Basic Concepts and Clinical Findings in the Treatment of Seizure Disorders with EEG Operant Conditioning

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EEG, Operant Conditioning
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INTRODUCTION

The first scientific paper applying EEG operant conditioning to the treatment of a clinical disorder was published in 1972.[1] This report was a case presentation involving a 23-year-old female with a 7-year history of generalized tonic-clonic seizures of unknown origin. There was no family history of seizures, and evaluation at two major medical centers had failed to demonstrate a localized lesion. An EEG study had shown generalized 5-7 Hz slowing and spike-wave activity, increased by hyperventilation. While the patient had proven refractory to numerous drug combinations, she was still being treated with a regimen of Dilantin and Mebarol, 200 mg. each, daily.

Observed daytime seizures in this patient consisted of a wrinkling of the brow associated with left lateral deviation of the eyes, crossing of the right arm to the left knee, and falling to the left with loss of consciousness, tonic-clonic movements, and occasional incontinence. The majority of incidents were nocturnal, occurring in the early morning hours. Carefully kept records over several years indicated a consistent pattern of at least 2 major-motor seizures per month that were unrelated to the menstral cycle.

During 3 months of twice-per-week EEG operant conditioning training, using light and tone rewards for enhancement of mid-central 11-15 Hz activity detected by band-pass frequency analysis, the patient's seizures essentially ceased. Additionally, quantitative analysis of the EEG over this period disclosed a significant increase in the 11-15 Hz band and a corresponding decrease in slower activity. These prolonged clinical and EEG changes were the basis for this report, which was from the author's laboratory. Treatment was continued with this patient within the context of an expanded, multi-subject study of this novel therapeutic approach.[2] She eventually became seizure free, was withdrawn from medications, and was issued a California driver's license.

This treatment was attempted as a result of findings in cats. Studies in our laboratory had documented a sustained increase in 11-15 Hz sensorimotor EEG rhythmic activity following prolonged operant conditioning of this pattern.[2] Further, this training provided protection against drug-induced seizures.[3] This protective effect was initially discovered by accident. We were studying the convulsive properties of toxic hydrazine compounds for the U.S. Air Force. These compounds are used as rocket propellants, and exposure of any kind has disastrous toxic effects. Hydrazine compounds form hydrazones with pyridoxal phosphate, a reaction which absorbs this essential coenzyme for the synthesis of glutamic acid decarboxylase (GAD) and gamma-aminobutyric acid (GABA), both primary central inhibitory neurotransmitters.[4-6] Animal studies determined that the resulting loss of inhibitory capacity resulted, after some delay, in thalamic and cortical hyperexcitability and explosive convulsions.[3,7,8] We had been working on the dose-response curve for the monomethylhydrazine (MMH) isomer, and had established the dose of 9.0 mg./kg. as 100% convulsive in the cat. It was customary to enter animals into this study after participation in other investigations. One of these other studies involved EEG operant conditioning to increase a specific 11-15 Hz EEG rhythmic pattern observed over the somatosensory cortex in alert but motionless cats.[9,10] Because of this localization, we coined the label Sensorimotor Rhythm, or SMR, for this activity. Since this rhythm was similar in frequency and localization to EEG sleep spindles, we sought to evaluate the possibility of a functional relationship between these patterns by facilitating the SMR during wakefulness and examining the effects on spindle activity during sleep.

The addition of these SMR-trained animals to the MMH dose-response study completely disrupted our curve. Despite showing the usual toxic prodrome, animals who had previously received prolonged SMR operant conditioning were resistant to MMH-induced seizures. This unexpected finding, resulting from what was perhaps the ulti-

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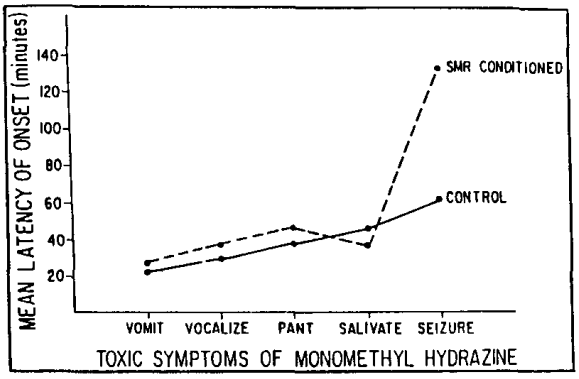

Figure 1.
Comparison of the time-course of visceral and behavioral symptoms in response to IP administration of monomethylhydrazine among SMR-trained and control cats (n = 8 each). A significant delay in the occurrence of generalized seizures was documented in the SMR-trained group (p<.05). Two animals in this group *failed to seize within 3 hours, despite showing all pre-convulsive* symptoms. (Modified from reference 11)

