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The thought translation device: a neurophysiological approach to communication in total motor paralysis

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Abstract A thought translation device (TTD) for brain-computer communication is described. Three patients diagnosed with amyotrophic lateral sclerosis (ALS), with total motor paralysis, were trained for several months. In order to enable such patients to communicate without any motor activity, a technique was developed where subjects learn to control their slow cortical potentials (SCP) in a 2-s rhythm, producing either cortical negativity or positivity according to the task requirement. SCP differences between a baseline interval and an active control interval are transformed into vertical or horizontal cursor movements on a computer screen. Learning SCP self regulation followed an operant-conditioning paradigm with individualized shaping procedures. After prolonged training over more than 100 sessions, all patients achieved self-control, leading to a 70–80% accuracy for two patients. The learned cortical skill enabled the patients to select letters or words in a language-supporting program (LSP) developed for inter-personal communication. The results demonstrate that the fast and stable SCP self-control can be achieved with operant training and without mediation of any muscle activity. The acquired skill allows communication even in total locked-in states.

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Introduction

Some neurological conditions, such as amyotrophic lateral sclerosis (ALS), polyneuritis with Guillan-Barré-Syndrom, or brain-stem infarct, can lead to severe motor disability. Such patients are referred to as “locked-in” because they are often completely paralyzed and not able to communicate with caregivers or to express their needs and feelings. In addition to tetraplegia, a lack of control over head and eye movements as well as facial muscles appears in some cases (Harvey et al. 1979; Hayashi and Kato 1989). Even when small muscle twitches are possible, they are often unreliable. Many patients cannot use conventional devices made for patients with severe motor disability, because these require consistent control over at least one muscle group.

Recent studies indicate that humans can learn to control certain components of their EEG and can use them as a new communication channel. Unlike conventional alternative communication methods, EEG-based communication requires no neuromuscular control. Therefore, computer mediated communication may be a possibility for locked-in patients (Birbaumer 1997; McFarland et al. 1993; Pfurtscheller et al. 1996; Wolpaw and McFarland 1994; Wolpaw et al. 1991, 1997).

Birbaumer and coworkers (Birbaumer 1984; Birbaumer et al. 1981b, 1990; Rockstroh et al. 1989) demonstrated that healthy subjects can attain reliable control over their slow cortical potential (SCP) amplitude at the vertex (Cz, according to the international 10-20 system), if it is reinforced for the brain response. Compared with other EEG signals, SCPs have two important advantages: first, they are present in the brain activity of every person, whereas rhythmic EEG components (such as alpha- or μ-rhythm) cannot be recorded in some subjects. Second, the physiological function of SCP shifts from

500 ms up to 10 s duration and the underlying neurophysiological mechanisms are better understood than oscillatory phenomena in the EEG and MEG (Birbaumer et al. 1990). Furthermore, the control of SCP was found to be highly specific; human subjects can produce positive or negative SCP shifts over the right versus the left hemisphere (Birbaumer 1984; Birbaumer et al. 1981b, 1990; Rockstroh et al. 1989) or over the anterior versus the posterior cortex (Birbaumer et al. 1992). A possible disadvantage of the SCP is the necessity of a low time constant and, hence, contamination by electrooculogram (EOG) artifacts. However, reliable techniques for on-line EOG-artifact control during SCP self-regulation have been developed since early 1980's (Birbaumer et al. 1981b; Kotchoubey et al. 1996b, 1997; Rockstroh et al. 1993).

For communication, however, the technique employed in those studies is too slow. The minimal duration of a trial is 6 s, and that of the inter-trial interval is about 4 s. Even a very efficient patient, who has learned to control his or her brain potentials perfectly, would need at least 10 s to perform one action. Therefore, a SCP self-regulatory method has been developed for communication purposes only (Kotchoubey et al. 1997). A timing paradigm was introduced, in which subjects can choose the brain polarity they intend to control. With this technique, as described below, a well-trained patient requires 4 s for one action.

Electrical potentials from the patient's brain operate a software system usually presented in a menu structure. The menu can contain words or whole phrases for functions to control the patient's environment (switches etc.). The brain signal can be used to choose letters and *to spell words*, which are then printed as text, or pronounced, or both. In the simplest case, the patient produces *one distinct brain response* (e.g., increase of the negative potential at vertex) or suppresses this response if necessary. This is sufficient to master a "passive" language-supporting program (LSP), in which letters are automatically presented for selection. Some patients can attain the next level of difficulty and generate two different cortical signals along the same dimension, e.g., either positive or negative SCP shifts. The additional second signal can be used for different functions (e.g., correction), accelerating the spelling process considerably. Alternatively, a second brain response may be employed in an "active" LSP, in which patients decide with their brain responses whether or not to proceed to a new function. The first response can indicate "go ahead" and the second "select". Humans can further learn to control several two-dimensional brain signals simultaneously. For example, Wolpaw and McFarland (1994) recorded the amplitudes of the Rolandic mu-rhythm of the right and the left motor cortex and trained their subjects to increase or decrease the sum and the difference of the Rolandic rhythm at these locations. Similarly, subjects of Kotchoubey et al. (1996a, 1997) learned to control positivity versus negativity at Cz and simultaneously to control the amplitude difference between C3 and C4. In this case, four brain responses (in two dimensions) allowed patients to operate a multi-level menu, using one dimension for forward and backward movements within the current level and using the other dimension for proceeding onto another level, i.e., "enter" and "escape" functions.

Subjects learn to self-regulate their SCP activity within a feedback paradigm. A feedback device provides prompt measurement of cortical activity and presents it in a simple, easy-to-perceive manner (e.g., ball movement on a screen) (Miller 1978). The training procedure is based on the operant-conditioning paradigm (Ferster and Skinner 1957). A feedback of the correct response serves as a reward. The desired reaction is systematically shaped. Shaping is a widely used training technique, in which a desired motor, physiological, or behavioral objective is approached in small steps by successive approximations (Taub et al. 1994). The technique has been used extensively in humans with mental retardation, self-injurious behavior, depression, motor deficits, children with autism, and for a variety of other conditions. Because different individuals have different characteristics of EEG activity and baseline performance, the shaping procedure must be adapted to each individual separately.

