Utilização de interfaces cérebro-computador em esclerose lateral amiotrófica: uma actualização

Use of brain-computer interfaces in amyotrophic lateral sclerosis: an update

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Resumo

Nos últimos anos tem-se assistido a um enorme investimento em investigação e desenvolvimento das chamadas interfaces cérebro-computador (ICC). Estes dispositivos adquirem sinais provenientes da actividade cerebral e, através de um computador, traduzem esses mesmos sinais em instruções que podem ser usadas para comunicar e/ou controlar dispositivos motorizados. A esclerose lateral amiotrófica (ELA) é a mais comum doença neuromuscular. À medida que a doença evolui, os doentes encontram cada vez maiores dificuldades em comunicar e mover-se até que, em estádios finais da doença se encontram totalmente paralisados. Assim sendo, os doentes com ELA são candidatos ideais para utilizarem esta nova e facilitadora tecnologia. Este artigo revê os mais recentes avanços da tecnologia ICC, dando enfoque à especificidade da utilização das ICC na ELA e nas aplicações desenvolvidas para estes doentes. São abordados os desejos e as necessidades dos doentes com ELA e dos seus cuidadores. São igualmente discutidas as limitações actuais da tecnologia ICC que restringem a sua maior disseminação a nível clínico. Por fim, são apontadas direcções para futura investigação no que diz respeito a equipamento, processamento de dados e aplicações, abordando-se ainda o potencial terapêutico dos ICC no âmbito da neuro-reabilitação.

Abstract

In recent years there has been an enormous amount of effort being put into the research and development of the so-called brain-computer interfaces (BCIs). These devices record brain signals and, via a computer interface, translate them into commands that can be used for communication and/or control of motorized devices. Amyotrophic lateral sclerosis (ALS) is the most dreadful neuromuscular disorder, and as disease progresses patients are faced with the inevitability of being paralyzed and loosing the ability to communicate. Therefore, ALS patients are ideal candidates for using this novel empowering technology. This paper reviews recent advances in BCI technology, focusing on the specificities of BCI use in ALS and the applications developed for ALS patients. Additionally, the needs and wants of ALS patients and caregivers are addressed along with current BCI technology limitations. Finally, future research directions are pointed out, covering aspects of hardware and software improvements and the potential of the BCI technology for neurorehabilitation.

Methods of the Review

In this review, information was retrieved from Pubmed search engine considering publications from 2006 to March 2012 and using as keywords amyotrophic lateral sclerosis together with brain-computer interface. Searched publications were evaluated according to their suitability to the review's goal and availability. Additionally, more general information related to the review theme and brain-computer interface devices was retrieved from Pubmed and Google Scholar search engines, and theme-related websites.

Introduction

Neuroprostheses are artificial devices that are used to replace or augment a missing or impaired function of the nervous system, such as a sense (hearing, sight), action functions such as movement or speaking, or even cognitive functions[1]. The most widely used neuroprosthetic device is the cochlear implant, which interfaces directly with the auditory nerves to restore the sense of hearing[2]. Other devices include retinal implants[3] and systems for restoring motor function in spinal cord injuries by interfacing with peripheral nerves[4].

Brain-Computer Interfaces (BCIs) are a class of neuroprosthetic devices, which specifically interface brain with computer systems, while generally neuroprosthetic devices can interface with cranial nerves, the spinal cord or the peripheral nerves[5]. BCIs acquire brain signals and, via a computer system, signals are analyzed and are translated into actions in a computer screen or in other devices for performing a desired function[6]. The main purpose of the use of BCIs is improving communication and control of patients with neuromuscular disorders such as amyotrophic lateral sclerosis (ALS), muscle dystrophies, multiple sclerosis, cerebral palsy, or motor impairments resulting from stroke, traumatic brain injury or spinal cord injury[7-11].

BCIs have gained increased interest in recent years reflecting an increased knowledge in animal and human brain functioning and technological advances, namely in computer technology, sensors and data processing and analysis[6,8,13,]. Also, BCIs are now entering the consumer electronics market, namely in the video-gaming industry, which is additionally fostering research in the field[14,15].

BCIs research and development have mostly focused on providing solutions to stroke, neurotrauma and neuromuscular disorders[16]. In particular, BCI have been studied to restore more effective motor control to stroke and traumatic brain injury patients by modulating activity-based brain plasticity[17-19]. Both stroke[20] and neurotrauma[21,22] have a higher incidence and prevalence than neuromuscular disorders[23], which may explain the larger development of BCI research in these fields. Additionally, neuromuscular disorders present their own specificities with respect to clinical presentation and disease progression[24], and these should be included in the design of a suitable BCI system[25].

ALS is the most common neurodegenerative disease of the motor neuron system. ALS renders patients paralyzed and often without ability to communicate as disease progresses to its fatal outcome 3 to 5 years in average after clinical onset of muscle weakness[26,27]. Therefore, these patients could highly benefit from research and development done on assistive technologies and BCIs to improve quality of life[19].

In this paper progresses in the field of BCIs applied to ALS disease will be reviewed. In the end, future research directions will be pointed out.

Amyotrophic Lateral Sclerosis

ALS, also known as motor neuron disease (MND), is a progressive neurodegenerative disease.

ALS is mostly a sporadic disease but 5-10% of cases are inherited as an autosomal dominant trait[23,26]. Familial ALS is clinically indistinguishable from the sporadic form and, most frequently, is associated with mutations in the superoxide dismutase (SOD1) enzyme[23,24,26]. Other known mutations include genes coding for proteins involved in detoxification, vesicular trafficking and axonal transport, DNA and RNA binding and processing, and ATP production[23,24,26]. The cause for sporadic ALS is unknown but recent studies on animal models also show the involvement of SOD1 enzyme. It is believed that non-inherited, post-translational modifications of the enzyme may also be responsible for the sporadic form of the disease[23]. In addition, it has been found that excitotoxic neurotransmiters such as glutamate participate in the death of motor neurons in ALS[23]. Additionally, family aggregation studies have identified an overlap between common neurodegenerative diseases such as Alzheimer's Disease and Parkinson's Disease, suggesting the existence of susceptibility genes that increase the risk for neurodegenerative disorders[26]. Known risk factors include exposure to pesticides and insecticides and smoking, which agree well with an increased exposure to oxygen radicals and impaired function of SOD1[23].

ALS has an incidence of 2-3 per 100,000 and a prevalence of 4-6 per 100,000[23,24]. Males seem to be more affected than women in the sporadic form[23]. Peak at age of onset is 58-63 years for the sporadic disease and 47-52 years for the familial form[26].

ALS is characterized by loss of both lower motor neurons (LMN) and upper motor neurons (UMN). The loss of LMN in the anterior horn of the spinal cord and in the brain stem leads to progressive muscle weakness and atrophy, while loss of corticospinal UMN can lead to spasticity and abnormally active and pathological reflexes. Other neurons at the prefrontal motor areas may be affected resulting in cognitive impairments and dementia[24,27].

Other motor neuron diseases affect predominantly the LMN or the UMN. In the first case the disease is called progressive muscular atrophy (PMA) and in the second case primary lateral sclerosis (PLS). Also, rarely the disease is restricted to the bulbar muscles, which in this case the disease is referred to as progressive bulbar palsy (PBP). Nevertheless, in most cases where patients present initially bulbar symptoms, the disease progresses to ALS. Although similar, these diseases may present clinical courses that differ from ALS[24,27].

