

Brain-computer interfacing in disorders of consciousness

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Abstract

Background: Recent neuroimaging research has strikingly demonstrated the existence of covert awareness in some patients with disorders of consciousness (DoC). These findings have highlighted the potential for the development of simple brain-computer interfaces (BCI) for the significant minority of behaviourally unresponsive patients who display consistent signs of covert awareness.

Objectives: In this article, we review current EEG-based BCIs that hold potential for assessing and eventually assisting patients with DoC. We highlight key areas for further development that might eventually make their application feasible in this challenging patient group.

Methods: We consider the major types of BCIs proposed in the literature, namely those based on the P3 potential, sensorimotor rhythms, steady state oscillations, and slow cortical potentials. In each case, we provide a brief overview of the relevant literature, and then consider their relative merits for BCI applications in DoC.

Results: Over the last few decades, a range of BCI designs have been proposed and tested for enabling communication in fully conscious, paralysed patients. Though many of these have potential applicability for patients with DoC, they share some key challenges that need to be overcome, including limitations of stimulation modality, feedback, user training and consistency.

Conclusion: Developing feasible BCIs for diagnostics and communication in DoC will require parallel strands of enquiry. Preliminary exploratory research will need to specifically tailor cognitive tasks that can tap into the forms in which patients could potentially express volition. Alongside, future work will need to address the technical and practical challenges facing reliable implementation at the patient's bedside.

1. Introduction

In recent years, research into disorders of consciousness (DoC) has seen some key advances, with the successful demonstration of modern neuroimaging techniques for diagnosis and prognosis [1, 2]. These disorders, encompassing the vegetative (VS; also called the unresponsive wakefulness syndrome (UWS) [3]) and minimally conscious states (MCS), are marked by inconsistent signs of awareness with standard behavioural tests of command following. As a result, misdiagnosis rates among patients have been relatively high, ranging between 37-43% [4]. Owen et al. [5] were among the first to use functional magnetic resonance imaging (fMRI) to show that command following purely by thought could be detected in such patients. In that study, a patient clinically diagnosed as being in a VS/UWS performed mental imagery tasks in response to command. These tasks produced neuroanatomically distinct patterns of haemodynamic responses that were very similar to those observed in healthy, awake controls performing the same tasks. Monti et al. [6] exploited the potential of the paradigm by mapping these imagery tasks to yes/no responses. Remarkably, this allowed a patient behaviourally diagnosed as vegetative/unresponsive to answer correctly a series of autobiographical questions in real-time, by producing clearly discriminable brain activations. This striking result has demonstrated the possibility of establishing binary communication using thought alone. Consequently, the further development of such techniques could have tremendous potential for use with the small but significant minority of patients with DoC who retain most of their higher cognitive functions, but are unable to produce any consistent overt behaviour.

Though fMRI has many advantages with regard to detecting neural activation, availability, affordability and ease of use are not among them. This is where the older science of cognitive electroencephalography (EEG) offers potential for the development of relatively cheap, simple, compact systems that can be readily deployed at the bedside to detect volitional brain activity in a patient with DoC, and then used to enable basic communication with the outside world. EEG offers further comparative advantages to fMRI in this context. Firstly, it can be used in the presence of metallic implants that would make fMRI impossible. Secondly, it is relatively more resilient to noise artifacts generated by frequent, uncontrollable physical movements observed in patients with DoC, something that can present a difficult problem for MRI data analysis. As a third point, EEG seems to be better suited for repetitive assessment for patient with fluctuating vigilance. Monti et al. [6] reported a behavioural misdiagnosis rate of 17% using their fMRI imagery paradigm; EEG could give us a better estimate of this by allowing for a much larger, geographically distributed population of patients with DoC to be evaluated.

To support this effort, there exists an extensive body of research into EEG-based brain computer interfaces (BCIs), conducted mostly over the last two decades. In the past, these technologies have employed neural responses detectable with EEG to provide patients with motor impairments, often affected by the locked-in syndrome (LIS), the ability to control a computer interface. These interfaces usually drive software for simple communication, or control devices that influence some aspect of patient's external environment. In addition, they provide the patient with valuable real-time feedback on their performance, enabling them to learn to use the interface better over time. The objectives of this article are to review this literature in order to

assess the challenges and possibilities for applications that could improve the quality of life for patients with DoC and their families. In particular, we will focus on non-invasive EEG-based BCIs, as they are likely to be applicable to the widest range of patients. We will not address the literature on invasive BCIs (based on, for example, on electrocorticography), as these are currently thought to be ethically and technically infeasible in this patient population.

This review is structured as follows: in section 2, we review the literature relating to the major types of EEG-BCI designs with an eye toward their suitability in DoC. In section 3, we discuss the comparative merits and demerits of the previously discussed BCIs, and highlight some general design constraints that will need to be addressed for feasible DoC applications. We conclude in section 4 with an outlook toward the key challenges for future research.

2. Brain-Computer Interfaces

BCIs, by definition, only use brain activity to drive external devices or computer interfaces, to enable communication without motor responses [7]. A typical BCI (see figure 1) is composed of several functional components linked together; beginning with the input originating from a user who initiates “thought actions”, indexed by brain signals (recorded by EEG, fMRI, ECoG or fNIRS) and ending with the output (e.g., commands for a spelling program or a simple yes/no response). As outlined in figure 1, these two components are connected by a sequence of hardware and software components to pre-process the signal, extract predictive features, and classify the signal into one of many response classes that represent the intent of the user [8, 9]. There is normally a training phase before any feedback is provided.

During this phase, key system parameters are tuned to the user's activation patterns, using supervised learning algorithms.

<Insert figure 1 and caption about here>

Before adapting a BCI design for a patient with DoC, the first step would be to establish, beyond reasonable doubt, that they are able to follow commands with adequate consistency. Indeed, some patients might be able to follow command, but not well enough to make BCIs feasible. Hence, BCIs in DoC will have to follow a two-step approach: the first would be to establish successful command following. The second would be to try and establish communication (simple binary communication to begin with). Ideally, software and hardware components used for the first step would be readily extensible for the second.

Toward this end goal, we describe specific BCI implementations published in the literature, which are based on characteristic brain signals that can be volitionally controlled by the user. Amongst the most popular examples are the P3 event-related potential [ERP; 10], sensorimotor rhythms [SMR; 11, 12, 13] steady-state evoked potentials [SSEP; 14, 15], and slow cortical potentials [SCP; 16, 17]. We discuss each of these in turn, with a view toward evaluating their suitability for use with patients with DoC.

2.1. P3-based BCIs

The P3 component of the ERP is a positive deflection in the EEG time-locked to salient stimuli, typically evoked over the parietal cortex, and occurs between 200-500ms after stimulus onset [18-20]. The P3 is considered to include two distinct subcomponents, the P3a and the P3b. Similar to the MMN, the 'bottom-up' P3a is elicited by novel, unpredictable stimuli, even if they are irrelevant to the task being performed. It is typically seen in oddball paradigms [21] in which participants are attending to a sequence containing frequent stimuli interspersed with rare deviant ones, usually referred to as targets [22]. The deviant stimulus will elicit different ERPs, the most prominent being the frontally centered P3a. However, if the deviant is deemed task-relevant (for example, if it is being counted), it evokes a posterior, later P3b (peaking at around 300-350ms). From a cognitive perspective, the P3b is seen as a marker of consolidation into conscious awareness of a task-relevant, unpredictable target. For the purposes of BCI design in DoC, we will focus on the P3b. This is because, unlike the P3a, the P3b is only evoked in the presence of 'top-down' selective attention, strongly indicative of conscious control. As an evoked response for use in BCIs, the P3 has the advantage of requiring minimal training on the part of the user.

Some of the earliest BCI systems were P3-based, designed with visual stimuli. Donchin and his colleagues [10, 23] implemented a visual BCI by presenting letters in a 6 x 6 matrix and repeatedly flashing each row and column. To make a selection, the user had to count the number of times the row or column containing the desired letter was flashed. To identify this letter, the BCI averaged responses to each row and column over multiple flashes. The ones containing the largest P3 responses were assumed to contain the letter, enabling the BCI to detect the user's choice.

