

Clinical efficacy of galvanic skin response biofeedback training in reducing seizures in adult epilepsy: a preliminary randomized controlled study

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Received 30 September 2003; revised 8 December 2003; accepted 11 December 2003

Abstract

We investigated the effect of galvanic skin response (GSR) biofeedback training on seizure frequency in patients with treatment-resistant epilepsy. Eighteen patients with drug-refractory epilepsy were randomly assigned either to an active GSR biofeedback group ($n = 10$) or to a sham control biofeedback group ($n = 8$). Biofeedback training significantly reduced seizure frequency in the active biofeedback group ($P = 0.017$), but not the control group ($P > 0.10$). This was manifest as a significant between-group difference in seizure reduction ($P = 0.01$). Furthermore, there was a correlation between degree of improvement in biofeedback performance and reduction of seizure frequency ($\rho = 0.736$, $P = 0.001$), confirming that the effect of biofeedback treatment was related to physiological change. Our findings highlight the potential therapeutic value of GSR biofeedback in reducing seizure frequency in patients with drug-resistant epilepsy.

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Keywords: Galvanic skin response; Biofeedback; Randomized controlled study; Drug refractory epilepsy; Seizure reduction

1. Introduction

Antiepileptic drugs are the mainstay in the management of epilepsy. However, despite optimal drug therapy, approximately 30% of patients continue to have seizures. Seizure occurrence is subject to a number of nonpharmacological influences [1]. Emotional and physiological challenges to the patient are often associated with the occurrence of breakthrough seizures [2,3]. Patients with epilepsy often report the use of individualized behavioral countermeasures, such as increasing arousal by walking, standing, clapping, or pinching themselves, inducing relaxation by being still or sitting quietly, and using nonspecific methods such as eating and drinking, to diminish the likelihood of seizure onset [4,5]. Vagus nerve stimulation, the newest nondrug treatment in epilepsy management, directly perturbs

afferent information about visceral states of arousal by stimulating the vagus nerve in the side of the neck [6]. Together, these lines of evidence suggest that in addition to pharmacological (or surgical) interventions, behavioral interventions that alter states of emotional and peripheral autonomic arousal may have a positive impact on seizure frequency in drug-refractory epilepsy.

In biofeedback, treatments are facilitated by the provision of on-line feedback, visually or auditorily, to a covert physiological response, such as heart rate, skin conductivity, or brain wave pattern, and the subject learns actively to control such a bodily response. A number of biofeedback approaches have been suggested for the management of epilepsy. These include different electroencephalographic (EEG) frequencies, cortical potentials, and peripheral activity such as respiration [7–15]. However, biofeedback using the galvanic skin response (GSR) has not previously been reported.

The GSR is an accessible and sensitive index of peripheral sympathetic nervous activity, reflecting

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peripheral autonomic change. Skin conductance increases with enhanced arousal level. In a previous study in healthy subjects, we investigated the relationship between peripheral autonomic change and cortical excitation indexed by the GSR and the contingent negative variation (CNV), respectively [16]. We demonstrated an inverse relationship between GSR and CNV amplitude, such that increases in peripheral sympathetic activity were associated with reductions in this EEG index of cortical neural excitation. A pilot study of GSR biofeedback in three patients with drug-resistant epilepsy revealed a remarkable reduction in seizure frequency in two of three patients [17]. Based on these findings, we designed this study to examine whether GSR biofeedback treatment of patients, aimed at increasing tonic levels of peripheral sympathetic arousal, would lead to seizure reduction. The present clinical investigation was undertaken with 18 patients with drug-refractory epilepsy.

2. Method

2.1. Patients

Inclusion criteria for this study were as follows: drug-refractory epilepsy, age between 16 and 60 years, a clinical history and EEG evidence of epileptic seizures; clinical history of epilepsy lasting more than 2 years; average minimum seizure frequency of two to three per month over 3 months; stable medication for more than a month prior to commencement of the study; likelihood that the medication would not need to be changed during the study; and ability to keep a seizure diary. Serum drug level monitoring was not performed. Patients with a history of psychiatric illness, severe head injury, drug abuse or difficulty in taking antiepileptic medication were excluded, as were those with significant learning disabilities. All patients gave written informed consent. The ethics committee of the National Hospital for Neurology and Neurosurgery approved this study.

