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Learning from brain control: clinical application of brain–computer interfaces

Introduction

Probably, the idea to convert thoughts directly into movement without the detour via the motor system is as old as mankind. Magic and religious thinking frequently assumes that we are able to influence or even control the processes around us with our thoughts and feelings. Interestingly enough this concept was classified as irrational since the Renaissance and later in the eighteenth and nineteenth century, when it became clear that the brain functions as carrier of our mental processes and had been pushed into the background of the philosophical and scientific considerations. Within western philosophy, influenced strongly in the eleventh and twelfth century by Arab and Jewish scientists, it was recognized early on that behavior and thinking are brain dependent, becoming a certainty in the early Renaissance. With this, however, a mechanistical concept moved into the foreground viewing the brain as internal organ with more or less autonomous function circles comparable to the gastrointestinal system. Therefore, the possibility to influence brain functions by voluntary procedures and learning was not considered to be relevant. This pre-medieval dream of direct manipulation of the environment by thinking and concepts was revived on the one side by the development of psychophysiology in human research of the twentieth century, on the other side by neurophysiological animal research, particularly the activity of individual neurons being made audible and visible and thus control machines and external devices.

The term "brain–computer interface" (BCI) was used for the first time by the French neurophysiologist Jaques Vidal, who has already foreseen in 1973 the potential applications of direct computer control by brain procedures. Approximately at the same time psychophysiology evolved researching how to control physiological procedures "biofeedback", which later, if brain processes were learned, was referred to as "neurofeedback". First scientific papers about the self-regulation of the alpha-rhythm were published in 1969, written by Joe Kamiya and showed that healthy test persons could quickly learn to voluntarily change the alpha activity (8–13 Hz) of their own electroencephalogram (EEG) if they were given continuous feedback, for example, by means of a rising and falling tone. These efforts, however, suffered a setback in the late seventies and early eighties of the previous century, after animal experiments on self-regulation and instrumental learning of bodily processes, originated from the laboratory of Neal E. Miller at Rockefeller University, turned out to be not replicable (see ▪ **excursion 1**). Only at the beginning of the twenty-first century, the rapid development of research in brain–computer interfaces began, again fuelled by two methodical approaches: on the one hand by single micro-electrode recordings in non-human primates and on the other hand by clinical successes of the neurofeedback research in humans.

It could be shown via implanted microelectrodes in the motor cortex of apes that the animals learned, within a relatively short period of time, to move light signals in given directions by changing their action potential sequences from individual motor cells on the screen of a computer respectively to steer complex arm and hand movements of a prosthesis with the activity of only a few motor cells [7]. The mathematical algorithms for the translation of the action potential sequences in targeted movements were thereby astonishing simple linear differential equations. These results of the primate research were transferred to humans, particularly by John Donoghue of Brown University and Andrew Schwartz of the University of Pittsburgh. Microelectrodes were implanted in patients with paralyses of the extremities after stroke or in the case of chronic neurological diseases into the motor cortex, which were connected with hand robots or hand arm orthosis. The patients could learn relatively rapidly to influence the firing of their motor cells by thinking of the movement in such a way that they could learn vitally important movement sequences with the peripheral neuro prostheses such as a drinking [6, 9, 10].

These human trials on partially paralyzed people show that complex natural movements can be steered directly by a few nerve cells of the brain whereby usually 30–100 cells are sufficient. This is surprising in view of the complexity of the motor system and the underlying neurophysiological processes, but it shows that the situation, at least as far as the movement control is concerned, is not as complicated as expected. These direct transmissions from the animal experiment to human patients, however, were of little therapeutic relevance, since the patients still had voluntary muscle control, partic-

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Excursion 1

The curare tragedy
In 1969 the well-known American experimental psychologist Neal E. Miller of the Rockefeller University in New York published a paper in "Science", where he asserted that it was possible to voluntarily control the autonomous nervous system and thus questioned the independence of this system from voluntary (somato-motor) influences. In order to support this theory, he and his employees performed experiments on rats in the late 1960s, 1970s, and 1980s of the past century, which were paralyzed with the Indian arrow poison curare, nourished artificially, and respirated artificially and for a surprisingly long time remained in this condition. Thus a voluntary muscular control of autonomous functions and brain functions was impossible via the paralyzed motor system. The animals were trained curarized to control different autonomous parameters, for example, peripheral blood circulation, kidney blood circulation, brain activity via instrumental conditioning: they received, for example, for each rise of the blood pressure a rewarding intracranial electrical self-stimulation. The first years of these experiments has shown that the animals also learned in a paralyzed condition by instrumental conditioning to control and "voluntarily" steer the different physiological autonomous parameters. In the middle of the 1970s, however, it became increasingly difficult in the laboratory of N. E. Miller to replicate their own results until finally at the end of the 1970s, at the beginning of the 1980s neither in the laboratory of Neal Miller nor in any other laboratory worldwide a replication of these initial results was possible. One of the project leaders of these investigations committed suicide, another one like, for example, Barry Dworkin (1989) tried to replicate the results via changes of the experimental arrangement and the curarization, however, without success. Thus Miller's original question, whether voluntary learning and the self-regulation of autonomous functions and probably also of brain functions without mediation of the motor system is possible at all, is still unresolved. This question, however, could be clarified with brain–computer interfaces in completely paralyzed, artificially nourished, and artificially respirated patients.

ularly within the area of the face and the eyes, which is much easier subjected to the voluntary control than the brain activity.

