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Clinical Neurophysiology 110 (1999) 683–686

Negative potential shifts and the prediction of the outcome of neurofeedback therapy in epilepsy

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Accepted 20 November 1998

Abstract

About two-thirds of epilepsy patients who learn to control their slow cortical potential shifts (SCP) reduce their seizure rate, but the remaining third does not demonstrate clinical improvement. In the present study, this finding was replicated in a group of 27 patients with focal epilepsy. We found that patients who consistently produced larger negative SCP in all conditions during the first phase of treatment, showed no decrease in seizure frequency during the six-month follow-up, as compared with the three-month baseline phase. The large negative SCP explained about one-third of the variance of the clinical outcome. Age, medication, seizure history, or the localization of focus were found to be unrelated to clinical improvement.

Keywords: Epilepsy; Outcome prediction; Self-regulation; Slow cortical potentials

1. Introduction

Birbaumer et al. (1991) hypothesized that patients with intractable epilepsy are characterized by an impaired ability to regulate their level of cortical activation using cortico-thalamic feedback loops. The cortical activation level is assumed to manifest itself in oscillations of slow cortical potentials (SCP), with negative SCP shifts reflecting an increase, and positive SCP shifts, a decrease in the excitability of the underlying cortical networks (Birbaumer et al., 1990, 1992). Studies with healthy subjects demonstrated the ability of humans to learn the cortical self-regulation (Elbert et al., 1980; Lutzenberger et al., 1980). This led to the idea that epilepsy patients can acquire the lacking cortical self-regulation during learning. According to this hypothesis, a neurofeedback method was developed in which actual SCP changes are presented to epilepsy patients in the form of a moving object on a screen. In fact, using this method, most patients with drug-resistant epilepsy could learn to control their SCP, resulting in a significant and lasting decrement of the seizure rate (Birbaumer et al., 1991; Daum et al., 1993; Rockstroh et al., 1993; Kotchoubey et al., 1996, 1997).

Some important questions, however, remained unanswered. Patients in this paradigm learned bi-directional SCP responses, producing either cortical negativity or cortical positivity in different trials. Further, they learned to transfer these skills to a condition in which they received no continuous feedback of their SCP. The results of the studies cited above were not consistent with respect to the factors accounting most for seizure reduction. This could be the ability to generate cortical positivity, or to differentiate between the positivity and negativity waves, or to apply any of these skills to a condition without feedback. About a third of the patients treated with this technique did not profit from SCP-neurofeedback training; factors which distinguish them from patients with clinical improvement are as yet unknown. One may speculate that different clinical outcomes were related to pre-existing individual differences in SCP responsivity, however, such consistent relationships were not found in the previous studies, probably because of the small number of patients or training sessions, or both.

2. Methods

In the present study, 28 patients with focal epilepsy (16

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1388-2457/99/$ - see front matter CLINPH 98693
PII: S1388-2457(99)00005-X

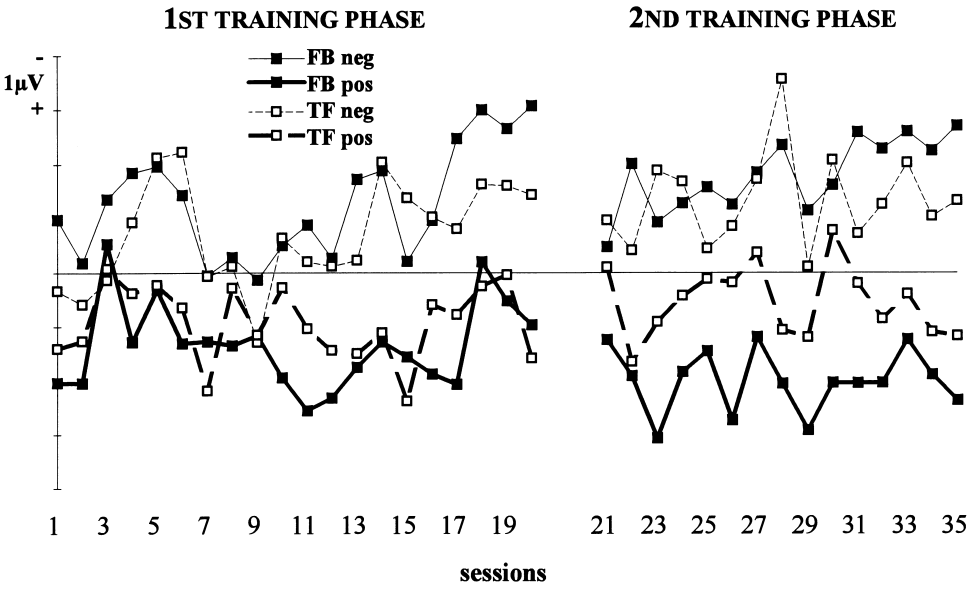

Fig. 1. Changes of the mean SCP amplitude (compared with the 1 s pre-stimulus time) during training. Each point represents the average for 27 patients. Negativity is up. Solid lines, black squares: feedback (FB) trials. Dashed lines, empty squares: transfer (TF) trials. Thin lines represent the negativity task, and thick lines, the positivity task. SCP values averaged across sessions were significantly negative during negativity task ($t = 11.02$, and $t = 3.79$, for FB and TF, respectively, both $P < 0.001$). Likewise, these values were significantly positive during positivity task ($t = 6.15$, $P < 0.001$, and $t = 3.36$, $P = 0.002$, for FB and TF, respectively).