Since then, a range of improvements has been proposed to the original interface [24-26] and the EEG signal processing techniques [27, 28]. Recently, a large group study by Guger et al. [29] reported that in 81 healthy users, 89% were able to successfully use a P3-based BCI for spelling, with accuracies of 80% and above. Alongside, many studies have shown that this system is feasible and practical for patient groups [see 30 for a review; also see]. Nijboer et al. [31, 32] showed that five out of six patients affected by Motor Neuron Disease or Amyotrophic Lateral Sclerosis (ALS) could use the P3-based BCI for communication after one training session. Thereafter, four of them continued using it for functional communication in a second phase of the study, and all were able to spell messages of considerable length when more features were extracted from the EEG [32]. Going further, P3-based BCIs have been applied for other thought-controlled tasks, including simple games [33], navigation [e.g. to move a mouse; 34] and even control of a virtual environment [35].

The question remains, however, as to whether these BCIs could be adapted for detecting command following in patients with DoC. To do so, the patient would need to be able to understand the task requirements, attend to stimuli, and selectively process the salient ones, while retaining information in working memory. Hence its presence can be used to test for command following, and then to set up a BCI. This final step is straightforward, as the patient can be asked to deem one amongst two or more equally frequent stimuli as being task-relevant. Counting their occurrences in an unpredictable stimulus stream will produce a P3b for the chosen stimulus. For example, the answer words “YES” and “NO” in a stream of unrelated words, will produce a P3b for the chosen word.

In recent years, there have been some prominent findings in the literature, suggesting that some patients with DoC might retain most of these high-level cognitive abilities. Firstly, fMRI evidence suggests that some patients might retain near-normal levels of language comprehension [36-38]. In addition, they appear to be able to selectively attend to and process their own names as compared to unfamiliar names [39-41]. This finding has been confirmed with EEG data: ERPs evoked by increased mismatch negativity (MMN) have been observed when some patients with DoC heard their own names presented infrequently amongst tones and other names [42]. Closer in design to P3 BCI-type active paradigms, Schnakers et al. [43] employed a setup where patients were instructed to count the number of instances of their own names presented within an auditory sequence consisting of other names. They found that 5 out of 14 (36%) MCS patients tested produced reliably larger P3 responses when actively counting the occurrence of their own name as compared to when only passively listening to them. From this important result, the authors inferred that these patients demonstrably retained the ability to volitionally follow command with EEG, even though unable to do so behaviourally with the same level of consistency. Moreover, they used this paradigm to detect signs of consciousness in a patient behaviourally diagnosed as being comatose [44]. Promisingly, this finding has been corroborated and extended by Monti et al. [45], though in fMRI. They found increased haemodynamic response when a MCS patient actively counted occurrences of an *arbitrarily chosen* target word, indicative of high-level cognitive functions like top-down attention and working memory.

Taken together, these findings are certainly encouraging for the development of P3-based BCI systems that tap into these volitional abilities retained by some patients

with DoC. However, active tasks will be required for such BCIs (e.g., requiring the patient to count target stimuli), as P3s in response to highly salient stimuli (like the patient's own name) have been observed in VS/UWS patients even in passive listening conditions [43].

Crucially, there is a practically motivated need for further research into auditory variants of P3 BCIs. It is often the case that patients with DoC lose the ability to fixate their gaze and attend visually. Consequently, auditory BCIs are more likely to be usable by a greater number of patients with DoC who could demonstrate signs of awareness. Recently, some auditory P3-based BCI designs have been proposed for patient groups unable to control eye movements. In one of the first of these, Hill et al. [46] allowed a healthy user to make a binary decision by focusing attention on one of two concurrent auditory stimuli differing in location (on the left or right of the subject) and pitch. The user's task was to report the number of deviant target beeps contained in the sequences. The study suggested that it is possible for users to generate a detectable P3 at the single-trial level by focused auditory attention. Using classifiers developed by Hill et al. [46], Sellers and Donchin [47] tested an auditory P3-based BCI asking severely physically disabled patients to pay attention on one of four randomly presented stimuli (yes, no, pass, end). Results suggested that it is a promising tool for use as a non-muscular communication device. To address the reduction in efficiency commonly found with auditory BCIs, Schreuder et al. [48] used spatial hearing as an additional auditory cue to enhance performance. By presenting target and non-target sounds from different spatial locations surrounding the user, they demonstrated P3 classification accuracies of over 90%. Halder et al. [49] demonstrated the viability of fast binary (yes/no) communication with an

auditory BCI based on a three-stimulus (two target stimuli, one frequent stimulus) paradigm, instead of the more common two-stimulus design.

Several studies have also investigated whether it is possible to operate the standard matrix P3 speller with auditory stimuli instead of flashes. Klobassa et al. [50] used six environmental sounds to represent the six rows and the six columns of a standard speller matrix. They reported online results and offline analyses showing that eight out of ten participants achieved accuracies of 50% or more. An alternative auditory adaptation of the visual speller was reported by Furdea et al. [51]. They coded the rows of a 5x5 matrix with numbers from 1 to 5, and the columns with numbers from 6 to 10. These numbers were then presented auditorily. To select a letter, users had to focus their auditory attention on the numbers corresponding to the row and then the column containing the desired letter. When tested with four severely paralyzed patients in the end-stage of a neurodegenerative disease, the system performed above chance level [52]. However, as one might expect, spelling accuracy was significantly lower with the auditory variant than with the original visual speller. Moreover, participants reported difficulties in concentrating on the auditory task, indicative of the increased difficulty.

An alternative paradigm for a two-choice auditory P3-based BCI, based on the phenomenon of auditory stream segregation has been described by Kanoh et al. [53]. When two or more repeating sounds differ in at least one acoustic attribute (e.g., the sequence ...ABAB...), they are perceived as two or more separate sound streams (i.e.,...AAA.. and ...BBB...). By randomly placing infrequent deviant tones within these streams, an oddball paradigm is created. The auditory N200 ERPs generated

when the user pays selective attention to one of the tone sequences can be detected and used to convey intent. Based on this idea, they developed a Morse code speller. To use it, the user focuses their auditory attention on the deviant tones in one of the two streams to generate one of two possible symbols (“dash” and “dot”), to effectively spell letters in Morse code.

To a relatively limited extent, researchers have explored the use of tactile stimulation. In a study by Brouwer and van Erp [54], two, four or six vibro-tactile stimuli were applied around the waist of healthy participants. These tactile stimuli have the advantage of not taxing the auditory or visual system, and being mostly unnoticeable to other people. The participants were asked to focus on one (target) stimulus and to ignore the rest. The statistically significant accuracy with which the tactile P3s could be classified demonstrated the feasibility of this approach. However, the authors pointed out that further improvements to the tactile interface and stimulation design would be required to improve accuracy to a level acceptable for use with patients.

Finally, it is worth noting that ERP components other than the P3 could potentially be used to improve performance of BCIs. Bianchi et al., (2010) reported preliminary results suggesting that sensors located over the occipital cortex provide classifiable information, highlighting the fact that some visual evoked components (e.g., the N100) might advantageously be combined with P3s for discrimination of targets from non-targets. The question about whether similar improvements can be made by incorporating early auditory evoked potentials in auditory BCIs remains to be explored in future work.

In summary, research into P3-based tasks is encouraging for DoC applications, and has demonstrated the possibility of selecting a stimulation modality sensitive to the patient's individual circumstances. However, the need for active tasks to differentiate volitional P3 responses from automatic ones will add to the cognitive load imposed on patients. On the technical side, machine learning algorithms will have to be adapted to the difficult problem of detecting a relatively small and often abnormal P3 response in patients, with usually only a few clean trials worth of signal. Furthermore, the performance limitations imposed by non-visual stimulation modalities need to be overcome. In this regard, future research will need to investigate potential benefits of multi-modal audio-tactile stimulation suitable for patients, alongside means for providing effective feedback with these modalities.

