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Review

Neurofeedback and epilepsy☆

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Abstract

Over the past three decades, researchers have examined various behavioral approaches to the treatment of epilepsy. One prominent line of inquiry concerns the effectiveness of neurofeedback, which entails the entrainment of specific electroencephalographic frequencies for the purpose of decreasing seizure frequencies in patients with epilepsy. This article reviews the current literature on the efficacy of neurofeedback in reducing seizure frequency. While it is clear that neurofeedback had a positive effect in most of the studies reviewed, these findings are limited due to multiple confounding factors. In the absence of any rigorously controlled studies, the relationship between neurofeedback and seizure frequency cannot be firmly established. Despite these limitations, the promising role of neurofeedback as a treatment for epilepsy is illustrated.

Keywords: Neurofeedback; Biofeedback; Epilepsy; Intractable epilepsy; Alternative therapy; Seizure control; Epilepsy therapy

1. Introduction

While the past few decades have been witness to major advances in the treatment of epilepsy, a significant percentage of patients continue to have seizures that are intractable to current medical and/or surgical therapies. For such patients, the availability of an additional therapy for seizure control has the exciting potential of positively impacting both health and quality of life.

In the search for alternative treatments, some researchers have begun to supplement medical regimens with behavioral treatments. One such modality is neurofeedback, which is a form of biofeedback therapy based on self-modulation of the electroencephalogram (EEG) by the patient. Using neurofeedback, entrainment of specific EEG frequencies is believed to influence seizure control as well as behavioral parameters. This entrainment is accomplished through operant conditioning, whereby patients are positively reinforced for the production of a specific EEG frequency. Various techniques of neurofeedback that have been used include entrainment of slow cortical potentials (SCPs) and, conversely, entrainment of the higher-frequency sensorimotor rhythm (SMR).

The purpose of this article is to provide a comprehensive review of the literature concerning the effects of neurofeedback on seizure frequency in patients with epilepsy.

2. Methods

Our initial intent was to perform a meta-analysis of neurofeedback for seizure control. Articles were identified using multiple computer-based search engines, including Medline and Pubmed. This review initially considered all studies conducted from 1960 to the present assessing the effects of neurofeedback on seizure frequency, while other outcomes, such as neuropsychological measures associated with neurofeedback, were not examined. Only studies with five or more subjects were reviewed. Additionally, multiple studies using overlapping patient populations were not included.

A preliminary review of the literature did not provide a sufficient number of large or controlled studies to satisfy the statistical requirements of meta-analysis.

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Therefore, we present here an overview of the present state of research concerning the efficacy of neurofeedback in reducing seizure frequency.

Seizure types are specified when available from the studies. However, as the classification of epilepsy and diagnostic techniques have undergone significant transition over the decades spanned by this review, the quality of the described seizure types is often limited. For the purposes of this review, seizures have been classified largely as partial (including simple partial, complex partial, and complex partial with generalization) or primary generalized (absence, primary myoclonic, and primary generalized tonic clonic).

3. Modification of slow cortical potentials

3.1. Biological basis

Negative slow cortical potential (SCP) shifts reflect widespread depolarization of apical dendrites of the cortical pyramidal cells. In the normal brain, it has been suggested that these negative SCP shifts reflect cortical arousal, attention, and information processing, while positive shifts reflect relaxation [1]. The behavioral approach that seeks to decrease negative slow cortical potentials for epilepsy is premised on the theory that negative SCPs represent paroxysmal depolarization of irritable cortical neurons, indicative of excessive neuronal excitability, as was noted in cats with pentylenetrazol- or penicillin-induced seizures [2]. In humans, cortical negative potential shifts have been recorded preceding seizure activity, and are thought to represent the overexcitability of cortical neuronal networks [3,4]. Based on such data, Birbaumer and colleagues [5] proposed that patients with intractable epilepsy may be characterized by a loss of feedback control over the level of cortical activation by the basal ganglia and thalamus. On the EEG, this level of activation may be visualized as oscillations of slow cortical potentials, with negative SCP shifts reflecting an increase, and positive SCP shifts reflecting a decrease in cortical activity. Consequently, by training a patient to reduce his or her level of cortical negativity, it can be assumed that seizure control may be attained.