2.2. Study design

The study represents a two-group, single-blind, randomized controlled, study. Intervention periods (treatment and “sham” control treatment) were undertaken in parallel for the two groups of patients with drug-refractory epilepsy. As a result of limited resources, a double-blind study could not be implemented, but extreme caution was exerted by the experimenter/trainer to ensure that all participants received the same verbal directions and feedback. Patients were unaware of the treatment group to which they had been randomized and they completed their own seizure diaries. From the pilot study, we found that the mean percentage seizure

frequency change was 64% in the biofeedback group (the SD of percentage change was 46%). Assuming that seizure frequency of the control group would not change (percentage change 0%), a sample size of 10 in each group would have 80% power to detect a difference in means of 64% with an effect size of 1.39 (effect size = [mean percentage change in biofeedback group – mean percentage change in control group]/SD of biofeedback group).

2.3. Procedure

Patients were randomly assigned to either the active biofeedback group or the noncontingent biofeedback (control) group using a random allocation sequence (random number tables) determined at the trial onset. Measurement of GSR and implementation of biofeedback sessions were undertaken using a biofeedback system (Inner Tuner: Professional, Ultrasis plc., London, UK) that had modifications for experimental use and was calibrated using a standard set of resistances to confirm linearity. Dry nickel-plated electrodes were placed on the palmar surface of the participant’s index and middle finger of the left hand. Biofeedback took the form of the same computer-generated graphics in both control and biofeedback conditions, presented visually on a computer monitor in front of the patient at eye level. In the active biofeedback group a reduction in the participant’s skin resistance (GSR) resulted in rightward movement through a series of animations that progressed through pictures of a fish, a mermaid, a female person, an angel, and a star when the participant’s GSR changed in the intended direction (Fig. 1). If the patient’s GSR reversed its resistance then the display returned to an earlier form. Thus, in the biofeedback session, the subject watched the “evolution” of the graphics as GSR sympathetic activity increased (skin resistance decreased).

In the control (sham biofeedback) group, patients were shown a video of the same computer-generated animation used in the active biofeedback condition. In the control group, the patients also tried to alter their GSR level using the sequence of video events on the computer screen. However, in contrast to the active treatment condition, in each sham control condition the patient unknowingly watched a video animation. The progress of the animation change was reasonably increased session by session so that patients in the control group would also have the impression of progress in each session. However, animation changes were unrelated to GSR change as the GSR monitor was not connected to the computer-generated animation.

The study was composed of three phases: a 3-month baseline period, a 1-month treatment period in which the respective groups of patients were given either active biofeedback treatment or sham control biofeedback, and a 3-month follow-up period. In all phases, patients were asked to keep a careful record of their number of seizures.