While the invasive brain–computer interfaces research on humans was driven forward in the USA, the clinical human research on applying self-regulation of the brain and the neurofeedback evolved in Europe, particularly in Germany. Thereby slow brain potentials of the human cerebral cortex reflecting the state of excitation of the apical dendrites, proved to be particularly useful, both for basic research on self-regulation of the brain as well as for clinical application (see Neuroforum 1998 as well as [1]). Healthy people and people with a neurological disease learn within a few hours to regulate slow brain potentials via direct feedback and positive reinforcement in the electrically negative (exciting) and electrically positive (restraining) directions. After a few hours of training, during which people observe the changes of the slow brain activities on a screen, clear behavioral changes can be seen in motor, cognitive, and emotional domains with self-generated cortical negativity (excitation), depending on the location in the brain where the person learned the self-generated brain change. In a series of studies of untreatable epileptics we could prove the fact that even seriously impaired people could learn not only to reduce the excitability of their brain in the laboratory but could also expand this to real life situations outside the laboratory environment. After 20–100 training hours a considerable number of the patients were able to suppress both the excitability of their brain as well as the onset of a seizure [12]. It has also been shown that some patients changed their brain potentials at any time into the desired direction. And so the idea emerged of using the learned brain control for direct communication with the outside world.

Brain control as skill-learning

The learning process behind acquiring brain control—irrespective of whether it concerns neuroelectric activities of the single cells or the electroencephalogram or metabolic changes of the cerebral circulation—is analog to those learning procedures examined for the acquisition of talents (e.g., sporty activities). These include at the beginning the conscious, explicit control with participation of the brain regions responsible for controlled, conscious attention and with increasing repetition and exercise the transition to the implicit automatic attention control with decreasing usage of attention resources. The automation and training process runs exponentially, whereby in the course of the automated acquisition increasingly less cortical areas are activated and the attention focus is restricted to the brain regions dealing with the behavior (**Fig. 1**).

In several investigations with simultaneous registration of slow cortical brain potentials in the electroencephalogram and functional magnetic resonance imaging (fMRI) with epileptic and healthy people it was shown that in people who learned the neuroelectric control of slow brain activities very fast and well, regions in the basal ganglia, above all in the anterior striatum, are activated during the learning process. People who do not learn neuroelectric self-regulation of the brain do not show simultaneous activation of the basal ganglia. These results were confirmed in an experiment on rats by Koralek et al. [11]. The animals learned to increase the intracellular firing rate of two neighboring cells in the motor cortex and simultaneously lower those of the neighboring cell: the reward was given, if the animals increased the action potential frequency in one cell and at the same time lower it in the other one. The learning process complies with the exponential learning process of skill learning. A cross correlation of the activity of the motor cortical cells and cells in the anterior striatum show an increasing connection of the oscillations in the process of learning. Furthermore animals without N-methyl-D-aspartate (NMDA) receptors (genetic knock out rats) necessary for the long-term potentiation of striatal neurons could not learn the neurofeedback task despite intact movement control.

These clear results, however, point out that disturbances of the cortico-thalamo-striatal loop, the instrumental, operant learning of skills is disturbed or completely impossible. The dependence of the self-regulation of the brain on reward and skill learning becomes particularly dramatic in people with instrumental learning deficits, for whom receiving rewards do not have any effect. This is probably the case with completely paralyzed patients, with whom reliable contingencies (temporal relations) between voluntary reactions and their consequences are not possible anymore.

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Learning from brain control: clinical application of brain–computer interfaces

Abstract

Brain–computer interfaces (BCI) use neuroelectric and metabolic brain activity to activate peripheral devices and computers without mediation of the motor system. In order to activate the BCI patients have to learn a certain amount of brain control. Self-regulation of brain activity was found to follow the principles of skill learning and instrumental conditioning. This review focuses on the clinical application of brain–computer interfaces in paralyzed patients with locked-in syndrome and completely locked-in syndrome (CLIS). It was shown that electroencephalogram (EEG)-based brain–computer interfaces allow selection of letters and words in a computer menu with different types of EEG signals. However, in patients with CLIS without any muscular control, particularly of eye movements, classical EEG-based brain–computer interfaces were not successful. Even after implantation of electrodes in the human brain, CLIS patients were unable to communicate. We developed a theoretical model explaining this fundamental deficit in instrumental learning of brain control and voluntary communication: patients in complete paralysis extinguish goal-directed response-oriented thinking and intentions. Therefore, a reflexive classical conditioning procedure was developed and metabolic brain signals measured with near infrared spectroscopy were used in CLIS patients to answer simple questions with a "yes" or "no"-brain response. The data collected so far are promising and show that for the first time CLIS patients communicate with such a BCI system using metabolic brain signals and simple reflexive learning tasks. Finally, brain machine interfaces and rehabilitation in chronic stroke are described demonstrating in chronic stroke patients without any residual upper limb movement a surprising recovery of motor function on the motor level as well as on the brain level. After extensive combined BCI training with behaviorally oriented physiotherapy, significant improvement in motor function was shown in this previously intractable paralysis. In conclusion, clinical application of brain machine interfaces in well-defined and circumscribed neurological disorders have demonstrated surprisingly positive effects. The application of BCIs to psychiatric and clinical–psychological problems, however, at present did not result in substantial improvement of complex behavioral disorders.