The diagnosis of ALS is primary clinical and is often impaired by the insidious nature of the disease and the diverse etiology for motor neuron dysfunctions which must be excluded. These differential diagnoses include structural lesions, infections, intoxications and effect of physical agents, immunologic mechanisms, metabolic changes and hereditary disorders[23]. ALS can be suspected when slowly progressive impaired function or painless muscle weakness is observed in one or more body regions without changes in sensitivity, and no other cause can be attributable[24,27].

Initial symptoms are generally observed in the limbs, 75-80% of cases, with both upper and lower limbs being equally affected. The remaining 20-25% of patients have initial bulbar symptoms such as slurred or decreased volume of speech, hoarseness, aspiration or chocking during meals, and excessive salivation. Additionally, the loss of LMN can initially present fasciculations, in particular of the tongue, and also gait changes, muscle cramps and loss of finger dexterity[24,26,27].

As disease progresses symptoms became more severe. Furthermore, the symptoms spread cumulatively to other body regions. This results, later on, in paralysis and ventilatory failure. This happens 3-5 years after the initial manifestations of the disease. Patients usually die of respiratory infections or complications of immobility, such as deep vein thrombosis and pulmonary emboli. In the meantime, some motor functions are usually spared, such as extraocular movements and bowel and bladder control. Sensory functions are usually preserved and only rarely patients present paresthesia[24,27].

In the diagnostic pathway other clinical methods can complement the clinical anamnesis and observation. Nerve conduction studies and needle electromyography (EMG) can be useful for confirmation of ALS diagnosis and for exclusion of other resembling entities[24,27]. Laboratory tests, on the other hand, are usually normal and are used to rule out other diseases[24,27]. Genetic testing can be used when there is a familial history[23,24,27]. Neuroimaging of the brain and spinal cord using computed tomography (CT) or magnetic resonance imaging (MRI) may also be useful for exclusion, as in general examinations are normal in ALS patients. Presently, the value of positron emission tomography (PET), and advanced MRI techniques such as diffusion tensor imaging (DTI), functional MRI (fMRI), and in-vivo magnetic resonance spectroscopy (MRS), are being assessed for diagnosis and monitoring of the disease[26]. Finally, muscle and nerve biopsy is rarely needed but may be used to confirm diagnosis when the presentation is atypical or it may also lead to an alternative diagnosis[24].

Until today, no treatment arrests the progression of ALS disease. Therapy with riluzole, a glutamate pathway antagonist, has shown to prolong the survival by 2 to 3 months in average[23,24], which is quite a modest accomplishment. In comparison, noninvasive ventilation (NIV) or the use of percutaneous endoscopic gastrostomy (PEG) extend life longer, possibly by an average of 6 months[27]. Several clinical trials are ongoing including: the study of cefriaxone, which may also be anti-excitotoxic; pramipexole and tamoxifen, which are neuroprotective; and anti-sense oligonucleotides that diminish the expression of mutant SOD1[24,27]. Research is also being conducted with stem cell therapy for nerve and muscle replacement, and curing treatment is only envisioned by means of genetic therapy[26,28].

Therefore, treatment of ALS is mainly symptomatic and can be divided in patient education, pharmacological treatment, and adaptive and supportive treatment[23,24,26-28]. Education relates to explaining the disease and the needs for life-style changes to patient, family and caregivers. This also includes smoking cessation, and dietary and physical activity recommendations. Medication may include anti-spastic drugs; anticholinergic, sympathicomimetics or botulinum toxin for sialorrhea; mucolytics for facilitating expectoration; anti-depressives and anxiolytics for psychiatric symptoms; and analgesics if needed. With respect to weakness and physical disability: physiotherapy; orthotics; and adaptive aids such as walking frames and wheelchairs are possible solutions. Regarding dysarthria symptoms, speech therapy or the use of communication aids is recommended. Other supportive cares include: chest physiotherapy for dyspnoea and poor cough; physiotherapy for musculoskeletal pain; and re-positioning and pressure-relieving cushions and mattresses. Finally, ventilatory support or PEG is usually required at later stages of the disease.

Of major importance to the improvement of the quality-of-life of these patients is the ability to manipulate, move and communicate. This is a role that BCIs are starting to fill.

BCI devices and systems

BCI have been designed using a number of different brain signals. These can be electrical, magnetic and metabolic in origin (see table 1). Electrical signals are the most commonly used signals in BCIs and result mainly from neuronal post-synaptic potentials. These signals are recorded using electroencephalography (EEG)-based methods such as scalp EEG (sEEG), electrocorticography or cortical surface EEG (ECoG) and intra-cortical EEG (ICE)[8,29]. The latter in fact, can record action potentials of individual neurons and local electric fields[8]. Also, magnetic signals generated from electric currents moving along pyramidal neurons can be detected using magnetoencephalography (MEG)[8,29,30]. Finally a third type of signal can be used, which is related to metabolic activity and therefore provides an indirect measure of neural activity[31]. Functional near-infrared spectroscopy (fNIRS)[32] and functional MRI (fMRI)[33] both measure the blood oxygen levels of brain regions.

All signal types and measurement techniques present both advantages and disadvantages[8] (see table 1 and figure 1). EEG- and MEG-based systems have temporal resolutions in the order of the millisecond, making them highly suitable for real-time or near real-time applications[29,34]. On the other hand, these methods present low spatial resolutions, which make signal source localization challenging[29,34].

Within EEG methods, scalp EEG is more limited than surface cortical or intra-cortical signal recording, with respect to signal quality. Signal amplitude diminishes considerably at the scalp due to distance from the cortical surface and due to distinct electrical conductivities of the dura, skull and scalp[8,29]. Additionally, cortical and intra-cortical signals appear to be more stable than scalp EEG, and therefore these methods may be interesting for long-term use applications. Nevertheless, scalp EEG is non-invasive while the other EEG methods are not, making scalp EEG particularly interesting by avoiding the need of intervention, with less surgical risks and in particular, almost non-existent risk of infection[8].

fNIRS and fMRI are also non-invasive. fNIRS has temporal resolutions in the order of 100's of ms but measures the hemodynamic response to neural activity, which peaks after ~5s of activity onset and lasts for ~10s[31]. This technique is also limited with respect to the depth of signal origin, but is able to localize cortical signal sources better than scalp EEG[8,31,34]. fNIRS is also less prone to movement artifacts than EEG.

fMRI also measures the hemodynamic response, but its temporal resolution is typically in the order of 1s. Nonetheless, of all the techniques fMRI is the one with the best spatial resolution, being able to localize both cortical and subcortical signal sources with millimeter resolution[31,34].

Finally, these methods have quite different associated costs and while the scalp EEG is the most affordable in terms of price of equipment and maintenance, fMRI is the most expensive technique[8].

A BCI device or system is a comprehensive apparatus, which includes both specific hardware and software[6,35]. It is comprised mainly of signal acquisition, signal processing and signal translation components, and device output[8] (see figure 2).

Signal acquisition is related to the specific brain signal recording technique and accounts for all electronics, including sensors, amplification, filtering and digitization modules, and also to the electronics for signal acquisition control.

