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Biofeedback in the Treatment of Epilepsy

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Abstract

This review traces the origin of the clinical application of EEG operant conditioning, or biofeedback, from empirical animal research to its emergence as an alternative treatment for the major types of seizure disorder. Initial animal studies that were focused on brain mechanisms mediating learned behavioral inhibition revealed a uniquely correlated 12-15 Hz EEG rhythm localized to sensorimotor cortex. We labeled this as the sensorimotor rhythm, or SMR. The similarity of the SMR to the known EEG "spindle" pattern during quiet sleep, both of which were associated with a state of motor quiescence, led to the novel idea of attempting to increase the SMR using EEG operant conditioning. It was hypothesized that this might produce a corresponding increase in sleep spindle activity, thus establishing a common underlying mechanism for this state. Results supported this hypothesis but also led accidentally to the discovery of an anticonvulsant effect as well. Continuing animal studies identified a physiological pattern of responses correlated with the SMR in primary motor pathways. Additionally, bouts of oscillating cellular discharge in the afferent somatosensory thalamic nuclei were found to mediate the cortical SMR pattern. All of these findings were indicative of reduced motor excitability. Simultaneously, we undertook a series of studies in human epileptic subjects which documented a significant reduction in seizure incidence and severity, together with EEG pattern normalization. This work expanded internationally, resulting in numerous well-controlled group and single case studies that are summarized in several recently published meta analyses of efficacy findings in this field. Further, exciting new findings in fMRI/EEG correlation studies have provided a rational model for the basis of these clinical effects. However, in recognition of the diversity of clinical applications of this method in general, and the complexity of seizure disorders in particular, the specific methods used in this authors program are reviewed here in detail.

Background

The attempt to alter EEG frequency/amplitude patterns and their underlying brain mechanisms

using contingent operant conditioning methods is today referred to variously as EEG biofeedback, neurofeedback, or neurotherapy. This application was officially added to the broader field of biofeedback with the publication in 1972 of a paper by Sterman and Friar titled "Suppression of seizures in an epileptic following sensorimotor EEG feedback training". [1] A sustained and progressive reduction of generalized nocturnal tonic-clonic seizures was documented in a 23 year old female epileptic with a 7 year history of frequent medically refractory seizures of unknown origin. Her clinical EEG showed left sensorimotor cortex spikes and slow 5-7 Hz activity. Seizure reduction occurred in response to an experimental course of EEG operant conditioning to increase 12-15 Hz EEG activity in left sensorimotor cortex, while suppressing slower activity at this same site. The 12-15 Hz EEG rhythm was discovered in animal research, and labeled as the Sensorimotor Rhythm, or SMR. Despite having previously been worked up and treated unsuccessfully with anticonvulsant medications at several prestigious medical institutions, during 2 years of twice per week EEG feedback training sessions she became essentially seizure free and was ultimately issued a California drivers license (fig.1).

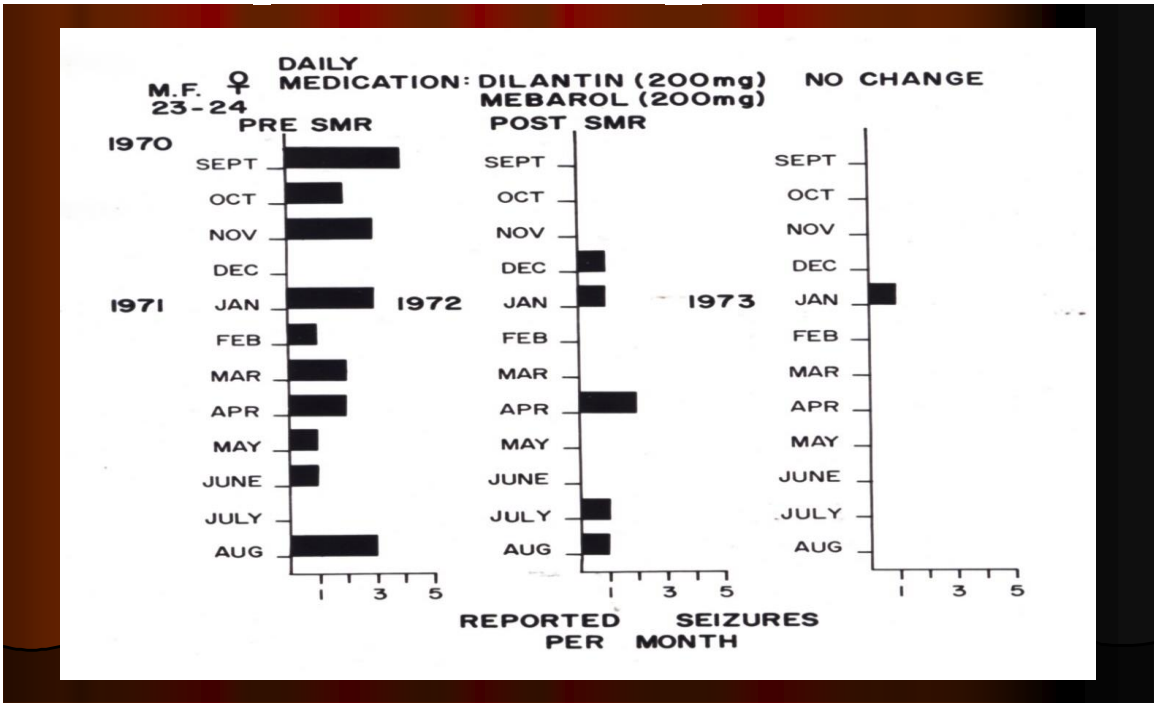

Figure 1. Carefully documented three-year seizure log data from an adult female subject with nocturnal tonic-clonic seizures, often with incontinence. These data document a progressive reduction of seizures after the initiation of EEG feedback training for increased 12-15 Hz sensorimotor cortex activity. In 1974 this patient was issued a California drivers license. (Modified From [2])