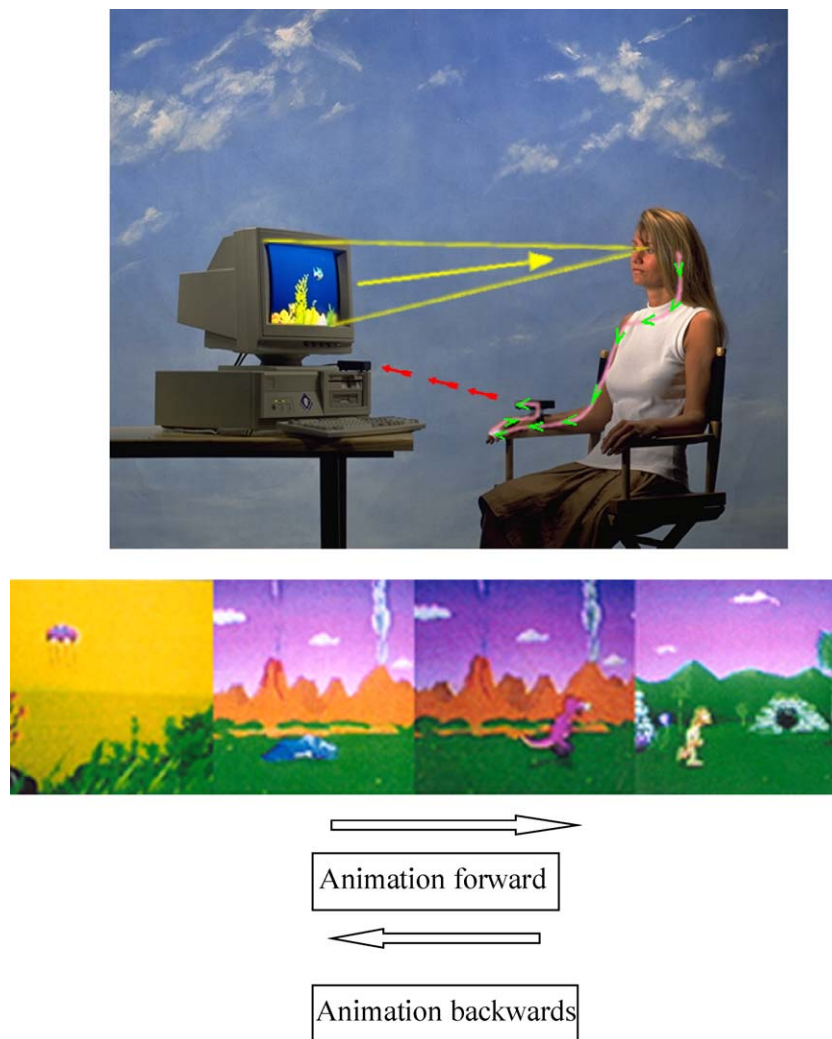


Fig. 1. Setup of biofeedback and the animation change on the screen. An animation moves forward with decrease in skin resistance and backward with increase in skin resistance.

During the treatment phase, participants attended a total of 12 sessions (3 sessions/week). Each session lasted 30 minutes during which patients assigned to the active treatment group received true biofeedback, and patients assigned to the control group received sham biofeedback. They were not informed as to whether they were given sham or contingent GSR biofeedback but were all instructed to actively attend to and change the animation on the computer screen by increasing their level of alertness. After completion of the treatment, patients were asked to continue to keep careful seizure records for another 3 months and to practice the skill they learned in the biofeedback sessions at home without the biofeedback machines, preferably on a daily basis. They were also asked to use this same skill as a countermeasure when they were aware that a seizure was about to start.

The primary outcome measure of this study was the change in seizure frequency after a month of GSR bio-

feedback treatment as a proportion of baseline seizure frequency. The secondary outcome measure was an increase in percentage GSR reduction over each treatment session which, in the active biofeedback group, provided an index of behavioral learning of GSR biofeedback skills over the 12 treatment sessions.

We thus hypothesized that the therapeutic effect of GSR biofeedback treatment would be physiologically based and not merely a placebo effect of the behavioral intervention. We predicted a significant reduction in seizure frequency after a month of treatment in the active biofeedback group in contrast to no significant benefit in the control group.

2.4. Statistical analysis

Seizure frequency was calculated as the number of seizures per week in the 3-month baseline period and the

3-month follow-up period. The main outcome was calculated as the percentage seizure change from the baseline period. As the data were not normally distributed, the Wilcoxon signed ranks test was used to analyze patients' mean seizure frequency before and after treatment in the active biofeedback and control groups. The Mann–Whitney *U* test was used to explore differences in percentage seizure frequency change between the biofeedback and control groups. To measure GSR change during the sessions, the individual's change in skin resistance level was calculated by subtracting the average GSR level for the first 2 min from the average GSR level for the final 2 min of each session. Percentage change in GSR was calculated in each session for each individual and averaged over the 12 biofeedback/control sessions. Repeated-measures ANOVAs were undertaken to investigate significant GSR change between the beginning and end of the biofeedback sessions in the active biofeedback and control groups. Then, to measure the progress in performance of biofeedback, the average percentage GSR change in the first three sessions (sessions 1–3) was subtracted from that in the last three sessions (sessions 9–12). Repeated-measures ANOVAs were performed in the same way between the average percentage GSR reductions in the first three sessions and the last three sessions for each group (active biofeedback and control) to determine whether the patients showed improvement in the degree to which they could change their skin resistance level over a month of (active or sham) biofeedback treatment. Degrees of freedom were corrected using the Greenhouse–Geisser estimate. Data were subsequently explored using post hoc *t* tests. To explore the relationship between physiological factors in the reduction of epileptic seizures, Spearman correlational analyses were undertaken between percentage seizure reduction, percentage GSR reduction, and percentage GSR change over treatment. The statistical significance level was generally set at 95% confidence in the analyses; however, in view of the number of variables, significance was set at 99% confidence in the correlation analyses.

