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Biofeedback in the treatment of epilepsy

ABSTRACT

This review traces the application of electroencephalographic (EEG) operant conditioning, or biofeedback, from animal research to its emergence as an alternative treatment for the major types of seizure disorder. Initial animal studies focusing on brain mechanisms that mediate learned behavioral inhibition revealed a uniquely correlated 12- to 15-Hz EEG rhythm localized to sensorimotor cortex. We labeled this the sensorimotor rhythm, or SMR. The similarity of the SMR to the known EEG spindle pattern during quiet sleep led to the novel idea of attempting to increase the SMR using EEG operant conditioning. The hypothesis was that this might produce a corresponding increase in sleep spindle activity, thus establishing a common EEG marker for the state of motor inhibition. Results supported this hypothesis but led also to the accidental discovery of an anticonvulsant effect on drug-induced seizures in cats and monkeys. Continuing animal studies identified a pattern of neurophysiologic responses correlated with the SMR in primary motor pathways. These and other findings were indicative of reduced motor excitability. Simultaneously, we undertook studies in human epileptic subjects that 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 summarized in recent meta-analyses. Exciting new findings in functional neuroimaging/EEG correlation studies provide a rational model for the basis of these clinical effects. In recognition of the diversity of clinical applications of EEG biofeedback and the complexity of seizure disorders, this review also details specific methods used in our EEG biofeedback program.

The attempt to alter electroencephalographic (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 article traces the history of the clinical application of EEG operant conditioning from empirical animal investigations to its emergence as a treatment option for major seizure types. In light of the diversity of the clinical applications of this method in general, and the complexity of seizure disorders in particular, I also present an overview of specific methods used in our EEG biofeedback program.

INITIAL APPLICATION IN HUMANS

This application was officially added to the broader field of biofeedback with the publication of a 1972 paper by Sterman and Friar titled, "Suppression of seizures in an epileptic following sensorimotor EEG feedback training."[1] In this paper we documented a sustained and progressive reduction of generalized nocturnal tonic-clonic seizures in a 23-year-old female epileptic with a 7-year history of frequent and medically refractory seizures of unknown origin. The patient's clinical EEG showed left sensorimotor cortex spikes and slow 5- to 7-Hz activity. Seizure reduction occurred in response to an experimental course of EEG operant conditioning aimed at increasing 12- to 15-Hz EEG activity in the left sensorimotor cortex while suppressing slower activity at this same site. The 12- to 15-Hz EEG rhythm was discovered in animal research and labeled as the sensorimotor rhythm (SMR). Although the patient had previously been worked up and treated unsuccessfully with anticonvulsant medications at several prestigious medical institutions, over the course of 2.5 years of twice-weekly EEG feedback training sessions she became essentially seizure free **(Figure 1)**[2] and was ultimately issued a California driver's license.

BACKDROP TO THE CLINICAL APPLICATION: KEY ANIMAL STUDIES

The above landmark study was predicated on the observation of a discrete 11- to 19-Hz EEG rhythmic pattern in cats, which occurred intermittently over the sensorimotor cortex during behavioral quiescence. When animals were trained to suppress a learned bar-press response for food if a tone was sounded in the chamber, a 12- to 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

FIGURE 1. A carefully documented 6-year seizure data log from an adult female subject (aged 23 years at the start of the log) with nocturnal tonic-clonic seizures, often with incontinence.[2] The log starts 1 year before initiation of electroencephalographic (EEG) feedback training ("Pre-SMR"), continues through 2.5 years of twice-weekly EEG training sessions ("Post-SMR"), and continues through 2.5 years after withdrawal from this training ("Withdrawal"). Training consisted of auditory and visual reward for increased 12- to 15-Hz EEG activity over the left sensorimotor cortex, which has been labeled the sensorimotor rhythm (SMR). Medications were held constant during training and adjusted downward after withdrawal from training. In 1977 this patient was issued a California driver's license.

Reproduced from Sterman MB, "Effects of sensorimotor EEG feedback training on sleep and clinical manifestations of epilepsy." In: Beatty J, Legewie H, eds. *Biofeedback and Behavior;* 1977:176 (figure 7). © 1977 Plenum Press. With kind permission of Springer Science and Business Media.

sleep spindle, was localized to the same cortical area at the same frequency **(Figure 2)**.[3] Our interest at the time was in the neurophysiological control of sleep. Because both of these patterns occurred uniquely in the absence of movement, we sought to determine if the underlying neural mechanisms were related.

