Brain-Computer Interfaces for Communication in Paralysis: A Clinical Experimental Approach

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3.1 Abstract

An overview of different approaches to brain-computer interfaces (BCIs) developed in our laboratory is given. An important clinical application of BCIs is to enable communication or environmental control in severely paralyzed patients. The BCI "Thought-Translation Device (TTD)" allows verbal communication through the voluntary self-regulation of brain signals (e.g., slow cortical potentials (SCPs)), which is achieved by operant feedback training. Humans' ability to self-regulate their SCPs is used to move a cursor toward a target that contains a selectable letter set. Two different approaches were followed to develop Web browsers that could be controlled with binary brain responses. Implementing more powerful classification methods including different signal parameters such as oscillatory features improved our BCI considerably. It was also tested on signals with implanted electrodes.

Most BCIs provide the user with a visual feedback interface. Visually impaired patients require an auditory feedback mode. A procedure using auditory (sonified) feedback of multiple EEG parameters was evaluated. Properties of the auditory systems are reported and the results of two experiments with auditory feedback are presented. Clinical data of eight ALS patients demonstrated that all patients were able to acquire efficient brain control of one of the three available BCI systems (SCP, /i-rhythm, and P300), most of them used the SCP-BCI. A controlled comparison of the three systems in a group of ALS patients, however, showed that P300-BCI and the /i-BCI are faster and more easily acquired than SCP-BCI, at least in patients with some rudimentary motor control left. Six patients who started BCI training after entering the completely locked-in state did not achieve reliable communication skills with any BCI system. One completely locked-in patient was able to communicate shortly with a ph-meter, but lost control afterward.

3.2 Introduction

Investigating the ability of humans to voluntarily regulate their own slow cortical potentials (SCPs) has been a major research focus in Tubingen since the eighties. The positive results obtained from initial experiments led to the development of clinical applications. An initial application was found in epilepsy therapy, training patients to voluntarily down-regulate their brain potentials toward a positive amplitude to reduce the amount of epileptic seizures (Kotchoubey et al. (1996)). The idea of developing a brain-computer interface

(BCI) for communication with patients suffering from "locked-in syndrome" was another challenging project, which started in 1996. A system was needed that allowed people to spell out letters with single trial responses given by the electroencephalographic (EEG) signals. This system was called the Thought-Translation Device (TTD), a BCI developed to enable severely paralyzed patients, for example, people diagnosed with amyotrophic lateral sclerosis (ALS), to communicate through self-regulation of SCPs (Birbaumer et al. (1999); Ktibler et al. (1999); Hinterberger et al. (2003b)) (sections 3.3.3-3.3.4) and chapter 22.

In contrast to our method of using SCPs, other groups have mostly followed the approach of using brain oscillations, such as the /i-rhythm activity of 8 to 15 Hz, recorded over the motor areas for brain-computer communication (Wolpaw and McFarland (1994); Sterman (1977); Pfurtscheller et al. (1995)). When performing or imagining a movement, the jj,-rhythm activity desynchronizes over the corresponding brain area (e.g., hand or tongue) (Sterman (1977)). Besides using SCPs to operate the TTD, our group developed an approach using oscillatory components as well. Instead of calculating an estimate of the spectral band power in a certain predefined frequency range, as most of the /i-rhythm-driven BCIs do, we attempted to classify the coefficients of an autoregressive model, which was sensitive to the predominant rhythmic activity. Using this approach, communication experiments were performed with signals from EEG, MEG, and ECoG derived from implanted electrodes (see sections 3.3.6-3.3.8) and chapter 14.

So far, the TTD and most of the other BCIs have been operated with visual feedback. Providing auditory feedback overcomes the limitations of visual feedback for patients in an advanced stage of ALS. Some of these patients have difficulties focusing their gaze; however, their audition remains intact, making auditory feedback the preferential feedback mode. Therefore, the TTD was modified to be entirely operated by brain signals as a voluntary response to auditory instructions and feedback. In section 3.3.4, we report the principles and experimental testing of a fully auditorily controlled BCI.

3.3   Methods

3.3.1   BCI Software

The Thought-Translation Device was first designed to train completely paralyzed patients to self-regulate their SCPs to enable verbal communication. The hardware of the device consists of an EEG amplifier, which is connected to a PC equipped with two monitors: one for the operator to supervise the brain-computer communication training, and one for the patient to receive feedback. For acquisition of the EEG, the TTD can be interfaced with a variety of EEG amplifiers that offer a high time constant (TcMOs) such as the EEG8 system (Contact Precision Instruments, Inc.) in connection with a 16 bit A/D converter (PCIM-DAS1602/16 from Measurement Computing, Inc.), the g.tec amplifiers, or the BrainAmp system (Brainproducts, Munich). Alternatively, interfaces exist for EEG amplifiers to be used in the MRI as well as MEG systems. For most of the BCI experiments, the EEG signal was sampled at 256 Hz and digitized with 16 bits/sample within an ampli-
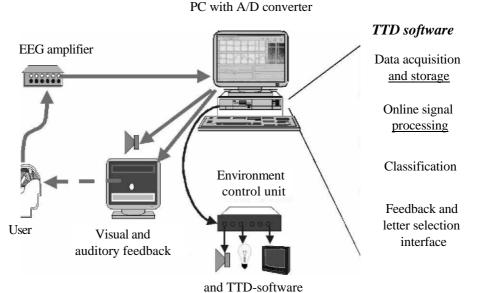
PC with A/D converter

TTD software

EEG amplifier

Data acquisition
and storage

Online signal
processing

Classification

Environment
control unit

Feedback and
letter selection
interface

User

Visual and
auditory feedback

and TTD-software

Figure 3.1 The TTD as a multimedia feedback and communication system. The EEG is amplified and sent to the PC with an A/D converter board. The TTD software performs online processing, storage, display, and analysis of the EEG. It provides feedback on a screen for self-regulation of various EEG components (e.g., SCPs) in a paced paradigm and enables a well-trained person to interface with a variety of tasks, e.g., a visual or auditory speller for writing messages or a Web browser for navigating through the World Wide Web using brain potentials only. All feedback information can be given auditorily to enable visually impaired patients to communicate with brain signals only.

tude range of at least $\pm$ 1 mV. The amplifier's low frequency cutoff was set to 0.01 Hz (i.e., a time constant of 16 s) and the high frequency cutoff to 40 to 70 Hz.

