Biofeedback as complementary treatment in patients with epilepsy – an underestimated therapeutic option? Review, results, discussion

Carmen Uhlmann[1], Walter Fröscher[2]

[1] Ulm University, Clinic for Psychiatry and Psychotherapy I
Centres for Psychiatry Suedwuerttemberg
Ravensburg-Weissenau, Germany

[2] Lake Constance Epilepsy Centre
Epilepsiezentrum Bodensee Centres for Psychiatry
Suedwuerttemberg Ravensburg-Weissenau, Germany

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Correspondence
Prof. Dr. Carmen Uhlmann
Clinic for Psychiatry and Psychotherapy I
Centres for Psychiatry Südwürttemberg
Weingartshofer Str. 2
D-88214 Ravensburg-Weissenau, Germany
Phone (49) 751 7601 2292
(49) 751 7601 2987
e-mail: carmen.uhlmann@zfp-zentrum.de

SUMMARY

Background. Biofeedback methods represent side effect free complementary options in the treatment of epilepsy. In this paper we review the current status of these methods in terms of clinical study results and their evaluation by systematic review papers. Possible mechanisms of action in biofeedback methods are discussed.

Aim. To present the current status of biofeedback methods applied to patients with epilepsy.

Material and Methods. With a literature search up to 10/2016 we screened publications containing the search terms "biofeedback", "neurofeedback" or "neurotherapy" and "epilepsy" or "seizure" for intervention and population search terms respectively.

Results. Four different techniques of biofeedback were used to improve seizure frequency in patients with epilepsy. Three of these techniques, measuring EEG (slow cortical potentials and sensory motor rhythm) or electrodermal activity (galvanic skin response, GSR) seem to be promising methods for successful seizure control. Nevertheless, methodological standards in the conducted trials were too low for assured empirical evidence in their efficacy.

Conclusions. Biofeedback methods could be applied to patients to a greater extent. Probably due to the missing empirical evidence of efficacy and the high demand on patients' and therapists' time and commitment and therefore low cost effectiveness, these methods are hardly offered. Especially the relatively new approach of GSR biofeedback represents a promising option here.

Key words: biofeedback • neurofeedback • epilepsy • self-control

BACKGROUND

Despite the introduction of many second-generation antiepileptic drugs over the past two decades, up to 40% of people with epilepsy fail to attain seizure freedom with appropriate medical treatment (Perucca et al., 2011). In a population-based study, 20 to 30% of diagnosed individuals with epilepsy were categorized as drug-resistant (Picot et al., 2008). Therefore, applications and enhancements of nondrug therapies are still necessary options in the management of seizures. Besides surgical treatment these include complementary

treatments. Biofeedback-methods represent one alternative in these possibilities (Kwan et al., 2011), notably since nowadays the availability of biofeedback-systems is better and initial costs are reduced because of progress in computer technology. Biofeedback typically includes the visual representation of internal physiological events on a monitor. The physiological responses are recorded by a sensor, usually a surface electrode, in case of respiration feedback by sample tubes of gas analyzers. The user is prompted to manipulate these otherwise involuntary physiological events with the goal of achieving control over the respective bodily process. Theoretically, the efficacy of biofeedback is caused through the enhancement of behavioral self-regulation in the displayed parameter, which is in case of epilepsy a countermeasure of epileptic activity.

AIM

The aim of the manuscript is to give an overview of biofeedback-methods offered to patients with epilepsy. Published review papers as well as study results with regard to seizure reduction will be presented and discussed. Also, the technique of different biofeedback methods and therapeutic procedures in the application with epilepsy patients will be explained.

MATERIAL AND METHODS

A literature search in Medline, Psychlit and Psychinfo databases was performed for the years 1965 until 10/2016 using the search terms "biofeedback", "neurofeedback" or "neurotherapy" as well as "epilepsy" or "seizure" for intervention and population search terms respectively.

RESULTS

Biofeedback techniques and study results

In the treatment of drug-resistant epilepsy four different physiological parameters have been studied over the last five decades. Two to them are considered as neurofeedback since the central parameters displayed include electroencephalographic signals of cortical activity: sensory motor rhythm (SMR) and slow cortical potentials (SCP). The other two peripheral parameters are considered to measure autonomic activity: galvanic skin response and respiratory signals.

