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# Brain–computer interface and semantic classical conditioning of communication in paralysis

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ABSTRACT

We propose a classical semantic conditioning procedure to allow basic yes–no communication in the completely locked-in state as an alternative to instrumental-operant learning of brain responses, which is the common approach in brain–computer interface research. More precisely, it was intended to establish cortical responses to the trueness of a statement irrespective of the particular constituent words and letters or sounds of the words. As unconditioned stimulus short aversive stimuli consisting of 1-ms electrical pulses were used. True and false statements were presented acoustically and only the true statements were immediately followed by electrical stimuli.

15 healthy participants and one locked-in ALS patient underwent the experiment. Three different classifiers were employed in order to differentiate between the two cortical responses by means of electroencephalographic recordings. The offline analysis revealed that semantic classical conditioning can be applied successfully to enable basic communication using a non-muscular channel.


## 1. Introduction

The aim of most brain–computer interface (BCI) research is to provide a non-muscular communication channel for individuals who are no longer able to communicate by any means due to severe motor impairment. Neurological diseases such as amyotrophic lateral sclerosis (ALS), muscular dystrophy, high spinal cord injury or brain-stem stroke may lead to severe or complete motor paralysis rendering communication hard or even impossible. The state of severely paralyzed patients with residual voluntary control of particular muscles (e.g. eye muscles, lips, fingers) is known as locked-in state (LIS) (Bauer et al., 1979; Kübler and Birbaumer, 2008). There are also patients who lose all motor control resulting in the completely locked-in state (CLIS) (Birbaumer et al., 2008). These patients have the greatest need for a BCI that restores communication and interaction with the social environment.

It has been repeatedly shown that patients with severe motor disability, including patients in the LIS, are able to control a BCI (e.g. to select characters and thus to communicate) by regulating their slow cortical potentials (SCP) or sensory-motor rhythm (SMR) or using the P300 event-related potential (ERP) component (Birbaumer et al., 1999; Neuper et al., 2003; Kübler et al., 2005a; Halder et al., 2010). However, up to now there are no documented cases of CLIS patients communicating by means of BCI. In their meta-analysis of 29 patients in different stages of physical impairment and trained with BCIs, Kübler and Birbaumer (2008) showed that none of the seven CLIS patients ever achieved BCI control despite intact passive cognitive functioning assessed with a battery of cognitive event-related potential-tests (Kotchoubey et al., 2002, 2003). Importantly, all of the completely locked-in patients were already in CLIS at the beginning of their BCI training. At the same time the analysis revealed that patients with some remaining muscle control learned to use the BCI (Kübler and Birbaumer, 2008). Murguialday et al. (2011) monitored the transition from LIS to CLIS of an ALS patient with electrophysiological measures and concluded that to achieve reliable BCI-based communication in CLIS afferent pathways which are different from the visual system must be employed for feedback and reward. Indeed, most patients

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with extended paralysis of eye-muscles develop disorders of fixation and vision due to necrosis of the cornea (Murguialday et al., 2011).

It has been speculated that the unsuccessful efforts to restore communication by means of BCI in CLIS patients could be explained by the loss of the contingency between goal-directed behavior such as intention and its consequences, which could lead to extinction of voluntary cognitive activity, goal directed thinking and imagery in CLIS (Birbaumer et al., 2008). Accordingly, it has been suggested that a paradigm shift from instrumental-operant learning, that has been dominating the existent BCI approaches, to classical conditioning could resolve the problem of insufficient BCI based communication in CLIS. Commonly, during classical conditioning a neutral conditioned stimulus (CS) is repeatedly paired with a biologically relevant (e.g. aversive) unconditioned stimulus (US). Once a CS–US association has been formed the CS produces a conditioned reaction (CR) in anticipation of the US. No voluntary-operant response effort is required in classical 'reflex' conditioning and only minimal semantic priming is necessary in classical conditioning. Therefore, this approach might re-open a remaining communication pathway in patients with more or less severe cognitive disorders as reported previously (Ludolph et al., 1992; Volpato et al., 2010).

Semantic classical conditioning refers to conditioning of a physiological or behavioral response to a meaningful word or sentence irrespective of the particular constituent letters or sounds of the words (Razran, 1961). Originated in Russian research of the 50s and 60s semantic conditioning is based on generalization of CRs along a semantic dimension (word-to-word transfer). It has been shown that CRs (e.g. saliva secretion, galvanic skin response, heart rate) to specific words or sentences can be transferred to other words or sentences with similar meaning (Razran, 1939, 1949a, 1949b; Lacey and Smith, 1954). These principles represent the framework of the proposed paradigm. Additionally, there are evidences for cortical correlates of semantic classical conditioning showing that words associated with aversive stimuli (through frequent pairing) evoke stronger cortical responses compared with words not associated with pain or discomfort (Montoya et al., 1996).

In one of our previous studies unpleasant auditory stimulation has been employed to condition cortical responses to the trueness or falseness of a sentence (Furdea et al., 2012). After frequent pairing, electroencephalogram (EEG) segments following true and false statements were classified with the aim to separate covert 'yes' from 'no' responses. Four different classifiers were employed offline in order to detect the most suitable algorithm for the analysis of the EEG data. Results indicated that discriminating between 'yes-' and 'no-responses' was not attainable, presumably due to similarities and lacking salience of both USs. Nevertheless, accuracies above chance level were found when the classifier was trained to distinguish either 'yes-' or 'no-responses' from the baseline, i.e. EEG segments before the onset of a sentence.

