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# **Endogenous Neuromodulation at Infra-Low Frequencies**

by Siegfried Othmer

This chapter is dedicated to my late wife and professional partner, Sue Othmer, whose discoveries are described herein. This is a lightly edited version of Chapter 17 in “Introduction to Quantitative EEG and Neurofeedback”, Third Edition (Elsevier, 2023)

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“Future medicine will be the medicine of frequencies.”

Albert Einstein

## **Abstract**

Cerebral regulation rests on the frequency-based organization of the glial/neuronal system, with primary responsibility falling on the infra-low frequency regime that lies below the EEG spectrum. Conventionally, enhancement of self-regulatory competence is pursued by challenge-based methods targeting either the EEG spectral range or the Slow Cortical Potential domain. They appeal to the fast and the slow control systems, respectively. The virtues of training the slow control system directly with a frequency-based schema is explored in this chapter.

## **1. Tonic State Regulation**

Cerebral activity relevant to the tonic regulation of state is typically studied in its phasic responses that fit into typical experimental time scales. The primary focus in this regard is on evoked potentials, and secondarily on the Contingent Negative Variation (CNV). Clearly, it is tonic regulation that establishes the conditions for phasic responding, and yet in the conventional studies its role remains implicit. That is largely because it is difficult to study directly. Any measure chosen to track tonic regulation globally reflects a variety of influences that are difficult to discriminate. And the signal would be relatively amorphous and featureless. This doesn't offer good prospects for success.

In principle, tonic state regulation presents an appropriate target for a self-regulation strategy, as it is foundational to everything else. This has long been understood, and that gave rise to a challenge-based method of neurofeedback known as Slow Cortical Potential training as far back as the 1980's (Rockstroh et al, 1989;

Birbaumer et al, 1990; Birbaumer, 1999). In this learning task, clients are challenged to alter the ambient level of the Slow Cortical Potential by several microvolts within nominally ten seconds (Strehl, 2009). An extensive research history exists for this method of training, and the clinical footprint largely overlaps with what can be accomplished with SMR-beta training, where SMR refers to the sensorimotor rhythm (nominally 12-15 Hz), and beta refers to the beta1 band (nominally 15-18 Hz). A core claim for the procedure is that it can readily moderate cortical excitability, with implications for epilepsy (Rockstroh et al, 1993; Kotchoubey et al, 2001), migraines (Siniatchkin, et al, 2000), and even schizophrenia (Schneider et al, 1992; Gruzelier et al, 1999). The predominant application has been to Attention Deficit Hyperactivity Disorder (ADHD), just as in the case of SMR/beta training (Strehl et al, 2006).

In all of these applications, the objective is diminished excitability as a learned response, and thus altered tonic state regulation. This objective is explicit in the last of the studies cited, by Gruzelier et al. Here a shift in the hemispheric asymmetry of negativity (i.e., excitability) is directly targeted by way of the differential signal at {C3 – C4}. The training is challenge-based, within the customary eight-second window. Thus, all the above neurofeedback techniques rely on phasic responding to train tonic activation and excitability. A limitation of the method is that it calls for significant cognitive engagement with the task; also, the training is relatively inefficient by virtue of the episodic nature of the process.

Just as in the case of evoked potentials and the Contingent Negative Variation, the tonic SCP is treated as a baseline in this feedback modality. It is merely the background against which the challenge takes place, and is not itself expected to yield useful information. In particular, the SCP is not expected to furnish evidence for the success of the training.

This is also what transpired in the field of functional magnetic resonance imaging. Measurements were typically challenge-based, against a presumptively stable background signal. It took some years before it was discovered that not only was the baseline not stable, but the fluctuating background was the principal signal of interest for the neurosciences at large—the key to our understanding of the intrinsic connectivity networks (Biswal, 1995).

The baseline in fMRI reflected primarily the hemodynamics of the Default Mode, our task-negative network (Raichle et al, 2001; Greicius et al, 2003; Raichle, 2010). The terminology reflected the mindset: this is the state to which the brain defaults when it is not being engaged or challenged. But that downplays what is in fact the main story, in

that the Default Mode, our resting state, accounts for the vast majority of cortical energy consumption, with task engagement typically accounting for only a few percent. Tonic regulation of state is the brain's predominant occupation, consuming the vast majority of its resources. And it is organized on the basis of frequency.

This is deserving of our attentions. Brain behavior in the infra-low frequency region is accessible to us via the tonic SCP, which is highly correlated with the BOLD (Brain Oxygen-Level Dependent) activity measured in fMRI (He and Raichle, 2009). Consider in that light what happens in the bioelectrical domain in the infra-low frequency region. Figure 1 shows spectral density over some six orders of magnitude in frequency. The data were acquired over a period of three hours of passive movie watching. Data are plotted logarithmically on both axes, which means that a straight line on that plot indicates a power-law relationship ( $1/f^\alpha$ , where  $f$  refers to frequency). Such a relationship is commonplace in natural phenomena, but in particular it characterizes self-organizing systems. The fact that a single coefficient in the power-law relationship covers both the EEG spectral range and the infra-low frequency range—over five orders of magnitude—adds weight to the proposition that a common organizing principle underlies both. Jointly the SCP and EEG range of frequencies constitute a seamless,