To accomplish this, we attempted to facilitate the SMR during wakefulness using an operant conditioning paradigm with a liquid food reward, and then study any resulting changes in sleep spindle activity and sleep structure. Necessary quality controls included alternate training to suppress this rhythm and a counterbalanced design employing two separate groups of cats. Six weeks of three 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. No changes occurred in the control condition.[3]

A more profound finding in the cat

As interesting as this finding was, the most profound outcome of the study emerged later. A different cat study under way in our laboratory, funded by the US Air Force, was seeking to determine the effects on behavior of low-dose exposure to monomethyl hydrazine (MMH).[4] This compound is a highly toxic component of the liquid rocket fuel used for launching virtually all space vehicles. Significant MMH exposure via any route causes profound nausea and gradual onset of convulsions, which are lethal at adequate doses. The mechanism for this effect was ultimately determined to be a disruption of the synthesis of gamma-aminobutyric acid, the primary inhibitory neurotransmitter in the central nervous system. We were investigating the effects of low-dose exposure 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 that species. We had succeeded in determining a curve showing that 9 mg/kg of MMH was the threshold dose for reliably producing
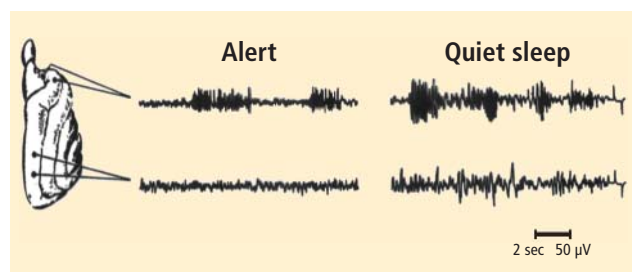
FIGURE 2. Bipolar electroencephalographic (EEG) samples from sensorimotor and parietal cortex in the cat during quiet (motionless) wakefulness (left) and quiet (non-REM) sleep (right). Both states are associated with bursts of 12- to 15-Hz EEG rhythmic activity in sensorimotor cortex. During sleep these bursts are higher in amplitude and associated with slower rhythmic patterns in parietal cortex. Figure reprinted from Sterman et al (Science 1970; 167:1146–1148).[3]

FIGURE 3. The sequence of prodromal events preceding generalized convulsions in two groups of 10 cats, all of which were injected intra-abdominally with 9 mg/kg of GABA-depleting monomethyl hydrazine. One group (dashed tracing) had received 6 weeks of electroencephalographic feedback training for sensorimotor rhythm (SMR) enhancement with food reward (see text). 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. In contrast, the SMR-trained group had a significantly prolonged mean latency to seizures (130 minutes), and several did not seize within the 4-hour test period. Figure modified from Sterman.[5]

nonlethal convulsions after a prodrome of approximately 40 to 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 to 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 **(Figure 3)**.[5] This finding then led to the test in the human epileptic subject described above.[1]

Platform for a dual research approach

These two studies provided several interesting conclusions that directed our subsequent scientific efforts. First, in the cat study we observed a common prodrome in both SMR-trained and control animals even though 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. Second, in our human epileptic patient, the seizures that were suppressed arose out of the unconscious state of sleep, a fact that eliminated the possibility of any voluntary countermeasure and again indicated a direct effect on the seizure mechanism. Accordingly, we undertook a dual approach to understanding the basis of this effect, involving both additional animal electrophysiologic 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, as reviewed in the following section, sought to further document the anticonvulsant effects of SMR operant conditioning and examine this effect on various seizure types. Possible alternative explanations, such as altered medication compliance and placebo effects,
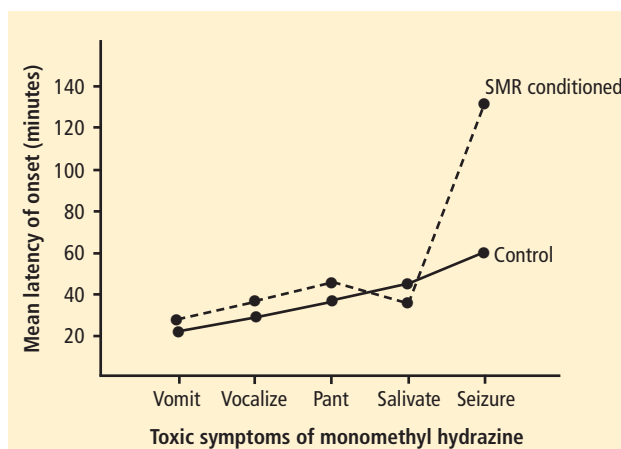
were also addressed in several comprehensive studies. Additionally, by this time other laboratories were beginning to add to the research literature in this new field.