2.2. SMR-based BCIs

The Sensorimotor or mu-rhythm (SMR) refers to the 8–15 Hz oscillatory EEG activity that can be recorded over primary sensory and motor cortical areas [12, 55–58]. It is usually accompanied by 18–26 Hz harmonics in the beta frequency band. In neural terms, the SMR is seen as an ‘idling rhythm’ of neurons in the motor cortex. Crucially, it has been known for many years that the SMR desynchronises, i.e., its power decreases, with the preparation of movement [59]. This power decrease, termed event-related desynchronization – ERD [60], is particularly prominent in the relevant motor regions contralateral to the limb movement being made. Often, an ipsilateral increase in SMR power, or ‘event-related synchronization’ (ERS), is observed after the movement [61].

For the purposes of BCI design, the most interesting feature of the SMR is that ERD and ERS do not require actual movement; as they are markers of well-developed motor competencies, they occur even when the user is asked to imagine performing a movement [62, 63] kinesthetically [64]. Furthermore, participants who are provided with visual or auditory feedback on their performance can learn to regulate the SMR amplitude [65]. Since the mid-1980s, several motor-imagery BCIs have been developed to tap into this phenomenon. These systems allow the user to select between two to four response choices by mapping pairs of complementary motor imagery tasks (e.g., right hand and left hand) to either bimodal responses or to continuous control of a computer cursor.

Detailed studies of motor imagery BCIs have been conducted, both with healthy controls [66] and paralysed patient populations [9]. In patients who could not perform actual limb movements due to severe motor disabilities, SMR modulation due to imagined movement could be detected and classified with accuracies above 70% [13, 67, 68]. In addition, several asynchronous spelling applications have been developed using motor imagery, and have shown promising results in healthy controls [69, 70]. Neuper et al. [71] trained a paralyzed patient diagnosed with severe cerebral palsy, to use a language support program [72] for communication. In their paradigm, the patient was presented with a virtual keyboard with a predefined set of letters, split into two equally sized subsets at the top and the bottom of the computer screen. The patient had to select the subset containing the target letter using a mental task. Following the detection of this choice, the chosen subset was split again. This successive splitting of the letter set continued until only one letter was selected. They showed that, after several months of training, the patient was able to control the

keyboard with 70% accuracy. Another study by Neuper et al. [73] showed that a patient suffering from ALS could learn to operate the virtual keyboard spelling application using SMR modulation.

Going beyond two-choice designs, Pfurtscheller et al. [74] studied the possibility of disentangling four different motor imagery tasks (pointing either to the left, right, up, or down), representing one of four different motor imagery tasks (left hand, right hand, both feet, and tongue, respectively) and one mental-calculation task. They found that it was difficult to discriminate between more than two mental states when only imagery-induced ERD patterns were available. This was mainly because of the large number of perceptual and memory processes that resulted in a non-specific desynchronization of alpha band rhythms [75], irrelevant for the classification task at hand. Wolpaw et al. [56, 76] have had some success in developing multi-class SMR-based BCIs, by having participants modulate mu- or beta-rhythm amplitudes separately. Using their system, healthy controls and patients with motor disabilities learned to control their brain activity to move a cursor in one or two dimensions toward targets on a computer screen.

This prior research in patients with motor disabilities has laid much of the groundwork for potential applications of motor-imagery BCIs to patients with DoC. In particular, researchers have developed sophisticated methods for extracting best possible classification performances to drive BCIs. Amongst these, Common Spatial Pattern (CSP) analysis is a popular technique suitable for use with increasingly popular high-density EEG hardware. Mathematically speaking, CSP analysis is a supervised Blind Source Separation algorithm. It is focused on improving the spatial

resolution of EEG data at the single-trial level [77]. CSP analysis aims to spatially filter high-density data from a large number of EEG sensors (electrodes) across the scalp to a relatively small number of task-relevant spatial patterns of activity. In a motor imagery setting, the scalp topographies of these spatial filters are selected on a per-user basis, selected so as to maximise the discriminability of the ERD patterns across a pair of motor imagery tasks. The spatial patterns generated by appropriate filters are well suited for improving classification performance with relatively simple linear approaches. Indeed, Blankertz et al. [78] have demonstrated that CSP analysis can assist in generating excellent (>84%) classification of motor imagery in 8 out of 14 BCI-naïve healthy participants after the first training session. Given these properties, CSP analysis could provide key advantages for dealing with the large amount of variability observed across patients with DoC. In particular, due to the aetiology (and subsequent atrophy) of their brain injuries, the cortex might have undergone significant functional remapping. These changes are likely to be significantly variable from one patient to the next; spatial filtering could account for this variability by isolating patient-specific spatial patterns (if any) that are likely to be generated by volitional motor imagery. This pre-processing step enables the subsequent single-trial classification procedure and the BCI in general, to be tailored to the patient's specific neuroanatomy and dynamics.

Preliminary evidence in the literature suggested that patients with DoC might be able to use some forms of motor imagery to express volitional intent. In particular, Bekinschtein et al. [79] showed that some VS/UWS and MCS patients were able to produce sub-threshold increases in hand electromyographic (EMG) activity in response to movement commands. This result pointed to the possibility of developing

of simple EEG BCIs based on two-choice imagery paradigms, which could afford such patients the means to demonstrate awareness. Goldfine et al. (2011) recorded EEG from three patients with severe brain injury (MCS and LIS), while they were asked to imagine motor and spatial navigation tasks. In one MCS patient and one LIS patient, they were able to show evidence of significant differences between the frequency spectra accompanying the two imagery tasks, though the pattern of changes observed in patients differed from those in controls [80]. Cruse et al. [81] investigated the ability of DoC patients to perform demanding motor imagery tasks that could be discriminated in their EEG at the single-trial level. They assessed 16 behaviourally VS/UWS patients while asking them to imagine either squeezing their right hand or moving all their toes. The results showed that in 19% (3) of the patients, a support vector machine was able to accurately predict the task being performed, with cross-validated accuracies between 61% and 78%. Cruse, Chennu et al. [82] performed the same test with MCS patients and found that 5 out of 23 (22%) MCS patients were able to follow command using motor imagery. Such paradigms could allow researchers to establish binary communication in patients who successfully perform the imagery tasks, by mapping imagination of right hand movement to 'YES' and toe movement to 'NO'.

These DoC studies with SMR are promising in their use of the auditory modality. However, learning to map intended responses to motor imaginations is a relatively complex task, and can be challenging to perform consistently even for healthy adults [66]. Hence SMR-based BCIs will probably be useful only for a minority of patients retaining high-level cognitive function. Along with the use of techniques like CSP to improve classification performance and reduce training time, suitable means of

providing feedback will need to be investigated. In this regard, past research into adapting SMR-based BCIs to other sensory modalities might well prove useful. Nijboer et al. [31] demonstrated that SMR-modulation could be learned and improved with auditory feedback, albeit slower than with visual feedback. Further, Cincotti et al. [83] showed that SMR could also be modulated with tactile feedback. In fact, they found no difference between the efficacies of tactile and visual feedback.

2.2.2. Alternative forms of imagery

Despite its popularity in BCI research, motor imagery is not the only task that can be used for volitional modulation of oscillatory rhythms in the brain. Mental arithmetic [84, 85], mental task rotation [86] and many others have been shown to lead to differentially specific patterns of spatially specific cortical activation and deactivation [87]. Given that some patients with DoC were able to follow command imagine playing tennis and spatial navigation with fMRI [5, 6], it might be fruitful to draw upon this previous work to explore novel imagery tasks that are well suited for use with EEG. The most suitable sorts of tasks in this context are likely to be based on well-established, long-term mental capabilities that might be preserved in DoC. Looking ahead, tapping into these capabilities might allow BCI design to move beyond the two-choice design, into the realm of complex and nuanced communication.

2.3. Steady-state evoked potential BCIs

We now consider a set of related BCI approaches based on the volitional modulation of steady-state electrical responses set up in the brain by the presentation of oscillatory stimulus sequences. Such BCI designs are distinguished based on the sensory modality used to present these stimuli, considered here in turn.

2.3.1. SSVEP-based BCIs

Steady-state visually evoked potentials [SSVEPs; see 88 for a review] are the oscillatory electrical responses of neurons in the visual cortex to stimuli that are repeatedly presented, or flashed, at frequencies above 6 Hz. For many years, it has been known that such rapid stimulus sequences set up stable and synchronised neural oscillations in the occipital cortex, at frequencies corresponding to that of the stimulus [89]. SSVEPs are easy to detect, as their frequency content is completely determined by the visual stimuli used to elicit them. These stimuli typically also elicit oscillations at harmonics of the stimulating frequency [89, 90].

