The Neurobehavioral Treatment of Epilepsy

Edited by David I. Mostofsky and Yngve Løyning
THE NEUROBEHAVIORAL TREATMENT OF EPILEPSY
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Traditionally, a volume concerned with the treatment of epilepsy restricts itself to alternatives and options that fall within the confines of pharmacological or surgical protocols. Indeed, the literature on the medical management of the epilepsies is vast, and such works often include reviews of basic neurophysiology and neurochemistry, technical issues of electroencephalography and related recording methodologies, and even animal models. Yet almost without exception, they fail to report the range of behavioral or psychological interventions and therapeutic programs that have been validated scientifically and that are available to contribute to the comprehensive management of epileptic disorders. Such techniques, properly applied, may well lead to significant reductions in the frequency and severity of clinical seizures, perhaps even with concurrent reduction or elimination of abnormal electrical discharges.

The evidence strongly suggests that the inclusion of behavioral methods in a comprehensive treatment program may offer much to the clinical neurologist. At the very least, they foster increased compliance with medication regimens and stem emotional and interpersonal crises that have been shown frequently to exacerbate seizure disorders. Conventionally separated from medical management, the psychological considerations have been relegated to what has become a minor role for clinical neurologists (i.e., enhancing quality of life, teaching a restrictive lifestyle, and monitoring sequelae of the patient’s condition on his or her family).

Contemporary neurology had its roots in anecdotal and clinical lore, which made frequent reference to the interplay of body and mind. Yet, paradoxically, many medical practitioners now express a seemingly hostile attitude toward
theories and techniques that appear to them to stray from the path. Remarkably, it is forgotten that Gowers (1901), a giant in epileptology, had no such compunctions when he advocated *limb ligation* to arrest seizures, for which there was empirical evidence dating back to the 17th century, but no scientific support.\(^1\) The academic training of most neurologists fosters a rigid dualism and a curious reluctance to examine controversial findings. This has resulted in few collaborations with other behavioral sciences—to the detriment of all, especially the seizure sufferer.

Nevertheless, an increasing number of these patients, on their own initiative, are seeking professional assistance from unconventional quarters. Increasing numbers of physicians are now joining the ranks of psychologists and other health-care workers who are scrutinizing the claims, promises, and limitations of these options. It is to their great credit, as well as to that of the many agencies, foundations, and hospitals, that such research has been pursued for some years, now resulting in a growing number of cases and a change of attitude among even the most hard-core nonbelievers. To be sure, there have been notable exceptions when illustrious neurologists and clinics have embraced and fought for the inclusion of behavioral strategies in their epilepsy clinical services, but their numbers are small.

The efforts of nontraditionalists are beginning to gain acceptance by the weight of their demonstrated successes, achieved most often in the face of patients intractable to surgery and/or conventional medication. Furthermore, the rapidly expanding neurosciences databases confirm the interactions between the *milieu internal* and the *milieu external*. Such factors as environment, conditioning, and personality, and such functions as thinking, imagining, and even breathing may have a rightful place in the therapeutic armamentarium of clinical epileptology.

This volume is the first of its kind, addressed principally to the professional reader. Although it is not intended to be exhaustive or comprehensive, its aim is to sketch a broad picture of some of the nondrug and nonsurgical treatment strategies with a demonstrated basis in conventional scientific method. Likewise, although it does not include all those who have contributed to the emergence of this exciting new field, it assembles those authors whose seminal work has earned them international reputations.

Our purpose in producing this volume is to provide a state-of-the-art guide to methods and techniques used in the behavioral treatment of epilepsy, and to their basis in theory. We hope that it will catalyze the evolution of their acceptance as standard elements, where appropriate, in the clinical activities of independent practitioners, clinics, and agencies that service those with convulsive disorders.

This book draws on a rich scientific and clinical history, including the bio-

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psychological links to epilepsy described by such early pioneers as Hughlings Jackson and William Lennox. Giants in this field, they fueled the courage of those who later conducted clinical investigative programs, such as those of the Seizure Unit at Boston Children's Hospital and the Norwegian National Center for Epilepsy, whose programs are notable for their humane and insightful concepts. All those who trained at such institutions were imbued with a special sensitivity to multidisciplinary treatment options.

The last 20 years, especially, have witnessed a dramatic increase in interest in biobehavioral approaches to the management of convulsive disorders, and a number of influential scientific journals have published comprehensive reviews of ongoing research and clinical applications. The creation of an international interest group, whose name was adopted as the title of this book, attests to the vitality of this new discipline. We, the editors of this volume, wish to express our warmest thanks to our many colleagues from all disciplines. We are particularly grateful to Peter Fenwick and Joanne Dahl for their encouragement of this project, and for their vigorous promotion of this topic area at international meetings. To them, and to the many others whose encouragement and advice made this book a valuable and appreciated addition to the epilepsy literature, we are most grateful.

—David I. Mostofsky

—Yngve Løyning
Sensorimotor EEG Feedback Training in the Study and Treatment of Epilepsy

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BACKGROUND

For the past three decades, my laboratory has investigated the nature, origin, and functional significance of both normal and pathological electroencephalographic (EEG) patterns in sensorimotor cortex. EEG studies in behaving animals supported the fact that well-defined rhythmic patterns, which appear in this area of cortex during immobility or after experimental interruption of afferent somatosensory pathways, are generated by gated ventrobasal thalamocortical volleys (Bowersox & Sterman, 1981; Harper & Sterman, 1972; Howe & Sterman, 1972; Shouse & Sterman, 1979; Sterman & Wyrwicka, 1967). This work with behaving animals was consistent with earlier findings based primarily on acute preparations and summarized comprehensively by the important conceptual treatise of Andersen and Andersson (1968). The dominant intrinsic thalamocortical 12–15 c/sec frequency was exclusive to alert but motionless waking states. Both the frequency and general distribution of this activity was similar to the well-known “spindle burst” seen during non-REM sleep. In deference to function, we labeled this band the Sensorimotor Rhythm, or SMR.

