The Thought-Translation Device (TTD): Neurobehavioral Mechanisms and Clinical Outcome

Niels Birbaumer, Thilo Hinterberger, Andrea Kübler, and Nicola Neumann

***Abstract*—The thought-translation device (TTD) consists of a training device and spelling program for the completely paralyzed using slow-cortical brain potentials (SCP). During the training phase, the self-regulation of SCPs is learned through visual-auditory feedback and positive reinforcement of SCPs; during the spelling phase, patients select letters or words with their SCPs. A psychophysiological system for detection of cognitive functioning in completely paralyzed patients is an integral part of the TTD. The neurophysiological and anatomical basis of SCP-regulation was investigated by recording of BOLD-response in functional magnetic resonance imaging. Results showed involvement of basal ganglia and premotor cortex for required SCP positivity. The clinical outcome of 11 paralyzed patients using the TTD and quality of life of severely paralyzed patients is described. First attempts to improve learning of brain regulation with transcranial magnetic stimulation were successful.**

***Index Terms*—Amyotrophic lateral sclerosis (ALS), locked-in-syndrome, physiological brain regulation, slow cortical potentials.**

This report provides an update of results obtained with the thought-translation device (TTD) since its first report in IEEE TRANSACTIONS ON REHABILITATION ENGINEERING in 2000 [1]. Methodological details and details of results can be found in Kübler *et al*. [2], [3], Wolpaw *et al*. [4], Kübler and Birbaumer [5], Kotchoubey *et al*. [6], and Hinterberger *et al*. [7].

I. TECHNOLOGY AND FUNCTIONING

In its present form, the core of the TTD consists of a single computer program that runs under all MS-Windows versions. This software contains the functions of electroencephalogram (EEG)-acquisition, storage, signal processing, classification, and various applications for brain–computer-communication such as spelling. It was written in C++ for Windows and uses the BCI-2000 common standard developed in cooperation with the Wadsworth Center group (see Wolpaw *et al*. [32]) The BCI-2000 software can be obtained free of charge from G. Schalk at http://www.bciresearch.org. The file format is fully compatible with the standard. The patient receives visual feedback on a separate monitor and/or auditory feedback. The TTD-software can be connected to several EEG amplifier systems. At the patient's home, an eight-channel EEG-amplifier (PsyLabs, EEG8) with a time constant of 16 s is connected to an A/D-converter (Computerboards, PCIM-DAS 1602/16) serving as the interface to the TTD. As this A/D-converter is also available for notebooks, a portable version of the TTD can also run on notebooks. An interface to an MRI-compatible 16-/32-channel EEG-amplifier (EMR16/32, Schwarzer, Munich) allows the TTD to be used in functional magnetic resonance imaging (fMRI)-studies investigating the basic mechanisms of EEG self-regulation.

The TTD also encompasses a psychophysiological system for detection of cognitive functioning in locked-in-syndrome, vegetative state, apallic syndrome, and coma [8]. This system for detection of cognitive functioning consists of a series of hierarchically ordered experiments using auditory event-related brain potentials (ERPs). The hierarchy of experimental paradigms begins with a simple auditory oddball using frequent and rare tones; it ends with complex sentences using semantic and syntactic errors for detection of the N400 and P600 waves reflecting higher processing capacities. Application of brain–computer interface (BCI) systems and the TTD in completely paralyzed patients is useful only if a minimum of cognitive and neuropsychological functioning is ensured. Only patients with intact ERP differentiation participate in TTD training.

The TTD and BCI-2000 permit recording and online-feedback and reinforcement of slow cortical potentials (SCPs), ERPs, mu rhythm, and other EEG signals in frequency bands up to 40 Hz. Feedback of brain activity in patients with closed eyes or impaired vision can be given auditorily or with bright light through closed eyes. The system for detection of cognitive functioning is available in Hebrew and French, and partly in English, Italian, and German. The spelling system consists of a letter selection system [9] combined with rapid word and sentence completion based on psycholinguistic principles. Letters are presented visually or auditorily by the computer and can be selected with one of the previously mentioned EEG activities. The TTD requires a learning phase of instrumental (operant) learning of physiological self-regulation of brain activity in which 1–8-s epochs of a particular potential (mainly SCP or mu) are fed back and the achieved brain changes are positively reinforced by a smiling face and a harmonic tone sequence. For patients unable to select letters and with no remaining visual function a digital "yes"—"no"version allows the patient to respond to external questions with a brain response, e.g., a negative or positive SCP polarization in a continuous fashion.

