Published in final edited form as:
Curr Neurol Neurosci Rep. 2017 May ; 17(5): 42. doi:10.1007/s11910-017-0752-z.

Cognitive and behavioral interventions in epilepsy

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Abstract

Purpose of review—Cognitive and behavioral treatments for epilepsy offer several advantages, as they are relatively low cost, are noninvasive, lack serious side effects, and facilitate patient participation. Their role in the management of epilepsy, however, is unclear. The following manuscript will critically review the efficacy data regarding psychological treatments for seizure reduction.

Recent findings—Encouraging results have been found for the cognitive behavioral therapy-based Reiter/Andrews approach and mindfulness or arousal-based programs (e.g. yoga, meditation, relaxation, and biofeedback). Most studies attained responder rates between 45-90%.

Summary—Cognitive and behavioral interventions may be considered as low-risk adjuncts to standard therapies. Efficacy data are limited, however, by small numbers of subjects, inadequate randomization, controls, and blinding, brief trial durations, varying methodologies, and variability in the presentation of results. Additional clinical trials are warranted.

Keywords

epilepsy; seizures; cognitive treatments; behavioral treatments; psychological treatments; cognitive behavioral therapy

Introduction

The treatment of epilepsy typically focuses on anticonvulsant medications, surgical interventions, and device implantations. Although likely effective for enhancing psychological well-being, the role of cognitive and behavioral approaches for seizure control is less clear. In 2008, a Cochrane review [1] determined that there was no reliable evidence to support cognitive and behavioral interventions, such as relaxation therapy, cognitive-behavioral therapy (CBT), EEG biofeedback, and educational interventions, as the number

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of randomized, controlled trials was limited. While the Psychobehavioral Treatments for People With Epilepsy Task Force focused on health-related quality of life as an outcome measure for the new, updated Cochrane review, the nine included studies do address seizure frequency, with results of the meta-analysis pending [2]. More data, however, are still needed. Although generally assumed to be less effective for seizure control than standard treatment options, non-pharmacologic methods pose less risk of side effects, avoid drug interactions, are of minimal cost, may be conducted remotely in many instances, and may present an attractive option to pregnant women, people who are refractory to medications, or others who are wary of medication trials. Given these possible benefits, it is important to critically review the existing data regarding psychological treatments for epilepsy.

Cognitive and behavioral techniques have been used alone and in combination, as well as adjunctive to medication, in patients with epilepsy. The mechanism of potential seizure frequency reduction is unclear, but may relate to decreased stress and its associated maladaptive responses, a reduction of co-morbid psychiatric symptoms, increased self-efficacy to improve seizure management, or learned behaviors altering the underlying epileptogenic neural networks. The following manuscript reviews the efficacy of psychological methods for the treatment of seizure disorders, focusing on the specific therapies for which there is the most available evidence: cognitive behavioral therapy (CBT) and mindfulness and arousal-based approaches (mindfulness, yoga and meditation, and biofeedback).

Cognitive behavioral therapy (CBT)

Cognitive behaviorism maintains that thoughts influence behavior and physiology. Cognitive behavioral therapy (CBT), often used in conjunction with mind-body approaches, examines the relationships between thoughts, emotions, and specific events (i.e. seizures). Patients learn to identify maladaptive thought patterns and replace them with healthier cognitive and behavioral responses. The goal is to foster an increased sense of self-control over seizure occurrence. The process typically involves an assessment of psychological stressors that can lower seizure threshold and identification of environmental or behavioral factors that impede healthy practices (e.g., behaviors that prevent sufficient sleep or medication adherence). Programs include education regarding epilepsy, mood regulation, cognitive and behavioral methods to abort seizures, resolution of conflicting thoughts and emotions (“cognitive dissonance”), stress management, and lifestyle modification to minimize triggers. Specific psychological and behavioral techniques used in such programs include the observation of triggers and development of countermeasures and self-control of seizures, thought restructuring, conditioning, behavioral activation, systematic desensitization, family systems therapy, and motivational interviewing (Table 1). Programs vary in their frequency of therapy sessions, duration of therapy, and methods of implementation, and may include individual or group sessions, with or without participation of family members or other caregivers [3].

CBT for the treatment of epilepsy may be effective due in part to resulting lifestyle changes that reduce the impact of seizure triggers or enhance adherence to treatment, but also to a direct relationship between cognition and seizure activity. In Matsuoka et al. [4], cognitive tasks (e.g., reading, speaking, mental or written calculation, writing, and spatial construction) inhibited or provoked epileptiform EEG discharges in 64% and 7.9% of participants, respectively. These results suggest that cognitive tasks could theoretically be designed to inhibit epileptiform activity, and that cognitive activity inducing epileptiform discharges could be altered for the purpose of reducing seizures. Such cognitive behavioral measures could also induce long-term changes in excitability. Tang et al. [3] proposed a model in which long-term practice of psychobehavioral strategies to reduce seizure precipitants ultimately leads to changes in neuronal circuits and a resultant decrease of the “epileptic disposition.”