Keywords

Brain–computer interfaces (BCI) · Amyotrophic lateral sclerosis (ALS) · Completely locked-in syndrome (CLIS)

Brain–computer interface (BCI) in patients with locked-in syndrome

Brain communication with loss of motor control

Locked-in syndrome occurring after subcortical stroke or with progressive chronic degenerative neurological diseases like amyotrophic lateral sclerosis (ALS) is of course the most important disease pattern to prove the benefits of BCI. It, however, has to be differentiated between locked-in (LI) syndrome and the completely locked-in syndrome (CLIS). With the locked-in syndrome all body muscles are paralyzed, but there is still control of the eye muscles or individual face muscles. The external sphincter is still voluntarily controllable in some individual cases as well. With the completely locked-in syndrome (CLIS) all muscles of the voluntary motor system are paralyzed.

The first patients, with whom a BCI was analyzed for direct brain communication, were patients with advanced amyotrophic lateral sclerosis, but preserved eye muscles [2]. The patients initially learned to steer voluntarily their slow brain activities via neurofeedback, that is, they received visual feedback for an increase or decrease of the cortical negativity (excitability). After learning the self-regulation of slow brain potentials the letters of the German alphabet in the order of their frequency were presented on a screen and patients had to learn to divide a board with brain potentials with approximately 8 and/or 16 letters until the desired letter appeared on the screen. They had to keep the desired letter in their memory and to manipulate the letter board with changes of their slow brain potentials. This is a difficult task requiring divided attention and was mastered by patients with locked-in syndrome after long training times (weeks to months) (**Fig. 2**).

Apart from excessive long training times, the first brain–computer interfaces naturally had the problem that these people could in principle select the letters on the letter board with eye muscles or individual face muscles, which requires no training times and does not need a lot of attentiveness because of the automation of the muscle control. Nevertheless, the proof of first direct brain communication represented a major progress being also tested successfully with patients suffering from locked-in syndrome after subcortical stroke: Sellers et al. [14] trained a patient after a pontine stroke with rudimentary eye control to select letters from a letter board with all letters of the alphabet by means of the P300-event-related potential. This by E. Donchin developed method has the advantage that it does not need lengthy training: the letters of the alphabet are rapidly lit up successively with light bars and the person concentrates only on the desired letter within the lit letters producing an increased P300-potential, then letting appear the desired letter at the top margin of the screen. Therefore it is obviously necessary to have an intact vigilance and attention as well as an intact visual fixation system. BCI systems, with which the presentation of the letters takes place acoustically, show far smaller precision, that is, there are more errors with the selection of letters, if they are presented acoustically. The best acoustic BCIs maximally reach a 65 % correct letter selection, which is problematic with locked-in patients, since many of these patients have only reduced visual capacity and weak concentration.

After proof of brain communication was obtained, the research naturally con-

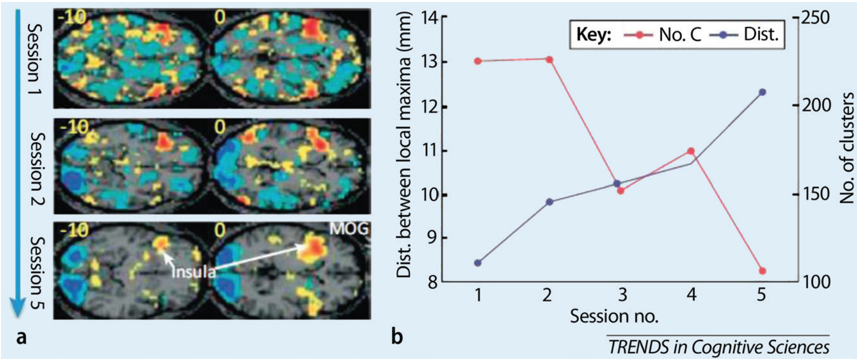

Fig. 1 ▲ Brain reorganization due to real-time-functional magnetic resonance imaging (rt-fMRI) neurofeedback training of the anterior insula. The results depicted in these two panels are from a multivariate analysis of the data from a previous study, in which participants were trained to regulate their own Blood Oxygen Level Dependent (BOLD) responses in the anterior insula with rt-fMRI feedback. **a** Neurofeedback training from session 1 to session 5 (*top* to *bottom*; sessions 3–4 are not shown) results in focusing of brain activity. **b** This effect is represented quantitatively as a decrease in the number of activation clusters and simultaneous increase in the average distance between the clusters. Reproduced, with permission from: Birbaumer et al. [3]