II. NEUROBEHAVIORAL MECHANISMS OF PHYSIOLOGICAL CONTROL OF SCPS

In a series of studies over the last 25 years, the neurophysiological basis of SCP and SCP-self-control was studied extensively (for a review see [10] and [11]). This led to a comprehensive psychophysiological model of SCP. More recent investigations used fMRI and transcranial magnetic stimulation (TMS) in healthy subjects and in patients at various stages of the learned acquisition of SCP self-control [7], [12]. The reported physiological mechanisms for SCP control might be generalized to physiological regulation of other EEG/magnetoencephalography (MEG) signals such as mu or P300, but there are, to date, no data available (see [4]).

As shown in Fig. 1, fMRI-recorded BOLD responses averaged over five trained subjects able to produce large ($> 8\ \mu$V) cortical positivities and negativities. The comparable results of a larger group of subjects with a different degree of performance were described in Hinterberger *et al*. [7]. Subjects were trained outside the fMRI scanner for 35 sessions to produce cortical negativities and positivities of 8-s duration in the presence of a discriminative stimulus (S^D) consisting of a single letter ("A" for negativity and "B" for positivity) centered on the computer screen. As a baseline for the fMRI analysis, a third condition (indicated with "C") instructed the patient for passive viewing only without feedback. Feedback of SCP was provided over the whole 8-s period in the form of a yellow ball moving toward the illuminated goal. Each trial session included 70 trials for positivity and 70 trials for negativity. After the last training sessions, subjects did the training in the 1,5 T MRI-scanner (Sonata,

Manuscript received July 9, 2002; revised February 30, 2003. This work was supported by the Deutsche Forschungsgemeinscchaft (DFG), by the Bundesministerium für Bildung und Forschung (BMBF), and by the National Institute of Health (NIH).

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Digital Object Identifier 10.1109/TNSRE.2003.814439