In a novel series of behavioral studies, we found that cats and monkeys could be trained to facilitate this 12–15 c/sec activity through the application of operant conditioning techniques (Sterman, Goodman, & Kovalesky, 1978; Wyrwicka & Sterman, 1968). Perhaps the most interesting aspect of this work was the serendipitous discovery that both cats and monkeys trained behaviorally to enhance the SMR were subsequently resistant to seizures induced by the injection of convulsant hydrazine compounds (Sterman, 1973; Sterman, LoPresti, & Fairchild, 1969; Sterman, Goodman, & Kovalesky, 1978).
A series of studies focusing on the neurophysiological basis for this effect showed that specific changes in somatosensory and motor excitability accompanied trained SMR activity. In particular, attenuation of somatic afferent discharge, related thalamic sensory relay transmission, and efferent motor and striate muscle activity were all seen in strict relationship to the appearance of this pattern in the sensorimotor EEG (see review by Sterman & Bowersox, 1981). Additionally, EEG dynamics indicated that physiological and pharmacological manipulations that facilitated SMR activity were associated with a corresponding decrease in slower 4–7 c/sec rhythmic patterns (Bowersox & Sterman, 1981; Sterman & Kovalesky, 1983). The opposite effects had been reported in epileptogenic conditions, where experimentally produced increases in cortical excitability replaced normal rhythmic EEG patterns with such slower frequencies and, ultimately, with spike-and-wave discharge (Gloor, Pellegrini, & Kostopoulos, 1979).

Collectively, these and other findings led us to propose that epileptogenic pathology involving motor manifestations is generically associated with a disturbance of normal sensorimotor regulation, with a consequent disturbance of conductive patterns and associated EEG manifestations. Under these circumstances, influences that further increase intracortical excitability and/or alter thalamocortical interactions (i.e., drowsiness, slow-wave sleep, metabolic changes, etc.) facilitate abnormal patterns as well as ictal and interictal discharge. Conversely, influences that decrease intracortical excitability and/or stabilize normal thalamocortical interactions attenuate abnormal discharge. Thus, EEG feedback training directed to an enhancement of normal thalamocortical regulation could potentially support the latter effect and increase seizure threshold.

In extending these investigations to man, we observed the so-called "wicket" or "mu" rhythm in the sensorimotor EEG during motor quiescence, as described earlier by Gastaut (1952) and Chatrian, Petersen, & Lazarte, (1959), among others. However, our analyses were dominated by quantitative rather than visual methods. Bandpass and spectral analysis techniques disclosed frequency components not clearly seen with visual scrutiny and confirmed the presence of sensorimotor patterns similar to those seen in our animal work (Sterman, 1977; Sterman, Macdonald, & Stone, 1974). However, the limitations of scalp rather than direct cortical recording and voltage differences in the human EEG made this higher frequency pattern difficult to observe visually. Operant conditioning could be used selectively to enhance 12–15 c/sec activity but sleep studies were the most effective means of characterizing changes in this frequency band due to the clear expression of a related pattern during Stage 2 sleep, the sleep spindle. When normal and poorly controlled epileptic subjects were compared in this regard, SMR and sleep-spindle patterns were found to be significantly attenuated and 4–7 c/sec activity increased in the epileptics, particularly when anticonvulsant medication influences were decreased or absent (Sterman, 1977, 1981).

In 1972, we reported our first attempt at EEG feedback-based enhancement of
the SMR pattern in a human epileptic patient (Sterman & Friar). Response acquisition was demonstrated over a 3-month period and was accompanied by a dramatic decline in reported seizures. This work was followed by expanded studies in 1974 (Sterman, Macdonald, & Stone), 1978 (Sterman & Macdonald), 1980 (Sterman & Shouse), and 1984 (Sterman). After the 1974 report, we began controlling for nonspecific effects and included noncontingent “placebo” training conditions as well as the suppression of abnormal EEG frequencies, together with enhancement of the SMR in contingent training conditions. Normalization of the EEG and significant seizure reductions were associated exclusively with contingent feedback training and response acquisition in all of these studies (see, for example, Fig. 1.1).

Neuropsychological assessment was included in a study of 24 patients with poorly controlled complex-partial seizure disorders (Lantz & Sterman, 1988). This study confirmed previously reported deficits in psychosocial and cognitive functioning in this population. Additionally, however, specific psychomotor disturbances were documented as well, and these were found to predict success with EEG feedback training. Further, patients who successfully normalized central cortical EEG patterns showed significant improvements in both cognitive and motor functioning. These improvements, unlike psychosocial changes, were specific to successful contingent training in this controlled, crossover design study.

Starting in 1975, many other laboratories began to explore EEG feedback training in relation to epileptic pathology. Numerous reports have appeared in the EEG and neurological literature from other laboratories, all of which documented significant seizure reductions with this approach (Cott, Pavloski, & Black, 1979; Ellertsen & Kløve, 1976; Finley, Smith, & Etherton, 1975; Kaplan, 1975; Kuhlman, 1978; Lubar & Bahler, 1976; Lubar et al., 1981; Quy, Hutt, & Forrest, 1979; Tozzo, Elfner, & May, 1988; Wyler, Lockard, Ward, & Finch, 1976; Wyler, Robbins, & Dodrill, 1979). Controversy arose, of course, over the “active ingredient” in this methodology. Despite the evidence already reviewed and the development of other theoretical explanations for this therapeutic effect (Kuhlman & Kaplan, 1979; Wyler, 1984), profound differences between the clinical epilepsies and animal models, together with the complexities of human epilepsy, have precluded a definitive resolution of this question.