The current version of the TTD software derived from the BCI2000 standard (see chapter 21). The parameter handling, state information, and file format is identical to the definitions in the BCI2000 description. The available filters can be freely wired together and configured by the user during run-time and the data source is chosen at run-time as well. Spatial, temporal, and spectral filters are available for signal processing. Online artifact detection and correction can be performed. Classification can be done either by linear discriminant analysis (LDA), simple threshold classification, or by using a support vector machine (SVM) classifier. Several applications are available with the TTD: a two-dimensional feedback task, a spelling interface to write letters and messages (Perelmouter et al. (1999)), an interface to select Web pages from the Internet (Mellinger et al. (2003)), and interfaces to control external devices, such as switches, a robot, or orthosis. To economize the development of algorithms, a socket interface to MATLAB is available to exchange data at run-time that allows for performing calculations with MATLAB routines.

The paradigm of the SCP control for brain-computer communication is also implemented in the BCI2000 software (Schalk et al. (2004)). A detailed description of the BCI2000 is given in chapter 21.

3.3.2 Self-Regulation of Slow Cortical Potentials

SCPs are brain potential changes below 1 Hz, which up to several seconds and are generated in the upper cortical layers. Negative potential shifts (negativity) represent increased excitability of neurons (e.g., readiness) while a positive shift (positivity) is recorded during the consumption of cognitive resources or during rest. Healthy subjects, as well as locked-in patients, can learn to produce positive or negative SCP shifts when they are provided with visual feedback of their brain potentials and when potential changes in the desired direction are reinforced.

For SCP self-regulation training the recording site for the feedback signal was usually Cz (international 10-20 system) with the references at both mastoids. EEG was usually recorded from 3 to 7 Ag/AgCl-electrodes placed at Cz, C3, C4, Fz, and Pz and the mastoids. Additionally, one bipolar channel was used to record the vertical electrooculogram (vEOG) for online and offline artifact correction. For FOG correction, a fixed percentage (between 10 and 15 percent) of the vEOG signal was subtracted from the SCP signal at Cz. Furthermore, to prevent participants from controlling the cursor with their eye movements, the feedback signal was set to baseline in case the signal used for EOG correction exceeded the actual SCP changes (Kotchoubey et al. (1997)). Feedback was provided from Cz referenced to the mastoids and was updated sixteen times per second to provide a smooth cursor movement. SCPs were calculated by applying a 500 ms moving average to the EEG signal. The SCP value, taken immediately before the feedback started, served as the baseline, defining the center cursor position on the feedback screen. The baseline was subtracted from all SCP values. All trials with strong movement artifacts (SCP variations exceeding 200 mV within one trial and vEOG variations exceeding 800 mV) led to an invalid trial.

With the visual feedback modality, participants or patients viewed the course of their SCPs as the vertical movement of a feedback cursor on the screen. Vertical cursor movement corresponded to the SCP amplitude. Their task was to move the cursor toward the polarity indicated by a red rectangle at the top or bottom half of the screen.

Figure 3.2 (top) illustrates the different phases of the training process in a trial. The first 2-4 s of a trial consisted of a target presentation interval during which the target was illuminated in red, indicating the feedback task for this trial, and allowing the person to prepare for the corresponding SCP regulation. In the following selection interval, feedback was provided by the vertical position of a steady horizontally moving cursor. Cortical negativity moved the cursor up; positivity moved the cursor down. The center of the screen corresponded to the baseline level. The task was to move the cursor into the red area. A response was classified as correct if the average potential during the response interval carried the correct polarity or was inside the target boundaries of the required goal. Additionally, automatic classification algorithms, such as a linear discriminant classification or SVM, can be used for improvement of the correct response rate (Lai et al. (2004)). At the end of the selection interval the selected target was illustrated with blinking. Finally, during the response interval a smiley face combined with a sound of chimes rewarded a correct trial.

Performance was measured by the percentage of correct responses on valid trials. After a rate of 75 percent correct responses was reached, patients were trained to select letters and write messages using their self-regulative abilities for spelling (Birbaumer et al. (1999);
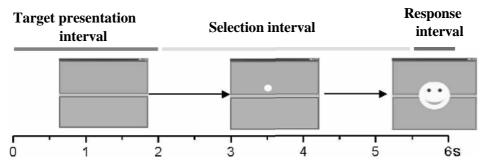
Figure 3.2 Illustration of the visual feedback information during SCP self-regulation training. Each trial is subdivided into intervals for target presentation, selection with feedback, and the report of the response.

Perelmouter et al. (1999)). Patients typically reach such levels of proficiency after one to five months of training, with one to two training days per week. A training day comprises seven to twelve runs, and a run comprises between 70 and 100 trials. With patients suffering from ALS, operant feedback training was conducted at the patients' homes with the users seated in wheelchairs or lying in bed.

The applications that will be described in the following paragraphs are a language support program including an advanced dictionary option, a fast communication program for basic desires, and an Internet browser. All these programs are driven by simple yes or no responses that serve as "select" or "reject" commands. These types of brain-computer communication also require three intervals in one trial: (1) the target presentation interval for presentation of the letter set, which was displayed in the target rectangle on the screen; (2) the selection interval, during which feedback was provided, and where self-regulation of SCP amplitudes was used to select or reject the letter set; and (3) a response interval indicating to the user the result of the selection. Selection errors require correction steps in the decision tree that were presented as "go back" options (see also figure 3.3).

