants had to maintain their gaze on the fixation point and to avoid head and eye movements. For eliciting brain potentials, on each trial we presented at the fixation point one out of four capital letters (duration: 900 ms, overall event probability for each letter: 25%), while the four icons, positioned in the periphery, remained always on the screen. Each letter was the initial of an Italian spatial directional word (“A”: *alto* = above, “B”: *basso* = below, “S”: *sinistra* = left, “D”: *destra* = right), each indicating the position of one icon.

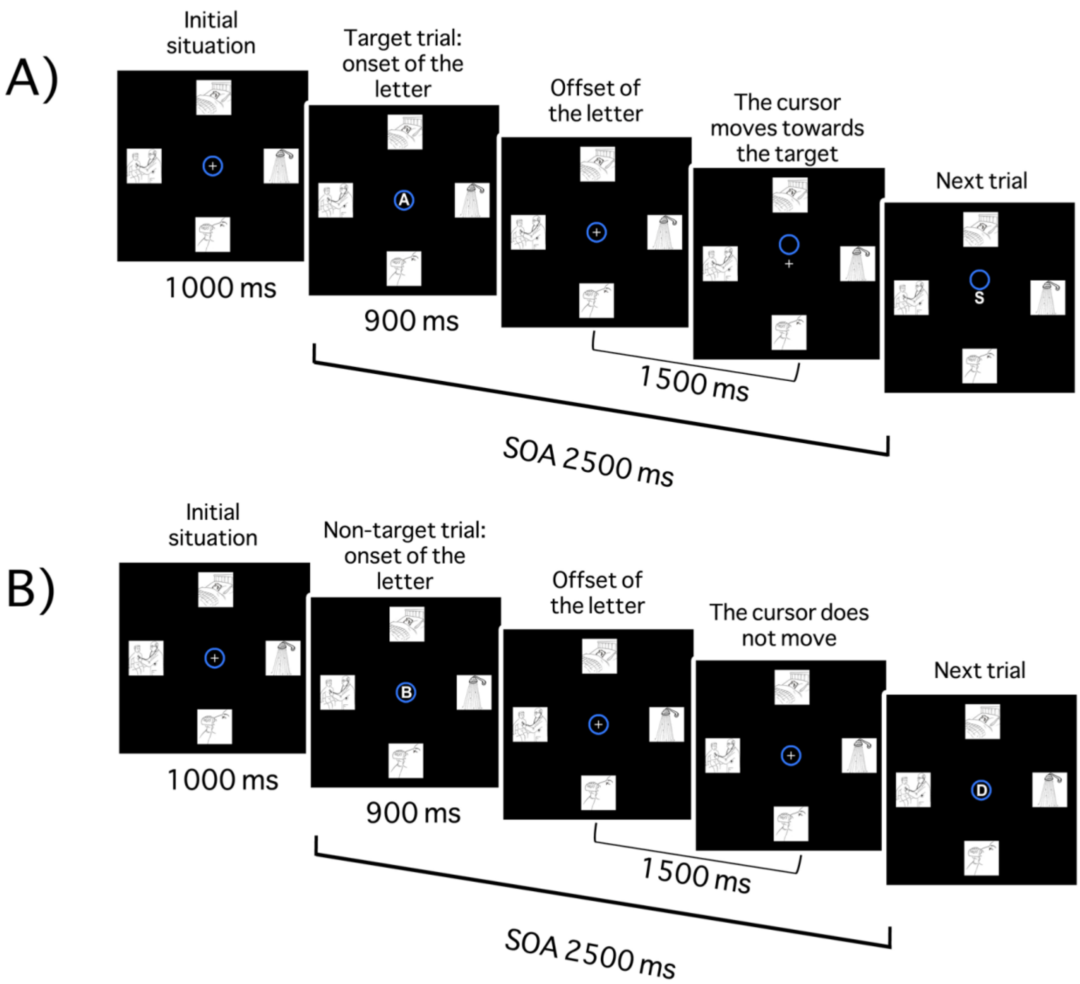

Figure 2.3 The “Vol” interface. A: Example of a target trial (i.e., a trial in which a target spatial position is cued; in this example the cued target spatial position is that above the fixation point). B: Example of a non-target trial (i.e., a trial in which a non-target spatial position is cued; in this example the cued non-target spatial position is that below the fixation point). The icons in the periphery of the visual field represented various activities of everyday life (e.g., eating, drinking, taking a shower, asking for a doctor, sleeping, listening to the radio).

A trial was defined as the time elapsed from the onset of a letter to the onset of the next letter. The order in which the letters were presented was semi-random, as it was in the other two interfaces. Participants were required to pay attention to the letter indicating the spatial position of the target icon that was indicated by the examiner before each session (e.g., the “eating” icon) and to ignore the other three letters, each indicating the position of a non-target icon. We assumed that the focus of visuospatial attention was endogenously oriented, because participants had to select the position of the target icon by cognitively interpreting the directional meaning of the centrally presented letters. The initial distance between the starting-point of the cursor and each of the targets encompassed four discrete steps in all interfaces.

During the presentation of the interfaces, participants’ EEG was recorded. The inter-trial interval (ITI) was 2.5 s. Each time the P300 was detected during the trial, presumably as the result of correct orientation of the visuospatial attention focus at the target icon location, the cursor moved one step on the screen, towards the direction of the target icon. A session was defined as the complete sequence of trials sufficient to reach the target icon (range: 13-92 trials). For each interface participants performed eight learning sessions (LS) in the first day and 16 testing sessions (TS) that were distributed over the following ten days (i.e., first day 8 LS → second day 4 TS → two days interval → fifth day 4 TS → two days interval → eighth day 4 TS → two days interval → eleventh day 4 TS). Finally, four follow-up sessions (FU) that took place, on average, 27 days after the last testing session (SD: 10 days).

The learning sessions were characterized by a “perfect feedback”, provided to the participants by a correct movement of the cursor. That is, each time the target stimulus occurred, the cursor made one step towards the target icon, independently of the presence of the P300. Note that “perfect feedback” represented what should have been the consequence of a correct P300 classification, and it was necessary for collecting the first sample of epochs related to target and non-target icons, in order to prepare the classifier for the first day of the testing sessions. In each learning session, the number of trials for each participant was the same (i.e., 13-16 trials). In contrast, during the testing sessions the cursor moved towards the target only as a response to the participants’ brain waves, once correctly classified as P300s (i.e., “real feedback” based on participants’ orienting of the visuospatial attention focus on the target). Thus, in each testing and follow-up session the number of trials was different for each participant, depending upon the performance of the classifier and the ability of the participant to reach the target icon. The follow-up sessions were the same as the sessions of the last testing day. The target icons and their positions were different in each session. The order of target positions was counterbalanced across testing sessions. The order of presentation of the three interfaces was counterbalanced across participants.

2.2.3. Electrophysiological data acquisition and processing

On each trial the EEG was recorded. Registration electrodes were placed according to the International 10-20 System at Fz, Cz, Pz, and Oz. The Electrooculogram (EOG) was recorded from a pair of electrodes below and laterally to the left eye. All electrodes were referenced to the left earlobe and the ground was on Fpz. Impendence was lower than 5 kΩ. The five channels were amplified, band-pass filtered between 0.15 Hz and 30 Hz, and digitized (with a

16-bit resolution) at 200 Hz sampling rate. Each ERP epoch, synchronized with the stimulus, began 500 ms before the stimulus onset and ended at 1000 ms after the cue (total duration: 1500 ms). Thus, after each cue presentation the system recorded a matrix of 300 samples per 5 channels, available for online and offline data processing. To test the BCI system we used a classification algorithm that has been extensively described elsewhere (Silvoni et al., 2009). Before each testing day and for each of the three interfaces a different classifier was trained and adapted *ad personam* through a three-step procedure: Independent Component Analysis (ICA) decomposition, fixed features extraction, and support vector machine (SVM) classification. The SVM classifier was updated with a 20-fold, cross-validation procedure except for the epochs of the last session (Wang et al., 2004). Of the remaining epochs, 80% were randomly selected as training set and the 20% composed the testing set. ERP epochs with artifacts greater than 100 μV with regard to each channel's activity (including EOG) were excluded from each training set (Cohen and Polich, 1997).

All available ERPs epochs were analyzed for each testing set. The epochs of the last session were used to perform a further validation of the updated SVM. After the last testing session, no other classifier updating was performed. Thus, the classifier used in the follow-up sessions was the same as that of the last testing sessions. The three-step classification procedure was applied during online operations to each single sweep synchronized with the cue. The output of the SVM classifier was converted into a binary value (1 = P300 detected; 0 = P300 absent) to control the discrete movements of the cursor. Performance of the analyzer (accuracy in %), was computed as in Piccione et al. (2006) and Wolpaw et al. (2002).

2.2.4. Experimental Design

Independent variables were manipulated within an experimental design for repeated measures. The independent variables were: Interface with three levels (“Arrows”, “Auto”, “Vol”) and Session with two levels (Testing sessions, Follow-up sessions). The dependent variable were Performance (%) and the transfer bit rate (TBR, measured in bit/min).

2.3. RESULTS

Trials affected by eye movements, detected through the EOG, were discarded from the statistical analyses.

Table 2.1 Mean (SD) for Performance (%) and TBR (in bit/min) reach by participants with the three interfaces.

Performance (%)	**“Arrows”**	**“Auto”**	**“Vol”**	**Tot.**
Testing Sessions	74.49 (7.31)	72.43 (8.98)	78.85 (5.76)	75.26 (7.74)
Follow-up Sessions	74.59 (5.43)	75.73 (8.93)	74.78 (5.41)	75.04 (6.61)
Tot.	74.54 (6.29)	74.08 (8.91)	76.82 (5.85)	75.15 (7.15)

TBR (bit/min)	**“Arrows”**	**“Auto”**	**“Vol”**	**Tot.**
Testing Sessions	5.52 (2.46)	5.88 (2.86)	7.1 (2.61)	6.17 (2.66)
Follow-up Sessions	4.39 (2.29)	6.23 (3.23)	5.56 (2.54)	5.39 (2.75)
Tot.	4.95 (2.39)	6.06 (2.99)	6.33 (2.64)	5.78 (2.72)

Both, the percentages of performance (Figure 2.4) and the transfer bit rate (Figure 2.5) of the four sessions of the last day (i.e., the 11th day) and of the four sessions of the follow-up day were entered into statistical analyses. System performance and TBR (Table 2.1) were separately introduced into a two-way analysis of variance (ANOVA) for repeated measures.

2.3.1. Performance

The main effects of Interface and Session were not significant (Interface: $F(2, 22) = 3.06$; Session: $F < 1$). In contrast, the Interface by Session interaction was significant, $F(2, 22) = 13.73$, $p < .001$, partial eta squared = .56. To investigate further this interaction, separate one-way ANOVAs for repeated measures were run for each Session level. The simple effect of Interface was significant in the testing sessions $F(2, 22) = 11.49$, $p < .001$, partial eta squared = .51, but was not significant in the follow-up sessions, $F(2, 22) = .39$. The simple effect of Interface for the last testing sessions was further evaluated using post-hoc comparisons corrected with Bonferroni.

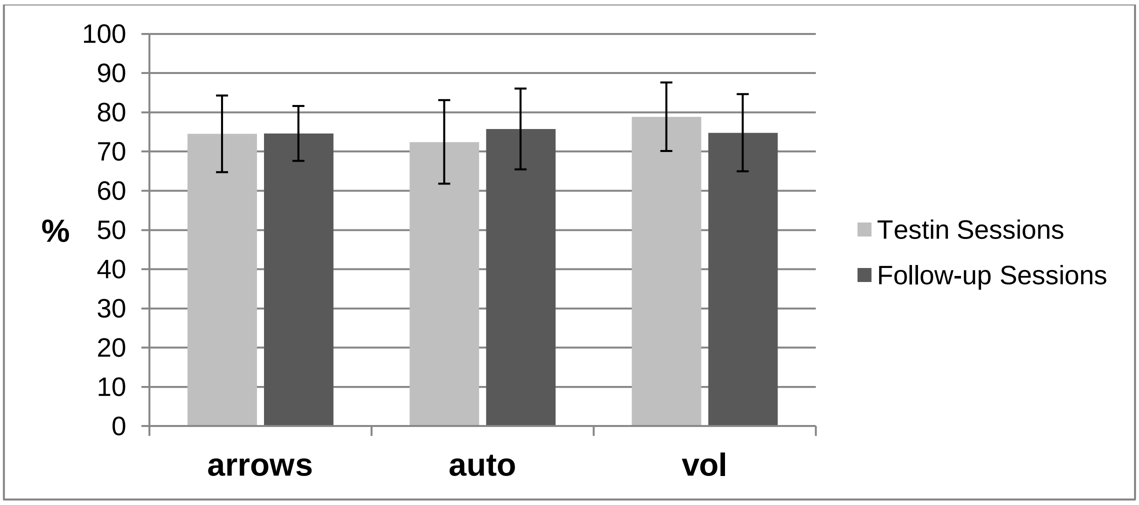

Figure 2.4 Mean BCI's performance (%) in the Testing and in the Follow-up sessions.

The differences between “Vol” (M = 78.86%; SD = 5.76) and “Arrows” (M = 74.49%; SD = 8.98) and between “Vol” and “Auto” (M = 72.43%; SEM = 2.46) were both significant, $p < .05$ and $p < .005$, respectively. In contrast, the comparison between “Arrows” and “Auto” was not significant, $p > .05$ (see Figure 2.4).

2.3.1. Transfer bit rate

The main effects of Interface and Session were significant, $F(2, 10) = 5.24$, $p < .05$ and $F(2, 11) = 7.48$, $p < .05$, respectively (Figure 2.5). Post-hoc comparisons Bonferroni corrected for Interface were significant only for “Vol” (M = 6.33 bit/min; SD = 2.64) versus “Arrows” (M = 4.95 bit/min; SD = 2.39), $p < .05$. The Interface by Session interaction was also significant, $F(2, 10) = 6.79$, $p < .01$. To further investigate the interaction, a separate repeated measure ANOVA was ran for each Session. The simple effect of Interface was significant in the testing sessions $F(2, 10) = 6.15$, $p < .01$.