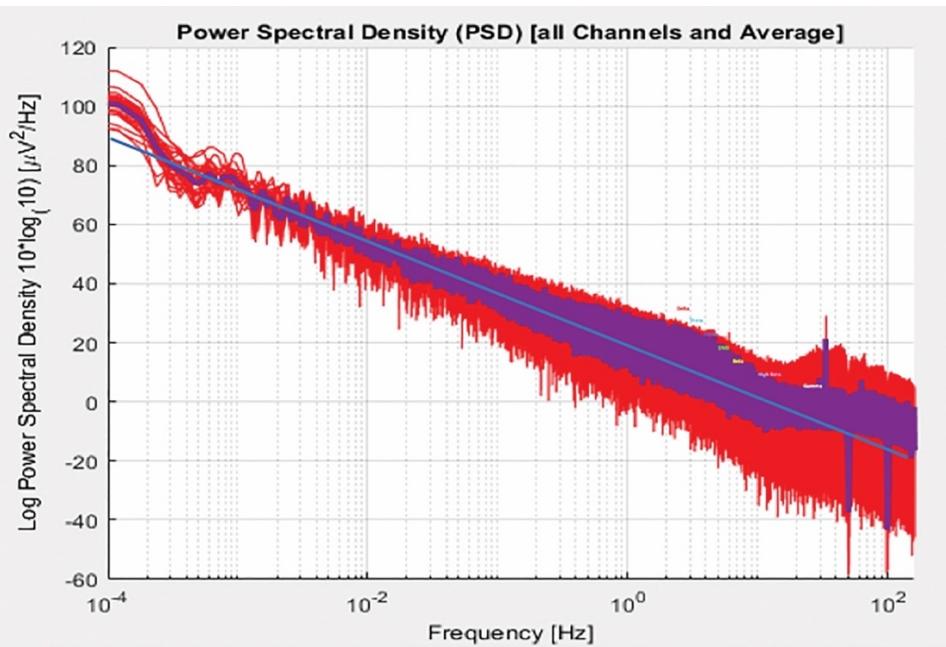


Figure 1. Shown is the spectral power (i.e.,  $[voltage]^2$ ) over six orders of magnitude in frequency, for the standard 19 sites. The average is shown in purple. The blue line is an eye-ball fit. A power-law relationship is indicated over the entire range. The power-law coefficient is nominally 1.5, which is the expected value, over five decades. The deviation at higher EEG frequencies may well be explained by scalp muscle activity, or by excitement attributable to the movie being watched by the volunteer over the course of three hours. (Data courtesy of Bee Medic.)

unitary entity. The  $\alpha$ -coefficient is nominally 1.5, which is the expected value for self-organizing systems at the edge of criticality (Beggs and Plenz, 2003; Kitzbichler et al, 2009). This is the state at which the brain marshals maximal responsiveness while retaining core stability.

The EEG regime reflects the text of our lives as the brain experiences it, whereas the SCP region reflects the context—tonic state regulation—in that it indexes cortical activation directly. And just as the Default Mode dominates in terms of energy consumption, the infra-low frequency region accounts for the largest signal dynamics. Thus, we now know from both fMRI and SCP data that the frequency-based organization of the brain extends deep into the infra-low frequency region, which is an invitation to extend frequency-based neurofeedback to lower frequencies.

Frequency-based training, which has served us well in the EEG spectral range, presents a viable option through mere extension into Slow Cortical Potential region. And yet because of the large time scales involved, tonic regulatory function does not lend itself readily to conventional threshold-based neurofeedback in the frequency domain. An alternative to standard operant conditioning is called for.

The available alternative is neurofeedback by way of endogenous neuromodulation, in which the brain executes the training process in an entirely self-referential manner. The feedback process is one in which the brain engages directly with signals tracking its own regulatory activity, and responds accordingly. This non-prescriptive manner of doing neurofeedback was first exploited by our group in the EEG range. This was accomplished straight-forwardly by making the EEG dynamics at the training frequency a prominent feature of the feedback. The brain is thus able to orient itself in the frequency domain much more specifically than is possible on the basis of discrete rewards alone.

The fact that exposure to its own real-time dynamics should make such a strong difference in the training is far from obvious. Consider the similarity in the filtered EEGs at neighboring frequencies illustrated in Figure 2. An observer has difficulty telling the difference between them, and yet the brain can react very differently to one versus another. What is a mere observation to the human observer is an experience for the brain—'augmented reality,' in effect. The brain can respond to subtleties in the signal that would be missed by an external observer who lacks the relevant context. The brain is immediately 'at home' with the signal, so to speak, and thus takes command of the process: exploiting the signal for its own purposes—enhanced state regulation. The feedback is effectively internalized. The brain is 'self-absorbed.'