For communication through brain activity, three major problems must be solved. First, the learning ability of completely paralyzed patients must be proven. It cannot be ruled out that healthy controls as well as neurological patients with intact motor abilities (e.g., epilepsy: Rockstroh et al. 1993) regulate their SCP by using peripheral strategies, for instance varying muscle tension to modulate the sensory input to the cortex. A paralyzed patient is obviously unable to employ such a strategy. Second, the EEG must be analyzed on-line for immediate reinforcement. The on-line analysis must include all the transformations necessary to extract the to-be-controlled signal from the background noise (e.g., filtering, spectral analysis, baseline correction, elimination or correction of artifacts, or both, etc.). The cortical process must be converted on-line into a signal (e.g., cursor movement) that can be observed by the user. Third, the software has to be flexible in order to adjust it to the individual shaping procedure. The study presented here proposes a solution to these problems.

Materials and methods

Selection of EEG channels for communication

The EEG was recorded from Cz, C3, and C4 (the left and the right hand cortical motor areas) of the 10-20 leads. SCP shifts from Cz (vertex) serve as the primary signal, which has to be controlled and used for operating the thought-translation device (TTD). Cz was recorded against both A1 (left mastoid) and A2 (right mastoid), instead of the standard recording against linked mastoids, or against the nasion (patient HPS). A simulated Cz-linked mastoid channel was calculated on-line as 1/2 [(Cz-A1) + (Cz-A2)]. This avoided problems of linked-mastoid references. For example, the calculated Cz-mastoid dipole is strictly sagittal in the midline, which implies that horizontal eye movements, being orthogonal to the sagittal plane, have no effect on the Cz amplitude. Thus, correction needed to be made only for the vertical EOG (vEOG), which was recorded with a pair of electrodes placed above and below the left or right eye.

Fig. 1 Training patient HPS in his home: on the *right side* is the PC, which controls the on-line system and shows the EEG and electrooculogram. In the *middle* is the trainer surveying the patient's behavior. In the *back*, one can see the amplifier, and on the *left side* is a PC giving slow-cortical-potential feedback to the patient

If a patient mastered two-dimensional self-regulation, SCP asymmetry between C3 and C4 could constitute the second dimension. C3 was recorded against C4 and C4 against Cz. This configuration allowed off-line potential amplitudes to be calculated in each channel in relation to any reference. When the bipolar C3-C4 channel was used as an operant response, the horizontal EOG (hEOG) had to be recorded by electrodes at the outer canthi of both eyes.

Using 8-m Ag/AgC1 electrodes and Elefix electrode creme, an impedance less than 5 kΩ could be attained. The presence of various electrical fields in the patient's private rooms, which are not, in contrast to electrophysiological labs, electromagnetically shielded, required such a low electrode impedance. The signals were amplified with an EEG amplifier set to a low-pass filter of 30 Hz and a time constant of 8 s and then digitized with a sampling rate of 100 Hz. Though different EEG amplifier systems can be used, the availability of a long time constant (corresponding to a high-pass of at least 0.2 Hz) is essential.

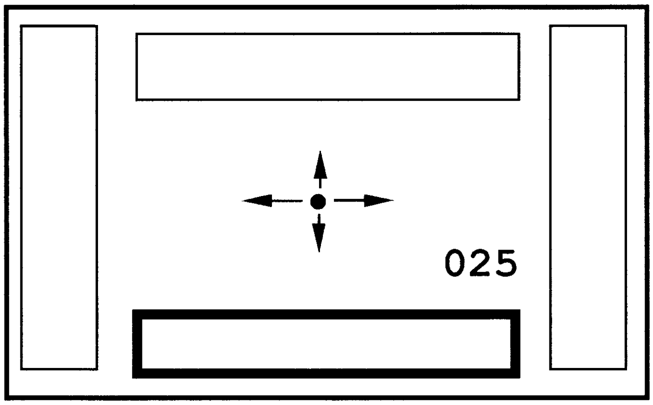

Fig. 2 A schematic drawing of the feedback display with a ball in the center, whose vertical and horizontal positions are controlled by the amplitude of slow cortical potentials at Cz-mastoids and C3–C4 channels, respectively (from Appl Psychophysiol Biofeedback, vol. 22, no. 2, 1997, with permission)

Procedure

Usually, patients sat in wheelchairs or beds and viewed a color PC (notebook) screen (Fig. 1), on which two rectangles (goals) and a small moving object (ball) were displayed. The viewing distance was about 140 cm. If the second (C3–C4) channel was used, two more goals (on the right and the left frame of the screen) were displayed in addition to the top and the bottom goals (Fig. 2).

A training session consisted of 100–200 4-s trials. Two alternating tones of different pitch, which followed each other in an interval of 2 s, held the patient to the rhythm of the program. The ball could only move during the 2-s phase between the low-pitch tone and the high-pitch tone (active phase) and remained in the center of the screen during the 2-s phase between the high-pitch tone and the low-pitch tone (baseline phase). The patient's task was to move the ball in a specified direction toward one of the goals during the active phase. To indicate the target direction, the goal into which the ball had to be transferred by the brain response was illuminated (in Fig. 2, bottom goal).

Only the last 500 ms of the so-called baseline phase served as an actual baseline for the SCP-feedback calculation, i.e., the mean EEG amplitude within this 500-ms window, was taken as zero. During the following 2-s active phase (feedback phase), the current SCP-amplitude was calculated every 100 ms as an average over the last 500 ms (sliding time window). The current position of the ball corresponded to the difference between every 500-ms time window and the 500-ms baseline. Vertical ball movements indicated SCP changes at Cz, whereas horizontal movements were controlled by the C3 minus C4 signal, thereby reflecting hemispheric differences at central regions (Fig. 3). The minimum SCP amplitude difference between baseline and active phase necessary to move the ball from the center of the screen into a goal was defined individually.