Some clues as to mechanism were provided by a preliminary study of complex-partial seizure patients who were candidates for neurosurgical treatment involving resection of anterior temporal lobe tissues (Sterman & Bloomfield, 1987). During Phase 2 of the neurosurgical protocol, these patients had fine-wire microelectrodes implanted bilaterally into deep anterior temporal lobe sites. Unit recordings, indicating cellular discharge behavior at these sites, were obtained from 3 patients during several EEG feedback training sessions for the enhancement of SMR activity. A comparison of cortical and subcortical EEG patterns showed a general and significant reciprocity, in that the presence of SMR trains
REPORTED SEIZURE RATES (n=24)

FIG. 1.1. Comparison of mean percent change from baseline seizure rates during the last month of four sequential experimental treatment conditions, as reported by 24 poorly controlled partial-complex seizure subjects. Three-month treatment periods included: (a) seizure tabulation with special seizure logs, (b) noncontingent, yoked control EEG feedback training, (c) contingent feedback training for EEG normalization (Cont. 1), and (d) gradual withdrawal from contingent training (Cont. 2). Data reported after a 6-month follow-up period are also shown. Rates registered during the Tabulation period were significantly elevated ($p = <0.05$). Rates reported following contingent training were significantly depressed ($p = <0.05$). Data reported during the final phase of contingent training and with follow-up were also significantly reduced ($p = <0.01$). No significant change was reported with noncontingent, yoked training (data from Sterman, 1984).

in the sensorimotor EEG was accompanied by normal electrical activity at deep sites. Conversely, subcortical paroxysmal discharge occurred almost exclusively in association with activated or slow-frequency EEG patterns. Feedback training sessions that produced an enhancement of the SMR across trials were accompanied by a sustained suppression of unit firing at many hippocampal recording sites (Fig. 1.2). These findings demonstrated a surprisingly consistent relationship between the sensorimotor cortical EEG and subcortical focal pathology.
Abnormal subcortical EEG patterns and related unit discharge were suppressed when normal sensorimotor rhythmic EEG activity was present or behaviorally enhanced through feedback training. This implies that cortical and/or thalamocortical regulatory mechanisms can have a significant effect upon limbic neuronal excitability.

In summary, several decades of animal and human research have established a relationship between thalamocortical EEG mechanisms and seizure pathology. These studies clearly showed that animals can be trained to produce discrete, discrete,

A. Training Session: SMR Production Rate
(R.N., 5/29/86)

B. Right Anterior Hippocampal Gyrus Cells

C. Right Mid Pes Hippocampi Cells

FIG. 1.2. Mean incidence of automatically detected cortical (C3) SMR activity is compared here with corresponding mean integrated extracellular unit discharge rates at limbic sites in a presurgical patient with partial-complex seizures. Data were collected before, during, and after four sequential 7-minute EEG feedback training trials. A clear enhancement of SMR activity across feedback trials was associated with a significant and sustained decrease in unit discharge rates at these sites.
voluntary changes in sensorimotor EEG patterns that are not directly mediated by behavioral events and that can alter susceptibility to experimental seizures. Numerous controlled studies evaluating the effects of sensorimotor EEG feedback training in epileptics documented a significant therapeutic effect and ruled out nonspecific factors. Neurophysiological evidence suggests that this methodology can produce significant changes in underlying neuronal regulation that can also alter seizure susceptibility.

RECENT DEVELOPMENTS

In recent years, work in this area has been greatly facilitated by the emergence of highly sophisticated computer-based quantitative EEG analysis systems. These systems provide a comprehensive analysis of background EEG abnormalities in epileptics, with the resulting advantage of objective and quantitative data for the development of appropriate EEG feedback training strategies. Our efforts with this new technology were initially directed to the development of an appropriate methodology for the application of the greatly expanded capability it provided.

We worked exclusively with the Lexicor NRS-24 topographical mapping system (Boulder, CO). This system performs a digital conversion of the analog EEG signal and calculates real-time spectral magnitudes, using the Fast Fourier Transform, for selected EEG frequency bands from 19 cortical recording sites. These quantified frequency magnitudes can then be displayed sequentially over time as compressed spectral arrays, trends, or topographic maps.

Despite the complex and attractive visual displays that this system provides, it was necessary to develop software for the organization of data within analytic spreadsheet programs that provide for appropriate quantitative comparisons and statistical analysis. It was necessary, also, to standardize procedures for system settings, data collection, and artifact removal. Most importantly, however, it was essential to collect a comprehensive body of EEG data with this system from a sufficiently large group of confirmed neurologically normal subjects. These normative data would provide the critical reference needed for the evaluation of epileptic pathology in the background EEG.

This was accomplished over an extended period during which 30 data sets were obtained from normal, right-handed male subjects participating in a standardized EEG study protocol (Sterman, Mann, Kaiser, & Suyenobu, 1993). Quantitative EEG data were tabulated for three standard test conditions, each lasting 2 min. These included: (a) eyes closed, (b) eyes open, and (c) numerical calculations. Standardized recordings were obtained from a fitted electrode cap, with leads placed according to the International 10/20 System at 19 cortical sites. A monopolar montage was used with reference to linked earlobes. Electrode impedances of less than 10 Kohms were required at all sites prior to recording. EEG signals were fed directly to the analysis system where they were digitized at
a rate of 512 samples per second. Input characteristics provided common mode rejection, Hanning window smoothing, and bandpass filtering between 2 and 16 Hertz. Data were acquired in 4 sec epochs to a hard disc for subsequent quantitative analysis.

For the past 2 years, we have entered a series of poorly controlled epileptic subjects into an identical assessment protocol, with the addition of a respiratory hyperventilation test. This assessment was used to confirm and characterize background EEG abnormalities in these subjects. The data obtained were used as the basis for selection of subjects for a new EEG feedback-training study and for determination of appropriate EEG training sites and strategies.

In addition to the hyperventilation test, which often activates EEG pathology in epileptics, we found that the eyes-closed, resting condition also provides valuable information for the assessment of background EEG abnormalities. Further, our normative database does not include a hyperventilation test, thus precluding quantitative comparisons. For these reasons, we focus here on assessment data obtained from the eyes-closed test condition. Further, we examine EEG spectral findings in the 4–8 Hz frequency band; as already mentioned, this activity has been most closely associated with epileptic pathology in the background EEG.

Figure 1.3 compares mean log magnitude values at 4–8 Hz with the eyes-closed condition from sites across the central coronal cortical plane in 6 epileptic subjects with the mean and mean plus one standard deviation for each of these sites from our database. The normative means are seen at the bottom of this figure as a solid curve with filled boxes, and the means plus standard deviations just above this as a solid curve with empty boxes. The values for epileptic subjects are arrayed primarily above these with various other curve and symbol formats. It is immediately apparent that each subject showed unique background EEG abnormalities but that all displayed significantly abnormal 4–8 Hz values at one or another of these sites. Not surprisingly, this reflects the variable pathologies underlying the seizure disorders manifested in these patients. Thus, 2 of these patients had partial-motor (Jacksonian) seizures secondary to focal cortical lesions, the sites of which were identified by unusually elevated 4–8 Hz activity. One other had partial-complex seizures with clearly lateralized enhancement of 4–8 Hz activity on the right. Finally, 3 had partial-complex seizures with generally increased 4–8 Hz activity.