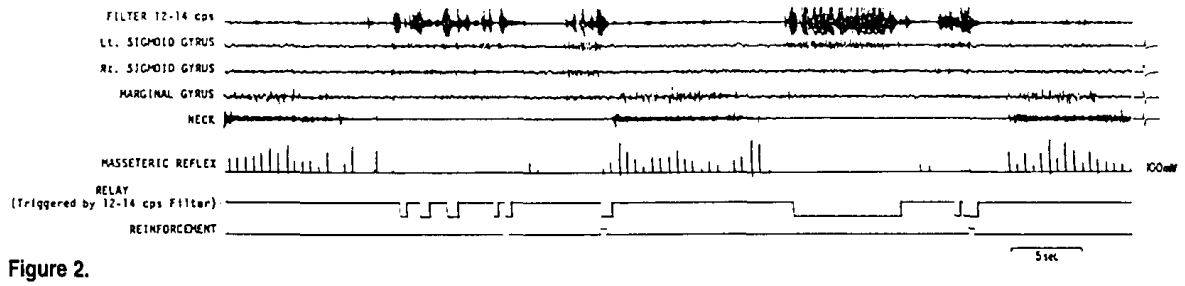

Figure 2.
Sample data from a cat trained to produce SMR for food reward *illustrates neck EMG and masseteric reflex changes during sustained* bursts of this EEG rhythm. Note simultaneous suppression of EMG and reflex amplitude exclusively during SMR. (Modified from reference 15).

mate in a double-blind design, suggested that seizure threshold had been raised in the SMR-trained animals. A focused examination of this hypothesis in a controlled group study[11] showed that 25% of trained animals were completely protected from MMH seizures, while the other 75% were able to resist these seizures for more than twice the latency of control animals (Figure 1).

These findings redirected our interest to an examination of the physiological correlates of the SMR, and led to a simultaneous series of human studies. These studies, in turn, stimulated many related efforts in other laboratories throughout the world. Looking back at this exciting flurry of research activity, one is puzzled by several conclusions being expressed today by individuals who have apparently never read this literature. These are: 1) that there is no evidence that EEG operant conditioning affects physiological substrates, and 2) that application of this modality to the treatment of epilepsy should still be considered as "experimental". These issues constitute the focus of the present review.

PHYSIOLOGICAL CORRELATES OF SENSORIMOTOR RHYTHM OPERANT CONDITIONING

Almost immediately after our initial papers, studies in several laboratories began examining the central and peripheral correlates of SMR activity. We had shown that the SMR response could be learned and its incidence significantly increased in the baseline EEG.[12] Further, the sleep studies mentioned above indicated that SMR-trained animals developed a reliable increase in sleep spindle density and showed decreased awakenings during non-REM sleep.[13] Since the rhythm relates behaviorally to sustained immobility, muscle discharge was one of the first areas evaluated. Chase and Harper[14] showed that neck muscle activity was suppressed in strict association with the emergence of this rhythm (Figure 2), a finding which confirmed our earlier observations.[12] This suppression, however, was independent of motor quiescence, since it occurred rather abruptly just prior to the appearance of the SMR bursts. Because posture did not change, this abrupt decrease in muscle discharge was attributed to a specific reduction in tone rather than a change in length. This observation implicated the gamma motor neuron pathway, a conclusion supported by the subsequent reflex study of Babb and Chase.[15] They showed that the monosynaptic masseteric (jaw closing) reflex was significantly reduced during SMR activity (shown also in Figure 2), while activity in the reciprocal polysynaptic digastric (jaw opening) reflex was not affected. Since the digastric muscle lacks muscle spindle afferents, they suggested that mechanisms regulating the gamma motor neuron/muscle spindle system were uniquely associated with the appearance of the SMR. On the basis of the behavior of cortical cells in and around chemically-induced seizure foci in primates, Wyler[16] also concluded that unloading of muscle spindle receptors through attenuation of gamma motor neuron activity might be related to the therapeutic effects of SMR-training.