Neurophysiologic 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 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 thalamic source of the cortical SMR pattern. These findings are summarized in **Figure 4**.[6] Details of the studies and resulting publications are provided in recent review articles.[7–9] They represent empirical evidence for significant reorganization of neuronal function when SMR activity appears in the sensorimotor EEG.

■ 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
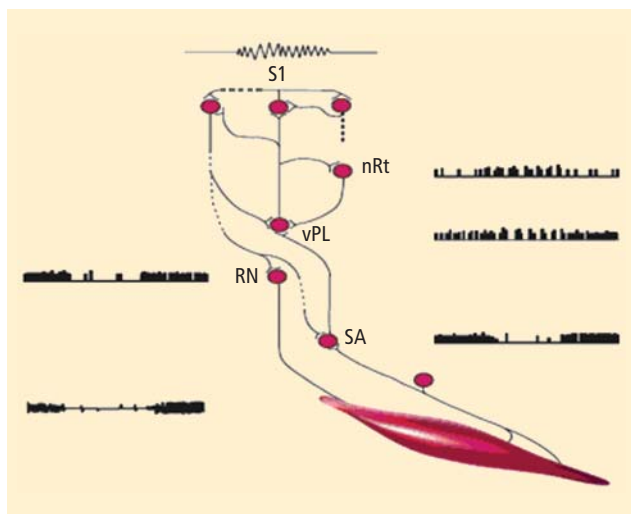
FIGURE 4. Trained sensorimotor rhythm (SMR) responses are associated with changes in both afferent and efferent pathways of the sensorimotor system. These include decreased red nucleus (RN) activity, stretch reflex excitability, and muscle tone. These changes produce reduced somatic afferent (SA) discharge 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.[6]

FIGURE 5. Reported seizure rates in three experimental groups of randomly assigned patients with medication-refractory complex partial seizures.[11] Each group of 8 subjects received 6 weeks of treatment consisting of either (1) detailed tabulation of seizures, (2) noncontingent sensorimotor rhythm (SMR) training ("yoked control"), or (3) contingent SMR training. Following this initial 6-week period, all 24 subjects were combined into one contingent SMR training group for 6 additional weeks and then gradually withdrawn from training. A final 6-week follow-up seizure tabulation period completed the 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. Data are from Lantz and Sterman.[11]

patients in response to reward for increasing sensorimotor EEG rhythmic activity.

Two independent meta-analyses of the peer-reviewed papers in this literature have appeared in the last decade.[8,10] In a review of 24 studies involving 243 patients with predominantly partial complex seizures provided with central cortical SMR feedback training, Sterman determined that 82% of these subjects registered seizure reductions greater than 50%.[8] More recently, Tan and colleagues evaluated data from 63 studies and selected for comprehensive analysis 10 studies that met stringent criteria for controls and population and seizure details.[10] They reported 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 of these systematic reviews are summarized in **Figure 5**. In this study, 24 subjects with complex partial seizures, 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 logging method.

• The second group received EEG feedback training for 1 hour three times a week for 6 weeks; however,
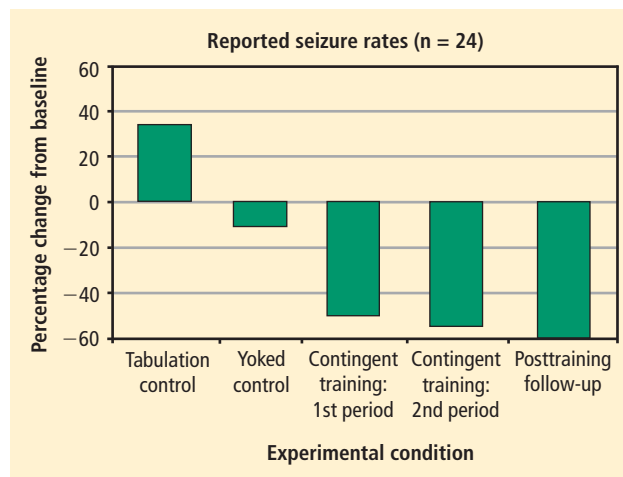
the EEG signal responsible for reward was previously recorded from a different individual. This noncontingent feedback constituted a "yoked control" group.