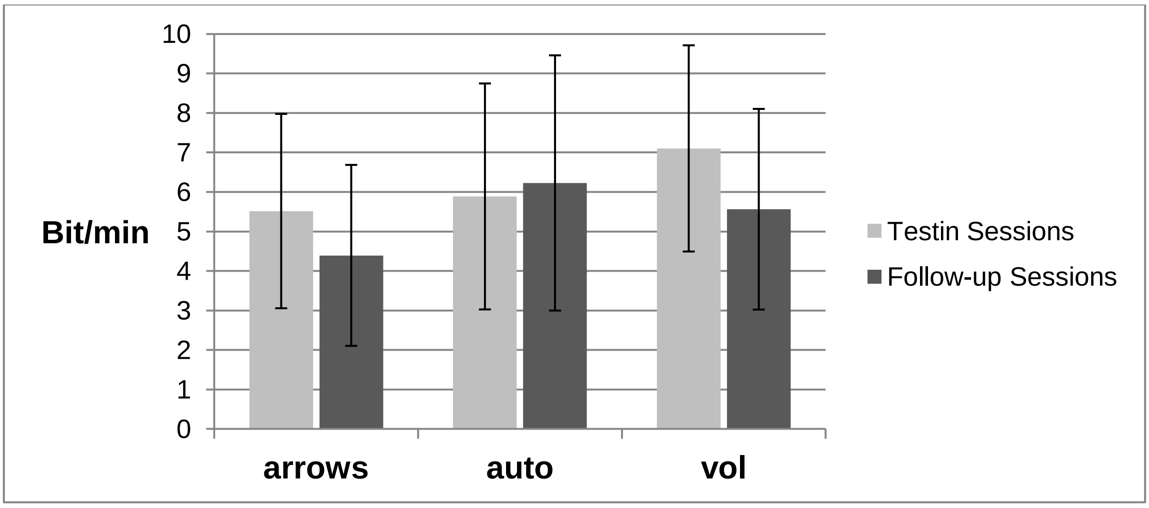

Figure 2.5 Mean BCI’s communication speed (TBR in bit/min) in the Testing and in the Follow-up sessions.

Post-hoc comparison Bonferroni corrected were significant only for Vol” (M = 7.1 bit/min; SD = 2.71) versus “Arrows” (M = 5.52 bit/min; SD = 2.46), $p < .05$. The simple effect of Interface was also significant in the follow-up sessions, $F(2, 10) = 5.22$, $p < .05$, but none pairwise comparison between Interface levels in the follow-up sessions were significantly different (all comparisons $p > .05$).

2.4. DISCUSSION

In the present study we described three P300-guided BCIs in which the effect of different modalities of visuospatial attention orienting (i.e., exogenous vs. endogenous) on BCIs’ performance was tested for the first time. We showed that the endogenous orienting of visuospatial attention lead to a better outcome than did the exogenous orienting of visuospatial attention. Nonetheless, this effect emerged clearly only for the Testing sessions. Indeed, this advantage of the “Vol” interface disappeared in the Follow-up session, where the performance of all three interfaces was virtually identical and stable (approximately 75%).

The difference between the testing and the follow-up sessions might be due to the fact that BCI skills guided by endogenous visuospatial attention orienting should be continuously trained in order to obtain optimal performance not only in the short term (i.e., testing sessions), but also in the long term (i.e., follow-up sessions or further). Indeed, it has been proposed that practicing BCI skills might be considered itself as a kind of cognitive training (Birbaumer, 2006). That is, practicing BCI skills (e.g., orienting visuospatial attention in order to communicate everyday life needs and activities) may allow patients with partial LIS to exercise and thus to maintain their conscious functions. This, in turn, might enable these patients to avoid the hypothesized “cognitive extinction” (i.e., “decrease of cognitive abilities and/or extinction of output-directed and goal-oriented thoughts”, Birbaumer, 2006; see also Silvoni et al., 2009).

In the present study we did not implement a “classic” Posner task in our interfaces, although we had implemented the general principles of endogenous and exogenous orienting of visuospatial attention (for reviews, see Corbetta and Shulman, 2002; Wright and Ward, 2008). Both our target and non-target spatial positions were always present on the screen. We used different cues for eliciting either endogenous or exogenous visuospatial attention orienting towards target or non-target positions. This happens all the time in many everyday life situations. For example, an observer, who looks for the face of someone (i.e., a “target”) in a highly crowded place, directs endogenously his/her visuospatial attention towards different spatial positions (above-below, left-right, near-far), in order to explore voluntarily the surroundings. Each time the observer focuses his/her visuospatial attention on a spatial position occupied by a face, he/she decides whether that face corresponds to the “target” one. If the face is not the “target” one, the observer restarts to orient voluntarily his/her visuospatial attention towards a new face. The “target” face is always there, among many non-target faces. Suddenly, an abrupt sensory change in the periphery of the visual field, and next to the “target” (e.g., a crashed glass), reorients exogenously, in this case, the visuospatial attention of the observer to the position of the “target”. In all the aforementioned cases the “target” was always present and the observer used both endogenous and exogenous cues to find the “target”. Independently of the modality of visuospatial attention orienting (endogenous vs. exogenous), the observer had to make a decision about the identity of a given face (“target” vs.

“non-target” face). In our interfaces, both target and non-target spatial positions were always present on the screen. Our participants used either endogenous or exogenous visuospatial attention orienting to select a given spatial position and decide whether that spatial position was a target or a non-target one. We assumed that the P300 would be elicited only for target positions, which the participants knew before starting each trial. Thus, what elicits the P300 is the comparison between target and non-target trials.

In our three interfaces only implicit (i.e., without head or eye movements) orienting of visuospatial attention was elicited, because participants were asked to keep their gaze on a fixation point, while they were screening for critical events in the periphery of the visual field (i.e., the movement of the cursor towards a target position). We suggest that effective communication can take place in this condition (i.e., implicit orienting). It is worth noting that this condition might be similar to that of LIS patients. These patients are unable to move purposefully their gaze but can, presumably, orient their visuospatial attention in order to communicate with their environment. In the present study healthy participants were able to orient their visuospatial attention towards targets representing activities of everyday life (see Figures 2 and 3). Studies on LIS patients are required, however, in order to verify and to extend the findings of the present study on healthy participants.

In conclusion, BCI’s performance can be modulated by different modalities of visuospatial attention orienting (exogenous vs. endogenous). It is suggested that more “attention” be paid on the role of cognitive functions (e.g., attention, working memory, spatial-response compatibility, etc.) in the effective design of future BCI systems.

3. EXPERIMENT 2

3.1. INTRODUCTION

Farwell & Donchin (1988) first investigated the possibility of communicating by means of event-related potentials (ERPs; e.g., P300), without the involvement of the peripheral nervous system and the voluntary muscle activity. This is possible thanks to the so called brain-computer interfaces (BCIs), systems that permit to translate the brain signals directly into commands for controlling external devices (Wolpaw et al., 2002). Briefly, a BCI comprises a system for acquiring brain signals (e.g., an electroencephalograph for recording ERPs). Once acquired, brain signals are digitized and analyzed by specific algorithms in order to extract specific features. Afterwards, these features are classified and then translated into commands. Finally, these commands are executed by a device (van Gerven et al., 2009). The execution of a command is a feedback for the users about their performance, and they have to try to modulate their mental states in order to obtain the desired effect on the device (i.e., concentrating on the target stimulus and ignoring a non target stimulus).

BCIs offer new perspectives regarding communication and control of devices for patients affected by severe motor impairment, who can be completely paralyzed, such as patients with amyotrophic lateral sclerosis (ALS). The ALS is a motor neurodegenerative pathology characterized by progressive paralysis resulting from selective death of both upper and lower motor neurones (Murray et al., 2010). In the latest stages of the illness, ALS patients can show a clinical condition called the locked-in syndrome (LIS). LIS is characterised by the presence of quadriplegia, head muscle paralysis, and mutism. Nonetheless, consciousness is preserved (Smith & Delargy, 2005). Usually, the last controllable muscles are the eye-muscles (Ramos Murguialday et al., 2011). When the control of all the muscles is lost, the patients enter in the completely locked in syndrome (CLIS), in which the communication abilities of the patients are abolished. To date, using the brain signals might be the only way for giving a chance to LIS patients to communicate (Birbaumer, 2006). For this reason, in the last years the development of efficient BCIs for communication has been an important scientific and clinical challenge.

Despite more than twenty years are passed, the P300 speller (i.e., the visual word spelling BCI proposed by Farwell & Donchin), remains the most used and studied interface. The P300 speller is composed by a 6 x 6 matrix of letters and numbers. Users have to concentrate their visuospatial attention on the target (i.e., a letter or an Arabic digit), while the brightness level of each row and column of the matrix is randomly and repeatedly changed briefly. When the brightness of the row and column which contain the target are changed, a larger P300 is elicited, than when the brightness of the rows and columns which contain non-targets are changed. Finally, the P300 with the expected feature (i.e., larger amplitude elicited by the target) is automatically detected by specific algorithms and the target (i.e., letter or number) is selected and displayed.

Several studies have been conducted on the P300 speller, to investigate the effects of different matrix sizes and inter-stimulus intervals (Allison & Pineda, 2003; Sellers et al., 2006), the effect of color contrast between the stimuli and the background (Takano et al., 2009), or the effect of arranging the matrix by the psycholinguistic frequency of the English letters (Li et al., 2011). To date, however, the most significant improvements have been achieved in the domain of signal processing and detection. Different efficient techniques are available now for signal classification: support vector machines (SVM; Rakotomamonjy & Guigue., 2008), stepwise linear discriminant analysis (SWLDA; Donchin et al., 2000; Krusienski et al., 2008), Bayesian linear discriminant analysis (Hoffman et al., 2008), hidden markov models (Rastjoo & Arabalibeik., 2009), neural networks (Cecotti & Gräser., 2010), and genetic algorithms techniques (Dal Seno et al., 2010a). In particular the approach proposed by Dal Seno et al., (2010a) is appealing as it merges in a closed loop the feature extraction task (by using a genetic algorithm (GA)) and the issue of classification task (by using a logistic classifier). GAs have been used already in the BCI field, although differently from the present work: in Boostani et al., (2007), the best combination among different features and classifiers is sought for a motor-imagery task, while in Citi et al., (2004), a classifier operating on P300 features, is selected by a GA.

In the classical approach (Wolpaw et al., 2002), the feature extraction component is separated from the classification component: the extracted features are used to feed a classifier; in Dal Seno et al., (2010a) there is not an *a priori* feature set, but the "goodness" of the single feature is measured during the running of the GA itself, using the performance obtained by the logistic classifier. In this way, the two components of the system are in a closed loop, which is stopped when the obtained feature set does not further improve the classification performance.

Recently, it has been reported that good performances with the P300 speller are due to the participants' possibility to move their eyes (Brunner et al., 2010; Treder & Blankertz, 2010). Both, Brunner et al. and Treder & Blankertz, have reported that the classification accuracy of the P300 speller, when participants cannot perform eye movements, is not sufficient for communication, even in healthy participants. The fact that the P300 speller performance depends on eyes movements can be a critical obstacle for the use of visual BCI by CLIS patients (Kübler & Birbaumer, 2008), although it seems to be still possible by LIS patients who might have some residual eye movements (Kübler & Birbaumer, 2008; Sellers et al., 2010). To overcome this problem, two different solutions have been proposed. The first solution was to develop P300-BCI systems based on other sensory modalities, such as the auditory BCI (Sellers & Donchin, 2006; Furdea et al., 2009; Klobassa et al., 2009; Halder et al., 2010) and the tactile BCI (Brower & van Erp, 2010). The second solution was to design a visual BCI based on the covert visuospatial attention principle (Hoffman et al., 2008; Liu et al., 2011).

In our recent study (Experiment 1), we tested a P300-based BCI for controlling the movement of a cursor on a screen with a four choice interface (Piccione *et al* 2006), in a covert visuospatial attention condition. In Experiment 1 our aim was to investigate whether there was an advantage by implementing the principles of covert orienting of visuospatial attention, described by Posner (1980), on these interfaces. Many studies in the last four decades (for a comprehensive, recent review, see Wright & Ward, 2008) have suggested that visuospatial attention can be oriented by two types of cues: peripheral cues, which elicit an exogenous (i.e., stimulus-driven, automatic, involuntary) orienting and central cues (i.e., displayed in the center of the screen), which activate endogenous orienting (i.e., goal-driven, non-automatic, voluntary). We investigated the possibility to modulate the performance of the above-mentioned BCI system, by designing and implementing three new interfaces in which participants were required to perform implicit (i.e., without eye movements) orienting of visuospatial attention (Posner, 1980; Posner & Petersen, 1990). The first interface ("Arrows") was similar to that of Piccione et al., (2006). The second interface ("Auto") was designed, by implementing the exogenous principles of visuospatial attention orienting. The third interface ("Vol") was designed, by implementing the endogenous principles of visuospatial attention orienting. Note that also the interface proposed by Piccione et al., was implicitly based on exogenous orienting of visuospatial attention. By using online classification, in Experiment 1 was showed that good performance can be reached using visual interfaces controlled without eye movements. Furthermore, it was reported that the interface based on voluntary visuospatial attention orienting could yield better performance than those based on automatic orienting of visuospatial attention.

To investigate whether the findings of Experiment 1 depended on the classification system that was used, in the present study we performed an offline reclassification of the EEG data. In the previous experiment was performed the online analysis of the epochs by means of Independent Component Analysis (ICA) and of subsequent fixed features extraction and support vector machines (SVM) classification (Silvoni et al., 2009). In the present study we performed offline epochs analysis by means of a genetic algorithm (GA) that permits to retrieve the relevant features of the signal, which can be classified, in turn, by means of a logistic classifier (Dal Seno et al., 2008). In summary, we tested whether the effects reported in Experiment 1 depended on the specific classification system used, and whether the offline classification performed with the GA could improve classification with respect to the previously used classification system by Silvoni et al., (2009). Moreover, we discussed here the results of the analysis on the electrophysiological data, which have not been previously reported, as a function of the two classification approaches.

3.2. METHODS

3.2.1. Participants

Twelve naïve healthy participants with normal or corrected-to-normal vision took part in the study (mean age: 37 years; range: 20-61 years; 5 males). All participants gave their informed consent to participate in the study, in accordance with the Declaration of Helsinki.

3.2.2. Apparatus, stimuli, and procedure

The experiment took place in a sound-attenuated chamber. Participants sat in an adjustable chair in front of a computer screen (HP L1906T Flat Panel LCD Screen; dimension: 38 x 30.5 cm; refresh frequency: 60 Hz; resolution: 1024 x 768), with their head positioned on a chinrest, that was fixed on the table. The distance between the center of screen and the chinrest was 57 cm. Three interfaces, two designed by following the principle of exogenous orienting of visuospatial attention and one designed by following the principle of exogenous orienting of visuospatial attention, were presented to all participants. All interfaces were based on the Piccione et al.'s (2006) paradigm, where participants had to control the movement of a cursor to reach a target position by paying attention to central or peripheral cues. The three interfaces have been extensively described in Experiment 1.

In each interface all stimuli were displayed against a black background. Each interface comprised a fixation point (i.e., a cross presented in the center of the screen) and a cursor placed in the center of the screen (i.e., a blue circle measuring 1° in diameter). During the experimental sessions with all the interfaces, participants were required to maintain their gaze on the fixation point and to avoid head and eye movements, while their EEG was recorded.

The “Arrows” interface (Figure 3.1) was similar to that of Piccione et al., (2006), and used a stimulation paradigm that elicited exogenous visuospatial attention orienting.