3.3.3 Spelling by Brain-Computer Communication

The spelling device allows the user to select letters from a language alphabet, including punctuation marks, and to combine letters into words and sentences. Because the number of characters in an alphabet (typically about thirty) exceeds the number of brain response classes (two) that the user can produce, the selection of a letter must be broken down into a sequence of binary selections. This leads to the concept of presenting the alphabet's letters in a dichotomous decision tree, which the user navigates by giving brain responses (Perelmouter et al. (1999)). This concept was realized in a module called "language support program". Figure 3.3 shows the structure of the decision process.

The presentation of letters for spelling is realized with a binary letter selection procedure as illustrated in figure 3.3. Each box contains a letter set that can be selected or rejected. In each, trial a single letter or a set of letters can be selected or rejected by a binary brain response that corresponds to a cortical negative or positive potential shift. The letters are arranged in a way that facilitates the selection of the more frequent letters, whereas the less
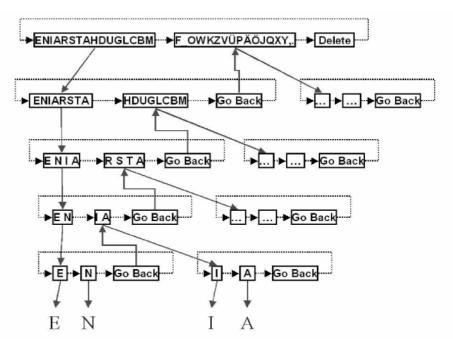
Figure 3.3 Schematic structure of the language support program. Boxes show letter sets offered during one trial; solid arrows show the subsequent presentation when a select response is produced; dotted arrows show the presentation following a reject response. When the level of single letters is reached, selection leads to the presentation of this letter at the top of the screen. Texts can thus be generated by adding letter to letter. At all except the uppermost level, failure to select one of the two choices results in the presentation of a "go back" option taking the user back to the previous level. At the top level, double rejection and selection of the delete function results in the deletion of the last written letter.

frequent letters require more steps to select. A selection will split the current letter set into two halves and present the first half for selection during the next trial (dotted arrows). A rejection response will present the second half for selection or proceed to the "go back" option (bold arrows). At the final level, the selection of a single letter will spell it. This paradigm can be used similarly for visual and auditory spelling.

In this system, writing the most conveniently situated letter, "E," takes five trials, that is, 20-25 s depending on the duration of a trial; whereas, writing the most remote sign takes nine trials, that is, 36-45 s. In an attempt to make free spelling less time-consuming, a simple personal dictionary has been introduced in which the experimenter may enter words that are frequently used by the patients (Hinterberger et al. (2001); Ktibler et al. (2001b)). With the dictionary option, a complete word is suggested after at least two letters have been written and a corresponding word is available. This word can then be chosen with a single selection response.

3.3.4 Approaches for Brain-Controlled Web Surfing

3.3.4.1 *Initial Approach: "Descartes"*

The methods described above help the patients to express their ideas, thoughts, and needs. The Internet offers instantaneous access to desired information. Providing paralyzed patients with a BCI, which allows them to navigate through the World Wide Web by brain responses, would enable them to take part in the information exchange of the whole world. Therefore, a special Web browser named "Descartes" was developed (Hinterberger et al. (2001)).

Descartes can be controlled by binary decisions as they are created in the feedback procedure described in section 3.3.3. The browser functions are arranged in a decision tree, as previously described for the spelling of words. At the first level the patients can choose whether to write letters, to write an e-mail, or to surf the Web. When they decide to write an e-mail, the e-mail address is spelled in the first line using this language support program. When the patients decide to surf the Web, they first receive a number of predefined links arranged in the dichotomous decision tree. Each Web page that the patients have selected with their brain signals will be shown for a predefined time of one to two minutes. The wait-dialog indicates the remaining viewing time for the page, after which the feedback procedure will continue to select a related page. After the viewing time is over, the current page is analyzed for links on it. Then a dichotomous decision tree is dynamically produced, containing all links to related sites, and so the trials continue. The patients now have the option to select a link out of this tree in a similar manner to the spelling task. The links are sorted alphabetically so the desired link in the new tree can be found quickly. For example, they are first presented with the links between A and K, and then with the links between L and Z, and if both were ignored they receive a cancel option for returning to the prior level. The lowest level contains the name of the single links loaded after selection (figure 3.4).

3.3.4.2 *An Improved Graphical Brain-Controllable Browser Approach: "Nessi"*

The spelling concept was also used for a hypertext (Web) browser. Instead of selecting letters from a natural language alphabet, sequences of brain responses are used to select hyperlinks from Web pages. In the previous project (Descartes), links were extracted and presented on the feedback targets. The current approach uses graphical markers "in-place", that is, on the browser's Web page display (see figure 3.5) (Mellinger et al. (2003)). Colored frames are placed around user selectable items, circumventing any need to maintain a separate presentation of choices. The frame colors are assigned to the possible brain responses. By default, red frames are selected by producing cortical negativity and green frames are selected by the production of cortical positivity. As an aid, feedback is displayed at the left rim of the screen by depicting the vertical movement of a cursor that can be moved upward into a red area or downward into a green area. The user simply has to watch the current color of the desired link's frame that indicates the brain responses that have to be produced for its selection. By presenting a series of brain responses, as indicated by the changing color of the frame around that link, the link can be chosen with binary

Figure 3.4 After an Internet page is loaded, a dichotomous decision tree is dynamically produced, containing all links to related sites. During the ongoing selection procedure, the patient has the option to select a link out of this tree. The links are sorted alphabetically. In this figure, the patient can decide whether to choose one of the six links named from "Info" to "Studienb...," or one of the five links named from "Studiere..." to "Wissensc...".

decisions, neglecting any knowledge about its position in a selection tree. Besides links, other interactive elements on Web pages are accessible to the user, particularly text fields, for which a virtual keyboard is provided, opening up a wide range of hypertext-based applications. In addition, the user can read and write e-mails. Care was taken to keep the graphical e-mail interface very simple to speed up the communication process: Four sections of the e-mail window show user commands (reply, compose, next), incoming e-mail list, text of current e-mail, and a section for the user's reply text, respectively. E-mail addresses can be predefined for faster selection and text is entered on a virtual keyboard. To record the user's advances when browsing with the graphical brain-controllable browser, Nessi, a task-based browsing mode is available. The supervisor highlights a link and the user's task is to select that link as quickly as possible. Nessi records the number of correct choices made for later analysis by the supervisor. Similarly to the spelling task, the user must manage a dual task situation: figuring out the task and performing the corresponding brain response. Initial tests with this system revealed difficulties only when a Web page contains too many links. One of our almost completely locked-in patients managed to navigate to sites of his favorite soccer team in the first runs with the system.