Thus, the subject's task was to produce SCP shifts in a 4-s rhythm paced by the alternation of the baseline phase and the active phase. If a negative potential had to be produced in the active phase, compared with the baseline interval, the ball moved upwards, and conversely, when the potential was more negative during the baseline interval than during the following active phase ("positivity"), the ball moved downwards. If there was no difference between the baseline interval and the SCP amplitude in the active phase, the ball remained in the center of the screen.

Artifact correction

Because it was used for both healthy controls and patients with varying degrees of eye movement control, the system needed to correct for eye-movement potentials that can influence the EEG.

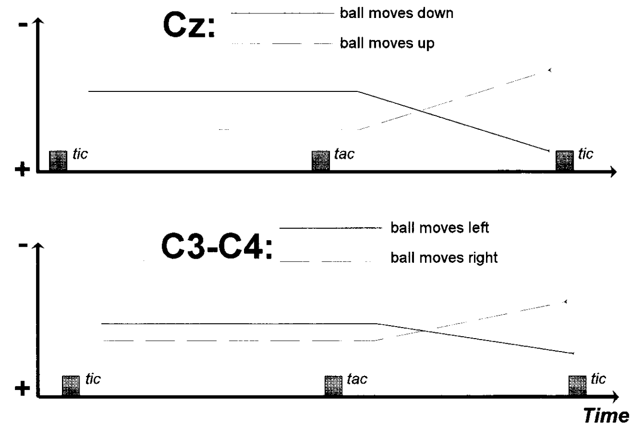

Fig. 3 Changes in slow cortical potentials (SCP) at Cz-mastoids (*above*) and C3–C4 channels (*below*) during a trial. Ball movements depend on the SCP change between *tac* and *tic* (i.e., in the *active phase*) subtracted from the baseline between *tic* and *tac* (from Appl Psychophysiol Biofeedback, vol. 22, no. 2, 1997, with permission)

Several reliable techniques for off-line EOG correction exist (Berg-Lenssen and Brunia 1990; Gratton et al. 1983). The following algorithm for on-line EOG-correction is based on the fact that neither the Cz-linked mastoid channel can be affected by horizontal eye movements, nor can the C3-C4 difference be affected by vertical EOG artifacts. Therefore, the Cz channel had to be corrected for vEOG only, and the C3-C4 channel for hEOG only. The Cz-linked mastoid channel was used for SCP feedback in all patients.

The maximum vEOG influence on the EEG signal at vertex was assumed to be 10% (Lutzenberger et al. 1985); therefore, the vEOG was multiplied by 0.1 (preset correction factor β) and then subtracted from the EEG at vertex. For the hEOG, β was assumed to be 20% (Lutzenberger et al. 1985). As we focussed on the feedback of slow waves, the correction was calculated for averages of EEG and EOG – referred to as A_{EEG} and A_{EOG} – in a sliding time window of 500 ms. To compute the ball position at a given time, the average current slow-wave signals $A_{EEG}(t)$ and $A_{EOG}(t)$ in the active interval were compared with the EEG and EOG values in the baseline interval – referred to as B_{EEG} and B_{EOG}:

$D_{EEG}(t)=k(B_{EEG}-A_{EEG}(t))$, and

$D_{EOG}(t)=k(B_{EOG}-A_{EOG}(t))$,

where $D_{EEG}(t)$ is the current ball position, and k is the transformation coefficient of μV into screen amplitude values.

For the EOG correction, three cases have to be distinguished:

1. No correction is necessary when $D_{EEG}(t)$ and $D_{EOG}(t)$ have different signs.
2. When $D_{EEG}(t)$ and $D_{EOG}(t)$ have the same sign and $|D_{EEG}(t)| > |\beta D_{EOG}(t)|$, $D_{EEG}(t)$ is calculated as described above. Thus,

   $D_{EEG}(t)=k[(B_{EEG}-A_{EEG}(t))-\beta D_{EOG}(t)]$

3. $D_{EEG}(t)$ and $D_{EOG}(t)$ have the same sign and $|D_{EEG}(t)|\leq|\beta D_{EOG}(t)|$: no ball movement occurs, i.e., $D_{EEG}(t)=kB_{EEG}$.

This algorithm corrects *only those EOG changes whose polarity coincide with the EEG shift, opposite-direction EOG potentials are not corrected*. It implies further that the value subtracted from the current EEG amplitude cannot be larger than the EEG amplitude itself [in case (3), the ball just remains in the center of the screen]. This avoids the risk of overcorrection.

For off-line EEG analysis, the exact correction factors for the vEOG were computed using the algorithm of Gratton et al. (1983). For the hEOG, the correction factors were calculated as EEG/hEOG regression coefficients after subtraction of averaged event-related activity from EEG and hEOG channels. Epochs contaminated with other artifacts (such as zero-activity epochs, out-of-scale values, or amplitudes >125 μV) were discarded. The preset correction factor used in the on-line correction could be adjusted in the following training session on the basis of the data obtained during off-line processing of the preceding sessions.

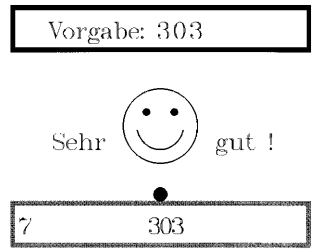

Fig. 4 An example of the feedback display during training at the moment when the patient has just completed the task “3 0 3”, i.e., hit, no hit, hit. The task is formulated in the top goal, and the cumulated frequency of reinforced trials in the bottom goal, left. The current performance within a task sequence appears in the center of the bottom goal. The appearance of the smily face and “sehr gut” (=”very good”) reinforces the patient’s performance

