TOPICAL REVIEW

Neuropsychological and neurophysiological aspects of brain-computer-interface (BCI) control in paralysis

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Ujwal Chaudhary graduated with PhD in Biomedical Engineering from Florida International University, Miami, Florida, in 2013. He was awarded the best doctoral student award at the end of his doctoral study. After his graduation he commenced his postdoctoral research under the supervision of Professor Birbaumer and later he formed his own group under the supervision of Professor Birbaumer and developed functional near infrared spectroscopy (fNIRS) and electroencephalogram (EEG)-based BCIs for communication in locked-in state (LIS) and CLIS patients. Over the last 6 years he has worked with several LIS and CLIS patients. Niels Birbaumer is a co-director of the Institute of Medical Psychology at the University of Tübingen, Germany. He has published several hundred scientific papers and 11 books, among them the bestselling Your Brain Knows More than You Think. He pioneered research on physiological self-control and regulation in epilepsy and other neurological and psychiatric disorders. He and his team developed and tested several brain computer interface systems for rehabilitation of paralysed patients, particular those with chronic stroke, and to re-establish communication in completely locked-in patients suffering from amyotrophic lateral sclerosis. Apart from clinical neurophysiological research, he has developed a theory on slow cortical brain potentials.
Abstract  Brain-computer interfaces (BCIs) aim to help paralysed patients to interact with their environment by controlling external devices using brain activity, thereby bypassing the dysfunctional motor system. Some neuronal disorders, such as amyotrophic lateral sclerosis (ALS), severely impair the communication capacity of patients. Several invasive and non-invasive brain-computer interfaces (BCIs), most notably using electroencephalography (EEG), have been developed to provide a means of communication to paralysed patients. However, except for a few reports, all available BCI literature for the paralysed (mostly ALS patients) describes patients with intact eye movement control, i.e. patients in a locked-in state (LIS) but not a completely locked-in state (CLIS). In this article we will discuss: (1) the fundamental neuropsychological learning factors and neurophysiological factors determining BCI performance in clinical applications; (2) the difference between LIS and CLIS; (3) recent development in BCIs for communication with patients in the completely locked-in state; (4) the effect of BCI-based communication on emotional well-being and quality of life; and (5) the outlook and the methodology needed to provide a means of communication for patients who have none. Thus, we present an overview of available studies and recent results and try to anticipate future developments which may open new doors for BCI communication with the completely paralysed.

Brain-computer interface (BCI)

Brain-computer interfaces (BCI) use brain activity to circumvent the (paralysed) motor system to control computers (case I) or external devices (case II), mostly prosthetic devices.

Case I, computer controlled by brain activity, is particularly relevant for the maintenance or restoration of communication in patients with more or less complete paralysis, such as advanced amyotrophic lateral sclerosis (ALS) (Chaudhary & Birbaumer, 2015; Chaudhary et al. 2015, 2016a,b). Case II using prosthetics or other external devices is reserved for partial paralysis, such as severe stroke or spinal cord injury. Regardless of the application, the signals extracted from the ongoing brain activity may be obtained using either invasive or non-invasive techniques (Chaudhary et al. 2016a; Coscia et al. 2019).

Invasive BCIs use spiking of single or multiple neuronal units (single-unit activity, SUA; multiple-unit activity, MUA) and local field potentials (LFP) (Chaudhary et al. 2016a; Coscia et al. 2019) and are typically reserved for the most severe and otherwise unresponsive patient groups, due to the associated risks. Most published reports of invasive BCI use in human patients employ the ‘Utah’ device (now available through Blackrock Inc.) (Hochberg et al. 2006, 2012; Chadb.wick et al. 2011; Simeral et al. 2011; Bansal et al. 2012; Gilja et al. 2012, 2015; Collinger et al. 2013; Bacher et al. 2015; Jarosiewicz et al. 2015; Pandarinath et al. 2017; Milekovic et al. 2018). The remaining invasive applications in patients include electrocorticographic (ECoG) arrays implanted epi- or subdurally in tetraplegic patients (Leuthardt et al. 2004; Schalk et al. 2008; Moran, 2010; Brunner et al. 2011; Wang et al. 2013, Vansteensel et al. 2016) and in epileptic patients (Schevon et al. 2008, 2009, 2012; Kramer et al. 2011; Dykstra et al. 2012; Weiss et al. 2013, 2015).