For the purposes of BCI design, the finding that the strength of the SSVEP is modulated by endogenous attention is crucial. Specifically, it has been found that when the visual system is presented with multiple stimuli flashing at different frequencies, the frequency of the stimulus being attended to generates the largest oscillatory response in the brain. Tapping into this knowledge, researchers have built BCIs that use stimuli at different frequencies to represent a set of responses from which the user selects one by paying attention to it. Such BCIs are particularly attractive because occipital SSVEPs have high signal-to-noise ratios and are nearly completely free of eye movement [91] and electromyographic (EMG) artifacts [92,

93]. Moreover, SSVEP-based BCIs allow the user to select from a relatively large number [up to 64 of different choices 15, 94] without adversely affecting classification accuracy, which tends to range between 64-96.5% [88].

Stimulation for modern SSVEP-based BCIs is delivered either on a computer screen, or using light-emitting diodes flickering at different frequencies [15, 94, 95]. The power at the stimulation frequencies over occipital electrodes is fed to a classifier, which is trained a priori to identify the stimulus frequency most likely to be focused on by the user. It has been found that the first three harmonics of the stimulus frequencies carry additional information, providing for a significant increase in classification accuracy [96]. Progressive improvements in the design have produced systems that allow for impressive rate of communication. Parini et al. [97] showed performance results from a SSVEP-based BCI that employed four cubic LED stimuli mounted at each side of a display. Seven healthy participants and four patients affected by muscular dystrophy at different stages were able to successfully use this system. In particular, the study reported the robustness of the system and the rapidity of user performance.

The ability to focus gaze and attention is an obvious requirement for using SSVEP BCIs. Hence, their use by a majority of patients with DoC, who often have little or no control of their eye movements, would seem infeasible. There has been some progress in addressing this limitation; paradigms based on covert spatial attention [98], selective attention to spatially overlapping stimuli [99] and superimposed illusory surfaces [100] have also been found to evoke changes in SSVEP activity. However,

preliminary tests with healthy controls have found significant increases in the variability of performance, making it difficult for a patient to reliably control the BCI.

2.3.2. SSSEP-based BCIs

Analogous to visually evoked SSVEPs, steady-state somatosensory evoked potentials (SSSEPs) are elicited by a continuous vibro-tactile stimulus of a constant carrier frequency and a modulation frequency applied to the skin [101]. Using this technique, early research reported that when the palm [102] or the palm and sole [103, 104] were stimulated, corresponding steady-state responses were recorded at the scalp. Such non-visual BCIs based on SSSEPs hold promise for patients with DoC unable to focus their gaze.

The first study showing attentional modulation of SSSEP amplitude in humans was done by Giabbiconi et al. [105], using tactile stimuli with different frequencies applied simultaneously to the left and right index finger. Following this, the usability of SSSEPs in BCI design was evaluated by Müller-Putz et al. [106]. They stimulated both index fingers using tactile stimulation in the resonance frequency range of the somatosensory system. Four healthy subjects participated in the experiments and were trained to modulate the induced SSSEPs by focusing their attention on either their left or their right index fingers. Two of them learned to modulate their SSSEPs with accuracies between 70% and 80%, demonstrating the initial possibilities of this approach.

Researchers have also attempted to combine multiple modalities to improve the classification accuracy of steady-state BCIs. Such BCIs, based on multi-modal attention, have been proposed by Zhang et al. [107]. They combined tactile and visual stimuli to realise a 3-class BCI based on SSSEPs and SSVEPs. The combination of the two modalities resulted in improved classification accuracies when compared to either modality alone. Further, they showed that steady-state evoked potential amplitudes were modulated not only by switching spatial attention within one sensory modality, but also by switching across different modalities.

2.3.3. ASSR-based BCIs

There have been a few relatively recent attempts to use steady-state responses produced by auditory stimulation, i.e., ASSRs [Auditory steady-state responses; 108, 109, 110] to drive BCIs. Cortically recorded ASSRs are generated presenting amplitude-modulated tones to the ear [111]. Ross et al. [112] showed that the amplitude of the prominent ASSR generated by 40Hz stimulation is modulated by selective attention. However, as of yet, there has been no demonstration of a BCI driven by such attentional modulation of ASSRs. The BCI design challenge yet to be overcome here is the relatively small size of this modulation effect, making it difficult to detect in real-time.

BCIs employing ASSRs would come with the important advantage of not requiring the visual modality. Hence, as with SSSEP-based BCIs, they could find applications for patients with DoC. However, a potential drawback, the seriousness of which is yet to be properly studied, might be related to sensory stress and irritation brought on by

continual steady-state stimulation. The problem of cognitive fatigue and short attention spans, common in patients with DoC, might be exacerbated with steady-state stimulation, limiting the viability of steady-state BCI applications in this context.

2.4. SCP-based BCIs

We finally consider the class of BCIs based on the modulation of Slow Cortical Potentials [SCPs, 113]. These slow voltage changes generated in the cortex are among the lowest frequency features of scalp-recorded EEG, occurring over periods of 0.5–10.0s. Usually, negative SCPs are associated with motor movement and other functions involving increased cortical activation, while positive SCPs are more associated with reduced cortical activation [113]. Over the last few decades, Birbaumer and colleagues have worked on the development of SCPs-based BCIs. Crucially, they have shown that people can learn to modulate their SCPs and use them to control the movement of an object on a computer screen [16, 114, 115]. Further, this system has been tested in people with late-stage ALS and has proved capable of providing basic communication capacities [17]. Often, these BCIs are based on visual feedback from a computer screen that shows one choice at the top and one at the bottom. Two seconds of baseline are necessary to provide the system the user's initial voltage level. In the next two seconds, the user selects either the top or bottom choice by attempting to decrease or increase their SCP voltage level by a criterion amount, leading to a vertical movement of a cursor in the chosen direction. In addition to the commonly used visual feedback mode, SCP BCIs have also been set up to provide auditory or tactile feedback [115]. However, a study by Pham et al. [116] in healthy

participants showed that auditory feedback resulted in a relative increase in the variability of performance.

SCP-based BCIs come with the advantage of being the most stable over longer periods of usage, and do not require the use of any specific sensorimotor functions. This is a potential advantage for patients with DoC. On the other hand, the speed of choice selection is low, owing to the slow rates at which SCPs manifest. More importantly, these BCIs require relatively long periods of user training, sometimes in the order of months for some LIS patients [30]. It will probably be a minority of patients with DoC, showing consistent signs of awareness, who will be able to exercise the cognitive control required to train their SCPs over extended periods of time.

3. Discussion

Currently, there still remain a number of barriers keeping patients with DoC from benefitting from novel BCI technologies. Three key challenges are identified below:

1. Firstly, there is the sensory dysfunction, arousal fluctuation and limited attention span commonly observed in DoC, and especially in MCS. Hence task/stimulus complexity is an important factor to consider when evaluating BCI applications for such patients.
2. Stimulation and feedback modality is another issue: the visual modality is infeasible for use with most patients with DoC, and it has proven difficult to

develop effective auditory and tactile BCIs that deliver relatively consistent performance [49, 52, 116].

3. In addition, the suitability of different BCI designs for individual patients is significantly variable, and will need to be comparatively assessed in each case. While some patients have been shown to be able to generate reliable P3s in response to task-relevant stimuli, others have demonstrated the ability to consistently perform motor imaginations in response to command.

Amongst the different designs, SMR BCIs are relatively less hindered by problems of stimulation modality. There is relatively little stimulation that needs to be presented, and this can be effectively delivered auditorily. Furthermore, such BCIs can be designed to be self-paced, further minimising intrusiveness and patient distress. Results on their use in some DoC patients have produced promising results [9, 81, 117]. This knowledge, along with the fact that other forms of mental imagery (e.g., playing tennis vs. spatial navigation imagery) in fMRI have already allowed some patients with DoC to communicate [6], bodes well for similar BCI variants.