Neurofeedback of slow cortical potentials

Slow cortical potentials (SCP) correspond to a slow type of event-related potentials and represent negative shifts of large neuronal assemblies over a couple of seconds after an eliciting event. They reflect the depolarization of apical dendrites of pyramidal neurons and indicate cortical excitability. Theoretically, SCP decrease the threshold of paroxysmal activity over cortical tissue. Therefore, the conscious suppression of the negative SCP shifts provides a way of controlling seizures in people with epilepsy, because epileptic discharge is restricted (Birbaumer et al., 1990; Strehl et al., 2006).

Biofeedback of SCP, nowadays so called neurofeedback, was introduced in the 1980s by the research group of Niels Birbaumer at the University of Tuebingen (Birbaumer et al., 1987). In several studies, the application and effectiveness of the method, when applied to patients with epilepsy, was investigated. In a first substantial study with 25 recruited patients with epilepsy, Rockstroh et al. (1993) found significant seizure reductions in 13 of the 18 patients, still included after one year of follow-up. A subsequent multicenter replication study confirmed these results (Kotchoubey et al., 2001). They revealed overall successful treatment in 34 patients in a 6 months follow up, but mostly in simple partial seizures. A follow-up study of this sample over 8 years was executed by Strehl et al. (2014). Sixteen of the originally 34 analyzed patients of the SCP-group participated in this follow-up, with 11 of the 16 patients not undergoing epilepsy surgeries. Seizure frequency decreased in 6 of the 11 patients > 50%. Seizure reduction following SCP neurofeedback could be predicted by a couple of variables that account for treatment success: First, higher amplitudes of negative SCP, i.e. cortical excitability at the beginning of the training as well lower SCP differentiation at the end of training were related to more seizure reduction. Other variables related to seizure reduction were locus of epileptic focus (right hemisphere) and some personality variables. The relation of success in seizure reduction to cortical excitability was an indication of SCP change representing the specific mode of action in neurofeedback (Strehl et al., 2005).

Treatment protocols for SCP biofeedback over the various studies consisted of 28 to 35 sessions with 110 to 145 trials per session, and every trial lasted for 8 seconds. The trials included parts with feedback and so called transfer trials without feedback. The aim of SCP biofeedback was to perform negative or positive shifts in SCP in each 8 second trial. Every session lasted therefore 60 to 90 minutes. SCP were recorded at the vertex (Cz) and referenced against left and right mastoid. Artifacts of eye movements were controlled for.

Neurofeedback of EEG frequencies

Another form of neurofeedback is the operant conditioning of EEG frequencies located over the sensorimotor cortex. Operant conditioning is a learning process of stimulus-response patterns where the frequency of a specific response changes as a function of reinforcement. In a biofeedback arrangement the contingent positive feedback of physiological changes is the reinforcement that leads to permanent behavior modification. The 12–15 Hz EEG rhythm appearing over the sensorimotor cortex is the so called sensory motor rhythm (SMR). Activity in this region is accompanied with the blockading of overexcitation in ventrobasal thalamic structures and is associated with inhibition processes in the sensorimotor system. Ultimately this form of neurofeedback has therefore also the goal of decreasing the threshold of paroxysmal activity over cortical areas. The enhancement of SMR amplitudes has shown to improve clinical epileptic conditions (Sterman and Egner, 2006).

The research body around SMR feedback in patients with epilepsy is large and started in the early 1970s by the research group of Barry Sterman. Since then, different research groups replicated the successful treatment of patients with epilepsy by SMR neurofeedback. Studies with clinical improvement published in this field mostly lacked controlled research designs and included only small sample sizes and short follow ups. But taken all studies together, a total of 174 patients were treated over the decades and 82% of all subjects showed a clinical improvement, defined as >30% seizure reduction (Sterman, 2000). In one higher quality study with a cross sectional and longitudinal control design, 24 patients with refractory epilepsy were treated (Lantz and Sterman, 1988). The results showed a seizure reduction of 60% after SMR feedback in a 6 week follow up. A meta analysis that included 9 published studies with SMR feedback conducted from different research teams and additionally one study with SCP feedback also showed highly significant seizure reduction for both kinds of neurofeedback (Tan et al., 2009). Especially the included SCP study of Kotchoubey et al., (2001) was of good methodological quality, even when it was not randomized controlled. The included studies using SMR feedback were not of convincing quality (see also section Biofeedback – treatment in epilepsy). Treatment protocols varied between the studies, mostly biofeedback session lasted between 60 and 90 minutes, executed a couple of times per week over a period of 6 to 24 weeks. SMR was recorded over electrode site C3, sometimes with multiple electrode placements over sites C1 to C5. Treatment goal was to increase SMR amplitude. In some studies, the feedback arrangement required a decrease of theta (5–7 Hz) besides the increase of 12–16 Hz.