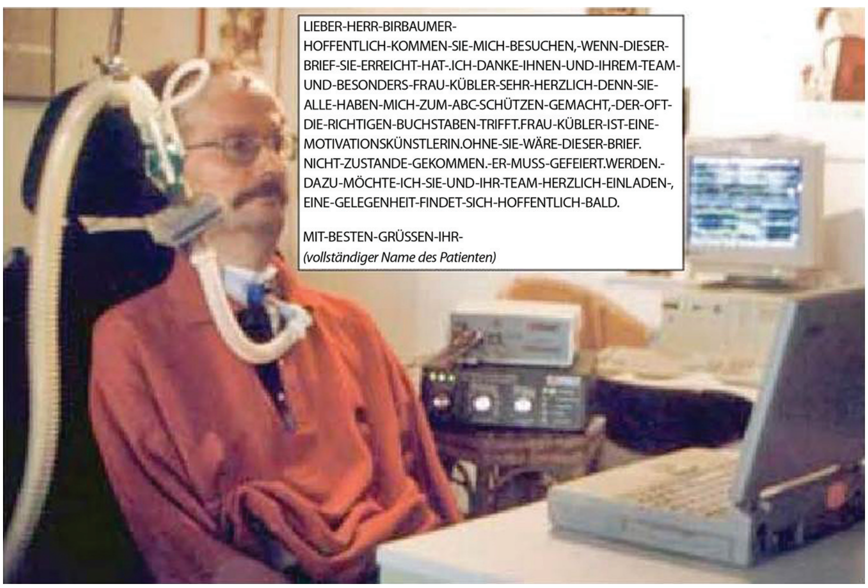

Fig. 2 ▲ The first full message written by subject HPS. With permission from Birbaumer et al. [2]. A spelling device for the paralyzed

centrated on the use of BCIs in patients with completely locked-in syndrome, with whom also other assisted communication systems do not function any longer, that is, eye movement systems or electromyographically steered communication systems. For these patients only the brain activity remains, at least potentially, subjected to the will, not depending on the intactness of the motor system. It, however, has been shown that in the case of completely locked-in patients (CLIS) with ALS that the BCI systems described, requiring intact attention functions and usually also intact volitional functions, do not enable satisfying communication rates with a correct letter selection over 65 %. An overview in the year 2008 [13] revealed that except a badly documented Japanese report no completely locked-in patient was able to communicate with a BCI using EEG signals.

We assumed initially that the cause for this lacking skill with CLIS was the bad signal-to-noise ratio of the EEG signals on the head surface. For this reason the EEG electrodes were implanted invasively at the cortex surface in two patients in our hospital, so that patients with the direct electrocorticographic signal of the cortex surface should learn to communicate with a very much broader frequency spectrum of 0–100 Hz. With two CLIS patients, the electrodes were implanted neurosurgically into the left frontal hemisphere; both patients should answer with two different images (e.g., image of a finger movement and image of a leg movement) to simple questions with "yes" (finger movement) or "no" (leg movement). Despite long training times, there was no sufficient training success in any of these two patients showing a useful communication rate of over 60–65 % of the answers during a longer period of several weeks. Obviously the problem of brain communication in completely locked-in patients is not a methodical–electrophysiological problem, but is connected with changes of the learning processes steering the control of brain activities.

Extinction of goal-oriented thinking

On the basis of the learning psychological literature we assume that in the completely locked-in state all goal-oriented intentional thoughts and concept are subject either to a partial or complete extinction process: all intentions and thought intentions in this state are not followed by the desired consequence, what in the course of weeks to months would have to lead to the slow disappearance of goal-oriented intentional thinking. It is also conceivable that there is a kind of forgetting and a cognitive atrophy in view of the lack of effects by which the general intention and the will to control the social environment diminishes. Such a pathopsychologic problem naturally also involves leaving or disappearance of controlled attention necessary for volitional actions. Over several years some CLIS patients were trained unsuccessfully with different electroencephalographic signals in order to voluntarily control and select letters or "yes"- "no"- answers. It, however, has been shown that in the state of completely locked-in, the normal circadian rhythm is partly lost and short, but frequent sleep phases and phases of dozing off with phases of attention alternate among patients (usually with closed eyes) also during the day and during the training sessions. Altogether the EEG shows a clear slowing down in these states, fre-