However, as SMR-based BCIs rely on the user's ability to learn mappings between intention and movement imagery, they require adequate training before reliable performance can be achieved. In this regard, the need for consistent SMR changes within the training procedure poses a significant challenge in the DoC context. The classification algorithms that drive BCIs naturally depend on the quality and inter-trial consistency of the data used to train them. This is problematic for most patients with DoC, especially those in MCS, who are prone to frequent and prolonged bouts of fatigue, accompanied by severe temporal variability in their levels of arousal and

awareness. This would effectively render them unable to pay attention for sufficiently long periods. For many patients, this limitation will adversely affect the statistical power of the classifiable patterns latent in their EEG data.

In comparison, P3-based BCI designs rely on ‘natural’ responses of the brain to salient stimuli, and hence require relatively little explicit user training. As highlighted earlier, previous findings by Monti et al. [45] and Schnakers et al. [43] have shown that some patients with DoC can generate consistent changes in fMRI and EEG when asked to selectively attend to task-relevant stimuli. These are promising for the development of simple, binary BCIs based on auditory/tactile stimulation. Eventually, if successful with a patient, a P3-based BCI for spelling words and sentences using a predictive language support program would provide a true, multi-class system with relatively high efficiency.

For any of the BCI designs discussed in this article, results from patients with DoC will need to be interpreted with great caution. In part, this is because, even in a large sample of the healthy controls, only 20% of users were able to drive a motor-imagery based BCI with accuracies greater than 80% [66]. In fact, between 40-50% of users only managed accuracies around 60-70%. In comparison, P3-based BCIs fared much better, with 89% of healthy controls able to use it with an accuracy between 80-100% [29]. Though these results do not invalidate the potential of these BCIs in DoC research, we must keep in mind that the likelihood that a covertly aware patient might go undetected (i.e., the false negative rate) is likely to vary significantly across different tests and patient groups. Hence, none of these tests applied individually to look for command-following can currently be used to interpret negative results,

without combining findings from multiple testing methods to mitigate against the level of uncertainty.

Furthermore, it is important to note that while the BCI designs reviewed in this article have seen many years of intensive development, much of this work has involved testing of various designs with healthy controls. As one might expect, it is often the case that results from controls do not generalise well to patient groups [118]. Hence, there is a need to conduct extensive testing with patients likely to benefit from various BCI systems in their daily lives [119]. To date, EEG and ERP responses demonstrating volitional brain activity in DoC have only been shown in relatively small cohort studies or case reports. Larger cohort studies by multiple, independent groups will need to test and validate these findings. A better understanding of variability in responses across a wider population of patients will certainly aid future BCI research.

Lately, there is increasing research interest in the question of ‘what it is like’ to be in an unresponsive or minimally conscious state [1, 120]. The development of methods for working towards empirically motivated answers to such questions will undoubtedly benefit from the latest BCI research. As neuroimaging contributes to our current understanding of mental states in DoC, we will be able to better evaluate the challenges, benefits and viability of the different BCI designs discussed in this review.

4. Conclusions

We have reviewed a range of BCI systems that might prove useful for enabling communication in DoC. The prior research into the development of these systems has done much of the groundwork to allow us to evaluate the relative merits and demerits of these designs, with a view to their viability for patients with DoC. These are, however, a particularly difficult group of patients for BCI research. Developing feasible BCIs in this context will require, in parallel, preliminary exploratory research into basic cognitive tasks that allow us to probe the forms in which patients could potentially express volition. This work might bring to light new paradigms, e.g., based on novel forms of mental imagery, which could then be applied to developing BCIs. Eventually, we would hope to have at our disposal an essential, broad-based battery of neuroimaging paradigms that tap into a wide range of cognitive functions with the potential to drive BCIs. The combination of knowledge therefrom will better enable us to tailor the mechanisms and complexity of future designs to the specific capabilities of individual patients with DoC most likely to benefit from them. However, it will take significant time and effort before current BCI technology can move from bench to the bedside, and reliably inform clinical practice for improving the quality of life in patients with DoC.

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Declaration of interest

The authors report no declarations of interest.

Figure Captions

Figure 1: A typical Brain-Computer Interface loop. Real-time neural signals acquired from the user are pre-processed before discriminative features are extracted therefrom. Machine learning techniques are then used to train classifiers to detect statistical patterns in the features that are reliably associated with pre-specified (supervised) volitional states of the user. The trained classifier can then be used to classify new features corresponding to states now selected by the user to communicate choices. Finally, the result of the classification is fed back to the user, to help them train themselves in the use of the BCI.

References

- [1] Cruse D., Owen A.M. Consciousness revealed: new insights into the vegetative and minimally conscious states. *Curr Opin Neurol* 2010; 23(6): 656-60.
- [2] Monti M.M., Laureys S., Owen A.M. The vegetative state. *BMJ* 2010; 341: c3765.
- [3] Laureys S., Celesia G.G., Cohadon F., Lavrijsen J., Leon-Carrion J., Sannita W.G., Szabon L., Schmutzhard E., von Wild K.R., Zeman A., Dolce G. Unresponsive wakefulness syndrome: a new name for the vegetative state or apallic syndrome. *BMC Med* 2010; 8: 68.

- [4] Schnakers C., Vanhaudenhuyse A., Giacino J., Ventura M., Boly M., Majerus S., Moonen G., Laureys S. Diagnostic accuracy of the vegetative and minimally conscious state: Clinical consensus versus standardized neurobehavioral assessment. *BMC Neurology* 2009; 9(1): 35.
- [5] Owen A.M., Coleman M.R., Boly M., Davis M.H., Laureys S., Pickard J.D. Detecting Awareness in the Vegetative State. *Science* 2006; 313(5792): 1402.
- [6] Monti M.M., Vanhaudenhuyse A., Coleman M.R., Boly M., Pickard J.D., Tshibanda L., Owen A.M., Laureys S. Willful Modulation of Brain Activity in Disorders of Consciousness. *New England Journal of Medicine* 2010; 362(7): 579-589.
- [7] Kübler A. Brain-Computer Interfaces for Communication in Paralyzed Patients and Implications for Disorders of Consciousness. *The Neurology of Consciousness* 2008: 217-234.
- [8] Mason S.G., Birch G.E. A general framework for brain-computer interface design. *IEEE Trans Neural Syst Rehabil Eng* 2003; 11(1): 70-85.
- [9] Kubler A., Neumann N. Brain-computer interfaces - the key for the conscious brain locked into a paralyzed body. *Progress in Brain Research* 2005; 150: 513-525.
- [10] Farwell L.A., Donchin E. Talking off the top of your head: toward a mental prosthesis utilizing event-related brain potentials. *Electroencephalogr Clin Neurophysiol* 1988; 70(6): 510-23.
- [11] Ingvar D.H., Philipson L. Distribution of cerebral blood flow in the dominant hemisphere during motor ideation and motor performance. *Ann Neurol* 1977; 2(3): 230-7.
- [12] Pfurtscheller G., Neuper C., Krausz G. Functional dissociation of lower and upper frequency mu rhythms in relation to voluntary limb movement. *Clin Neurophysiol* 2000; 111(10): 1873-9.
- [13] Kubler A., Nijboer F., Mellinger J., Vaughan T.M., Pawelzik H., Schalk G., McFarland D.J., Birbaumer N., Wolpaw J.R. Patients with ALS can use sensorimotor rhythms to operate a brain-computer interface. *Neurology* 2005; 64(10): 1775-7.
- [14] Regan D. Steady-state evoked potentials. *J Opt Soc Am* 1977; 67(11): 1475-89.
- [15] Cheng M., Gao X., Gao S., Xu D. Design and implementation of a brain-computer interface with high transfer rates. *IEEE Trans Biomed Eng* 2002; 49(10): 1181-6.
- [16] Birbaumer N., Ghanayim N., Hinterberger T., Iversen I., Kotchoubey B., Kubler A., Perelmouter J., Taub E., Flor H. A spelling device for the paralyzed. *Nature* 1999; 398(6725): 297-8.
- [17] Kubler A., Kotchoubey B., Hinterberger T., Ghanayim N., Perelmouter J., Schauer M., Fritsch C., Taub E., Birbaumer N. The thought translation device: a neurophysiological approach to communication in total motor paralysis. *Exp Brain Res* 1999; 124(2): 223-32.
- [18] Walter W.G., Cooper R., Aldridge V.J., McCallum W.C., Winter A.L. Contingent Negative Variation: An Electric Sign of Sensorimotor Association and Expectancy in the Human Brain. *Nature* 1964; 203: 380-4.
- [19] Sutton S., Braren M., Zubin J., John E.R. Evoked-potential correlates of stimulus uncertainty. *Science* 1965; 150(700): 1187-8.