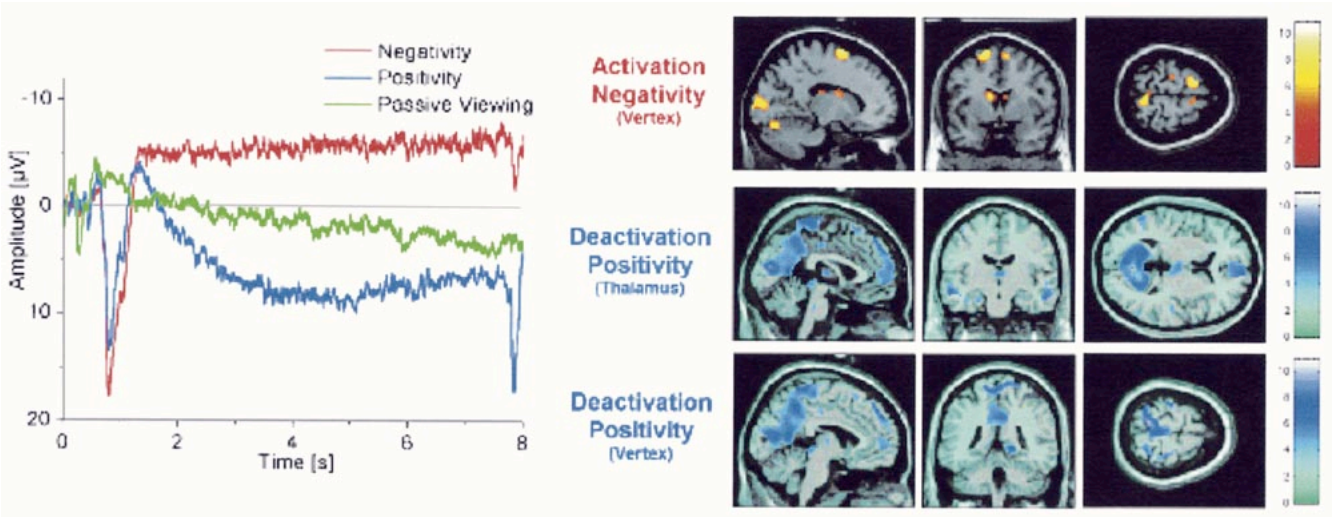

Fig. 1. Left diagram shows the EEG slow waves during the voluntary production of cortical negativity (red), positivity (blue), and the passive viewing (green). The fMRI images on the right show highly significant areas of activation (yellow, red) during required electrocortical negativity (upper row). During required negativity BOLD-response increased in premotor areas and under the EEG electrode (vertex). During required positivity, BOLD-response decreased in medial thalamus, posterior visual areas, medial prefrontal areas, and under the EEG electrode (vertex)(blue).

Siemens, Erlangen) which recorded BOLD responses during the task for performing cortical negativity, positivity, and passive viewing. (For methodological details see [7]). A reference session immediately before the fMRI session was carried out in a dummy-fMRI consisting of a tomograph without magnetic fields. (This enabled us to do the feedback session and record the EEG in the same environment as that in a real scanner without the scanning artifacts.) As shown in Fig. 1 on the left, in these reference sessions, the five subjects achieved an average differentiation of 13.3 μV ($\mathrm{N} = 620, \mathrm{t} = 11.3$). A clear pattern of differential metabolic responses of self-produced brain responses emerged: cortical negativities resulted in a general *increase* of metabolic activity; cortical positivity resulted in a widespread *decrease*. Increases during negativity were located primarily at vertex near the electrode position in the feedback training, premotor regions and precentral areas [supplementory motor area (SMA)]. Decreases during positivities were centered at vertex, thalamus, and medial precentral cortex (see Fig. 1, right). Successful regulation of cortical SCP-positivities could be predicted with an accuracy of $\mathrm{r} = 0.93$ from activation of Globus pallidus and putamen and deactivation of SMA (right) with an accuracy of 0.98 from dorsomedial prefrontal areas. Negativity versus positivity was predicted with $\mathrm{r} = 0.80$ from parahippocampal BOLD-activations.

These data confirm an earlier preliminary report [13] strengthening and broadening the excitation-threshold-regulation theory developed by Birbaumer *et al*. [10]: negative SCPs reduce neural excitation thresholds of upper cortical layers while positive SCPs increase it through a negative feedback circuit involving the basal ganglia and reticular nucleus of the thalamus. With increased cortical excitation (negativity), inhibitory striatal nuclei increase the excitation threshold of the involved cortical assemblies. Activation of these nuclei during cortical positivity not only reduces cortical excitation, but may also activate a (dopaminergic) positive reinforcement zone of the ventral striatum that is responsible for the learned stabilization and maintenance of the self-produced cortical positivity [14]. During SCP-negativity, thalamic and reticular activation systems are activated. Therefore, regulation of attentional modulation seems to constitute the cognitive strategy in the physiological regulation of SCPs and probably other brain responses such as mu or beta rhythms as well.

Awareness of these cognitive-attentional strategies, however, is not necessary for successful operant brain regulation. Kotchoubey *et al*. [8] found that in successful SCP-regulators, awareness of the neural brain response, i.e. their SCPs, *follows* the actual (operant) control of that response and is usually delayed by several sessions. This and other results, such as absence of temporal-hippocampal involvement in the fMRI study reported previously and inconsistent verbal report data [15], clearly indicate that physiological regulation of SCP and probably other neuroelectric phenomena can be viewed as an instrumentally learned *implicit-procedural response* acquired through a cognitive mechanism of repetition priming [16].