Signal processing involves two steps: feature extraction and feature translation. Feature extraction involves processing of the signals in order to extract a relevant meaning or intention of the user to perform a certain action. Naturally, this process involves also recognizing what is spurious, artifactual and unintentional signal information. Feature extraction may be accomplished by using a number of time-series processing methods, such as Fourier transform, autocorrelation, and independent component analysis[37]. Signal features are then translated into intentions or commands for output devices. For this purpose machine-learning and classification algorithms, such as Bayesian methods, artificial neural networks, genetic algorithms and support vector machines can be used[38,39].

Finally, commands are used to operate an external device, either for communication, including letter selection, cursor control, or control of mobile devices such as motorized wheelchairs and robotic arms[7,8].

A fundamental issue in BCI research and development is adaptation of the user-BCI dyad, as communications and control applications are interactive processes. Therefore, BCI systems should provide real-time feedback to the user in order for actions to be smooth, and also for providing a means for the user to maintain and reinforce good performance and to correct for mistakes[40]. Three approaches can be considered in BCI design and operation[7,12,40]: the BCI adapts to the user; the user adapts to the BCI; user and BCI adapt to each other. So far no best approach as been defined. Additionally, these adaptation approaches can further relate to the choice of brain signal type/technique that is most suitable to user. This is equally valid in the case of use of multimodal brain signals or hybrid BCIs. In the latter case, BCIs are used to enhance conventional assistive devices operated by residual muscular functionality and therefore, a optimal adaptation should dynamically choose which is the best interaction channel at any time[40]. In the case of EEG signals, adaptation involves also the choice of EEG phenomena that best fits the user, namely, evoked potentials, spontaneous signals, and rhythmic activity[40]. Adaptation also involves online brain signal calibration, as EEG signals are inherently non-stationary[40]. Finally, adaptation is a dynamic process and requires the development of novel training protocols to fit user and BCI[7,12,40].

A number of distinct BCI systems based on electric (see figure 3), magnetic and metabolic phenomena have been developed. BCI's have explored the use of event-related potentials (ERP), in particular the P300 potential[41]. ERP signals are features within the EEG signals, which are elicited upon the presentation of a stimulus and therefore are related to brain processing. Two types of ERPs are considered: early and late. The former are recorder within 150 ms after stimulus presentation, and are also called exogenous. The latter are recorder later after the stimulus and are related to cognitive processes. Therefore late ERPs are also called endogenous. These include the P300 potential, as usually it is recorder 300 ms post-stimulus. The P300 potential is elicited by a specific set of circumstances know as Oddball Paradigm, which has 3 essential attributes: a subject is presented with a series of events (stimuli), each of which falling into one of two classes; the events that fall into one of the classes are less frequent or rare in comparison with the ones that fall into the other class; the subject has the task of classifying each event into one of the classes[41]. The events that fall into the less-frequent (or oddball) class elicit a P300 potential. The P300 potential is therefore elicited by a decision-making process, which may or may not be a conscious one. Typically, visual or auditory stimuli are used for BCI applications, such as in the form of spelling devices for typing, internet browsing and wheelchair control[8,12,41].

Other frequently studied BCI systems make use of sensorimotor rhythms (SMR). This method is based on the evidence that limb movement or motor imagery (MI) result in changes in rhythmic activity over the sensorimotor cortex[12,42,43]. SMR are observed mainly at frequency bands of mu (8-12 Hz), beta (18-30Hz) and gamma (30 to>200 Hz) activity. These signals can be detect by EEG, but high-frequency gamma frequencies can only be recorder using ECoG[44,45] or MEG techniques[30]. SMR show reduced activity during motor behaviors, a phenomenon called event-related desynchronization (ERD), which correlates with activation of cortical networks[42,43]. SMR can also show an increase of activity immediately after movement, a phenomenon called event-related synchronization (ERS), which is thought to be associated with deactivation or inhibition of cortical networks[42,43]. SMR have been extensively researched and a number of applications have been developed, such as the control of cursors in 1, 2 or 3 dimensions, and integrated in spelling devices and conventional assistive devices, including wheelchairs, limb functional electrical stimulation (FES), and prosthetic and robotic devices[8,12,42,43].

Other EEG signals that have been used in BCI applications, although less frequently, include steady-state visual evoked potentials (SSVEP) and slow cortical potentials (SCP)[46]. SSVEP are stable oscillations that result from repetitive visual stimulation. In the BCI implementation, concurrent stimuli are placed in different locations of the visual field and run at different frequencies. These stimuli are related to different intentions such as a letter for spelling or a direction for wheelchair control. When the user gazes at a desired stimulus, the recording EEG signals from the occipital lobe present a peak at the frequency of the chosen stimulus[46]. SSVEP have been used for control of cursors in 2 dimensions, spelling, environmental control, FES, and prosthesis control. This technique is then highly dependent on eye-movement control and intact visual functions. In patients with visual impairments, auditory and tactile stimuli substitutes have been used[8].

SCP, like SMR, also relate to changes in the sensorimotor cortex, but unlike SMR, SCP are observed at low frequencies. Typically, SCP precedes in 500-1000 ms a self-initiated actual or imagined movement, the so-called readiness potential. SCP is also observed 200-500 ms after a stimulus that requires a following action to be taken, either motor or cognitive[46]. This potential is called contingent negative variation and is distributed in the frontal areas or over the regions involved directly in the action[46]. Since SCP may be modulated by cognitive activities, the use of these potentials in BCI application requires extensive adaptation of the user, frequently over weeks or months and generally is not very effective. Applications using these systems include cursor control, spelling, and internet browsing[8,12,45]. Due to its operational difficulty this approach as mostly focused on research, in particular in combination with fMRI and Transcranial Magnetic Stimulation (TMS).

ICE devices can measure individual neuronal action potentials and local electric field[8,45]. These systems make use of electrode microarrays for recording neuronal populations. By recording motor imagery activity they have been used in the control of robotic arms, computer cursors, environment (lights and television). Additionally, they have shown accurate cursor control for more than 1000 days after implantation[8,46].

In spite of most of the research and development on BCIs has been made on EEG-based systems, metabolic-based BCIs may offer interesting choices. fNIR systems are both non-invasive, relatively affordable and can be made portable[31,32,47]. They also may be less prone to movement artifacts and to limitations of electrode-scalp impedance matching, as optical technology is used. For the time being, one of the downturns is that fNIR systems have moderate temporal resolutions, limiting their use to application where real-time signal evaluation is not an absolute requirement[32,47]. Applications using fNIRS-based BCIs have been scarce so far and have focused on binary choice systems, and a spelling system. fNIRS as a BCI technology is still in its infancy, and new developments both in hardware and processing are expected and may someday turn to be useful for day-to-day life[47].

fMRI based systems are also non-invasive and present a high spatial resolution, but they have poor temporal resolution, are non-portable and very expensive[47]. Therefore, BCI applications based in this technique have focused mainly on neuropsychiatric research[33] and demonstrations of feasibility, with the 2-dimensional control of a robotic arm[47], for instance. Of particular interest could be the use of fMRI in the assessment of a patient's state of consciousness and also for communication with severely impaired patients[48].