These findings demonstrate the value of the background EEG in characterizing epileptic pathology and the utility of this approach in localizing (and verifying) that pathology. The potential accuracy of this localization is demonstrated in Fig. 1.4, which compares CT scan findings with topographic EEG findings in one of the patients with Jacksonian seizures. These seizures persisted despite the removal of a right, parasaggital central-parietal hamartoma, shown as the bright region in the CT study of the cerebral hemispheres (horizontal perspective). On the right is a comparable EEG topographic map based on a 2-min average of
FIG. 1.3. Mean log spectral magnitudes at 4–8 Hz are shown here for a standardized 2-min eyes-closed period at recording sites across the central cortical coronal plane. Data from 6 subjects with varying seizure disorders are compared with mean and mean plus one standard deviation values from a normal database population. Normative data are represented by the two parallel solid line curves at bottom of graph, showing means (filled boxes) and means plus standard deviation (empty boxes). Values greater than two standard deviations from normal were considered to reflect epileptic pathology.

sequential 4-sec spectral-magnitude estimates at 4–8 Hz, with eyes closed. The topographic EEG image was originally in color and showed a single region of incrementing 4–8 Hz density in the right central-parietal area. This is shown in this black-and-white rendition as the large bright region with a dark center on the right. Given the slightly different horizontal planes of the head in these two images, the topographic EEG findings were in very close agreement with the CT study in localizing this pathology. Additionally, however, the EEG findings disclosed more than just morphology by also indicating an expanded extent of functional abnormality.

These considerations demonstrate again the importance of a quantitative frequency assessment of the topographic EEG in selecting appropriate sites for the application of a frequency-based EEG feedback procedure in what is always a
diverse population of epileptic patients. In earlier studies, we did not have the advantage of the rapid and relatively inexpensive collection of such comprehensive data. Instead, we standardized training to left central cortex, using a bipolar lead from C1–C5. Further, feedback was based on bandpass filter analysis of this signal, with electronic relays activated when both positively and negatively rewarded frequencies reached criterion levels. The new topographic equipment allows for feedback to be applied selectively to previously determined sensorimotor sites of maximal abnormal background activity. This localization is made possible through the use of monopolar (referential) recording methods and bases feedback on real-time spectral-magnitude values calculated in frequency bands matched to patient pathology. High- and low-pass filters and adjustable band frequencies provide for attenuation and continuous monitoring of signal artifacts. Session data can be stored digitally for further analysis. Additionally, feedback modalities can be varied with ease and adapted for different patient groups. As a result of these advances, such important factors as localization, feedback accuracy, and data retrieval are all greatly facilitated.

This new capacity for “customized” training makes the rigid experimental protocols used previously both difficult and inappropriate, particularly if the

FIG. 1.4. Comparison of computer tomography (CT) image and topographic spectral analysis of 4–8 Hz EEG activity in a subject with severe focal-motor seizures secondary to a right central-parietal, parasagittal hamartoma. Tumor location is indicated by the bright area on the right in both studies. EEG study also discloses expanded region of functional disturbance.
patient's welfare is considered. The objective of training remains the same, namely normalization of the disturbed epileptic EEG. Confirmation of EEG abnormalities in sensorimotor cortex is still essential to our approach because it is based on animal and human research focused on sensorimotor mechanisms and pathological manifestations. However, this objective can now be addressed in a more individualized manner. The cortical site or sites primarily implicated can be identified objectively, the abnormal frequencies specified, and the optimal format of feedback for response acquisition determined. Further, flexibility with regard to frequency bandwidth and complexity of displays facilitates the shaping of desired responses.

Some discussion of the new and rather remarkable feedback modality capabilities is in order. All formats achieve essentially the same objective, that of portraying both desired and undesired frequency components in a manner that best facilitates their learned enhancement or suppression, respectively. This can be done separately or together, from one or several sites, and with a number of different displays. For example, it may be beneficial initially to focus on the suppression of abnormally elevated, and often dominant, slow activity in the 4–8 Hz range. Sequential mean spectral magnitudes for samples ranging from 0.5 to 2 sec can be represented by modulated bars, circles, or real-time trends. These can be displayed in any color the subject desires. Maintenance of the signal below predetermined magnitude threshold levels can be rewarded by auditory or numerical reinforcement. Subsequently, attention can be directed to the enhancement of the desirable higher frequencies. A different, perhaps more soothing, color and tone is used for shaping frequencies within the 12–16 Hz range component in this phase. One can then alternate between low-frequency suppression and high-frequency enhancement. Finally, the two can be displayed together in any of these formats and the subject rewarded for their differentiation. Experience has indicated that subjects respond best to the more recently achieved capacity for real-time frequency trend displays.

Quantitative spectral magnitude data for each trial can be stored for later evaluation and are also used to summarize the trial for the subject. Two trial summary sets (approximately 1 min in duration) are shown in Fig. 1.5 and Fig. 1.6, which present smoothed, trended outputs in 12–16 Hz (upper curve in each graph) and 5–7 Hz (bottom curve) bands for 2 different subjects. Figure 1.5 presents data from a normal subject recorded at C3 and taken from an early (top) and late (bottom) trial in a single training session. These data demonstrate the frequency differentiation that can sometimes be achieved fairly quickly with nonepileptic subjects.

Figure 1.6, on the other hand, presents data from two different sites (C4 top and C3 bottom) at approximately the same point in a training session but in an epileptic subject. Note that these two frequency bands show variable but significant reciprocity at each site. They also show very different magnitudes at each site and in comparison to Fig. 1.5. Finally, it is clear that at the point in training
FIG. 1.5. Summary trends of 12–16 (dashed) and 5–7 Hz (solid) EEG spectral data from two 1-min EEG feedback trials at the beginning (top) and end (bottom) of the same training session. Subject in this case was a 27-year-old nonepileptic male. Ordinate is spectral magnitude and abscissa time in seconds. Reinforcement was for increasing 12–16 Hz and decreasing corresponding 5–7 Hz activity. Early trials were characterized by lack of differentiation and parallel modulation. With repeated trials, these frequency bands became differentiated and showed increased reciprocity.

depicted here, the subject was able to follow reward contingencies more effectively at the more normal C3 site.