This landmark study was predicated on the observation of a discrete 11-19 Hz EEG rhythmic pattern in cats, which occurred intermittently over sensorimotor cortex during behavioral quiescence. When animals were trained to suppress a learned bar-press for food if a tone was sounded in the chamber a 12-15 Hz version of this EEG pattern always accompanied inhibition of the bar-press response. If animals later fell asleep, a similar rhythmic EEG pattern, known as

the sleep spindle, was seen to be localized to the same cortical area at the same frequency (fig. 2). Our interest at the time was in the neurophysiological control of sleep. Since both of these patterns occurred uniquely in the absence of movement, we sought to determine if the underlying neural mechanisms were related.

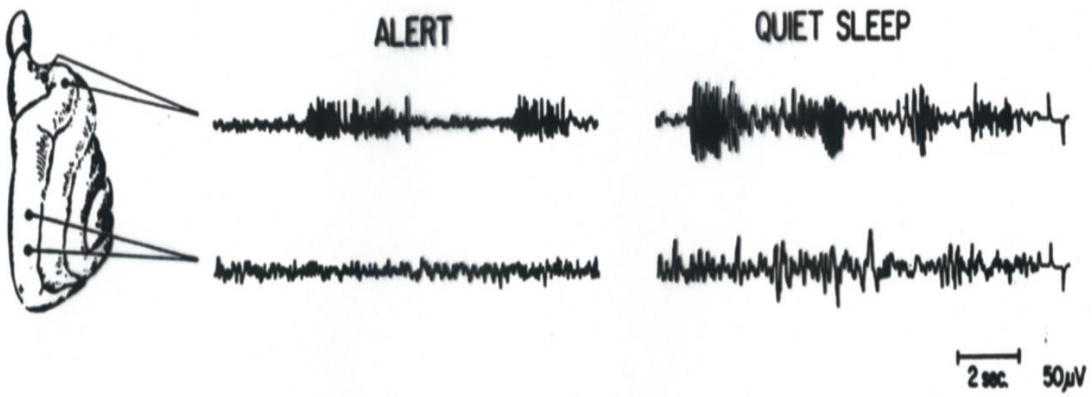

Figure 2 Bipolar EEG samples from sensorimotor and parietal cortex in the cat during quiet (motionless) wakefulness (left) and quiet (non-REM) sleep (right). Both states are associated with bursts of 12-15 Hz EEG rhythmic activity in sensorimotor cortex. During sleep these bursts are higher in amplitude and associated with slower rhythmic patterns in parietal cortex. (From [3])

To accomplish this we attempted to facilitate the SMR during wakefulness using an operant conditioning paradigm with a liquid food reward, and study the changes in sleep spindle activity and sleep structure that might result. Necessary quality controls included alternate training to suppress this rhythm, and a counterbalanced design employing two separate groups of cats. Six weeks of 3 training sessions per week to satiation led to profound and differential changes in sleep EEG and sleep architecture. SMR training, whether it preceded or followed suppression training, led to a significant increase in EEG sleep spindle density, as well as a significant reduction in sleep period fragmentation due to arousals [3]. No changes occurred in the control condition.

As interesting as this finding was the most profound outcome of the study emerged later. A different cat study underway in our laboratory, funded by the US Air Force, was seeking to determine the effects on behavior of low dose exposure to monomethyl hydrazine [4]. This compound is a highly toxic component of the liquid rocket fuel used for launching virtually all space vehicles. Significant exposure via any route causes profound nausea and the gradual onset of convulsions, which at adequate doses are lethal. The mechanism for this effect was ultimately determined to be a disruption of the synthesis of GABA, the primary inhibitory neurotransmitter in the Central Nervous System. We were investigating the effects of low dose exposure in order to determine the possible disruption of cognitive functions such exposure might cause in flight crews. Our first objective for studies in cats was to establish the dose-response curve for convulsive effects in this species. We had succeeded in determining a curve showing that 9 mg/kg of MMH was the threshold dose for producing non-lethal convulsions reliably after a

prodrome of approximately 40-67 minutes. This prodrome consisted of a sequence of reliable autonomic and behavioral events. When data from animals provided with SMR operant conditioning as the final training procedure were added to this curve the same prodrome was observed but there were no seizures at 60 minutes. Instead, the latency to seizures was delayed to a range of 80-220 minutes, and several animals failed to seize at all[4]. A subsequent systematic study of this effect with animals as their own controls in a counterbalanced design confirmed this effect (fig. 3). This finding then led to the test in the human epileptic subject described above.

