Brain–computer interface in paralysis

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Purpose of review

Communication with patients suffering from locked-in syndrome and other forms of paralysis is an unsolved challenge. Movement restoration for patients with chronic stroke or other brain damage also remains a therapeutic problem and available treatments do not offer significant improvements. This review considers recent research in brain–computer interfaces (BCIs) as promising solutions to these challenges.

Recent findings

Experimentation with nonhuman primates suggests that intentional goal directed movements of the upper limbs can be reconstructed and transmitted to external manipulandum or robotic devices controlled from a relatively small number of microelectrodes implanted into movement-relevant brain areas after some training, opening the door for the development of BCI or brain–machine interfaces in humans. Although noninvasive BCIs using electroencephalographic recordings or event-related-brain-potentials in healthy individuals and patients with amyotrophic lateral sclerosis or stroke can transmit up to 80 bits/min of information, the use of BCIs – invasive or noninvasive – in severely or totally paralyzed patients has met some unforeseen difficulties.

Summary

Invasive and noninvasive BCIs using recordings from nerve cells, large neuronal pools such as electrocorticogram and electroencephalography, or blood flow based measures such as functional magnetic resonance imaging and near-infrared spectroscopy show potential for communication in locked-in syndrome and movement restoration in chronic stroke, but controlled phase III clinical trials with larger populations of severely disturbed patients are urgently needed.

Keywords

amyotrophic lateral sclerosis, movement restoration, stroke

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Introduction

A brain–computer interface (BCI) or brain–machine interface uses brain signals to drive external devices without participation of the spinal and peripheral motor system. BCIs permit action through brain signals such as spike trains from single neurons [1••,2], extracellular local field potentials (LFPs) [3], electrocorticograms (ECoG) [4], electroencephalogram (EEG) oscillations [5], event-related brain potentials (ERPs) [6], real-time-functional magnetic resonance imaging (rt-fMRI) [7], and near-infrared spectroscopy (NIRS) [8]. In most BCIs the user's brain activity is acquired via amplifiers and filters and decoded using an on-line classification algorithm. In turn, this output is fed back to users, which allows them to modulate their brain activity. The feedback may consist of sensory stimuli, such as visual [7], auditory [9] or vibrotactile, varying proportionally to the classified brain activity, a discrete reward for a particular brain response, a verbal response (such as 'yes' or 'no'), the movements of a prosthesis or wheelchair, or direct electrical stimulation of muscles or brain. Thus, feedback of the consequences of the brain activity carried out to control the device is likely an essential part of a successful BCI.

Most of the research devoted to BCI development consists of methodological studies comparing different on-line mathematical algorithms, ranging from simple linear discriminant analysis (LDA) [10•] to nonlinear artificial neural networks (ANNs) [10•] or support vector machine (SVM) classification [11]. Single cell spiking for the reconstruction of hand movements requires different statistical solutions [12] than EEG rhythm classification for communication [9]. In general, the algorithm for BCI applications is computationally simple and differences in classification accuracy between algorithms used for a particular purpose are small [13]. Only a very limited number of clinical studies with neurological patients are available, most of them single case studies [14].

The clinical target populations for BCI treatment consist primarily of patients with amyotrophic lateral sclerosis (ALS) and severe CNS damage including spinal cord injuries and stroke resulting in substantial deficits in communication and motor function. However, an extensive body of literature started in the 1970s using neurofeedback training [15]. Such training implemented to control various EEG measures provided solid evidence of positive effects in patients with otherwise pharmacologically intractable epilepsy [16] and attention deficit and hyperactivity disorder (ADHD) [17]. More recently, the successful introduction and testing of real-time fMRI [18] and NIRS-BCI [8] opened an exciting field of interest in patients with psychopathological conditions.

Learned regulation of brain states

Most clinical applications of BCI research rest on the tradition of neurofeedback and biofeedback, both consequences of technological achievements in rapid computer analysis of EEG patterns that allow on-line feedback and reward of different types of neuroelectric activity [19]. BCIs aimed at restoration of movement, however, were built in the tradition of tuning functions of sensory–motor neurons representing different directions of movements [20].