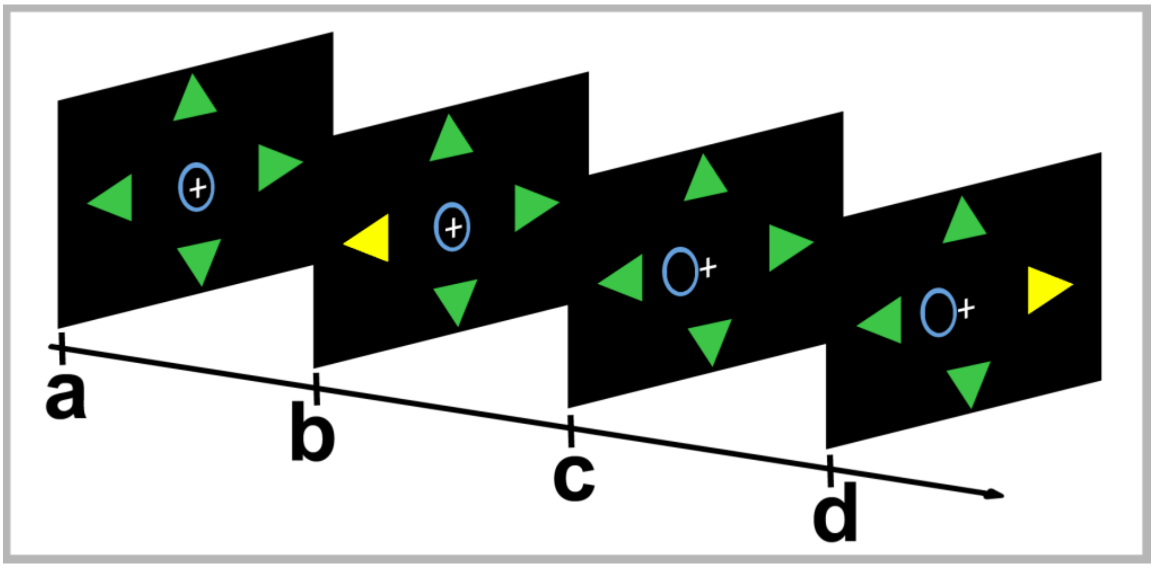

Figure 3.1 The “Arrows” interface. Scheme of a “target” trial: a) initial situation of a session: the fixation point, the cursor (blue circle) and the four “Arrows” were displayed on the monitor; b) one arrow changed color for 150 ms; c) if the classifier recognized the “target” ERP pattern, then the cursor was moved one step towards the direction of the arrow that had changed color; d) next trial (ITI 2.5 sec): an arrow in a different spatial position changed color.

Four “Arrows” were presented in the periphery of the screen at a distance of 7° from the fixation point. Each arrow indicated one out of four possible directions: above, right, below, and left. On each trial, a red cross indicating the target position was displayed close to a specific arrow. For eliciting brain potentials, we used a fast change of the color of each arrow from green to yellow and then back to green (color change duration: 150 ms; overall event probability for each arrow: 25%). A trial was defined as the time elapsed between the color changes of two “Arrows”. Participants were required to pay attention to the arrow next to the red cross (target) and to ignore the other three “Arrows” (non targets), in order to control the movement of the cursor for reaching the red cross.

The “Auto” interface (Figure 3.2) used a stimulation paradigm that elicited exogenous visuospatial attention orienting.

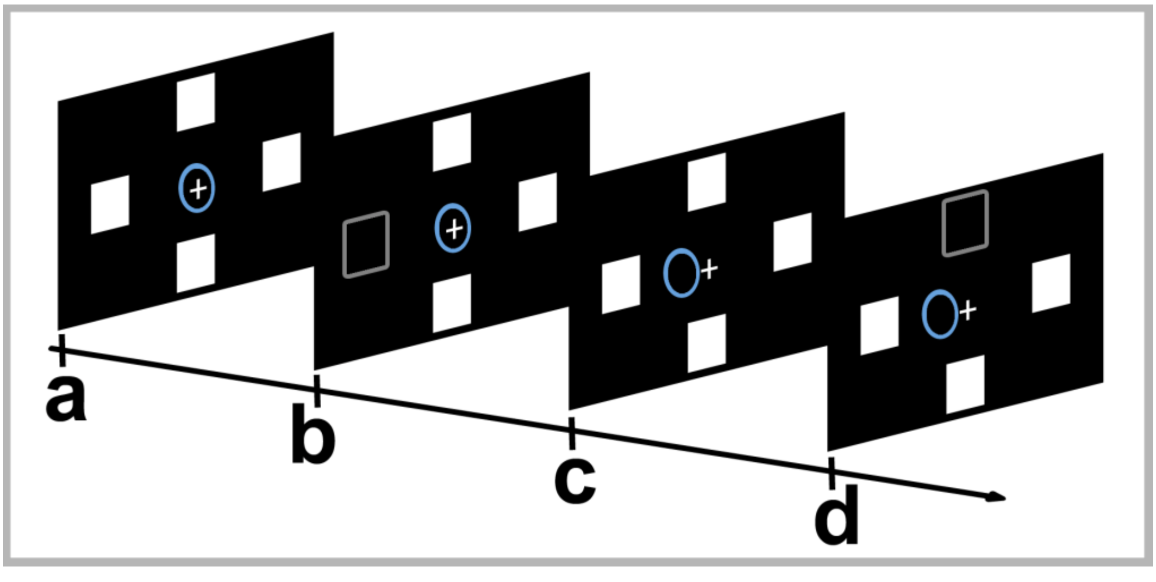

Figure 3.2 The “Auto” interface. Scheme of a “target” trial: a) initial situation of a session: the fixation point, the cursor (blue circle) and the four icons were displayed on the monitor; b) one icon disappeared (represented by the grey shape) for 75 ms and reappeared in the same position; c) if the classifier recognized the “target” ERP pattern, then the cursor was moved one step towards the direction of the icon which disappeared; d) next trial (ITI 2.5 sec): an icon in a different spatial position disappeared.

Instead of the “Arrows”, four icons were presented in the periphery of the screen at a distance of 7° from the fixation point. The icons were four squared, (side: 3.5°) black and white drawings depicting everyday life activities (eating, drinking, etc.), which had been adapted from a battery for the assessment of aphasic disorders (Miceli et al., 1994*)*. For eliciting brain potentials, we used a brief offset of one icon (duration: 75 ms; overall event probability for each icon: 25%) and its onset in the same position. A trial was defined as the time elapsed from the offset of an icon to the offset of the next icon. Participants were required to pay attention to a target icon, previously indicated by the examiner, and to ignore the remaining three non-target icons, in order to control the movement of the cursor for reaching the target.

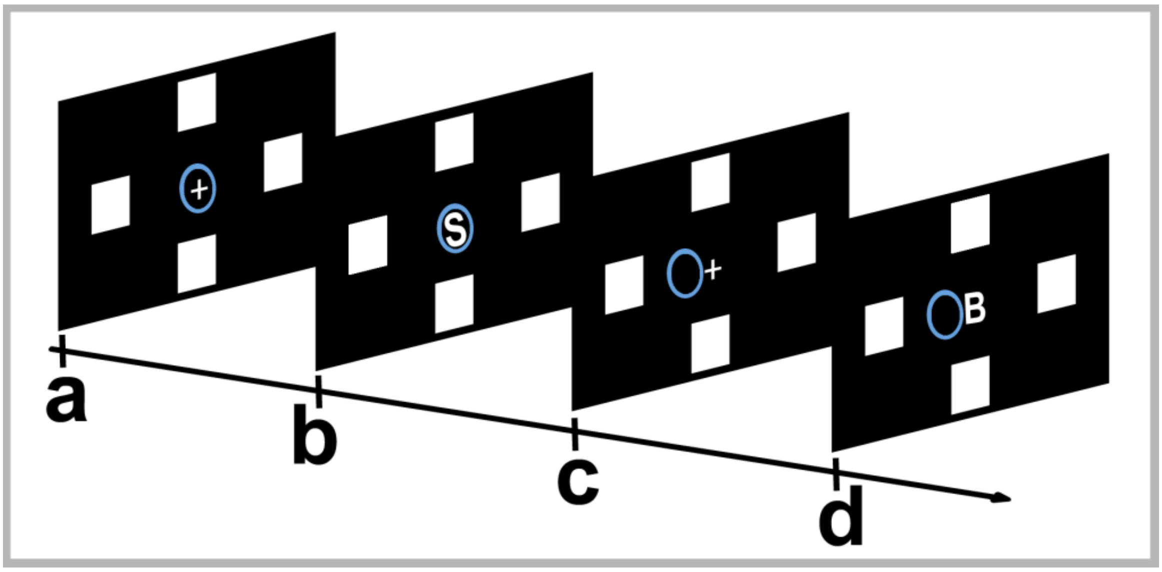

Figure 3.3 The “Vol” interface. Scheme of a “target” trial: a) initial situation of a session: the fixation point, the cursor (blue circle) and the four icons were displayed on the monitor; b) one capital letter indicating a spatial position appeared for 900 ms; c) if the classifier recognized the “target” ERP pattern, then the cursor was moved one step towards the direction indicated by the letter; d) next trial (ITI 2.5 sec): a capital letter indicating a different spatial position appeared.

In the “Vol” interface (Figure 3.3) we used a stimulation paradigm that elicited an endogenous orienting of visuospatial attention. In this interface was used the same stimuli configuration as that for the "Auto" interface. For eliciting brain potentials, on each trial we presented at the fixation point one out of four capital letters (duration: 900 ms, overall event probability for each letter: 25%), while the four icons remained always on the screen. A trial was defined as the time elapsed from the onset of a letter to the onset of the next letter. Each letter was the initial letter of an Italian spatial directional word (i.e., "A": *alto* = above, "B": *basso* = below, "S": *sinistra* = left, "D": *destra* = right), each indicating the position of a specific icon. Participants were required to attend the onset of the letter indicating the spatial position of the target icon, which was indicated by the examiner before each session, and to ignore the other three letters.

The order of the events for eliciting the brain potential in all the interfaces was semi-random. That is, within each block of four consecutive trials, each of the four possible events (i.e., "Arrows" interface = brief color change of one arrow, "Auto" interface = offset-onset of one icon, "Vol" interface = onset-offset of one letter) occurred randomly. The first trial of the next block of four trials, however, could have been either the same or different from that of the last trial of the preceding block. The inter-trial interval (ITI) was 2.5 s. The initial distance between the starting-point of the cursor (i.e., center of the screen) and each of the targets, encompassed four discrete steps in all interfaces. Each time the target ERP was detected during the trial by the online classification system, the cursor moved one step on the screen towards the target spatial position. A session was defined as the sequence of trials sufficient to reach the target icon (range: 13-92 trials; after the 92th trial the session was ended). For each interface participants performed eight learning sessions in the first experimental day, 16 testing sessions that were distributed over the following ten days (second experimental day: 4 testing sessions; two days without BCI sessions; third experimental day: 4 testing sessions; two days without BCI sessions; fourth experimental day: 4 testing sessions; two days without BCI sessions; fifth experimental day: last 4 testing sessions), and four follow-up sessions which took place, on average, 27 days after the last testing sessions. The learning sessions were characterized by a “perfect feedback”, provided to the participants by a correct movement of the cursor which did not depend on the online classification system. It was necessary for collecting the first sample of epochs related to target and non-target trials, in order to prepare the online classifier for the first day of the testing sessions. In contrast, during the testing sessions the cursor was moved only as a response to the participants’ brain waves, once classified as target ERPs. Thus, in each testing and follow-up session the number of trials was different for each participant, depending upon the performance of the classifier and the ability of the participant to control the cursor movements. Within an experimental day, the position of the targets was different for each session. The target positions in the follow-up sessions were the same as those in the sessions of the last testing day. The order of target positions was counterbalanced across testing sessions. The order of presentation of the three interfaces was counterbalanced across participants.

3.2.3. Electrophysiological data acquisition and online processing

On each trial the EEG was recorded. Registration electrodes were placed according to the International 10-20 System at Fz, Cz, Pz and Oz. The Electrooculogram (EOG) was recorded from a pair of electrodes below and laterally to the left eye. All electrodes were referenced to the left earlobe and the ground was on Fpz. Impendence was lower than 5 kΩ. The five channels were amplified, band-pass filtered between 0.15 Hz and 30 Hz, and digitized (with a 16-bit resolution) at 200 Hz sampling rate. Each ERP epoch, synchronized with the stimulus, began 500 ms before the stimulus onset and ended1000 ms after the cue (total duration: 1500 ms). Thus, after each cue presentation the system recorded a matrix of 300 samples per 5 channels, available for online and offline data processing.

3.2.3.1. Online data classification

To test online the BCI system, we used a classification algorithm that has been extensively described elsewhere (Piccione et al., 2006; Silvoni et al., 2009). Before each testing day and for each of the three interfaces a different classifier was trained and adapted *ad personam* through a three-step procedure: Independent Component Analysis (ICA) decomposition, fixed features extraction, and support vector machine (SVM) classification. The ICA decomposition was used for splitting up the EEG signals into statistically independent sources of signal (Cover & Thomas, 1991; Jung et al., 1998), with the specific hypothesis that one of the sources reflected the ERP. Then the source that was more similar to the target ERP was automatically selected using a fuzzy method (Beverina et al., 2004). Considering the selected source, a single-sweep normalized data set was obtained for each trial of the testing sessions, and it was used for feature extraction (Jung et al,. 2001). The features extracted were a data set of 78 values representing a concise description of the ERPs. The extracted features were used for the classification of the testing-session trials with a SVM classifier. The SVM classifier was updated after each testing day with a 20-fold, cross validation procedure except for the epochs of the last session (Wang et al., 2004). Of the remaining epochs, 80% were randomly selected as training set and 20% composed the testing set. ERP epochs with artifacts greater than 100 μV, with regard to each channel's activity (including EOG), were excluded from each training set (Cohen & Polich., 1997). All available ERPs epochs were analyzed for each testing set. The epochs of the last session done by the participants were used to perform a further validation of the updated SVM. After the last testing session, no other classifier updating was performed. Thus, the classifier used in the follow-up sessions was the same as that of the last testing sessions. The three-step classification procedure was applied during online operations to each single sweep synchronized with the cue. The output of the SVM classifier was converted into a binary value (1 = target ERP; 0 = non target ERP) to control each movement of the cursor.

3.2.3.2. Offline data analysis

For the offline classification of target vs. non-target ERPs, we used a method which combines a genetic algorithm for both feature extraction and selection, and a logistic classifier for classification. A detailed description of the method can be found in (Dal Seno et al., 2010a), here only the fundamental aspects are presented.