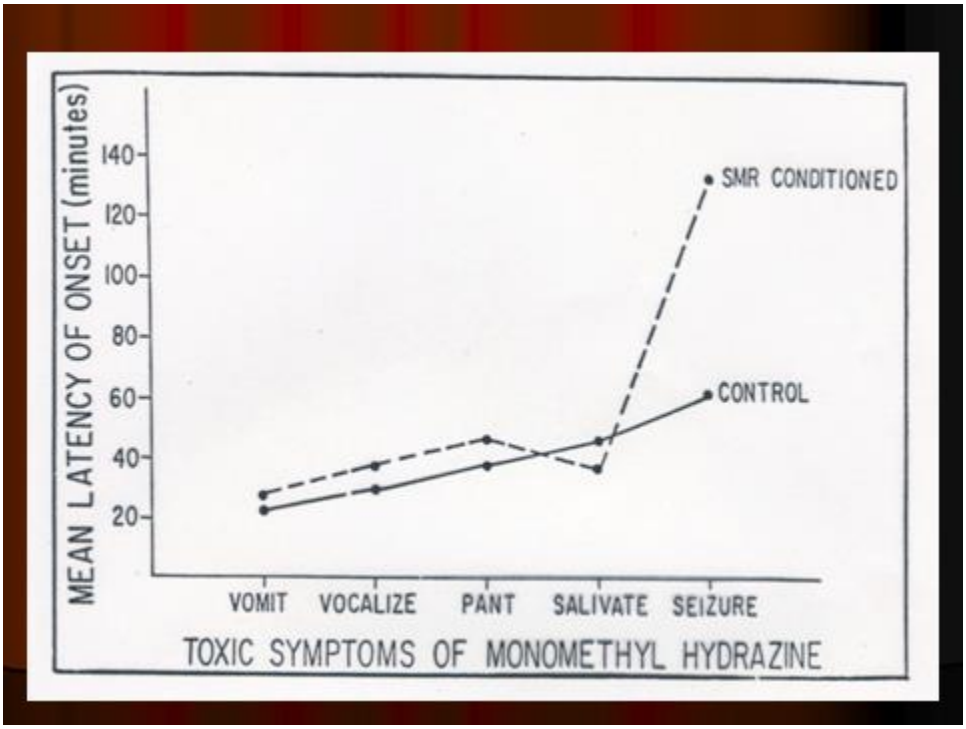

Figure 3. The sequence of prodromal events preceding generalized convulsions is shown here for two groups of 10 cats each injected intra-abdominally with 9 mg/kg of GABA depleting monomethyhydrazine. One group (dashed curve) had received 6 weeks of EEG feedback training for SMR enhancement with food reward, as described here. The two groups did not differ statistically in the latency to prodromal symptoms. All control animals seized reliably at approximately 60 minutes, as had been previously documented. However the SMR trained group had a significantly prolonged mean latency to seizures of 130 min., and several did not seize within the 4 hour test period. (Modified from [5]).

These two studies provided several interesting conclusions which directed our subsequent scientific efforts. First, in the cat study, we had observed a common prodrome in both SMR trained and control animals, despite the fact that the SMR trained animals had acquired protection against seizures. This suggested a direct effect on the seizure process and not on MMH toxicity in general. Secondly, in our human epileptic patient, the seizures which were suppressed arose out of the unconscious state of sleep, a fact which eliminated the possibility of any voluntary countermeasure, and again indicated a direct effect on the seizure mechanism. Accordingly, we under-took a dual approach to understanding the basis of this effect, involving both additional animal electrophysiological and human clinical studies.

Animal studies evaluated motor behavior, motor reflexes', motor and thalamic unit firing, and somatosensory pathway correlates of the SMR response. Clinical studies sought to further document the anticonvulsant effects of SMR operant conditioning, and to examine this effect on various seizure types. Possible alternative explanations such as altered medication compliance and placebo effects were also addressed in several **c**omprehensive studies. Additionally, by this time, other laboratories were beginning to add to the research literature in this new field.

Neurophysiological studies in cats revealed a convergent pattern of changes that were directly correlated with the SMR pattern in the EEG, and clearly indicated reduced motor excitability. These included a specific attenuation of cellular activity and reflex excitability in the motor pathway, a reduction in muscle tone and associated motor unit firing, and the cessation of behavioral movements. Further, unit studies in afferent nuclei of the somatosensory pathway revealed evidence of reduced somatic afferent firing and the onset of reciprocal burst oscillation between the thalamic reticular nucleus and the adjacent ventrobasal relay nucleus. This oscillation provides the thalalmic source of the cortical SMR pattern. These findings are summarized in figure 4. Details of the studies and resulting publications are provided in recent review articles [6-8]. They represent empirical evidence for significant reorganization of neuronal function during when SMR activity appears in the sensorimotor EEG.