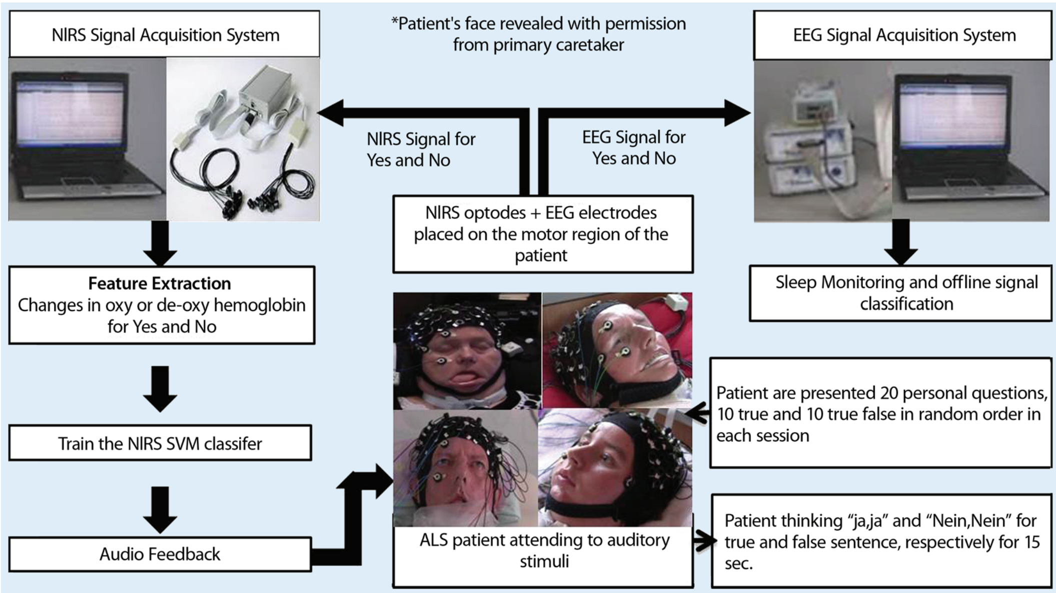

Fig. 3 ◄ A brain–computer interfaces (BCI) system for completely paralyzed. The setup and flow diagram of the BCI for communication in amyotrophic lateral sclerosis (ALS) patients. *Left*: near-infrared spectroscopy device (*NIRS*)-BMI for classification of imagined yes or no-answers. *Right*: electroencephalogram (EEG)-BMI to interrupt questioning during lack of vigilance and sleep. *Middle*: four completely paralyzed patients (CLIS) with ALS using this combined BMI for communication. See text for explanation. From Chaudhary et al. [5]

quencies over 10 Hz disappear usually after long-lasting CLIS. This means that many communication attempts must fail because of the vigilance fluctuations and the extinction of goal-directed thinking.

Thinking and movement

In this situation the close connection between thinking and movement in the development of cognitive and language-related processes becomes particularly clear. Already Aristoteles voiced the suspicion that intentional thinking is linked to the development of a goal-oriented movement subjected to the will:

Soul (psychological procedures) is identical to the production of movement of animals… we can gather from movements of the body to similar movements of the soul … the thought processes and conceptions of the soul are attached as movement to avoidance and approach; and like that it is with all kinds of movements (Aristoteles 384–322 B.C.)

In the nineteenth century Carpenter and others and finally William James has further developed this idea from antiquity to a "motor theory of thinking". Therefore experimental arrangements had to be tested for CLIS patients avoiding intentional voluntary attention and goal-oriented thinking. As a result we developed, following a long experimental phase, an experimental arrangement functioning on reflexive, classical conditioning without voluntary attentional focus (see below). Furthermore we could show in a series of investigations with neurofeedback of the BOLD-effect in the functional MRI scanner [3] that healthy and sick people learn very much faster the change of the cerebral perfusion of individual cortical and subcortical areas with the help of the functional MRI scanner than controlling neuroelectric procedures and the electroencephalogram. Although the cause for this superior controllability is unclear, it could be connected with the fact that our thought processes (that are neuroelectric procedures of the nerve cells) do not possess sensory systems and receptors for their own electric activity in the brain. Nerve cells seem to be "immune" concerning the feedback via their own activity. Formulated colloquially, we do not perceive our thought processes. In contrast to this, the vascular system of the brain has extensive pressure and flow sensors informing the brain continuously about the vascular status of even the smaller blood vessels, so that the brain itself can regulate via this feedback the flow condition and thus the oxygen and glucose transport within a restricted range.

Fig. 3 shows the structure of a portable BCI system as it is successfully used today with CLIS patients. It is characterized by reflexive, simple learning procedures and by control of the blood circulation of the brain as important response parameter. As CLIS patients are not transportable, artificially nourished, and artificially respirated in family care, the BCI system must be applicable in the domestic environment. For the controlling and measurement of the cerebral perfusion a portable near-infrared spectroscopy device is used (NIRS) measuring changes of the oxygenation and deoxygenation of larger brain areas via the reflection of light. Small laser light sources are attached to the head of the patient. The light penetrates scalp and the top of the skull and, depending on the absorption—due to the blood circulation—the reflection of the light from the cortex surface is registered by sensitive sensors measuring the reflected absorption. At the same time our system registers the EEG brain oscillations and interrupts the communication process, if signs of falling asleep or reduction of the vigilance in the EEG sample (usually waves with a frequency under five cycles per second) are detected. Thus the communication process is limited to time units, in which there is no sign of fatigue or sleep. The BCI system consists of simple questions, which the patient is to answer "in the head" reflectively with "yes" or "no". At first the patient receives many hundreds questions with well-known answers, mostly knowledge-based questions or questions related to the personal area ("Berlin is the capital of Spain", "Berlin is the capital of Germany"). The change of