The data regarding efficacy of CBT in seizure control, however, are mixed. Tan et al. [5] conducted a randomized, controlled trial of CBT, involving stress control, relaxation and coping skills training, cognitive restructuring of maladaptive thinking, rehearsal of positive social behaviors, and problem-solving discussions. While therapist's measures of psychological adjustment improved, there were no significant changes in seizure frequency, ratings of seizure control, or medication adherence with CBT. Similarly, an uncontrolled trial of CBT involving trigger identification, healthy lifestyles, relaxation, seizure interruption techniques, cognitive techniques to counteract negative thoughts and cognition or mood-related seizures, and graded exposure to phobic situations had some psychological benefits but failed to alter seizure frequency in six adults with refractory epilepsy and comorbid psychiatric and/or psychosocial difficulties [6].

Motivational interviewing (MI), a counseling approach often used in CBT, has demonstrated promise, however, with respect to improved medication adherence. In MI, the therapist uses open-ended questions, reflective listening, interpretive and encouraging comments, and reinforcement of the patient's statements regarding positive health behaviors to help the patient identify barriers to and create plans for positive changes. The therapist does not provide direct advice, but rather guides the patient to his/her own conclusions. In a large, randomized, controlled trial, MI combined with complementary behavior change techniques yielded significantly better medication adherence at 3- and 6-month follow-up than a standard care control group. The MI group was also more likely to have lower seizure severity ratings, better quality of life, and drug levels within a therapeutic or supratherapeutic range following the intervention, among improvements in many other psychological measures [7]. Project EASE (Epilepsy, Awareness, Support, and Education), which included principles of MI, was a telephone-based program that emphasized social support, self-efficacy, and goal setting, to enhance self-management related to medication use, seizure control, safety, and lifestyle issues [8]. The program, and its successor, WebEase [9,10], also led to improved adherence, but data suggesting that this translates to reduced seizure frequency has not been published to date.

Perhaps holding the most promise with respect to seizure reduction is the Reiter/Andrews method, which relies heavily on the concepts of CBT. The Reiter/Andrews approach proposes that all seizures have an underlying predisposing factor and that the emotions predisposing to seizures can reflect underlying cognitive processes that are amenable to CBT. This method often combines CBT with relaxation, visual imagery, EEG biofeedback, counseling, and aura interruption techniques. The treatment model is formalized in the workbook, *Taking Control of Your Epilepsy: A Workbook for Patients and Professionals* [11]. In an uncontrolled study, Spector et al. [12] evaluated a group intervention combining a variety of psychological techniques in seven adults with refractory epilepsy, based partly on the Reiter et al. workbook [11]. The group attained an average seizure frequency reduction of 74%, with two subjects becoming seizure-free, benefits which were largely maintained at three months after program completion. McLaughlin et al. [13] modified these methods for a group CBT program in adults over 60 years of age. In a randomized study, seizure frequency was significantly reduced in the CBT group compared to a relaxation control, maintained at 3 months following treatment. Furthermore, both groups improved on psychological measures including depression, dysthymia, psychosocial function, and psychological adjustment. In Andrews et al. [14], a trial of the Reiter/Andrews approach in patients with complex partial seizures led to 79.5% of subjects attaining seizure-freedom for 6 months or longer when followed for 2 years. Seizures were reduced by a mean of greater than 90%, albeit in the absence of an untreated control group for comparison. In an uncontrolled trial of a 5-day residential treatment program based upon this method in 11 patients with complex partial seizures, the nine patients who experienced less than four seizures per month prior to treatment became seizure-free, and seizure frequency was reduced to less than two per month in the other two patients [15]. Subjects were also able to reduce medication dosages following the intervention. In Elsas et al. [16], a behavioral approach based on the Reiter et al. workbook [11] was applied in eight subjects with localization-related epilepsy. Their trial led to one subject attaining seizure-freedom, one subject experiencing a 90% reduction in seizures, and two participants achieving a greater than 50% reduction in seizure frequency at one year after initiation of CBT, as well as improvements in quality of life and temporary improvements in mood in subjects who were adherent to the program. Finally, Michaelis et al. [17] conducted a retrospective study of patients using the Reiter/Andrews approach, including trigger avoidance and desensitizing strategies, with 37% of the sample becoming seizure-free, sustained for a median of 2.2 years, and a 50% responder rate (the percentage of subjects with a >50% reduction of seizures).

While the Reiter/Andrews approach demonstrated positive results in these studies, the trials were often uncontrolled, and it remains unclear which components are most effective. In addition, the mechanism of benefit is unknown, and could relate to increased medication adherence in some patients.

Mindfulness and Arousal-based Approaches

Mindfulness training

Mindfulness refers to a form of mental meditation in which the patient develops mindful attentional control, with a focus on present stimuli and a nonjudgmental and accepting approach [3]. The methods emphasize the mind-body connection and promote greater awareness of bodily sensations and thoughts associated with seizures. This approach may allow for improved seizure anticipation and better stress management, with acceptance serving as a coping mechanism for seizure-related symptoms. Basic techniques include mindful breathing, eating, awareness of sensations, and thought and emotional labeling.