Biofeedback of electrodermal activity

One newer and peripheral biofeedback in the treatment of epilepsy is the application of the galvanic skin response (GSR), also known as skin conductance levels. The GSR is a measure of the autonomic nervous system reflecting sympathetic activity. Therefore the GSR is a sensitive indicator of autonomic arousal related to emotional and cognitive/attention processes. The signals are recorded at the sweat glands of the hand. In the research group of Yoko Nagai, the relationship of GSR and the already described slow cortical potentials (SCP) were studied. They found an inverse relation of the amplitudes of GSR and SCP. Therefore, an increase of peripheral sympathetic arousal as measured by GSR at the sweat gland of the hand is thought to reduce cortical excitation as measured by decreased negativity of SCP (Nagai et al., 2004a). This relationship was confirmed in a clinical study in 10 patients with epilepsy after 12 training sessions of GSR biofeedback (Nagai et al., 2009). Cortical excitability was there measured by the contingent negative variation (CNV), which reflects SCP.

Autonomic arousal feedback recorded by GSR is therefore thought to decrease seizure frequency. In a randomized biofeedback study, 18 patients with drug-resistant epilepsy were either assigned to GSR biofeedback or to sham control feedback (Nagai et al., 2004b). The results show clearly that the GSR feedback active group was able to improve seizure frequency by 49% in a 3 months follow-up period, with 6 of the 10 patients having seizure improvements >50%. Also a strong positive correlation of 0.7 could be found between GSR feedback improvement and seizure reduction, consistent with the theoretical model. In a case report with 2 patients the effect was maintained over 3 years (Nagai and Trimble, 2014). The results of GSR biofeedback could be confirmed by a different, French research group as well. Micoulaud-Franchi et al. (2014) also found promising results in 11 patients with drug-refractory temporal lobe epilepsy and stress-triggered seizures 3 months after GSR feedback training.

In different studies the protocols of feedback fre-

quency varied: GSR feedback sessions lasted 30 minutes with an additional time for preparation and debriefing before and after feedback training. Training consisted of 1 to 3 sessions per week until in sum 12 GSR feedback sessions were completed. Treatment duration required therefore 4 to 12 weeks. Treatment goal was to enhance GSR, i.e. skin conductance levels. Feedback of skin conductance levels was recorded from the index and middle finger of the participants' left hand.

Biofeedback of respiration parameters

The idea of respiration feedback was established because of the interrelation of breathing, brain waves and epileptic activity. The link between these factors is hyperventilation (HV). Chronic or acute HV can cause hypocapnia which leads to respiratory alkalosis and changes in the EEG. To measure these factors, end-tidal carbon dioxide ($ETCO_2$) and the respiration rate (RR) were picked as control parameters to regulate breathing. Robert Fried et al. (1984) developed a self-regulation program for patients with idiopathic epilepsy. In their study, 18 patients with epilepsy and chronic hyperventilation underwent respiration biofeedback (and diaphragmatic respiration training) with the parameters percent $ETCO_2$ and RR, both measured by a gas analyzer. In 13 control persons breathing parameters were recorded without feedback and training. They found significant seizure reductions and EEG normalization as well as improvements in chronic hyperventilation. A problem in interpretation the study results is the lack of baseline pre treatment and the lack of follow up data after treatment. Fried et al. report seizure data in 10 patients with 7 months of biofeedback training, but none of them had stopped the training. Therefore unspecific effects as attention, general relaxation, stress reduction and others cannot be excluded. Another problem is that the patients did not reach improvements in hypocapnia, only in respiration rate and therefore it remains unclear, if there was any specific treatment factor of breathing regulation involved in the seizure improvements. In a study reported earlier, respiration feedback was one of the control conditions for neurofeedback of slow cortical potentials (Kotchoubey et al., 2001). The results were not encouraging in this retrial. No significant changes in seizure frequency were found in a one year follow up.