- [20] Donchin E., Smith D.B. The contingent negative variation and the late positive wave of the average evoked potential. *Electroencephalogr Clin Neurophysiol* 1970; 29(2): 201-3.
- [21] Fabiani M., Gratton G., Karis D., Donchin E. Definition, identification and reliability of the P300 component of the event-related brain potential. in: P. Ackles, J. Jennings, M. Coles, editors. *Advances in psychophysiology.2* New York: JAI Press; 1987. p. 1-78.
- [22] Squires K.C., Donchin E., Herning R.I., McCarthy G. On the influence of task relevance and stimulus probability on event-related-potential components. *Electroencephalogr Clin Neurophysiol* 1977; 42(1): 1-14.
- [23] Donchin E., Spencer K.M., Wijesinghe R. The mental prosthesis: assessing the speed of a P300-based brain-computer interface. *IEEE Trans Rehabil Eng* 2000; 8(2): 174-9.
- [24] Martens S.M., Hill N.J., Farquhar J., Scholkopf B. Overlap and refractory effects in a brain-computer interface speller based on the visual P300 event-related potential. *J Neural Eng* 2009; 6(2): 026003.
- [25] Salvaris M., Sepulveda F. Visual modifications on the P300 speller BCI paradigm. *J Neural Eng* 2009; 6(4): 046011.
- [26] Townsend G., LaPallo B.K., Boulay C.B., Krusienski D.J., Frye G.E., Hauser C.K., Schwartz N.E., Vaughan T.M., Wolpaw J.R., Sellers E.W. A novel P300-based brain-computer interface stimulus presentation paradigm: moving beyond rows and columns. *Clin Neurophysiol* 2010; 121(7): 1109-20.
- [27] Lenhardt A., Kaper M., Ritter H.J. An adaptive P300-based online brain-computer interface. *IEEE Trans Neural Syst Rehabil Eng* 2008; 16(2): 121-30.
- [28] Krusienski D.J., Sellers E.W., McFarland D.J., Vaughan T.M., Wolpaw J.R. Toward enhanced P300 speller performance. *Journal of Neuroscience Methods* 2008; 167(1): 15 - 21.
- [29] Guger C., Daban S., Sellers E., Holzner C., Krausz G., Carabalona R., Gramatica F., Edlinger G. How many people are able to control a P300-based brain-computer interface (BCI)? *Neurosci Lett* 2009; 462(1): 94-8.
- [30] Birbaumer N. Breaking the silence: Brain-computer interfaces (BCI) for communication and motor control. editors. *Psychophysiology.43* Blackwell Publishing; 2006. p. 517-532.
- [31] Nijboer F., Furdea A., Gunst I., Mellinger J., McFarland D.J., Birbaumer N., Kubler A. An auditory brain-computer interface (BCI). *J Neurosci Methods* 2008; 167(1): 43-50.
- [32] Nijboer F., Sellers E.W., Mellinger J., Jordan M.A., Matuz T., Furdea A., Halder S., Mochty U., Krusienski D.J., Vaughan T.M., Wolpaw J.R., Birbaumer N., Kubler A. A P300-based brain-computer interface for people with amyotrophic lateral sclerosis. *Clin Neurophysiol* 2008; 119(8): 1909-16.
- [33] Finke A., Lenhardt A., Ritter H. The MindGame: a P300-based brain-computer interface game. *Neural Netw* 2009; 22(9): 1329-33.
- [34] Citi L., Poli R., Cinel C., Sepulveda F. P300-based BCI mouse with genetically-optimized analogue control. *IEEE Trans Neural Syst Rehabil Eng* 2008; 16(1): 51-61.
- [35] Bayliss J.D., Ballard D.H. A virtual reality testbed for brain-computer interface research. *IEEE Trans Rehabil Eng* 2000; 8(2): 188-90.
- [36] Coleman M.R., Davis M.H., Rodd J.M., Robson, Ali, Owen A.M., Pickard J.D. Towards the routine use of brain imaging to aid the clinical diagnosis of disorders of consciousness. *Brain* 2009; 132(9): 2541-2552.

- [37] Fernandez-Espejo D., Junque C., Vendrell P., Bernabeu M., Roig T., Bargallo N., Mercader J.M. Cerebral response to speech in vegetative and minimally conscious states after traumatic brain injury. *Brain Injury* 2008; 22(11): 882 - 890.
- [38] Davis M.H., Coleman M.R., Absalom A.R., Rodd J.M., Johnsrude I.S., Matta B.F., Owen A.M., Menon D.K. Dissociating speech perception and comprehension at reduced levels of awareness. *Proc Natl Acad Sci U S A* 2007; 104(41): 16032-7.
- [39] Di H.B., Yu S.M., Weng X.C., Laureys S., Yu D., Li J.Q., Qin P.M., Zhu Y.H., Zhang S.Z., Chen Y.Z. Cerebral response to patient's own name in the vegetative and minimally conscious states. *Neurology* 2007; 68(12): 895-9.
- [40] Qin P., Di H., Liu Y., Yu S., Gong Q., Duncan N., Weng X., Laureys S., Northoff G. Anterior cingulate activity and the self in disorders of consciousness. *Hum Brain Mapp* 2010; 31(12): 1993-2002.
- [41] Staffen W., Kronbichler M., Aichhorn M., Mair A., Ladurner G. Selective brain activity in response to one's own name in the persistent vegetative state. *J Neurol Neurosurg Psychiatry* 2006; 77(12): 1383-1384.
- [42] Qin P., Di H., Yan X., Yu S., Yu D., Laureys S., Weng X. Mismatch negativity to the patient's own name in chronic disorders of consciousness. *Neurosci Lett* 2008; 448(1): 24-8.
- [43] Schnakers C., Perrin F., Schabus M., Majerus S., Ledoux D., Damas P., Boly M., Vanhaudenhuyse A., Bruno M.A., Moonen G., Laureys S. Voluntary brain processing in disorders of consciousness. *Neurology* 2008; 71: 1614-1620.
- [44] Schnakers C., Perrin F., Schabus M., Hustinx R., Majerus S., Moonen G., Boly M., Vanhaudenhuyse A., Bruno M.A., Laureys S. Detecting consciousness in a total locked-in syndrome: An active event-related paradigm. *Neurocase* 2009: 1-7.
- [45] Monti M.M., Coleman M.R., Owen A.M. Executive functions in the absence of behavior: functional imaging of the minimally conscious state. *Prog Brain Res* 2009; 177: 249-60.
- [46] Hill N.J., Lal T.N., Bierig K., Birbaumer N., Sch\"o l, B. An Auditory Paradigm for Brain-Computer Interfaces. *Advances in Neural Information Processing Systems* 2005; 17: 569-576.
- [47] Sellers E.W., Donchin E. A P300-based brain-computer interface: initial tests by ALS patients. *Clin Neurophysiol* 2006; 117(3): 538-48.
- [48] Schreuder M., Blankertz B., Tangermann M. A new auditory multi-class brain-computer interface paradigm: spatial hearing as an informative cue. *PLoS One* 2010; 5(4): e9813.
- [49] Halder S., Rea M., Andreoni R., Nijboer F., Hammer E.M., Kleih S.C., Birbaumer N., Kubler A. An auditory oddball brain-computer interface for binary choices. *Clin Neurophysiol* 2010; 121(4): 516-23.
- [50] Klobassa D.S., Vaughan T.M., Brunner P., Schwartz N.E., Wolpaw J.R., Neuper C., Sellers E.W. Toward a high-throughput auditory P300-based brain-computer interface. *Clin Neurophysiol* 2009; 120(7): 1252-61.
- [51] Furdea A., Halder S., Krusienski D.J., Bross D., Nijboer F., Birbaumer N., Kubler A. An auditory oddball (P300) spelling system for brain-computer interfaces. *Psychophysiology* 2009; 46(3): 617-25.
- [52] Kubler A., Furdea A., Halder S., Hammer E.M., Nijboer F., Kotchoubey B. A brain-computer interface controlled auditory event-related potential (p300) spelling system for locked-in patients. *Ann N Y Acad Sci* 2009; 1157: 90-100.