Limited data suggest that mindfulness may decrease seizure frequency and improve quality of life in patients with epilepsy.

In a randomized, assessor-blinded, controlled trial of mindfulness with social support compared to social support alone in patients with medication-refractory epilepsies, the mindfulness training group demonstrated greater improvements in seizure frequency, depression, anxiety, and verbal memory [18]. Others have formulated standardized psychotherapy programs based on mindfulness training, such as Mindfulness-Based Cognitive Therapy (MBCT) and Acceptance and Commitment Therapy (ACT), which have been applied to patients with epilepsy.

Mindfulness-Based Cognitive Therapy (MBCT) forms the basis of the “Using Practice and Learning to Increase Favorable Thoughts” program (UPLIFT), which aims to prevent depression in patients with epilepsy. UPLIFT focuses on increasing knowledge about depression, altering maladaptive thought patterns, improving coping skills, attaining relaxation and pleasure, preventing relapses, and importantly, mindfulness. The program, consisting of telephone and internet-based cognitive/behavioral group therapy, was noted to reduce seizure frequency in patients with epilepsy at risk for depression, in addition to reducing the incidence of depressive episodes, decreasing symptoms of depression, and improving life satisfaction [19].

ACT is based on the same theory of learning as CBT, in addition to a new theory about language and cognition called relational frame theory (RFT). In ACT, patients accept the tendency for seizures to occur, along with the associated thoughts and fears, and choose actions that further their life goals. ACT can also be combined with behavioral techniques to control seizures. Randomized, controlled trials of ACT in patients with refractory epilepsy demonstrated sustained benefits of ACT over control conditions (yoga or supportive therapy with reflective listening) at 6- and 12-month follow-up, with respect to seizure frequency and duration [20,21]. Improvements in quality of life were also reported. More recently, an uncontrolled, non-randomized, prospective study found that ACT yielded positive effects on depression, anxiety, quality of life, self-esteem, and work and social adjustment, but no significant effect on seizure frequency [22]. No records of medication changes, seizure duration, or seizure severity, however, were included.

The acceptance of seizure occurrence may have a paradoxical inhibiting effect in some patients. This is akin to the common experience of patients with frequent seizures suddenly becoming seizure-free when admitted to the epilepsy monitoring unit, where seizures are desired and expected. The mechanism of this effect is unknown, but may relate to stress reduction, improved psychiatric symptoms, and resilience against other precipitating factors. Such programs appear to have some degree of efficacy with low cost and minimal side effects, and provide a promising alternative for patients who prefer non-pharmacological treatments or do not have access to costly medications.

Yoga and meditation

Yoga may induce relaxation, diminish stress, and influence the EEG and the autonomic nervous system, thereby controlling seizures. Commonly performed yogic practices include breathing exercises (pranayama), postures (asanas), devotional sessions, and meditation (dhyana). Yoga teaches participants to respond to internal stimuli in a conscious way and decrease behaviors that are led by the fears, thoughts, and emotions associated with epilepsy. A Cochrane review [23] of yoga in adults with refractory epilepsy found only two unblinded, controlled trials [21,24] and was unable to draw reliable conclusions about the efficacy of such treatment due to the limited number of studies, small number of participants, and lack of blinding. Nevertheless, there was a beneficial effect in control of seizures, with better efficacy of yoga when compared to no intervention or "sham yoga" (e.g., postural exercises mimicking yoga or muscle relaxation). The meta-analysis recommended that yoga should only be used as an adjunct to antiepileptic drugs (AEDs).

In Lundgren et al. [21], ACT was compared to yoga, consisting of deep breathing, postures, and meditation, as well as the psychological dimensions of yama ("harmony with others") and niyama ("harmony with yourself"). While the average magnitude of the effect on seizure index (a combined measure of frequency and duration) was greater for ACT than for yoga, each group attained benefit. Half of each group was seizure-free after one year, with a 50% or greater reduction in seizure frequency in 9 of 10 participants in the ACT group and 7 of 8 participants in the yoga group.

Panjwani et al. [24] evaluated the efficacy of Sahaja yoga for the treatment of seizures, primarily in patients with active idiopathic primary generalized epilepsy. Sahaja yoga represents a simple form of meditation, in which participants acquire a state of "thoughtless awareness." It was practiced at bedtime, with the feet dipped in warm saline water. Subjects with epilepsy were randomized to either Sahaja yoga, a yoga mimic (sham yoga/exercise), or no additional treatment. Data demonstrated a significant reduction in seizure frequency with yoga, with a 62% and 86% decrease in seizure frequency at 3 and 6 months of follow-up, respectively. Four out of the 10 participants became seizure-free at six months of follow-up, compared to none in the sham yoga (n=10) and no treatment (n=12) control groups. Four out of five subjects practicing yoga with epileptiform discharges at baseline also had normalization of the EEG, with such improvement evident in only one of nine control subjects. The Cochrane meta-analysis [23] obtained additional, unpublished data regarding responder rates. A more than 50% reduction in seizure frequency was found in 9 of 10 participants practicing yoga, but only in 1 of 10 in the sham yoga group and in none of the 12 untreated controls. Furthermore, seven participants in the yoga treatment arm had more than 50% reduction in seizure duration compared to none among the two control groups. This study was limited, however, by the lower baseline seizure rate in the "no treatment" control group.