3. Results

Of 150 patients who were screened at the National Hospital for Neurology and Neurosurgery, 22 patients agreed to take part in the study. Of the 22 patients, 18 patients with drug-refractory epilepsy actually enrolled and were randomly assigned to the active biofeedback group ($N = 10$, 7 with complex partial seizures [localization-related symptomatic epilepsy], 2 with generalized tonic–clonic seizures [symptomatic generalized epilepsy], 1 with generalized absence seizures [idiopathic generalized epilepsy]) and control group ($N = 8$, 5 with complex partial seizures [localization-related symptomatic epilepsy], 2 with generalized tonic–clonic seizures [symptomatic generalized epilepsy], 1 with myoclonic seizures [idiopathic generalized epilepsy]). Two patients were on no medication by choice. All of the other patients were receiving polytherapy. The main combination of anti-epileptic drugs was carbamazepine and sodium valproate. Data from the three patients in the pilot study were not analyzed; however, in Fig. 2, seizure frequency from these pilot study participants is provided.

Statistical analysis showed that there were no group differences between control and biofeedback groups with respect to age (mean \pm SD, 41.38 ± 13.287 , 42.50 ± 6.80 ; $P = 0.82$, independent *t* test) and baseline seizure frequency median number of recorded seizures per week (1.92 for control, 3.38 for biofeedback; $P = 0.23$, Mann–Whitney *U* test). The numbers of males and females in the two groups were equal (control M (4), F (4); biofeedback M (5), F (5)). Of 18 patients, all 10 in the biofeedback group completed biofeedback treatment; however, 3 patients assigned to the control group did not complete the study. Of the three, two patients stopped treatment (after 2 and 10 sessions) due to a slight increase in seizure frequency, and an antiepileptic drug change was undertaken after a month of follow-up assessment in both patients. Another patient withdrew from the study after seven sessions due to lack of motivation. The study was terminated based on analysis

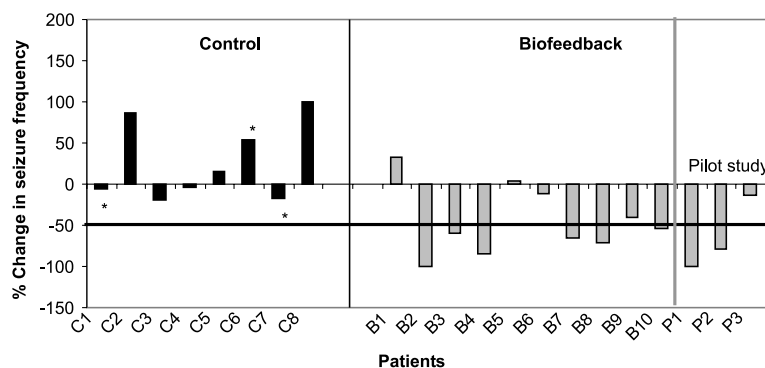


Fig. 2. Percentage seizure frequency change after GSR biofeedback treatment in control and biofeedback groups. *Patients who dropped out of the study in the middle of training.

that was undertaken when data concerning seizure frequency had been collected on these patients, the biofeedback group ($N = 10$) and the control group ($N = 8$), motivated in part by the ethical issue as to whether it was appropriate to continue the sham treatment control sessions.

Patients who withdrew from the study provided incomplete data sets, and data were included in the statistical analyses where appropriate. In other words, the seizure frequency information was included but no GSR data were. Thus, seizure frequency was analyzed on an intention-to-treat basis.

3.1. Seizure frequency change

There was a significant between-group difference in seizure reduction following GSR biofeedback treatment ($P = 0.01$). In the active biofeedback group patients, a month of GSR biofeedback training was associated with a significant decrease in seizure frequency comparing baseline seizure frequency with that in the follow-up period ($P = 0.017$). Of 10 patients in the biofeedback group, 6 patients had more than a 50% seizure reduction compared with their seizure frequency before treatment. The mean percentage change in seizure frequency was -49.26% ($SD = \pm 41.64$, median = -56.4%) for the biofeedback group. One patient became seizure-free. In contrast, no significant reduction was seen in the control patients who received sham biofeedback training (mean reduction of seizures = $+24.59\%$ [$SD = \pm 45.64$, median = $+9.53\%$]) (Fig. 2). Table 1 lists individual patients' mean seizure frequencies prior to and after treatment.