• The third group received 6 weeks of contingent training for increasing SMR activity in somatosensory cortex while simultaneously suppressing slower 4- to 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 by a final tabulation of seizure incidence during a 6-week period after training was terminated. As can be seen in **Figure 5**, the seizure tabulation control was associated with an increased seizure count and the "yoked control" noncontingent SMR training was associated with no significant change in seizure incidence, whereas contingent SMR training was associated with a statistically significant reduction in seizures. The statistical significance of this 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 following withdrawal from training. In addition to this exclusive seizure reduction after SMR contingent training, pre-/post-training neuropsycho-

FIGURE 6. This 12-year-old girl has suffered since early childhood from frequent multiple seizure types and myoclonic jerks that are unresponsive to pharmacologic treatments. She currently functions at about third-grade level but is aware and behaviorally compliant. Here she is responding to visual feedback in the context of sensorimotor rhythm training. Her mother assists by providing raisin and candy rewards when certain response criteria are achieved. Her seizures have declined in frequency and severity.

logical testing showed that responding SMR-trained subjects also improved significantly in performance of tasks specific to the hemisphere contralateral to their frontotemporal lesion, indicating a reduced corrosive disturbance from the seizure focus.[11]

■ EEG BIOFEEDBACK IN PRACTICE: PROFILE OF THE AUTHOR'S PROGRAM

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

Patients are subjected to a quantitative multichannel 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 is used consistently throughout the treatment period, which consists of one or two 60- to 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 pieces of candy **(Figure 6)**.

The display that subjects see can varies 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 four 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 the objective is to suppress that frequency band, the display must drop below the threshold line. The duration of the required response can be adjusted and is typically 0.25 to 0.5 seconds. 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, 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 by one unit. The timing of each performance set (typically 3 minutes) is indicated by a moving blue bar at the bottom of the screen.

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 the far left is set at 12 to 15 Hz (SMR) for the C3 electrode site, and the remaining three bands to the right are set to 3 to 5 Hz at the left medial frontal location Fz, with successively lower thresholds to promote suppression of this band at this site.

Performance outcome is measured systematically by tracking the scoring rate per trial, together with associated EEG patterns. Data from the 12-year-old female subject described above provide an example. The top of **Figure 8** shows a plot of reward rate across four successive 3-minute EEG feedback trials. The patient was rewarded for simultaneously increasing 12- to 15-Hz

FIGURE 7. Primary display used in our sensorimotor rhythm biofeedback program. The display conforms strictly to operant conditioning principles while still promoting cognitive engagement in the human subject. Reward here is for two different EEG frequencies at two different cortical sites. The far left "green" site shows reinforced 12- to 15-Hz band-pass activity at the C3 electrode site. Low-frequency suppression of abnormal 3- to 5-Hz slow activity at Fz is addressed here through "successive approximation" and consumes the final three display units from left to right. See text for more details. Display results are for the subject depicted in Figure 6.
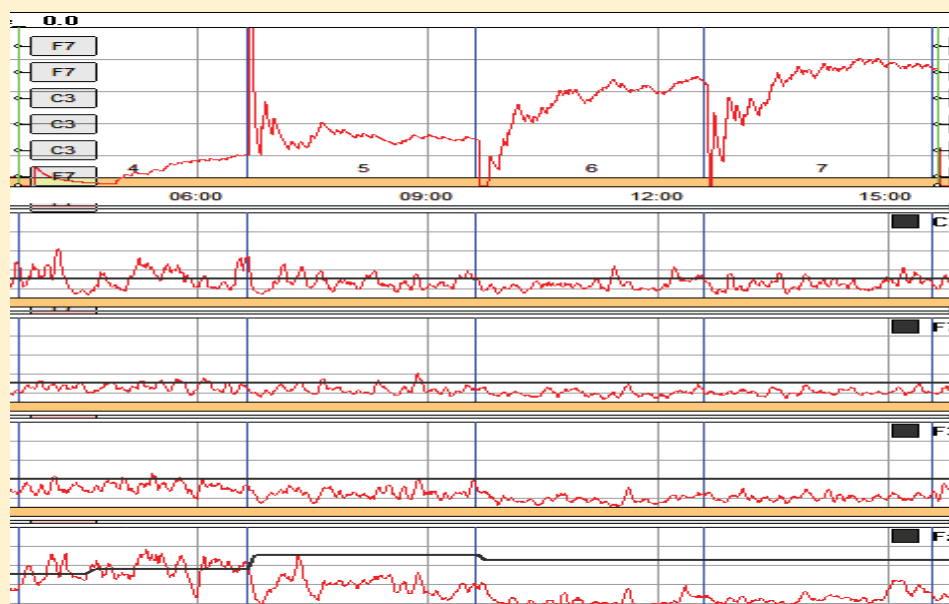

FIGURE 8. Performance plot from the patient represented in Figures 6 and 7. The plot registers the scoring rate per 3-minute trial at top, along with corresponding smoothed amplitude output in the band-passed frequencies set for each electrode placement. In this case the patient was rewarded for increasing 12- to 15-Hz sensorimotor rhythm (SMR) activity (top EEG trace) and decreasing 3- to 5-Hz slow activity at Fz (bottom EEG trace) The subject showed response acquisition both within and across 3-minute feedback trials, together with a stabilization of the SMR frequency and a reduction in frontal slow activity.