The meta-analysis only included randomized trials comparing yoga to a behavioral arm or no intervention. Non-randomized trials have also been published and contribute additional data.

Sathyaprabha et al. [25] conducted a short-term, unblinded, controlled study of the impact of yoga, which included postures, meditation, and breathing exercises, on autonomic function in epilepsy. The yoga group had a decrease in seizure frequency after 10 weeks of daily sessions, not seen in a simple routine exercise control group. This study was not included in the meta-analysis, however, as seizure frequency was not a primary outcome measure, responder rates were not provided, and group allocation was performed by alternation rather than true randomization.

Fehr [26], Swinehart [27], and Deepak et al. [28] have also reported positive results with yoga meditation. Case reports by Fehr [26] and Swinehart [27] documented three young women who attained seizure-freedom with meditation. In a randomized, controlled clinical trial, Deepak et al. [28] found that patients with refractory epilepsy who practiced meditation, repeating a word while comfortably seated for 20 minutes per day, showed significant decreases in seizure frequency and duration. No significant changes were evident in a waitlist control group. Responder rates of those who performed meditation were 3/11 at 6 months (27%) and 7/9 at 12 months (78%). These data were not included in the Cochrane meta-analysis, however, as the authors of the review lacked access to the quantitative results.

Rajesh et al. [29] conducted a pilot non-randomized, unblinded study of yoga meditation as an adjunctive treatment in patients with drug-resistant chronic complex partial seizure disorders. The intervention was performed for 3 months, followed by optional continuation of the protocol. The meditation program required patients to sit in a relaxed posture with legs crossed and breathe in a controlled manner, followed by silent meditation which involved concentrating on a region on the forehead. A reduction in seizure frequency was noted in 19 out of 20 participants at 3 months, six of whom had ≥50% seizure reduction (“responders”). Responder rates increased with longer duration of participation, and 15 out of 20 subjects were responders at the time of their last follow-up. In addition, 25% of subjects attained seizure-freedom.

Jaseja [30–33], in contrast, proposed that the hypersynchrony and EEG fast oscillations induced by meditation, the complex partial epilepsy-like signs and experiences reported in meditators [34], and the accompanying serotonergic and glutamatergic activation may predispose to epileptic activity. One published case report may loosely support this hypothesis, in that the onset of mesial temporal lobe epilepsy occurred in a lifelong meditator who lacked known risk factors for epilepsy [35]. No reliable provocation of seizures by her continued practice of transcendental meditation occurred, however, such that meditation may have been a coincidental association rather than a cause. In addition, the types of synchrony and gamma rhythms produced by epilepsy and meditation are fundamentally different in frequency, amplitude, distribution, and evolution [36]. Furthermore, the sensations experienced by meditators (e.g. psychic or religious phenomenology, automatic behaviors, altered subjective awareness, and myoclonus) have not been shown to result from abnormal neuronal firing as is evident with seizures. Meditation induces ketosis, which may increase brain gamma-aminobutyric acid (GABA), and hence would be expected to inhibit epileptiform activity. Others have also argued that this hypothesis contradicts the epidemiological data drawn from the millions of people who practice meditation without a known increase in the incidence of epilepsy [26,27,36]. Fehr [26] and Orme-Johnson [36,37] reported no epileptic seizures in 707 and 2000 people practicing transcendental meditation, respectively, lower than the baseline frequency in the general population. Nor do the data on meditation in patients with epilepsy suggest an overall increase in seizure frequency.

The possible benefits of yoga and meditation, which promote relaxation, suggest that simple relaxation therapies could also be effective. In an early pilot study [38], eight patients were randomized to progressive relaxation therapy using a Differential Relaxation training tape or sham treatment of quiet sitting, with the sham control group later receiving the active therapy. All subjects demonstrated a decrease in seizure frequency after three weeks of relaxation therapy, as well as improved subjective well-being, with a 50% responder rate.

Using a more individualized approach, Dahl et al. [39] examined the effects of relaxation in a small study of patients with refractory epilepsy. Patients learned progressive muscle relaxation and the ability to envision states that were low-risk for seizure occurrence, to be applied when the imminent risk of a seizure was high. Three groups were compared: relaxation therapy, an attentional control consisting of supportive therapy, and no treatment. A significant reduction of seizure frequency was evident only in the group performing relaxation, maintained at 30 weeks of follow-up. The authors noted a 66% reduction in median seizure frequency for the relaxation group**,** a 68% increase for the supportive therapy group, and a 2% reduction for the waitlist controls. No patient was seizure-free for the duration of the 10-week follow-up period. Four out of five subjects had a ≥ 50% reduction in seizure frequency with relaxation, compared to none of the 11 subjects in the control groups. Seizure frequencies also decreased in the attentional control and no treatment groups when they were provided relaxation therapy in a second phase of the study.