Shaping

An individual schedule of reinforcement and an individualized shaping procedure were both necessary for rapid learning. Each subject had to learn to produce a reliable brain signal that included two distinct brain responses, i.e., negativity versus positivity at vertex (ball moves up or down), more negativity versus less negativity (ball moves up or not), or more positivity versus less positivity (ball moves down or not). At the very beginning, the baseline performance of the patient had to be determined (i.e., the noise in the response system). In the first step, patients had to respond with correct negativity for 50% and correct positivity for 50% of the trials. The object was to determine which polarity was easier for the patient. As patients usually preferred one direction (i.e., positivity or negativity), training started by shaping the signal only for the preferred goal. To simplify the feedback, ball movement produced by the opposite brain responses (e.g., ball movement in the top goal when the bottom goal is the target) was damped by a factor 0.3. When the ball had to be kept in the center of the screen, no ball-movement damping occurred. For every correct response, patients were presented with an illuminated smiling face on the screen saying “very good”, “fine”, “fantastic”, etc. as a positive reinforcement, and a running tabulation of correct responses, kept on the bottom left of the screen, was increased by one in order to allow patients to keep track of their correct responses.

The current task was shown in the goal box at the top of the screen (Fig. 4). The task “hit the top goal” was referred to as “1”, “hit the bottom goal” as “3”, and “keep the ball in the center of the screen” as “0”; thus, different task sequences were, for example, “hit the bottom goal, then keep the ball in the center of the screen” or “hit the bottom goal, then keep the ball in the center of the screen and then hit the bottom goal again”, etc.

Two different types of errors can occur in the patient’s performance: misses or type-I errors were counted when a goal should have been hit and was not; false alarms or type-II errors were counted when a goal was erroneously hit. Misses caused no change in the program, they only slowed down the patient’s performance. For patients who are completely dependent on others, even the possibility of controlling the realization of an action in several seconds is perceived as a significant achievement. However, false alarms are worse, as non-intended commands could be performed, i.e. selecting an erroneous letter. Thus, the procedure was arranged to decrease type-II errors.

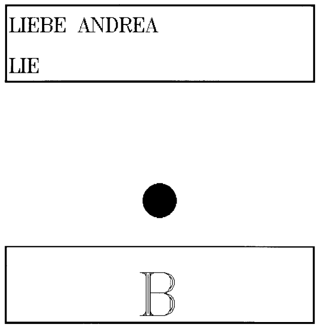

Fig. 5 The display viewed during the language-supporting program. The top goal indicates the required letters or words ("DEAR ANDREA") as well as the already written letters. The set of letters for selection is shown in the bottom goal. In the case depicted, the patient has to select the letter "B". In order to do this, the patient has to move the ball into the bottom goal. If the characters shown should not be selected (if it doesn't contain the required letter), the patient's task would be to keep the ball away from this goal

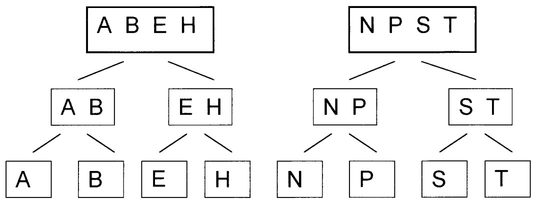

Fig. 6 Dichotomic spelling structure of the language-supporting program with eight letters on three levels. First, patients have to choose, on the first level, between A-B-E-H or N-P-S-T. If, e.g., A-B-E-H is selected, patients then have the choice between A-B or E-H on the second level. If, e.g., A-B is selected, patients now have, on the third level, the possibility to write the letter A or B. If A is selected, it appears in the top goal of the screen

When the patient achieved the desired level of competence, which is about 70% correct responses, the criterion was raised. When this criterion was stably attained, it could be raised again. Specifically, two response criteria were shaped in the training procedure: first, the length of a task sequence, e.g., hit, no hit, hit (see Fig. 4); second, the minimum number of trials during which the particular task sequence had to be completed. For example, the patient first had to perform the task-sequence "hit the bottom goal and then keep the ball in the center of the screen" within 10 trials, then within 9, 8, ... 2 trials.

When patients mastered a three-component task sequence (e.g., "keep the ball in the center of the screen, again keep the ball in the center of the screen, and then hit the bottom goal") in about 70% of the trials over two sessions, they were shifted to the language supporting program (LSP).

Production of language with slow cortical potentials

The same goals used in the preceding training period here presented a word or letter sequence (the lower goal) and a space for the patient's own text (the upper goal). The ball movements continued to reflect the patient's current brain responses. The appearance of the screen during selection of letters, syllables, or words was quite similar to the training condition, as shown in Fig. 5, to aid the transfer of the acquired self-regulation skill.

Severely paralyzed patients frequently use commercial devices operated by finger or eye movement, with letters being automatically presented and the patient selecting the desired letter with a muscle twitch. In most devices, either the entire alphabet is presented and the letters are arranged according to their frequency in the corresponding language, as described by Bauby (1997), or the letters are alphabetically ordered in 4–7 rows, 4–6 symbols in each row, where the last row may include digits, punctuation marks, or both (Beukelmann and Mirenda 1992). In the latter case, the letter selection consists of two stages, i.e., the patient first chooses the row, then the symbol in the particular row. In the former case, the selection process entails only one step, but requires extensive waiting before a low-frequency letter is presented. A Monte-Carlo simulation of the language production has revealed, however, that both methods are efficient if the accuracy of the patient's physiological responses is very high (above 95%) (Perelmouter et al., submitted). Even if voluntary somatic responses are available, some paralyzed patients cannot attain a high level of accuracy because of EMG noise due to myoclonic twitches or rapid fatigue. When EEG responses reach an accuracy of 80–85%, the method of choice is a dichotomic LSP structure. At the first level, the alphabet is divided in two parts, at the second level each half is divided into two quartiles, etc., up to the last level containing only one letter (see Fig. 6). The number of necessary levels in most European languages is 5, as the entire alphabet and the most important punctuation marks consists of 2^5=32 symbols. Artificial languages can operate with fewer symbols; e.g., the Morse alphabet consists of only two symbols (i.e., one level).