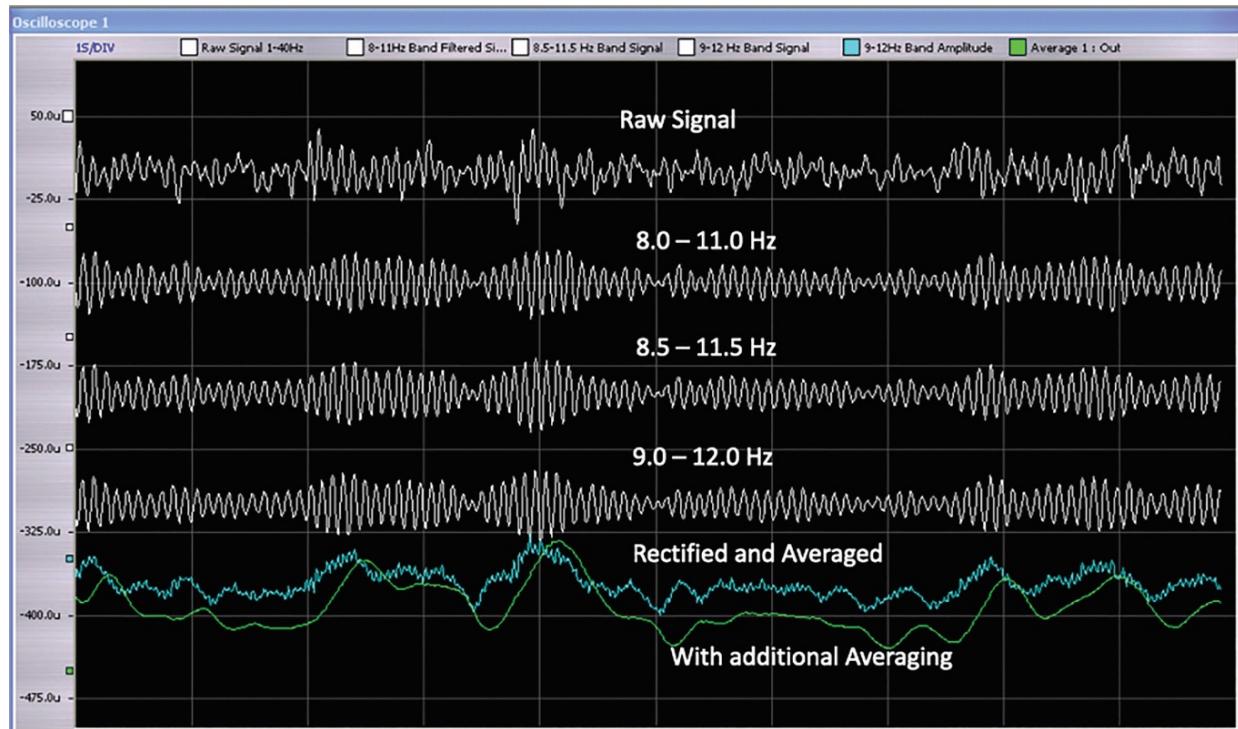


Figure 2. Filtered EEG traces are shown for three neighboring frequencies, illustrating their essential similarity. For purposes of feedback these signals are rectified and smoothed. The bottom trace illustrates the waveform that is utilized in feedback. Despite the loss of detail involved in the smoothing procedure, the brain may nevertheless respond differentially to the three signals. This speaks to the subtlety of discernment of which the brain is capable when given the opportunity.

The natural extension of this kind of training into the infra-low frequency region simply involves tracking the surface potential, suitably narrow-band filtered. It turns out that the brain has no difficulty discerning the significance of the signal, just as in the case of the EEG, and on that basis it immediately recruits the signal as an additional control loop. There are no rewards; there are no nudges; there is no human guidance of the process itself. Instead, the critical role of the clinician lies in establishing the parameters under which this training yields optimal results in each case. Yet even here the brain plays the lead role, in that it is the brain's real-time response to the training that cues the clinician as to the path forward in the therapeutic journey.

Over the last seventeen years, neurofeedback by way of endogenous neuromodulation has been extended deep into the infra-low frequency region (Othmer et al, 2013). The Slow Cortical Potential is utilized as the dynamic variable in the feedback (which is complemented typically by a conventional inhibit scheme). Just as training in the EEG band is generally accomplished by zeroing in on a particular frequency and its dynamics, the same strategy pays off in the SCP domain. Selecting a

particular frequency enhances the signal-to-noise ratio to the point where it more readily engages the interest of the witnessing brain. This work has now been successfully extended to extremely low frequencies. These appear to be still relevant to brain regulation across the entire frequency spectrum, and indeed they appear to be foundational to the dynamic organization of the entire cerebral regulatory regime.

Work with this method has been conducted almost entirely in the clinical realm, and very few clinical studies have been published to date. An early study tracked outcomes in complex regional pain syndrome (CRPS) (Jensen, 2007); reports on PTSD were first published in 2009 (Othmer and Othmer, 2009; Othmer, Othmer, & Legarda, 2011). Case reports on application to pediatric epilepsy have also been published (Legarda et al, 2011). Carol Kelson evaluated ILF NF in application to PTSD of long-standing in Vietnam era veterans in her Ph.D. dissertation (Kelson, 2013). The Swedish Red Cross conducted a pilot study on five treatment-resistant victims of torture among their refugees, with excellent results (Metso and Duberg, 2016). The research group at the Institute for the Human Brain in St. Petersburg published on application to depression with three case histories (Grin-Yatsenko et al, 2018).

A large, multi-site outcome study with children and adolescents with ADHD was reported in 2019 (Schneider et al, 2019). And recently rapid recovery from a case of complex PTSD and DIDNOS has been reported (Gerge, 2020). The book “Restoring the Brain” is now in its second edition. It is concerned exclusively with this method (Kirk, 2015, 2020), and reports on a variety of conditions. More broadly, the method has been in active use at military bases for more than a dozen years, and it is in active use at the hands of thousands of clinicians in over forty countries.