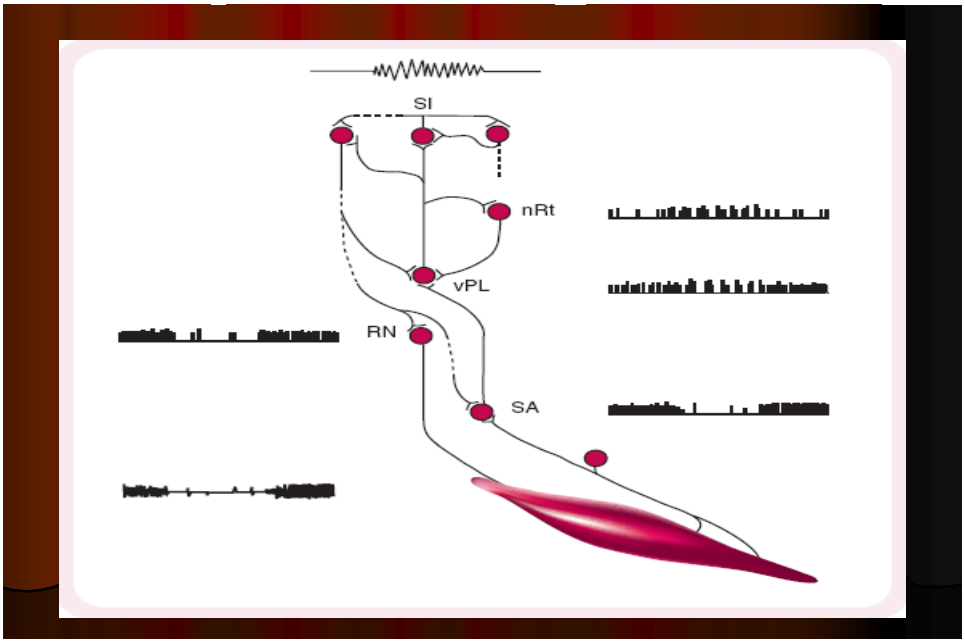

Figure 4. Trained SMR responses were associated with changes in both afferent and efferent pathways of the sensorimotor system. These included decreased red nucleus (RN) activity, stretch reflex excitability, and muscle tone. These changes produce reduced somatic afferent (SA) discharge, and lead to thalamic hyperpolarization and reciprocal oscillatory burst activity between the ventrobasal (VPL) and reticular (nRt) nuclei of the thalamus. This burst activity is propagated to sensorimotor cortex (S1) and initiates corresponding bursts of SMR activity [9].

Clinical Studies

A series of human studies followed our initial clinical report, including group studies involving crossover and placebo controlled designs. These studies consistently reported significant seizure reductions in epileptic patients in response to reward for increasing sensorimotor EEG rhythmic activity. Two independent meta analyses of the peer-reviewed, published papers in this literature have appeared in the last decade. Sterman[7] reviewed 24 studies involving 243 mostly partial complex seizure patients provided with central cortical SMR feedback training, and determined that 82% of these subjects registered seizure reductions greater than 50%. Tan et al.[10] evaluated data from 63 studies and selected 10 for comprehensive evaluation that met stringent criteria for controls and population and seizure details. They report that 79% of the patients treated with SMR feedback training experienced a statistically significant reduction in seizure frequency, despite a collective history of failed medication therapy.

Data from one of the studies [11] evaluated in both reviews are summarized in figure 5. Here, 24 complex-partial subjects, many with seizure foci confirmed through depth recordings, were randomly assigned to three experimental treatment groups. One group simply tabulated their seizure experiences for 6 weeks using a comprehensive seizure logging method. A second group received EEG feedback training for one hour three times a week for 6 weeks. However, the EEG signal responsible for reward was previously recorded from a different individual. This non-contingent feedback constituted a "yoked control" group. The third group received 6 weeks of contingent training for increasing SMR activity in somatosensory cortex while simultaneously suppressing slower 4-8 Hz activity. After the initial 6 weeks all 24 subjects were combined into one group that received 6 more weeks of contingent training only. This was followed by a 4 week period of gradual withdrawal from training, and then a final tabulation of seizure incidence during a 6 week period after training was terminated. As can be seen in figure 5, enhanced seizure tabulation resulted in an increased seizure count, yoked-control, non-contingent SMR training produced no significant change in seizure incidence, and contingent SMR training resulted in a significant reduction in seizures. This statistical reduction increased progressively as subjects from the other two groups were added to a second 6 week period of contingent training, and after an additional 6 weeks post-withdrawal from training. In addition to this exclusive seizure reduction after SMR contingent training, pre-post neuropsychological testing showed that responding SMR trained subjects also improved significantly in performance of tasks specific to the hemisphere contralateral to their fronto-temporal lesion, indicating a reduced corrosive disturbance from the seizure focus.

EEG operant conditioning methods for EEG biofeedback training have diversified as differing hardware and software products have emerged, and as individuals with differing backgrounds and credentials have entered the field. A lack of methodological standards and professional regulations has contributed to an undesirable inconsistency in the competence and effectiveness of therapeutic applications. Nevertheless abundant peer-reviewed research conducted by qualified individuals has proven the worth of this method as a viable alternative treatment for seizure disorders. As a result, an attempt will be made here to provide some idea of a systematic and evidence-guided approach to treatment, as used in the authors program.

Patients are subjected to a quantitative multi-channel EEG evaluation (QEEG), using hardware and software complying with both technical and learning theory principles critical to valid data collection and operant conditioning applications. Data obtained from this study are combined with medical reports from other studies and information gained in a comprehensive intake interview. QEEG and background information guide the design of an empirical protocol, often with several training components, that will be used consistently throughout the treatment period, in our case consisting of one or two 60-90 minute treatment sessions per week for at least 20 weeks. Subjects are seated in front of a large monitor screen and instructed on the requirements for reward. Reinforcement consists of visual images and tones, as well as a numeric display of scores achieved and the time remaining in a trial. On rare occasion a committed parent may be seated next to a more challenged patient and provide additional reinforcement in the form of earned treats, such as raisins and M&Ms (fig.6).