In Whitman et al. [40], 12 subjects with epilepsy were taught progressive relaxation techniques with a before-and-after, within-subject design. Changes in median seizure frequency were not statistically significant over the first four months of follow-up, but reached significance at six months, with a decrease of 54% and a responder rate of 50%. This study was limited, however, by the lack of a randomized, controlled design and changing AED regimens in some patients.

Finally, in Puskarich et al. [41], progressive muscle relaxation was compared to quiet sitting. The number of subjects reporting a decrease in seizure frequency was significant in the treatment group, but not in controls. Similarly, the mean decrease in seizure frequency was significant in the subjects performing relaxation (29%) but was not significant in the control group (3%). Unlike the yoga trials, no subject attained seizure freedom. Responder rates were 38% and 18% for the treatment (n=13) and control (n=11) groups, respectively. AEDs did not necessarily remain stable and reports of the changes were inconsistent, however, which may have skewed results.

This small amount of data suggests that simple relaxation, while perhaps beneficial for seizure control, may be less effective with more variable responder rates than yoga. Larger trials are needed, with further investigation of the effect of intervention duration.

The mechanism by which relaxation and yoga may reduce seizure frequency is unclear, but may relate to direct physiochemical or electrographic changes, changes in the autonomic nervous system and vascular tone, alterations of CO_2 and O_2 concentrations, or indirect effects on the limbic system. Brown et al. [42] have proposed that stimulation of the vagus nerve may mediate the positive effects of yoga. Benefits may also stem from modulation of seizure triggers (i.e. improved sleep) or reduction in sensitivity to seizure triggers (i.e. shifting attention away from triggering stimuli to focus internally) [39].

Overall, the studies of yoga are small and bound by certain limitations. The nature of these interventions, for example, makes double-blinding largely impossible. In addition, the studies often fail to meet the standards of high level evidence due to small sample sizes, inadequate randomization methods, or uncontrolled designs. Unlike drug studies in which blood levels or pill bottle opening may be tracked, protocols are based on home practice for which adherence cannot be verified. Some studies were also potentially confounded by changes in AEDs and differing baseline characteristics across groups. Despite these constraints, the data regarding yoga are promising and deserve further study. Yoga has been associated with multiple health benefits and poses little risk; we would consider its use in medically refractory patients whose seizures may be exacerbated by stress and who are not candidates for, or do not desire, further medication trials, surgery, or implantable devices, with the understanding that current empirical support is limited.

Biofeedback

Biofeedback employs behavioral control strategies based on operant conditioning to regulate physiological activity. Through visual and auditory feedback, patients learn how to voluntarily modulate physiological responses, such as heart rate, respirations, electrodermal activity, or EEG frequencies, in real time. All types of biofeedback are thought to act by influencing thalamocortical regulation [43]. When applied to patients with epilepsy, the goal is to voluntarily reduce cortical excitation or increase peripheral sympathetic arousal to decrease seizure threshold.

A common physiological target for biofeedback is electrodermal activity, termed the "galvanic skin response" (GSR), an index of sympathetic activity that reflects centrally-induced changes in peripheral autonomic arousal. High GSR corresponds to increased conductance, decreased resistance, increased sympathetic tone, and an aroused state. Changes in GSR have been associated with modulation of Contingent Negative Variation (CNV) amplitudes, a specific type of slow cortical potential, for which greater negative amplitudes suggest cortical excitability. Nagai has proposed that sympathetic arousal and CNV amplitudes have, counterintuitively, an inverse relationship: *decreased* sympathetic arousal correlates with greater CNV negative amplitudes, indicating cortical excitation. This finding led researchers to postulate that increased GSR, reflecting increased sympathetic arousal, could lead to an increased seizure threshold. It was hypothesized that a reduction in CNV amplitude would be mediated by GABAergic inhibitory neurons of the reticular nucleus, which may modulate seizure threshold by altering excitatory input to the cortex via thalamocortical neural circuits [44].

In a small randomized, controlled, single-blinded study of patients with medically refractory seizures, subjects performed either visually-guided GSR-based biofeedback or sham control training and were asked to use the acquired skill to abort seizures at onset [45]. The authors reported significantly reduced seizure frequency with biofeedback, while no significant change was evident in the sham control group after one month of training and three months of follow-up. The mean percentage change in seizure frequency was -49.26% with biofeedback, compared to a 24.59% increase in controls. Of 10 patients in the biofeedback group, 6 had a greater than 50% reduction in seizure frequency, and one patient became seizure-free. Furthermore, there was a correlation between the degree of improvement in biofeedback performance and reduction of seizure frequency. Two of the participants were followed long-term [46]. Both showed a marked reduction in seizure frequency (54.9% and 59.8%) during biofeedback treatment, which was maintained over approximately three years of follow-up. The author also found that the degree of seizure reduction correlated with electrophysiological and neuroimaging studies demonstrating GSR biofeedback-induced modulation of networks controlling cortical excitability, although no quantitative data were presented in that brief abstract [47].

