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# Self-regulation of slow cortical potentials in epilepsy: A retrial with analysis of influencing factors

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**Abstract**

Twenty sessions of biofeedback training were carried out with 12 drug-resistant patients with focal epilepsy who learned to produce either negative or positive shifts of their slow cortical potentials (SCPs) at vertex. Feedback trials were interspersed with transfer trials in which only a discriminative stimulus (signalizing whether positivity or negativity was required) was presented, without feedback signal. Patients were able to differentiate significantly between the conditions of cortical positivity and cortical negativity, with larger differentiation scores being obtained in feedback trials than in transfer trials. The amplitude of positivity generated in the positivity condition increased linearly across sessions both in feedback and in transfer trials. The largest negativity was produced in the 5th session; after this, more transient negativities were generated, whose amplitude decreased towards the end of trial. The mean severity of seizures, estimated as the frequency of seizures weighted by their subjective 'strength', decreased significantly after training as compared to the pre-training phase. The data suggest that (1) patients could learn to achieve a state of cortical disfacilitation and (2) with progressed learning, they became less motivated for (or afraid of) producing considerable negative shifts, since extensive negativity may reflect cortical over-excitation and therefore be associated with early signs of seizures. The inability of producing cortical negativity is however not necessarily a bad predictor.

*Keywords:* Biofeedback; Drug-resistant epilepsy; Slow cortical potentials

## 1. Introduction

The ability of epileptic patients to regulate their slow cortical potentials (SCP) in biofeedback training was found to be inferior to healthy subjects [2,3]. Since SCPs are regarded as an indicator of cortical excitability [1,13], the impairment of these regulative processes in patients in the biofeedback condition may be a manifestation of their insufficient ability to modulate the excitability thresholds of cortical areas and to avoid over-excitation of these areas [5]. Although seizure-like EEG activity and the superficial

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cortical negativity may dissociate for various reasons (e.g. neurons of the epileptic focus may be located in different depth), in most patients large superficial negativities precede seizure activity and remain at extreme amplitudes during seizures. These seizure-related negativities and SCPs share a common mechanism of dendritic depolarization (e.g. [10,14]). Birbaumer et al. [1,2] suggested that the mechanisms of negative feedback loops between cortex and basal ganglia, which restrain hyperactivation of neuronal pools, are partially defective in epileptic patients, and this can lead to explosive over-excitation of large cortical areas or even the entire cortex.

While Birbaumer et al. [2] and Rockstroh et al. [12] demonstrated that after a prolonged biofeedback training, patients can acquire the self-regulation skill, the question remains open why some patients do not achieve self-control. This might result from individual characteristics of patients (e.g. age, type of epilepsy, intellectual abilities, or personality traits). Therefore predictive studies differentiating between groups with heterogeneous biofeedback training abilities are urgently needed. However, since behavioral training procedures for epilepsy require extremely long training periods and extensive clinical experience of well educated personal, such studies will remain exceptions rather than the rule [15]. Previous studies have not answered the question whether a lack of significant differentiation between two kinds of biofeedback trials (i.e. those where cortical negativity is required and those in which positivity is required) was due to subject's inability to achieve positivity, or to achieve negativity, or both. In these three cases, different underlying mechanisms could be supposed, and different counter-measures could be suggested.

The study reported here was intended to clarify some of these questions concerning both electrophysiological and clinical effects of biofeedback training. As regards EEG findings, Birbaumer et al. [2] and Rockstroh et al. [12] found a consistent training effect across sessions for SCP differentiation. However, it remained unclear to what extent the overall significant effect was achieved due to learned positivity or learned negativity. In addition, the impact of learned negativity and learned positivity may be different for feedback condition and transfer condition. To answer these questions is of utmost clinical importance: subjects may be informed about possible difficulties in course of training and can therefore avoid deleterious frustrations appearing on early stages of learning. It is also unclear whether subjects achieved the SCP differentiation during the very first seconds of a feedback trial or toward the end of the trial. If this is known, the timing of feedback can be modified on an empirical basis in order to maximize training effects.