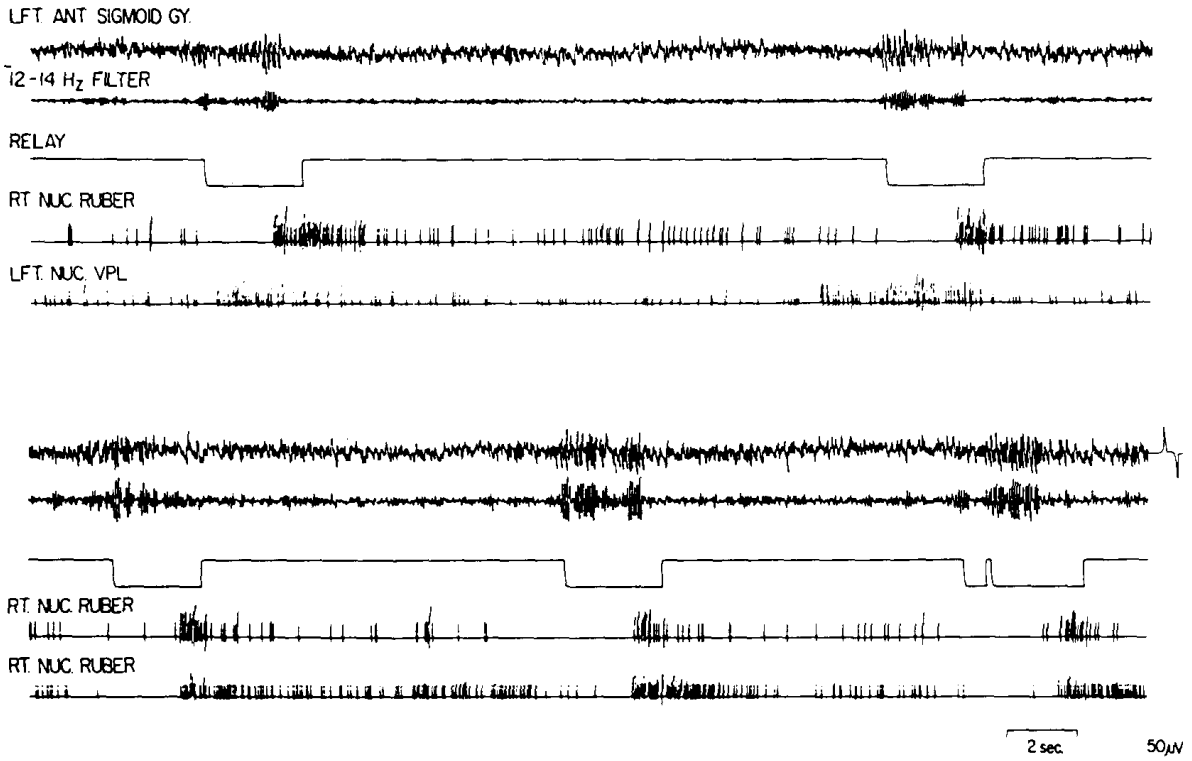

Figure 3.
Fine wire microelectrodes were used to record extracellular unit discharge rates from the red nucleus and ventrobasal (VPL) thalamic nucleus in cats. Three different red nucleus cells are shown from 2 animals, together with VPL cell in top tracing. Cell discharge rates in the red nucleus were suppressed during SMR activity. In contrast, cell firing changed to bursting pattern in VPL. (Modified from references 22, 23)

It has long been known that movement immediately abolishes anterior cortical EEG rhythmic activity[17] in animals and humans.[10,18-20] Rougeul and colleagues[21] found that SMR activity was suppressed only by movement and not by cutaneous stimulation. This unique relationship to motor regulation was supported in our laboratory by microelectrode studies of cellular behavior in the voluntary motor pathway. In particular, extracellular recordings from the red nucleus, an important midbrain structure linking motor cortex, cerebellum, brainstem, and spinal cord for voluntary movement coordination, disclosed a specific and sustained suppression of cellular discharge during trained SMR activity.[22,23] As shown in Figure 3, unit discharge essentially ceased during the learned expression of the SMR. Combined with the evidence for specifically reduced excitability in both alpha and gamma motor neurons reviewed above, this finding suggested that the SMR was associated with a functionally discrete alteration in the basic physiological substrates of motor control.

Other work disclosed that the SMR was generated in the thalamic relay nuclei of the somatosensory pathway, known collectively as the Ventrobasal (VB) complex.[24] This finding was in agreement with an earlier body of evidence suggesting a thalamic origin for sensorimotor EEG rhythms, summarized in the popular text by Andersen and Andersson.[25] The Andersen and Andersson model has been confirmed and clarified recently by a series of elegant cellular studies which establish the thalamus as the site of generation for these rhythms.[26-29] These investigations have shown that EEG spindle rhythms arise in the thalamus from an intrathalamic and corticothalamic interplay leading to synchronized and recurrent bursting in thalamic relay cells, and imposing a concurrent synchronous discharge on cortical neuronal pools. We also found that thalamic VB relay cells changed their behavior to recurrent bursting during SMR activity,[22] an example of which is shown also in Figure 3. This shift to oscillatory bursting results in part from hyperpolarization of relay cells, and leads to an attenuation of the conduction of somatosensory information to cortex.[28, 30, 31]

In summary, findings from these animal studies have provided several major clues concerning both the origins and functional significance of sensorimotor rhythmic EEG activity. These findings, and a model of their putative relevance to the development of SMR activity, are reviewed in Figure 4. First, there is evidence for an abrupt attenuation of motor excitability, apparently involving reduced cortical output to thalamus, brainstem, cerebellum, and spinal cord. This shift is manifested by a reduction in motor pathway cellular[22,23] and reflex[15] excitability, and in muscle tone.