Genetic algorithms (GA) belong to the class of evolutionary algorithms, i.e. optimization algorithms inspired by the theory of evolution (Holland, 1975). In particular, in a Genetic Algorithm, the solutions of the optimization problem are coded in strings called chromosomes: the best chromosomes are selected, combined together and modified in a process which mimics how evolution works, including mutation, cross-over and natural selection. Generation-by-generation, the best solution will emerge from a population of sub-optimal solutions (Goldberg, 1989). In our implementation, each chromosome encodes the set of features to be used by the logistic classifier for the classification of target vs. non-target ERP sweeps. Each feature is computed by the dot product between the EEG signal and a weighting function (a Gaussian curve in this paper) coded in one *gene*; indeed, the gene is composed by four parameters: two parameters characterize the Gaussian curve (the timing of the peak within the epoch, and its width); one parameter identifies the EEG lead used; and a forth parameter activates/deactivates the gene (i.e. it states if the related feature must be used for classification or not). The length of the single chromosome (i.e. the number of its genes, is not defined *a priori* but it may change from generation to generation), as it is used in Goldberg et al. (1989). A constant population of 120 individuals, randomly initialized, was used. The maximum number of generations was set to 20 and the evolution was stopped if both the maximum value and the average value of a performance metric (i.e. the F measure, defined below) did not increase for at least 4 generations. Concerning the selection criterion, tournament selection with elitism was used (Goldberg, 1989). A tournament size of 10 chromosomes and an elitism of 2 individuals were used for each generation. After selection, individuals underwent crossover and mutation. Crossover was applied to pairs of chromosomes randomly chosen with a probability of 0.7: the chromosomes were randomly divided in two segments (without breaking any gene), and then the four parts recombined. Mutation was applied to any single element of the gene with a probability of 0.005 and it consisted in small perturbations of its value. The output of our GA consists in a set of chromosomes. It includes all the chromosomes with a performance above 99% of the maximum performance value obtained during the whole evolution. In our implementation, the features extracted from the GA are used as input for a logistic classifier (le Cessie & Houwelingen, 1992). For each single interface, learning and testing sessions (Section 2.2) were used as training set for the logistic classifier; last testing and follow-up sessions (Section 2.2) as testing set; to avoid overfitting in the optimization of features by the GA, k-fold cross-validation (k=4) was used (Stone, 1974).

3.2.4. Experimental Design

Independent variables were manipulated within an experimental design for repeated measures. The independent variables manipulated for separately testing the effects on both, online and offline classification, were: Interface with three levels (“Arrows”, “Auto”, “Vol”) and Session with two levels (Testing sessions, Follow-up sessions). To assess classification performances, the F-measure (van Rijsbergen, 1979) was chosen. Most commonly used in Information Retrieval, F-measure is the harmonic mean of recall (Re) and precision (Pr): the recall is the rate of correct target classification with respect to the actual target sweeps, whereas the precision is the rate of correct target classification with respect to all target labeled sweeps. The traditional F-measure (or balanced F-measure) equally weights precision and recall and it is defined as (1):

$$F_1 = 2\frac{\mathrm{Pr}\cdot \mathrm{Re}}{\mathrm{Pr}+\mathrm{Re}} \tag{1}$$

We have used F measure instead of the classical accuracy mainly because of the unbalanced number of targets and non-targets in our experiments. We could have artificially balanced the training and the testing, but besides being not realistic it does not take into account the presence of false positives and false negatives.

The independent variables manipulated for testing the experimental effects on the ERP were: Interface with three levels (“Arrows”, “Auto”, “Vol”), Session with two levels (Testing sessions, Follow-up sessions), Channel with four levels (Fz, Cz, Pz and Oz) and Trial Class (Target, Non-target). The dependent variable was the amplitude of the P300 and the LNC. The amplitude of the P300 was defined as the averaged ERP amplitude from 300 to 500 ms. The amplitude of the LNC was defined as the averaged ERP amplitude from 500 to 900 ms. The time windows used for the amplitude definition were identified trough visual inspection of the grand average ERP (see Figure 3.5) by the experimenters.

3.3. RESULTS

3.3.1. Performance: online system classification

The analysis of the online classification data showed that participants’ performance was modulated by the main effect of Interface (see Figure 4), $F(2,22) = 8.57$, $p = .002$. Post hoc comparison, corrected with Bonferroni, revealed that the performance on the “Arrows” interface (M = 0.39, SD = 0.05) was lower than that on the “Auto” (M = 0.45, SD = 0.06; $p = .005$) and on the “Vol” (M = 0.46, SD= 0.04; $p = .008$) interfaces. There was no difference between the “Auto” and the “Vol” interface ($p = 1$). The main effect of the Sessions was not significant, $F(1,11) = 3.90$, $p = .074$. Moreover, the Interface by Session interaction was not significant, $F(2,22) = 3.19$, $p = .061$.

3.3.2. Performance: offline system classification

The analysis of the offline classification data revealed that participants' performance differed in the three interfaces (see Figure 4); Interface, $F(2,22) = 14.22$, $p < .001$. Participants' performance were higher on the "Vol" interface (M = 0.63, SD= 0.03) than on the "Auto" (M = 0.55, SD = 0.02; $p = .01$) and on the "Arrows" (M = 0.54, SD = 0.02; $p = .001$) interfaces; post hoc comparisons were corrected with Bonferroni. No significant difference was found between the "Vol" and "Auto" interfaces ($p = 1$). The main effect of the Session, $F(1,11) = 3.43$, $p = .091$, and the Interface by Session interaction, $F(2,22) = 3.25$, $p = .058$, were not significant.

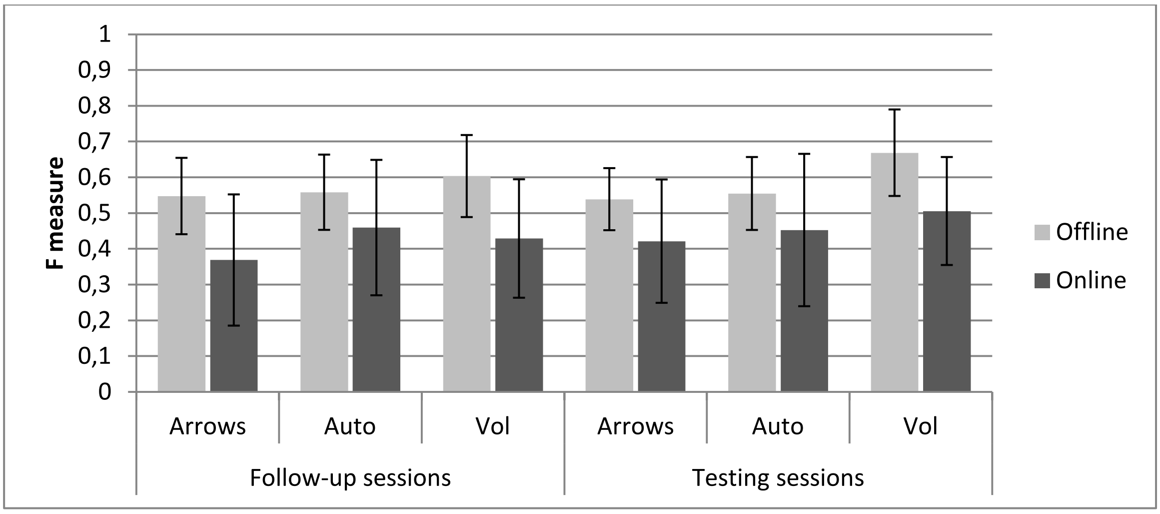

Figure 4. Means and Standard Deviations of the performance (F-measure) for online and offline classification.

3.3.3. P300 amplitude analysis.

The ANOVA results for the mean amplitude of the P300 are shown in Table 3.1. For reason of clarity, only the results relevant for the experimental hypotheses of the present study were extensively reported in the paragraph below, especially those where the Trial Class factor was involved.

Table 3.1 Results of the ANOVA for the P300 amplitude. In the first column are reported the main factors and the interactions. In the following columns are reported, respectively, the *F* values, the related degrees of freedom, the associated *p* values (in bold are reported those which are < .05) and the Greenhouse-Geisser correction coefficient when the assumption of sphericity was violated.

Factors	***F***	**df**	***p***	**E**
Interface	.34	(2, 22)	.62	.64
Channel	4.95	(3, 33)	**.006**	-
Session	3.07	(1, 11)	.11	-
Trial Class	9.76	(1, 11)	**.01**	-
Interface x Channel	1.24	(6, 66)	.31	.29
Interface x Session	.89	(2, 22)	.42	-
Channel x Session	.45	(3, 33)	.71	.43
Interface x rial Class	2.84	(2, 22)	.08	-
Channel x Trial Class	2.89	(3, 33)	.05	-
Session x Trial Class	.59	(1, 11)	.68	-
Interface x Channel x Session	.77	(6, 66)	.5	.43
Interface x Channel x Trial Class	.59	(6, 66)	.74	.33
Interface x Session x Trial Class	1.94	(2, 22)	.17	-
Channel x Session x Trial Class	.99	(2, 22)	.41	-
Interface x Channel x Session x Trial Class	2.86	(6, 66)	.8	.56

The main effect of the Trial Class was significant, $F(1,11) = 9.76$, $p = .01$. A larger P300 was elicited following the Target trials (M = 4.83 μV, SD = .86) than following the Non-target trials (M = 3.32 μV, SD = .45). The distribution of the P300 increased in amplitude from the frontal to the posteriors sites (Channel, $F(3,33) = 4.95$, $p = .006$; see Figure 5). The three interfaces elicited P300s of similar amplitudes on Target and Non-target trials. In fact, the interaction effects of Interface by Trial Class ($F(2,22) = 2.84$, $p = .08$) and Interface by Channel by Trial Class ($F(6,66) = .59$, $p = .74$, $\varepsilon = .33$) were not significant. Moreover, none of the effects involving the Session factor was significant.

To investigate whether the differences between the interfaces' performance found in the EEG data classification were due to differences in P300 amplitude, a Target vs. Non-target trials planned contrast was performed within each interface. There was a significant difference in P300 amplitude in the "Vol" interface (Target: M = 4.99 µV, SD = 2.36; Non-target: M = 2.78 µV, SD = 1.32; $t(11) = 4.98$, $p < .001$), but not in the "Auto" (Target: M = 4.78 µV, SD = 3.7; Non-target: M = 3.54 µV, SD = 1.94; $t(11) = 1.91$, $p = .083$) and in the "Arrows" (Target: M = 4.72 µV, SD = 3.33; Non-target: M = 3.61 µV, SD = 1.78; $t(11) = 1.88$, $p = .087$) interfaces (see Figure 3.5).

3.3.4. LNC amplitude analysis

The ANOVA results for the mean amplitude of the LNC are shown in Table 3.2. Only the results relevant for the experimental questions of the present study were extensively reported, with particular reference to the Trial Class factor.

There was a larger negativity in the last portion of the epochs on the Target (M = -2.22 µV, SD = .51) than on the Non-target trials (M = -.05 µV, SD = .2), Trial Class, $F(1,11) = 21.43$, $p = .001$. This difference was significantly larger in the frontal site and progressively decreased towards the posterior sites along the midline (see Figure 5), Channel by Trial Class $F(3,33) = 11.05$, $p = .002$, $\varepsilon = .49$. The Interface by Trial Class interaction was significant, $F(2,22) = 8.97$, $p = .001$, revealing that the LNC amplitude related to the Target and Non-target trials was differently modulated among the three interfaces. To further investigate this interaction effect, two separate ANOVAs were performed for testing the simple effect of the Interface on each level of the Trial Class (e.g., Target and Non-target). No different modulation in LNC amplitude was found on the Target trials, *F*(2,22) = .24, *p* = .63. In contrast, there was a significant effect of the Interface on the Non-target trials, *F*(2,22) = 25.56, *p* < .001. Post hoc comparisons, corrected with Bonferroni, showed that the amplitude values related to Non-target trials on the "Vol" interface (M = .87 µV, SD = .29) were different than those on the "Auto" (M = -.47 µV, SD = .18, *p* < .001) and those on the "Arrows" (M = -.57 µV, SD = .22, *p* = .001) interfaces. In contrast, there was no significant difference between the "Auto" interface and the "Arrows" one, *p* = 1.

Table 3.2 Results of the ANOVA for the LNC amplitude. In the first column are reported the main factors and their interactions. In the following columns are reported, respectively, the *F* values, the related degrees of freedom, the associated *p* values (in bold are reported those which are < .05) and the Greenhouse-Geisser correction coefficient when the assumption of sphericity was violated.

Factors	***F***	**df**	***p***	**ε**
Interface	3.97	(2, 22)	**.034**	-
Channel	4.63	(3, 33)	**.008**	.55
Session	.02	(1, 11)	.89	-
Trial Class	21.43	(1, 11)	**.001**	-
Interface x Channel	1.07	(6, 66)	.39	.26
Interface x Session	.14	(2, 22)	.87	-
Channel x Session	.82	(3, 33)	.49	.44
Interface x Trial Class	8.97	(2, 22)	**.001**	-
Channel x Trial Class	11.05	(3, 33)	**.002**	.49
Session x Trial Class	.8	(1, 11)	.39	-
Interface x Channel x Session	.89	(6, 66)	.5	.28
Interface x Channel x Trial Class	1.15	(6, 66)	.34	.45
Interface x Session x Trial Class	.69	(2, 22)	.93	-
Channel x Session x Trial Class	.28	(2, 22)	.84	-
Interface x Channel x Session x Trial Class	.59	(6, 66)	.59	.42

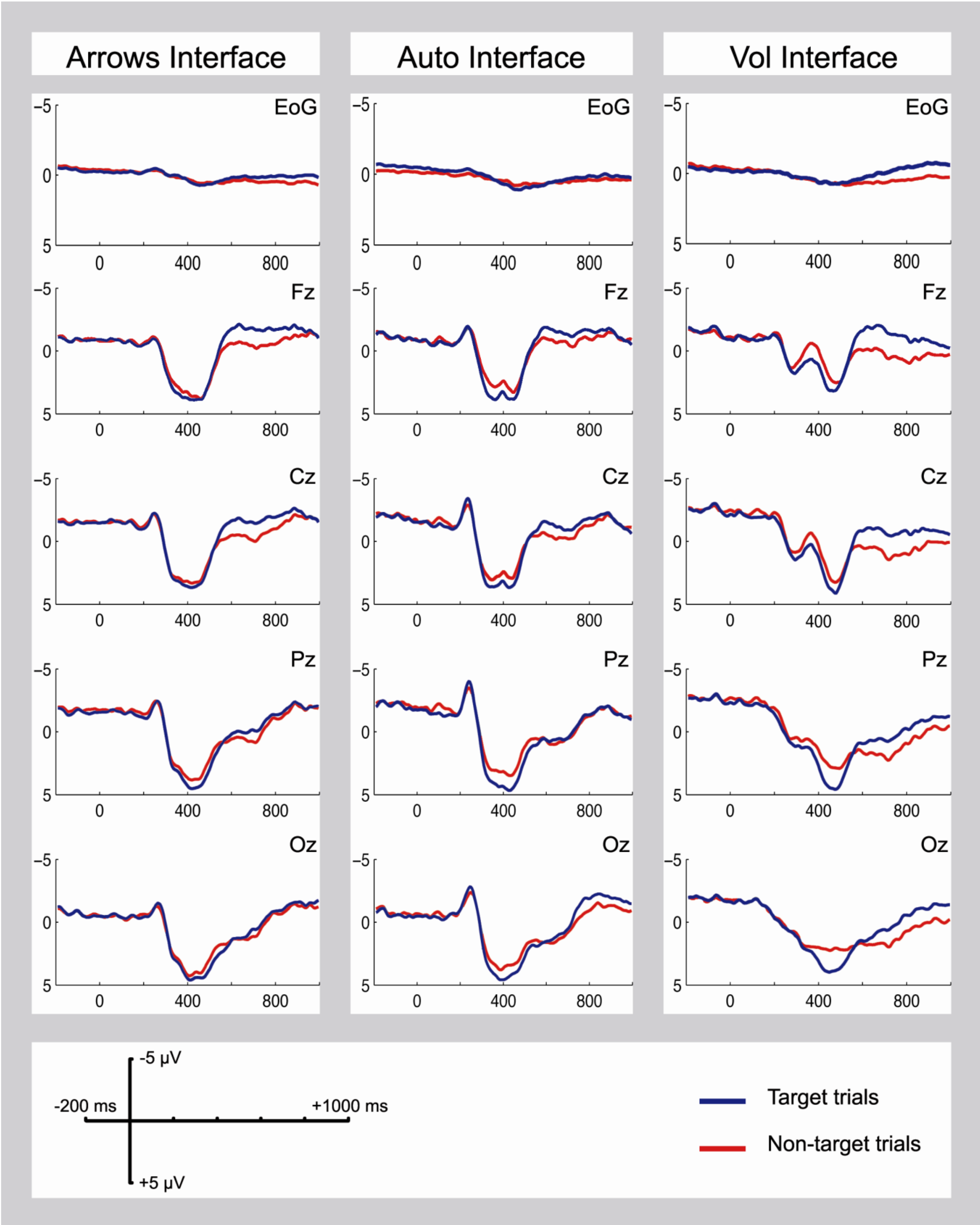

Figure 3.5 Grand Average of the ERPs elicited by the three interfaces on the last testing and follow-up sessions.