Non-invasive BCIs focus on different parameters of the EEG: oscillatory frequency components or evoked brain potentials such as the P300 or the steady-state visually evoked potential (SSVEP) (Birbaumer et al. 1999; Cipresso et al. 2012; Farwell & Donchin, 1988; Kübler et al. 2001, 2005; Nijboer et al. 2008; Halder et al. 2010; Sellers et al. 2010, 2015; McCane et al. 2015; Wolpaw et al. 2002, 2018; Wolpaw & McFarland, 2004, Okahara et al. 2018). A minority of applications favour functional near-infrared spectroscopy (fNIRS), measuring mainly oxygen saturation of large superficial cerebral arteries (Naito et al. 2007; Gallegos-Ayala et al. 2014; Chaudhary et al. 2017). The majority of information on non-invasive BCIs has been collected in healthy young persons; the generalization of these results to severe neurological diseases is questionable, and therefore we exclude publications with healthy participants from this review article.

The field of BCI is relatively new and the research focus has largely been on improving the quality of the extracted signals.
signals by reducing the signal-to-noise ratio through improved technology or development of advanced algorithms. Relatively few studies have explored the underlying neurophysiological correlates of the brain signal features used for BCI control. An important limitation is that there is a lack of biomarkers that assess disease progression (Kiernan et al. 2011; Nowicka et al. 2019).

An understanding of the underlying neurophysiology becomes particularly important when considering the application of BCI technology to patient populations as they progress through a disease (such as in ALS) or recover from an insult (such as in stroke). The importance of adaptive algorithms that incorporate the state of the user has recently received increased attention, with efforts being made to understand the effects of plasticity induction on the extracted brain signals.

In the current review we focus on the application of BCIs for communication in ALS patients. We will initially present the fundamental neuropsychological learning factors and neurophysiological factors determining BCI performance in clinical applications – these factors seem not to be different for invasive and non-invasive approaches, and we thus discuss them together. We will then describe the recent developments in BCIs for communication in CLIS patients, along with the limitations and challenges facing such developments. Following that, we will describe the effect of BCI use on the quality of life of an individual without any means of communication. Finally, we will conclude looking at the developments needed to provide a means of communication to patients who have none.

**Physiological self-regulation and learning**

To achieve BCI-based communication and rehabilitation in the clinical environment, the patient has to learn to produce – contingent upon an external command, i.e. a question or upon internal intention and decision – a particular brain response which is followed by an external feedback and reward (Birbaumer et al. 2013; Sitaram et al. 2017). Brain responses (whether metabolic blood oxygenation level-dependent (BOLD) in fMRI or oxygenation in NIRS or neuroelectric such as EEG, evoked brain potentials, cellular firing and synaptic activity) are not perceived consciously and the learning of voluntary control is comparable to motor skills where most elements and components are learned implicitly and do not require conscious experience or conscious memory access for their operant-instrumental control. Implicit learning and memory of skilled responses such as brain signals involve the cortico-thalamic-basal ganglia loop responsible for the regulation of cortical preparation and excitation of motor or cognitive responses (“thinking”) (Birbaumer et al. 1990). The reward and feedback endpoint node of that loop involves the anterior and dorsal striatum receiving dopaminergic input from the positive reinforcement areas: blockade of this part of the loop with NMDA receptor inhibitors interrupts and destroys learning of a brain self-regulation skill such as learning to differentially activate two adjacent cortical cells (Koralek et al. 2013). In human epileptic patients, we have shown that patients capable of learning self-regulation of slow cortical potential (SCP) (“brain athletes”), in comparison to patients who do not acquire this brain regulation skill, activate the anterior striatum and adjacent basal ganglia structures confirming the animal data (Hinterberger et al. 2005). During the first phases of BCI-neurofeedback, prefrontal executive structures guiding working memory, particularly the dorsolateral PFC and the medial prefrontal and orbitofrontal regions for conscious anticipation and storage of the memory content, need to be involved, while in a later post-consolidation phase these structures may not be critical and the cortical-subcortical dopaminergic striatal loop may suffice.

In the sections below, we first describe the difference between LIS and CLIS and the neurophysiological parameters used in the study of these conditions because the experimental procedures and methods of analysis of BCI-control differ according to specific brain signatures, i.e. self-control of and communication with the P300-component of the evoked brain potential are not comparable with control and communication using oscillatory EEG activity. We also discuss the limitations of BCIs for communication in CLIS, as well as the technical challenges.

**BCIs for communication: differentiating between LIS and CLIS in ALS**

BCI results seem to differ sharply between patients in the locked-in state (complete paralysis with intact voluntary eye-movements) and patients in complete locked-in states (CLIS, all motor control lost). Thus, before discussing this unresolved problem we have to define or at least circumscribe the differences between these two states, which are currently not clearly separated from each other.