3.3.5 An Auditory-Controlled BCI

A limitation was soon evident with the visual version of the TTD. For patients in an advanced stage of the disease, focusing gaze to sufficiently process the visual feedback or read the letters in the verbal communication paradigm is no longer possible. In this case, a nonvisual feedback modality such as auditory or tactile feedback had to be implemented. The implementation of auditory feedback is shown in the following section.
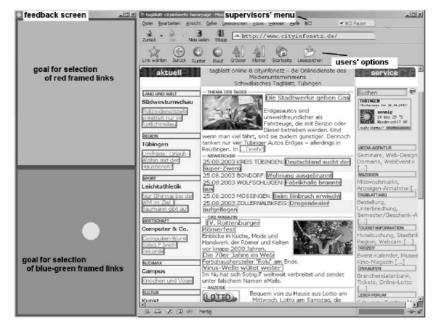
Figure 3.5 A screenshot of the Nessi browser. On the left, the feedback window is displayed with a red and a green field for the two brain responses. All links on the browser window have frames with one of the two colors that might change from trial to trial. By concentrating, viewing a specific link, and giving the corresponding brain response, the computer can identify the desired link and open it within only a few trials.

3.3.5.1 Auditory Brain-Computer Communication Paradigms

Figure 3.6 (bottom) describes the transformation of the visual feedback information to the auditory channel. For auditory feedback, the SCP amplitude shifts were coded in the pitch of MIDI sounds that were presented with sixteen notes, or "touches," per second. High-pitched tones indicated cortical negativity, low-pitched tones cortical positivity. The task was presented by a prerecorded voice spelling "up" or "down" to indicate that the patient has to increase or decrease the pitch of the feedback sound. If the result was correct, a harmonious jingle was presented at the end of the feedback period as positive reinforcement. In addition, the TTD can be operated providing combined visual and auditory feedback. For this purpose, the same instructions, feedback, and reinforcement as used for visual or auditory feedback were employed but presented simultaneously in both modalities. Successful regulation of an auditorily presented SCP or ^-feedback signal enables a locked-in patient to communicate verbally.

Figure 3.6 demonstrates four experimental paradigms that were tested with ALS patients: (1) the copy-spelling task in which a predefined word has to be spelled—the task is presented visually and visual feedback is provided; (2) training of self-regulation of SCPs in the auditory mode; (3) spelling in a completely auditory mode according to the selection paradigm; and (4) the question-answering paradigm for receiving yes no answers in less skilled patients.
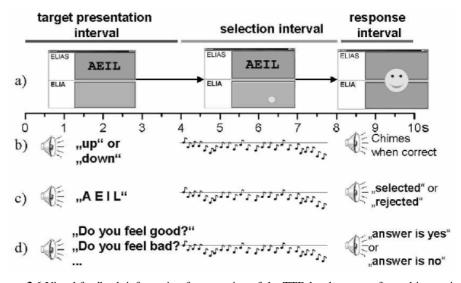
Figure 3.6 Visual feedback information for operation of the TTD has been transformed into voices and sounds to operate the TTD auditorily. Four communication paradigms are illustrated. For training a "locked-in" patient with the copy-spelling mode a predefined word has to be spelled, a) shows the visual stimuli for spelling, b) shows the stimuli for the auditory training of self-regulation of auditory displayed SCPs. c) depicts the stimuli in an auditory spelling system for brain-computer communication. In each trial a single letter or a set of letters can be selected or rejected by a binary brain response that corresponds to a cortical negative or positive potential shift. A voice informs the user at the end of a trial by saying "selected" or "rejected." In the auditory mode, a patient can spell words by responding to the suggested letter sets trial by trial, d) The question-answering paradigm allows for receiving yes no answers even in less skilled patients.

In the auditory mode, the letter sequence to be selected is presented by a prerecorded, computer-generated voice at the beginning of the preparation interval. After the feedback period, the selection or rejection response is confirmed by a voice saying "selected" or "rejected," respectively. Words are spelled by responding to the suggested letter sets trial by trial until all letters of the word to be spelled have been selected. The auditory letter-selection communication paradigm was tested with a completely paralyzed patient without any other means of communication. Despite the fact that his performance for SCP self-regulation was at average only about 60 percent, he could spell words using a set of eight letters. To keep the patient motivated it was important to start spelling with personally meaningful words or ask personally relevant questions. However, to achieve a reliable answer from the less-skilled patients, a question-answering paradigm was developed that presented questions instead of letters (figure 3.6d). Repetitions of the same question allow detection of a statistically significant brain response and thus a reliable answer. The presentation of almost 500 questions to this patient showed that even with unreliable brain control (55 percent performance) a significant answer can be obtained after averaging the responses of all identical questions ($t(494) = 2.1$, $p < 0.05$) (Hinterberger et al. (2005a)). In other words, this equals an information transfer rate of 1 bit per 140 trials.
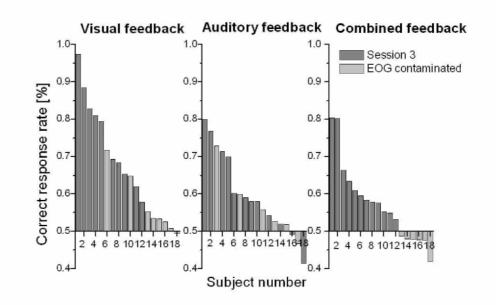
Figure 3.7 Comparison of performance of SCP self-regulation with visual, auditory, and combined visual and auditory feedback. The correct response rate (chance level 50 percent) is depicted for the third training day (session 3) for each of the 18 subjects per group. The grey bars indicate that the standardized mean differentiation of the two tasks of the EOG exceeds the differentiation of the SCP and could therefore be responsible for the SCP regulation effect as an artifact. The graph shows that visual feedback is superior in learning SCP self-regulation compared to auditory feedback, but successful SCP regulation can be achieved with auditory feedback as well.