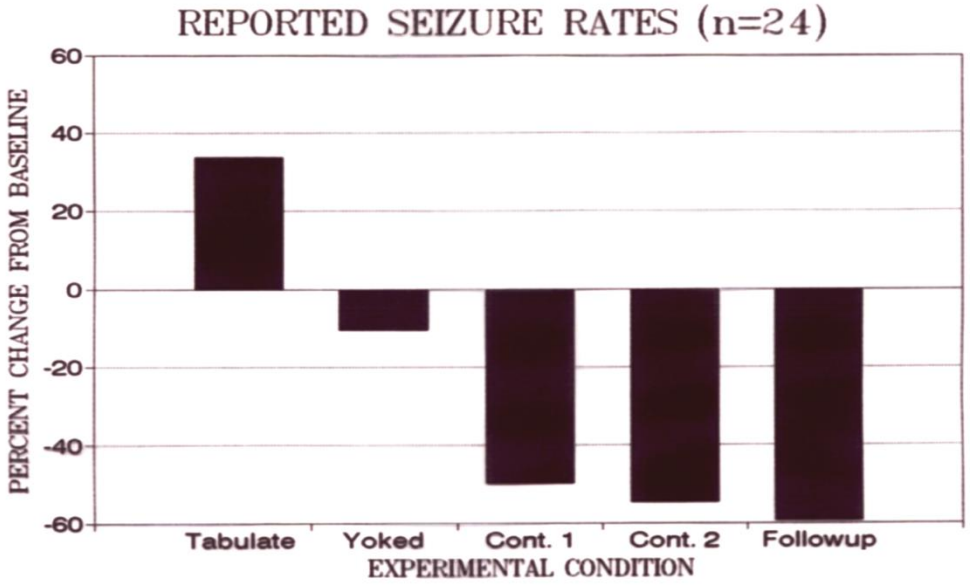

Figure 5. Plot of reported seizure rates in three experimental groups of 8 randomly assigned complex-partial epileptic subjects with medication-refractory seizures. The groups received one of the following treatments each for 6 weeks, including 1) detailed tabulation of seizures, 2) non-contingent SMR ("yoked") training , and 3) contingent SMR training. Following this initial period all 24 subjects were combined into one SMR contingent training group for 6 additional weeks, and then gradually withdrawn from training. A final 6 week follow-up seizure tabulation period completed this analysis. Data are plotted against group baselines. A significant reduction in seizures was registered after contingent training only, and this effect increased progressively across subsequent conditions. (Modified from [11]).

The display that subjects see can vary within limits but must always be as simple as possible and must provide information exclusively relevant to achieving the desired EEG changes. One such display is shown in figure 7. It consists of a series of 4 rectangular boxes, each with a segment of band-passed EEG data for selected frequency bands and enclosed by reward threshold guidelines. If the objective is to increase the amplitude and/or incidence of a particular

frequency band the band-pass display must exceed the upper threshold guideline. If it is to suppress that frequency band it must drop below the threshold line. The duration of the required response can be adjusted and is typically a quarter to one-half of a second. When the desired response is achieved a small horizontal bar at the upper right of each band-pass display turns from red to green, and a large blue ball appears above the band-pass, together with a chime or other tone. The display is frozen for 2 seconds and then becomes active again, thus providing for discrete trials. A yellow score bar at the bottom of the screen advances one unit. The timing of each performance set (typically 3 min.) is indicated by a moving blue bar at the bottom of the screen.

Figure 6. This 12 year old female patient has suffered from frequent multiple seizure types and myoclonic jerks since early childhood. She has not responded to pharmacologic treatments. She currently functions at about 3rd grade level but is aware and behaviorally compliant. Here she is responding to visual feedback in an SMR training context. Her mother is assisting by providing raisin and M&M rewards when certain response criteria are achieved. Her seizures have declined in frequency and severity.

With each box monitoring the same electrode site and each frequency tuned to the same band thresholds can be set to promote facilitation or suppression through "successive approximation", or sequencing from left to right with sequentially more difficult thresholds. Numerous other configurations are possible. In the case shown in figure 7 the band-pass at far left is set at 12-15 Hz (SMR) for the C3 electrode site, and the remaining three bands to the right set to 3-5 Hz at left medial frontal location Fz, with successively lower threshold to promote suppression of this band at this site.

Performance outcome is measured systematically by tracking scoring rate per trial together with associated EEG patterns. Data from the case described above provide an example. Figure 8 at top shows a plot of reward rate across 4 successive three-minute EEG feedback trials. The patient was rewarded for simultaneously increasing 12-15 Hz SMR activity at C3 and reducing 3-5 Hz activity at Fz, as described above. Smoothed EEG plots for the targeted frequency bands are shown below these reward curves, starting with the C3 12-15 Hz channel. Activity in this band became increasingly stable across trials. Data from three frontal recording sites are also shown, with the targeted Fz 3-5 Hz band output at the bottom. Amplitudes decreased progressively at all frontal sites but most markedly at the bottom Fz location. Thus, SMR stabilization and simultaneously suppressed frontal slow activity resulted in progressively a pattern of incremental reward both within trials and across the session. The resulting profiles are indicative of learning.