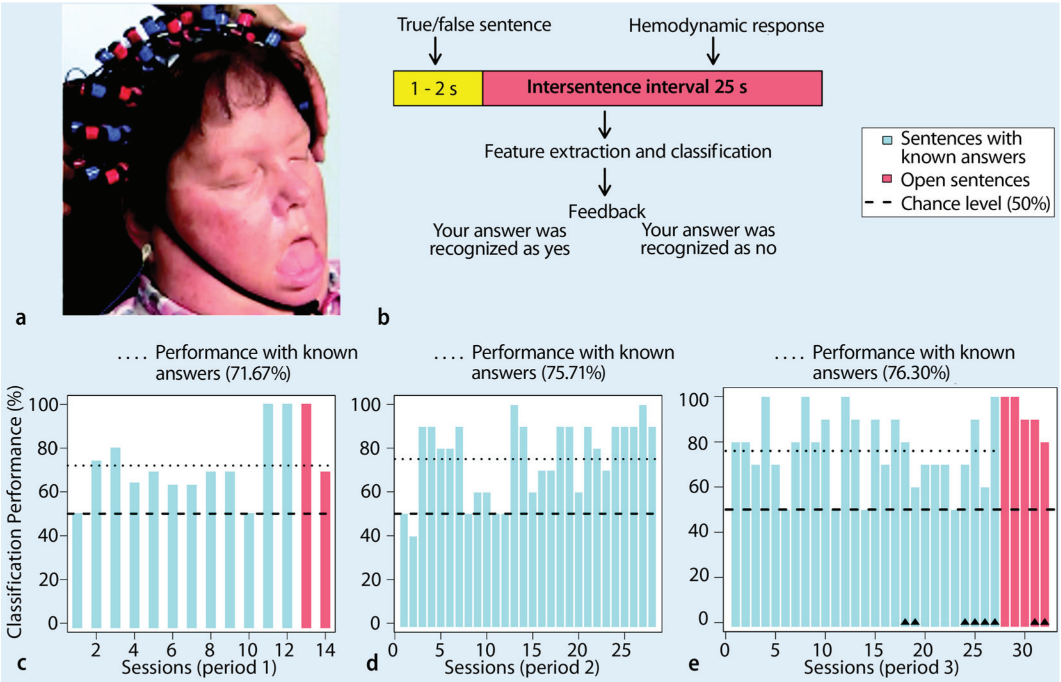

Fig. 4 ▲ Communication with a completely locked-in patient using bedside near-infrared spectroscopy. **a** Brain oxygenation and deoxygenation changes in hemoglobin were recorded with an ETG-4000 Optical Topography System (Hitachi Medical Co., Tokyo, Japan) covering the sensorimotor cortex and temporal areas. The figure shows the patient with the near-infrared spectroscopy sensors and receivers attached to her head. **b** The structure of sentences, as presented by the near-infrared spectroscopy-based brain–computer interface. **c** Classification performance based on the questions with known answers in period 1, which consisted of 12 sessions spread over 14 days with 105 true and 95 false sentences. Sessions with questions requiring a known answer are *blue*. Sessions 13 and 14 contained 20 open questions that are *orange*. **d** Classification performance of each session with known answers in period 2 (28 sessions distributed across 8 days with 140 true and 140 false sentences). **e** Classification performance of each session with known answers in period 3 (27 sessions spread over 2 weeks with 135 true and 135 false sentences). Sessions 28–32 contained 50 open questions. Sessions marked with a small *black triangle* consisted of sentences recorded with an unfamiliar voice; all other sessions were recorded with the voice of the husband. The classification results of the open sentences in parts 1 and 3 were derived from the assumed correct answers the husband had noted before the sessions. The session sequence for sessions with known answers follows the numbers below the respective *bars*. The sessions with open answers were interspersed in time between the sessions with known answers in period 3 but were moved to the end of the figure to underscore their importance. The chance level is marked by a *black horizontal line*; the average performance level is marked in *blue*. With permission from Gallegos-Ayala et al. [8]

oxygenation to these questions will be recorded over 10–15 s after completion of the question and the difference in the oxygenation between the brain responses "yes" and "no" is calculated with linear and nonlinear classification algorithms. Is there a response accuracy of over 70 % during a longer question period to questions with well-known answers, open questions can be asked ("You would like to be turned", "do you have pain?"). Naturally the correctness of the responses to open questions cannot be validated with absolute certainty with a completely locked-in patient; however, the correctness of the responses can be determined, at least approximately, with the help of the following criteria (**excursion 2**):

a. The answer has face validity, for example, the patient has an open wound causing pain and answers to the question "Are you in pain?" with "yes".
b. The relatives confirm the correctness of the response because of the personal knowledge of the patient
c. Temporal stability: the question, for example, about the quality of life, receives always the same answer over a longer period of time
d. Internal validity: questions with similar semantic meaning ("the life is e.g., beautiful" or "I enjoy every day") receive consistently the same answer.

Quality of life in completely paralyzed patients

The application of a BCI system with CLIS patients makes naturally sense only if thereby a sufficient quality of life can be achieved in this severe medical state. The results to this question are completely clear: with family care the quality of life of patients with ALS, even in the LIS state, is good to very good, even after initiation of the artificial respiration and artificial nutrition. With the previously examined CLIS patients, all questions at any time querying positive or negative quality of life were answered with positive quality of life. Altogether, in our laboratory and in the neurological hospital of A. Ludolph in Ulm with the largest ALS-outpatient clinic in South Germany, several 100 ALS-patients in different stages of the illness were questioned in representative surveys with questionnaires about the quality of life and a newly developed questionnaire on

Excursion 2 describes the principle of the near-infrared spectrophotometry (NIRS) within a BCI system