SMR activity at C3 and reducing 3- to 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- to 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- to 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 sup-

pressed frontal slow activity resulted in a progressive pattern of incremental reward both within trials and across the session. The resulting profiles are indicative of learning.

■ A RATIONAL MODEL FROM RECENT NEUROIMAGING STUDIES

While it is difficult to evaluate neurophysiologic changes in human subjects to a degree similar to that in animals, certain parallels can be drawn. Further, new imaging
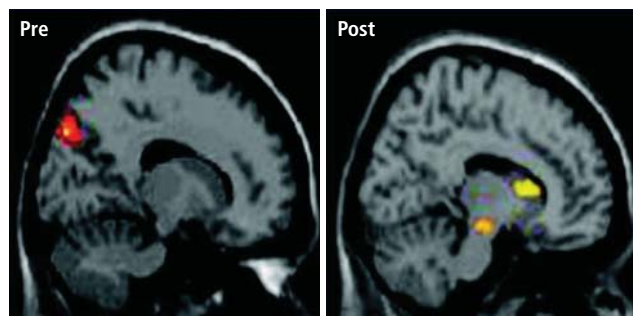
FIGURE 9. Functional magnetic resonance images before (left) and after (right) sensorimotor rhythm (SMR) feedback training in a study of the effect of SMR training in learning-disabled children.[13] The images are sagittal sections for the data averaged across subjects, who either received SMR feedback training (experimental group) or did not (control group). In the pretraining condition, significant loci of activation were noted in the left superior parietal lobe for both groups. In the posttraining condition, activations were again seen in this cortical region for both groups. In addition, the experimental group also showed stronger and statistically significant loci of activation in the left striatum and substantia nigra.

Reprinted from *Neuroscience Letters* (Lévesque J, et al. Effect of neurofeedback training on the neural substrates of selective attention in children with attention-deficit/hyperactivity disorder: a functional magnetic resonance imaging study. Neurosci Lett 2006; 394:216–221), Copyright © 2006, with permission from Elsevier. www.sciencedirect.com/science/journal/03043940

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 intrathalamic 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 observed increased striatal metabolic activity with functional magnetic resonance imaging (fMRI) analysis in subjects producing SMR activity (personal communication, 2005). Further, Lévesque and colleagues studied pre-/post-fMRI blood oxygenation level–dependent 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 **(Figure 9)**.[13] The SMR-trained subjects showed significant academic improvement as well.[13]

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 gan-

glia (principally acetylcholine, gamma-aminobutyric acid, and dopamine), the overall effect on thalamus and premotor 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 if responsible circuits can be potentiated by this association, motor inhibitory regulation would be generally facilitated.

■ CONCLUSIONS

Despite the encouraging findings and concepts reviewed here, 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, in light of the complexity of seizure disorders, accurate history and seizure classification must be evaluated and understood.

Alternative explanations for therapeutic results include such considerations as short-lasting expectation effects and changes in patient behavior. However, it must again be noted that the prolonged anticonvulsant effect documented in our animal studies, as well as in relation to nocturnal seizures arising out of sleep in a human subject, would seem to rule out placebo or nonspecific effects. This conclusion is supported further by the finding of improved neuropsychological 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 EEG biofeedback research studies, along with many who seek this treatment today, represent unquestionable failures of anticonvulsant drug therapy. Notably, positive outcomes have frequently been achieved in patients with complex-partial seizures, an extremely difficult-to-treat seizure type. It is therefore unfortunate that some professionals still criticize neurofeedback therapy for a lack of more consistent or successful outcomes. On the contrary, as noted here, evidence has shown that most of these difficult-to-treat patients benefit beyond any chance or placebo outcome, in some cases dramatically so. In light of the frequent adverse effects and costs associated with lifelong pharmacotherapy, we view EEG biofeedback therapy not as a "last resort" option to be restricted solely to pharmacotherapy-resistant cases but rather as a

generally viable consideration for any patient suffering from seizures. Moreover, in contrast to drug-dependent management approaches, the altered modulation of striatal and thalamocortical inhibition that is possible through neurofeedback training may sufficiently raise seizure thresholds to greatly increase the prospects for the long-term *nondependent* management of epilepsy.

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