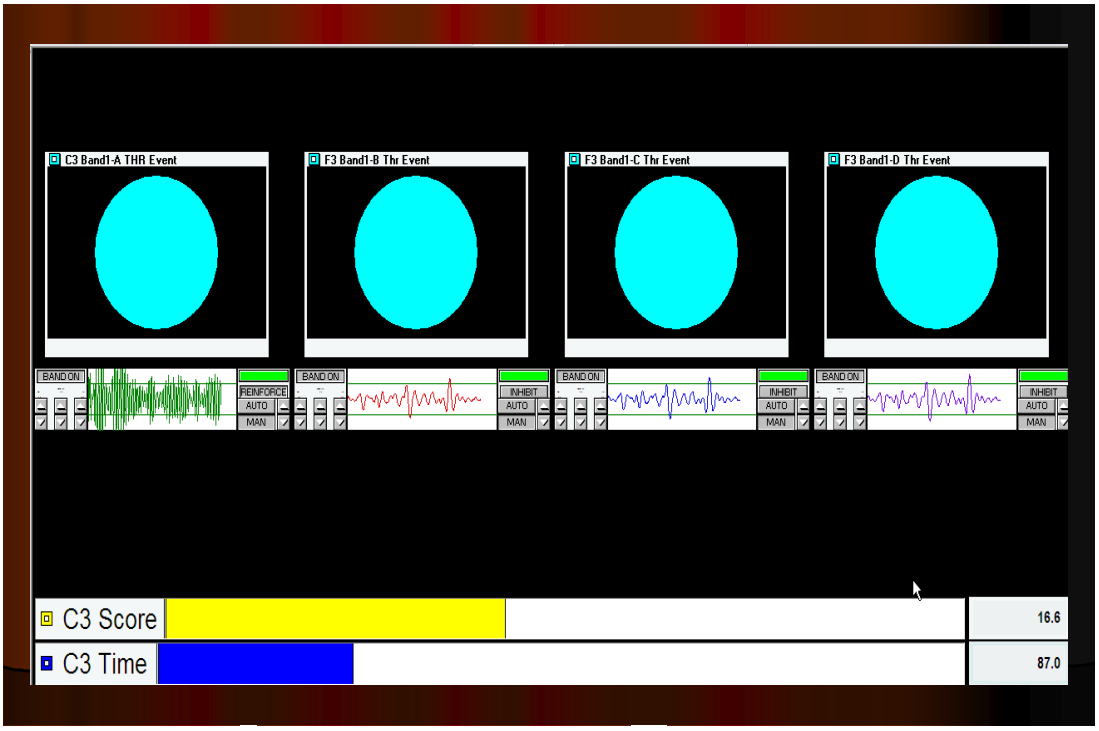

Figure 7. This primary display used in our SMR biofeedback program conforms strictly to operant conditioning principles, while still promoting cognitive engagement in the human subject. Reward here is for 2 different EEG frequencies at 2 different cortical sites. The Far left "green" site shows reinforced 12-15 Hz band-pass activity at C3. Low frequency suppression of abnormal 3-5 Hz slow activity at Fz is addressed here through "successive approximation", and consumes the final 3 display units from left to right. See text for more details. This subject is described in figure 6.

While it is difficult to evaluate neurophysiological changes in human subjects similar to what was accomplished with animals, certain parallels can be drawn. Further, new imaging methods

allow for assessment of localized metabolic changes in the human brain during and after EEG feedback training. Behaviorally, during successful SMR training, human subjects become behaviorally quiet and direct their attention to the task. It is safe to presume that the SMR response develops as a result of reduced motor excitation and resulting intra-thalamic ventrobasal oscillations, since this mechanism is well established as a basis for mammalian sensorimotor EEG rhythm generation [12]. These changes, as well as others documented in our animal studies, set the stage for the development of SMR activity, and are likely collectively initiated by altered input from some other executive system. Several recent studies have suggested a specific pattern of motor inhibition output from the striatum of the basal ganglia as the source of these changes. Birbaumer (personal communication, 2005) observed increased striatal metabolic activity with fMRI analysis in subjects producing SMR activity. Further, Bouregard and Levesque [13] studied pre-post fMRI BOLD response patterns in learning disabled children trained to increase SMR activity and found a specific increase in the metabolic activity of the striatum and substantia nigra. The SMR trained subjects showed significant academic improvement as well.