The present study aimed at developing a semantic classical conditioning paradigm which, by taking into account the findings of our previous attempt, should secure a better discriminability of the cortical conditioned responses of covert 'yes' and 'no' answers and thus enable basic affirmative and negative communication in all states of paralysis including CLIS. For this, we used an aversive electrical pulse delivered over the left thumb as US and acoustically presented true and false sentences as CSs (denoted as $CS_1$ and $CS_2$, respectively). The use of electrical stimulation and of a paradigm which consumes less attentional resources and voluntary effort may be an alternative for LIS patients to learn BCI skills and to transfer the skills to the CLIS and may be even applicable in patients already in the CLIS. In the current study we explored the proposed paradigm in a healthy sample and exemplified its efficacy with a patient in LIS.

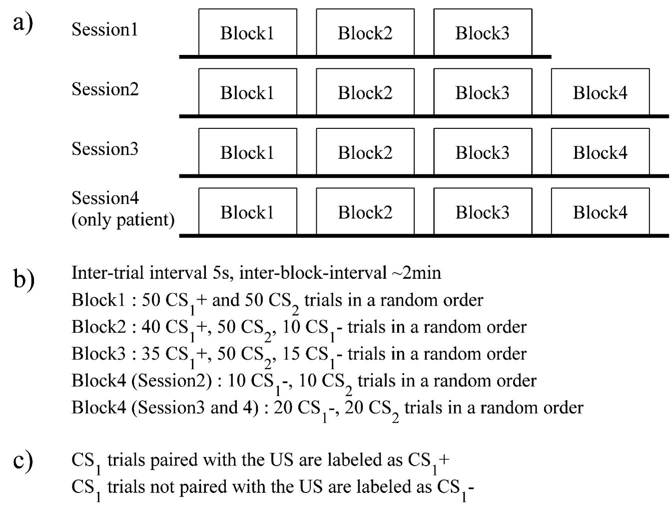


**Fig. 1.** Description of the experimental design. The structures of the sessions (a) along with the number and types of sentences per blocks (b) and the definition of the labels used in the picture (c) are introduced.

## 2. Methods

### 2.1. Participants

A total of 15 right-handed healthy participants (mean age: 26.1 years; range: 19–38 years, 7 men, 8 women) and one ALS patient (55-year-old male, score 0, out of 48, in the ALS Functional Rating Scale-Revised (Cedarbaum et al., 1999)) were included in the study. Participants gave informed consent for the study. The study was approved by the Internal Review Board of the Medical Faculty of the University of Tübingen. Participants were required to complete a demographic and screening questionnaire, and only those with normal hearing participated. Individuals with a history of seizures, psychiatric illness or severe head injury were excluded, as those currently taking psychotropic drugs. Each healthy participant sat in a reclining chair facing loudspeakers placed at a distance of 1.5 m and was asked to remain motionless and to keep the eyes open during the performance. All measurements with the healthy participants were performed in a sound-attenuated chamber, whereas the patient was measured at home.

The patient was diagnosed with ALS 6 years before this study. He was artificially ventilated and fed through a percutaneous endoscopic gastrostomy. His motor abilities were reduced to minimal eye movements and extension of the left forefinger. No depression and average quality of life was reported as for those patients included in a previous study (Kübler et al., 2005b).

### 2.2. Experimental setup

True and false sentences were used to elicit affirmative and negative responses. The trueness or falseness of each sentence was determined by its last word. Each of the sentences was used for both affirmation and negation (e.g. 'Berlin is the capital of Germany' or 'Berlin is the capital of Italy'). The statements were played through loudspeakers placed 1.5 m in front of the participant.

According to the meaning of the statement the participant was asked to intensively think 'yes' or 'no' as an answer to each statement. The sentences served as the conditioned stimuli ($CS_1$ for 'yes' and $CS_2$ for 'no' thinking).

An electrical pulse was employed as US and delivered to the left thumb of the participant immediately following the end of the $CS_1$-sentence. The pulses were generated by a bipolar direct current stimulator (DS5, Digitimer Ltd., United Kingdom) and delivered through two Velcro strap electrodes positioned over the distal and proximal phalanx of the left thumb with a distance between electrodes of approximately 2 cm. The intensity of the stimulus was subjectively set at the beginning of each session using a procedure aimed to monitor the somatosensory and pain threshold of the participant. The duration of the pulse was 1 ms and the magnitude was determined individually for each participant using a gradually increasing stimulus intensity approach. The participant was asked to successively rate the stimulus magnitude of each stimulus by using a visual analog scale (VAS) ranging from 0 (no sensation) to 10 (pain tolerance threshold, 'unbearable pain'). The intensity rated as 8 in the VAS was selected to be employed throughout the session. This procedure was applied for both the healthy participants and the ALS patient.

The experiment consisted of three sessions performed on separate days (Fig. 1): the first two sessions on two consecutive days and the third session one week later. The first session included three conditioning blocks, each consisting of 100 statements, 50 true and 50 false presented in a pseudo-random order. In the second and third sessions a fourth block was added. The fourth block of the second session consisted of 20 statements whereas in the fourth block of the last session a total of