Micoulaud-Franchi et al. [48] replicated the methods of Nagai et al. [45] in 11 adults with drug-resistant, stress-activated temporal lobe epilepsy (TLE). The authors assessed skin conductance with visual biofeedback in an effort to increase levels of peripheral sympathetic arousal and reduce cortical excitability, and patients were encouraged to practice these self-regulation skills in seizure-prone situations. GSR biofeedback training significantly decreased seizure frequency, with a mean reduction of 48.61%. When evaluated three months after training, the responder rate was 45%, although no subjects attained seizure freedom. The mean change in skin conductance during treatment correlated with the reduction of seizure frequency.

Conversely, Scrimali et al. [49] described a patient with secondary generalized tonic-clonic seizures, exacerbated by stress and sympathetic arousal, who was treated for two years with GSR biofeedback to *reduce* sympathic arousal. In addition, problem-solving and coping strategies based on cognitive and behavioral approaches were applied. This training resulted in a significant reduction in generalized seizures, from an average of 5.3 to 0.75 per month.

The advantages of using a GSR target include an increase in patient self-control, and compared to some other types of biofeedback, easy operation of equipment, lesser expense, and the targeting of a specific relevant physiological activity [48]. The literature in this area seems to be contradictory, however, and the direction of the association between GSR and seizure threshold is not always clear [50]. The data are also fraught with limitations, including the simultaneous use of multiple treatment modalities.

Other forms of peripheral modulation have demonstrated less success in seizure control. In Kotchoubey et al. [51], for example, subjects with drug-refractory, predominantly partial seizures learned to control end-tidal carbon dioxide and breathing rate, with behavioral therapy to translate the skills to everyday life. Respiratory biofeedback was compared to EEG-based biofeedback and alterations of anticonvulsant medication regimens with psychosocial counseling, including daily sessions of art therapy, occupational therapy, physiotherapy, individual and group psychotherapy, and training for social competence. Groups receiving EEG-based biofeedback and medication adjustment showed a significant decrease in seizure frequency, largely driven by a decrease in focal seizures, not evident in the respiratory biofeedback group.

EEG-based biofeedback, also called “neurotherapy” or “neurofeedback,” received more attention in the early literature than at present. A number of targets of neurofeedback have been used in the treatment of epilepsy, which involve modulation of the amplitude or power of specific frequencies in specified locations. Classically, neurofeedback involved an increase in amplitude and occurrence of the sensorimotor rhythm (SMR), a 12–15 Hz pattern over central electrodes (C3, C4, or Cz). The amplitude of the SMR is greater when the sensory-motor areas are inactive (i.e. when the subject is immobile) and decreases when the regions are activated (i.e. during motor tasks). Animal data suggest that this rhythm is generated in the ventrobasal nucleus of the thalamus, which relays afferent somatosensory information. By increasing the amplitude and rhythmicity of the SMR, it is thought that somatosensory information is suppressed and muscular tension is reduced, impacting thalamocortical information flow to prevent cortical overexcitement.

The common alternative approach involved targeting of slow cortical potentials (SCPs). SCPs are event-related potentials or evoked responses of approximately 0.01 Hz, generated over several seconds after an eliciting event. The potentials are typically surface negative, such that shifts in the positive direction indicate inhibition of activation, while shifts in the negative direction (i.e. the Contingent Negative Variation), represent increased cortical activation. Generation of the SCP is likely related to widespread depolarization of apical dendrites in pyramidal cells. Modulation of the SCP, like SMR-based methods, may serve to reduce thalamocortical excitation.

In the first scientific report of neurofeedback for the treatment of epilepsy, Sterman et al. [52] described a patient with medically refractory nocturnal left fronto-parietal seizures with secondary generalization. The patient's baseline EEG revealed left sensorimotor cortex spikes and 5- to 7-Hz theta slowing. Abrupt seizure reduction occurred with EEG operant conditioning aimed at increasing 11- to 13-Hz EEG activity in the left sensorimotor cortex. With the EEG feedback training sessions she became, with one exception, seizure-free. The success of this patient prompted further research in this area.

Two independent meta-analyses have assessed the peer-reviewed literature on neurofeedback. The first summarized SMR-based studies from 1972 to 1996 [53]. Eighteen unique data sets were included, although the inclusion criteria for the review were unclear, many studies were small (including single case reports and case series), and the trials were often uncontrolled. The review suggested that 82% of participants had >30% seizure reduction, with an average exceeding 50% reduction. Five percent attained seizure-freedom for up to one year. Responder rates were not reported. The author wished to challenge the notion that neurofeedback is “experimental” in comparison to AEDs “through an assessment of over 25 years of peer-reviewed research demonstrating impressive EEG and clinical results….” The counter-argument, however, is that a total of 174 patients, many from uncontrolled, non-blinded, and non-randomized studies, cannot be compared to well-designed AED clinical trials involving thousands of patients who contribute data during pre- and long-term post-marketing experience.