3.3.5.2 *Comparison between Visual and Auditory Feedback*

An experiment was carried out to investigate the use of auditory feedback for controlling a brain-computer interface. The results of this study were reported in Hinterberger et al. (2004a) and Pham et al. (2005). Three groups of healthy subjects *(N = 3*18)* were trained over three sessions to learn SCP self-regulation by either visual, auditory, or combined visual and auditory feedback. The task to produce cortical positivity or negativity was randomly assigned. Each session comprised 10 runs with 50 trials each. Each trial of 6 s duration consists of a 2 s preparation interval and a 3.5 s selection interval followed by 0.5 s for presentation of the result and the reinforcing smiley associated with a jingle sound. As shown in figure 3.2, the task was presented either by an illuminated red or blue rectangle into which the feedback cursor should be moved, by a voice telling whether the feedback sound (the pitch reflected by the SCP-amplitude) should be high or low, or by the combination of both modalities. The performance of the third session was analyzed for each subject for each feedback condition. The results in terms of the correct response rate (chance level is 50 percent) are shown in figure 3.7.

All groups showed significant learning for their modality for the majority of the subjects. More than 70 percent correct responses in the third session were achieved by six (out of

eighteen) subjects with visual feedback, by five subjects with auditory, and only by two with combined feedback. The average correct response rate in the third session was 67 percent in the visual condition, 59 percent in the auditory, and 57 percent in the combined condition. Overall, visual feedback is significantly superior to the auditory and combined feedback modality. The combined visual and auditory modality was not significantly worse than the auditory feedback alone (Hinterberger et al. (2004a)). The results suggest that the auditory feedback signal could disturb or negatively interfere with the strategy to control SCPs leading to a reduced performance when auditory feedback is provided.

3.3.6 Functional MRI and BCI

3.3.6.1 *Investigating Brain Areas Involved in SCP-Regulation*

To uncover the relevant areas of brain activation during regulation of SCPs, the BCI was combined with functional MRI. EEG was recorded inside the MRI scanner in twelve healthy participants who learned to regulate their SCP with feedback and reinforcement. The results demonstrated activation of specific brain areas during execution of the brain-regulation task allowing a person to activate an external device: successful positive SCP shift compared to a negative shift was closely related to an increase of the blood oxygen level dependent (BOLD) response in the anterior basal ganglia. Successful negativity was related to an increased BOLD in the thalamus compared to successful positivity. The negative SCP during the self-regulation task was accompanied by an increased blood flow mainly around central cortical areas as described by Nagai et al. (2004).

These results may indicate learned regulation of a cortico-striatal-thalamic loop modulating local excitation thresholds of cortical assemblies. The data support the assumption that human subjects learn the regulation of cortical excitation thresholds of large neuronal assemblies as a prerequisite for direct brain communication using an SCP-driven BCI. This skill depends critically on an intact and flexible interaction between the cortico-basal ganglia-thalamic-circuits.

The BOLD activation pattern during preparatory neuroelectric signals that was supposed to reflect the SCP was at the vertex (in line with Nagai et al. (2004)), in the midline medial prefrontal cortex, including the SMA, and cingulate cortex. Activations in our study were focused on the SMA, the precentral gyrus, and the inferior frontal gyrus and the thalamus. BOLD activation at vertex corresponded with the position of the electrode used for training where the strongest slow potential shifts were expected. These results demonstrated that the negative SCP reflects an anticipatory activation of premotor and motor areas independent of whether a motor act was required or not. In the present experiment, no overt motor response was observed; subjects prepared for a cognitive task only. The positioning of the electrodes at central regions of the scalp was therefore also supported by fMRI data.

3.3.6.2 *Real-Time Feedback of fMRI Data*

Real-time functional magnetic resonance imaging allows for feedback of the entire brain with a high spatial resolution. A noninvasive brain-computer interface (BCI) based on

(fMRI) was developed by Weiskopf et al. (2003, 2004a). Data processing of the hemodynamic brain activity could be performed within 1.3s to provide online feedback. In a differential feedback paradigm, self-regulation of the supplementary motor area (SMA) and parahippocampal place area (PPA) was realized using this technique. The methodology allowed for the study of behavioral effects and strategies of local self-regulation in healthy and diseased subjects.

3.3.7 Support-Vector-Machine Classification of Autoregressive Coefficients

In contrast to the SCPs that are denned by the frequency range below 1 Hz and classified according to their time-domain representation, EEG correlates of an imagined-movement are generally best represented by considering the amplitude of oscillatory components at higher frequencies in the 8-15 and 20-30 Hz ranges, which are modulated due to the desynchronization of the /i-rhythm over motor areas when imagining movements. For this, we use the coefficients of a fitted autoregressive (AR) model, which can capture the dominant peaks in the amplitude spectrum of a signal adaptively. While in the SCP training, the SCP constitutes one parameter whose behavior should be influenced in a predefined manner (producing positivity or negativity); the AR coefficients are a multidimensional feature representation whose numerical values are not related to fixed time- or frequency-domain features in a straightforward way. Therefore, a classifier must be trained to identify how the AR coefficients change during two or more tasks (e.g., imagination of finger movement versus tongue movement). We used a regularized linear support vector machine (SVM) classifier for classification of the AR coefficients.