III. Clinical Outcome of TTD Application in Locked-in Patients

Since our first report in this journal [1], six new patients have been trained, bringing the total to 11 patients trained over extended periods ranging from 6 mo to 6 yr. Nine of the 11 patients were diagnosed with end-stage amyotrophic lateral sclerosis (ALS) and were artificially ventilated and fed. One had subcortical hemorrhage and one was diagnosed with polyneuropathy and Guillan-Barré syndrome and has been locked-in for five years. Four of the six new patients are completely locked in with no motor activity and no eye-movements. In these patients, locked-in syndrome was confirmed through lack of eye and lid-movements, and lack of EMG-measured face or body muscle activity. EMG measurements for anal sphincter musculature were not done. All patients satisfied cognitive-ERP detection for cognitive functioning by completing complex processing tasks. Their ERPs were intact. One of the four new locked-in patients died from pulmonary complications before achieving any communication. The remaining seven (not completely locked-in) patients were able to communicate yes-no signals only with eye or face muscles at the beginning of training. Two of these seven patients subsequently lost all motor responses and are still communicating with the TTD. None of the patients who were already completely locked-in at the beginning of training have yet been able to gain control over SCP, mu, or eye movement. Training with two of these patients is still in progress. The already substantial obstacles in trying to train these four initially completely locked-in patients are complicated by the considerable geographical distances between the home laboratory in Tuebingen, Germany, and the patients' places of residence (Patient LB lived in Berlin, Germany; patient NB lives in Los Angeles, CA; patient EL lives in Lima, Peru; and patient AG, the closest, lives 120 km from the home lab). Since all patients have to be visited at home, have TTD devices installed in their homes, and have on-going training, distance presented a considerable problem. Of the remaining seven patients (who live closer to the home lab), two

currently use the TTD for communication, with an average selection speed for a letter or completed word of 1/min. The learning curves and performance of these patients can be found in [2], [17]–[20].

These results suggest that patients who learn physiological control will be able to use the spelling device and select letters and words with their brain response alone. Learning curves for acquisition of SCP control are extremely variable and rarely show exponential learning as reported for the acquisition of implicit skills or even explicit-declarative knowledge. Regression analysis of performance in five patients [21] revealed significant prediction of spelling success only in those patients demonstrating improvement during the first 30 training runs. One run consists of 70–100 single trials (see [33].)

In an effort to improve learning of physiological control of SCPs, TMS was used before each trial. In the first study [12], a single magnetic pulse was given at the vertex and at a lateral scalp position in ten healthy subjects prior to each trial of feedback-assisted differential acquisition of negative and positive SCP changes. The outcome of this study was inconclusive, main effects pointed toward a nonsignificant enhancement of negative SCP after vertex stimulation and a significant increase of positive SCP after stimulation over the lateral scalp position. An ongoing experiment, again with healthy subjects, used high-frequency TMS (15 Hz) and low-frequency TMS (1 Hz) delivered for 2 and 30 s, respectively, in a balanced sequence prior to trials of required positivity and negativity. Results clearly indicate that low-frequency TMS improved learning of SCP positivity and high-frequency TMS accelerated learning of negativity [22].

IV. Quality of Life and Depression in Severely Paralyzed Patients

Ninety to ninety five percentage of patients diagnosed with ALS (or similar debilitating diseases) decide not to be ventilated and die under undocumented circumstances. Legal regulations concerning assisted suicide vary within Europe, from state to state in the U.S., and in other countries. Moreover, in some developing countries, common practice does not necessarily correlate with legal regulations. Most patients are not fully aware of the possible benefits of assistive communication devices and BCI, and do not have a fully accurate view of quality of life after tracheotomy and artificial respiration. Since there have been, to date, no neuropsychological and psychometric instruments for measurement of psychological variations in severely paralyzed patients, the results of published data on cognitive and emotional functioning in severely paralyzed people are unclear. The data that do exist do not confirm the negative expectations of ALS patients, families, and health professionals, but, instead, indicate satisfying or good quality of life even in artificially respirated ALS patients [23], [24].

Fig. 2 shows how a sample of 22 ALS patients rated their general quality of life, as measured by the scales to assess quality of life [25]. Patients were everything from mildly impaired to almost completely paralyzed and artificially ventilated and fed. Quality of life was not correlated with the degree of physical impairment as measured with the modified Norris Neuroscale [26]. Admittedly, these are preliminary results that await replication, but they underline the need for functioning BCIs for these groups. The data also suggest that patients', doctors', and family members' fears of low quality of life and suffering in locked-in states are unfounded and question the widespread decline in choosing of artificial respiration.