As regards clinical findings, Rockstroh et al. [12] found a clear relationship between the success of training and the size of clinical improvement. The reduction of seizures was attributed to the acquired skill to achieve positivity or to suppress negativity preceding a seizure. Positivity was found to indicate a state of disfacilitation in the respective cortical cell assemblies [1,6]. Previous studies left it open, however, whether patients really achieved relative positivity or only learned to inhibit rising negativity. Therefore, particular attention was paid in the present study to the process of learning cortical positivity.

## 2. Methods

### 2.1. Patients

Twelve epileptic patients (4 males), aged 21–44 ($M = 32.2 \pm 2.4$), took part in the training program. The average duration of the illness was 21.4 years (range 4–40 years). Simple focal seizures was the prevailing type of epileptic fits in 5 patients, 5 suffered from complex partial seizures, and the other two, from secondary generalized tonic–clonic seizures. In 6 patients, clinical and EEG data pointed to a right hemispheric focus, in 5 of them in the temporal lobe. In the remaining six patients, no focus could be found. None of the patients suffered from generalized epilepsy. Patients with any kind of non-epileptic seizures, or progressive neurological or psychiatric complications, were excluded.

All patients were on anti-epileptic medication from the very beginning of their disease. Ten of them took more then one type of medication. All patients were defined as drug resistant, since the medication had no effect on seizure frequency for more than 2 years. Medication regimes were kept constant for at least 5

months prior to the beginning of the biofeedback therapy, as well as during the training.

### 2.2. Training schedule

Data reported here comprise twenty biofeedback sessions, the first phase of the thirty-five session training. The 20 sessions were carried out during two weeks, with two sessions daily, and a weekend pause between the 10th and the 11th session. In addition to biofeedback training, behavioral therapy was conducted regularly with the following objectives: (1) increasing the subject's perceptual sensitivity to early signs of seizures, as well as to their immediate antecedents; (2) preventing potential seizure triggers and revealing reinforcing contingencies; (3) overcoming possible frustration after intermittent failures on the early stages of biofeedback learning and (4) transfer of the self-regulation skills from the laboratory to everyday life conditions.

Each training session consisted of 145 trials. In most trials, subjects had to produce an SCP shift while continuous feedback on the SCP amplitude was provided (feedback trials). In other trials, they had to produce SCP shifts without feedback (transfer trials). The percentage of transfer trials varied from 30% to 58%, according to individual performance. The first 30 trials in each session were always feedback trials.

### 2.3. Procedure

Each feedback trial began with the presentation of a letter 'A' or 'B' on a screen of a computer monitor together with a stylized rocket ship (Fig. 1). The position of the rocket was determined by the EEG potential integrated over 500 ms time intervals sliding with a 100 ms shift. The EEG amplitudes were referred to a baseline of 2 s prior to the appearance of the rocket and the letter. Depending upon the letter ('A' or 'B'), subjects were asked to modulate their SCPs in either a negative or a positive direction. In both cases, the correct SCP shift was signalled in forward (i.e. rightward) rocket movement, whereas the inadequate change of the potential (e.g. a negative shift as compares to the pre-stimulus baseline when positivity was required) yielded a backward (i.e. leftward) rocket movement. After 8 s, the rocket and the letter disappeared, marking the end of the trial.

Fig. 1. Examples of patterns viewed on the subject's monitor. A large letter and a small rocket ship can be seen. Left: a trial with required negativity. The performance in this trial was good, as the rocket was moving forward. Right: in this trial, the required positivity was not produced — the rocket was moving backward.