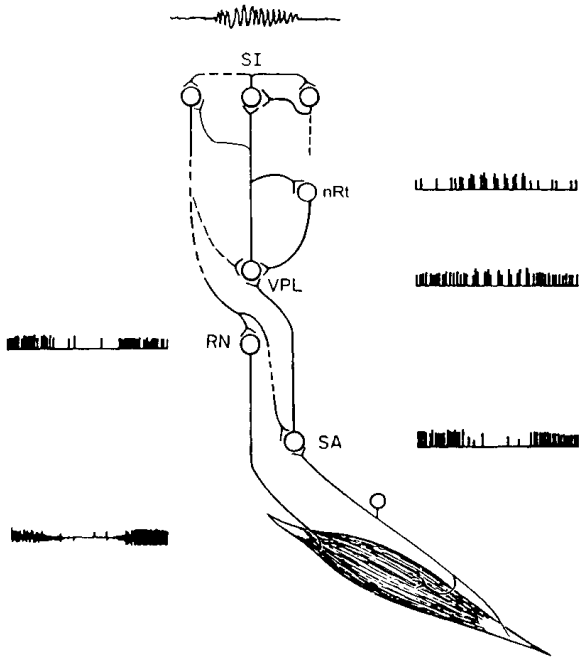

Figure 4.
Summary of events providing theoretical model for the generation of SMR. Motionlessness in the context of attention produces altered motor output to thalamus and brainstem, resulting in decreased red nucleus (RN) activity, stretch reflex activity, and muscle tone. This results in an attenuation of somatic afferent (SA) activity, oscillatory bursting activity between ventralis-posterior-lateralis (VPL) and nucleus reticularis (nRt) of thalamus, and development of fast sensorimotor EEG rhythmic activity.

[12,14] Second, these changes appear to favor a reduction in sensory bombardment of VB thalamus,[32] hyperpolarization of VB relay cells,[22,23] altered somatosensory conduction,[28,30,31] and the emergence of sensorimotor EEG rhythmic activity due to oscillatory discharge projected to cortex. Finally, the behavioral exercise of these events through directed operant conditioning can produce sustained changes in physiological regulation, as documented by increased sleep spindle density and stabilized sleep states.[13] These findings provide irrefutable evidence that operant conditioning of the sensorimotor EEG indeed does alter physiological substrates!

Epileptic syndromes arise from many different causes, classified as either ideopathic (presumed genetic predisposition), symptomatic (secondary to other pathology), or cryptogenic (of unknown etiology) by the International League Against Epilepsy.[33] These syndromes have in common the favoring of recurrent abnormal and excessive synchronous discharge in neuronal populations. Prevailing theory attributes this response to hyper-excitability in or hyper-excitation of cortical cellular pools. These conditions make the epileptic central nervous system particularly vulnerable to alterations in functional state,[34,35] and to intrinsic electrophysiologic transients.[27, 36, 37] Presumably therefore, irrespective of the cause of hypersynchronous discharge, effective therapeutic intervention might be expected to 1) reduce neuronal excitability in relevant tissues, 2) blunt the impact of transient neuronal discharge, and 3) stabilize state characteristics. As reviewed above, a body of competent and diverse scientific evidence indicates that the exercise of appropriate thalamocortical regulatory mechanisms via operant conditioning of sensorimotor EEG rhythms can potentially impact each of these requirements.

CLINICAL APPLICATIONS IN THE TREATMENT OF SEIZURE DISORDERS

After our initial clinical report in 1972[1] we expanded our preliminary investigations,[2] and initiated a series of controlled studies with progressively larger groups of epileptic subjects.[38-41] Additionally, since that report, there have been numerous peer-reviewed journal publications from other laboratories exploring this treatment (Tables 1 and 2). These are very difficult investigations to conduct, given the complications of history, seizure types, and medications that characterize the severely epileptic patients available for such studies. Despite these facts, and notwithstanding the many important issues raised by this body of work, every single study reported significant clinical benefits exceeding expected placebo effects.

Several review articles have attempted to dissect the available literature in terms of the research and mechanistic issues they raised.[19,41] Each of these efforts, however, created a formidable and perhaps soporific tomb of technical reading material. The present review will take a more practical clinical approach, tabulating these studies for archival purposes and focusing on the convergence of salient findings.

Drug Compliance

Due to the high level of structure and motivation associated with these studies, it has been suggested that subjects may become more compliant with medication schedules. In order to examine this possibility, many of the studies listed in Tables 1 and 2 have drawn blood samples for evaluation of anticonvulsant levels prior to and after experimental treatments[39-42-44] All of these investigations have failed to find any relationship between anticonvulsant drug levels and study outcomes.

Seizure Rate Changes

The patients participating in these studies represent a most difficult subset of epileptics. These are typically individuals with severe seizure disorders of relatively long duration, often with significant co-morbidities, and uniformly refractory to anticonvulsant medications. Further, they remain on medications, a condition that not only distorts the EEG but also impacts significantly on their ability to acquire new information.[45]

Given these facts it is rather remarkable that so many different studies have reported positive outcomes. Table 2

Table 1

Peer-reviewed journal articles on the clinical effects of sensorimotor EEG operant conditioning treatment of epilepsy (1972-1980).