Before these methods were included in the TTD, a real-time socket connection to MATLAB was established to let MATLAB do the job of calculating the AR model from the received EEG-data, classifying the coefficients and then sending the result back to the TTD that controls the application (e.g., spelling interface). Later, after the approach had been successfully tested, the AR module and SVM were included in the TTD so that the MATLAB environment was no longer needed (see figure 3.8).

This approach was applied successfully to signals from EEG (Lai (2005); Lai et al. (2005a)), ECoG (Lai et al. (2005a)), and MEG (Lai et al. (2005b)). A comparison of these datasets, and more details on the automatic classification approaches we have applied to them, is given in chapter 14 by Hill et al.

3.3.8 Brain-Computer Communication Using ECoG Signals

BCIs can be used for verbal communication without muscular assistance by voluntary regulation of brain signals such as the EEG. The limited signal-to-noise ratio in the EEG is one reason for the slow communication speed. One approach to improve the signal-to-noise ratio can be attempted by the use of subdural electrodes that detect the ECoG signal directly from the cortex. ECoG signals show an amplitude up to 10 times higher with a broader frequency range (0.016 to approximately 300 Hz, sampled at 1000 Hz) from a more focused area than EEG signals. The increased signal-to-noise ratio of invasive
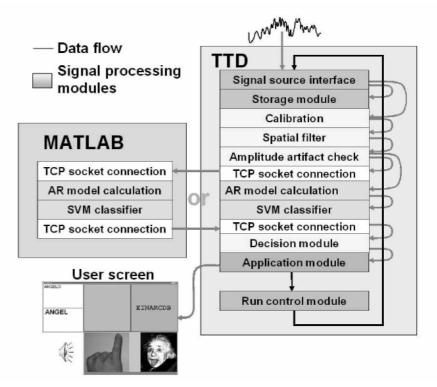
Figure 3.8 Interfacing MATLAB with a real-time cortical system: At the beginning of the experiments the calculation of the AR-coefflcients as well as the SVM-classifler was not included in the TTD. A TCP/IP socket connection between the TTD and the MATLAB application allowed real-time data exchange and classification with MATLAB. After successful testings the algorithms were inserted into the TTD application. Online classification and training of the classifier now does no longer require MATLAB.

electrocorticographic signals (ECoG) is expected to provide a higher communication speed and shorter training periods.

Here, it is reported how three out of five epilepsy patients were able to spell their names within only one or two training sessions. The ECoG signals were derived from a 64-electrode grid placed over motor-related areas. Imagery of finger or tongue movements was classified with support-vector classification of autoregressive coefficients of the ECoG signal (see 3.3.7). In each trial, the task was presented to the patient for four seconds by an image of either Einstein's tongue or a finger (see figure 3.9).

The first stage of the session consisted of a training phase of at least 100 trials. The data between second 1.5 and 5 were used to calculate 3 AR-coefficients for each of the 64 channels. After training of the SVM classifier, the binary responses could be used for selection of letters. Before that, in the second stage, the classifier was tested by displaying the task images in the same way as in the training but with immediate feedback (correct or incorrect) after each trial. In the letter selection paradigm, two boxes were shown, one associated with the tongue picture and one associated with the finger picture. The sets of letters offered to be selected in a certain trial were displayed inside the box with the
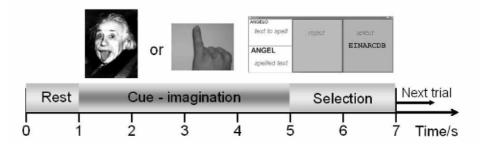
Figure 3.9 Overview of the trial structure during the data collection phase. Each trial started with a one second resting period. During the following four seconds imagination phase a picture of Einsteins tongue or a hand was shown as a cue to inform about the task. The period used for classification started 0.5 seconds after the cue onset. Each trial ended with a two seconds resting period.

Sub-ject	Sess-ions	Training		Testing with online classification		Spelling with online classification		
		Trials	CRR %	Trials	CRR %	Trials	CRR %	Letters spelled
1	1	210	*74*	120+8	**94**	-	-	
1	2	378	*87*	78+20	**80**	157	**64**	"ANGELO"
2	1	100	*63*	-	-	-	-	–
2	2	100	*60*	100	**56**	244	**73**	"MOMO"
4	1	200	*74*	-	-	164	**77**	"SUSANNE"
4	2	164	*88*	-	-	73	**88**	"THÖRNER"

Table 3.1 Bold: actual online performance. Italic: offline SVM cross-validation result.

finger picture. Therefore, patients had to imagine a finger movement in order to select a letter. The dichotomous letter selection procedure as described in section 3.3.3 was used. As the patients were not accustomed to the unusual order of the letters they were helped by indicating the imaginary task by highlighting the corresponding box. This assisted-spelling paradigm is referred to as copy spelling. Table 3.1 shows the correct response rate (CRR) for those patients who succeeded writing their names in the first two sessions.

Five epilepsy patients were trained in one or two sessions for only spelling with ECoG signals from their motor area. Three of them could write their name successfully within the first two sessions. The short training periods offer completely paralyzed patients the opportunity to regain communication using a BCI with invasive ECoG signals. However, this highly invasive method is suggested to be applied only to paralyzed patients without success in EEG-driven BCI training.

3.3.9 Comparison of Noninvasive Input Signals for a BCI

Although invasive brain-computer interfaces are thought to be able to deliver real-time control over complex movements of a neuroprosthesis, several studies have shown that noninvasive BCIs can provide communication and environmental control for severely paralyzed patients (Birbaumer et al. (1999); Wolpaw and McFarland (2004); Ktibler et al. (2005a)). Most current noninvasive BCIs use sensorimotor rhythms (SMR), slow cortical potentials (SCPs), or the P300-evoked potential as input signals. Although these signals have been studied extensively in healthy participants and to a lesser extent in neurological patients, it remains unclear which signal is best suited for a BCI. For this reason, we compared BCIs based on slow cortical potentials (SCPs), sensorimotor rhythms (SMR), and the P300-evoked potential in a within-subject design in collaboration with the Wadsworth Center in Albany, New York (Schalk et al. (2004); Wolpaw et al. (2002)). A patient's best signal was chosen to serve as input signal for a BCI with which the patient could spell, so-called Free Spelling. Previous research has shown that a minimal performance of 70 percent correct is needed for communication (Kiibler et al. (2001b)) (see also chapter 22).