Table 1
Change in number of seizures per week before and after the GSR biofeedback training^a

Patients	Pretreatment (per week)	Posttreatment (per week)
C1 ^b	5.1	4.8
C2	0.7	1.3
C3	0.5	0.4
C4	5.8	5.5
C5	2.8	3.3
C6 ^b	3.9	6.0
C7 ^b	1.0	0.8
C8	0.8	1.4
B1	3.3	4.3
B2	0.9	0.0
B3	82.3	33.1
B4	15.7	2.4
B5	3.5	3.7
B6	0.8	0.7
B7	1.7	0.6
B8	33.8	9.6
B9	1.4	0.8
B10	4.1	1.9

^a C, control group; B, biofeedback group.

^b Patients who dropped out of the study in the middle of training.

3.2. GSR change

Patients in both the active biofeedback and control groups were given the same instructions to attend to the visual feedback display and to try to influence the animation by increasing their alertness level. As a result, both groups of patients were able to change their GSR (by demonstrating an increase in sympathetic arousal). In fact, change in GSR reached significant levels in both the biofeedback ($P = 0.001$) and control ($P = 0.028$) groups. The mean change in percentage GSR was greater in the biofeedback group (42.58 ± 30.16) than in the control group (25.27 ± 26.9); however, no significant between-group difference was found.

To examine the degree of improvement in GSR biofeedback performance, the average percentage GSR change over the first three sessions was subtracted from that of the last three sessions. The greater the value of this subtraction, the better the performance in GSR biofeedback toward the end of treatment. Patients in the biofeedback group showed significant improvement in performance of GSR biofeedback ($P = 0.007$), whereas patients in the control group did not show significant improvement in GSR biofeedback with time. Fig. 3 illustrates the difference (mean \pm SD) in across-session GSR biofeedback performance between the biofeedback (51.98 ± 12.17) and control (20.50 ± 27.88) groups. Statistical analysis revealed a significant difference in improvement of biofeedback performance between the two groups ($P = 0.004$).

3.3. Correlation between GSR and seizure frequency change

Consistent with our hypothesized causal relationship between the efficacy of GSR biofeedback training and a reduction in seizure frequency, we observed a significant correlation between the reduction in seizure frequency and the degree of patients' improvement in GSR biofeedback performance (i.e., GSR change over sessions) in both biofeedback and control groups together ($\rho = 0.736$, $P = 0.001$). The correlation between absolute magnitude of GSR reduction in each session and seizure frequency in both groups did not reach significance, suggesting that the learning of the biofeedback technique is a greater therapeutic factor in reducing epileptic seizures than perhaps the overall change in GSR arousal itself (Fig. 4).

4. Discussion

Our results provide preliminary evidence that the GSR biofeedback treatment was associated with a successful reduction in seizure frequency in patients with drug-resistant epilepsy. Despite the relatively small

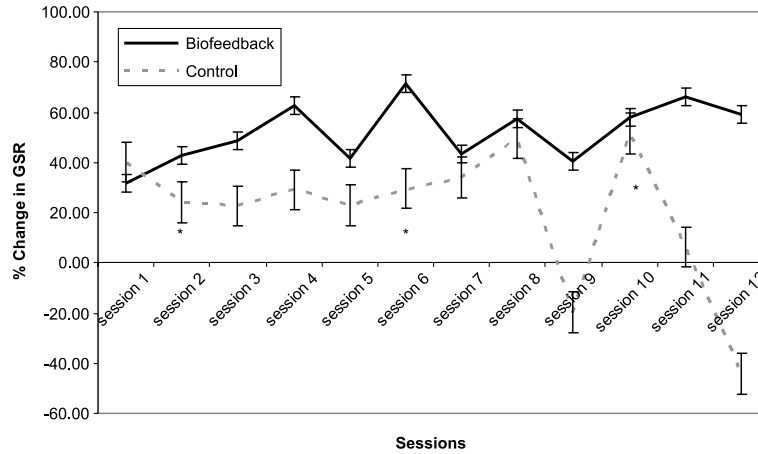


Fig. 3. Improvement in GSR biofeedback performance over 12 sessions in the control and biofeedback groups. For each session, percentage GSR change was calculated by subtracting the average GSR level for the first 2 min from the average GSR level of the last 2 min. Means and standard errors are shown for each group. *Week during which a patient in the control group dropped out of the study.