Author(s)/Journal	# Subjects	#Showing Clin. Improvement	#Showing EEG Improvement	Controls
Sterman & Friar[1] EEG Clin. Neuro., 1972	1	1	1	pre-treat. baseline
Sterman et al.,[2] Epilepsia, 1974	4	4	4	pre-treat. baseline
Finley et al.,[62] Biol. Psych., 1975 Also Finley,[61] Pav. J. Biol. Sci, 1977	2	2	2	non-contingent feedback
Seifert & Lubar[63] Biol. Psych., 1975	6	5	4	pre-treat. baseline
Kaplan[47] EEG Clin. Neuro., 1975	3	2	nr	pre-treat. baseline
Wyler et al.,[44] EEG Clin. Neuro., 1976	4	4	nr	non-contingent & EMG
Ellertsen & Klove,[46] Scan. J. Behav. Ther., 1976	1	1	nr	start-stop-start
Lubar & Bahler,[64] *Biofeedback & Self-Reg., crossover 1976*	8	7	6	ABA
Kuhlman & Allison[65] Pav. J. Biol. Sci., 1977 Also Kuhlman[66] EEG Clin. Neuro., 1978	5	3	3	non-contingent feedback
Cott et al.,[57] *Science, 1979*	7	5	4	pre-treat. baseline
Quy & Hutt,[48] Biol. Psych., 1979	3	3	nr	random feedback
Sterman & Macdonald,[40] Epilepsia, 1978 Also Sterman & Shouse,[41] EEG Clin. Neuro., 1980	8	7	5	ABA crossover

indicates that 82% of the subjects studied demonstrated significant (>30%) seizure reduction, with an average value exceeding 50%. Many of the studies also report reductions in seizure severity. Approximately 5% of patients have experienced complete control for periods of tabulation up to 1 year. This has been true even when anticonvulsants were subsequently reduced or entirely withdrawn.

It should be pointed out, however, that in a number of these studies significant seizure reductions were registered regardless of the EEG feedback contingencies rewarded.[46-48] But the vast majority of patients responded only when feedback contingencies provided reward for SMR activity and normalization of the sensorimotor cortex EEG. Training exclusively for the reduction of paroxysmal events, higher frequencies, or EMG activity, or for the enhancement of lower frequencies has been ineffective.[43,44,49,50] Additionally, Wyler et al,[51] exploring the hypothesis that localized cortical activation was the operative factor in SMR training, attempted enhancement of higher frequency activity over variable sites of identified focal abnormality. Only 27% of these patients showed meaningful seizure reductions.

EEG Changes

Not all of these studies examined EEG changes associated with training. However, among those that did, 66% of patients showed significant effects (bottom of Table 2). These EEG changes were examined primarily during training. However, some evaluated independent clinical records

Table 2

Peer-reviewed journal articles on the clinical effects of sensorimotor EEG operant conditioning treatment of epilepsy (1981-1996).

Author(s)/Journal	# Subjects	#Showing Clin. Improvement	#Showing EEG Improvement	Controls
Lubar et al.,[43] Arch. Neurol., 1981 Also Whitsett et al.,[52] Biofeedbk. & Self-Reg., 1982	8	5	5	non-contingent + ABA with 3-8Hz reward condition
Sterman in Engel et al.,[38] Ann. Internal Med., 1982 Also Lantz & Sterman,[39] Epilepsia, 1988	23	17	12	yoked non-contingent and waiting list
Tansey,[67] Int. J. Psychophys., 1985	1	1	1	pre-treat. baseline
Tozzo et al.,[49] Int. J. Psychophys., 1988	6	5	5	relaxation training with EEG electrodes
Andrews and Schonfeld,[68] Seizure, 1992	83	69	nr	pre-treat. baseline
Hansen et al.,[69] J. Neurotherapy, 1996	1	1	1	pre-treat. baseline
Totals (Tables 1 and 2)	174	142 (82%)	(66% of reported cases)	

as well, and both Sterman and Shouse[41] and Whitsett et al.[52] focused also on effects registered in standardized sleep EEG recordings after differential periods of training.

Before reviewing these findings it should be pointed out that sensorimotor rhythms are difficult to study in the human EEG. This is because in humans these higher frequencies must be recorded from the scalp rather than the dura, as in animal studies. These factors result in a significant attenuation of amplitude, as shown in Figure 5. Here, bilateral EEG recordings are compared in a patient with the bone removed over the right centrotemporal cortex. This bipolar montage, referenced to Cz, shows suppression of rhythmic activity bilaterally during movement and the emergence of clear sensorimotor rhythms over the exposed dura when movement ceases. This activity is barely visible on the intact contralateral side. This problem has been overcome through the use of sensitive quantitative analysis (FFT and band-pass filters), and by the study of the selective suppression of this activity during movements.[53-55]

In our initial paper[1] we compared trends in the 11-13 Hz and 8-10 Hz bands across the first 12 training sessions. Initially both frequency bands were gradually increased. By session 12, however, these frequencies moved in opposite directions, with 11-13 Hz activity trending upward and 8-10 Hz gradually suppressed. Additionally, the mean incidence of 11-13 Hz activity had increased significantly from earlier levels. This patient showed clinical EEG abnormalities when drowsy and in classic manner during sleep, with paroxysms progressing into trains of spike-wave discharge across the non-REM sleep-state stages.[35] These EEG manifestations were greatly attenuated as her clinical condition improved. In subsequent studies, where both laboratory spectral analysis and independent clinical analysis of the EEG were obtained, patients showed reliable reductions in epileptiform activity and a normalization of EEG patterns.[2,40] Because of the finding that many epileptics have attenuated sensorimotor rhythmic activity and elevated 4-7 Hz activity in both the sleep and waking EEG,[56] later studies also employed reward for suppressing slow activity while simultaneously enhancing the SMR. Nonepileptic subjects have little EEG slow activity, and spectral analysis can often clearly document a significant SMR increase during training (Figure 6).