Finally, a number of studies are now being focused on the use of BCIs for neurorehabilitation, based on the hypothesis that BCIs can reinforce conventional rehabilitation therapies by modulating brain plasticity[8,16,18,19]. Applications have been developed for sensorimotor rehabilitation in stroke[30] and neurotrauma patients[17] using BCI training and motor imagery. Also, combination of BCI devices with FES and assistive robotics seem to help motor function recovery[8,12]. BCI systems might, therefore, reduce rehabilitation costs by reducing time to recovery and also by reducing the need for a constant therapist to be present alongside the patient[8].

Use of BCIs in ALS

ALS inexorably progresses to ever more challenging communication and motor control, resulting later on in complete paralysis with a fatal outcome[23,24,26,27]. In fact, the progressive nature of the disease is a distinctive feature of ALS in comparison with other diseases, such as stroke and neurotrauma, for which BCI applications have been researched and developed. In particular, in the final stages of the disease patients progressively loosed their ability to communicate as they transition from locked-in to completely locked-in state, when communication through voluntary eye movements is no longer possible[49]. In this case, the remaining means of communication would be auditory and proprioceptive BCI systems[49,50].

ALS patients are therefore natural candidates for using assistive BCI devices. Additionally, both individual clinical evolution and individual personal choices and believes should be taken into account in the development and use of such devices[50].

Pubmed search results using as keywords amyotrophic lateral sclerosis in combination with brain-computer interface resulted in 81 articles (see figure 4), 12 of which corresponded to reviews, and 50 to regular papers published after 2006, inclusively. These were further scrutinized in the present review.

Regarding BCI applications in ALS, these have mainly focused on using P300 signals, and in particular the P300 speller application[41,51-67,69,70].

The P300 speller application, as first developed[41], showed all letters of the alphabet, one at a time, in random order. The user was asked to count the number of times the desired letter appeared. This elicited a P300 potential that could be measured and translated into letter selection. Since this system was too slow, a newer version of the speller was designed, which consisted of briefly intensifying each row and column of a 6x6 matrix of letters and other commands (see figure 5). The subject was also asked to count the number of times the desired letter appeared, corresponding to a rare event in an oddball paradigm and therefore eliciting the P300 potential[41].

Initial studies on ALS patients who enrolled an intensive training comprised of 10 training sessions during 6 weeks showed that both visually and auditory evoked P300-based BCI systems could be useful as non-muscular communication devices[51,52]. A later study investigated the efficacy of such systems for patients with advanced ALS and showed spelling rates of 1.2-2.1 characters/min and efficacies of 62-79%[53]. Additionally, it was observed that patients' performance was stable for more than 40 weeks, showing that these devices could have potential for long-term use.

Nevertheless, it was found, in a number of studies, that the P300 spelling system was challenging for some ALS patients[9,51-54], in particular those with high muscular artifacts (for instance due to fasciculations) or decreased visual functions[54]. Overall, in one study using visually evoked P300 potentials, patients' average accuracy reached 70% in comparison with 91% accuracy in a healthy control group[54]. These limitations are particularly true as during ALS disease progression patients may have visual functions affected[49], further impairing the use of BCI systems[55]. Proposed alternatives include the use of auditory stimuli[51,52,56-60], such as using cues varying in pitch (high, medium, low) and location (left, middle, right)[58].

In order to improve the usability of BCI devices in patients with ALS and/or severe motor impairments, several strategies have being used besides using auditory stimuli. These include development of simpler and more efficient paradigms, such as: 4-choice system based on auditory and/or visual stimuli[51,52]; using the Latin square structure to intensify non-neighboring characters simultaneously in the row-column matrix[61]; a checkerboard paradigm[62]; or lateral single-character speller[63] (figure 5).

Additional methods to improve the performance of the P300-BCI include the use of error-related potentials (ErrRP)[12,64]. These are observed when the subject perceives a wrong outcome of the BCI system. One study showed that, by using feedback from ErrRP, ALS patients were able to increase the bit rate in the spelling application[64].

Besides using complementary EEG signal information for performance boosting, studies have also addressed feature translation by testing the optimum classifier[65,66]. In a study comparing 7 different classifiers, including both linear and non-linear methods[39], it was observed that the Bayesian linear discriminant analysis method provided the best accuracy, followed by the support vector machines method[65]. Both these methods were also shown to be comparable in terms of reliability[66,67].

Another study proposed the use of electrooculography (EOG), instead of P300 potentials for spelling[68]. The authors compared EOG and P300-based BCI systems and claimed performances in writing a 5-letter word of 25 seconds on average with the EOG-based system and 105 seconds with the EEG-based device. Results show that the EOG system is superior, although restricted to patients with conserved ocular movements[68].

Besides spelling, another P300-based application developed for ALS patients is the control of an internet browser[69]. In this study, authors showed that the implementation of such a system is an added-value to patients. Patients showed an average accuracy of 73% and an information transfer rate (ITR) of 8.6 bits/min, while healthy participants with no prior BCI experience had over 90% accuracy with an ITR of 14.4 bits/min[69].

P300 potentials were further used for tele-control of a robotic system[70]. The goal of this work was to provide patients with a means to perceive, explore and interact with the environment. As such, the developed system offers navigation, exploration and bidirectional communication using brain activity alone. The system was tested with an ALS patient with promising results, demonstrating the feasibility of such approach. Further, researchers expect benefits to patients in the context of neurorehabilitation and maintenance of neural activity[70].

In addition to P300 potentials, SMR/beta-rhythm has been used for 2-dimensional control of a cursor in a gaming context[71]. Event-related desynchronization and synchronization was observed when patients sustained or stopped either motor execution or motor intentions. Additionally, it was observed that the EEG beta activity over the sensorimotor area provided the largest discrimination. The observed accuracy for an ALS patient was 80%[71].

Overall, patients require long-term training in order to accurately control a BCI system. This is due to fatigue caused by demands of focused attention during prolonged BCI operation[72]. As such, a later development of the previous work intended to develop a user-friendly BCI system in the sense that it would require minimal training and less mental load[72]. In this study, researchers further explored the use of ERD and ERS in the beta frequency band to monitor ALS and PLS patients motor execution or motor imagery. Binary control of cursor movement showed average accuracies of 82% with motor execution and 80% with MI, while a four directional cursor control was achieved with 50-60% accuracies for both motor modalities[72].

SCPs have also been used in ALS. In one application a 1-dimensional cursor was controlled by self-regulated SCPs in the assessment of cognitive functions of completely paralyzed ALS patients[73]. Patients moved the cursor to one of two targets to discriminate between odd/even numbers, consonants/vowels, nouns/verbs, and large/small numbers. They were also tested for the ability to perform simple calculations. The authors showed that such a system had the potential to be used to assess maintenance or decline of cognitive abilities in individual ALS patients[73]. The same authors used the SCP-based device to specifically assess conditional associative learning in one severely paralyzed late stage ALS patient[74].

Another application using SCPs included the development of a system for web browsing based on slow cortical potentials[46,75]. This system rendered a locked-in ALS patient to be the first paralyzed person to web browse using brain waves alone. Here, the amplitude shift of SCP at the vertex was monitored and feedback was provided to the patient, while training. Each training day consisted of 10 to 20 runs, with 100 trials per run. After training 2 to 3 times per week during one moth, the patient was able to produce positive and negative SCP amplitudes. After 2 months training the patient was able to select letters, and within the following year he wrote the first message. After control of SCP amplitudes the patient was also trained to web browse by using a dichotomous decision tree. The mean accuracy of the system was 80% (68-95%, varying on the days)[75]. The authors of this study claim that P300 appear to be more accurate 90-100% in patients with intact eye fixation with the additional advantage of no requiring neurofeedback for learning. Nevertheless, P300 is only an option when patients show pronounced P300 responses[75]. Finally, the authors also mention that a web-browser based on self-regulation of SMR/beta-rhythm would be an alternative also[75].