Using this model, studies have been designed to train patients to suppress negative SCP shifts. In these studies, patients with epilepsy received feedback for their surface-recorded SCPs and were reinforced for decreasing or increasing their SCPs below or above their baseline levels.

3.2. Technique

Feedback for SCPs is typically delivered for a dc shift toward reduced surface negativity as recorded from the Cz electrode referenced to linked ear electrodes. Subjects are presented with feedback (reward) which is typically visual, with reward for the required positivity versus negativity. Session duration and frequency vary, and total session number ranged from 28 to 35 in the reported studies [3,4].

3.3. Studies

Much of the investigation into self-regulation of SCPs has been performed by two groups. In 1993, Rockstroh et al. [3] reported a study of 25 patients with epilepsy who were trained to self-regulate SCPs. Seizure type was predominantly partial, although patients with primary generalized seizures were included. Of the 18 patients with at least 1 year of follow-up, a significant decrease in seizure frequency as compared with baseline levels was reported ($P < 0.01$). Six patients became seizure-free, seven patients had reductions in seizure frequency relative to baseline, and five patients showed no change in seizure incidence.

Kotchoubey et al. [4] have similarly trained patients with intractable epilepsy to self-regulate their SCPs. In their most recently reported study, SCP self-regulation was compared with respiratory self-regulation and new antiepileptic drug (AED) treatment. Seizure types were predominantly partial, but patients with absence, myoclonic, and primary generalized tonic–clonic seizures were also included. Results showed a significant decrease in overall seizure rates for the SCP group ($P = 0.027$) and the AED group ($P = 0.023$), with no significant difference between these two groups. Self-regulation of SCPs, therefore, was as effective for seizure control as the addition of a new AED.

Not all patients are capable of regulating their SCPs. In determining whether or not to recommend such treatment to a patient, assessment of factors that may predict the likelihood of positive outcome can be valuable. Rockstroh et al. [3] noted that factors such as increasing age, lack of motivation, and life stresses may have a negative impact on one's ability to train their SCPs.

4. Sensorimotor rhythm

The second major behavioral technique that has been used in the conditioning of certain central cortical EEG patterns is sensorimotor rhythm training. Although studies assessing SMR self-regulation are more numerous than self-regulation of SCPs, study design varies significantly, and few controlled studies have been performed.

4.1. Biological basis

The sensorimotor rhythm was initially described in cats. During behavioral inhibition, a 12- to 20-Hz fre-

quency rhythm was noted over the sensorimotor cortex, with maximal amplitude between 12 and 16 Hz [6]. Initial studies demonstrated that cats were capable of learning, through operant conditioning, to increase this predominantly 12- to 16-Hz EEG rhythm over their somatosensory cortex while remaining alert and motionless [7,8]. This effect was later demonstrated in humans [9]. Sterman and colleagues have extensively studied the mechanisms underlying SMR, and a theoretical model has been proposed [10]. Lack of motion in the context of attention may alter motor output to the thalamus and brainstem, resulting in decreased red nucleus activity and a reduction in the stretch reflex and muscle tone. The reduction results in a decline in somatic afferent activity and a shift to increased oscillatory bursting activity between the ventralis posterior lateralis and reticularis nuclei of the thalamus. This correlates with the development of sensorimotor electrographic activity, which is considered to "normalize" the EEG [10]. The SMR bears similarity in location and characteristics to sleep spindles, and SMR training has been demonstrated to enhance spindle activity during quiet sleep [11].

4.2. Technique

Feedback for SMR is typically delivered for bipolar EEG components of left sensorimotor cortex, with electrodes placed at C3 and CZ. Subjects are presented with feedback (reward) which may be auditory, visual, or both, with reward for an increase in SMR. Some protocols include reward for a decrease in feedback for theta (5–7 Hz) and higher beta frequencies, or excessive EMG activity. Session duration and frequency and total session number vary among studies, but generally consist of 30- to 45-min sessions delivered two to three times per week for a number of months.