Since this book chapter was written two years ago (2021), a special topics issue on “Endogenous Neuromodulation in the Infra-Low Frequency domain” has been published by Frontiers of Human Neuroscience under my editorship (Othmer, 2023). It contains eighteen papers covering both research and case reports on neurofeedback in the ILF domain.

While we are concerned here with therapeutics, this kind of feedback is of scientific interest as well. Karl Friston asked rhetorically in 2009: How does one study resting states without interfering with them? "One view of resting-state correlations is that they forego hypothesis-testing because they preclude experimental manipulations" (Friston, 2009). Endogenous neuromodulation can meet the condition of non-interference because the feedback is continuous. Once the brain accommodates to the process in first instance, it unfolds entirely within the resting state configuration. The

method has already yielded findings that most likely would not have been discovered any other way.

## 2. Resonance Frequency Training

There is a second critical element of feedback via Endogenous Neuromodulation. The clinical work using this method has revealed the existence of considerable ‘parametric sensitivity’ of the conditions under which optimal regulatory performance may be achieved. This concerns primarily the target frequency in the training, but secondarily also the electrode placement. The process is best conducted at particular frequencies that optimize the response in each individual. Specific frequencies can usually be identified across the EEG and ILF spectral ranges at which functionality is optimized and disregulation status is minimized. At these frequencies the client feels as calm, alert, and as euthymic as the nervous system is capable of at that moment. The variables being tracked are necessarily those on which the client can report in real time, which among others include pain symptoms and any other specific complaints such as tremor, spasticity, dystonia, tinnitus, rumination, bruxism, etc. Yet other complaints, such as sleep quality, are tracked from session to session. We refer to this as optimal response frequency (ORF) training. The ORF principle is illustrated in Figure 3.

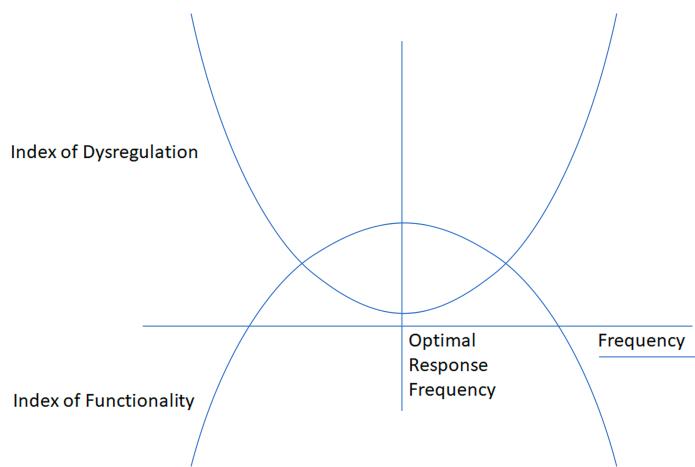


Figure 3. The dependence of two measures, the index of functionality and the index of dysregulation, is illustrated. A frequency exists at which functionality is optimized and the state of dysregulation is minimized. This optimal response frequency specifies the condition under which favorable outcomes may be anticipated for the training, and training efficiency is maximized. Several such frequencies may be found distributed over the spectral range.

Here's how we described the process in the second edition of this series, published in 2009 (Othmer et al, 2009): “It is the responsiveness to optimized-frequency

training that makes this training approach practical. The immediate response to the reinforcement is in terms of state shifts in the arousal, attentional, and affective domains. These state shifts are readily perceived within a matter of a minute or two or three by anyone who responds sensitively to this training. Reports on perceived state change are elicited by the therapist, and on this basis the reward frequency is adjusted on the timescale of minutes to hours. As the optimum reward frequency is approached, the trainee achieves a more optimal state in terms of arousal, vigilance, alertness, and euthymia. At the same time, the strength of the training increases perceptibly. For those familiar with the theory of resonant systems, this maps out a conventional resonance curve, and it is our impression that the person's felt states and the responsivity to reinforcement map out essentially the same curve." The resonance curve is illustrated in Figure 4. (See also Othmer, S., Othmer S.F., 2017).