As for the P300, planned contrasts on target vs. non-target trials were performed within each interface. There was a significant difference between the two levels of the Trial Class in each interface: the “Vol” interface (Target: M = -2.24 μV, SD = 2.29; Non-target: M = .87 μV, SD = 1.01; $t(11) = -5.87$, $p < .001$), the “Auto” interface (Target: M = -2.42 μV, SD = 1.64; Non-target: M = -.47 μV, SD = .64; $t(11) = -4.07$, $p = .002$) and the “Arrows” interface (Target: M = -1.98 μV, SD = 1.99; Non-target: M = -.57 μV, SD = .78; $t(11) = -2.53$, $p = .028$).

3.4. DISCUSSION

We analyzed whether the different performances obtained by 12 healthy participants with three new interfaces for an ERP-based visual BCI (Experiment 1) were influenced by the use of different classification systems. For this purpose, we performed a new offline classification with a GA for the features extraction and a logistic classifier for epoch categorization (Dal Seno *et al* 2010a). The F-measure was calculated and used as the dependent variable for both, online and offline classifications, because the F-measure is an accuracy index that takes into account the unbalanced number between targets and non-targets (i.e., 1/3 ratio). By using the F-measure, we overcame some intrinsic limitations of the classic measures used for testing discrete BCIs (Dal Seno *et al* 2010b, Bianchi *et al* 2007).

The result of the offline classification revealed different performances among the three interfaces. Participants reached better accuracy with the “Vol” interface than with both, the “Auto” and the “Arrows” interfaces. The offline analysis performed using the GA and the logistic classifier permitted to underline the experimental manipulation that we have done by implementing different principles of visuospatial attention orienting on the three interfaces. These results are in line with those reported in the Experiment 1, in which was used an online classifier with a fixed features extraction algorithm, and the total accuracy as dependent variable (i.e., the percentage of correct classified trials on the total number of trials, Wolpaw *et al* 2002, Piccione *et al* 2006).

Also the result of the online classification revealed different performances among the three interfaces. From the statistical analysis emerged that participants reached a lower performance using the "Arrows" interface with respect to the other two interfaces. Instead, no difference was found between the "Auto" and "Vol" interfaces. This result is not in line with (A) the results reported in Experiment 1, with (B) the results of the offline classification, and with (C) the neurophysiological data recorded.

(A) From the online analysis of classification accuracy (Experiment 1) emerged that participants had an advantage by using the "Vol" interface whit respect to both the "Auto" and the "Arrows" interfaces. Instead, while performing the same analysis in Experiment 2, but using the F-measure as dependent variable, the advantage in using the "Vol" interfaces disappeared, and emerged that lower performance are associate to the "Arrows" interface with respect to the other two interfaces. This different pattern of result underline that the results obtained with the online classification are not consistent when using different measure of performance (i.e., accuracy in % and F-measure).

(B) The different pattern of results between the offline and online classification system reported in the present study might depend on the use of a fixed features extraction, which seemed to be less sensible on detecting the differences among the interfaces due to the experimental manipulation. Even if the result did not disconfirm the advantage of using the “Vol” interface, it did not underline the difference between the interface which used the endogenous principle of visuospatial attention orienting (“Vol”) and those which used the exogenous principle of visuospatial attention orienting (“Auto” and “Arrows”). This experimental manipulation, instead, clearly emerged while using the offline classification system, based on *ad personam* features extraction through GA procedures.

(C) The online classification results using the F-measure were not in line with those about the ERPs analyzed in the present study. There were no specific differences in the ERPs elicited by the “Arrows” interface with respect to those elicited by the other two interfaces that might explain the online classification results. Instead, the planned contrast performed within each interface resulted into a significant target vs. non-target difference for the “Vol” interface, but not for the “Auto” and “Arrows” interfaces. Furthermore, we found a different modulation of the LNC amplitude on non-target trials between the three interfaces. In detail, a significant less pronounced LNC was elicited in the “Vol” interface than in the “Auto” and in the “Arrows” interfaces. The results from the ERPs analysis were in line with those of the offline classification and they could explain the different efficacy of the “Vol” interface with respect to the other two interfaces.

The level of classification reached differed as a function of the two classifying systems. We did not test the differences on classification between the online and the offline classifiers used in this study with a statistical procedure, because only a comparison of the classifiers in the same condition (i.e., both tested online) could permit to directly compare their efficacy. But the higher performances obtained and the smaller standard deviation (see Figure 4), suggest that the use of the GA classifier might be a better solution for epochs categorization within our BCI system.

In summary, the results showed that the control of a visual ERP BCI is possible in a condition of covert visuospatial attention, without gaze movements, that is particularly relevant for patients, whose eye muscle control is impaired. Moreover, subtle differences in interface design, such as the implementation of the endogenous and exogenous principles of visospatial attention orienting, produced significant differences on the ERP elicited and, consequently, on BCI performance. This result represents a further evidence of the fact that the implementation of cognitive principle on BCI design and development can modulate the brain signal, leading to advantages in device control for the user. Nonetheless, to take full advantages of such design implementations, classifying systems which do not operate on *a priori* feature extraction are required. For this purpose, the use of genetic algorithms might represent an efficient *ad-hoc* solution for detecting the most relevant features deriving from both, different interfaces modulation and interpersonal brain signal differences.

4. EXPERIMENT 3

4.1. INTRODUCTION

Amyotrophic lateral sclerosis is a neurodegenerative disease with adult onset that leads to paralysis and death typically within 2-5 years from initial diagnosis. Pathological features of ALS include the loss of motor neurons in the spinal ventral horns, most brainstem motor nuclei, and motor cortex (Kunst, 2004).No treatments are available, to date. The progression of the disease brings the patients to lose their ability to breath independently, and they have to face the critical decision of accepting artificial respiration or to die because of respiratory problems. The patients who decide for the artificial respiration survive longer, and progressively enter in a condition of paralysis in which only the eye muscles or the external sphincter control are spared (i.e., LIS condition; Birbaumer, 2006a). In the latest stages of the illness, when no muscle control is possible, ALS patients enter in the so-called completely locked-in state (CLIS). The motor impairments in ALS could be accompanied by preserved comprehension, because the sensory and the cognitive functions might be spared or impaired in minor degree (Irwin et al., 2007; Lakerveld et al., 2008). ALS affects the patients' quality of life (QoL) not only by reducing their autonomy in everyday life, but also by preventing their possibility of communicating and interacting with the environment. Independently of the fact to use a ventilator or not, half of ALS patients are mildly depressed or experience depressive symptoms due to their clinical condition, even if their QoL-related perceptions is higher than that supposed by their caregivers (Kübler, 2005a). In the last years, new clinical approaches have been proposed for treating the ALS patients' symptoms, which are due to paralysis. The depressive symptoms may be clinically treated with psychotherapy (Matuz et al., 2010), while the QoL of ALS patients may be raised by maintaining or restoring basic communication and autonomy (Wolpaw, 2010).

BCIs represent a possible solution to the problems of communication and interaction with environment (e.g., BCIs for word spelling and BCIs for wheelchair movement control; Wolpaw et al., 2002). ALS patients have been the most investigated clinical population in BCI research so far (Birbaumer et al., 2008), and their ability to control a BCI system does not remain the same in all the stages of the illness. In their meta-analysis on the use of BCIs by patients, Kübler and Birbaumer (2008) proposed a classification of five different levels in relation to different degrees of impairment:

- *minor* impairment, is referred to patients who have only slightly impaired limb movement and normal speech;
- *moderate* impairment, is referred to patients with restricted limb movement (wheel-chair-bound) and unaffected speech or with intact limb movement, but without speech (such as the bulbar form of ALS that first affects speech and swallowing);
- *major* impairment, is referred to patients who are almost tetraplegic with restricted speech,
- LIS, patients in the locked-in state;
- CLIS, patients in the completely locked-in state.

The majority of the BCI systems tested with ALS patients, relies on EEG signals (i.e., P300, SCP, SMR) and on visual interfaces. It has been reported that ALS patients with *minor*, *moderate*,or *major* impairment were successfully able to control online a visual BCI through P300 (Nijboer et al., 2008; Silvoni et al., 2009), SCP (Kübler et al., 2004; Iversen et al., 2008) and SMR (Kübler et al., 2005b; Bai et al., 2010).

Some reports of effective communication in ALS patients with LIS can be found in the literature. Birbaumer et al. (1999) first described two ALS-LIS patients who successfully used the SCP in order to communicate through a word spelling system, the TTD. Few other examples have been reported so far. The efficient control (i.e., above chance criterion or higher) of a BCI was reached by ALS-LIS patients in the studies of Kübler et al. (2001: one patient, SCP-based BCI; 2005b: one patient, SMR-based BCI; 2009: three patients, P300-based BCI), Nijboer et al. (2008: one patient, P300-based BCI[1]; 2010: one patient, SMR-based BCI), Iversen et al. (2008: two patients, SCP-based BCI), Gu et al. (2009: one patient, SMR-based BCI), and Townsend et al. (2010: two patients, P300-based BCI). A remarkable longitudinal study has been reported by Sellers and colleagues (2010). They described an ALS-LIS patient (ALSFRS-R score = 1) who used the P300-speller for communication, and, thus, he was able to manage his work (i.e., leading a research group) for more than two years. Nevertheless, there are also some studieswhere the unsuccessful use or the inability of learning to use a BCI have been reported: Hill et al. (2006: one patient, SMR- and P300 based BCI), and Nijboer et al. (2010: one patient, P300-based

[1] The patient reported by Nijboer et al. (2008) was the same one described in Kübler et al. (2005b)

BCI). The lower number of ALS-LIS patients who were not able to control a BCI could be underestimate indeed, due to scientific publication biases (e.g., the tendency of researchers to publish only “successful” studies, and the tendency of the journal editors and reviewers to reject “unsuccessful” ones).

The findings of studies on ALS-CLIS patients are less encouraging. There are very few cases described in the literature, and none of them was able to reach an acceptable level of success, in order to control independently a BCI (Neumann and Birbaumer, 2003: two patients, SCP-based BCI; Kübler et al., 2004: one patient, SCP- and SMR- based BCI; Hinterberger et al., 2005b: one patient, SCP-based BCI). In their meta-analysis, Kübler and Birbaumer (2008) have hypothesized that the reason of this failure could be attributed to the extinction of goal direct thinking in the completely paralyzed condition. An alternative explanation for the unsuccessful BCI use in the cases reported, which in any case does not disconfirm Kübler and Birbaumer’s hypothesis, is that the use of a visual interface for controlling a BCI is not suitable for an ALS-CLIS patient. Murguialday et al. (2011) have described the case of an ALS patient who was deteriorating from the LIS to the CLIS. In the latter condition, the visual sensory modality of the patient was compromised, both because of eye-muscle paralysis and of cornea dryness. In contrast, auditory and proprioceptive information processing was preserved, remaining the only possible channels for developing a BCI in this ALS patient.

There are examples of auditory BCI (Sellers and Donchin, 2006; Furdea et al., 2009; Klobassa et al., 2009; Halder et al., 2010; Schreuder et al., 2010) or tactile BCI (Brouwer & van Erp, 2010) designed for communication, but none of them has been tested with CLIS patients. Kübler et al. (2009) compared the use of a visual and of an auditory P300-based BCI with four ALS patiens. Three of these patients were LIS, and one of them was described to be close to the CLIS condition. All patients reached good performance (i.e., above 70%) with the visual BCI, whereas their performance with the auditory BCI was very poor. It has to be mentioned that these four ALS patients had previous experience with the visual P300-based BCI, but not with the auditory one.

In summary, visual BCIs for communication seem to be suitable for ALS patients with *minor*, *moderate*, and *major* impairment, but not for those who are in the CLIS condition. More controversial is the case of LIS: BCIs based on the visual modality have been successfully used by ALS-LIS patients in some cases, but not in others. It is clear that the degeneration of the illness leads the ALS-LIS patients to progressively lose their eye-movement control. This fact must be taken into account when designing efficient visual interfaces for communication or motor control. Recent studies have demonstrated that the use of the P300 speller depends on the possibility of the participants to focus their gaze on the target (Treder & Blanckertz, 2010; Brunner et al., 2010). The need of moving the eyes might represent a limit for ALS-LIS patients, when their illness stage advances. Thus, the development of gaze-independent visual BCIs is required.

In Experiment 1 we proposed three new visual interfaces, in which healthy participants used their covert visuospatial attention orienting (i.e.; implicit shifting of the attentional focus without eye movements) for controlling a virtual cursor on a monitor, by means of their ERPs (i.e., P300 and LNC). The results have revealed that it is possible to use a BCI in a covert visuospatial attention orienting condition (see also, Liu et al. 2011; Treder et al., 2011). Moreover, in our experimental manipulation we modulated participants' BCI performances, by implementing different principles of covert visuospatial attention orienting (exogenous vs. endogenous). Healthy participants reached higher performance with the interface that required endogenous visuospatial attention orienting ("Vol" interface) than with the interfaces that required exogenous visuospatial attention orienting ("Arrows" and "Auto" interfaces). These findings were confirmed with both online and offline analysis, which were performed by means of two classifiers (see Experiment 2).

In Experiment 3 we aimed to investigate the online effect of the "Auto" and "Vol" interfaces with a group of ALS patients, who showed different levels of motor impairment (i.e., from *minor* to *major*). We wanted to investigate whether the use of the "Vol" interface would result in a more efficient control of the ERP-based BCI, as it was observed with healthy participants (see Experiment 1). Moreover, we investigated whether there was an effect of pathology's level, measured through the revised ALS functional rating scale (ALSFRS-R, Cedarbaum et al., 1999), on the performance obtained with the BCI. In the literature, it has been reported that there is no relation between the level of impairment and BCI performances (Kübler & Birbaumer, 2008; Silvoni et al., 2009). In Experiment 3, we tested, for the first time, the effects of different modalities of visuospatial attention orienting on the performance of ALS patients, by means of a "covert attention BCI", by means of the analysis of performance and neurophysiological data. In addition we investigated whether their performance was affected by their illness' severity.