In an early replication study, Cott and colleagues[57] rewarded poorly controlled seizure patients for increasing 12-14 Hz while simultaneously suppressing 4-7 Hz activity in the central cortical EEG. They tracked seizure incidence and digital output in these 2 frequency bands across 3 months of EEG biofeedback training. Five of 7 patients registered a significant reduction in seizure incidence and severity from start to finish. Three of these patients showed a reliable increase in 12-14 Hz activity, while 4 showed a reliable reduction in 4-7 Hz activity. One patient who showed a reduction in seizures demonstrated no change in the EEG,

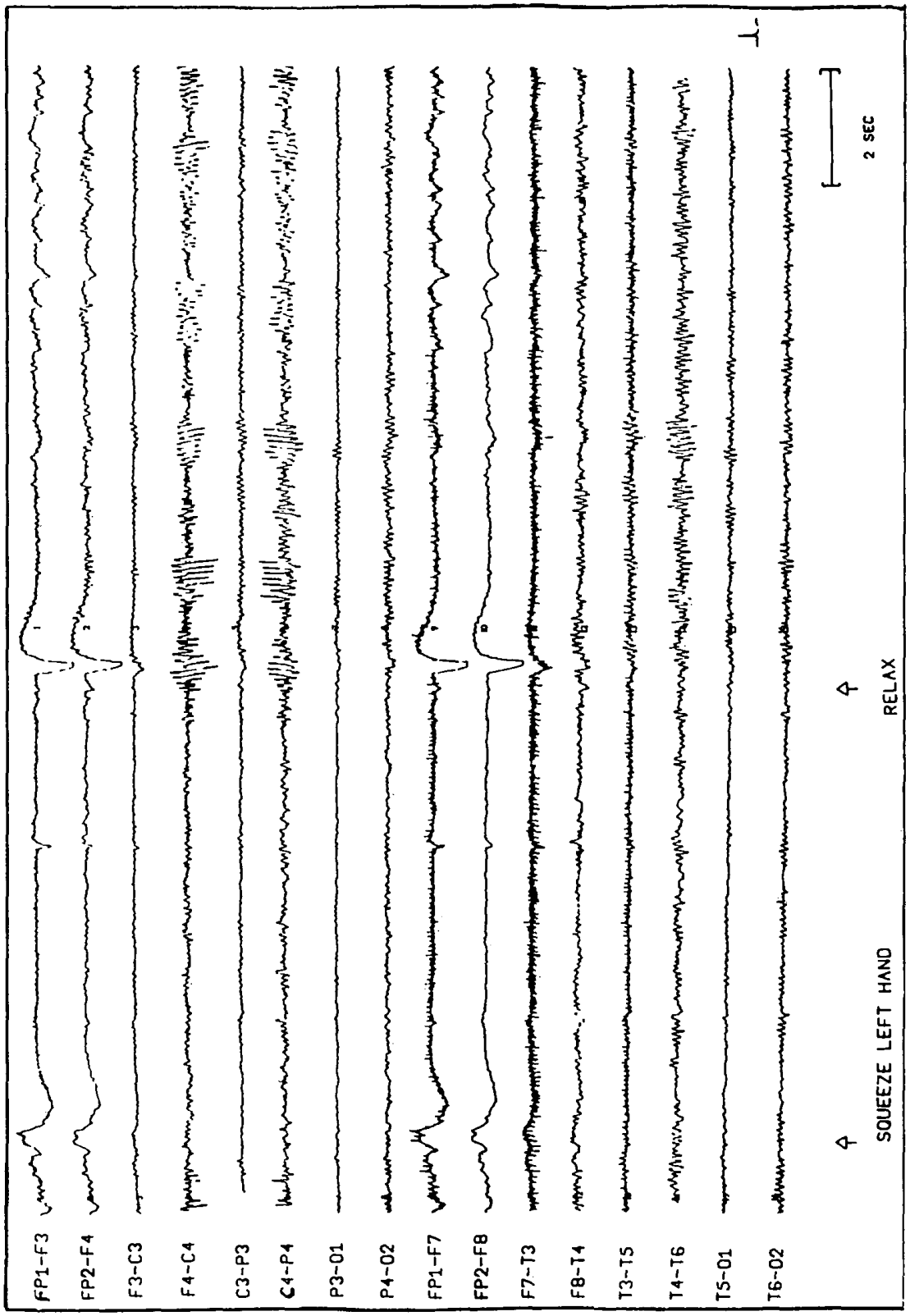

Figure 5.
Bipolar EEG montage showing sample tracings from a non-epileptic patient with bone surgically resected over right centro-temporal area of calvarium. Electrodes at C4 and T4 are placed directly on dura. Subject is shown while first squeezing the left fist and then terminating the squeeze and holding the hand still. Note development of high voltage 10-12 Hz rhythmic activity, particularly in relation to C4, when muscle contraction is terminated. Similar activity in traces derived from C3 is greatly attenuated. (Modified from reference 11)