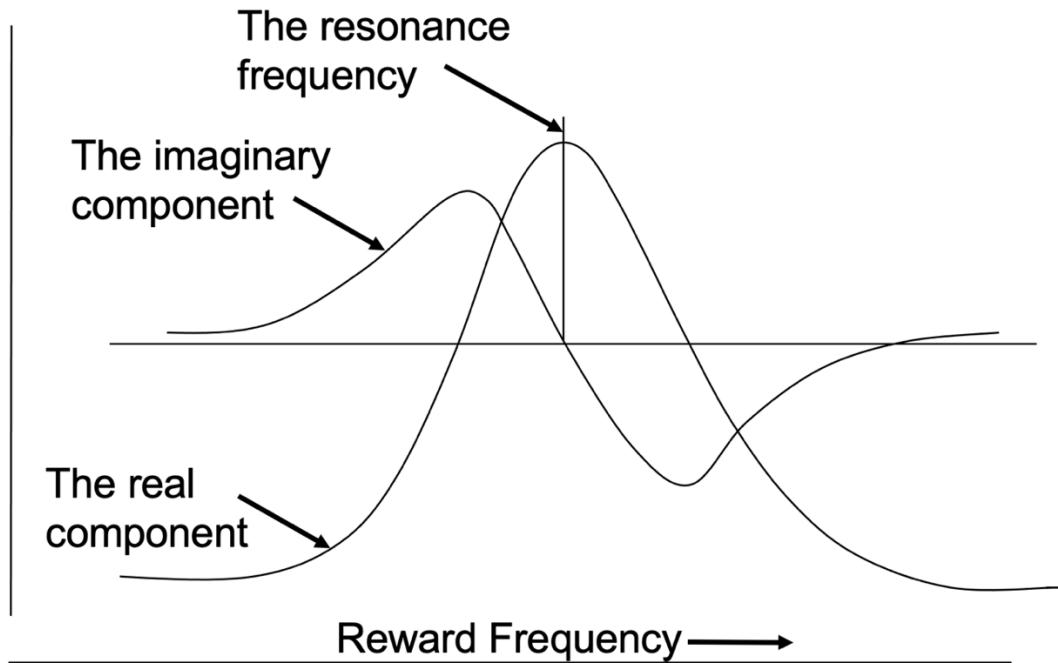


Figure 4. The frequency response is shown here for a resonant system. Both the real and imaginary components of the complex signal are illustrated. The clinically significant import is that response to the training changes significantly over a narrow range in frequency, which calls for careful optimization (Othmer, 2009).

Of course, not everyone responds sensitively to the training, but in practice that does not pose much of a problem. Sensitivity to the training scales with dysregulation status. Those who are most symptomatic are also the most sensitive to the particulars of the training, by and large. Conversely, those who are endowed with a well-regulated nervous system may have difficulty identifying any ORF at all within session. They can still benefit from the training, of course, but for them operating at the ORF is less critical.

The range of responses is illustrated in Figure 5. Those who react strongly to the training may experience equivocal responses in the immediate vicinity of the ORF. That is in the nature of the resonance curve: The system response can vary dramatically over a narrow range of frequencies near the ORF, and the ORF may have to be tuned in rather precisely in some cases for best results---down to the 1% level in the EEG range, and the 5% level in the ILF.

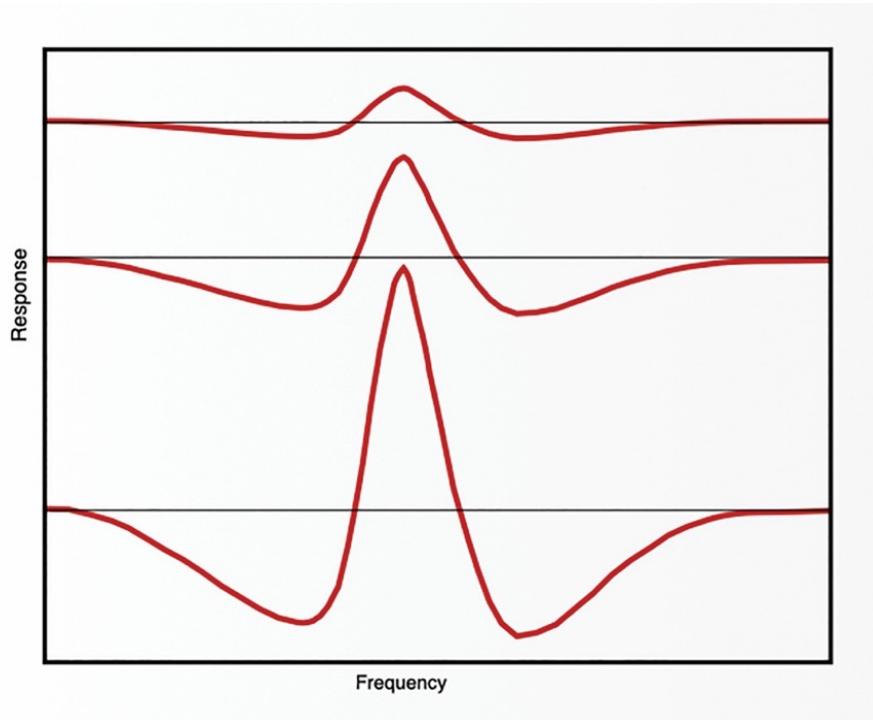


Figure 5. Response characteristics as a function of frequency are shown here for three levels of 'sensitivity' to the training. At one extreme it may be a challenge for the clinician to even identify the ORF within session, and at the other extreme the trainee may experience mixed results when operating in the immediate neighborhood of the ORF, making optimization critical. That's in consequence of the nature of the resonance response.

Clinical experience testifies to the proposition that training in the slow cortical potential region holds great promise in remediation of functional deficits in cerebral regulation. The clinical reach of the method is comprehensive, and the explanation for this is straight-forward. Training at extremely low frequencies takes us to the foundations of our regulatory hierarchy, to what we consider to be core regulation. A successful intervention necessarily impinges on all systems that rest upon that foundation.

Restoration of regulatory competence more generally is then achieved with additional protocols that appeal to other critical aspects of the regulatory hierarchy. The

method largely remains the same: the brain's engagement with its own signal is facilitated, and it responds with an inherent bias toward favorable outcomes. The process of functional recovery, then, is iterative and sequential, a kind of scaffolding process in which the training of core regulatory function lays the basis for progress with higher functions. In each case, the real-time response of the system to this challenge guides the practitioner to its most propitious outcome.