4.3. Studies

4.3.1. 1970s

SMR training was applied to patients with epilepsy in the early part of the 1970s, which produced numerous initial reports on the effects of neurofeedback training [12–14]. Lubar and Bahler [15] were the first group to use SMR feedback in more than five patients. By use of biofeedback, eight patients with intractable epilepsy were trained to increase production of 12- to 14-Hz activity and decrease production of 4- to 7-Hz slow-wave activity. Seizures were predominantly partial. After a treatment duration ranging from $6\frac{1}{2}$ to 8 months during which time medication adjustment was allowed, six of the eight patients showed a postconditioning reduction in seizure frequency, although two of these patients showed transient increases in seizure frequencies when the feedback sessions were stopped and during stressful events in their lives.

In 1978, Kuhlman [16] investigated whether reduction in seizure frequency was due to EEG feedback training and not to other contingencies such as placebo and changes in medications. This study compared seizure frequency during periods of random feedback to periods of positive feedback contingent on the production of 9 to 14 cps activity. Of the five patients included, four had partial and one had generalized myoclonic epilepsy. Three of five patients showed a significant reduction in seizure frequency during contingency training when compared with random feedback ($P < 0.05$). Subsequently, two of these three patients did not return to their posttreatment seizure frequencies after a break in training, while one patient remained improved.

Also in 1978, Sterman and Macdonald [17] studied eight patients with refractory seizures and mixed seizure types, using an ABA crossover design, with medications kept constant. During the first 3 months, each subject was conditioned to increase one EEG frequency and decrease another. The next months of training included the reversal of the above schedule, and during the last 3 months, the original conditioning schedule was reinstated. The eight subjects received reinforcement for different combinations of three frequencies (6–9, 12–15, and 18–23 Hz). Six of the eight subjects had a significant reduction in seizure frequency when they were reinforced for either the 12- to 15-Hz or 18- to 23-Hz frequencies in the absence of 6- to 9-Hz activity. The response to the 18- to 23-Hz training remained even when the reinforcement contingencies were reversed, while the response to the 12- to 15-Hz training did reverse with contingency reversals.

4.3.2. 1980s

Lubar and his colleagues [18] reported the first double-blind ABA crossover study on eight patients with intractable epilepsy and various seizure types in 1981. Four of eight patients had an increase in seizure activity during training to produce slow 3- to 8-Hz activity, whereas reinforcement for faster frequencies appeared to be associated with seizure reductions, with or without affecting the slow-wave activity.

In 1988 Tozzo et al. [19] studied six patients refractory to medical therapy, in a study consisting of relaxation training, neurofeedback training 1, and neurofeedback training 2, separated by baseline periods. Four patients had Lennox–Gastaut and two had atonic/tonic–clonic seizures. Treatment consisted of receiving positive feedback contingent on the production of 12- to 14-Hz activity and withholding feedback for production of epileptiform activity (4- to 8-Hz frequency). Five of six patients showed a reduction in seizure frequency during at least one of the neurofeedback training periods, but only three of the six showed this reduction in both. The sixth patient had a reduction in seizure frequency during the relaxation period.

In that same year, Lantz and Sterman [20] reported a double-blind controlled study with 24 intractable epilepsy patients. Subjects were matched for age and seizure types and then assigned to three groups: group 1—contingent training for enhancing 11- to 15-Hz frequencies while decreasing 0- to 5-Hz and 20- to 25-Hz frequencies; group 2: noncontingent training; group 3: tabulation group, consisting of seizure tabulation only. Following an initial study period, groups 2 and 3 received contingent feedback training. Seizure types were predominantly partial. A statistically significant reduction in seizure frequency during the contingent training phase as compared with the control phases was reported ($P = 0.005$). Individual responses ranged from 0 to 100%, with the median seizure reduction being 61%.