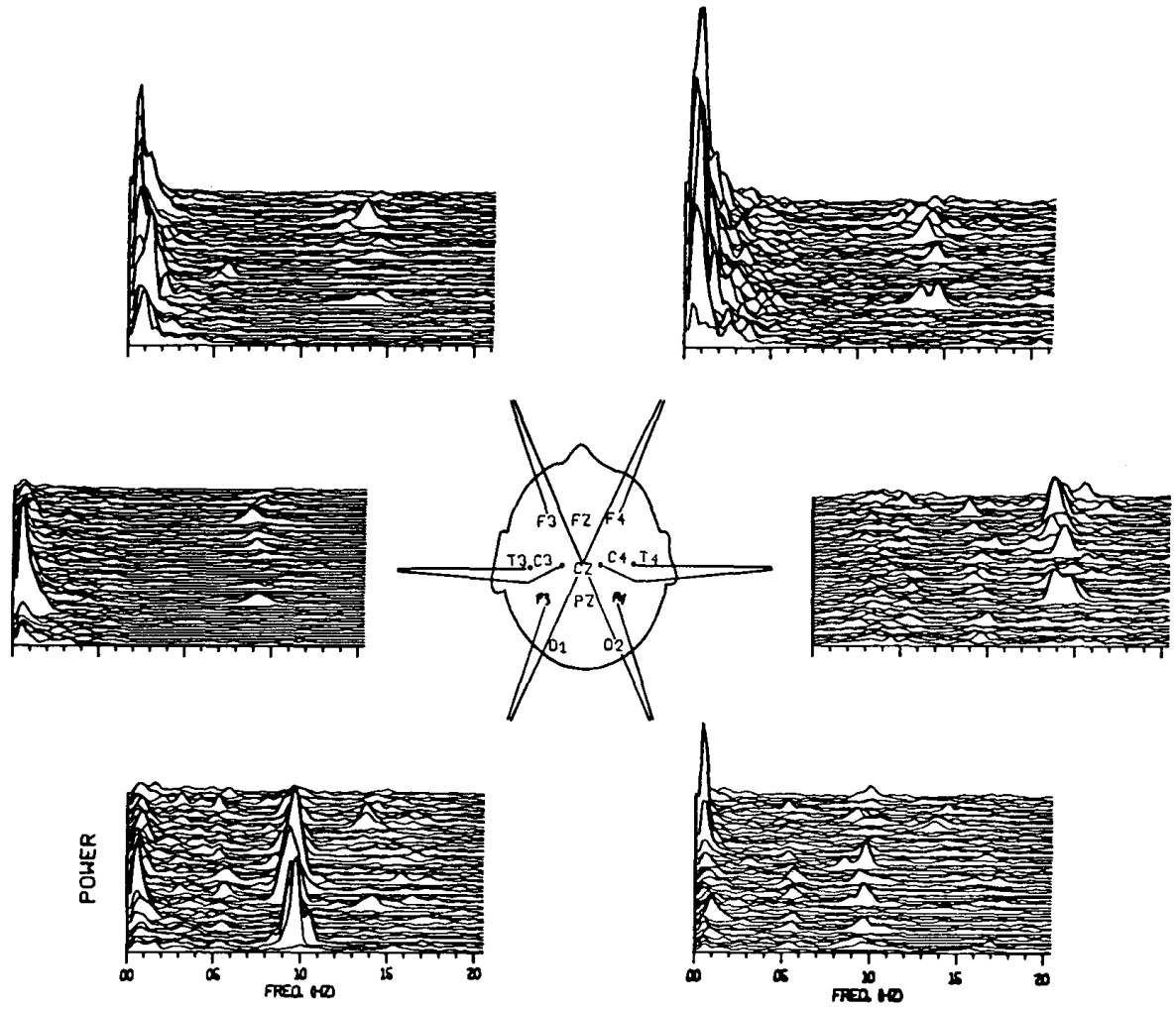

Figure 6.
Compressed spectral arrays showing 10 minutes of spectral analyzed EEG data from bipolar montage referenced to Cz during right central SMR training session in a nonepileptic subject. Successive 8 sec. epochs are shown. Note spectral density peaks at 13-15 Hz from central and frontal recordings, greatest on the right. Parietal 9-11 Hz activity is seen also, greatest on the left. Peaks at 0.5-2 Hz reflect eye-blink artifact. (Modified from reference 19)

and 1 patient who experienced no change in seizures had significant EEG changes. However, 4 patients showed both seizure reduction and a significant, training-contingent normalization of the EEG. In a more recent replication study, *Tozzo et al*[49] provided 8 weeks of EEG biofeedback reward for the simultaneous enhancement of central 12-15 Hz and suppression of 4-7 Hz activity in 6 severe seizure disorder patients. A control condition utilizing verbal relaxation training preceded EEG biofeedback. While relaxation training had no EEG and only limited clinical effects, 5 of the 6 patients showed a significant reduction in seizures by the end of EEG biofeedback training. Digital filter analysis of the EEG indicated that all of these patients significantly increased percent SMR with training ($p < .01$). In 4 of the subjects there was also a significant negative correlation between percent time SMR and seizure incidence.