There is no accepted quantitative and reliable method available to discriminate CLIS from LIS. The widely cited and used description of Bauer et al. (1979) is based on clinical–observational criteria with doubtful reliability: presence of voluntary eye-movements or any other somatic-motor muscle under voluntary control separates LIS from CLIS. No specific measurement strategy to confirm the clinical diagnostic procedure is proposed. In ALS, even in the fast progressing forms of the disease, the transition from LIS into CLIS is gradual and time periods alternating motor control with loss of control and short periods of spontaneous recovery are the rule (Kiernan et al. 2011). Extensive repeated testing measuring eye movements with electrooculography (EOG) is necessary
to indicate permanent CLIS. The time course of this transition process is patient and disease specific and no general valid rule exists (Kiernan et al. 2011; Nowicka et al. 2019). In theory, voluntary muscles other than those used in eye movements could be used for EMG (electromyography)-based communication attempts. In particular, facial muscles outside the eyeballs remain under voluntary control in some rare cases even after loss of eye-muscle control. Thus, in addition to eye-movements, measurement of surface-EMG from several face muscles and the external sphincter (also sometimes preserved) may be required to define the existing state of paralysis. EOG recordings during BCI performance requesting motor control to simple questions should be available for an extended time period or during the course of non-invasive BCI attempts. External sphincter control measurement can be excluded if the patient is permanently incontinent. Spontaneous recovery of eye control needs to be documented with continuous EOG recordings while the patient tries to answer repetitive questions with ‘yes’ and ‘no’ eye movements. In addition, absence of communication with the caretakers needs to be documented. Particular family members often insist that they perceive some voluntary response of eyes and face muscles to auditorily presented questions, even after negative EOG recording results, and this information should be taken seriously, since collaterals from surviving motor axons have been shown to reinnervate denervated muscle fibres. Even if CLIS is diagnosed after all the above documentation, it is still possible that at some point in the future, more sensitive measurements of somatic-motor control may reveal some form of volitional control, which would render the diagnostic statement of CLIS obsolete.

BCIs for communication

The vast majority of published reports of clinical BCI applications for communication in paralysis concern patients who have ALS at different stages of disease progression (for review see Chaudhary et al. 2016a). In a single case study of a locked-in state (LIS) patient with pontine stroke, the patient learned to use a non-invasive EEG-BCI (Sellers et al. 2015), and in several cases using invasive BCIs in the Brain Gate trial employing the Blackrock microelectrode system (Hochberg et al. 2006, 2012; Jarosiewicz et al. 2015; Pandarinath et al. 2017) and an electrocorticogram (ECoG)-based BCI (Vansteensel et al. 2016), BCI communication in LIS patients was demonstrated with positive results. However, none of the patients in those reports were in the complete locked-in state (CLIS), i.e. they still had control over some muscles of the body, with some means of communication left, and most of them were using commercially available eye-trackers. BCIs based on microelectrodes implanted in the motor cortex of patients in LIS and pre-LIS states allowed rapid voluntary selection of visually presented letters from a speller-type computer program comparable to eye-tracking spelling. However, as recently as 2008, Kübler & Birbaumer (2008), in a review of the BCI literature for CLIS patients with ALS, concluded in summary that no successful BCI-based communication of any type, neither invasive nor non-invasive, was possible. This statement remained unchanged and valid until 2014 when Ayala (Gallegos-Ayala et al. 2014) reported an average of 70% correct ‘yes-no’ answers to questions in one ALS patient in CLIS. The patient could communicate successfully for more than one year employing a NIRS-based BCI system. However, with the NIRS-based BCI system, voluntary selection of letters or words from a speller was not possible because of the high error rate of the classifier and the slow nature of the NIRS signal. A paper by a Japanese group in 2018 reported a single case of a CLIS patient using an SSVEP (steady-state visual evoked potential) BCI, where the patient was able to control the amplitude of the VEP for a short period (Okahara et al. 2018). However, again, while ‘yes-no’ responses to simple questions with BCIs were demonstrated, the voluntary spelling of words was not possible. The schematic layout of a typical auditory non-invasive BCI for communication in CLIS is shown in Fig. 1.

Several explanations for the inability of CLIS patients to voluntarily select letters and words employing BCI technology have been suggested, including the patient’s physiological limitations and technological limitations. These are interrelated and thus require both a better understanding of the physiological consequences as the disease progresses and more advanced technology, as outlined in the following paragraphs.