Scalp EEG signals were further used for the development of powered wheelchair control[76]. In this application a late ERP paradigm was created for assessing left and right movement intentions. EEG signals were recorded at the posterior parietal cortex in both hemispheres and were analyzed regarding power spectral density in the alpha (7-14Hz) and beta (18-30Hz) frequency bands. The system showed an accuracy of ~82% and results suggested that hemispheric asymmetries in amplitude changes at 200 and 320 ms latencies could be used for a single trial indication module for left and right intended movements[76].

Intra-cortical neural interface systems have been applied as well to ALS[45]. Microelectrode arrays were used to record cortical spiking activity to control a computer cursor in 2 dimensions[77,78]. This system extracts both discrete (click) and continuous (cursor velocity) signals from a small population of ~40 neurons in the motor cortex, while the patient is imagining actions. Furthermore, a pilot system called BrainGate (http://www.braingate.com) was tested in the M1 area of an ALS patient years after onset of paralysis. Researchers observed that M1 neurons were immediately engaged by imagining limb actions even without training[45]. Additionally, they have demonstrated accurate control of the computer cursor after 3 years following electrode implantation[8].

Finally, the fNIRS technique has also been applied to ALS[79]. The applications developed have been so far quite simple with a dichotomous response (yes/no) and moderate accuracy (average of 80%). Of great importance are the classification algorithms used, whereas in one study the use of Support Vector Machines resulted in 73% of accuracy in healthy volunteers, using the Hidden Markov Model held 89% accuracy[80]. As such, it is expected that fNIRS systems can be further optimized regarding data processing in order to become more useful[81].

Table 2 shows a resume of BCI applications in ALS. Globally, the table shows that most research applications developed to date are related to communication. In the top of the list is the speller device, which enables patients to text; other related applications are internet browsing and binary choice/cursor control, which may be used also for communication and eventually for device control. The most complex systems for control of external motorized devices such as wheelchairs and robots were only developed more recently.

Regarding signal type, the sEEG is the most frequently used and the most frequent stimulus to be processed is the visually-evoked P300 potential. Average accuracies and ITRs for visually-evoked P300-based BCI spelling devices are around 80% and 20bits/min, respectively. The most recent studies, though, show improved performances with accuracies up to 90% and higher ITRs.

Finally, alternative approaches using auditory stimuli and action potentials measured by ICE are also being developed and may be useful for particular ALS patients.

Needs and Wants: Research directions

The latest research on BCIs shows that they are promising tools for functional recovery of ALS patients and patients with severe motor impairments alike. A number of applications are being developed, ranging from spelling, internet browsing, and motor control of external devices such as wheelchairs and robots. These will certainly improve patients' communication skills and motor control. In this section, patients' needs and wants will be further explored, along with present BCI technology limitations and future avenues of research.

Generally, the needs of BCIs potential users, that is, those with severe motor disabilities due to neuromuscular disease, stroke, or trauma fall into three broad categories: communication, mobility and autonomic function[82]. Most BCIs, as discussed, are being developed for communication purposes mainly, or for mobility, but for autonomic (bladder, bowel and sexual) function control are rare[82].

Regarding ALS patients' specific needs, a research survey showed that patients prioritize in the first place accuracy of commands of at least 90% (84% of respondents); speed of operation comparable to at least 15-19 letters per minute (satisfying 72%); and accidental exits from standby mode not more than once every 2-4h (84% of respondents). Furthermore, 84% of respondents would accept using an electrode cap, while 72% would undergo outpatient surgery or 41% would undergo surgery with a short hospital stay in order to obtain an implantable BCI[25]. In another study, regarding impaired mobility patients prioritize regaining arm and hand function rather than walking[82].

Additionally, focus group research of patients and caregivers has identified the barriers to and mediators of BCI acceptance for practical day-to-day use[83]. Two categories of human factors were identified: relational factors and personal factors. Relational factors, which were prioritized by participants, included corporeal, technological and social relations[83].

Corporeal issues translated the dissatisfaction with the gel-based electrode cap, considering it cumbersome and uncomfortable. Technological issues were related to the interaction of the BCI with existing hardware and software in a functional perspective. The group manifested the wish to have BCI-mediated interface with the telephone, TV, and other communication devices. In particular for texting, by means of a spelling device, users desire accuracy. The main important fact considered was the relationship between the patient and the caregiver. While, the BCI may give the patient the ability to communicate with the caregiver, the group manifested concern for the time required to set-up the BCI accordingly. The training may be quite time-consuming and an extra workload on the caregiver. Finally, regarding social relationship issues the concern is for appearance[83].

Personal factors included physical, physiological, and psychological concerns. The most important personal factor considered was psychological, which involved cognitive fatigue in using the BCI. In addition, anxiety, attitude and managing distractions were also issues expressed by the group[83]. In another study, the psychological state and motivation were also suggested to be factors of importance in BCI performance[84]. In particular, authors suggest that motivational factors as well as well-being should be assessed in standard BCI protocols[84].

Physiological considerations included concerns with fatigue and endurance as some patients complained of fatigue after using a P300 spelling device for only half-an-hour[83].

Physical factors relate to pain and discomfort while using the BCI system. This issue though was only pointed out by less than half of the patients[83].

In spite of limitations of present devices, participants in both studies were quite positive towards BCI use, describing feelings of freedom, hope and connection[83].

Given user and caregiver's feedback, an ideal BCI would have the following characteristics[12,82]: be safe, affordable; reliable in terms of day-to-day operation; reliable in the long-term; independence, in terms of not requiring the support of a caregiver, technician or scientist; should restore normal communication in terms of text or speech; restore real-time control of one's own limbs or prosthetic devices; be aesthetically acceptable or invisible; restore normal autonomic functions (bladder, bowel, sexual); have a natural operation, not requiring more effort or concentration in a task than a healthy individual.

In resume, studies reach the conclusion that patients with ALS have a strong interest in obtaining a BCI, but current devices do not yet fulfill the desired performance[25].

Other BCI limitations that should be bore in mind are related to the disease evolution. A recent study has shown that as motor disability advances, more cortical areas are recruited to perform the BCI task. This indicates reduced cortical differentiation and specialization in these patients, and may pose limitations to BCI performance[85].

Additionally, it is known that at late stages of the disease, ALS patients loose eye voluntary movements (completely locked-in state), and therefore the use of visual-based BCIs is compromised[82,86]. Recent studies, nevertheless, suggest that auditory[49,56-60], proprioceptive[49], and invasive BCIs[45,77,78] could be the remaining possible communication channels for these patients.

Further, it has also been observed that some ALS patients have cognitive impairments[24,27,82], which also limit the use of BCI systems. In this case, BCI systems could also be used for assessment of cognitive function[73,74] and test for suitability of BCI functional operation.

Given the present BCI limitations and user inputs one can define three main areas for research and development: hardware, software and applicability[8,12].