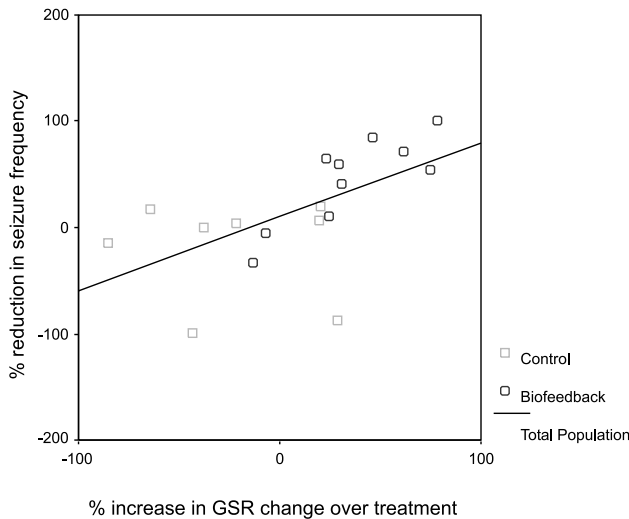


Fig. 4. Correlation between seizure frequency change and performance improvement in GSR biofeedback.

sample size, GSR biofeedback was observed to have a high response rate of 60% (60% of patients in the active biofeedback group had a reduction in seizure frequency of greater than 50%).

In this study, following a 3-month baseline seizure frequency level, a reduction in the occurrence of seizures was seen immediately during the treatment period for 5 of 10 patients in the biofeedback group. The effect of biofeedback-related seizure reduction was well maintained during the follow-up period for all patients. On the other hand, no significant seizure reduction was observed in the control group. Three control patients dropped out during the sham treatment period. This was partly due to lack of motivation (patients' self-report) because of the absence of reduction in seizures together with the high demands of the study protocol whereby patients were required to travel to the hospital three

times a week. This is not an issue in drug trials. It is of interest that in trials of drug therapy, the dropout rates for placebo and active treatments are often equivalent, or, because of side effects, more patients drop out of the active treatment group. In biofeedback, patients actively engage with the therapy rather than passively receive prescribed medications. The added reward of improving performance in the treatment group therefore probably explains this difference. Although patients were blind to the treatment group to which they were randomly assigned, it is still possible that, unrewarded by a reduction in seizures, they either realized or assumed they were in the sham group and withdrew from the study, although no patients in the control group questioned if they were receiving sham control at the end of the treatment.

In the current study, patients were not asked if they knew they were receiving sham treatment at the end of the study. Thus, the reliability of the blindness of the patients cannot be confirmed in this study. The inclusion of a simple questionnaire asking patients if they felt that they were allocated to the control or biofeedback group will be important in any planned future and more extensive clinical trials.

An important issue to consider is whether or not the biofeedback treatment group's results were due to a nonspecific placebo effect as a consequence of the attention and success in changing the computer graphics they experienced rather than as a consequence of specific changes occurring in neural mechanisms. An argument in support of the latter explanation is our observation that the reduction in seizure frequency was significantly correlated with an increase in performance of GSR biofeedback over the duration of the treatment for both active biofeedback and control groups (Fig. 4). In other words, patients who showed increases in GSR change throughout the sessions benefited most in terms of seizure reduction. This suggests that GSR change

combined with the receipt of accurate feedback by patients concerning their own physiological response is a key component underlying the apparent efficacy of GSR biofeedback in reducing epileptic seizures. It is possible that the acquisition (and consolidation through accurate feedback) of skills for controlling physiological arousal through biofeedback training is a particularly important aspect in seizure reduction and needs to occur in addition to the change in sympathetic arousal reflected by GSR change. Our imaging studies showing that GSR biofeedback modulates cortical and subcortical brain areas that are closely linked to homeostasis and the enhancement of bodily control [18–20] also suggest the results are due to physiological effect in the central nervous system beyond a placebo response.