Subjects were provided with two 1-hour training sessions per week, and reevaluated at approximately 3-month intervals. The objective of training in all cases was the normalization of sensorimotor EEG frequencies, focused on a structured suppression of abnormal components within the 4–8 Hz range and a corresponding enhancement or stabilization of higher frequencies within the 12–
FIG. 1.6. Summary EEG spectral magnitude trends as in Fig. 1.5 but showing, instead, data from two different sites studied during the same session in epileptic subject. At this point in training, this subject had significantly higher spectral magnitude values at C4 (top) and was able to follow reward contingencies better at C3 (bottom). Note some degree of frequency band reciprocity at both sites.

16 Hz range. Because this review is based on cumulative data from a recent outpatient series, quantitative findings concerning EEG and seizure effects are limited. In fact, only 2 of these patients have had sufficient training for review at this time. Both were high functioning females in their late 50s.

As in previous studies, seizure logs have documented significant attenuation in the intensity and frequency of seizures. Further, these clinical improvements have been registered despite meaningful reductions in anticonvulsant medications. Details from each case will be reviewed separately.

Figure 1.7 compares baseline, eyes-closed sensorimotor EEG data from these 2 patients with comparable normative data from laboratory studies, both prior to
FIG. 1.7. Repeated baseline assessments (eyes closed) showing central cortical EEG spectral magnitudes at 4–8 Hz are compared here with normative data in 2 epileptic subjects at different stages of EEG feedback training. Database means (filled box) plus one standard deviation (empty box) at bottom can be contrasted to epileptic subject values (triangles). For subject in top graph, initial assessment (dashed curve) is compared with identical data acquired 6 months into EEG feedback training for normalization (solid curve) and shows decline of 4–8 Hz activity at most sites to within normal range. Data for subject in bottom graph reflect initial (dotted) and two sequential 6-month follow-up assessments (dashed and solid curves). This subject has shown a progressive attenuation of 4–8 activity, particularly at the site of epileptogenic tumor focus (C4).
training and at regular assessment intervals after training began. The patient in the top graph suffers from relatively frequent partial-complex seizures and showed a significant, general increase in 4–8 Hz background activity across the central cortical plane in pretraining, eyes-closed data. Training was alternated between C3, CZ, and C4 in this subject. After approximately 6 months of training, this subject demonstrated a significant attenuation of central 4–8 Hz activity during a retest eyes-closed assessment. Because normative data are very stable over time, this change is best explained as a result of the EEG feedback training. Seizure rate decreased and became stable at a significantly lower level in this patient, which encouraged the responsible neurologist to allow a subsequent withdrawal from Tegretol anticonvulsant therapy. The patient has sustained these gains and is currently on monotherapy, having continued with a relatively low dosage of Mysoline only.

The second patient (bottom graph, Fig. 1.7) experienced frequent Jacksonian focal-motor seizures secondary to right central cortical-tumor pathology (see Fig. 1.4). The initial pretreatment, eyes-closed assessment EEG data for this patient showed a remarkable and highly significant elevation of background 4–8 Hz activity, with a specifically elevated secondary peak at C4. After approximately 6 months of training focused on the primary C4 site, these levels declined across the central strip, most dramatically at C4. An additional 6 months of training resulted in a further reduction, bringing some sites within two standard deviations of normal mean values. Training emphasis during this period alternated between C4, C3, and T4. Although 4–8 Hz magnitudes on the right remained elevated compared to the left, the specific discrepancy at C4 was abolished.

This patient maintained comprehensive seizure logs before and since the initiation of EEG feedback training. These logs have documented an irregular but progressive decline in the rate and intensity of focal motor seizures during the course of training. She now experiences unique seizure-free periods and can abort many seizures in their earliest phase. During this same period, and as a result of these gains, she has been permitted to reduce her Phenobarbital and Tegretol medications by 30 and 40%, respectively.

Although proper application of this new computer technology is still in its infancy, initial findings are very encouraging. The ability to achieve a facile quantification of background EEG abnormalities and changes associated with training fortifies documentation significantly. Later reports will expand on these initial findings.

GENERAL CONCLUSIONS

It has been difficult to summarize 20 years of research on the voluntary control of sensorimotor EEG patterns, not to mention the complications added with its application to the clinical morass of epilepsy. We take some pleasure in the fact
that our animal findings were rather straightforward. Healthy cats and primates showed a distinct, behaviorally significant EEG rhythmic pattern recorded from implanted electrodes placed directly on sensorimotor cortex. Well-controlled studies showed that cats and monkeys could, indeed, learn to regulate the incidence of this EEG pattern and, in so doing, provide a basis for the disclosure of relevant underlying neuronal dynamics. Changes in cell-firing patterns, sensory conduction, and motor excitability were all objectively demonstrated. So, too, was the fact that seizure thresholds could be raised.

In applying this methodology to human seizure disorders, the circumstances were very different. The EEG was recorded from surface electrodes in subjects whose signals were often characterized by an inherent deficiency in the EEG patterns of interest. Additionally, the influence of medications and the variety of epileptic pathologies further complicated matters. Finally, and of equal importance, was the impact of such factors as history, expectations, and, for lack of a better term, personal styles, on the effectiveness of behavioral intervention. Certainly, none of these issues burdened our animal work.

Despite these problems, we and others have demonstrated that EEG feedback training for normalization can have a lasting effect on brain electrical activity and on the clinical manifestation of seizure pathology. Achieving these outcomes, however, is no easy matter. Because effective EEG feedback training probably depends on the gradual alteration of underlying neural substrates achieved through voluntary learning, it is not surprising that success requires a serious and sustained effort. The cost in terms of time and resources for such an effort is not trivial. Neither, however, are the alternatives.