Neurofeedback allowed, for the first time, voluntary self-regulation of brain activity through feedback and reward. Expectancies ran high and many premature announcements of clinical success based on single case studies or uncontrolled observations discredited the field early on. In the 1970s NE Miller's demonstrations of operant control of autonomic (and CNS) functions [21] in curarized rats, supposedly proving 'voluntary' operant regulation of many bodily functions excluding mediation of the motor system through curarization, turned out to be difficult to replicate [22]. Together with the clinical overstatements in the field of biofeedback, this historic incident virtually halted funding from public sources and blocked large controlled clinical studies despite some indications of its efficiency. However, more recent studies suggested that some patients with drug-resistant epilepsy (mostly with secondarily generalized seizures) experienced a reduction in the number of ictal events during and after training consisting of self-regulation of slow cortical potentials (SCPs) [23,24], an effect also reported using biofeedback of skin conductance responses (GSR) [25]. Nagai *et al.* [25] showed that learned increase in autonomic arousal through reduction of skin conductance decreased negative SCPs at the cortical level and thus increased seizure thresholds, confirming earlier reports [23,24,26].

In those studies with training and visual feedback of positive SCPs in focal epilepsies, some patients achieved virtually 100% accuracy in the control of SCPs after extensive training of 30 to 50 sessions, thus paving the way for application to BCIs for communication. Still, well controlled trials with larger samples of epileptic patients have not been implemented.

Another promising line of neurofeedback in neurology is the self-regulation of SCPs and mu-rhythm (also called sensorimotor rhythm, SMR) in ADHD. SMR occurs over the sensorimotor rolandic brain regions with a frequency of 8–15 Hz indicating motor quiescence and a functionally inhibitory mode of the thalamocortical loops [27]. Motor imagery or motor action desynchronises SMR (event-related desynchronization, ERD). Well controlled studies with relatively small samples of ADHD children showed potential, pointing to lasting effects on attention and vigilance comparable to those achieved through pharmacological treatment with stimulants [28]. Neurofeedback training to increase negative SCPs in prefrontal regions or training to increase SMR may influence secondarily functions at subcortical sites in this condition. As recent studies suggested a pivotal role of basal-ganglia-thalamo-frontal circuits during neurofeedback of SCPs [29,26], the exact neurophysiological mechanisms underlying these training-induced effects remain to be determined. All in all, these pioneering studies underlined the possiblity of controlling human electrocortical activitiy and of influencing motor and cognitive functions in health and disease.

Communication with locked-in syndrome

Patients with progressive motor neuron disease, particular ALS, Guillain-Barré syndrome and subcortical stroke, as well as patients with traumatic brain damage in vegetative state [30] may suffer from locked-in syndrome (LIS) or total locked-in syndrome (TLIS). LIS is defined as complete paralysis with one or a few voluntary functions left (usually small eye movements). TLIS consists of complete cessation of volitional control of all voluntary somatic–motor functions. Both LIS and TLIS show intact auditory and tactile perception and intact cognitive functions, usually measured with ERPs [30] or fMRI [31]. Visual perception is also frequently compromised through paralysis of eye muscles. Therefore, BCIs using the auditory or tactile modality are mandatory for use in TLIS patients.

Since the first report [14] of two LIS patients with ALS selecting letters from computer-presented letter strings using learned voluntary decrease of SCPs, several papers with small samples of ALS patients have appeared that demonstrate BCI-controlled communication in LIS and advanced stages of ALS. In a thorough review of the literature it was proposed that BCIs using P300 ERPs [32,33], SCPs [14] and SMR control [34] could provide

slow but effective verbal communication in all stages of ALS, except the TLIS. It is of interest that in two patients with TLIS, not even an invasive BCI controlled from epidural electrodes at left frontal sites improved their ability to communicate (unpublished data, available from the authors). Only one study [35] reported more optimistic results from a NIRS-based BCI in 17 patients with TLIS. Patients were trained to respond with an increase in blood oxygenation ('yes') or decrease in oxygenation ('no') to various questions displayed on a computer screen. Using an elaborate off-line classification method, a separation of 'yes' and 'no' of 70% correct was reported in seven out of 17 patients with TLIS. One weakness of this study is the relative lack of quantitation and definition of clinical criteria used for the TLIS patients. It remains to be determined whether BCIs using EEG, ECoG or NIRS allow voluntary brain responses and communication in TLIS. One possible explanation for the failure to replicate operant control of autonomic functions in the curarized rat [21,22] and for the lack of learned brain regulation with BCI in TLIS is that goal directed and voluntary thought processes may over time extinguish in the absence of reinforcement contingencies, a hypothesis worth testing in the future [5]. If this hypothesis is true a transfer of training success with a BCI from the LIS to the TLIS should be possible.