Aim of respiration feedback was to reach 5% $ETCO_2$ and a RR of 12 to 14. Each feedback session lasted 10 minutes with a pre-training session of also 10 minutes for baseline recording and measuring effects of the previous feedback session. In sum 35 feedback sessions were carried out in the study of Kotchoubey et al. (2001). In the study of Fried et al. (1984), respiration feedback was ongoing by the time of publication. No statement was made about the conducted amount of sessions at the time of study analyses.

Biofeedback – treatment in epilepsy

Several reviews were published to evaluate biofeedback methods in the treatment of epilepsy in view of seizure reduction. A Cochrane review of 2008 with an update 2011 included only a total of 2 biofeedback studies in their review of psychological treatments for epilepsy (Ramaratnam et al., 2008), the earlier described study of Lantz et al. (1988) applying SMR biofeedback and the study of Nagai et al. (2004b) using GSR biofeedback. The study with SMR feedback was not analyzed and rated in terms of seizure reductions because of lack of information about the control group. In case of the GSR study, the conclusion was that there is no reliable evidence to support the application of the treatment due to limited number of individuals studied. This statement was issued for all psychological treatments in epilepsy, namely relaxation training or cognitive behavioral therapy. For 2016, a new Cochrane review for the topic of psychological treatments in epilepsy including biofeedback methods was announced. The intervention protocol for the upcoming review was already published by the Cochrane Collaboration (Michaelis et al., 2016).

A comparable statement was declared in the BMJ reviews of Clinical Evidence. In the report about behavioral and psychological treatments in epilepsy, it was also stated that there is no evidence for biofeedback to represent an effective treatment for seizure reduction in people with epilepsy (Maguire et al., 2011). They did not analyze the study about GSR feedback (Nagai et al., 2004b) and the SMR feedback study of Lantz et al. (1988) because of insufficient quality or missing information and referred to the Cochrane review of Ramaratnam et al. (2008). In an updated specific overview of Clinical Evidence for alternative therapies in epilepsy, the evaluation was unchanged (Cross, 2015). The author confirmed furthermore unknown effectiveness of biofeedback since no well conducted studies were found in their search up to April 2014.

The earlier mentioned specific meta analysis about EEG biofeedback included 10 published studies (Tan et al., 2009), nine studies about SMR feedback and one

study applying SCP feedback, involving a total of 87 participants. The authors found a significant reduction of seizure frequency in the analyzed studies and interpreted this as evidence of the effectiveness of neurofeedback. The statement is limited however, because most included studies have small sample sizes and they lack follow up recordings longer than 6 weeks. Therefore, the Center for Reviews and Dissemination (CRD) commented that the authors' conclusions should be treated with caution (Center for Reviews and Dissemination, 2015).

In sum, while the authors of the studies found significant seizure reductions, none of the studies completely corresponded to the high methodological quality standards for clear empirical evidence. These standards include study design aspects like sample size and homogeneity, control conditions, randomization, blindness, time of follow up and outcome parameters. Therefore it was concluded that it is difficult to interpret the results of the conducted studies over the last decades from a scientific perspective (Monderer et al., 2002).

Mechanisms of action in biofeedback and the framework of cognitive behavioral therapy

There are three different broad models about possible modes of action in biofeedback. The first and most important assumption is a specific influence of physiological self-control due to feedback through operant conditioning processes. Authors of all presented biofeedback techniques argue that this is the main mode of action, because they found significant correlations between outcome success and biofeedback performance in respect of specific physiological changes. Therefore, they stated seizure improvements due to changes occurring in neural mechanisms. Examples of studies presenting this relation are available for 3 of the 4 described kinds of biofeedback. Consistent with the theoretical model, researchers found a strong positive correlation between GSR feedback improvement (defined as increased electrodermal activity) and seizure reduction (Nagai et al., 2004b; Micoulaud-Franchi et al., 2014). In SCP neurofeedback, the relation of success in seizure reduction and cortical excitability was interpreted as an indication of SCP change as the specific mode of action (Strehl et al., 2005). Seizure reduction following SCP neurofeedback was predicted by the SCP amplitude at the beginning of the training and SCP differentiation at the end of training. Also, in the study of Lantz and Sterman (1988) a significant correlation between SMR feedback and seizure reduction of $r = 0.46$ confirmed a specific mode of action in this kind of biofeedback.