Eight severely paralyzed patients (five men and three women) with amyotrophic lateral sclerosis were recruited. Background information of the patients can be found in figure 3.2. Eight patients participated in twenty sessions of SMR training. Six patients had ten sessions with the P300 BCI. In addition, five patients participated in twenty sessions of SCP training, whereas data from two other patients (D and G) were taken from previous studies (Ktibler et al. (2004)). All patients but one were trained at home. For an overview of the design see figure 3.3. During each trial in SCP training, the patient was confronted with an active target at either the top or the bottom of a computer screen. A cursor moved steadily across the screen, with its vertical movement controlled by the SCP amplitude. The patient's task was to hit the target. Successful SCP regulation was reinforced by an animated smiling face and a chime. During each trial of SMR training, the patient was presented with a target consisting of a red vertical bar that occupied the top or bottom half of the right edge of the screen. The cursor moved steadily from left to right. Its vertical movement was controlled by SMR amplitude. During each trial of P300 training, the patient was presented with a matrix containing the alphabet (Farwell and Donchin (1988)). Rows and columns flashed randomly and sequentially, and the participant was asked to count the number of flashes of a certain target symbol (e.g., the letter "p"). Target flashes elicit a large P300 response while nontarget flashes do not.

Results show that although one patient (D) was able to learn successfully to self-regulate his SCP amplitude, performance was not sufficient for communication (Kiibler et al. (2004)). None of the seven patients had a sufficient performance for communication after twenty sessions of SCP training. In contrast, half the patients *(n = 8)* learned to control their SMR amplitude with an accuracy ranging from 71 to 81 percent over the last three sessions (Kiibler et al. (2005a)). Performance with the P300 ranged from 31.7 to 86.3 percent as an average over the last three sessions. Only two patients were able to achieve an online performance over 70 percent correct (patient A and G).

These data suggested that a brain-computer interface (BCI) based on sensorimotor rhythm (SMR) is the best choice for our sample of ALS patients. However, after evalu-

Patient	Age	Sex	ALS type	Time since diagnosis (months)	Artificial		Limb function	Speech
					Nutrition	Ventilation		
A	67	M	bulbar	17	yes	no	yes	no
B	47	F	spinal	24	yes	yes	none	slow
C	56	M	spinal	9	yes	yes	none	slow
D	53	M	spinal	48	no	no	weak	yes
E	49	F	spinal	12	no	no	weak	slow
F	39	M	spinal	36	yes	no	none	slow
G	36	F	spinal	96	no	no	minimal	slow
H	46	M	spinal	120	yes	yes	none	no

Table 3.2 Background information for all patients: patient code, age in years, sex, type of ALS, time since diagnosis in months, artificial nutrition and ventilation, limb function, and speech ability. Weak limb function refers to a patient who can still walk although very slowly and with risk of falling. Minimal limb function means that the patient already is in a wheelchair, but has some residual movement left in one foot or hand. Slow speech refers to a patient who speaks slowly and needs to repeat often what he or she says.

	SMR study	SCP study	P300 study	Free Spelling
Number of sessions	20	20	10	undefinded
Task	one-dimensional cursor control	one-dimensional cursor control	copy-spelling a 51-character sequence	Free Spelling
Patients	A,B,C,D,E,F,G,H	A,B,C,D,E,F,G	A,B,D,E,F,G	A,B,E,G

Table 3.3 Within-subject cross-over design of the comparison study. Undefined number of sessions means that the sessions are still ongoing.

ating the P300 data again with new classification methods (Sellers et al. (2006a)) it was found that performance could improve significantly by changing the configuration of the electrodes, the number of electrodes included into the online analysis, and the number of features of the signals.

The P300 matrix configuration was changed to a 7 x 7 format with more characters (i.e., the German letters a, 6, ii, comma, and full stop). An "end" button was inserted to terminate the run. Four patients (A, B, E, and G) continued with the P300 sessions after completion of the study. These patients now achieve more than 70 percent correct and use the P300-BCI for Free Spelling, that is, they write words or short messages. For example, one patient (G) wrote: "Ich war am Samstag in Freiburg. Ich habe neue Klamotten gekauft" (translating to: I was in Freiburg last Saturday. I bought new clothes). These two sentences needed 76 selections (including correction of 4 errors). For this patient we reduced the number of sequences to 5, meaning that the columns and rows flashed 5 times leading to

10 flashes of the target character. The total time needed for writing these sentences was 13.3 minutes.

These results suggest that the P300-BCI might be the most efficient BCI for ALS patients, and it has the advantage of no training. However, most current BCIs require intact vision, which may be a problem for patients in the late stages of their diseases. For this reason, we are also investigating the feasibility of auditory BCIs.

3.3.10 Auditory BCI Systems Based on SMR and P300

Recently, we compared auditory and visual SMR feedback in a group of sixteen healthy subjects. They received auditory or visual feedback of SMR in three consecutive daily sessions comprising nine blocks of eight runs each (three blocks per daily session). High-SMR amplitude (relaxation, thinking of nothing in particular) was fed back by harp sound and low-SMR (movement imagery) by bongo sound. The intensity of the sounds was proportional to the alteration of SMR. Participants who received visual feedback were significantly better compared to those who received auditory feedback. Most interestingly, participants provided with visual feedback started in the first session with an accuracy of already 70 percent, whereas in the auditory group performance was at chance level. Later, training led to an improvement of performance in seven of eight participants in the auditory group, so that after three daily sessions no performance difference was found between the visual and the auditory group.