Over the course of some years, patterns have been observed that relate optimal response frequencies for different electrode placements. The frequency rules are observed to be consistent across the entire frequency domain that has been explored, which by now extends over ten orders of magnitude, from  $10^2$  to  $10^{-8}$  Hz. These results are shown in Figure 6 for lateralized placements. Systematically, the left hemisphere placements optimize at higher frequencies than the right. The relationship is arithmetic in the EEG range and geometric in the ILF regime. The transition region lies in the Delta band. Different rules apply to inter-hemispheric placements, with frontal placements optimizing at 2 Hz (a factor of two lower in ILF) lower than central placements, and posterior placements optimizing at 4 Hz lower (a factor of four lower in ILF).

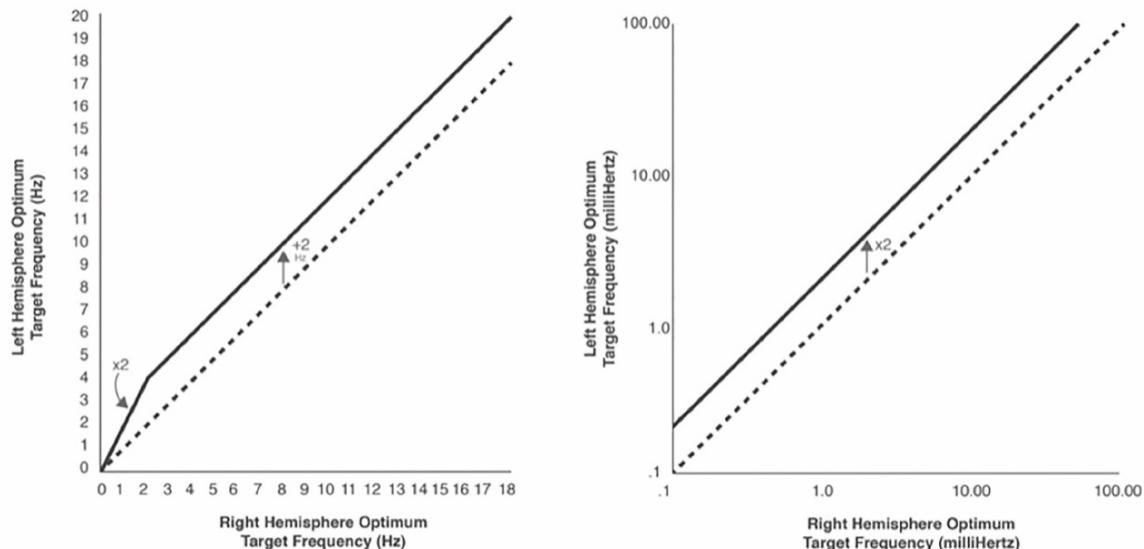


Figure 6. The relationship of optimal response frequencies for lateralized placements is illustrated here. The frequency domain divides into the EEG spectral range and the infra-low frequency range. In the EEG range the relationship is arithmetic, as shown in the linear plot. In the ILF range it is geometric, as shown in the logarithmic plot. In each case, the relationship holds over the entire frequency range that has been investigated. The upper Delta band of 2-4 Hz is the transition region between the two domains.

The existence of these relationships, which have the consistency of observation across a large practitioner network in their favor, testifies to a hierarchical organization in the frequency domain that governs both the glial and the neuronal systems. The stability of the optimal response frequencies throughout the training process further supports the hypothesis of a unitary organizing principle that covers both the glial and the neuronal spectral regimes. Relative invariance of the optimal training frequencies through the training process lends support to the view that these are key frequencies that underpin the organization of the entire frequency regime.

The clinical import of these findings is potentially immense. The history of development of this therapeutic process essentially scripted itself over the years, as the impetus to migrate to ever lower frequencies in the training—which is an ever-increasing challenge as one goes lower—was the imperative of training at the ORF. It is by way of the parametric sensitivity of the target frequency that her clients' brains led Sue Othmer to expand the range of target frequencies. The most challenging clients tended to train optimally at the lowest frequencies provided for in the software. Repeatedly the software would have to be modified to permit access to ever lower frequencies. Systematic exploration of the infra-low frequency domain has by now taken some seventeen years.

If this pace of progress looks slow in retrospect, it must be considered that ours was a clinical operation. It was not organized for research. We were not looking for opportunities to push boundaries. New initiatives could be undertaken only when a particular clinical situation demanded it because existing protocols were unavailing. On top of that, however, Sue Othmer was always cautious, prudent, and conservative in how she proceeded, as a matter of temperament. Everything that was learned had in fact been learned according to a controlled design, in that every clinical trajectory was a sequence of A/B choices, with every protocol choice entailing a contingency subject to redirection or fine-tuning. In complex cases, clients must serve as their own control, as the context for clinical decision-making is itinerant and irreproducible. Over the course of months to years, confidence in provisional hypotheses waxed or waned by the principle of Bayesian inference encompassing many case histories.

In the course of these developments, we found resolution for clinical presentations that had been refractory to earlier protocols. At the lowest frequencies we are targeting core regulatory function, which is organized early in development. In this manner, developmental trauma and other developmental dysfunctions became accessible to us. They remain reachable at any age. With the resolution of core regulatory deficits, other functional deficits seemed to resolve in the bargain. Others

became more manageable with complementary protocols—protocols that might very well not have been tolerated earlier.

Whereas it was the nervous systems in greatest deficit that forced our hand to explore ever lower frequencies, perhaps the greater surprise was to find that nearly everyone responded favorably to the principal protocols that had emerged to remediate core regulatory function. We all appear to be subject to the same principal failure modes; just some are more catastrophically compromised functionally than others. In consequence, the protocols that have proved to be most efficacious are applicable across the entire range of function, extending also to the realm of optimal functioning.