A more recent meta-analysis with strict inclusion criteria reviewed 10 studies from 1970 through 2005, each providing detailed information on patient selection, utilizing SMR- or

SCP-based biofeedback, and reporting individual subjects' pre- and post-treatment seizure data [54]. Nine studies were of SMR in participants with refractory epilepsy, with within-subject designs [55–63], while one study utilized SCP-based biofeedback [51]. All studies reported an overall mean decrease in seizure frequency following treatment, and 74% of all participants reported fewer weekly seizures in response to EEG biofeedback. When examined separately, SMR training reduced seizure frequency in 79% of participants. Effect sizes for all studies ranged from -0.21 to -1.38, but responder rates were not reported. Based on this meta-analysis, EEG operant conditioning was said to produce a significant reduction in seizure frequency, albeit based on very small numbers of subjects with mixed seizure types, varying levels of intellectual function, multiple methodologies (i.e. differing target frequencies), a lack of separate control groups, and some studies without randomization. To our knowledge, outside of isolated cases, there have been no trials of SMR-based neurofeedback for seizure control since this time.

A unique aspect of the Kotcoubey et al. [51] cohort was the duration of follow-up. Nearly 10 years later, 11 patients in the SCP biofeedback group, without subsequent resections, provided information regarding seizure frequency and took part in three follow-up biofeedback sessions [64]. All patients were still able to modulate their SCPs with feedback. Seizure frequency had decreased in 8 of 11 patients, from a mean baseline of 3.49 seizures/week to means between 0.8-2.1 seizures/week over the follow-up period, with a 55% responder rate. One of the 11 patients was seizure-free. Limitations of the data must be considered, however, including multiple confounding variables in each patient over time, the small number of participants, and the lack of long-term control group data.

Two notable neurofeedback studies were not included in the aggregated data of the meta-analyses, one SMR-based and one SCP-based. An early example of SMR modulation demonstrated reduction in seizure frequency with neurofeedback in a randomized, controlled study of 24 medication refractory patients with seizures involving a motor component [65]. This study was one of the most comprehensive in this field, with a comparatively large number of subjects with well-documented drug-refractory seizure histories and drug regimens kept constant and monitored through periodic blood levels. The study divided subjects into three groups: no intervention, a non-contingent training control in which the feedback display and rewards were derived from another participant, and a biofeedback intervention group. Feedback included lights and tones with rewards for increasing 11-15 Hz, while suppressing 0-5 Hz and 20-25 Hz, over left sensorimotor cortex (Cl-C5). Control groups received the contingent feedback training after the 6-week control period had ended. A statistically significant reduction in seizure frequency occurred following the contingent training condition that was not evident following control conditions. Individual responses to neurofeedback ranged from 0 to 100% reduction, with a median seizure reduction of 61%. Responder rates, however, were not reported. Although a larger and perhaps more well-designed study, the data still suggested variability in response across subjects. SMR biofeedback was more commonly reported in the 1970s and 1980s, but given the resulting variability in response and lack of seizure-freedom, the technique has largely been supplanted by newer methods.

Based upon their earlier findings in which SCP biofeedback resulted in significantly reduced seizure frequency compared to modulation of alpha frequencies, Rockstroh et al. [66] conducted a study of SCP biofeedback in 18 patients with drug-refractory epilepsies of various types. The participants demonstrated significant reduction of seizure frequency on average, with six subjects achieving seizure freedom and an additional seven subjects attaining some degree of benefit. The responder rate was 50% at three months of follow-up. Factors predictive of success included younger age and better SCP modulation (with and without feedback). While results are encouraging, this was a small, uncontrolled, unblinded, non-randomized trial, and the impact of anticonvulsant regimens and seizure types is unclear. Not all patients were able to achieve SCP amplitude control, and not every patient who demonstrated reliable SCP control experienced a reduction in seizure frequency.

More recently, Walker et al. [67,68] proposed the use of quantitative EEG (QEEG), a mathematical approach to analyzing EEG data and developing maps of the targeted type and location of EEG activity. This neurofeedback protocol most commonly rewarded inhibition of slow activity in the areas where there was excessive slowing (1–10 Hz), enhancement of 15–18 Hz activity, and normalization of coherence in the most significantly abnormal coherence pairs. The author stated that his 2005 data demonstrated that "….in all 12 patients….within 20–35 sessions, all the patients became seizure-free. They have remained so for an average of 7 years now (range 4–9)." Some discrepancy exists with the published data, however, in that Walker et al. [67] list 10 patients trained in this approach, with nine clearly becoming seizure-free after performing up to 82 sessions.

Three additional groups of patients have been trained in QEEG neurofeedback since that time [68]. In the first group, 18 out of 20 subjects with intractable epilepsy attained seizure-freedom over 3-7 years of follow-up. The two participants with continued seizures were improved, with "momentary lapses of attention" or infrequent partial seizures, but a resolution of generalized events. In a group of nine women who wished to discontinue anticonvulsants in preparation for pregnancy, all became seizure-free and remained so for an average of 6 years. In the final group, consisting of five patients who wished to discontinue anticonvulsant therapy due to side effects, all attained seizure-freedom off medication, for an average of 5 years. The authors interpreted the results to suggest enhanced efficacy for the QEEG approach as opposed to standard protocols. The latter two groups, however, had been controlled on medications prior to participation in the trials, and hence it is not clear whether they would have remained seizure-free regardless of any intervention or whether there was a floor effect of low baseline seizure frequency. Furthermore, no control data were reported. It is also unknown if specific target frequencies, locations, or durations of training are most efficacious, with variable protocols across patients making comparisons challenging.