females, mean age 32.4 years (range 21–45), mean seizure history 22.7 years (range 6–40)) participated. As one patient failed to complete his seizure diary, the data of 27 patients were analyzed. Nine of them had a right temporal focus, 7 patients had a left temporal focus, and the remaining suffered from multi-focal epilepsy. All patients were regarded as drug-resistant with at least 2 years of well-balanced pharmacological treatment without improvement (Bourgeois, 1994). Patients remained medicated during neurofeedback treatment, with the medication regime being constant at least 3 months prior to the beginning of training up to 6 months after its end.

Details of the training procedure have been described elsewhere (Rockstroh et al., 1993; Kotchoubey et al., 1996) and will only be repeated here in brief. The training course consisted of 35 sessions. After the first 20 sessions (two per day) patients had a break for 8 weeks before the start of the second phase of 15 training sessions. Each session included 140 trials that required cortical negativity or positivity, which was signalized by the discriminative letters A or B, respectively; these two tasks were presented in pseudorandom order. In feedback (FB) trials, the actual SCP amplitude at Cz, compared with a 1 s baseline prior to the letter presentation, was fed back in the form of a moving object on a computer screen. Mastoid electrodes, shunted with a resistance of 15 kΩ, served as reference. Each trial lasted for 8 s, after which both the letter and the feedback stimulus disappeared. Inter-trial intervals varied between 2.5 and 4 s. In transfer (TF) trials only the letters A or B were presented, without feedback.

3. Results

As shown in Fig. 1, differences between the SCP obtained with negativity task versus positivity task increased across sessions, particularly in trials with feedback. In FB trials, the amplitude difference between the two tasks (SCP differentiation) increased linearly as a function of session number ($F(2, 33) = 20.3$, $P < 0.001$). In TF trials, this linear trend did not reach significance ($F(2, 33) = 1.9$, $P = 0.18$), while the cubic trend was significant ($F(3, 31) = 3.0$, $P = 0.045$), indicating that periods of improvement were interspersed with periods of stagnation. The average seizure frequency during the 6 month follow-up was 2.9/week, as compared with 4.0/week during the 3 month baseline phase ($P < 0.05$, Wilcoxon test, two-tailed).

A sequence analysis (Künkel, 1979) was carried out to estimate the reliability of changes in seizure frequency for each individual patient. This technique allowed us to subdivide the sample into 3 groups: (a) patients with a significant (with $\alpha < 0.05$) reduction of seizure frequency (improvement group, $n = 8$), (b) patients with a significant (with $\beta < 0.10$) lack of the change in seizure frequency (failure group, $n = 8$), and (c) patients whose tendency to seizure reduction remained non-significant during the 6 month follow-up (indefinite group, $n = 11$). The mean number of seizures in the improvement group was 6.5/week during the baseline phase and 2.7/week during the 6 months after training. The corresponding numbers for the indefinite group were 1.2 and 0.9 seizures, and for the failure group, 5.0 and 5.4 seizures. An ANOVA with Group as a between-