Our experience indicates that this therapy modality is not for everyone. Studies have shown that outcomes vary as a function of seizure type, intelligence, and social adjustment. Generalized motor, focal motor, and partial-complex seizures with motor manifestations respond best. As with medications, good mental and social competence are associated with better results. Perhaps most important, however, is the personal variable previously mentioned. Successful patients are those who are best able to immerse themselves effectively in the task and to achieve awareness and control of their subjective state. This is difficult territory to chart objectively but clearly deserves more systematic attention. It must, in reality, be a simple skill, because cats seem quite competent in this regard.

REFERENCES


1. SENSORIMOTOR FEEDBACK TRAINING AND EPILEPSY


Breathing Training for the Self-Regulation of Alveolar CO₂ in the Behavioral Control of Idiopathic Epileptic Seizures

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In the United States, *idiopathic* seizure sufferers are estimated to constitute about 75%–80% of the total population of individuals said to have epilepsy—about 16 million or more persons, and growing by about 100,000 cases annually. In this subpopulation, seizures typically first emerge in the late teens, or about the time that most of them enter the labor market. A genetic predisposition to idiopathic seizures has been postulated, but no convincing scientific evidence suggests that it is strong. But there may be a cluster of related inherited disorders such as migraine, Raynaud’s, and angina, principally involving the vascular and oxygen transport systems, that they and their family seem to share (Deutsch, Ehrentheil, & Pierson, 1941; Fried, 1990, in press; Hauptmann & Meyerson, 1948).

Seizures are classified by etiology, manifestations, and physiological correlates; those of readily determinable origin are said to be “symptomatic.” They may take various forms (i.e., petit mal, grand mal, psychomotor, etc.) and may be accompanied by premonitory sensations (auras) that may take different forms, such as auditory, visual, abdominal, and so forth (Gastaut, 1970).

WHAT IS EPILEPSY?

In antiquity, seizure sufferers were variously admired or reviled, praised, or persecuted. The “falling disease,” the “sacred illness,” was often said to be demonic possession—hence the word *seizure*—or caused by winds (*aura*). It was described in considerable detail by Hippocrates (460–357 B.C.) and Galen (130–200 A.D.) and references to it may be found in the New Testament (Mark 9.17). With time, the treatment of epilepsy came to be the concern of neurology.
The theory of seizure etiology currently in vogue in neurology stipulates spontaneous individual brain neuron dysfunction, with subsequent recruiting of an aggregate whose critical mass results in total brain involvement in electrical seizure discharge. This theory is based on the electroencephalographic (EEG) observations during the seizure. But, in fact, it satisfactorily explains neither why the seizure starts nor why it stops. Wolfe and Elliott (1962) were typical:

Convulsive activity may now be conceived, not as an enhancement of the normal excitation of neurons, but as the partial or complete block of normal inhibition. A biochemical abnormality of some neurons is thought by many investigators to underlie the initiation of gradually increasing depolarization in their dendritic fields so that minimal stimuli may initiate a seizure discharge. The spread to adjacent neurons and the propagation axonally to other areas of the nervous system of the discharge results in the striking manifestation of the convulsion. (p. 694)

This elaborate definition raises more questions than it answers. Which biochemical neuronal abnormality? In well over 5,000 books and research articles available on the subject, there is little more than speculation. Ginter (1955) cited “inherent metabolic defects carried on transmissible genes;” birth defects, or birth injury traceable to “definite pathologic evidence [of] microgyri or glial scars;” disturbance in prenatal or neonatal oxygen (O₂) or foodstuffs supply; “poisoned” enzyme or hormone disturbance; and last, although by no means least, latent viruses that “may cause a decrease in the rate of glycolysis and inhibit glucose phosphorylation, or later the formation of amino acids from protein.” Himwich (1951) also cited hypoglycemia, but Maccario, Messis, & Vastola (1965) proposed hyperglycemia. Cogan, Schulman, Porter, & Mudd (1980) suggested methylmalonic aciduria and homocystinurea. There are suggestions that inhibitory mechanisms, such as those involving gamma-aminobutyric acid (GABA; Tower, 1968) and more recently taurine (Rozen, Goodyer, & Scriver, 1982), may play a role. They are diverse and cover a broad spectrum of metabolic processes.

The study of seizures as brain events dates from about the middle 19th century. Wilks (1859, cited in Penfield & Jasper, 1954) introduced the therapeutic use of bromide—the term later came to mean a universal palliative—and distinguished between functional (idiopathic) and focal seizures. But Merritt & Putnam (1938), who pioneered the use of dilantin, brought to our attention that:

Good results in the treatment of patients with convulsive seizures have been obtained by a variety of methods, such as medical treatment with bromides or barbituric acid compounds, the ketogenic diet, restriction of fluids, and the surgical excision of scars or irritable cortical foci. (p. 1068)

This would lead one to believe that uncontrolled seizures are, excepting extremes, a thing of the past. They continued, “In spite of these various therapeutic
means, there are a great number of patients who are not relieved of their attacks or are helped only temporarily by treatment” (p. 1068). In 1952, Yahr, Sciarra, Carter, & Merritt, reporting on the effectiveness of dilantin, concluded that it was about “87% effective” in the 319 patients they studied, but that 87% included only 48% whose seizures were controlled, whereas 37% showed varying degrees of improvement. Technically, this is “87% effective.”

Hughlings Jackson (1870, cited in Taylor, 1931) rejected the possibility of seizures in the absence of histopathology. Gowers (1881, 1901), supporting Wilks, disagreed:

The naked eye appearance of the nerve-centers in idiopathic epilepsy is for the most part that of healthy organs. . . . Great as is the aid which the microscope has afforded in the investigation of the structural changes in many diseases of the nervous system, it cannot be said to have thrown much light on the nature of idiopathic epilepsy. Of the minute histological changes which have been described, most, if not all, of those which are not common to many other diseases, are simply secondary. . . . (Gowers, 1901, p. 213)

Disciples of Hughlings Jackson were left to hope that histopathological evidence would emerge as technology advanced. It is not surprising that the EEG discoveries of Berger (1929) and Bremer (1938) resurrected the faithful; for here, finally, was the evidence for histopathology, (i.e., the biochemical lesion). But, they might have done well to heed Gower’s (1901) warning:

[T]he subject of the pathology of epilepsy resolves itself, in the main, into four questions: What is the seat of the discharge which thus produces the symptoms of the fit? Is the seat of the discharge the seat of the disease? How far does such discharge explain all the symptoms of the attack? What is the nature of the morbid change which causes the discharge? (p. 215)

According to tradition, neurology, like the youngest son, did not seem to know that there were questions to be asked. Berger (1929) and Bremer (1938) were, parenthetically, entirely at odds. The first held the EEG to be due to the electrophysiology of the vascular bed of the brain; the latter assigned it to neurons. No one else seemed to have paid much attention to this critical distinction, and thus it faded from view.