In a previous study of slow cortical potential biofeedback [14], the key component of the effect of biofeedback in reducing patients' seizures was the patients' ability to modulate cortical excitability in the follow-up sessions without the actual use of the biofeedback instrument. This suggests that successful transfer of the biofeedback skill to daily life situations is a very important therapeutic factor. This observation also applied to our study of GSR biofeedback training, showing that the patients who learned the GSR biofeedback skill progressively over the 12 sessions benefited more from that training in the follow-up sessions. Patients reported that after biofeedback treatment, they used their biofeedback skills as a countermeasure at seizure onset and this helped to limit seizure severity. Recall of biofeedback skills on a daily basis was suggested to the patients in both the biofeedback and control groups. The forms of countermeasure used were an image of the animation they watched on the computer screen during the biofeedback session or provoking the sensation of the biofeedback skills.

In the current study, the GSR biofeedback was given to the patients to increase sympathetic arousal. The rationale behind this new approach for treating epilepsy derives from the fact that negative cortical potentials are closely related to the abnormal cortical activity that is present in epilepsy, and reduction in amplitude of slow cortical potentials (SCP) has been associated with the occurrence of fewer seizures [14,21,22]. Most importantly, an inverse relationship between CNV amplitude and peripheral sympathetic arousal was found in our previous study [16]. A volitional increase in sympathetic arousal using GSR biofeedback reduced cortical negative potentials (CNV amplitude). In our previous study, it was hypothesized that the reduction in CNV due to arousal biofeedback was mediated by regulation of the sensory input to the cortex via the thalamus, especially the reticular nucleus (RN) neurons. The RN neurons, which are GABAergic inhibitory neurons, regulate ongoing flow of the sensory information in thalamocortical neural circuits and possibly modulate the seizure threshold by altering excitatory input to the cortex.

Although only speculative at this stage, taken together with data from our recent imaging study using functional MRI and EEG, in which we have shown that the thalamus and its associated structures were strongly involved in generation of the CNV and the GSR [23], it is possible that the thalamus plays an important role in the effect of GSR biofeedback on reducing seizures in patients with epilepsy.

Finally, the current study has a number of important limitations in its design and analysis. Recruitment of a larger sample size was difficult due to the high demands of the study protocol. As a result it was not possible to recruit a homogenous sample of patients with similar seizure types. In addition, only one investigator was available to undertake the biofeedback/control sessions and thus was not blind to the interventions being used for each patient. This could be solved by having a different biofeedback trial coordinator and biofeedback trainer so that the trainer is blind to which groups he or she is instructing in biofeedback. It would have been helpful to have monitored patients' compliance with their antiepileptic drugs by means of blood serum samples taken at regular intervals; this would have ensured that differences in compliance between the two groups could not have accounted for the findings. Finally, in view of potential differences in people with different seizure types benefiting from this type of biofeedback training, future studies based on larger seizure samples will permit between-seizure type comparisons in outcome, analysis of which was not possible in the current study because of small numbers of patients with specific seizure types. Although these limitations mean that caution is needed in data interpretation, the current study provides the basis for wider investigations of this type of biofeedback in seizure reduction.

5. Summary

In this preliminary study, GSR biofeedback training was associated with successful reduction in epileptic seizure frequency in patients with drug-refractory epilepsy. There was an apparently marked effect of this intervention, in that 6 of 10 patients had a greater than 50% reduction in seizure frequency. Most importantly, the efficacy of treatment was related to learning of the behavioral technique and surpassed placebo or non-specific therapeutic interactions that were controlled for in the control condition. In contrast to other technically demanding biofeedback treatments of epilepsy, such as EEG and respiratory control, GSR biofeedback training represents an accessible and easy-to-implement behavioral procedure. Our findings strongly suggest that GSR biofeedback has potential as a potent adjunctive non-pharmacological means of reducing seizure frequency in drug-resistant epilepsy.

Acknowledgments

This work was supported by the Bial Foundation, Ultrasis Plc, and the Raymond Way Fund. We thank Professor John Duncan, Professor Ley Sander, Dr. She-lagh Smith, Dr. Matthew Walker, and Dr. Hannah Cock for their help in identifying suitable patients for this study. The statistical advice of Dr. Sabine Landau is gratefully acknowledged. The principal investigator was awarded two prizes in 2003 for this work (British Neuropsychiatry Association, ILAE UK; Young Scientific Investigator's Award).

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