This serves to highlight the fact that endogenous neuromodulation is inherently function-focused rather than deficit-focused. This follows directly from the fact that by its very nature the process places the brain in charge of the journey. And the brain will naturally utilize every available feedback on its own activity to improve its own function. The most accessible model for this process is the development of motor skills. The brain must witness the execution of the motor skill in order to improve the performance of the skill. In the case of self-regulation, the brain is already in possession of a plethora of internal feedback paths. Under most ordinary conditions, these suffice even to effectuate self-recovery from many disorders—addiction, depression, PTSD, and minor traumatic brain injury among them—even without instrumental support. Adding instrumental support merely augments the brain's robust self-recovery capacity.

Self-recovery has not only been the default remedy throughout human history, but it remains the predominant path to recovery to this day for most people. The field of medicine even pays homage to self-regulation in a back-handed way through making the placebo the critical hurdle factor in medication efficacy studies. And as we know, many medications such as the anti-depressants barely pass the threshold. The addition of an external feedback path can now empower the brain to resolve even conditions that have not benefited by way of unaided self-recovery and may also be refractory to medical interventions.

When working with deregulated nervous systems, adverse responses are commonly encountered as well. These are attributed to adverse attractors in the attractor landscape as the brain migrates through state space under the impetus of the feedback signal. The process itself serves to increase the velocity of the state vector, thus enhancing the likelihood of encountering adverse attractors. We also must allow for the possibility that adverse responses may be evoked by the training process itself. With highly deregulated systems, it is even likely. That follows from the fact that rapid state

shifts may be induced, and even if such state shifts are in the desired direction, they may be sufficient by themselves to destabilize a disregulated system in the moment.

Examples are well known in the field of biofeedback. Rapid relaxation in a person susceptible to asthma may trigger an episode. Migraines are unlikely to arise while someone is actively engaged. More than likely, they make their appearance during a subsequent period of relaxation. That risk prevails in relaxation training as well. In neurology, seizures can be evoked by a simple change in dosing, even if the new dosing level is more appropriate in the steady state. Fortunately, these excursions into disregulation are typically transient, and they are reversible with appropriate adjustment of the training parameters. Obviously, this calls for great clinical skills, and these can be acquired only over the course of extended practice of the method.

One of the principal virtues of the method is that it rests on the skill set that mental health professionals have already cultivated—namely the relationship to the client and broad experience with the varied clinical presentations of mental dysfunctions. Once clinicians are equipped with the neurophysiological model that underpins endogenous neuromodulation, the state of the client is viewed in that new perspective. Symptom profiles are interpreted in terms of key failure modes of cerebral regulation, which then specifies the starting protocol. This facilitates the optimization procedure and the sequencing of successive protocols. The process is nomothetic in design, but idiographic in execution. Sue Othmer describes it as a “dance with the brain, but the brain gets to lead.” Excellent observational skills are called for to discern even the subtleties of the response by the client in this journey.

We have here a promising new method of engaging even with highly functionally compromised nervous systems. However, the challenge presented to the supervising clinician is commensurate with the state of disregulation. The path to recovery is more tightly constrained in severe cases, and this calls for an experienced clinician to navigate the terrain without subjecting the client to further distress in the journey to recovery. Because the method targets core regulatory mechanisms in the cerebrum, potential benefits of the training range across the entire domain of mental health concerns. In the remainder of this chapter, the method is introduced by way of recounting the history of its development, followed by some considerations regarding mechanisms.

### **3. Historical Roots of Feedback via Endogenous Neuromodulation**

As it happens, this topic traces back to the very first neurofeedback sessions that I experienced in the office of Margaret Ayers in 1985. Ayers had learned the method from Barry Sterman, the original researcher in clinical neurofeedback, and she was using the instrumentation that had been developed for his research. Feedback was by way of a green-yellow light that reflected the amplitude fluctuations in the low beta band of 15-18 Hz. This feedback was punctuated by a beep whenever threshold crossings met a persistence criterion, and these were rate-limited at two beeps per second.

Significant gains were achieved within four sessions, but that became fully apparent only over the course of time. For some years I had been suffering episodic vertigo related to a prior minor head injury. These happened rarely, so it took some while to be sure that they were no longer occurring. Other symptoms of the TBI disappeared as well. Sue Othmer experienced a first-session “clear windshield” effect, and our younger son Kurt also experienced an obvious first-session effect. Such rapid gains are inconsistent with an operant conditioning model. But there was more. My EEG amplitude in the beta band was so low that the threshold criterion was only rarely met even on the most sensitive setting on the instrument. So there hadn’t been very many beeps during my sessions.

To assign my functional improvements to that low incidence of beeps stretched credulity. But there was even more. I developed the sense of having a degree of voluntary control over the beeps during those four sessions. Reflecting back on that experience after gathering more experience with the method, I realized that I must have inadvertently cheated the system by slightly turning my head during the session, creating just enough neck muscle tension to trigger the threshold. This occurred beneath my awareness, but it could account for my having some sense of control over the signal. My brain was obviously generating beeps any way that it could. The beeps I was listening to were not honestly come by, so they cannot have been responsible for my dramatic recovery.