Taken together these results indicate that with visual feedback, participants have strategies immediately available to regulate SMR, whereas auditory feedback seems to retard learning. We speculate that this may be due to an increased demand for attentional resources in auditory feedback as compared to visual feedback. Learning to regulate SMR is possible, however, when provided with auditory feedback only.

We recently implemented an auditory P300 into the BCI2000 because patients in the locked-in state have difficulties looking at the entire P300 matrix and fixating on a target long enough to detect a P300. We provide such patients with an auditory P300 BCI, which will allow them to answer yes or no questions.

3.4   Summary and Conclusion

This chapter focussed on a number of different aspects that help develop BCI systems to be of use for paralyzed patients in a locked-in state. As illustrated in figure 3.10, different approaches aim at the improvement of the signal type, signal analysis, different designs of user applications, the patient-system interaction, and finally the understanding of the brain mechanisms underlying the successful regulation of SCPs. The major results of these five aspects of successful SCP-driven brain-computer communication are summarized.

(1) BCI systems were tested with a variety of different types of data sources. Besides the standard applications in which ALS patients use EEG signals, BCI approaches using classification of oscillatory activity were also carried out in the MEG, and with
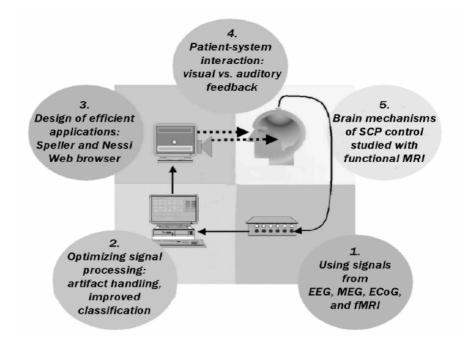
Figure 3.10 For successful brain-computer communication using SCPs, not only the properties of the system as a signal translation device must be investigated but also the interaction between the user and the system and finally the brain mechanisms themselves responsible for the systems' behavior.

ECoG in epilepsy patients implanted with electrode grids prior to surgery. In all these setups, users could operate a copy-spelling system by the use of motor-related /x-rhythm. FMRI feedback required a different software approach and was not used with a spelling application or environmental control.

(2) Signal processing and classification: In SCP self-regulation training, the computer does not adapt dynamically to the EEG response curve of a desired negative or positive potential shift. It requires the subjects' learning to produce reliable SCP shifts in both polarities. After the patient has reached a certain performance level without further improvement, the computer could optimize the number of correct responses by adapting to the response curve for example, by using additional classification algorithms. An improvement in the information transfer rate from 0.15 to 0.20 could be reached on average (Hinterberger et al. (2004b)). However, many of the highly successful SCP regulators adapt to the task without the need of further classification. Classification of autoregressive parameters using an SVM classifier was implemented as a method of classifying oscillatory activity of sensorimotor rhythm (SMR).

(3) Advanced applications from spelling to Web surfing: A wide range of applications have been developed that allow patients to communicate even in a locked-in state. A language support program with a dictionary enables paralyzed patients to communi cate verbally. Patients can switch the system on and off without assistance from others, which provides the option to use the system twenty-four hours per day (Kaiser et al. (2001)). An environment-control unit allows the patients to control devices in their

environment. All applications are independent of muscular activity and are operated by self-control of slow cortical potentials only. A further improvement of the quality of life in locked-in patients can be provided by voluntary control of information available through the World Wide Web. Two types of binary controllable Web browsers were developed allowing the access to Web sites by a selection procedure using SCP feedback (Hinterberger et al. (2001)). In the "Nessi" browser based on the open source browser Mozilla, all links on a site were marked with a colored frame. Each color was associated with a brain response (e.g., green for cortical positivity and red for negativity). This program created a hidden internal binary selection tree and changed the colors of the links accordingly each trial. The task for the patient was simply to view the desired link and respond to the current color frame with the associated brain response (Mellinger et al. (2003)). Nessi was successfully tested in two ALS patients with remaining vision. The modular design of this system and its compatibility with both the TTD and the BCI2000 means that it can be used easily with more than two response conditions and with brain responses other than SCPs.

(4) Visual versus auditory feedback: As locked-in patients such as patients in end-stage ALS are sometimes no longer able to focus visually on a computer screen, a BCI should have the option to be controlled auditorily. Therefore, the TTD was modified to present all information necessary for brain-computer communication in the auditory channel. To investigate how well SCP regulation can be achieved with auditory feedback compared to visual feedback and combined visual and auditory feedback, a study with eighteen healthy subjects and each of the three modalities was carried out. The result showed that auditory feedback enabled most of the subjects to learn SCP self-regulation within three sessions. However, their performance was significantly worse than for participants who received visual feedback. Simultaneous visual and auditory feedback was significantly worse than visual feedback alone (Hinterberger et al. (2004a)).

(5) Brain mechanisms for successful SCP regulation: Two studies with functional MRI were carried out to investigate the blood oxygen level dependent (BOLD) activity during SCP control. In the first study, the patients were asked to apply the strategy they used for SCP regulation in the MRI scanner. In a second study, the EEG was measured and the SCP fed back in real time inside the scanner. A sparse sampling paradigm allowed simultaneous measurement of EEG and BOLD activity. An online pulse artifact correction algorithm in the TTD allowed undisturbed feedback of the SCP in the scanner (Hinterberger et al. (2004c)). Twelve trained subjects participated. Success in producing a positive SCP shift compared to a negative shift was related to an increase of the BOLD response in the basal ganglia. Successful negativity was related to an increased BOLD in the thalamus compared to successful positivity. These results may indicate the learned regulation of a cortico-striatal-thalamic loop modulating local excitation thresholds of cortical assemblies. The initial contingent negative variation (readiness potential) as a major component of the SCP was associated with an activation at the vertex where the feedback electrode was located. The data support the conclusion that human subjects learn the regulation of cortical excitation thresholds of

large neuronal assemblies as a prerequisite for direct brain communication using an SCP-driven BCI (Hinterberger et al. (2005b)).

Acknowledgments

Notes

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