- [53] Kanoh S., Miyamoto K., Yoshinobu T. A brain-computer interface (BCI) system based on auditory stream segregation. *Conf Proc IEEE Eng Med Biol Soc* 2008; 2008: 642-5.
- [54] Brouwer A.M., van Erp, J. B. A tactile p300 brain-computer interface. *Front Neurosci* 2010; 4: 19.
- [55] Babiloni C., Carducci F., Cincotti F., Rossini P.M., Neuper C., Pfurtscheller G., Babiloni F. Human movement-related potentials vs desynchronization of EEG alpha rhythm: a high-resolution EEG study. *Neuroimage* 1999; 10(6): 658-65.
- [56] Wolpaw J.R., McFarland D.J., Neat G.W., Forneris C.A. An EEG-based brain-computer interface for cursor control. *Electroencephalogr Clin Neurophysiol* 1991; 78(3): 252-9.
- [57] Wolpaw J.R., Birbaumer N., McFarland D.J., Pfurtscheller G., Vaughan T.M. Brain-computer interfaces for communication and control. *Clin Neurophysiol* 2002; 113(6): 767-91.
- [58] Niedermeyer E., Goldszmidt A., Ryan D. "Mu rhythm status" and clinical correlates. *Clin EEG Neurosci* 2004; 35(2): 84-7.
- [59] Chatrian G.E., Petersen M.C., Lazarte J.A. The blocking of the rolandic wicket rhythm and some central changes related to movement. *Electroencephalogr Clin Neurophysiol* 1959; 11(3): 497-510.
- [60] Pfurtscheller G., Lopes da Silva, F. H. Event-related EEG/MEG synchronization and desynchronization: basic principles. *Clin Neurophysiol* 1999; 110(11): 1842-57.
- [61] Pfurtscheller G., Aranibar A. Evaluation of event-related desynchronization (ERD) preceding and following voluntary self-paced movement. *Electroencephalogr Clin Neurophysiol* 1979; 46(2): 138-46.
- [62] Pfurtscheller G., Neuper C., Flotzinger D., Pregezer M. EEG-based discrimination between imagination of right and left hand movement. *Electroencephalogr Clin Neurophysiol* 1997; 103(6): 642-51.
- [63] Jeannerod M. Neural simulation of action: a unifying mechanism for motor cognition. *Neuroimage* 2001; 14(1 Pt 2): S103-9.
- [64] Neuper C., Scherer R., Reiner M., Pfurtscheller G. Imagery of motor actions: differential effects of kinesthetic and visual-motor mode of imagery in single-trial EEG. *Brain Res Cogn Brain Res* 2005; 25(3): 668-77.
- [65] Neuper C., Muller-Putz G.R., Scherer R., Pfurtscheller G. Motor imagery and EEG-based control of spelling devices and neuroprostheses. *Prog Brain Res* 2006; 159: 393-409.
- [66] Guger C., Edlinger G., Harkam W., Niedermayer I., Pfurtscheller G. How many people are able to operate an EEG-based brain-computer interface (BCI)? *Neural Systems and Rehabilitation Engineering, IEEE Transactions on* 2003; 11(2): 145-147.
- [67] Kotchoubey B., Lang S., Winter S., Birbaumer N. Cognitive processing in completely paralyzed patients with amyotrophic lateral sclerosis. *Eur J Neurol* 2003; 10(5): 551-8.
- [68] Buch E., Weber C., Cohen L.G., Braun C., Dimyan M.A., Ard T., Mellinger J., Caria A., Soekadar S., Fourkas A., Birbaumer N. Think to move: a neuromagnetic brain-computer interface (BCI) system for chronic stroke. *Stroke* 2008; 39(3): 910-7.

- [69] Millan Jdel, R., Mourino J. Asynchronous BCI and local neural classifiers: an overview of the Adaptive Brain Interface project. *IEEE Trans Neural Syst Rehabil Eng* 2003; 11(2): 159-61.
- [70] Scherer R., Muller G.R., Neuper C., Graimann B., Pfurtscheller G. An asynchronously controlled EEG-based virtual keyboard: improvement of the spelling rate. *IEEE Trans Biomed Eng* 2004; 51(6): 979-84.
- [71] Neuper C., Muller G.R., Kubler A., Birbaumer N., Pfurtscheller G. Clinical application of an EEG-based brain-computer interface: a case study in a patient with severe motor impairment. *Clin Neurophysiol* 2003; 114(3): 399-409.
- [72] Perelmouter J., Birbaumer N. A binary spelling interface with random errors. *IEEE Trans Rehabil Eng* 2000; 8(2): 227-32.
- [73] Wijnen V.J.M., Heutink M., Boxtel G.J.M.v., Eilander H.J., Gelder B.d. Autonomic reactivity to sensory stimulation is related to consciousness level after severe traumatic brain injury. *Clinical Neurophysiology* 2006; 117(8): 1794-1807.
- [74] Pfurtscheller G., Brunner C., Schlogl A., Lopes da Silva, F. H. Mu rhythm (de)synchronization and EEG single-trial classification of different motor imagery tasks. *Neuroimage* 2006; 31(1): 153-9.
- [75] Klimesch W. EEG alpha and theta oscillations reflect cognitive and memory performance: a review and analysis. *Brain Res Brain Res Rev* 1999; 29(2-3): 169-95.
- [76] Wolpaw J.R., McFarland D.J., Vaughan T.M. Brain-computer interface research at the Wadsworth Center. *IEEE Trans Rehabil Eng* 2000; 8(2): 222-6.
- [77] Blankertz B., Tomioka R., Lemm S., Kawanabe M., Muller K. Optimizing spatial filters for robust EEG single-trial analysis. *IEEE Signal Processing Magazine* 2008; 25(1): 41.
- [78] Gjerstad A.C., Wagner K., Henrichsen T., Storm H. Skin Conductance Versus the Modified COMFORT Sedation Score as a Measure of Discomfort in Artificially Ventilated Children. *Pediatrics* 2008; 122(4): e848-853.
- [79] Bekinschtein T.A., Coleman M.R., Niklison J., Pickard J.D., Manes F.F. Can electromyography objectively detect voluntary movement in Disorders of Consciousness? *Journal of Neurology, Neurosurgery & Psychiatry* 2007; 79: 826-828.
- [80] Goldfine A.M., Victor J.D., Conte M.M., Bardin J.C., Schiff N.D. Determination of awareness in patients with severe brain injury using EEG power spectral analysis. *Clin Neurophysiol* 2011.
- [81] Cruse D., Chennu S., Chatelle C., Bekinschtein T.A., Fernandez-Espejo D., Pickard J.D., Laureys S., Owen A.M. Bedside detection of awareness in the vegetative state: a cohort study. *Lancet* 2011.
- [82] Cruse D., Chennu S., Chatelle C., Fernández-Espejo D., Bekinschtein T.A., Pickard J.D., Laureys S., Owen A.M. Relationship between etiology and covert cognition in the minimally conscious state. *Neurology* 2012; 78(11): 816-822.
- [83] Cincotti F., Kauhanen L., Aloise F., Palomaki T., Caporusso N., Jylanki P., Mattia D., Babiloni F., Vanacker G., Nuttin M., Marciani M.G., Del R.M.J. Vibrotactile feedback for brain-computer interface operation. *Computational Intelligence and Neuroscience* 2007; 2007: 48937.