With NIRS, the hemodynamic reaction can be measured after brain activation: this neuronal activation is closely bound to the vascular reaction-–—"neurovascular coupling". The neuronal activation after stimulation is followed by the release of neuro-transmitters, changes of the cell environment (e.g., glial cells), vasodilation and constriction, and blood flow changes. NIRS measures the vascular reaction of the cerebral blood vessels: Light in the infrared spectrum (650–900 mm) is used in order to record blood flow changes and oxygenation of the cerebral blood. Light in this wavelength penetrates more deeply into the brain tissue and is absorbed by oxy (HbO) and deoxyhemoglobin (HbR), the extent of the back reflected light to the NIRS sensors (optodes) measures HbO and HbR of cerebral blood flow. The light penetrates cranial bones and—brain skins (if it is not based directly on the cortex) and emits—depending on the absorption—and is taken up by the detector optode. The local dissolution is measured in centimeters from the skull, at the cortex in millimeters. Temporal resolution lies in the seconds range, the temporal latency after stimulation amounts from one to several seconds. The connection between neuronal cell responses and the NIRS change measured in the neighborhood is very high and therefore illustrates well the accumulated activity of the nerve tissue (**Fig. 4**).

depression all coming to the result that of an average quality of life of ALS-patients which does not differ from healthy people. It, however, has been shown that relatives and care-takers as well as medical staff evaluate the quality of life clearly more negatively than the patients themselves. Depressive states are extraordinarily rare. In an examination at the psychiatric university clinic in Tübingen, the results concerning the quality of life for depressive patients were clearly worse than for ALS-patients.

The potential causes for this surprisingly high quality of life has not yet been adequately examined, but with the LIS and CLIS patients, it is obvious that these patients accept the artificial nutrition and artificial respiration only in a positive family context. In this respect a preselection takes place. Only patients who are cared for in such a positive family relationship are examined. As a result of the focusing and restricting of the attention to the positive family interaction the natural consequence is a positive evaluation of the life circumstances. Furthermore we experimentally follow up the suspicion that the complete paralysis of the muscles and the partial extinction of intentional voluntary motivation cause a balanced "relaxed" brain state. The brain does not receive a feedback on changes in tension from the periphery, so that an activation of defensive systems is avoided. In an examination with positive and negative emotional visual and acoustic material we observed that emotional sensory material evaluated clearly more positive and less negative emotionally by ALS-patients than by healthy control persons. At this time, we also experimentally examine CLIS-patients in order to establish to what extent the thought and imagery process of these patients focus on sensory emotional information and outwardly directed, reaction-oriented conceptions, also within the linguistic–semantic area, are increasingly subject to extinction. Also this could be cause for a response to the apparently paradoxically good quality of life.

Brain–machine interface (BMI) and rehabilitation of chronic stroke

Chronic stroke is the most frequent cause for permanent handicap and therefore financial losses. A third of the affected patients recover spontaneously, one third remains paralyzed on one side contralateral to the lesion. A third does not recover even after several years, the affected arm and hand will remain completely paralyzed. For patients with limited movement in their arms and hands as the most promising and most successful treatment measure proved to be the so-called "constraint movement therapy" (CMT) by Edward Taub ([15], The EXCITE trial). This therapy is based on experiments involving primates, with which after lesion of the afferent pathways from the periphery, particularly from hand and arm, a chronic "disuse" of the affected arm was noticeable despite intact motor skills. The animals use primarily the healthy arm, because it leads to the desired success and "neglect" the arm contralateral to the affected brain hemisphere. In the psychological literature, this phenomenon is called "Learned Non-Use". By fixation of the healthy part of the body, particularly the arm and the hand during a period of several weeks the animal or the person is brought to realize the limited movements of the paralyzed hand and thus reactivate the brain areas adjacent to the lesion, at least at the motor cortex. The remaining third that are not able to move their hands at all and with those no change was ascertained even after 1 year of constraint movement therapy or physical therapy, did not show any permanent improvements and had to accept their severe disability also a sharp decline in quality of life and freedom of action and movement.

Based on the abovementioned animal and human experiments with the controlling of peripheral prostheses with the firing rates of motor cells of the motor cortex, a noninvasive BMI-system for controlling a hand orthosis was developed in our laboratory [4]. Already in 1969 Eberhard Fetz had shown in non-human primates that these animals can voluntarily regulate relatively fast (within 2 weeks daily training) rhythm and frequency of cortical action potentials via positive feedback. This pioneering research was then repeated in humans by Hochberg et al. and Collinger et al. in partly paralyzed patients with stroke. The patients learned to use an extra-corporal prosthesis or an artificial hand with the help of a relatively small number of cortical cells in such a way that thereby directed volitional acts such as grasping, drinking, and eating became possible.

These findings were implemented in our laboratory and in the laboratory of Leonardo Cohen at the National Institutes of Health in cooperation with our institute in stroke patients with complete paralysis of the side of the body opposite the lesion. This showed that patients are able within 20 h to steer an orthosis fastened to the hand and fingers with the help of their brain activity in the electroencephalogram in such a way that voluntary opening and closing of the hand or forward and sideward movements of the arm are possible. The patients receive feedback via the brain rhythms, derived from the motor cortex,