Regarding hardware, some of the requirements are already being tackled. The use of dry electrode technology[14] (http://www.gtec.at) should solve the issues related to the use of gel-based electrodes regarding comfort and stability of acquired EEG signals due to electrode contact. Further development of EcoG and intra-cortical EEG-based systems could also be a solution as long as infection risk, electrical safety and durability are assured.

Additionally, nowadays there are safe and affordable commercial non-invasive BCI devices (http://www.intendix.com), and there has been an increased interest in affordable, portable and ergonomic devices being developed for the video-gaming industry[14,15] (http://www.neurosky.com; http://www.emotiv.com; see figure 6). This is fostering a great deal of research in the field and may hold promising results in healthcare applications[8].

Regarding software, novel applications and functionalities may spurn in the coming years based on improved signal feature extraction and translation algorithms. Algorithms may take into account multimodal EEG signals such as P300, SMR, and SCP, as well as information coming from EOG, EMG, fNIRS or other physiological signals. For instance, a recent study showed that EEG signal features such as root-mean square amplitude and EEG theta frequency (4-8Hz) could predict P300-based device performance[87]. Also, authors propose that by optimizing such EEG features the BCI performance could be improved[87]. The major goal of improving software is then to enable real-time operation of communication devices and assistive devices[12], such as robotic arms, prosthetic limbs and exosqueletons[88].

Additionally, research efforts in this field should also be undertaken to reduce the training time required for operation of a BCI[72,84]. Ideally, no intensive training would be necessary and adaptation between user and BCI would be the most natural as possible[7,77,78]. Of particular interest would be the use of the mirror neuron system (MNS), as hypothetically, MNS could provide a robust way to map neural activity to behavior in severely limited patients[89].

Regarding applicability, larger long-term studies are required for testing BCI validity and reliability in every-day-use. So far studies with individual patients showed encouraging results with substantial and long-term improvements in functionality and quality-of-life [45,90]. An issue that should be taken into account is to tailor the BCI device to the stage of ALS, as it has been shown that BCI performance is greatly diminished in patients with late stage ALS[49,82,91].

Future research trends may yet include the topics of neurorehabilitation and neuroplasticity. As some studies suggest, BCIs alone could be used as a tool for rehabilitation by inducing changes in the brain networks of ALS patients[18,19,92].

BCIs could also be used in combination with physical therapy, assistive devices[12] such as prostetic limbs, or medical robots to synergistically promote brain plasticity[70,88].

Although fMRI-based BCIs would not be feasible for day-to-day use, they allow volitional control of anatomically specific regions of the brain. Therefore fMRI has the potential to be used for treatment by enabling modulation of brain activity[93]. Additionally, fMRI could be combined with other BCI types, as by monitoring brain changes due to disease evolution[85], electrode positioning could be optimized[94] and BCI protocols could be designed[95]. As a study showed, ALS patients have increased activity in precentral and frontoparietal networks in motor imagery. This information can, therefore, be used to optimally translate intentions into BCI commands[95].

Finally, non-invasive brain stimulation (NIBS) modalities such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) allow both the study of human brain activity in real-time but also could guide plastic changes[96,97]. It would be interesting to combine NIBS techniques with BCIs. They could be used for mapping functions or plastic changes induced by the BCI itself, leading to a better understanding of BCI operation and functional recovery processes[98]. It is also suggested that NIBS techniques could be used to modulate plasticity in order to improve brain signals per se. This could lead to improved BCI performance, eventually with shorter training times required and higher accuracy[99].

Conclusions

Research has shown that BCI technology holds great potential for improving communicational and motor functionalities of ALS patients. Though, in order for the technology to be disseminated clinically, some of the current limitations have to be overcome, namely: accuracy and reliability in the short- and long-term usage; real-time feedback; portability; and user-friendliness of both the equipment and applications. Ideally, the BCI would be used “naturally”, with as much natural appearance as possible and without much training or effort required for operation.

Also, ALS poses particular challenges to BCI usage, as in late stage ALS patients lose oculomotor control and may also present cognitive changes. In these cases, BCI devices should be adapted to each individual patient. For instance, auditory or intra-cortical EEG-based BCI devices may be used to surpass the oculomotor limitation, and other BCI systems may be used to assess cognitive functions. Additionally, research on BCI-mediated neuroplasticity may hold some hope for these patients. In this regard, BCIs are not only a means for communication and control but they could also become therapeutic.

Finally, with the advent of BCI technology entering the video-gaming industry, a novel generation of researchers is joining the field. It is expected that they could help bring this technology to maturity so that BCI devices could be used routinely by patients and the general population alike.

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Figure Captions

Figure 1. Comparison of the different brain signal recording techniques with respect to temporal and spatial resolution, portability, affordability and stage of BCI development. The area of each technique in the plot corresponds roughly to the closeness to clinical use. EEG=electroencephalography; MEG= magnetoencephalography; fNIRS=functional near infrared spectroscopy; fMRI=functional magnetic resonance imaging.

Figure 2. EEG-based BCI system components: scalp, cortical surface or intra-cortical electrodes are used to record electric signals form neuronal populations; signals undergo processing and conditioning such as amplification, digitization and filtering; features are then extracted from processed signals and translated into commands that feed external devices for communication, environmental control, movement of prosthetic limbs or robotic arms or control of locomotion using wheelchairs, and finally for neurorehabilitation (from [8] Shih *et al*. (2012) Mayo Clinic Proceedings 87: 268-279).

Figure 3. EEG-based signals used in BCI applications. (a) sensorimotor rhythms; (b) P300 evoked potentials and (c) cortical neuronal activity. Both sensorimotor rhythms and P300 potentials can be measured using scalp EEG, ECoG or MEG techniques. Cortical neuronal activity is measured using brain intraparenchymal depth electrodes (from [7] MacFarland and Wolpaw (2011) Communications of the ACM 54: 60-66).

Figure 4. Number of scientific peer-reviewed publications per year containing as keywords brain-computer interface in combination with amyotrophic lateral sclerosis.

Figure 5. P300-based BCI spelling devices: (a) standard row-column speller with highlighted row; (b) lateral single-character speller with highlighted letter (from [63] Pires *et al.* (2012) Clinical Neurophysiology doi:10.1016/ j.clinph.2011.10.040).

Figure 6. A portable and affordable, 14-channel BCI device developed for the video-gaming industry, now being used for the development of biomedical applications (http://www.emotiv.com).

Table Captions

Table 1. Possible brain signals for use in BCIs and respective techniques for signal recording, their advantages and disadvantages. EEG=electroencephalography; sEEG=scalp EEG; ECoG=cortical surface EEG; ICE=intra-cortical EEG; MEG=magnetoencephalography; fNIRS=functional near infrared spectroscopy; fMRI=functional magnetic resonance imaging.

Table 2. Current BCI applications for ALS patients. Refer to text for details. Otherwise noted, findings correspond to studies with ALS patients. sEEG=scalp EEG; ECoG=cortical surface EEG; ICE=intra-cortical EEG; VE=visually evoked; AE=auditory evoked; ERP=event related potentials; ErrRP=error related potentials; SMR=sensorimotor rhythm; SCP=slow cortical potentials; EOG=electrooculogram; RC=row-column; Checkerboard; LSC=lateral single character; Acc=Accuracy; ITR=information transfer rate; 1D=one dimensional; 2D=two dimensional; Ref.=Reference.