Non-invasive measures such as EEG or NIRS are too noisy – they represent activity from broad and functionally overlapping brain regions, and patients in CLIS do not possess the necessary analytical skills within the acoustic attentional system to select auditorily presented letters or words using a neurophysiological signal with bad signal-to-noise ratio. Auditory presentation is paramount for CLIS patients because of compromised vision due to the drying of the eyeballs along with subsequent necrosis of the cornea. Thus, although visual presentation of the BCI task, as realized in most BCI studies with non-CLIS patients, results in superior physiological control of the BCI compared to auditory presentation, visual tasks cannot be implemented in CLIS patients. Whether invasive BCIs implementing auditory cues may allow voluntary selection of letters or words in CLIS is unknown. Cellular activity recorded from microelectrodes in the motor and sensorimotor cortex, such as spikes or local field potentials (LFP), possess a high degree of specificity. Within a particular sensory or motor cortical map, the probability of overlapping noise seems to be much lower than for the more global measures such as
EEG or ECoG. Thus, invasive BCIs using microelectrode recordings like those successfully used in LIS patients (Hochberg et al. 2006, 2012; Milekovic et al. 2018) may allow voluntary communication in CLIS patients using auditory cues. Such a case awaits confirmation and will determine whether free voluntary spelling, in addition to ‘yes-no’ communication, is possible in CLIS using a BCI. Experiments to confirm this possibility are underway in our laboratory.

Even when auditory cues are used, there remains the problem of implementation of the machine learning algorithm. Algorithms such as the support vector machine (SVM) model used in BCI communication require extensive training with stimulus material such as auditory presentation of many questions with known answers or copy spelling of words. This may create boredom, habituation, and consequent lack of attention in the CLIS patient. These attentional problems result in frequent episodes of sleep and lack of vigilance during BCI attempts (Malekshahi et al. 2019). Despite healthy sleep and a normal circadian rhythm (Malekshahi et al. 2019) during the night, frequent episodes of sleep occur during the day in CLIS patients. In any design of a BCI for communication, such patterns need to be recognized by the patient, and the system should be able to detect and adjust to these patterns.

**Figure 1. Schematic layout of the auditory non-invasive brain-computer interface (BCI) for communication by completely locked-in state (CLIS) patients.**

The patient’s EEG, EOG and NIRS are recorded and preprocessed (filtered), and features for each measure differentiating a ‘yes’ from a ‘no’ answer are extracted (left). A machine learning algorithm (for example, support vector machine (SVM) or linear discriminant analysis (LDA)) is employed to train the classifier to explicate the most significant separation of ‘yes’ and ‘no’ answers after several training trials. During subsequent ‘feedback’ trials, the patient receives feedback on the predicted answer. Letter selection from an auditory speller is only provided if a stable, correct ‘yes’ and ‘no’ answer classification with more than 70% accuracy is achieved.
the algorithm otherwise these sleep episodes will prohibit communication.

A more general explanation of what hinders all communication attempts, but mainly voluntary spelling of letter sequences, in CLIS has been described by Birbaumer in several papers (Birbaumer, 2006; Kübler & Birbaumer, 2008; Chaudhary et al. 2016a). Extinction of semantic learning and thinking may occur in the course of development and maintenance of CLIS because of the lack of social reinforcing contingencies to all voluntary responses in CLIS. Caretakers cannot perceive any thought (‘I want . . .’) of the patient because of the total paralysis and therefore the schedules of reinforcement become random and consequently lead to extinction (Kübler & Birbaumer, 2008). Ardali et al. (2019) reported that the semantic content of sentences presented to a CLIS patient could affect BCI performance. Semantic concepts are mostly associated with executive words, which may be prone to extinction due to non-use of motor response networks, and thus communication attempts are extinguished. Extensive lack of muscular activity can cause language attrition in the cortical areas for language and the motor cortex, due to complete immobility in CLIS patients (Ardali et al. 2019).

The failure to replicate instrumental learning of visceral responses in the curarized completely paralysed rat (Dworkin & Miller, 1986) may also indicate such a general extinction phenomenon. CLIS, in which the patient is completely paralysed and artificially respiration fed over extended periods in some instances, can be considered analogous to the curarized state, and lack of learning or re-learning of BCI performance of any voluntary act may be the consequence. A single case of a CLIS patient selecting letters and building word sequences with a BCI will disprove this speculation. However, extinction of operant responses such as speech and language in communication is not an all-or-none phenomenon and often occurs slowly: the early periods of CLIS may thus allow some residual voluntary communication with brain activity and patients with long-lasting chronic CLIS over months and years need to be investigated.