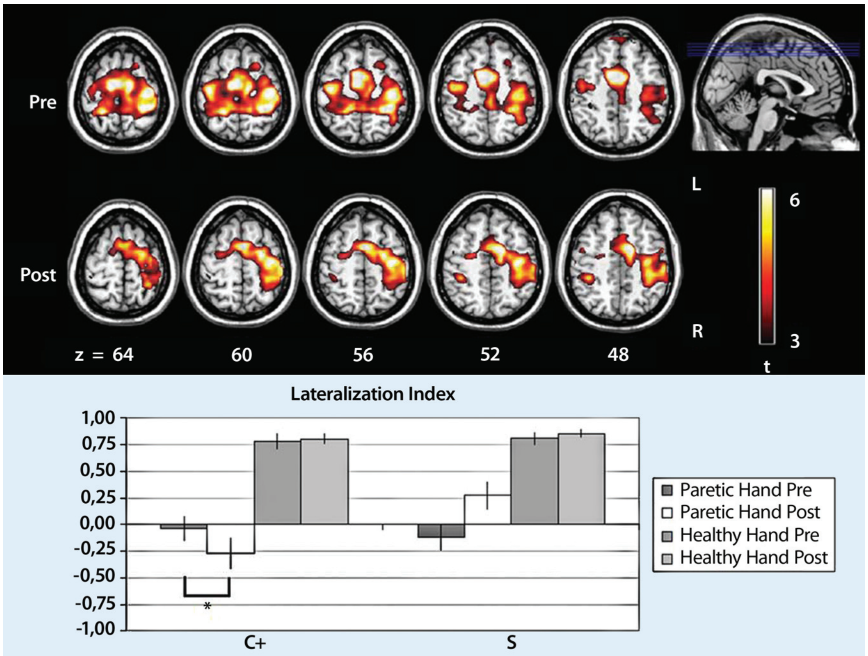

Fig. 5 ▲ Lateralization index of blood oxygenation level-dependent activity (1 = entirely contralesional, – 1 = entirely ipsilesional) was calculated for pre and post-training functional magnetic resonance imaging (fMRI) sessions during hand-opening attempts by patients with the paretic and with the healthy hand in the experimental or contingent positive group (C+) and control or sham group (S). Top images show brain activations during paretic hand movements versus rest before and after brain–machine interface (BMI) training ($p < 0.001$ uncorrected for visualization). fMRI maps were obtained from mixed effect analysis on the experimental group with subcortical lesion only ($n = 14$; maps of patients with lesion on the left hemisphere were flipped to the right hemisphere). The data for the control group are not shown, as no significant changes were observed between pre and post-training sessions. *Bottom* graph shows lateralization index of active voxels in the ipsilesional and contralesional motor and premotor areas during the actual movement condition for the paretic and healthy hand in the experimental and control group before and after BMI training (only for patients with subcortical lesions). *$p < 0.05$. *L* left, *R* right, *t* t value. With permission from Ramos-Murguialday et al. [14]

of 8–13 Hz or their harmonious frequencies of approximately 22 Hz (sensomotor rhythm, SMR). They learn to reduce gradually the sensomotor rhythm (SMR) by thinking of a voluntary movement and the extent of the reduction moves the peripheral orthosis and thus passively the paralyzed hand. It became clear, however, after the first examinations that despite 80–90 % of correct movements carried out with the help of the BMI and the fixed neuroprosthesis that this learned activity success did not generalize in the social reality: the patients were not able to realize the treatment success outside of the laboratory without being attached to the BMI. For this reason, the patients of the experimental group were trained in a further controlled study (Ramos-Murguialday et al. [14]) to steer hand and arm movements with the help of the desynchronization of the sensomotoric rhythm. After each BMI meeting, an intensive training of the same movement took place without help of the technical BMI. With the help of this behaviorally oriented physiotherapeutic training continuous treatment successes could be achieved, even with completely paralyzed patients who remained stable even 1 year after conclusion of the treatment (◘ **Fig. 5**).

Conclusion

The clinical–experimental research on brain–computer interfaces showed that with well-defined neurological diseases, with which clear relations between changed brain activity and movement exist, for example, amyotrophic lateral sclerosis where the complete paralysis for communication can be circumvented and in stroke where the blockade of the transmission of the movement impulse to the periphery initiated by the lesion, can have permanent effects. The results are particularly impressive with the completely locked-in syndrome, when up to now the concept that an alert mind is imprisoned in a completely paralyzed body, incapable of communication, worried generations. This fear seems to be eliminated by the results of the BCI research. If the results of the BMI training on chronic stroke should work satisfactorily and will be replicated and if, with the help of invasive surgery, the BCI system can remain within the body, then we would have achieved a further substantial step in the permanent rehabilitation of stroke.

The situation of the clinical BCI research is less simple—and have not been described in detail in this short article—if BCI is used with behavioral disorders from the psychiatric and clinical-psychological area. Even though the self-regulation of the brain produced positive and replicatable results with individual psychological disorders like attention deficit disorder and neurofeedback was tried again and again in connection with psychiatric disorders (e.g., in our laboratory people with antisocial personality disorder and crime, obsessive–compulsive disorders, schizophrenia, and very successfully with epilepsy), the results in view of the complex relations between brain changes and behavior are much less clear. Here the development of brain-based training measures will strongly depend on the technological development as well: miniaturized, cable-free implantable systems for the steering of the brain control, or for the stimulation of individual brain areas will also lead in this area to improved results. However, the invasive or noninvasive BCI application only makes sense in psychological–psychiatric disorders, if it does take place in the context of environmental changes and is not oriented towards the present rigid diagnostic categories in psychopathology.

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