Table 1.

Brain signal	Technique	Advantages	Disadvantages
Electrical	sEEG	Non-invasive High temporal resolution Most researched	Low spatial resolution Lower signal than other EEG methods
Electrical	ECoG	High temporal resolution	Need of intervention Low spatial resolution
Electrical	ICE	High temporal resolution	Need of intervention Low spatial resolution
Magnetic	MEG	Non-invasive High temporal resolution	Low spatial resolution Expensive
Metabolic	fNIRS	Non-invasive Medium temporal and spatial resolutions	Does not localize sources in depth
Metabolic	fMRI	Non-invasive High spatial resolution	Low temporal resolution Expensive

Table 2.

Year	Application	Signal/Stimulus	Main findings	Ref.
2006	Speller	sEEG VE/AE P300	A 4-choice system of Yes/No/Pass/End is more suitable than RC for ALS patients	51,52
2008	Speller	sEEG VE P300	RC speller Acc=62-79%; ITR=9.6-16.8bits/min Performance stable for 40 weeks	53
2010	Speller	sEEG VE P300	Healthy subjects performance depends on eye gaze	55
2010	Speller	sEEG VE P300	CB speller show higher performance than RC RC Acc=77%; ITR=17bit/min; CB Acc=92%; ITR=23bit/min	62
2011	Speller	sEEG VE P300	Healthy subjects show higher acc than patients Healthy Acc=91%; Patients=70%	54
2011	Speller	sEEG VE P300	Linear classifier methods showed higher acc than non-linear methods	65
2012	Speller	sEEG VE P300	LSC speller show higher performance than RC RC Acc=88.4%; ITR=21.9bit/min; LSC Acc=89.9%; ITR=26.1bit/min	63
2012	Speller	sEEG VE P300	Use of ErrRP improves ITR	64
2012	Speller	sEEG VE P300	Latin squares arrangement can be used	61
2010	Speller	sEEG AE P300	Use of 2D auditory stimuli: pitch and location is feasible	58
2010	Speller	EOG	EOG speller show higher performance than P300 P300 Acc=81%; ITR=22.9bits/min EOG Acc=100%; ITR=96bits/min	68
2006	Internet browsing	sEEG SCP	System is feasible. Acc=80%	75
2010	Internet browsing	sEEG VE P300	Healthy subjects acc >90%; ITR=14.4bits/min Patients acc=73%; ITR=8.6bits/min	69
2007	Binary choice	fNIRS	System is feasible. Acc=80%	79
2010	Binary choice	sEEG AE P300	Loudness, pitch, or direction. Healthy subjects acc=78.5%; ITR=2.5bits/min	57
2010 2008	1D/2D Cursor control	sEEG SMR/beta rhythm	1D Motor execution acc=82%; motor imagery=80%; 2D motor execution/imagery acc=50-60%	71,72
2011 2008	2D Cursor control	ICE Action potentials	Small numbers of cortical neurons can be used for cursor control using cursor position and velocity parameters, with small error rates	77,78
2008	Cognitive function	sEEG SCP	System is feasible for cognitive function assessment	73,74
2010	Powered mobility	sEEG Late ERP alpha/beta bands	Left and right movement intentions classified with acc=82%	76
2010	Robotic Telepresence	sEEG VE P300	System is feasible	70

Figure 1.

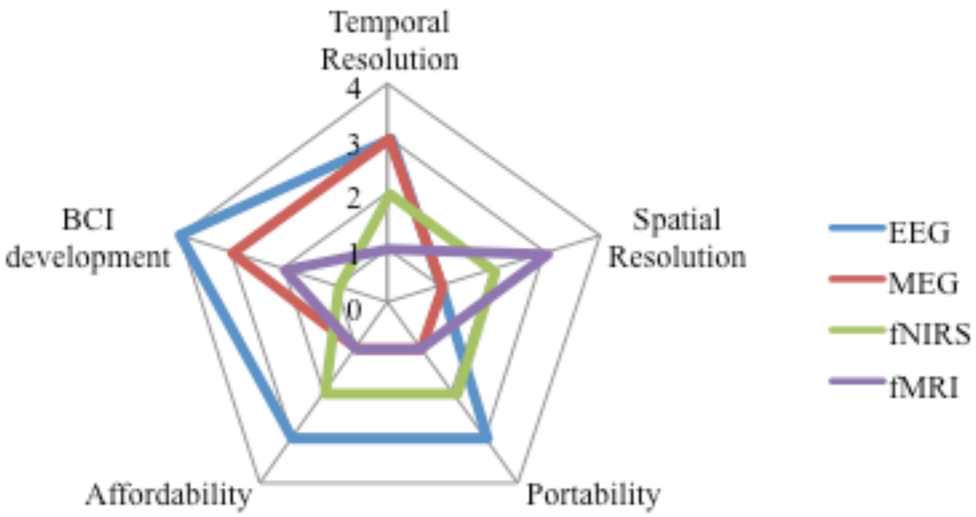

Temporal Resolution
Spatial Resolution
Portability
Affordability
BCI development
0
1
2
3
4
EEG
MEG
fNIRS
fMRI

Figure 2.