4.2. METHODS

4.2.1. Participants

Ten ALS patients gave their informed consent in order to participate in the study. Their demographic and clinical data are reported in Table 4.1. The participants were recruited from the ALS patients who were spending a period of clinical treatment at the IRCCS San Camillo Hospital, Venice-Lido. Experiment 3 was designed in accordance with the principles of the Declaration of Helsinki, and was approved by the ethical committee of the hospital.

Table 4.1 Demographic and clinical data of the ALS patients.

Id	Age	Sex	Education (years)	ALS diagnosis [a]	Level of impairment [b]	ALSFRS-R scale [c]	Disease duration (months) [d]
P01	44	m	13	bulbar	moderate	28	24
P02	51	m	13	spinal	minor	35	24
P03	68	m	8	spinal	moderate	14	29
P04	56	f	8	spinal	minor	36	96
P05	53	m	8	bulbar	minor	41	14
P06	53	m	8	bulbar	minor	39	10
P07	65	m	13	bulbar	major	10	8
P08	60	f	13	spinal	minor	32	12
P09	49	m	17	spinal	minor	42	6
P10	64	m	5	spinal	major	14	16

[a] *ALS diagnosis is referred to the initial symptoms manifested by patients. The term "bulbar" refers to the motor neurons located in the brain stem and is used when speaking, swallowing or breathing are first impaired. The term "spinal" refers to motor neurons of the spinal cord (2nd motor neurons), and is used when the limb movement is firs affected.*

[b] *Level of impairment according to Kubler & Birbaumer (2008).*

[c] *The revised ALS functional rating score (ALSFRS-R, Cedarbaum et al. 1999) evaluates the physical impairment on ascale from 0 (completely LIS) to 48 (not impaired).*

[d] *The duration of the disease was calculated in months from the occurrence of the first symptoms.*

4.2.2. Apparatus, stimuli, and procedure

The apparatus of Experiment 3 was identical to that of Experiment 1, except for the use of a chinrest in Experiment 1. This difference was due to the fact that patient P01 was tracheostomized, and patients P04, P08, P09, and P10 sat on a wheelchair; for these reasons it was impossible for them to position their head on the chinrest. The monitor was placed at a distance of about 60 cm in front of each participant's eyes. On the one hand, this procedure did not permit to control exactly the distance between the monitor and the patients' eyes. On the other hand, this experimental setting had the advantage of permitting us to test the use of a BCI system in a more ecological situation, which was closer to that required for BCI's use in everyday life.

Two of the three interfaces described in Experiment 1 were presented to the participants: the "Auto" interface (Figure 4.1) and the "Vol" interface (Figure 4.2). Both interfaces were designed for controlling the movement of a virtual cursor on a monitor. The cursor's control was used for reaching target icons displayed on the monitor. The icons showed everyday life activities, which may be used by the patients for communicating their needs (e.g., the icon of a doctor for requiring the presence of a doctor, the image of a drinking man for requiring a glass of water, etc.).

In the "Auto" interface the principle of exogenous visuospatial attention orienting was implemented. Four icons were placed in the periphery of the monitor, all at the same distance 7 cm from a central fixation point. During the experimental sessions, the icons disappeared for 75 ms and reappeared at the same spatial position. The offset/onset order of the icons was semi-random. The task of the participant was to pay attention to the icon that was in the target spatial position (i.e., the icon to be reached with the cursor, as it was indicated by the experimenter at the beginning of each experimental session), in order for the participant to guide the cursor towards the target spatial position. Moreover, the participants were required to keep their gaze on the central fixation cross and to ignore the offset of the icons in the non-target spatial positions.

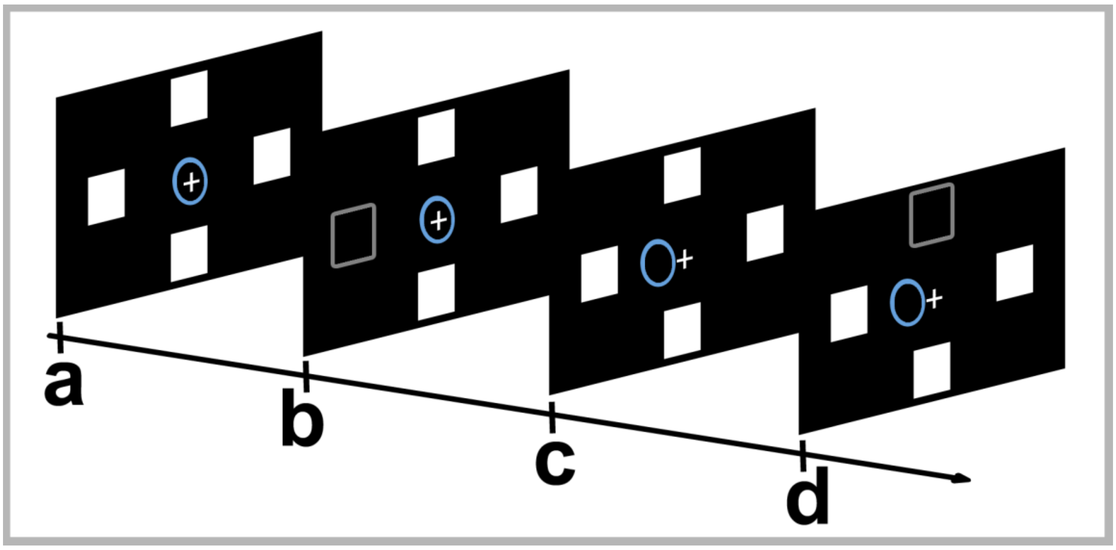

Figure 4.1 The “Auto” interface; schematic representation of a trial: a) initial situation; b) offset of an icon for 75 ms; c) feedback; if the target ERP was detected, the cursor moved of one step towards the target icon; d) offset of the next icon.

In the “Vol” interface the principle of endogenous orienting of visuospatial attention was implemented. The four icons remained always displayed on the monitor. Four capital letters were presented at the central fixation cross, one at a time, for 900 ms, in a sequential semi-random order, and then they disappeared. Each letter was the initial letter of an Italian directional word, and it indicated the spatial position of one among the four icons. Participants were required to pay attention to the letter indicating the direction of the target spatial position (i.e., the icon to be reached with the cursor, as it was indicated by the experimenter at the beginning of each experimental session), and to ignore the others. Moreover, participants were required to keep their gaze fixed on the central fixation cross.

The participants' EEG was recorded, during the presentation of the trials with the "Auto" interface (i.e., the offset of an icon for 75 ms) and during the presentation of the trials with the "Vol" interface (i.e., the onset of a letter for 900 ms).

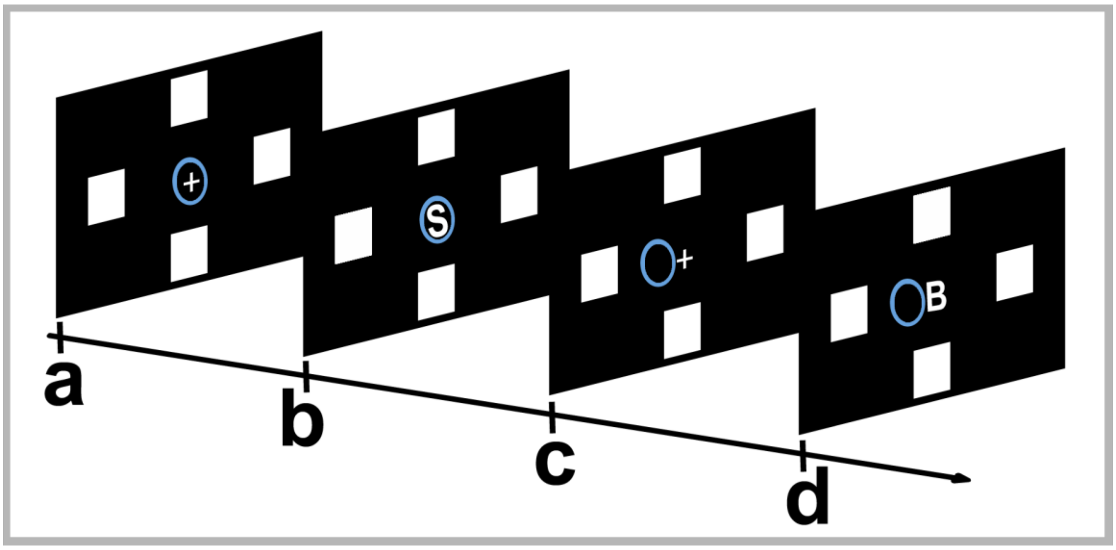

Figure 4.2 The "Vol" interface; schematic representation of a trial: a) initial situation; b) onset of a 'directional' letter for 900 ms; c) feedback; if the target ERP was detected, the cursor moved of one step towards the target icon; d) onset of the next letter.

The ERPs related to each trial were processed online by an *ad hoc* classifier. If the participants were correctly performing the attentive task, different ERPs were elicited by the target trials with respect to the non-target trials. The classifier was trained for detecting the difference between the features in the ERPs related to the target trials and those related to the non-target trials. When the classifier detected the features of a target trial, the cursor was moved one step according to the direction of the spatial position of the trial that elicited the ERPs. Otherwise, the cursor was not moved. The detailed description of both the interfaces and of the participants' task is extensively reported in paragraph 2.2.2.

The experimental procedure consisted in nine consecutive experimental days. In the first experimental day participants performed eight learning sessions with each interface (the definitions of a learning session and of a testing session are fully described in paragraph 2.2.2.). In the following eight experimental days, participants were required to perform four testing sessions, with one interface per day. The target spatial position (i.e., the spatial position occupied by the to-be-reached icon) differed in each of the four testing sessions. The order of the target positions was counterbalanced across the experimental days. The interfaces were presented to each participant among the experimental days with the following schema: A-B-B-A - B-A-A-B. The order of presentation of the two interfaces was counterbalanced among the participants: half of them started with the “Auto” interface, and the other half started with the “Vol” interface. At the end, participants performed 8 learning sessions in the first experimental day, and 16 experimental sessions in the four following experimental days (four sessions per experimental day) with each interface.

4.2.3. Electrophysiological data acquisition and online processing

The EEG was acquired and processed as in Experiment 1. The electrodes’ montage was performed according to the International 10-20 System at Fz, Cz, Pz, and Oz. The Electrooculogram (EOG) was recorded from a pair of electrodes below and laterally to the left eye. All electrodes were referenced to the left earlobe and the ground was on Fpz. Impedance was lower than 5 kΩ. The five channels were amplified, band-pass filtered between 0.15 Hz and 30 Hz, and digitized at 200 Hz sampling rate. The ERP epochs were synchronized with the occurrence of the stimulus (i.e., the offset of the icon in the “Auto” interface, and the onset of the letter in the “Vol” interface). Each epoch began 500 ms before the stimulus occurred and ended 1000 ms after the stimulus occurred (total duration: 1500 ms). The classification procedure has been extensively described in Silvoni et al. (2009). Before each testing day and for each of the two interfaces the classifier was trained and adapted *ad personam* through a three-step procedure: Independent Component Analysis (ICA) decomposition, fixed features extraction, and support vector machine (SVM) classification (for a detailed description, please see paragraph 2.2.3.). The three-step classification procedure was applied online to each single sweep synchronized with the trials. The output of the SVM classifier was converted into a binary value (1 = P300 present; 0 = P300 absent) to control the discrete movements of the cursor.

4.2.4. Experimental Design

The independent variables manipulated for testing the experimental effects on the BCI performance were: Interface with two levels (“Auto”, “Vol”) and Session with four levels (the four experimental days, in which the experimental sessions for each interface were performed: Day1, Day2, Day3, Day4. The dependent variables were the performance (total classification accuracy in %, computed as in Piccione et al., 2006), the percentage of error in the classification in the target trials, and a measure of the communication speed (the transfer bit rate [TBR] measured in bit/min, computed as in Piccione et al., 2006)..

The independent variables for testing the experimental effects on the ERPs were: Interface with two levels (“Auto”, “Vol”), Channel with four levels (Fz, Cz, Pz and Oz), and Trial Class (Target, Non-target). The dependent variable was the amplitude of the P300 and the LNC, taken from the epoch grand average of all the experimental sessions for each ALS patient. The amplitude of the P300 was defined as the averaged ERP amplitude from 300 to 600 ms. The amplitude of the LNC was defined as the averaged ERP amplitude from 600 to 995 ms. The time windows used for the amplitude definition were identified trough visual inspection of the grand average ERP (see Figure 4.6).

In order to test whether there was any influence on performance due to the level of the illness, we performed a linear regression using the ALSFRS-R score as predictor of the above-listed dependent variables, for each interface.

4.3. RESULTS

We ran ANOVAs for repeated measures. The Greenhouse-Geisser correction coefficient is reported when the assumption of sphericity was violated.

4.3.1. Performance

There was an improvement of the performance (figure 4.3) as a function of

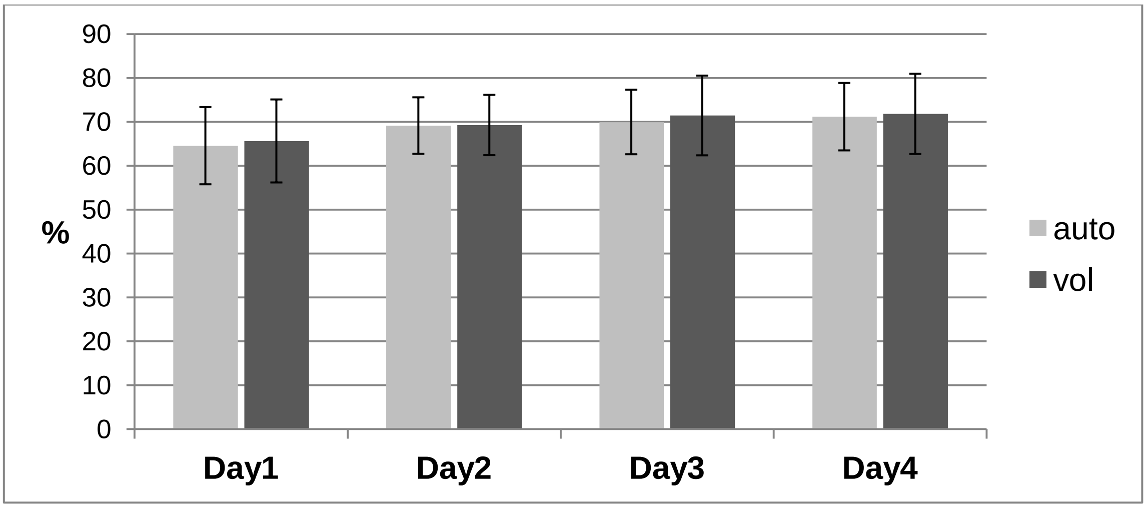

Figure 4.3 Mean and Standard Deviation of the performance (total accuracy in %) for the "Auto" and the "Vol" interfaces along the four days of testing sessions.

the experimental days (Day1: *M* = 65.08%, *SD* = 9.1; Day2: *M* = 69.18%, *SD* = 6.6; Day3: *M* = 70.68%, *SD* = 8.2; Day4: *M* = 71.46%, *SD* = 8.3), resulting in a significant main effect of the Session, $F(3,27) = 11.69$, $p < .001$. On the contrary, the main effect of the Interface and the Interface by Session interaction were both non-significant, respectively $F(1,9) < 1$ and $F(3,27) < 1$.