The benefit of QEEG in children with epilepsy is even less clear. In their review, Hurt et al. [69] determined that "pediatric epilepsy has no controlled studies, and preliminary data are not promising, but it might be considered for uncontrolled seizures unresponsive to anticonvulsants" in patients who have the time and resources to invest. Clearly, QEEG should not replace anticonvulsant medications for the treatment of pediatric epilepsy.

Overall, there are a limited number of small studies, often with a lack of randomization, controls, adequate blinding, and long-term follow-up. Many studies lack statistical analyses to assess whether the observed changes were greater than chance alone, and few studies have directly compared neurofeedback to other interventions. Methodologies were not consistent across trials (i.e. differing SMR frequency ranges), making comparisons and the identification of best techniques difficult. While biofeedback seems to carry a low risk of serious adverse events, side effects, which may include fatigue, feelings of detachment or fogginess, anxiety, headaches, insomnia, and irritability, have not been systematically studied. Worsening of seizure frequency is also a theoretical risk, should the wrong frequency be reinforced or suppressed. Biofeedback is neither easy nor inexpensive, requiring a significant commitment of time, effort, and funds. Training of professionals is also a key variable to consider. Despite these limitations, results were quite similar across studies, showing beneficial effects in many patients. In general, however, there is insufficient evidence to make a recommendation regarding the role of biofeedback in epilepsy. While neurofeedback devices are FDA-approved, there is no American Academy of Neurology guideline regarding their use. We believe that neurofeedback may be considered as low-risk for serious adverse events in the hands of experienced professionals, and it may be used as an adjunct to standard treatments in interested patients, but with relatively little data to support efficacy.

Conclusions

Many uncertainties remain regarding psychological treatments for epilepsy, including the optimal cognitive or behavioral approaches, the ideal duration of treatment, the time course of potential improvement, and the types of patients who may benefit most. Unfortunately, participation in such research may be limited by the need to travel for training or therapy, unlike the ease of taking a pill. Nevertheless, behavioral methods offer certain advantages. They tend to be less expensive, are noninvasive, lack serious side effects, require little technology, are easily comprehensible, and facilitate patient participation.

Overall, drawing definitive conclusions from the present data regarding cognitive and behavioral treatments for epilepsy is difficult, given the lack of sufficiently randomized and controlled trials, limited trial durations, small numbers of subjects, varying protocols, and variability in the presentation of results. The assessment of behavioral interventions also faces a unique constraint, in that adequate blinding may be impossible due to the nature of the intervention. Furthermore, many therapies also combine different modules, techniques, and psychological approaches, making it challenging to discern the specific methods that are most effective. Of the psychological therapies for epilepsy, the largest body of literature with the most encouraging results has been found for the CBT-based Reiter/Andrews approach and mindfulness or arousal-based programs (e.g. yoga, meditation, relaxation, and biofeedback), which warrant larger clinical trials.

As Reiter and Andrews noted, “the solution for each patient was unique” [15]. Ultimately, it may be that an individualized, flexible combination of approaches will be most effective. Patients may have different seizure syndromes, predisposing factors and triggers, and psychosocial circumstances, and perhaps a single behavioral approach should not be applied to everyone. At present, cognitive and behavioral interventions may be considered as low-risk adjuncts to standard therapies in interested patients.

Acknowledgments

Disclosures: This work was supported in part by Career Development Award number IK2 CX-001255-01 from the United States (U.S.) Department of Veterans Affairs Clinical Sciences R&D (CSRD) Service (Dr. Leeman-Markowski).

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Table 1

Cognitive behavioral therapeutic techniques

Thought restructuring	The patient learns to identify, understand, and dispute irrational or maladaptive thoughts and feelings and reframe negative thoughts to respond in a healthier manner
Operant conditioning	Relies on rewards or punishments for seizure absence or occurrence, respectively
Behavioral activation	A treatment approach for depression that 1) refocuses patients on their goals by using activity scheduling to encourage engagement in activities that they are avoiding and 2) analyzes the function of cognitive processes that serve as a form of avoidance
Systematic desensitization	The patient is exposed to progressively more anxiety-provoking stimuli and taught relaxation techniques to counteract the negative emotions (“habituation training”); may be applied to the anxiety elicited by seizure onsets or seizure provoking conditions
Family systems therapy	The underlying theory posits that individuals cannot be understood in isolation from one another. An individual must be viewed in the context of his/her family, with the family comprising an emotional unit
Motivational interviewing	A therapeutic style in which the patient is questioned and encouraged to develop his/her own ideas and plans regarding behavioral change, as opposed to the therapist providing direct advice