Although the selection process with a dichotomic LSP needs more stages than in the two above-mentioned structures, each stage requires considerably less time, because only two sets of symbols are presented at each step for selection. A correction sign is presented at each level, on every third trial. Thus, if the frequencies of both type-I and type-II errors are 0.2, the probability of writing at least one letter within 1000 trials in the dichotomic structure is larger than 0.99, and the mean number of trials per letter is 23.95 (using the German alphabet plus three punctuation marks and the space symbol). With the same error frequency, the probability of writing one letter in 1000 trials would be only 0.14 and 0.53 in the frequency-ordered structure and in the two-step structure, respectively. The mean number of trials per letter in both structures exceeds 100.

As in the training condition, learning to use the LSP proceeded from easy to more-difficult tasks. It started with a two-level dichotomic structure, i.e., with four letters. Syllables and short words, such as "man", "color", or "attain", could be written in this easy mode. After the patient had mastered the task (100% correct), the program progressed to three levels (i.e., eight letters), which substantially enlarged his or her vocabulary. With four levels (16 letters), virtually all words and word combinations could be written.

Subjects

Healthy subjects

Thirteen subjects, (four female), aged 22–54, all right-handed, took part in a one-session SCP self-regulation training. Two male and three female subjects participated in additional prolonged SCP asymmetry training. Specifically, subject VIII participated in six daily sessions, subject XVI took part in 13 sessions, and subject XII, XIV, and XV, had 16 sessions each. All subjects had normal vision, a Wechsler IQ>115, and no history of neurological or psychiatric diseases. Subjects were paid DM 20 (about US$ 13) per session.

Patients

Patient JB: male, 50 years old, diagnosed with ALS since 1994 (bulbar familiar form), artificial ventilation and feeding since 1994, followed by tetraplegia. Small eye movements, hardly visible and error prone because of rapid exhaustion, are used for communication.

Patient MP: male, 37 years old, diagnosed with ALS since 1985, severe tetraparesis with expressive speech disorder (only his wife can understand some of his utterances). Head movement and minor hand movements are used for communication.

Patient HPS: male, 42 years, diagnosed with ALS since 1989, artificial ventilation and feeding since 1993, almost totally paralyzed except for two facial muscles (M. levator labii superioris alaeque nasi and M. depressor anguli oris) and unreliable eye movements.

Statistical analysis

In order to demonstrate the extent and significance of self-regulation of healthy participants with the above described TTD, the mean amplitudes of ball movements in both vertical and horizontal dimensions were calculated for each single trial. Thus, for each of the four conditions (i.e., top target, bottom target, right target, and left target), a distribution of ball positions on the screen was obtained. These amplitude values were then normalized by division by the standard deviation of the corresponding distribution. The mean value of the resulting normalized distribution indicated the stability of production of a particular response (e.g., positivity at vertex). Another measure was needed for estimation of the significance of differentiation between two opposite responses (e.g., positivity vs. negativity at vertex). For this purpose, a point-biserial correlation between the ball position and target location (e.g., top versus bottom) was calculated according to Wolpaw and McFarland (1994).

As patients MP and JB learned only one signal (positivity vs. less positivity at vertex), and, thus, in any particular trial only one of four outcomes could occur [i.e., correct hits (bottom goal), correct rejection (i.e., to not hit the bottom goal), miss, or false alarm], the significance of individual results within a session was simply estimated by a chi-square test for a 2×2 table. Patient HPS, in contrast to the two other patients, learned both kinds of signals (i.e., positivity and negativity); but, as he performed much better with the positivity response, only this response was used in the following language production with LSP. For comparison, only positivity responses were taken for statistical analysis in all patients. To estimate the accuracy across sessions, two levels of responses were specified: first, goal responses, which had an amplitude equal to or larger than the threshold required to reach the goal; and, second, minimal response, i.e., minimum SCP changes in the target direction (all responses larger than 0.5 μV were considered). The minimal responses were used because the threshold μV values were set arbitrary, and, therefore, a biased result might be obtained if only the goal responses were calculated. For instance, if too high a threshold was set, the patient might have produced increasingly more responses in the target direction across sessions, but the values used in the analysis would remain zero if the patient did not reach this arbitrary threshold. However, this hypothetical case did not take place. In fact, both hits and minimal responses in the target direction changed in parallel, indicating that the threshold values were either too high nor too low. The correlation between the goal response and the minimal response in the target direction being (for the three patients) 0.89, 0.72, and 0.91. Thus, the information on both correct hits and minimal target responses was redundant, and only correct hits will be reported below.

Results

Healthy subjects

The overall, average slow cortical potentials of the healthy subjects are presented in Fig. 7. As can be seen, the differentiation between negativity and positivity at the vertex was about 7 μV and between C3 and C4 was about 5 μV. The normalized mean amplitude of ball-movements for upward and downward conditions, respectively, which indicates the consistency of ball-movements in the particular direction, and the point-biserial correlations between SCP-amplitude and direction of ball-movement, indicating how consistent the differentiation between the two directions were, are shown in Table 1. As can be seen in this Table, 10 out of 13 subjects participating in the single-session positivity-versus-negativity training attained significant SCP control. Four of them were able to produce significant positivity responses, three generated significant negativity responses, and three produced both kinds of responses.