- [84] Sakurai Y., Momose T., Iwata M., Sasaki Y., Kanazawa I. Activation of prefrontal and posterior superior temporal areas in visual calculation. *J Neurol Sci* 1996; 139(1): 89-94.
- [85] Dehaene S. *The Number Sense: How the Mind Creates Mathematics* Oxford, UK: Oxford University Press; 1997.
- [86] Rappelsberger P., Petsche H. Probability mapping: power and coherence analyses of cognitive processes. *Brain Topogr* 1988; 1(1): 46-54.
- [87] Curran E.A., Stokes M.J. Learning to control brain activity: a review of the production and control of EEG components for driving brain-computer interface (BCI) systems. *Brain Cogn* 2003; 51(3): 326-36.
- [88] Vialatte F.B., Maurice M., Dauwels J., Cichocki A. Steady-state visually evoked potentials: focus on essential paradigms and future perspectives. *Prog Neurobiol* 2010; 90(4): 418-38.
- [89] Regan D. *Human Brain Electrophysiology: Evoked Potentials and Evoked Magnetic Fields in Science and Medicine* New York: Elsevier; 1989.
- [90] Herrman C.S. Human EEG responses to 1-100 Hz flicker: resonance phenomena in visual cortex and their potential correlation to cognitive phenomena. *Experimental Brain Research* 2001; 137: 346-53.
- [91] Perlstein W.M., Cole M.A., Larson M., Kelly K., Seignourel P., Keil A. Steady-state visual evoked potentials reveal frontally-mediated working memory activity in humans. *Neurosci Lett* 2003; 342(3): 191-5.
- [92] Regan D. Some characteristics of average steady-state and transient responses evoked by modulated light. *Electroencephalogr Clin Neurophysiol* 1966; 20(3): 238-48.
- [93] Gray M., Kemp A.H., Silberstein R.B., Nathan P.J. Cortical neurophysiology of anticipatory anxiety: an investigation utilizing steady state probe topography (SSPT). *Neuroimage* 2003; 20(2): 975-86.
- [94] Wang Y., Wang R., Gao X., Hong B., Gao S. A practical VEP-based brain-computer interface. *IEEE Trans Neural Syst Rehabil Eng* 2006; 14(2): 234-9.
- [95] Middendorf M., McMillan G., Calhoun G., Jones K.S. Brain-computer interfaces based on the steady-state visual-evoked response. *IEEE Trans Rehabil Eng* 2000; 8(2): 211-4.
- [96] Muller-Putz G.R., Scherer R., Brauneis C., Pfurtscheller G. Steady-state visual evoked potential (SSVEP)-based communication: impact of harmonic frequency components. *J Neural Eng* 2005; 2(4): 123-30.
- [97] Parini S., Maggi L., Turconi A.C., Andreoni G. A robust and self-paced BCI system based on a four class SSVEP paradigm: algorithms and protocols for a high-transfer-rate direct brain communication. *Computational Intelligence and Neuroscience* 2009; 2009: 864564.
- [98] Kelly S.P., Lalor E.C., Reilly R.B., Foxe J.J. Visual spatial attention tracking using high-density SSVEP data for independent brain-computer communication. *IEEE Trans Neural Syst Rehabil Eng* 2005; 13(2): 172-8.
- [99] Allison B.Z., McFarland D.J., Schalk G., Zheng S.D., Jackson M.M., Wolpaw J.R. Towards an independent brain-computer interface using steady state visual evoked potentials. *Clin Neurophysiol* 2008; 119(2): 399-408.
- [100] Zhang D., Maye A., Gao X., Hong B., Engel A.K., Gao S. An independent brain-computer interface using covert non-spatial visual selective attention. *J Neural Eng* 2010; 7(1): 16010.

- [101] Müller G.R., Neuper C., Pfurtscheller G. "Resonance-like" Frequencies of Sensorimotor Areas Evoked by Repetitive Tactile Stimulation. *Biomedical Engineering* 2001; 46(7-8): 186-190.
- [102] Snyder A.Z. Steady-state vibration evoked potentials: descriptions of technique and characterization of responses. *Electroencephalogr Clin Neurophysiol* 1992; 84(3): 257-68.
- [103] Tobimatsu S., Zhang Y.M., Kato M. Steady-state vibration somatosensory evoked potentials: physiological characteristics and tuning function. *Clin Neurophysiol* 1999; 110(11): 1953-8.
- [104] Tobimatsu S., Zhang Y.M., Suga R., Kato M. Differential temporal coding of the vibratory sense in the hand and foot in man. *Clin Neurophysiol* 2000; 111(3): 398-404.
- [105] Giabbiconi C.M., Dancer C., Zopf R., Gruber T., Muller M.M. Selective spatial attention to left or right hand flutter sensation modulates the steady-state somatosensory evoked potential. *Brain Res Cogn Brain Res* 2004; 20(1): 58-66.
- [106] Muller-Putz G.R., Scherer R., Neuper C., Pfurtscheller G. Steady-state somatosensory evoked potentials: suitable brain signals for brain-computer interfaces? *IEEE Trans Neural Syst Rehabil Eng* 2006; 14(1): 30-7.
- [107] Zhang D., Wang Y., Maye A., Engel A.K., Gao X., Hong B., Gao S., editors *A Brain-Computer Interface Based on Multi-Modal Attention*. *Neural Engineering, 2007. CNE '07. 3rd International IEEE/EMBS Conference on;* 2007; 414 -417 p.
- [108] Ross B., Borgmann C., Draganova R., Roberts L.E., Pantev C. A high-precision magnetoencephalographic study of human auditory steady-state responses to amplitude-modulated tones. *J Acoust Soc Am* 2000; 108(2): 679-91.
- [109] Ross B., Picton T.W., Herdman A.T., Pantev C. The effect of attention on the auditory steady-state response. *Neurol Clin Neurophysiol* 2004; 2004: 22.
- [110] Pastor M.A., Artieda J., Arbizu J., Marti-Climent J.M., Penuelas I., Masdeu J.C. Activation of human cerebral and cerebellar cortex by auditory stimulation at 40 Hz. *J Neurosci* 2002; 22(23): 10501-6.
- [111] Picton T.W., John M.S., Dimitrijevic A., Purcell D. Human auditory steady-state responses. *Int J Audiol* 2003; 42(4): 177-219.
- [112] Giacino J. The vegetative and minimally conscious states: consensus-based criteria for establishing diagnosis and prognosis. *Neuro Rehabilitation* 2004; 19(4): 293 - 298.
- [113] Birbaumer N. Slow cortical potentials: their origin, meaning, and clinical use. in: van Boxtel GJM, B. KBE, editors. *Brain and behavior past, present, and future*. Tilburg: Tilburg University Press; 1997. p. 25-39.
- [114] Elbert T., Rockstroh B., Lutzenberger W., Birbaumer N. Biofeedback of slow cortical potentials. I. *Electroencephalogr Clin Neurophysiol* 1980; 48(3): 293-301.
- [115] Birbaumer N., Kubler A., Ghanayim N., Hinterberger T., Perelmouter J., Kaiser J., Iversen I., Kotchoubey B., Neumann N., Flor H. The thought translation device (TTD) for completely paralyzed patients. *IEEE Trans Rehabil Eng* 2000; 8(2): 190-3.
- [116] Pham M., Hinterberger T., Neumann N., Kubler A., Hofmayer N., Grether A., Wilhelm B., Vatine J.J., Birbaumer N. An auditory brain-computer interface

based on the self-regulation of slow cortical potentials. *Neurorehabil Neural Repair* 2005; 19(3): 206-18.

- [117] Cruse D., Chennu S., Chatelle C., Bekinschtein T., Fernández-Espejo D., Junqué C., Pickard J., Laureys S., and Owen A. Bedside detection of awareness in the vegetative state. *The Lancet* in Press.
- [118] Hill N.J., Lal T.N., Schroder M., Hinterberger T., Wilhelm B., Nijboer F., Mochty U., Widman G., Elger C., Scholkopf B., Kubler A., Birbaumer N. Classifying EEG and ECoG signals without subject training for fast BCI implementation: comparison of nonparalyzed and completely paralyzed subjects. *IEEE Trans Neural Syst Rehabil Eng* 2006; 14(2): 183-6.
- [119] Kübler A., Mushahwar V.K., Hochberg L.R., Donoghue J.P. BCI Meeting 2005-workshop on clinical issues and applications. *IEEE Trans Neural Syst Rehabil Eng* 2006; 14(2): 131-4.
- [120] Demertzi A., Schnakers C., Ledoux D., Chatelle C., Bruno M.A., Vanhaudenhuyse A., Boly M., Moonen G., Laureys S. Different beliefs about pain perception in the vegetative and minimally conscious states: a European survey of medical and paramedical professionals. *Prog Brain Res* 2009; 177: 329-38.