In transfer trials, only the letters 'A' or 'B' were presented for 8 s, without rocket. Trials containing artifacts (eye movements $> 150$ $\mu$V, body movements, blinks, muscular artifacts, electrode displacements) were stopped while the screen was illuminated for 500 ms. Small eye movements were on-line corrected by point-to-point subtraction of a certain amount of the vertical EOG amplitude from the EEG amplitude. Specifically, the EEG amplitude which was fed back to patients ($EEG_f$) was equal to

$$EEG_f = EEG_r - 0.1 \times EOG,$$

$$\text{if } EEG_r > 0.1 \times EOG;$$

$$EEG_f = 0, \quad \text{if } EEG_r \leq 0.1 \times EOG,$$

where $EEG_r$ is raw EEG amplitude, EOG is simultaneous vEOG amplitude. This implies that the corrected EEG could in no case have the opposite sign than the raw EEG, and thus, the over-correction (in which patients might use eye movements in the opposite direction in order to control rocket movements) was completely ruled out. Furthermore, the subtraction procedure was only employed if the EOG potential shift was in the required direction and thus, eye movement potentials were allowed to block the subjects performance but not to contribute to it. We conducted a series of control experiments with healthy subjects who tried to move the rocket using eye movements, and none of them was successful.

### 2.4. EEG recording

The EEG was recorded from Cz using a Neurofax (Nihon Kohden) amplifier with amplitude resolution

of about 0.05 μV. The high-frequency cut-off filter was set at 30 Hz and the time constant at 10 s. Two mastoid electrodes linked through a 10 kΩ shunt served as reference. Ag/AgCl electrodes were affixed by means of Elefix (Nihon Kohden) electrode paste. EOG electrodes filled with TECA (Vickers) electrode jelly were placed 1 cm above and below one eye. Electrode resistance was kept below 5 kΩ. Data were digitized with a sampling rate of 100 Hz.

### 2.5. Data analysis

#### 2.5.1. EEG data

Prior to averaging, an off-line EOG artifact correction was performed using the method described in [7]. Then, SCPs were averaged within each session according to the two conditions (required negativity versus required positivity) separately for feedback and transfer trials. In the resulting average waveforms (4 for each subject per session), area under the curve was measured within the last 6 s of the 8 s trial. Since one of our aims was replication, the statistical technique which had been employed by Rockstroh et al. [12] was used in the present study too. Namely, the mean SCP differentiation (difference between the condition of required negativity and that of required positivity) was statistically ($t$-test) evaluated for every subject across 20 sessions, separately for feedback and transfer trials, and then, $z$-transformed $t$-values for the entire group were agglutinated. In order to further explore the dynamics of SCPs with training, the 6 s interval was subdivided into three subsequent 2 s time windows, and then, a 4-way within-subject ANOVA was conducted with factors condition (positivity versus negativity), feedback presentation (feedback versus transfer), time window (3 levels), and session (20 levels). For the session factor and all interaction involving this factor, Greenhaus–Geisser epsilons ($e$) were used for non-sphericity correction. Effects of factors containing two levels (i.e., task and feedback) were further checked using non-parametric Wilcoxon test. Since this always revealed the same results as the ANOVA, the Wilcoxon data are omitted in the present text as redundant. Finally, SCP changes across sessions were evaluated by means of a trend analysis.

#### 2.5.2. Clinical data

Patients carried on a diary during twelve weeks before the beginning of training (pre-training phase) as well as during eight weeks following the last training session (post-training phase). They estimated the strength of each seizure on a 10 point scale. Since being included in a large study could have a placebo effect even before the training started, seizure incidence for the last twelve weeks prior to the first conversation about the training program (baseline phase) was taken from subjects' own diaries or, if possible, from ambulatory documentation. Mean seizure frequency per week was calculated for the baseline, pre- and post-training phases, whereas mean severity of seizures (seizure frequency multiplied by average seizure strength) was calculated for the pre- and post-training phases only (no data was available about seizure strength in the baseline phase). Because of large individual variability in seizure frequency, clinical data were analyzed using non-parametric tests. Specifically, Wilcoxon test was used for paired comparisons, and Freedman's one-way ANOVA was applied to the frequency data where three phases of the study were compared.

## 3. Results

### 3.1. Cortical self-regulation

Averaged SCP waveforms are presented in Fig. 2. Individual $t$-values for the SCP differentiation between the negativity condition and the positivity condition varied in feedback trials from 0.5 ($p > 0.50$) to 6.96 ($p < 0.0001$), resulting in a highly-significant agglutinated $z$-value of 3.62 ($p < 0.01$) which implies that epileptic patients achieved control over their SCPs with feedback. In transfer trials, individual $t$-values varied from −0.8 (non-significant opposite tendency) to 3.24 ($p < 0.005$), and the resulting $z$-value agglutinated over the entire group was marginally significant ($z = 1.96$, $p = 0.05$).