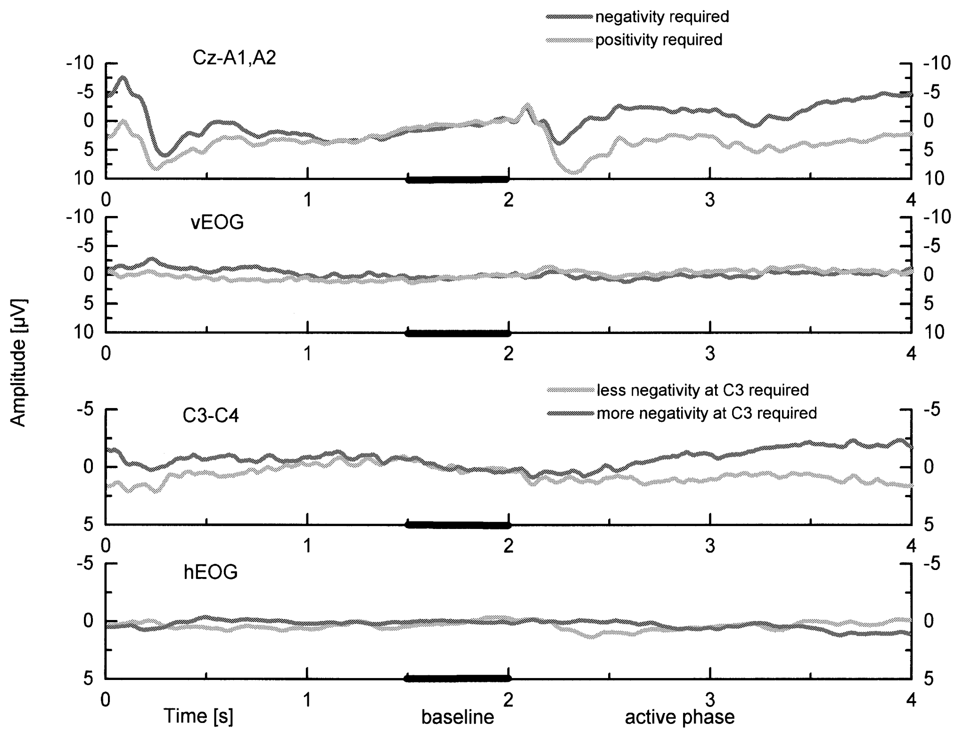

Fig. 7 Overall mean slow-cortical-potential (SCP) waveforms of healthy subjects. *Upper panel* The SCP at vertex and the vertical electrooculogram (EOG), averaged during the single training session over 13 subjects. *Lower panel* The SCP difference between the left (*C3*) and the right (*C4*) motor cortex and the horizontal EOG, averaged across the last three training sessions for the five subjects participating in prolonged training. *Thick lines* between 1.5 s and 2 s indicate the baseline. *Cz* EEG at the vertex, *vEOG* vertical EOG

Table 1 Results of the single-session slow-cortical-potential amplitude in 13 healthy subjects

	Subject												
	I	II	II	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII
M_{up}[a]	0.85	4.18*	2.95*	–0.56	1.07	3.08*	–0.49	2.75*	1.38	1.14	5.66*	2.74*	4.13*
M_{down}[a]	0.14	1.73	–2.24*	–4.37*	–3.22*	0.49	–1.05	–0.69	0.33	–3.00*	–2.84*	–1.22	–3.51*
R_{pbis}[b]	0.110	0.339*	0.424*	0.284*	0.339*	0.422*	0.115	0.371*	0.167	0.349*	0.461*	0.374*	0.455*

*P<0.05

[a] M_{up} and M_{down} represent normalized mean amplitude of ball movements for upward and downward conditions, respectively; they indicate how consistent the ball movements in the particular direction were; upward movements are positive, and downward movements are negative

[b] R_{pbis} indicates how consistent the differentiation between the two directions was

Table 2 Mean percentage of hits and false alarms at the beginning and the end training for patients HPS, JB, and MP

	First 20 sessions	Last 20 sessions	Mann-Whitney test, 2-tailed
HPS			
Hits	66.8%[a]	86.7%	z=4.90*
False alarms	69.0%	48.5%	z=5.41*
JB			
Hits	11.8%	46.2%	z=5.23*
False alarms	26.1%	26.0%	z=0.54
MB			
Hits	25.7%	66.1%	z=5.33*
False alarms	66.4%	23.8%	z=5.17*

*P≤0.0001

[a] From these numbers, percentages of other kinds of responses can be calculated (i.e., misses = 100 minus hits; correct rejections = 100 minus false alarms)

Table 3 Average time (in s) to select a letter in a session

Session	Time per letter	
	Patient HPS	Patient MP
1	125 (2)[a]	96 (2)
2	47 (2)	35 (2)
3	39 (2)	12 (2)
4	79 (2)	156 (2)
5	39 (2)	148 (2)
6	52 (2)	65 (2)
7	129 (2)	88 (2)
8	51 (2)	10 (2)
9	96 (2)	11 (2)
10	31 (2)	37 (2)
11	37 (2)	12 (3)
12	87 (3)	38 (3)
13	42 (3)	66 (3)
14	49 (3)	88 (3)
15	192 (3)	45 (3)
16	90 (3)	46 (3)
17	32 (3)	31 (3)
18	43 (3)	92 (3)
19	54 (4)	72 (3)
20	70 (4)	54 (3)

[a] The number in brackets indicates the number of levels of the language-supporting program: two levels = four letters, three levels = eight letters, four levels = 16 letters

Three out of five subjects who participated in prolonged brain-asymmetry training demonstrated highly significant self-control over the asymmetry of SCP amplitudes between the right and the left motor cortex after 10–13 sessions. The point-biserial correlations between SCP amplitude and direction of ball movement for subject XII in the last three sessions were 0.65, 0.56, 0.48, respectively (all P<0.01). For subject XIV, these correlations were 0.43, 0.60, and 0.47, respectively (all P<0.01), and for subject XVI, 0.31, 0.37, and 0.40, respectively (all P<0.05). The fourth subject (VIII), who only took part in six asymmetry training sessions also achieved a large asymmetry in the last two sessions (r_{pbis}=0.19 and 0.17, respectively); however, this tendency did not reach the 5% significance level.