**Effects of emotional factors and quality of life**

All available epidemiological and empirical studies investigating quality of life and depression in ALS have found a sufficient, even good, quality of life (Lulé et al. 2009, 2013) and positive mood and emotional processing at all stages of the disease. Even in LIS (Linse et al. 2017) when only assisted communication via computer menus with eye movements is possible. Before entering the LIS state, communication with more reliable muscle responses such as finger twitches and eye movements is still possible. Quality of life is, of course, negative during a limited period after diagnosis of the fatal disease and around the period when respiratory symptoms occur and the decision to artificially ventilate is made. The observation of standard sleep patterns in CLIS (Malekshahi et al. 2019) supports the positive results from these psychological studies since depression and healthy sleep patterns are incompatible. In order to accept artificial ventilation and to maintain a positive mood state, a functioning family environment with a willingness to accept patient care seems to be a prerequisite: All CLIS patients investigated so far, and most surviving LIS patients with ALS are in such a supportive family environment. Age, gender, cognitive abilities, etc., have not been systematically investigated as factors influencing BCI performance and do not seem to play a significant role, as no systematic differentiation is thus far visible in the published BCI literature.

Cognitive decline (partly attributed to frontotemporal dementia) cannot be measured in CLIS as long as BCI systems are not able to reliably allow at least ‘yes-no’ responses to challenging cognitive questions. For patients in LIS or pre-LIS stages no studies have reported severe cognitive deficits. It is clear, however, that, except in the Wolpaw et al. (2018) paper, the patients selected for BCI experiments constitute a positive selection, thus introducing a positive bias, since cognitively compromised patients were one of the exclusion criteria. This question can only be answered in future studies when long-term CLIS patients are recruited for BCI use in clinical trials. As a caveat, we emphasize that, except for one report (Wolpaw et al. 2018) of EEG-based BCIs in ALS patients, no controlled clinical group trial exists; all clinical applications rely on collections of single cases, prohibiting any quantitative statistical conclusion and generalization. However, even in the absence of statistical group data, some crucial points, albeit preliminary, can be derived.

**Conclusion and future directions**

Despite an exponential increase of BCI-related publications and significant financial investment efforts (i.e. Neurolink) during the last 20 years, the clinical and economic success of BCI applications is still pending. Research has mostly been technical and methodological, and there are few reported clinical-neurological and psychological studies despite communication with the paralysed and movement restoration in motor disabilities being among the most daunting medical problems. A review of the literature showed that patients in CLIS who depend on a functioning BCI for communication achieved up to 70% correct ‘yes’ and ‘no’ answers with a non-invasive NIRS-based BCI system but did not succeed in voluntary spelling of words. However, this summary is based on a few single cases and awaits replication with larger samples. This sobering conclusion applies
also to the invasive approaches; while all published reports demonstrate relatively fast spelling using microphone-electrode arrays or implanted ECoG-BCIs, none of them has shown this for patients in CLIS. However, there is no reason to assume that at least in the early stages of CLIS, invasive approaches that have shown the most promising results in LIS should not also allow flexible spelling with cellular activity in CLIS patients. Whether, as speculated, the extinction of contingency dependent thinking and intention in CLIS may impede BCI performance is an empirical question that cannot be answered based on present fragmentary knowledge. Further research into this question is thus necessary. Invasive approaches, however, must become economically viable, and long-term implants, i.e. present for several years, need to demonstrate safety, with no adverse events, related to implant, during and after implantation and explantation, particularly in CLIS patients.

While the non-invasive devices allow home use, they still require supervision by highly competent research personal. Home use of invasive BCIs is not yet feasible but should become a priority for research and commercialization. With invasive BCIs voluntary spelling is possible at a higher speed than with the non-invasive devices because of their excellent signal-to-noise ratio, particularly for spike recordings and LFPs. Until that can be achieved, non-invasive devices are the method of choice, and their simplification and automatization for home use with severely paralysed people and CLIS patients needs to accelerate, and public funding and health-promoting organizations should focus on controlled clinical trials of non-invasive wireless BCIs for home use. This is particularly important because of their low health risks and low cost. Non-invasive BCIs remain the method of choice for CLIS patients, since many of these patients are at an advanced age and in a state of fragile health. Thus, the development and application of (1) invasive BCI systems that enable free voluntary communication for CLIS patients and (2) home-based non-invasive BCI systems are two important issues for current state-of-the-art BCI research and neurotechnology.

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**Additional information**

**Competing interests**

Authors declare no competing interests.

**Author contributions**

U.C.: conceptualization, writing, literature search, figures; N.M.-K.: writing; N.B.: initiation, conceptualization, writing. All authors have approved the final version of the manuscript and agree to be accountable for all aspects of the work. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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