V. Future Developments

After final tests of the common hardware and software platform for TTD and BCI-2000 developed in cooperation with the Wadsworth group (see [32]), we will conduct a controlled international study comparing acquisition and spelling between SCP- and mu-control, first in healthy persons and later in ALS patients. These studies should allow a more individualized training protocol, faster acquisition of physiological control, and reduction of dropouts. Acceleration of training of

Fig. 2. Quality of life in a sample of 22 ALS patients (in different stages of the disease).

SCP- and mu-control with TMS and external dc currents [27] constitutes another priority for experimentation with healthy populations and, in case of successful completion with the healthy population, with the paralyzed. A study of metabolic and neuronal mechanisms underlying TTD-assisted acquisition of SCP control in nonrespirated ALS patients began in mid-2002.

To address issues concerning quality of life and emotional organization, a series of experiments (unpublished) using the International Affective Picture System (IAPS, [28]) will be replicated. Studies to date show that paralyzed and respirated ALS-patients, patients with high spinal cord lesions, professional athletes, and healthy controls have similar neural, psychological, and autonomic processing of emotional material. These studies should allow for more efficient selection and use of *positive reinforcers*, and an investigation of their neuronal basis, in persons with extremely restricted positive reinforcers. Knowledge of the effects of remaining positive reinforcers is critical for learning of physiological self-control and BCI use.

Simultaneously with these EEG-centered BCI-approaches, two newly developed BCI systems will be tested, first in healthy subject groups and then in patients in the initial stages of ALS and other progressive neurological diseases. These include an online fMRI-BCI for physiological regulation of cortical and subcortical metabolic BOLD-responses [29] and a 151 whole-head MEG-BCI system using conditioning and physiological control of very early ($<$80 ms) somatosensory components and low-gamma frequency range MEG oscillations. These noninvasive multisensor and multielectrode extensions of the current BCI research in humans will complement invasive multielectrode animal BCI systems for neuroprostheses [30], [31]. For a variety of reasons, comparable precision and classification of brain states can be achieved with noninvasive methodologies for BCI such as fMRI, MEG, and high-density EEG.

In summary, BCI-research and BCI systems consist not only of clinical or engineering approaches to direct brain control, but will also open new horizons for basic systemic and behavioral neuroscience and the classification of brain states.

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Current Trends in Brain-Computer Interface Research at the Neil Squire Foundation

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***Abstract*—The Neil Squire Foundation (NSF) is a Canadian nonprofit organization whose purpose is to create opportunities for independence for individuals who have significant physical disabilities. Over the last ten years, our team in partnership with researchers at the Electrical and Computer Engineering Department, the University of British Columbia, has been working to develop a direct brain-controlled switch for individuals with significant physical disabilities. The NSF Brain Interface Project primarily focuses on the development of brain–computer interface switch technologies for intermittent (or asynchronous) control in natural environments. That is, technologies that will work when the User intends control but also remains in a stable off state when there is no intent to control. A prototype of such a switch has successfully been developed. This switch has demonstrated classification accuracies greater than 94%. The initial results are promising, but further research is required to improve switch accuracies and reliability and to test these switch technologies over a larger population of users and operating conditions. This paper provides an overview of the NSF brain-switch technologies and details our approach to future work in this area.**

***Index Terms*—Assistive technology, asynchronous control, brain-computer interface (BCI), functional model, intent, intermittent control, neuroprosthesis, pattern recognition, standards, statistical signal processing, taxonomy.**

I. Introduction

The Neil Squire Foundation (NSF)—in partnership with the Electrical and Computer Engineering Department, the University of British

Manuscript received June 20, 2002; revised January 22, 2003. This work was supported by The Natural Sciences and Engineering Research Council of Canada under Grant 90278-02, by The Rick Hansen Neurotrauma Initiative under Grant 00008, by The Government of British Columbia's Information, Science, and Technology Agency, by The National Science Foundation under Grant IIS-0118917, and by the G.F. Strong Rehabilitation Centre.

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Digital Object Identifier 10.1109/TNSRE.2003.814450