Patients

SCP curves of the three patients, averaged according to the task, are presented in Fig. 8. The left panels show patients' EEG changes at vertex and vEOG for the very first ten training sessions, i.e., an average over at least 1000 trials: there was no differentiation between the two tasks. Patient JB tried to control the signal with eye-movement, but was, of course, not successful. The right panels show EEG curves of ten sessions (1000 trials) for all patients more than 100 sessions later. All patients differentiated between the two task requirements "hit required" (bottom goal) and "no hit required" and produced a positive SCP shift compared with the baseline in order to hit the bottom goal. Patient JB generated an EEG amplitude difference of only 5 μV at the end of the trial, whereas patient HPS achieved about 10 μV in the 2.5- to 3.5-s time window. The highest EEG amplitude difference could be seen in patient MP, who achieved 17 μV 3.2 s after the high-pitch tone and could maintain this difference until the end of the trial. In the Cz panels of patients JB and MP, the auditory-evoked potentials on the high-pitch and low-pitch tone, respectively, can be seen 200 ms after the tone. In the EEG curves of patient HPS, these potentials can hardly be seen, probably due to a different reference (nasion). The patients required 20–40 sessions to achieve significant SCP control. After this, the chi-square test was highly significant in practically every session, indicat-

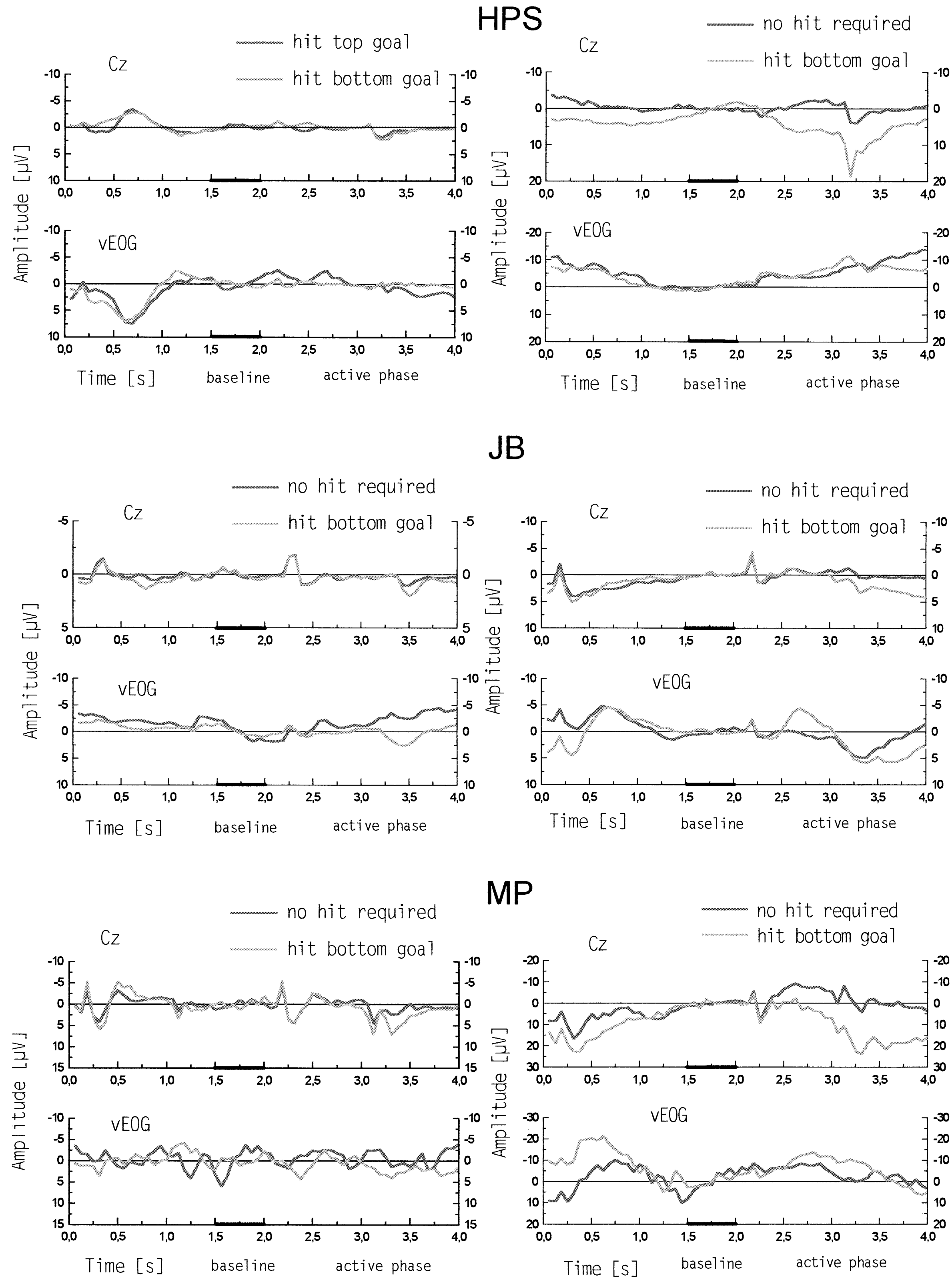

Fig. 8 Slow-cortical-potentials (SCP) waveforms of the three amyotrophic-lateral-sclerosis patients (*HPS*, *JB*, and *MP*) at the beginning of training (*left side*) and during writing sessions using the language-supporting program (*right side*). Each waveform represents the average of ten consecutive sessions. Obviously, all patients could not control their SCP at the beginning of training. After several months of training, SCP curves of all three patients demonstrated significant differences in the required direction. *Cz* EEG at the vertex, *vEOG* vertical electrooculogram. Note the different scaling on the y-axis