Even though specific physiological mechanisms of action were found in the studies, physiological nonspecific and/or cognitive placebo factors might as well be involved. In a 2×2 table with learning of feedback yes/no and seizure reduction yes/no on a single case level, nonspecific common mechanism must be at work when biofeedback was not successfully learned, but improvement of seizure frequency was high (Uhlmann and Fröscher, 1997). Therefore a second model about possible mechanism of action in biofeedback states nonspecific physiological factors. These could be existent due to a decrease of sympathetic arousal during biofeedback sessions, where patients sit quietly and concentrate on the biofeedback task. Therefore, biofeedback represents some kind of relaxation training as well. Interestingly, in the paradigm of GSR biofeedback, the opposite is the case: Successful performance was given, when arousal as measured by GSR was increased. This was considered as the specific mode of action since it covaried with decreased cortical arousal (see section Biofeedback of electrodermal activity). When the modes of action in biofeedback would consist of nonspecific physiological factors, sympathetic arousal should decrease, and therefore electrodermal activity as well. That means a nonspecific physiological relaxation factor as the mode of action is not possible in GSR biofeedback application (Nagai et al., 2004b; Micoulaud-Franchi et al., 2014). But a third possible mechanism of action type may be involved in all techniques of biofeedback. Cognitive processes should be at work in terms of expectations and attitudes of patients. Therefore, effectiveness is probably also mediated by cognitive changes induced by contingent performance feedback, i.e. success perception. Especially the theory of self-efficacy (Bandura, 1977) and the cognitive biofeedback approach of Meichenbaum (1976) established a whole era of cognitive mechanisms in behavioral modification. The variation of cognitive variables in the course of biofeedback treatment in patients with epilepsy was confirmed for GSR feedback (Nagai et al., 2004b) and also for respiration and SCP biofeedback (Uhlmann and Fröscher, 2001). Uhlmann and Fröscher present a cognitive model about the relation of control orientation, depression and biofeedback as a therapeutic option to improve helplessness and depression due to change in locus of control and self-efficacy in patients with epilepsy.

In sum, it seems difficult to extract the diverse active mechanisms in different biofeedback treatment approaches and there is a lack of clear conceptual distinction between common, nonspecific factors and specific factors of neural/physiological change. Lately, a promising approach of Gaume et al. (2016) tried to identify and separate possible mechanisms of action in the view of different scientific disciplines. Certainly, the debate about efficacy of biofeedback is in line with the controversy of mechanisms of action in psychotherapy in general (Wampold, 2015). This is specifically true considering that most researchers in biofeedback for epilepsy used a cognitive behavioral therapy framework when treating patients. Especially in SCP biofeedback, the method is embedded in a framework of cognitive behavioral treatment elements for seizure control (Schmidt-Schönbein and Heinen, 2013). Also in SMR biofeedback, some authors applied a complex self-control model for seizure improvement. Specifically in the study of Andrews and Schonfeld (1992) SMR biofeedback was one part of a multifaceted behavioral medicine approach for psychological seizure management. In a sense, biofeedback therapy seems to be a part of a complex self-control strategy in non-pharmacological seizure treatment and not the other way round (Kotwas et al., 2016).