Using spectral analysis of standardized stage 2 sleep samples, we also found a negative correlation between the incidence of sensorimotor rhythmic activity in the sleep EEG and seizure rate after training.[41,42] That is, seizure reduction was accompanied by a significant increase in sleep spindle activity. Figure 7 shows these relationships graphically. In a similar sleep study, Whitsett et al.[52] also found that increases in 8-11 Hz and decreases in 4-7 Hz frequencies were both significantly correlated with seizure reduction after EEG biofeedback training. Moreover, half of these subjects showed reduced nocturnal paroxysmal activity after appropriate normalization training in a cross-over design.

The consensus arising from these findings is that most epileptic patients who show clinical improvement with EEG biofeedback also show contingency-related EEG changes and a shift towards EEG normalization. However, not all

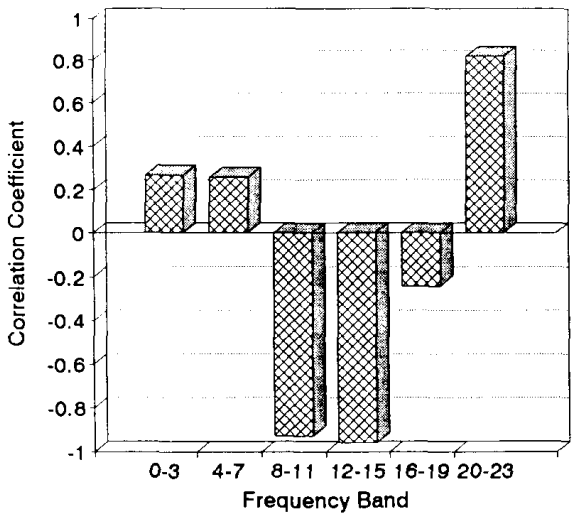

Figure 7.
Pearson product-moment correlations between spectral densities in 6 frequency bands and seizure rate changes in 8 epileptic patients after 3 months of training to increase 12-18 Hz and decrease 6-9 Hz EEG activity in central cortex. Seizure rates were negatively correlated with increases in 8-11 and 12-15 Hz activity ($p<.05$). Opposite contingencies in ABA design failed to produce these relationships. Data obtained from analysis of standardized samples of stage 2 sleep. (Modified from reference 42)

patients who respond to this treatment show expected EEG changes, and a few patients who show EEG changes experience little clinical improvement. One is reminded of the fact that a similar percentage of patients undergoing anterior temporal lobectomy for the surgical treatment of complex-partial seizures failed to show the expected hippocampal sclerosis or other lesions in microscopic studies of the tissue removed.[58] Further 27% of those patients with documented lesions showed little clinical improvement. Both EEG neurofeedback and anterior temporal lobectomy treatments are confounded by our relatively primitive comprehension of neural regulation and seizure pathology, and by the limitations of current analytic methodology.

CONCLUSIONS

Estimates of adequate control with medications in the largest subset of epileptics, namely those with localization-related partial seizures, have been as low as 30%.[59] With nocturnal primary generalized myoclonic epilepsy, control has also been estimated at 30%.[60] Anyone who has worked with these drug-refractory seizure patients knows that they pose a difficult clinical conundrum. Since available medications have not been effective, further titration of dosage will likely not be productive. Turning to new "experimental" drugs is no certain panacea, and can introduce serious risk factors. Given that a nonspecific 30% reduction in seizures can be expected with any new or novel treatment in this population, is it fair to label drug therapy as an "experimental" treatment? Yet a similar logic has been expressed in relation to EEG operant conditioning outcomes, which have been judged with this same patient population.

Clearly, the number of patients that have been studied with this method is relatively small. This research is both labor and cost intensive, and has not been well funded. In truth, however, the impressive success rate documented in a relatively substantial population estimate suggests, instead, that it may be the current treatment of choice with these patients. More research is needed in all areas to improve the treatment of this difficult patient population. But to continue to single out EEG operant conditioning as "experimental" seems neither rational, objective, or in the best interest of these patients.

SUMMARY

Two issues concerning sensorimotor EEG operant conditioning, or biofeedback, as a therapeutic modality for the treatment of seizure disorders are the focus of this review. The first relates to the question of whether relevant physiological changes are associated with this procedure. This question is addressed through review of an extensive neurophysiological literature that is likely unfamiliar to many clinicians but that documents both immediate and sustained functional changes that are consistent with elevation of seizure thresholds. The second focuses on the clinical efficacy of this method and whether it should carry the designation of "experimental". This designation is challenged through an assessment of over 25 years of peer-reviewed research demonstrating impressive EEG and clinical results achieved with the most difficult subset of seizure patients.

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