In fact, for some time it seemed not to matter much what the etiology of seizures actually was. As late as 1965, the renowned British neurologist, Lord Brain, stated, in what is considered by many the classic textbook of neurology, that we do not yet understand the physiological relationship between cortical dysrhythmia and the epileptic attack. Elsewhere, such an assertion would have been taken as parochial, if not curious agnosia, for the publications of countless scientists, especially in the United States, which promulgated quite creditable specifics (Gibbs, Lennox, & Gibbs, 1940; Gibbs, Williams, & Gibbs, 1949;
Himwich, 1951; Lennox, Gibbs, & Gibbs, 1938; Madsen, 1943; Meyer & Waltz, 1961; Millichap & Ulrich, 1962; Penfield & Jasper, 1954; Schwab, Grunwald, & Sargent, 1941; Swanson, Stavney, & Plum, 1958; Tower, 1960; Wolfe & Elliott, 1962). Brain (1965) continued:

There seems no doubt, however, that whatever its immediate or remote cause, an epileptic attack is that manifestation of a paroxysmal discharge of abnormal electrical rhythms in some part of the brain. If one adds that such discharges are likely to be repetitive, one has defined the cardinal features of epilepsy. (p. 129)

Epilepsy . . . “whatever its immediate or remote cause!” (p. 129). He might have cited Penfield (1933): “The vasomotor spasms and changes seen so characteristically in the cerebral cortex of epileptics are due to vasomotor reflexes . . .” (p. 310), right or wrong. Barolin (1966) was as vague as Brain and postulated an initial “pathological activity in the nervous cells” (p. 56). So was Merritt (1979), codeveloper of dilantin, who explained that seizures are due to “. . . excessive repetitive firing of [a] single or small group of neurons in the brain . . . [with] recruitment of adjacent neurons spreading to the entire system until it is out of control.” So if a few brain neurons seize and enough of them do it at the same time, a seizure results. If recruitment is how they get each other to join in the act, what limits recruitment to a lesion, or focus, that can be excised surgically?

Metabolic etiology of seizures, most notably where the body’s CO₂ economy plays a central role, has been proposed by numerous investigators (Brill & Seidmann, 1942; Caspers & Speckmann, 1972; Gotoh, Meyer, & Takagi, 1965; Meyer & Gotoh, 1960; Meyer & Waltz, 1961; Morrice, 1965; Raichle & Plum, 1972). But its division from electroclinical seizure etiology is demarcated so sharply that Gastaut & Tassinari (1966), proponents of the electroclinical view, assigned just one paragraph to “hyperpnea” and six short paragraphs to metabolic factors, limited to hypocalcemia in infants. All other research was dismissed with: “[Epileptogenic metabolic disorders] . . . are not only particularly interesting from the physiopathogenic point of view, but very important from the clinical point of view and must always be considered and studied in each subject. . . .” (p. 96). So why not tell us what they are? Even the paragraph on hyperpnea mentions nothing about CO₂, dismissing hundreds of respected investigations into its link to seizures.

Most metabolic theories of seizure etiology implicate hypoxia, relating it to the body’s CO₂ economy and the way that economy affects the O₂ transport system. They stem from observations of brain blood flow and metabolism, EEG, and seizures, following hyperventilation (HV) (Caspers & Speckmann, 1972; Gibbs, Williams, & Gibbs, 1949; Kerr, Dalton, & Gliebe, 1937; Penfield & Jasper, 1954; Raichle & Plum, 1972; Withrow, 1972). Brody and Dusser de Barenne (1932) may have been the first of many investigators to have reported inducing seizures with HV, and it has been verified repeatedly (Darrow & Graf, 1945). Gibbs, Lennox, and Gibbs (1940), stated unequivocally that:
Considering all those links between carbon-dioxide and epilepsy, namely that (1) the influence of carbon dioxide on the EEG, (2) the abnormal values of carbon dioxide in arterial and jugular blood of patients with petit mal and grand mal, and (3) the abnormal variation of carbon dioxide preceding grand mal seizures in such a way as to indicate a causal relationship, we may conclude that carbon dioxide plays a significant role in the etiology of epileptic convulsions. (p. 109)

Himwich (1951) supported this position: “In addition to exerting physiological effects, carbon dioxide may also be involved in pathological conditions, for instance, epilepsy” (p. 103). Holmberg (1953) asserted that “hypocapnia is probably the essential factor which produces slow waves in the EEG” (p. 374). Penfield and Jasper (1954) also allowed the possibility that etiological variables might include a spectrum of events broader than just “vasomotor reflexes,” or the prevailing theories of neuronal hyperexcitability: “The possibility that there may be intermediary metabolic defects, or abnormal reactivity of certain cerebral vessels . . . must also be considered. . . . It might be related to migraine . . . or to some obscure metabolic defect” (p. 495). With hypocapnia, they also saw brain arterial vessels “blanching,” but they did not cite Darrow and Graf (1945), who previously had produced it experimentally by HV in cats. The latter must have been astonished at the sight, because they reported, “A striking effect of hyperventilation was the occasional appearance of waves of constriction passing along the vessels, giving them the appearance of sausage links” (p. 456). Penfield and Jasper (1954) actually witnessed what Lennox et al. (1938) had hypothesized (i.e., paroxysms of cerebral arterioles during seizures in the brain exposed to view) and likened it to a small thread tied around the artery. But, they ultimately more or less dismissed vascular and metabolic variables:

The mechanism whereby hyperventilation elicits changes in the EEG and seizures in epileptic patients is still unknown; it may act by causing a partial ischemia due to cerebral vasoconstriction, and there may be some increase in excitability accompanying the lowered CO₂ concentration. (p. 230)

The links between low alveolar CO₂ (hypocapnia), alkalosis, brain arterial paroxysmal vasoconstriction, ictal EEG patterns, and seizures did not turn most investigators toward a metabolic dysfunction theory of the seizure etiology. Even today, neurophysiological theory of the etiology of idiopathic seizures involves the hypothetical destabilization of one or more hyperexcitable brain neurons, which, in concert, recruit surrounding such neurons until a critical mass has been achieved. Such a critical mass of destabilized neurons is thought to result in the local paroxysmal discharge called a focus, though in some cases it may involve the brain as a whole. The destabilization of the neurons is attributed by some to indeterminate chemical factors, which alter cell membrane characteristics. The seizure terminates when the activity is exhausted:

Review of the literature reveals that most experimental studies are concerned with the problem of initiation. . . . It is well known that seizure activity is accompanied
by a considerable increase in energy metabolism of the brain. . . . [I]t has been suspected that each convulsive discharge outlasting a certain period ceases automatically when the supply of energy is exhausted. . . . [P]articular attention has been directed to changes in gas tension in blood and tissue. (Caspers & Spec­kmann, 1972, p. 699)

This *hybrid* tells us that seizures end because they are self-terminating; but, in case they do not, they run out of steam—steam lost because of blood gas levels. In such theories, seizure activity is likened, by analogy, to the action potential of individual neurons, but on a grand scale.

The search for metabolic etiology has led many to compare biochemical factors in seizure sufferers and nonsufferers, reporting detectable differences (Batt et al., 1975; Davis & Wallace, 1941, 1942; Faurbye, 1943; Glaser, 1979; Groen, 1975; Himwich, 1951; Ikonomoff, 1970; Laidlaw & Richens, 1976; Latham, 1975; Lowenthal, 1965; Lubin & Price, 1942; Madsen, 1943; Meyer & Waltz, 1961; Millichap & Ulrich, 1962; Shinozaki & Furutani, 1968). It would not add immeasurably to this report to detail each finding. But, the most consistent is that concerning the body's CO₂ economy and the acid–base balance of the blood.

THE EFFECT OF CO₂ ON THE EEG AND SEIZURE THRESHOLD

It has been known for over 50 years that arterial blood CO₂ concentration (PaCO₂) is the most powerful intrinsic influence on cerebral blood flow and metabolism (Gibbs et al., 1940; Himwich, 1951; Holmberg, 1953; Lennox et al., 1938; Meyer & Waltz, 1961). Some maintained that the autonomic nervous system (ANS) plays little role in cerebral vasotonus, and that CO₂, therefore, is the only such factor (Heistad, Marcus, & Abboud, 1978).

Figure 2.1 shows the relationship between cerebral blood flow (CBF) and PaCO₂. At normal PaCO₂—38 torr (about 5%)—CBF is about 45 cc/100g/min. When PaCO₂ decreases to 30 torr, a value commonly observed in chronic HV (Fried, 1987a, 1992), CBF drops to about 35 cc/100g/min—a decrease of over 20%.

Figure 2.2 shows the relationship between pulmonary (alveolar) ventilation and alveolar and blood CO₂, O₂, and blood pH levels. *Alveolar ventilation* (i.e., respiration volume) is conventionally expressed as minute volume (Vmin), and is given here in liters/minute. When ventilation increases above the reference norms line at a little below 5.4 l/min, alveolar CO₂ (PCO₂), (A), and arterial blood CO₂ (PaCO₂), (B), decrease; oxyhemoglobin (OHb) saturation (SaO₂), (C), remains constant, although alveolar O₂ concentration (PO₂), (D), rises; and pH rises (alkalosis), (E). With increased Mv, PCO₂ and PaCO₂ decrease; SaO₂ remains unchanged, whereas pH rises. Some investigators erroneously focus on
breathing rate (RR) as the measure of HV. Although logically related to pulmonary ventilation, varying activity level makes it an unreliable measure of CO₂ loss. For instance, an individual who is running and breathing rapidly to reduce excess CO₂, or one with metabolism accelerated by cocaine, is not hyperventilating simply because he or she may be breathing rapidly (hyperpnea).

Cerebral blood flow is affected directly by alkalosis. Figure 2.3 shows the
relationship between CBF and pH: At normal alveolar ventilation, arterial blood pH is about 7.38, and CBF is about 45 cc/100g/min. If alveolar ventilation doubles—which is not uncommon in chronic HV—arterial blood pH rises to 7.6 (see Fig. 2.2) and CBF drops to about 35 cc/100g/min—a little over 20%. There is a parallel relationship between alveolar HV and arterial blood CO₂ in their adverse effect on CBF. This adversity is aggravated further by the
effect of alkalosis on the OHb-dissociation curve (Bohr-effect).

In 1904, Bohr, Hasselbach, and Krogh noted the effect of blood CO₂ concentration on the affinity of hemoglobin (Hb) for O₂. CO₂, contributing to the acidification of blood by biochemically affecting its concentration of hydrogen ion (H⁺), and therefore its acid–base balance, is critical in Hb function. Figure 2.4 shows the OHb-dissociation curve (ODC) at three values for pH. When pH rises, the curve shifts to the left; when it drops, the curve shifts to the right. A left-shifted ODC means higher affinity, which is detrimental to metabolism because O₂ and Hb are more tightly bound and therefore less is released to tissues. A right-shifted ODC favors O₂ release. According to Woodson (1979), one of the reasons for an acute increase in in vivo oxygen affinity in man is respiratory alkalosis due to inadvertent HV. He added, "Hyperventilation may likewise be hazardous, because, in addition to increasing oxygen affinity, it appreciably reduces cerebral and coronary blood flow" (p. 372).

Other pH-dependent factors further jeopardize the O₂ transport system. Alkalosis promotes decreased red blood cell calcium efflux, making them rigid and less able to traverse capillaries; and increased production of organic phosphates, including 2,3-diphosphoglycerate (DPG), which competes with O₂ for binding on

FIG. 2.4. Oxyhemoglobin (OHb) dissociation curve (ODC).