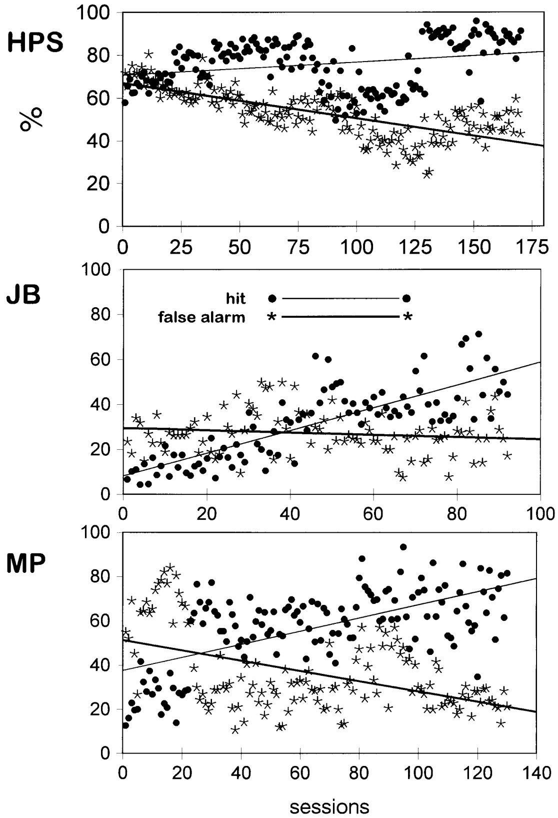

Fig. 9 Percentage of correct responses (hits: •——•) and wrong responses (false alarms: ∗——∗), as a function of session, in the three amyotrophic-lateral-sclerosis patients (*HPS*, *JB*, and *MP*)

ing that patients were able to produce the required cortical signals.

Figure 9 represents learning curves for the three patients in terms of their hit and false-alarm rates. Both kinds of responses changed during training, indicating the learning process. Specifically, highly significant linear trends were found in patients HPS ($F_{168,2}$=19.0, and 181.1, for hits and false alarms, respectively; both P<0.001) and MP ($F_{128,2}$=65.6, and 41.9, for hits and false alarms, respectively; both P<0.001), as well as for hit responses (only) in patient JB ($F_{90,2}$=177.5, P<0.001).

To further check learning effects, we conducted a 2-by-2 ANOVA for each patient, where the response-type (i.e., hits versus false alarms) was taken as a repetition factor, and time (i.e., the first 20 sessions versus the last 20 sessions) served as a group factor. A main effect of response-type was significant only in patient HPS ($F_{38,1}$ =146.5, P<0.0001), indicating that he made, generally, more hits than false alarms. A main effect of time was significant in patient JB ($F_{38,1}$=57.1, P<0.0001), indicating that he produced more positivity responses (regardless of them being correct or wrong) at the end of training than at the beginning. Most interesting was, however, the response-type by time interaction, which would suggest that patients learned to produce more hits or fewer false alarms or both with time. This interaction was, in fact, highly significant in all patients ($F_{38,1}$=185.9, 114.7, and 312.0 for HPS, JB, and MP, respectively; all P<0.0001). These data are presented in Table 2.

Interestingly, the changes of correct and wrong responses across sessions were not related to each other. The bivariate correlations varied between –0.08 (ns) and 0.22 (P=0.015); when the session number was partialled out, these values were between –0.09 and 0.11 (all ns). This suggests that learning to produce appropriate responses and to suppress inappropriate ones constitutes two different processes.

With the accuracy level attained after 40–120 training sessions, patients HPS and MP could use a dichotomic LSP structure (Fig. 6) for writing single words and combinations of three to four words. Table 3 shows the results of the first LSP sessions for these two patients. As can be seen, the average time needed per letter varied from 31 to 129 s for patient HPS and from 10 to 148 s for patient MP in writing with four letters on two levels. With eight letters on three levels (Fig. 6), this time varied from 32 to 192 s for patient HPS and from 12 to 92 s for patient MP. Patient JB did not yet consistantly have the response accuracy needed to be shifted to the LSP.

Discussion

The data demonstrate that both healthy subjects and nearly completely paralyzed locked-in patients with preserved cognitive functions can achieve an accuracy level of 65–85% in self-control of their slow cortical potential shifts with the thought translation device. Two patients using TTD can already write words and short sentences. In addition, the present software can easily be used for control of patient's environment (e.g., call attendant, switch a light on or off, etc.) by means of short task sequences (as described) being linked with corresponding technical devices. Such devices are now in construction.

Although locked-in patients are enthusiastic about new possibilities for communication, even if they require effort, acceleration of the communication process is the most important problem in the present stage of TTD development. Whereas patients using TTD can produce less than one word per minute, the speed of communication for subjects who can use at least one motor channel varies from 5 to 25 words per minute (Mizuko and Esser 1991).

The first and most obvious strategy for achieving a higher speed of LSP communication would be a reduction of the error rate. Previous data indicate that healthy subjects and patients with intractable epilepsies can achieve SCP changes up to 120 μV in amplitude (e.g., Birbaumer 1984; Birbaumer et al. 1981a; Rockstroh et al. 1993). However, data about maximum accuracy of self-control of the SCP are not available. As these potentials play an important role in the regulation of cortical excitability (Birbaumer et al. 1990, 1991; Elbert and Rockstroh 1987), one may suppose that the ability to change SCP "on command" should be limited by some protective mechanism that prevents the cortex from voluntary over-excitation (like the ability to voluntary control respiration is limited by the necessity to maintain a constant gas equilibrium in the blood).

The second possibility to accelerate the spelling speed might be a reduction of the time necessary for each single response. Presently, 4 s are required (i.e., a 2-s baseline phase and a 2-s active phase for selection). Pilot data indicated that healthy subjects and patients experienced a more rapid pace (1.5 s baseline phase and 1.5 s active phase) as being too exhaustive. However, Figs. 7 and 8 show that subjects are able to produce the required response in the active phase within the first 500–800 ms. They may need the time for the baseline phase in order to "prepare" the brain for a rapid response production after the low-pitch tone. If this assumption is correct, an "asymmetrical" rhythm with a 2-s baseline phase and a 1- to 2-s active phase could be tried.

Finally, as the duration of the spelling process is to a large extent caused by the complexity of the alphabet and language structure, *improvement of the language-supporting program* appears promising. Natural languages are redundant; thus, the number of necessary symbols can be decreased. In German, for example, "Umlaut" letters (ä, ö, ü) and ß can be omitted without information loss. Vowels are not necessary (like in Hebrew), and the program can fill in vowels. The program can also take into consideration the conditional probabilities of letters provided by one or two preceding letters and make corresponding suggestions to the patient.

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