Movement restoration in stroke and spinal cord injury

In 2003, Pfurtscheller *et al.* [36] reported a tetraplegic patient who, after extensive training to increase and decrease central mu-rhythms was able to control an electrostimulation device (FES) applied to hand muscles. The patient was able to grasp a glass and bring it to his mouth after he had learned with feedback and reward over a period of 4 months to regulate his mu-rhythm. Hochberg *et al.* [37] implanted a 96-microelectrode array into the hand region of the motor cortex of another tetraplegic patient. The patient learned to open and close a prosthetic hand distant from his own hand with intention-driven neuronal ensemble activity. No improvements in voluntary motor function in the paralyzed hand were reported.

Motor disability resulting from chronic stroke represents the main cause of long-term disability among adults and has substantial social, financial and psychological impact on patients, families and society. Approximately one third of all stroke patients are not able to use the paralyzed hand for activities of daily living one year after the stroke. No treatment is available for that condition. A recent study [38•] using a neuromagnetic BCI showed as a proof-of-principle successful BCI control of opening and closing grasping functions of an orthosis attached to the plegic hand in six out of eight patients. The orthosis was controlled by activity in three of the 275 magnetoencephalography (MEG) sensors. Increase of 9–12 Hz mu-rhythm in these three sensors opened the hand as decrease closed it. In six of the eight patients mu activity was derived from central ipsilesional location close to the subcortical lesion. After 13 to 22 1-h training sessions, patients were able to control hand opening–closing functions through the orthosis, in the absence of clinical improvements in the completely paralyzed hands. Training resulted in refocusing of MEG activity, providing first evidence that BCI training may result in well defined cortical reorganization. Whether an invasive BCI with implanted electrodes and internalized connection to the peripheral nerves, or noninvasive BCIs connected to prosthetic devices or rehabilitation robots may move from these 'bench' types of study to the clinic awaits further research.

Still, the gap between what can be achieved with implanted microelectrode arrays in motor or parietal cortex [39] in healthy nonhuman primates versus a paralyzed human patient is wide: as the monkey learns in relatively short time periods to use a small neural assembly to feed himself without any motor mediation, the human patient needs many training hours to open and close a paralyzed hand. The fact that a pattern of spiking neurons in the appropriate brain region is 'closer' to the origin of movement production alone does not explain the explanatory gap: with a dense sensor array of MEG a complex four-directional hand movement was possible to reconstruct with an accuracy of 70% [40•] in healthy individuals. The prediction accuracy was only slightly smaller for EEG data.

Experiments with lesioned animals and simultaneous recording of spike patterns, local field potentials and ECoG are urgently needed to explore the precise parameters at each level of observation necessary to reconstruct movements in the lesioned brain, the paralyzed body parts, or both.

Brain–computer interface using metabolic changes

NIRS measuring changes in oxygenation and in deoxygenation of the cortical surface is a relatively cheap noninvasive technology whose regulation can be learned within a few training sessions with contingent feedback only. Sitaram *et al.* [8] trained healthy human individuals successfully to maximize the difference between right and left sensorimotor regions. The regulation of the BOLD (blood oxygenation level dependent) response with real-time fMRI (rt-fMRI) constitutes a particularly exciting development in BCI research [18]. In contrast to all other noninvasive BCI measures, regulation of circumscribed cortical and subcortical structures is possible. Several experimental studies, mostly with young healthy volunteers, revealed an amazing anatomical resolution in

the characterization of the cortical region to be 'trained' and a good correlation of these changes with behavioural changes. For example, regulation of premotor and motor areas led to changes in motor response speed [18], of anterior cingulated regions to downregulation of pain [41], of parahippocampal areas to changes in explicit memory performance [18] and of the anterior insula to changes in the valence of negative emotional slides without affecting neutral or positive emotions [7]. Healthy individuals are able to increase and decrease BOLD activity in a region of interest within one to three 1-h training sessions: usually they receive positive visual feedback within a second after the BOLD change (which itself has a latency of 2–3 s to the neural response). Experiments manipulating the connectivity between different brain areas and real-time control of selected metabolic substances in specific brain regions using magnetic resonance spectroscopy-feedback are underway.

Magnetic resonance technology use is expensive and applications in large clinical groups may not be feasible, but it represents a powerful tool to explore the mechanisms underlying BCI effects and brain–behavior–pathology relationships in emotional disorders such as psychopathy and substance abuse as well as in other neuropsychiatric conditions.

Conclusion

Despite a growing animal literature demonstrating online control of functional hand movements from spike patterns recorded with microelectrodes in the motor cortex, BCI applications in neurological patients are rare and hampered by methodological difficulties. BCIs using EEG measures allow verbal communication in paralysed patients with ALS; BCI-communication in totally locked-in patients, however, awaits experimental confirmation. Movement restoration in chronic stroke without residual movement capacity using noninvasive BCI is possible but generalization of improvement to real life needs further experimentation.

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