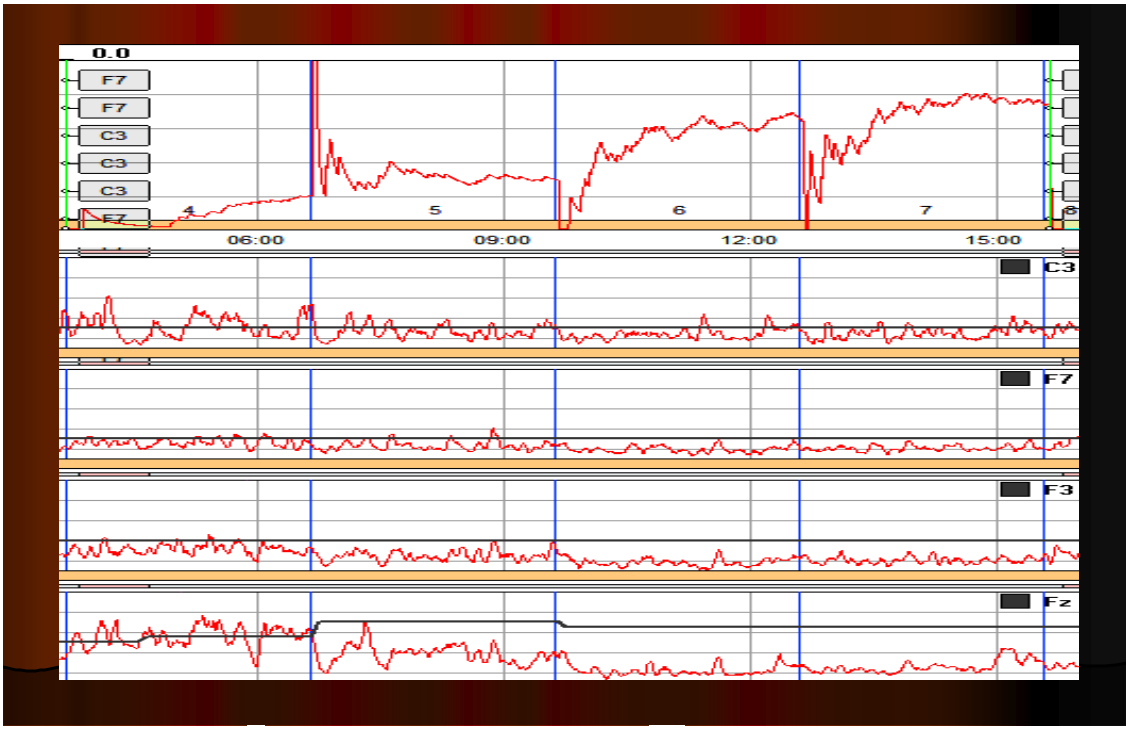

Figure 8. This performance plot from the patient and feedback display shown above registers scoring rate per 3 minute trial at top, and corresponding smoothed amplitude output in the band-passed frequencies set for each electrode placement. In this case the patient was rewarded for increasing 12-15 Hz SMR activity (top EEG trace), and decreasing 3-5 Hz slow activity at Fz (bottom EEG trace) The subject showed response acquisition both within and across 3 min. feedback trials, together with a stabilization of the SMR frequency and a reduction in frontal slow activity.

These facts provide a rational model for a threshold altering process that could affect seizure discharge propagation to motor networks. Although there are many different neurotransmitters

used within the basal ganglia (principally ACh, GABA, and dopamine), the overall effect on thalamus and pre-motor networks in the mesencephalic tegmentum and superior colliculus is inhibitory [14-16]. If activation of these inhibitory basal ganglia networks can become labeled by the SMR through contingent feedback training, and responsable circuits potentiated by this association, motor inhibitory regulation would be generally facilitated.

Conclusions

Despite the encouraging findings and concepts reviewed here it must be remembered that there are significant issues at virtually every step of the thinking and practice behind this new therapy. This method depends on a comprehensive understanding of the EEG signal and the technical requirements of valid quantitative analysis and feedback applications. This includes a basic knowledge of the principles essential for effective operant conditioning, Further, due to the complexity of seizure disorders, accurate history and seizure classification must be evaluated and understood.

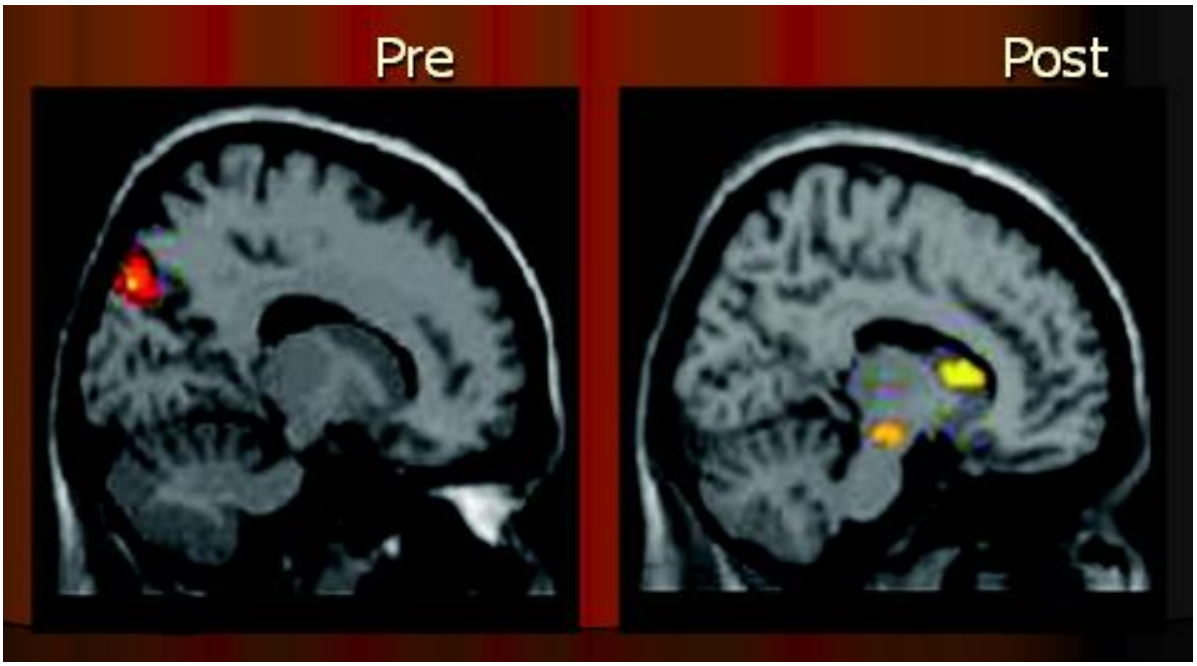

Figure 9. Functional MRI images shown here are sagittal sections for the data averaged across experimental subjects in a study comparing experimental (SMR feedback training) and control (no feedback training) groups. In the pre-treatment condition significant loci of activation were noted in the left superior parietal lobe for both control and experimental groups. In the post training condition activations were again seen in this cortical region for both groups. In addition, however, the experimental group also showed stronger and statistically significant loci of activation in the left striatum and substantia nigra. (Modified from [13]).