5. Operant conditioning: negative studies and alternate techniques

Over the course of many years of study, the SMR technique has been both justified by physiological data and supported by successful trials. However, not all studies have reported a positive effect. Cott and his colleagues [21] performed a study of subjects with intractable epilepsy, with partial and generalized seizures equally represented. They observed that three of four subjects receiving negative reinforcement for the production of epileptiform frequencies and no SMR reinforcement had as significant a decrease in seizure frequency as two of three subjects who were receiving both negative reinforcement and SMR positive reinforcement. The authors concluded that SMR training is neither necessary nor sufficient to cause a reduction in seizure frequency.

Certain study groups set out to challenge the traditional use of the 12- to 16-Hz activity training. Wyler et al. [22] posited that it was not the specific production of certain EEG frequencies that was responsible for a decrease in seizure activity, but it was simply the production of activity surrounding the seizure focus that caused the observed effect. They reported a study of conditioning patients to increase EEG frequencies above 14 cps over the area best approximating their seizure focus. Seizure type was predominantly partial. Patients were exposed to alternating periods of conditioning, nonconditioning, and pseudoconditioning. Medication adjustments were permitted. Two of four patients receiving training had a reduction in seizure frequency, two others had a decrease in their more "severe" seizures, and an increase in their "less severe" seizures, and a control patient had no change in seizure frequency.

In a follow-up study of 23 patients with poorly controlled epilepsy [23], patients were reinforced for 18-Hz activity over the approximated seizure focus, while reinforcement was withheld for low-frequency high-voltage EEG activity and EMG activity. Patients had predominantly temporal lobe epilepsy, but patients with generalized epilepsy and "hysterical seizures" were included. Ten patients showed a reduction in seizure frequency, eleven patients showed no change in seizure frequency, and two patients had equivocal responses, defined as a decrease in secondarily generalized seizures and an increase in simple partial seizures.

Finally, in 1992, Andrews and Schonfeld [24] reported the largest study, using a behavioral approach, which included EEG biofeedback for 83 subjects with medically uncontrolled seizures. Seizure types were not described. Patients were trained to identify preseizure warnings and triggers, perform diaphragmatic breathing techniques, and use EEG biofeedback to induce therapeutic alpha activity (8–12 cps at 50 mV). Sixty-nine of the eighty-three subjects (83%) achieved total seizure control, which was defined as no seizures during the time of this multifaceted behavioral treatment.

6. Conclusion

This review has attempted to synthesize the currently available literature on the use of neurofeedback for the treatment of epilepsy. Studies performed over three decades suggest a positive effect on seizure control. The extent of this positive effect, however, is very difficult to assess from the available literature. There is no consensus regarding the neurofeedback technique that yields optimal results. Furthermore, many of the available studies are beset by methodological deficiencies, including a small number of subjects, nonuniformity of subject selections, and the absence of a rigorously controlled study design. Finally, many of these studies permitted medication adjustments, potentially confounding the treatment effect of the neurofeedback.

To date, no large, randomized, controlled study of neurofeedback in epilepsy has been reported. This likely reflects the labor-intensive character of EEG feedback training and a historical preference of funding agencies toward "mainstream" rather than "alternative" research. In the absence of such a study, however, the relationship between EEG contingency training and seizure reduction cannot be unequivocally established, as the reduction in seizure frequency may be related to confounding factors.

Despite these limitations, the use of neurofeedback treatment for patients with epilepsy is an intriguing option. The addition of an alternative therapy with the potential to reduce seizure frequency is an innovative contribution, of importance to clinicians and patients alike. This review highlights the need for rigorously designed studies to investigate these potentially promising results.

References

[1] Elbert T, Rockstroh B, Lutzenberger W, Birbaumer N. Biofeedback of slow cortical potentials, I. Electroencephalogr Clin Neurophysiol 1980;40:293–301.

[2] Caspers H, Speckmann EJ. DC-potential shifts in paroxysmal states. In: Jasper HH, Ward AA, Pope A, editors. Basic mechanisms of the epilepsies. Boston: Little Brown; 1969.