DISCUSSION

Biofeedback methods represent a well established treatment option for drug-resistant epilepsies on a level of practicability and acceptance by patients. Feedback containing central parameters like SMR or SCP – nowadays called neurofeedback – has a research and application history of at least over 20 years. In contrast, GSR feedback comprising peripheral physiological response is a relatively new method. Despite the fact that study results are encouraging for the application of biofeedback and neurofeedback, the optimistic conclusions of the researchersin terms of seizure reduction could not be confirmed in reviews and meta-analyses due to methodological shortcomings in the clinical research designs. High-level methodological research designs are still missing in terms of biofeedback studies; therefore efficacy and effectiveness are still not completely confirmed since the conducted studies are mostly not included in the reviews because of these methodological shortcomings. Studies often lack of adequate sample size and homogeneity, randomization, controlling for placebo effects, long term follow ups, and sufficient outcome information. To improve clinical research protocols, biofeedback research studies are needed preferably with 1. homogenous, well described patients groups, 2. controlled randomized designs, possibly with 2 competing feedback modalities instead of sham feedback as control condition, 3. explicit seizure diaries, possibly electronically for reliable outcome measuring, 4. follow ups of at least 1 year, 5. adequate sample sizes to avoid underpowered trial results, 6. possibly blinded therapists and patients or highly motivated and convinced therapists and patients for the specific treatments.

Many researchers in biofeedback have stated the impossibility of randomization because of the uselessness of sham feedback. Especially therefore the application of 2 active feedback groups could be an option. Randomization will continue to remain the key factor for evidence of biofeedback studies. One problem in the research and application of biofeedback is the considerable period of time that must be provided for therapists and patients. The duration of feedback sessions and of overall treatment is enormous and implies a high demand on patients' and therapists' time and commitment. Also, there are innumerable options in feedback set up, including length and types of trials and sessions, physiological parameter settings, instructions for patients and feedback modalities. Additionally, patient characteristics for possible treatment success in terms of epileptogentic focus, seizure type, medication or age are hardly described.

GSR feedback in comparison to neurofeedback is less time consuming, less error-prone, less expensive, and easier to learn. Therefore, cost effectiveness is better in GSR feedback. On the other hand, even neurofeedback systems are nowadays easier to handle and there are complete system configurations available in Europe as well as in the US. At the same time this might be a problem, because not all equipment providers seem to be reliable partners working with evidence based knowledge. The application of neurofeedback for example is primarily successful in the treatment of young patients with attention deficit hyperactivity disorder (ADHD). In this field, occupational therapists are specialized for this kind of treatment, but application standards often remain unclear. Likewise, mechanisms of action in biofeedback therapy remain not untangled. Common cognitive and nonspecific physiological effects play an important – possibly additional – role in the effectiveness of biofeedback as well as in psychotherapy generally.

CONCLUSIONS

Despite its limitations, biofeedback represents an alternative treatment option for people with drug-resistant epilepsies. Even when the efficacy remains unclear in drug-resistant patients without option for surgery, biofeedback continues to be an additional possibility for seizure improvement and also for improvement of health related quality of life. Negative side effects of biofeedback are not described and biofeedback can be practiced at home and mediates a feeling of control. Perceived self-control is an important issue for well-being, especially in patients experiencing seizures, i.e. states with feelings of loss of control. Therefore the described study results are still notable and stay encouraging, considering that the included patients were drug-resistant without further options of other therapeutic possibilities. But even in nonresistant patients with epilepsy, biofeedback would be an option as adjunctive treatment that could be offered in epilepsy centers during adaptation of drug regimen. Biofeedback methods are not expensive compared with the enormous cost of the development of antiepileptic drugs, their chronic ingestion and the costs arising from side effects. In a survey of German epilepsy centers conducted in the year 2011, none of the 11 replying centers provided biofeedback for their patients on a regular basis (Uhlmann, 2012). Birbaumer et al. (2007) stated a general disinterest of the medical science institutions in psychological methods for somatic disorders as reason for the unacceptability of biofeedback as therapeutic option. The research of side-effect free behavior medicine methods should be supported by public research grants to a considerable greater extent. Nevertheless, the awareness of biofeedback methods is growing, also in the field of epileptology (Nagai, 2011). At the moment, we have a new cycle with an extreme hype around the topic of biofeedback, mostly on the side of patients with psychological disorders and their relatives (Marzbani et al., 2016). Let us hope that the motivation involved in this hype spreads for the treatment in patients with epilepsy.

CONFLICT OF INTEREST DISCLOSURE

The authors declared no conflict of interests.

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