Alternative explanations for therapeutic results include such considerations as short-lasting expectation effects, and changes in patient behavior. However, we must once again point out that

the prolonged anticonvulsant effect documented in our animal studies, and in relation to nocturnal seizures arising out of sleep in a human subject, would seem to rule out placebo or non-specific effects. This conclusion is supported further by the finding of improved neurosychological performance after SMR training in tasks mediated by the hemisphere contralateral to disrupting localized epileptogenic lesions. Additionally, an alternative explanation for improved seizure control based on increased medication compliance has been rejected through studies that carefully monitored blood levels of prescribed anticonvulsant drugs before, during, and after training.

Finally, the epileptic patients who have demonstrated clinical improvement in neurofeedback research studies, and many who seek this treatment today, represent unquestionable failures of anticonvulsant drug therapies. It is particularly noteworthy that positive outcomes have often been obtained treating complex-partial seizure disorders, an extremely difficult sub-population of epilepsy patients. We view it as unfortunate, therefore, that some professionals still criticize neurofeedback treatment for the lack of more consistent or successful outcomes. On the contrary, as noted here, evidence has shown that most of these difficult patients benefit beyond any chance or placebo outcome, and some do so dramatically. Considering the common side effects and costs associated with life-long pharmacotherapy, we do not view neurofeedback treatment as a "last resort" option for drug treatment-resistant cases only, but rather as a generally viable alternative consideration for any patient suffering from seizures. Furthermore, in contrast to drug-dependent symptom-management, the altered modulation of striatal and thalamocortical inhibition through neurofeedback training may raise seizure thresholds sufficiently to greatly improve the prospects for the long-term, nondependent management of epilepsy.

References

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

2. Sterman, MB Neurophysiologic and clinical studies of sensorimotor EEG biofeedback training: Some effects on epilepsy. In: L.Birk (Ed.), Biofeedback: Behavioral Medicine 1973; Grune and Stratton, New York (Chapter 9): Reprinted In: Seminars in Psychiatry 1973; 5(4):507-525.

3. Sterman, MB, Howe, RD, Macdonald, LR. Facilitation of spindle-burst sleep by conditioning of electroencephalographic activity while awake. Science 1970; 167:1146-1148.

4. Sterman, MB, LoPresti, RW, Fairchild, MD. Electroencephalographic and behavioral studies of monomethyl Hydrazine toxicity in the cat. Aerospace Medical Research Laboratory 1969; AMRL-TR-69-3:1-8.

5. Sterman, MB. Studies of EEG biofeedback training in man and cats. In: Highlights of 17th Annual Conference: VA Cooperative Studies in Mental Health and Behavioral Sciences 1972; 50-60.

6. Sterman, MB. Physiological origins and functional correlates of EEG rhythmic activities: Implications for self-regulation. Biofeedack. Self Reg. 1996; 21:3-33.

7. Sterman M.B. Basic concepts and clinical findings in the treatment of seizure disorders with EEG operant conditioning. Clin. Electroenceph. 2000; 31(1):45-55.

8. Egner T, Sterman MB. Neurofeedback treatment of epilepsy: From basic rationale to practical application. Expert Reviews in Neurotherapeutics, 2006; 6:247-257

9. Sterman, MB, Bowersox, SS. Sensorimotor EEG rhythmic activity: A functional gate mechanism**.** Sleep 1981; 4(4):408-422,

10. Tan, G, Thornby, J, Hammond, D, et al. Meta-analysis of EEG biofeedback in treating epilepsy. Clin. EEG Neurosci. 2009; 40(3):173-179.

11. Lantz, D, Sterman, MB. Neuropsychological assessment of subjects with uncontrolled epilepsy: effects of EEG biofeedback training. Epilepsia 1988; 29 (2):163-171.

12. Steriade M, McCormick DA, Seinowski TJ. Thalamocortical oscillations in the sleeping and aroused brain. 1993, Science, 262: 679-685.

13. Levesque J, Beauregard M, Mensour Boualem. Effect of neurofeedback training on the neural substrates of selective attention in children attention-deficit/hyperactivity disorder: A functional magnetic resonance imaging study. Neuroscience Letters 2006; 394:216-221.

14. Brodal P. The basal ganglia. In: The Central Nervous System: Structure and Function. Oxford University Press 1992: New York: 246-261.

15. Chevalier G, Deniau JM**.** Disinhibition as a basic process in the expression of striatal functions. Trends Neurosci. 1990; 13:277-280.

16. DeLong M.R. Primate models of movement disorders of basal ganglia origin. Trends Neurosci. 1990; 13:281-285.