[3] Rockstroh B, Elbert T, Birbaumer N, et al. Cortical self-regulation in patients with epilepsies. Epilepsy Res 1993;14: 63–72.

[4] Kotchoubey B, Strehl U, Ulmann C, et al. Modification of slow cortical potentials in patients with refractory epilepsy: a controlled outcome study. Epilepsia 2001;42:406–16.

[5] Birbaumer N, Elbert T, Rockstroh B, Daum I, Wolf P, Canavan A. Clinical psychological treatment of epileptic seizures: a controlled study. In: Ehlers A, editor. Perspectives and promises of clinical psychology. New York: Plenum; 1991. p. 81.

[6] Roth SR, Sterman MB, Clemente CD. Comparison of EEG correlates of reinforcement, internal inhibition and sleep. Electroencephalogr Clin Neurophysiol 1967;23:509–20.

[7] Sterman MB, Wyrwicka W. EEG correlates of sleep: evidence for separate forebrain substrates. Brain Res 1967;6:143–63.

[8] Howe RC, Sterman MB. Cortical–subcortical EEG correlates of suppressed motor behavior during sleep and waking in the cat. Electroencephalogr Clin Neurophysiol 1972;32: 681–95.

[9] Sterman MB. Effects of sensorimotor EEG feedback training on sleep and clinical manifestations of epilepsy. In: Beatly J, Legewie H, editors. Biofeedback and behavior. New York: Plenum; 1977. p. 167–200.

[10] Sterman MB. Basic concepts and clinical findings in the treatment of seizure disorders with EEG operant conditioning. Clin Electroencephalogr 2000;31:45–55.

[11] Sterman MB, Howe RC, McDonald LR. Facilitation of spindle-burst sleep by conditioning of electroencephalographic activity while awake. Science 1970;167:1146–8.

[12] Sterman MB, Friar L. Suppression of seizures in an epileptic following sensorimotor EEG feedback training. Electroencephalogr Clin Neurophysiol 1972;33:89–95.

[13] Sterman MB, Macdonald LR, Stone RK. Biofeedback training of the sensorimotor EEG rhythm in man: effects on epilepsy. Epilepsia 1974;15:395–416.

[14] Finley WW, Smith HA, Etherton MD. Reduction of seizures and normalization of the EEG in a severe epileptic following sensorimotor biofeedback training: preliminary study. Biol Psychol 1975;2:189–203.

[15] Lubar JF, Bahler WW. Behavioral management of epileptic seizures following EEG biofeedback training of the sensorimotor rhythm. Biofeedback Self Regul 1976;1:77–104.

[16] Kuhlman WN. EEG biofeedback training of epileptic patients: clinical and electroencephalographic analysis. Electroencephalogr Clin Neurophysiol 1978;45:699–710.

[17] Sterman MB, Macdonald LR. Effects of central cortical EEG feedback training on incidence of poorly controlled seizures. Epilepsia 1978;19:207–22.

[18] Lubar JF, Shabsin HS, Natelson SE. EEG operant conditioning in intractable epileptics. Arch Neurol 1981;38:700–4.

[19] Tozzo CA, Elfner L, May JG. EEG biofeedback and relaxation training in the control of epileptic seizures. Int J Psychophysiol 1988;6:185–94.

[20] Lantz D, Sterman MB. Neuropsychological assessment of subjects with uncontrolled epilepsy: effects of EEG feedback training. Epilepsia 1988;29:163–71.

[21] Cott A, Pavloski RP, Black AH. Reducing epileptic seizures through operant conditioning of central nervous system activity: procedural variables. Science 1979;203:73–5.

[22] Wyler AR, Lockard JS, Ward AA, Finch CA. Conditioned EEG desynchronization and seizure occurrence in patients. Electroencephalogr Clin Neurophysiol 1976;41:501–12.

[23] Wyler AR, Robbins CA, Dodrill CB. EEG operant conditioning for control of epilepsy. Epilepsia 1979;20:279–86.

[24] Andrews DJ, Schonfeld WH. Predictive factors for controlling seizures using a behavioral approach. Seizure 1992;1:111–6.