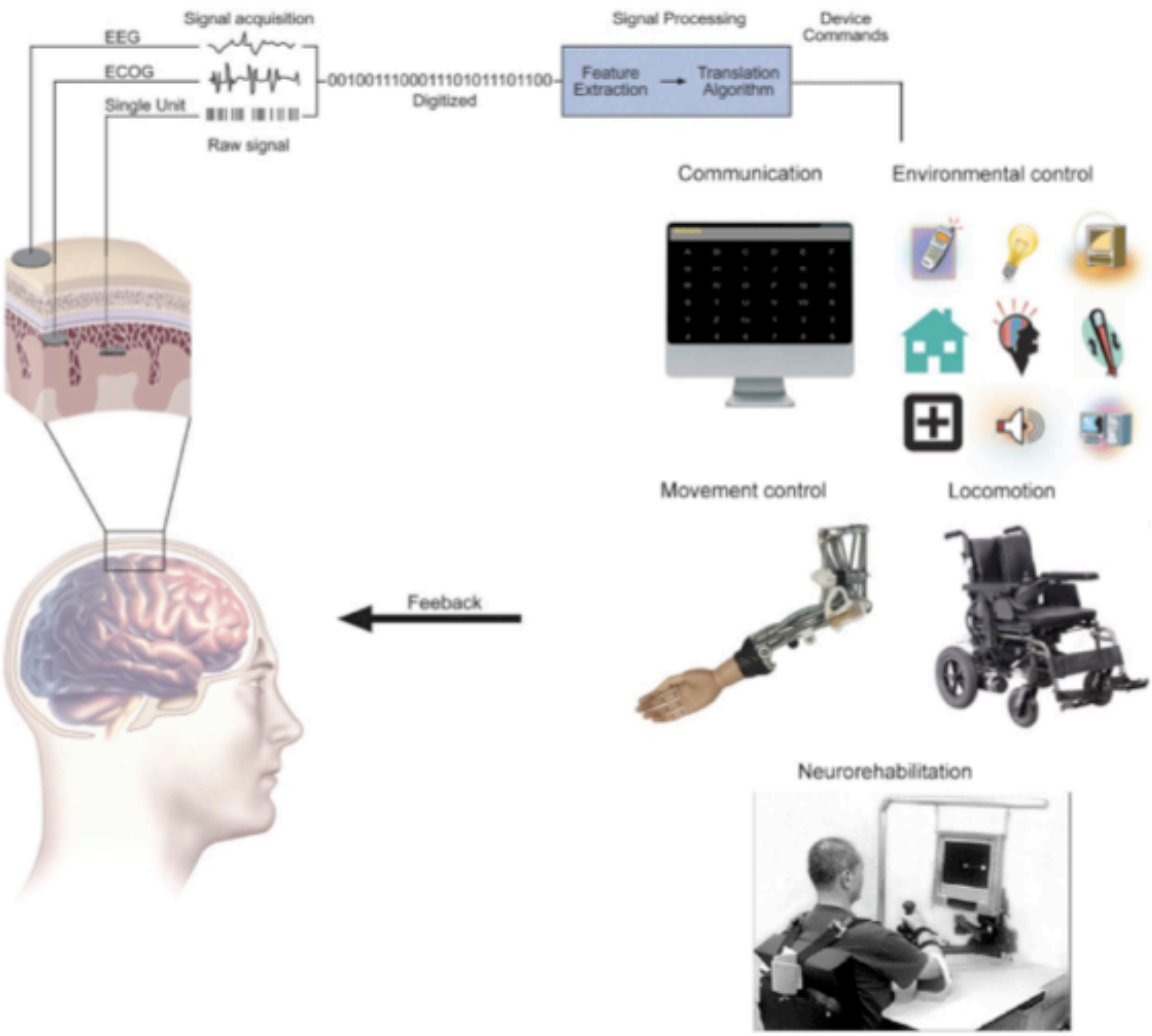

Signal acquisition
EEG
ECOG
Single Unit
Raw signal
001001110001110101110110O
Digitized
Signal Processing
Feature Extraction
Translation Algorithm
Device Commands
Communication
Environmental control
Movement control
Locomotion
Feeback
Neurorehabilitation

Figure 3.

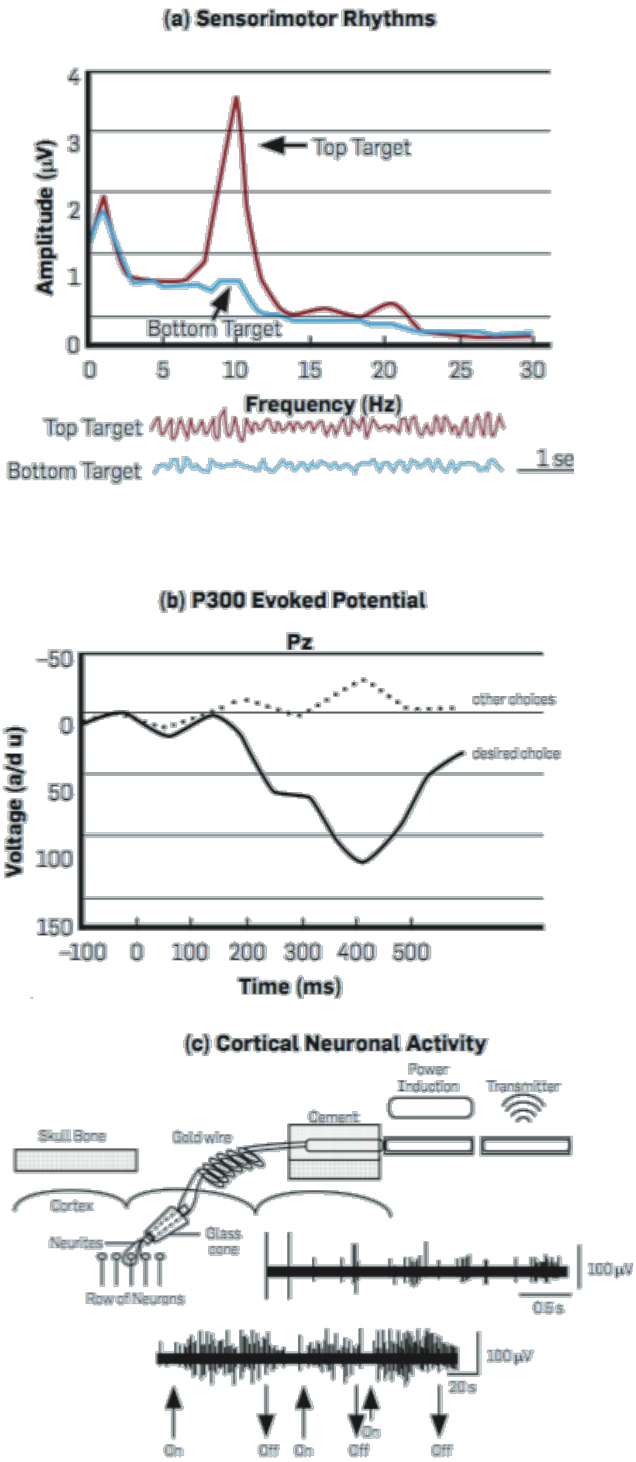
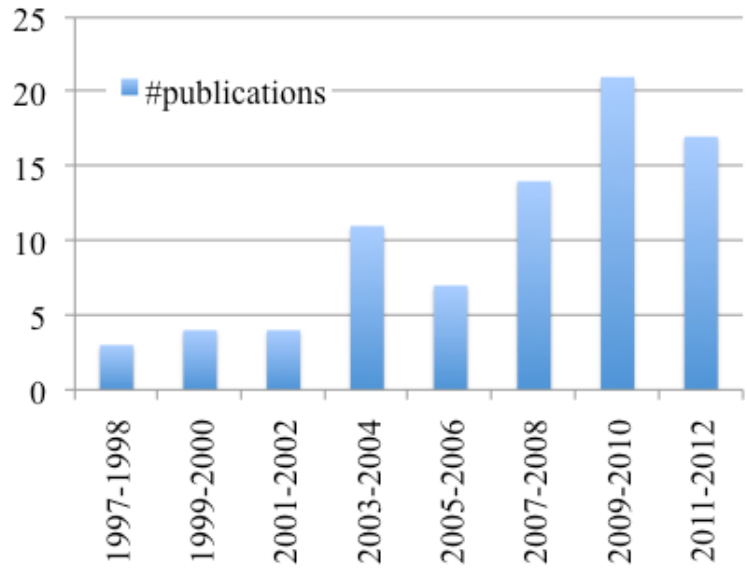

(a) Sensorimotor Rhythms
Amplitude (µV)
4
3
2
1
0
Top Target
Bottom Target
0
5
10
15
20
25
30
Frequency (Hz)
Top Target
Bottom Target
1 se
(b) P300 Evoked Potential
Pz
Voltage (a/d u)
-50
0
50
100
150
other choices
desired choice
-100
0
100
200
300
400
500
Time (ms)
(c) Cortical Neuronal Activity
Power Induction
Transmitter
Cement
Skull Bone
Gold wire
Cortex
Neurites
Glass cone
Row of Neurons
100 µV
0.5 s
100 µV
20 s
On
Off
On
Off
On
Off

Figure 4.


25
20
15
10
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#publications
1997-1998
1999-2000
2001-2002
2003-2004
2005-2006
2007-2008
2009-2010
2011-2012

Figure 5.

Figure 6.