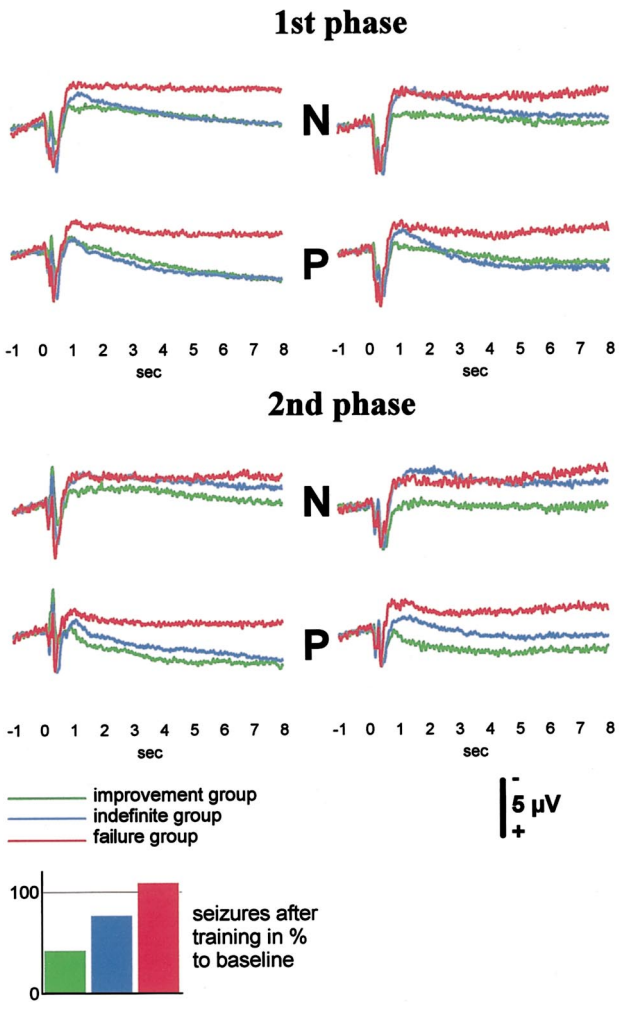

Fig. 2. SCP waveforms averaged across 20 sessions in the 1st training phase (top) or 15 sessions of the 2nd training phase (bottom) in patients with significant decrease of seizure frequency (green), those whose improvement tendency remained non-significant (blue), and patients without clinical improvement (red). The time point zero indicates the beginning of the task. Negativity is up. Left column: FB trials. Right column: TF trials. N: negativity task. P: positivity task. Bars below, indicate average seizure frequency after treatment in all 3 groups in percent to seizure frequency during baseline.

subject factor and Trial-type (feedback vs. transfer), Task (positivity vs. negativity), and Phase-of-training (1st vs. 2nd) as within-subject factors revealed two significant main effects (Task: $F(1,24) = 14.0$, $P = 0.001$; Group: $F(2,24) = 4.05$, $P = 0.03$), as well as a Task × Trial-type interaction ($F(1,24) = 7.27$, $P = 0.01$). A further analysis of the Group effect using a one-way ANOVA with post-hoc Tukey tests, indicated that the failure group differed from the two other groups by large negative SCP shifts produced in all conditions, regardless of the task and trial-type (Fig. 2). In fact, this difference was significant ($P = 0.008$) in the first training phase, but did not reach significance in the second phase. No difference was found between the improvement group and the indefinite group.

When patients were classified on the basis of their SCP after the first training phase, they could be correctly attributed to either the failure group or to one of the other groups in 24 cases out of 27 ($\chi^2(2) = 8.77$, $P = 0.013$). Despite the lack of difference between the indefinite group and the improvement group, the patients' SCP explained 31% of the variability of clinical outcome. Furthermore, the tendency for the failure group to larger negative SCP shifts also approached significance ($F(2,24) = 3.26$, $P = 0.056$) if only the first 5 sessions, rather than the first 20 sessions, were entered into the analysis.

The 3 groups with different clinical outcomes did not differ in age, sex, seizure history, medication, or localization of the focus (all $F < 1$). Age and seizure history were positively correlated ($r(27) = 0.49$, $P = 0.01$).

4. Discussion

In the present study, epilepsy patients learned to control their SCP (main effect of Task), with the amount of control increasing across sessions (significant linear and cubic trends). They were more successful with than without feedback (interaction Task × Trial-type). The average seizure rate decreased, on average, by 25% (about 60% in the improvement group), but no tendency for clinical improvement was observed in about a third of the sample. These results closely replicate those obtained in the previous studies in our laboratory (Birbaumer et al., 1991; Daum et al., 1993; Rockstroh et al., 1993; Kotchoubey et al., 1996).

A new finding of this study is the large and highly significant difference obtained during the first training phase between the patients without later clinical improvement and the remaining patients. The former were characterized by extremely large negative SCP shifts in all conditions and types of trials. This measure alone explained about a third of the variance of clinical outcome. This is comparable with outcome prediction for medicamental (Livingston et al., 1987), and surgical therapy of epilepsy (Faught et al., 1992; Hufnagel et al., 1995). Interestingly, the unsuccessful patients were able to learn to regulate their SCP during training as well as the remaining patients: the difference between the 3 groups in terms of the SCP differentiation was minimal ($F < 1$).

Considering the high costs of neurofeedback therapy and of insufficient medication, it seems important to be able to predict the outcome of different kinds of treatment. The present data are a first step in this direction, since they open the possibility to select patients who do not respond to SCP neurofeedback therapy. One strategy to improve outcome prediction, might be the analysis of SCP shifts on a trial-by-trial basis resulting in an estimation, after each session, of the probability that a particular patient would benefit from further training. A trial-by-trial analysis, as opposed to the session-by-session analysis employed here, is expected to increase the reliability of the prediction.

Additionally, other potential predictors should be sought (e.g. personality and neuropsychological variables).

At present, only tentative interpretations of the obtained relationships between the large negative SCP at the beginning of training and the subsequent lack of clinical improvement can be proposed. First, although the 3 groups did not differ in terms of medication or seizure history, other disease-related differences are not ruled out. These differences can, for example, be due to structural changes in hippocampus and other affected brain areas. One might also speculate that the slow negativities in all conditions reflect the patients' tendency to respond to any demanding condition, regardless of the task, with a stereotypic increment of cortical excitability. Although these patients can learn to suppress this response, to some extent, in the laboratory conditions, the supposed tendency to generalized cortical mobilization in challenging situations may still prevail in their real life, thus preventing them from controlling the spread of epileptic discharges with large enough inhibitory positive SCP. While the former conjectural explanation is morphological, the latter is functional, and they do not exclude one another.

Acknowledgements

The study was supported by the German Research Society (DFG). The authors are very much indebted to Michaela König for her valuable technical help.

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