Similar results were obtained using ANOVA. A significant main effect of condition ($F_{1,11} = 6.76$, $p < 0.05$), as well as a condition × feedback interaction ($F_{1,11} = 11.05$, $p < 0.01$) indicate that, first, our patients (as a group) were able to produce directed

SCP shifts, and second, they did it more effectively when they were presented with continuous SCP feedback than in transfer trials.

The ANOVA revealed another highly-significant effect, namely a condition × time-window interaction ($F_{2,22} = 8.25$, $p < 0.01$, $e = 0.61$). In order to analyze this interaction, 3-ways ANOVAs were carried out for the negativity and positivity conditions separately. The effect of time was significant in the former condition ($F_{2,22} = 7.01$, $p < 0.025$, $e = 0.68$), but non-significant ($p > 0.10$) in the latter. In both conditions, however, the time effect had the same direction: the largest negativity was observed in the 1st time window (roughly speaking, in the middle of the trial); towards the end of the trial, the negativity decreased.

This decreasing tendency can be seen in Fig. 3, where the waveforms obtained in the negativity condition are presented. One can also see Fig. 3, that the shape of the SCP curve changed with sessions. The first several sessions were characterized by rather stable negativity, while in following sessions, a sharply increasing and then decreasing waveform was typical [1].

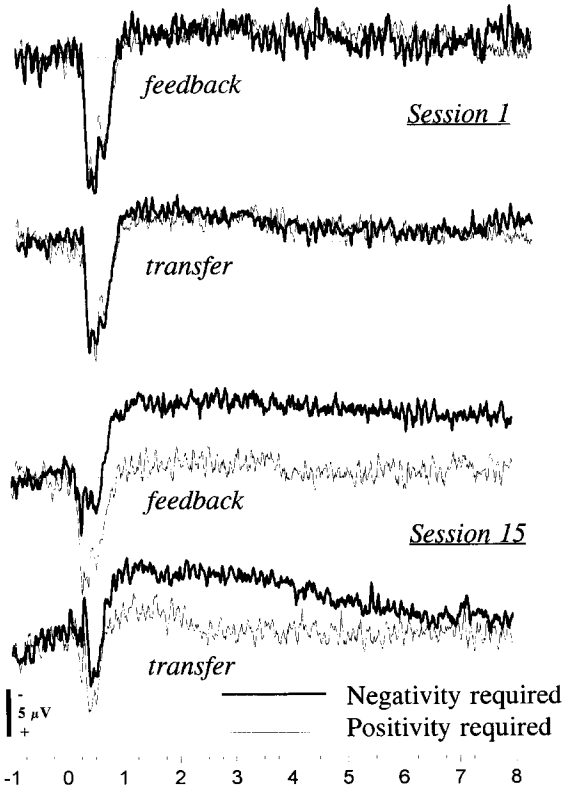


Fig. 2. Cortical potentials in two training sessions, averaged across 12 subjects. The zero point on the abscissa indicates the presentation of the stimuli. Thick line: negativity required. Thin line: positivity required.