4.3.2. Classification errors on target trials

The analysis of the classification errors on target trials (figure 4.4) revealed that there was a main effect of the Interface, $F(1,9) = 5.99$, $p = .037$. There were less classification errors on target trials in the "Vol" interface (M = 59.65%, SD = 23.4) with respect to the "Auto" interface (*M* = 67.34%, *SD* = 21.7).

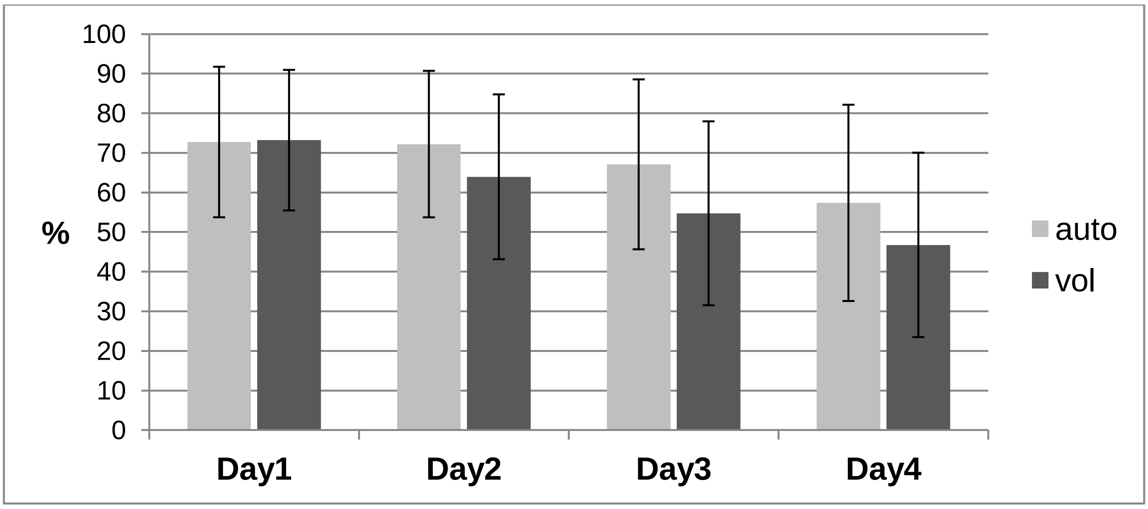

Figure 4.4 Mean and Standard Deviation of the classification errors on target trials (in %) for the "Auto" and the "Vol" interfaces along the four days of testing sessions.

Moreover, the number of incorrectly classified target trials diminished significantly with the progress of the experimental days, Session, $F(3,27) = 8.9$, $p < .001$. From the Bonferroni-corrected, post hoc comparisons emerged that there was a significant difference in the percentage of incorrectly classified target trials between the Day4 (M = 52.05%, SD = 24.5) and both the Day1 (M = 72.95%, SD = 18.3) and the Day2 (M = 68.07%, SD = 19.9). Instead, there was no difference between Day4 and Day3 (M = 60.91%, SD = 23.1). The Interface by Session interaction was not significant, $F(3,27) < 1$.

4.3.3. Transfer bit rate

The analysis of the communication speed data (Figure 4.5) showed that patients reached a significantly higher TBR using the “Vol” interface (M = 4.99 bit/min, SD = 3.01) with respect to the “Auto” interface (M = 4.02 bit/min, SD = 2.8), $F(1,9) = 6.03$, $p = .036$.

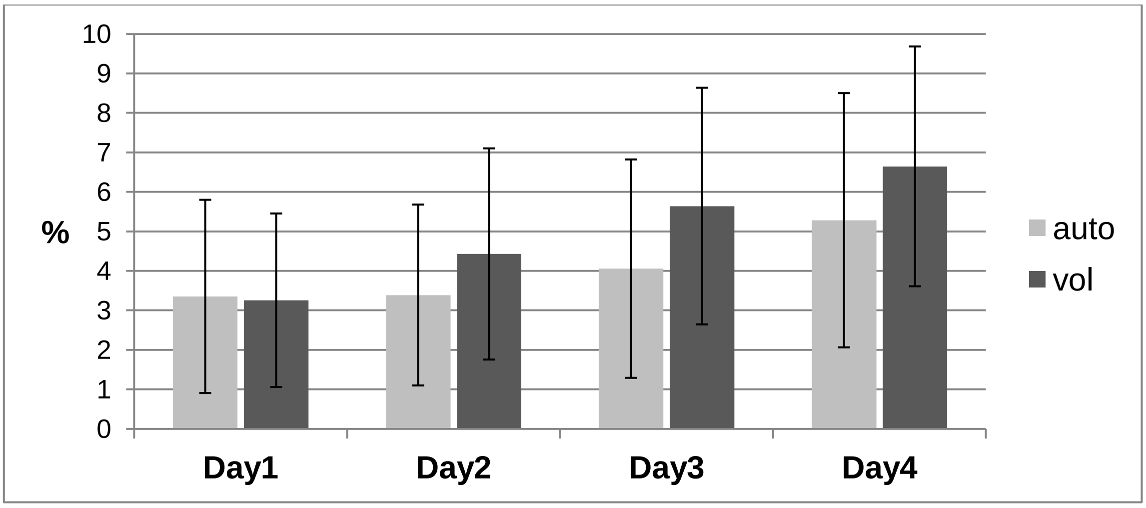

Figure 4.5 Mean and Standard Deviation of the communication speed (TBR in bit/min) for the “Auto” and the “Vol” interfaces along the four days of testing sessions.

Moreover, the main effect of the Session was significant, $F(3,27) = 9.26$, $p < .001$. As in the case for the performance and the classification errors on target trials, with the progress of the experimental days, ALS patients improved also on the TBR (Day1, M = 3.3 bit/min, SD = 2.3; Day2, M = 3.9 bit/min, SD = 2.5; Day3, M = 4.8 bit/min, SD = 2.9; Day4, M = 5.9 bit/min, SD = 3.2). From the Bonferroni-corrected, post hoc comparisons emerged that there was a significant difference in the TBR between the Day4 and both the Day1 (p <.001) and the Day2 (p = .027). Instead, there was no difference between the Day4 and the Day3 (p = .35). The Interface by Session interaction was not significant, $F(3,27) < 1$.

4.3.4. P300 amplitude

The ANOVA results for the mean amplitude of the P300 are shown in Table 4.2. For reason of clarity, only the results that were relevant for our experimental hypotheses were extensively reported within the text below, with particular regard to the Trial Class factor.

Table 4.2 Results of the ANOVA for the P300 amplitude. In the first column, are reported the main factors and all the interactions. In the following columns are reported, respectively, the F values, the related degrees of freedom, the associated p values, and the Greenhouse-Geisser correction coefficient when the assumption of sphericity was violated.

Factors	***F***	**df**	***p***	**ε**
Interface	2.67	(1, 9)	.14	-
Channel	1.50	(3, 27)	.23	-
Trial Class	3.12	(1, 9)	.11	-
Interface x Channel	2.88	(3, 27)	.054	.45
Interface x Trial Class	.22	(3, 27)	.65	-
Channel x Trial Class	2.59	(3, 27)	.073	-
Interface x Channel x Trial Class	.46	(3, 27)	.59	.51

The P300 amplitude was not differently modulated by the target (M = 1.07 µV, SD = .91) and the non-target epochs (M = 1.02 µV, SD = .95), resulting in a non- significant main effect of the Trial Class, $F(1,9) = 2.67$, p = .14. This was true for both the interfaces (Interface by Trial Class interaction, $F(3,27) < 1$) and among all the channels (Channel by Trial Class, $F(3,27) = 2.59$, p = .073).

Moreover, the Interface by Channel by Trial Class interaction was not significant, $F(3,27) < 1$.

4.3.5. LNC amplitude

The ANOVA results are reported in Table 4.3. As for the P300 amplitude, only the results concerning the modulation of the LNC because of the Trial Class factor were described in detail.

There was a larger negativity in the LNC epoch window on the Target (M = -.44 µV, SD = .68) with respect to the Non-target (*M* = -.04 µV, *SD* = .59) trials, resulting in a significant main effect of the Trial Class, $F(1,9) = 84.21$, $p < .001$. The LNC amplitude on Targets and Non-targets was differently modulated, in the "Auto" and in the "Vol" interfaces, resulting in a significant Interface by Trial Class interaction, $F(3,27) = 10.18$, $p = .011$. For further investigating this interaction effect, pairwise comparisons between the LNC amplitude in the "Auto" and "Vol" interfaces were performed, separately for the Targets and the Non targets. There was a significant difference between the LNC amplitude elicited by the Non-targets trials, $t(9) = -2.89$, $p = .018$ ("Auto": *M* = -.28 µV, *SD* = .32; "Vol": *M* = .18 µV, *SD* = .51), but not by Targets, $t(9) = -.68$, $p = .52$ ("Auto": *M* = -.53 µV, *SD* = .44; "Vol": *M* = .41 µV, *SD* = .58). Moreover, the LNC amplitude was affected by the Channel factor. That is, there was a larger difference between Targets and Non-targets amplitude in the fronto-central sites, which decreased in the parieto-occipital sites; resulting in a significant Channel by Trial Class interaction, $F(3,27) = 7.41$, $p < .001$. This effect, in turn, was differently modulated in the two interfaces, resulting in a significant Interface by Channel by Trial Class interaction, $F(3,27) = 3.97$, $p = .018$ (see Figure 4.6).

Table 4.3 Results of the ANOVA for the LNC amplitude. In the first column, are reported the main factors and all the interactions. In the following columns, are reported, respectively, the *F* values, the related degrees of freedom, the associated *p* values (in bold are reported those which are < .05) and the Greenhouse-Geisser correction coefficient when the assumption of sphericity was violated.

Factors	*F*	df	*p*	ε
Interface	3.4	(1, 9)	.098	-
Channel	5.55	(3, 27)	**.004**	.58
Trial Class	84.21	(1, 9)	**< .001**	-
Interface x Channel	.16	(3, 27)	.92	.5
Interface x Trial Class	10.18	(3, 27)	**.011**	-
Channel x Trial Class	7.41	(3, 27)	**.001**	.67
Interface x Channel x Trial Class	3.97	(3, 27)	**.018**	-

4.3.6. Disease level

The effect of disease level on the BCI use was tested by means of linear regression. The ALSFRS-R score was used as the predictor for each of the following dependent variables in both the interfaces: performance, classification errors on target trials, and TBR. The disease level measured with the ALSFRS-R scale did not predict ALS patients' ability to control the BCI. The parameters of the statistical analysis are reported in table 4.4.

Table 4.4 Non-standardized coefficient (B), t-test (*t*), and associate probability (*p*) values of the linear regressions performed using the ALSFRS-R score as the predictor for the results obtained by ALS patients with the BCI, listed in the 'Dependent variable' column, for both interfaces.

Interface	Dependent variable	B	$t_{(8)}$	*p*
"AUTO"	*Performance*	.04	.501	.630
	Tragets classification errors	.002	.905	.392
	TBR	-.026	-.932	.379
"VOL"	*Performance*	-.023	-.162	.875
	Tragets classification errors	.002	.998	.348
	TBR	-.024	-.887	.401

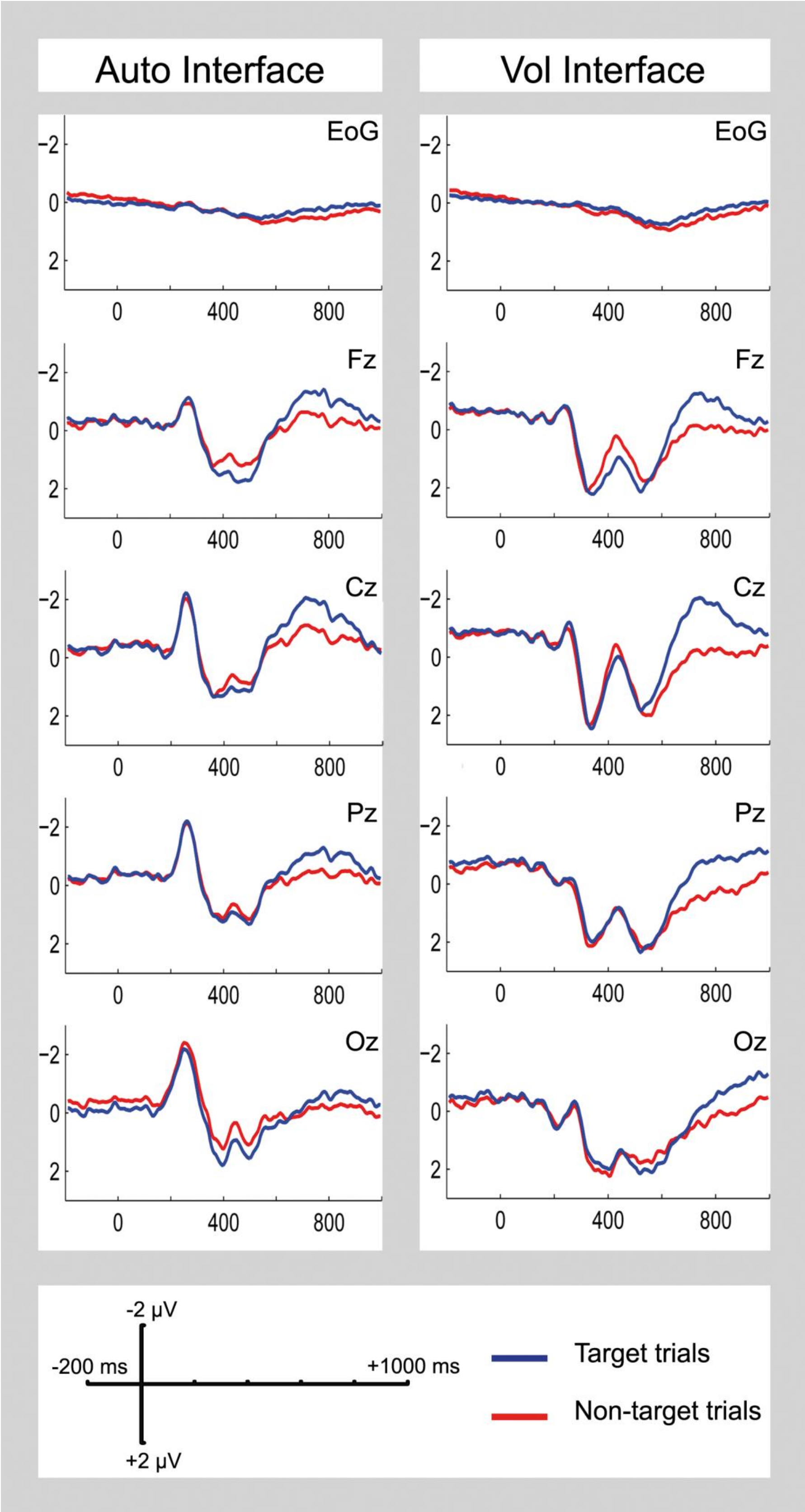

Figure 4.6 ALS patients' grand average of the ERPs elicited by the two interfaces.