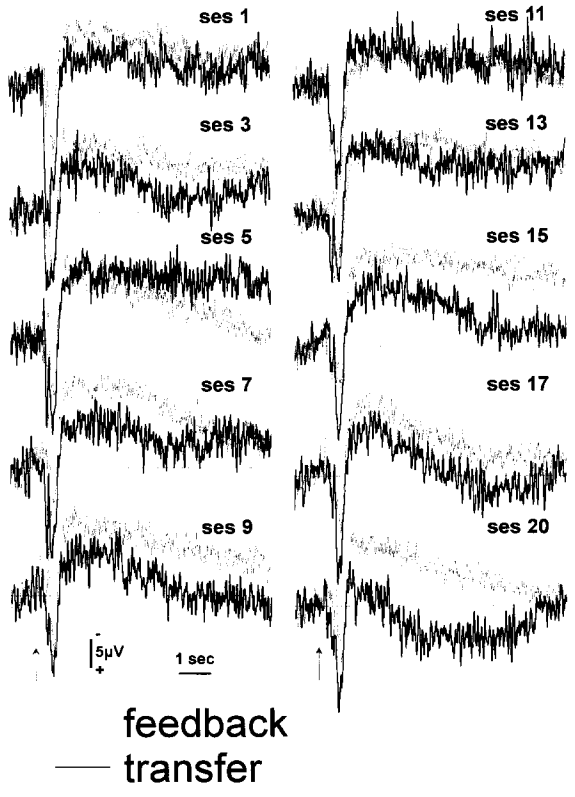


Fig. 3. Changes of the SCP waveform with sessions in *negativity* trials. Dotted line: feedback. Solid line: transfer. Note the falling negativity curve in some sessions, especially with transfer.

As a result of this 'fall of negativity' towards the end of the trial, the overall negativity developing in trials when the negative SCP shift was required was not found to vary significantly as a function of

[1] A significant time × session or condition × time × session interaction might be expected. Indeed, the interactions would be significant given uncorrected degrees of freedom, but with Greenhaus–Geisser correction, none reached the 0.10 level. It should be taken into consideration that all epsilons for the session factor and its interactions were less than 0.20. With such a low homogeneity, ANOVA results with respect to the session factor can hardly be regarded as reliable.

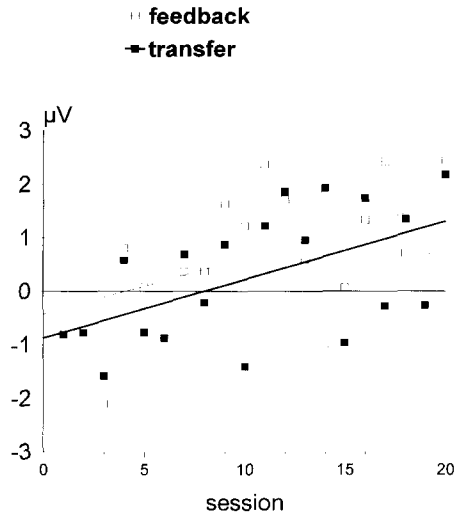


Fig. 4. Dynamics of the SCP amplitude when cortical *positivity* was required, in feedback trials (empty squares, approximated with a thin line) and in transfer trials (filled squares, thick line). The corresponding linear regression equations are $y = -0.43 \pm 0.105$ $\mu$V and $y = -0.87 \pm 0.109$ $\mu$V, for feedback and transfer, respectively.

session number. In this condition, the linear trend proved to be non-significant, nor quadratic, cubic, and S-formed trends were. One can see in Fig. 3 that maximal negativity was obtained, on average, in the 5th session; after this, the negativity tended to decrease with session number, albeit non-consistently. Conversely, the SCP amplitude in the condition of required positivity did demonstrate a consistent linear trend in both feedback trials ($F_{1,18} = 6.45$, $p < 0.025$) and transfer trials ($F_{1,18} = 7.28$, $p < 0.025$). Thus in the positivity condition, the SCP shift in the required direction grew with sessions (Fig. 4), whereas no such growth was observed in the negativity condition.

### 3.2. Seizures

Average seizure frequencies varied significantly as a function of the phase of training (chi-square = 12.54, df = 2, $p = 0.0019$) being 9.25, 6.88, and 4.33 (weekly) in the baseline, pre-training, and post-training phases, respectively. This finding allowed paired post-hoc comparisons between phases. Wilcoxon test revealed highly significant difference between the baseline phase and the post-training phase ($p = 0.003$). Patients tended to have fewer seizures in the pre-training phase than in the baseline phase ($p = 0.084$), whereas the difference between the pre- and post-training phases was non-significant.

The biofeedback training yielded a significant decrease of the mean severity of seizures (frequency of seizures weighted by their strength), as indicated by comparison between the pre- and post-training phases ($p = 0.019$).