4.4. DISCUSSION

In Experiment 3 we tested the effect of two visual interfaces, which were based on different principles of covert attention orienting (i.e., exogenous and endogenous orienting of visuospatial attention), with ALS patients. The participants reached good performance (about 70%) with both the interfaces. Moreover, from the data analysis emerged that ALS patients had some advantages using the "Vol" interface with respect to the "Auto" interface. That is, higher TBR and lower errors in target classification were associated with the "Vol" interface. The better results obtained with the "Vol" interface might be due to a different modulation in the ERPs. In fact, there was a significantly different modulation of the LNC between the two interfaces: a lower LNC amplitude on Non-target trials was associated with the "Vol" interface, whereas there was no significant difference in the amplitude of LNC elicited by the Target trials. This resulted in a larger difference between Targets and Non-targets with the "Vol" interface, that might explain the advantages of ALS patients, while using the "Vol" interface (i.e., the interface designed by means of the endogenous principle of visuospatial attention orienting).

Then we tested whether there was an effect of the ALS patients' impairment level on BCI use (i.e., performance in %, error in targets classification in %, and TBR in bit/min). There was no significant relation between ALS patients' level of impairment and the results obtained using the two new visual interfaces. This result is in line with the data previously reported in the literature (Kübler and Birbaumer, 2008; Silvoni et al., 2009).

The visual interfaces are the most used for developing BCIs, improving communication in ALS patients. Recently, it has been reported that the performance of the most used visual BCI, the P300 speller, depends on the possibility of the users to move their gaze (Treder & Blanckertz, 2010; Brunner et al., 2010). This fact makes difficult the use of visual interfaces for patients with impaired eye-muscle control, such as the ALS patients in the latest stages of the illness. Thus, there might be the need of new interfaces that do not depend on eye movements. Our results in the Experiment 2, however, support the idea that ALS patients can use the covert visuospatial attention orienting, in order to avoid their problems in BCI use, because of eye-movement impairment. Moreover, with the two new interfaces described in Experiment 3, different modalities of covert visuospatial attention orienting were tested (i.e., endogenous or voluntary vs. exogenous or automatic; Posner, 1980). The ALS patients who participated in the study obtained good online performances with both the interfaces. We cannot foresee, however, which cognitive abilities would be spared in the ALS-LIS/CLIS condition. Testing interfaces, which are based on different cognitive principles, might be a good strategy: if the patients learn to control a BCI by using interfaces, which are based on different cognitive processes, we can augment the patients' probability to maintain an efficient BCI's control through at least one of the tested interfaces. The advantages which ALS patients obtained with the interface that required endogenous orienting of visuospatial attention (i.e., "Vol") let us suppose that its use could be most appropriate, but longitudinal studies are required to definitively test to this hypotesis.

In conclusion, in Experiment 3 we reported results, from ALS patients, regarding the successful use of visual interfaces, which are based on cover visuospatial attention orienting. On the one hand, our ALS patients, were neither in the LIS nor in the CLIS condition. On the other hand, both the findings from other studies (Liu et al., 2011; Treder et al., 2011) and our findings in Experiment 3, have suggested that there is no relation between illness level and BCI performance, at least after CLIS patients are excluded. This allows us to hypothesize that our new interfaces may be efficient also for ALS-LIS patients. Nevertheless, only a study on ALS-LIS patients might definitively confirm or not this hypothesis. In addition, interfaces, which are based on different modalities of covert visuospatial attention orienting leaded to different level of efficacy on BCI performance in Experiment 3. This represents an advantage for the patients, because they can obtain better system control just by using the most suitable interface for them. Developing interfaces, which based on different cognitive principles is a further advantage for the patients because with the progression of the illness, their cognitive abilities might not be all spared in the same measure. For these reasons, we believe that more “attention” must be paid to the exploitation of cognitive principles, when designing the interfaces, in order to develop more ergonomic and more efficient BCI for ALS patients.

5. CONCLUSIONS

The brain computer interfaces (BCI) are systems which allow the users to interact with their environment, by translating the brain signals into direct commands for controlling devices. The main characteristic of a BCI is that neither the nerves nor the muscles are involved in the devices' control. Among all the possible applications of BCIs, the most important has been their development as efficient prosthesis for communication and control (Wolpaw et al., 2002), in order to overtake the physical limits of patients affected by severe motor disorders. So far, the most investigated clinical population, by means of BCIs, is that of patients affected by amyotrophic lateral sclerosis (ALS). The ALS is a neurodegenerative disease that leads the affected patients to progressively lose the voluntary control of all their muscles. In the latest stages of the illness ALS patients enter in a condition of paralysis named the locked-in state (LIS). LIS patients can execute only a few movements (i.e., in most cases eye and sphincter movements; Laureys et al., 2005). Thus, they have severe communication impairment. Then, when no voluntary movement control is possible, the patients enter in the completely LIS. For these reasons, ALS patients are one of the clinical populations that can most benefit of the BCI use, in order to communicate and to restore basic autonomy in their everyday activities.

There is increasing evidence supporting the successful control of BCIs by ALS patients before they enter in the LIS condition. The majority of these systems are based on visual interfaces (Kübler & Birbaumer, 2008), because of their usability. With respect to interfaces that are based on acoustic or vibro-tactile stimuli processing, visual interfaces permit users to select a high number of commands (e.g., the P300 speller system, Farwell and Donchin, 1988) and to explore all commands at the same time. It has been recently reported in a single case description, that visual perception is impaired in CLIS patients (Murguialday et al., 2011). This could be the reason why no case of ALS-CLIS patient, who was able to use a visual-based BCI, has been reported to date. Murguialday et al. (2011) have suggested that acoustic- or the tactile-based BCIs might be the only suitable ones for ALS-CLIS patients. More complex is the situation for the ALS-LIS patients. Successful use of visual interfaces was described by several authors (see paragraph 4.1 in Experiment 3 chapter), but this is possible when the LIS is *incomplete*, which means that residual eye movements are still possible (Smith & Delargy, 2005). Sellers et al. (2010) described an ALS-LIS patient, who was able to use successfully the P300 speller in everyday life, restoring some of his autonomy and permitting him to continue to manage his job (i.e., leading a research group). Two recent studies, have suggested that the efficient use of the P300 speller (i.e., the most studied visual interface), is impossible without overt visuospatial attention control, even for healthy users (Treder & Blanckertz, 2010; Brunner et al., 2010). Thus, the ALS-LIS patient described by Sellers et al. (2010) would be able to use the P300 speller system, until he has sufficient eye movement control. Indeed, after the loss of eye movements, the crowding effect of the stimuli would make impossible the use of the P300 speller (Treder & Blanckertz, 2010). For this reason, the development of efficient BCIs guided by covert visuospatial attention orienting, is needed for exploiting the advantages of the visual modality.

We designed three experiments in order to test whether it was possible to develop visual interfaces that did not require overt visuospatial attention orienting. A visual interface that does not require gaze shifts to be efficiently controlled might be used by ALS-LIS patients, even when their control of eye movements is impaired. Moreover, we investigated the effect of different modalities of covert visuospatial attention by designing new interfaces, in each of whom a different principle of covert visuospatial attention orienting was implemented (i.e., exogenous or endogenous; Posner, 1980). Thus, three visual interfaces for guiding the movement of a virtual cursor towards peripheral positions in a monitor were created. All the interfaces had a central fixation point, where the participants were required to point their gaze during the experimental sessions. This characteristic of the interfaces allowed us to test covert visuospatial attention orienting used in our ERP-based BCI. The first interface was named “Arrows”, and it was designed modifying the visual interface proposed by Piccione et al. (2006). Four arrows were displayed on the four sides of a monitor and were randomly flashed (for a detailed description, please see paragraph 2.2.2.). Participants were required to concentrate their visuospatial attention on the flashed arrow that indicated the direction towards which they had to guide the cursor, while maintaining their gaze on the fixation point. Because the ERPs were elicited by abrupt visual sensory changes in the periphery (i.e., the flash of an arrow), this interface required the use of exogenous orienting of visuospatial attention, in order for the participants to concentrate their visuospatial attention on the flashed target arrow and to ignore the flashed non-target arrows. The second interface was named “Auto”. Four black and white icons were displayed on the four sides of a monitor, and they were, then, randomly disappeared and rapidly reappeared at the same position (for a more detailed description, please see paragraph 2.2.2.). Participants were required to pay attention to the rapid offset-onset of the icon that was placed in the target spatial position, towards which they had to guide the cursor, while maintaining their gaze on the fixation point. The ERPs for controlling the cursor were elicited by abrupt visual sensory changes in the periphery (i.e., icons' offset-onset). Thus, the "Auto" interface required the use of exogenous visuospatial attention orienting, as it was the case of the "Arrows" interface. The third interface was named "Vol". Four black and white icons were displayed on the four sides of the monitor, while four letters, each one indicating the spatial position of one icon, were randomly presented at the center of the monitor (for a more detailed description, please see paragraph 2.2.2.). Participants were required to attend the letter indicating the direction of the icon towards which they had to move the cursor. The ERPs were elicited by directional symbols presented in the center of the screen (i.e., capital letters), which had to be interpreted in order to associate them to the peripheral spatial positions, while maintaining the gaze on the central fixation point. For this reason, and in contrast with the first two interfaces, the "Vol" interface required the use of endogenous visuospatial attention orienting.

In Experiment 1, the efficacy of the three interfaces was tested online with 12 healthy participants. Accuracy of about 75% was obtained with all interfaces, during both the testing sessions, performed just after a first day of training, and the follow-up sessions, performed about one month later. The central fixation point did not prevent the healthy participants from efficiently guide the cursor with the visual ERP-based BCI. Moreover, we tested whether the healthy participants' performance was modulated as a function of the interface used. From the data analysis emerged that the “Vol” interface, which was designed for exploiting the endogenous visuospatial attention orienting principle, leaded the participants to obtain significant better accuracy and faster communication speed with respect to both the other two interfaces.

In Experiment 2 we performed an offline classification of the BCI data collected in Experiment 1, with different algorithms in order to reach epoch categorization. By doing so, we wanted to investigate whether the interface effect reported in Experiment 1 depended on specific characteristic of the methods used for data processing (i.e., the classification algorithms and the method of performance calculation used). The online analysis of the epochs in Experiment 1 was performed via Independent Component Analysis (ICA), which was followed by fixed features extraction and support vector machines (SVM) classification. The offline epochs analysis was performed by means of a genetic algorithm (GA), which permitted to retrieve the relevant features of the signal to be classified, and to categorise the signal with a logistic classifier. As the dependent variable, was used the F measure, a performance measure that accounts for the specific characteristics of the interfaces used (e.g., the unbalanced number of target and non-target trials; for details, see paragraph 3.2.4.). The offline analysis performed using the F-measure in Experiment 2 confirmed the advantages of the use of the “Vol” interface, which were found in Experiment 1. As a further evidence of the interface manipulation effect, we found that also the neurophysiological data analyses were in line with the performance results. There was significant lower LNC amplitude related to non-target trials on the “Vol” interface with respect to that elicited by the “Arrows” and the “Auto” interfaces. This resulted in a larger difference between target and non-target ERPs with the “Vol” interface, which could explain the higher performance associated to that interface.

The results obtained in Experiment 1 and 2 supported the hypothesis that it is possible to use the principle of covert visuospatial attention orienting for controlling efficiently an ERP-based BCI system (see also Liu et al., 2011; Treder et al., 2011). Furthermore, better performance was associated with the use of the “Vol” interface, which required endogenous visuospatial attention orienting, with respect to the other two interfaces. This result was supported also by neurophysiological data analysis, and it was independent from the algorithm used for epoch classification.

On the bases of results in Experiment 1 and 2, we decided to test our experimental manipulation with ALS patients. In Experiment 3 we tested the effect of the “Auto” and the “Vol” interfaces in a group of 10 ALS patients with different degrees of impairment, although none of them was in the LIS condition. After a first day of training, ALS patients were required to perform 16 online sessions with each interface along 8 consecutive experimental days. The ALS patients reached good online performances in the last experimental day with both the interfaces (above 70%). From the comparison of the results obtained with the two interfaces, resulted that both higher communication speed (TBR) and fewer errors in target epoch classification were associated with the “Vol” interface, than with the “Auto” interface. As resulted with the healthy participants (see Experiment 2), the analysis on the neurophysiological data recorded with ALS patients was in line with their performance: significant lower LNC amplitude was elicited by non-target trials in the “Vol” interface than in the “Auto” interface.

The results of Experiment 3 supported our hypothesis. That is, ALS patients can successfully control an ERP-based BCI through visual interfaces under covert visuospatial attention orienting. Although the efficacy of visual interfaces, which require covert visuospatial attention orienting in ERP-based BCI has been reported in healthy participants, to our knowledge, this is the first time that this result is reported in ALS patients. This fact lays the groundwork for new perspectives about the use of visual-based BCIs by ALS-LIS patients, even when their eye movement control is impaired. One might argue that no ALS patient in the LIS condition was tested with the paradigm described in Experiment 3. Nevertheless, the data reported in the literature (see also Experiment 3), are encouraging toward the direction of our hypothesis. In fact, it has never been reported any significant correlation between BCI performance and degree of impairment (Kübler & Birbaumer, 2008; Silvoni et al., 2009). Thus, we can hypothesize that there are good chances for ALS-LIS patients, who have impaired eye muscles control, but can be still using the visual modality, to successfully communicate through interfaces, which are based on covert visuospatial attention orienting.

A further consideration regards the interface effect, which emerged with both the healthy participants and the ALS patients. Indeed, our second hypothesis was the possibility of modulating BCI performances by designing interfaces that required the use of different modalities of covert visuospatial attention orienting (i.e., exogenous and endogenous). In our experimental manipulation both better performance and communication speed were associated with the interface that required the use of endogenous visuospatial attention orienting (i.e., the “Vol” interface). This advantage was independent of the classification system used. Furthermore, the “Vol” interface advantage was obtained without any improvement of recording or of processing parts of the BCI system, and without any additional costs. To our view this is a relevant result: ALS patients can benefit from more efficient systems without the need of more expensive equipment or additional costs. Furthermore, it has been demonstrated that not all the cognitive functions are equally spared in ALS patients with the progress of the illness (Lakerveld et al., 2008). Thus, ALS patients can benefit from the development of BCI designed exploiting different principles taken from cognitive psychology, by using the principle that results the most ergonomic for them. We suggest that more attention must be paid to the cognitive principles when designing the interfaces, for augmenting BCI usability according to the patients’ needs.

The investigation of different modalities of covert visuospatial attention orienting effects on visual BCIs is a further step in order to overtly study specific cognitive aspects involved in BCIs, for increasing their efficacy and efficiency. Different cognitive processes can be investigated with the same goal, expanding our approach also to interfaces that are based on other sensory modalities. For example, new acoustic interfaces that exploit specific cognitive process advantages could be designed, with the advantage that such interfaces might be suitable for CLIS patients. We believe that the research approach we stressed within the present dissertation can offer real advantages to the improvement of BCI systems, and it has to be performed in closer relation with the technical advancement on signal recording and classification.

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