## 4. Discussion

The results obtained in the present study replicate most of the data previously reported [2,12] in the extent that epileptic patients were found to be able, albeit somewhat slower than normals, to learn to control their SCPs within several sessions of biofeedback training. They can also transfer the acquired skill and attain SCP differentiation even in trials during which no continuous SCP feedback is presented, although the performance in those trials is worse. A lower degree of control found in the present study for transfer trials compared to Rockstroh et al. [12] can easily be explained by the fewer number of training sessions in this study.

As in the study of Birbaumer et al. [2], large session-to-session and subject-to-subject variability in terms of the SCP differentiation has been found, especially in transfer trials. The presented data shed some light on the possible origin of this variability. If the observed instability in the course of the training results from the subjects' inability to reduce the activation of their over-excited cortex, a worse performance might be expected during required SCP positivity. This was not the case, as only in the positivity condition a distinct linear trend was found, with the performance improving gradually as a function of session number. This finding indicates that subjects consistently mastered the positivity skill as training progressed.

On the other hand, when the SCP negativity was required, only a transient negative wave after 3–4 s was produced, particularly during the second part of the training. The drop of negativity towards the end of the trial became more pronounced in the last sessions, and in the 20th session even a positive average SCP curve was obtained in transfer trials.

How can this lack of negativity immediately preceding the end of the trial be explained? Since this 'event-preceding negativity' is regarded as reflecting the preparation for the coming event (e.g. stimulus or a subject's own action) [4,11], a deficit of these preparation (gating) processes may be suggested. Such a deficit may be speculated as reflecting the inability or lack of motivation to allocate resources required for voluntary maintenance of the preparatory state manifested in the cortical negativity. Conversely, Kornhuber [8,9] suggested a direct relationship between the amplitude of slow negativities and subject's volitional qualities. As can be seen in Fig. 3, most subjects could produce a large negativity, if required, already after 3–5 training sessions, and they might have been bored with repeated negativity demands in the following sessions. Perhaps subjects were not motivated enough to repeatedly concentrate on negativity that was obviously deleterious in respect of seizure reduction.

In the present study, no effort was made to separate the effect of biofeedback training from that of behavioral therapy since both rest on the same principles of operant learning. Thus we regarded them as virtually one method, not a combination of two. This issue should be clearly distinguished from that of possible placebo effect. Surely, any particular part of the method employed (as well as any new method) might have a placebo component. The present study was not aimed to control placebo effects. This should be kept in mind, although we know from [2] that prolonged training to control the alpha-rhythm does not result in any clinical change in epilepsy patients, which would be the case if the effect of biofeedback might be reduced to the placebo effect. The (non-significant) tendency to a decrease of the seizure frequency in some patients already in the pre-training phase, indicating that the very fact of being observed can have some positive effect, may be regarded as a placebo component of the present method; however, significant change of the seizure frequency was obtained only after training. Further, mean severity of seizures was considerably lower after training than before it.

Interestingly, more than twofold decrement of seizure severity was found in two patients who demonstrated the smallest SCP negativity at the end of training. Owing to it, they did not show large SCP differentiation between the conditions of cortical negativity and cortical positivity. This observation is in line with the idea that the lack of cortical differentiation due to insufficient negativity does not have to indicate a therapeutic failure if a good performance in the positivity condition is observed. In the course of training, patients can notice that positivity trials are incompatible with seizures and therefore avoid negativity with increasing success.

To summarize, the data indicate that the improvement observed in patients with epilepsy in the course of SCP biofeedback training is largely achieved due to their increasing ability to produce positive versus negative, SCP shifts. They further indicate that producing cortical negativity may be irrelevant in respect of seizure reduction. Although it can not be definitely concluded from these data that generating positivity, rather than any other mechanism of the method employed, is the seizure-controlling factor (some additional controls are needed to rule out other interpretations), the idea that the mechanism of cortical positivity plays an important role may be regarded as a very probable working hypothesis, on the basis of which further techniques to help drug-resistant patients can be developed.

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