The brain was clearly engaging with its own dynamics as displayed by the fluctuating green-yellow light, and that encounter had to be mediating the change in my case. Still, there was every reason to believe that the threshold crossings were also clinically relevant. They gave direction to the proceedings at the brain level, and they helped to engage and to motivate trainees at the conscious level. So, we remained fully invested in the operant conditioning model for many years, despite our awareness that

matters were more complex in execution. This was, after all, the only plausible theoretical model for neurofeedback at the time. But we always took great care to tend to the pleasing representation of the EEG dynamics in our three generations of instrumentation design. And that turned out to make all the difference.

It should be remarked at this point that although Sterman must have included this feature in the design of his research instrumentation quite deliberately, he never drew attention to its existence or clinical relevance in any of his lectures. He was a Skinnerian purist with respect to operant conditioning. All that mattered were the discrete rewards. Accordingly, a later instrument design in his laboratory featured only the discrete rewards.

Another critical element of the process was the exclusive reliance on bipolar montage. This had been standard in both Sterman's and Lubar's early research, as indeed it was standard at the time throughout the field of EEG characterization. But the advent of 19-channel QEEG analysis shifted the perspective to single-site training. We yielded to the Zeitgeist for a time, but soon returned to bipolar montage because it was clearly more potent. This was effectively connectivity-training in the network model, a departure from the localization hypothesis that was still current at the time—the early nineties.

The observation that higher training frequencies in the SMR-beta band moved people to higher arousal level—and vice versa—inspired the arousal model for characterizing our work with these protocols. Clients were characterized in terms of their arousal status and behavior, aided in each instance by their response to the respective protocols, SMR training at {12 – 15} Hz and low beta training at {15 – 18} Hz. A third filter with a 15 Hz center frequency was added later, and thus it became evident that there was virtue in fine-tuning the target frequency for everyone. At first, we provided for 1-Hz steps in the software, then 0.5 Hz, and finally 0.1 Hz. Some individuals needed to have their training frequency tuned to within 0.1 Hz for the optimal training experience. In such highly sensitive individuals, the within-session response to the training was usually sufficient to get us to the optimal response frequency, the ORF. In poor reporters, one depended on session-to-session reports for convergence to the ORF.

With this level of fine-tuning of the target frequency, our clinical reach extended to many individuals who in an earlier day might well have given up on the training. In consequence, the clinical scope extended to a wider range of conditions. The ORF was serving as a guide to the terrain. Training at the ORF was always well tolerated, and then one had a chance to observe what the brain could accomplish with that

opportunity. More specifically, targeted training made for significant advances in working with migraines and other such sudden, episodic excursions into disregulation—seizures, asthmatic episodes, and panic attacks. We subsumed all of these into the category of ‘brain instabilities’, as all of them responded to the same electrode placement, and all depended on precise targeting of the ORF for their most efficient resolution. Good inter-hemispheric coordination was a condition for successful recovery in all of them.

It is perhaps useful at this point to reflect back on the earlier attempt to shift hemispheric dominance in negativity in schizophrenia (Gruzelier et al, 1999). The shift was easier to achieve when it was in the direction that was clinically appropriate. Those with mainly positive symptoms were better able to shift negativity to the right hemisphere, and withdrawn patients to the left. Even under top-down control of the process, the brain asserted itself. If one imagines applying that same method in Bipolar Disorder, the result would be to shift from the depressive to the manic state or vice versa. Control would be perpetually elusive. Not so with endogenous neuromodulation, in that with inter-hemispheric placement, the bipolar montage has no hemispheric bias.

A situation analogous to the above does, however, arise with endogenous neuromodulation as well: training too low in frequency moves the person toward the depressive state, and training too high induces movement toward mania. This can even happen within minutes. The difference is this: A frequency can always be found that tends toward system stability; that frequency is unique to the person, and it is their optimal response frequency. To find it, however, one needs to let the brain take the lead in the process. Once there, one needs to let the brain find its own way toward more lasting stability.

Over the course of seeing several hundred clients per year, the ORF’s of the various clients provided the opportunity to explore much of the EEG spectral region. A bias toward the lower frequencies soon became obvious. The search for the ORF led us predominantly downward in frequency from its starting point in the SMR/beta range. At first, it took some courage to do the training within the theta band, which we were also inhibiting. Colleagues who became aware of what we were doing were aghast. But training with bipolar montage should not be confused with conventional amplitude training. Bipolar training is biased toward de-synchronization at the training frequency, which tends to promote system stability. Hence there is no conflict with the objectives for the inhibit training.

There was even more nervousness in the gallery when later it came to training the delta band, but the story turned out to be similar. Bipolar training at the ORF was

clearly a different matter than amplitude up-training at an arbitrary frequency. By this point in our protocol development, the focus had shifted entirely to what was happening with the reward-based training, because that fully engaged the attentions of the therapist. The inhibits served as a mere grace note, augmenting training efficiency but largely running on autopilot in the background.

By 2002, the lowest frequency of 1.5 Hz (consistent with the 3-Hz bandwidth of the filter) had been reached. By 2005, it became clear in the data that there was a bias toward the lowest frequency in the distribution of ORFs among our clients. This is shown in Figure 7. Here the data are plotted for 3-Hz wide bins, but in the case of the lowest-frequency bin we have only one frequency, 1.5 Hz, not three. So, if the same data had been plotted with 1-Hz bins, the lowest frequency would have stood out by about a factor of three. It was clear that we needed to get to lower frequencies, but for some while we were constrained to function with the software that we had.

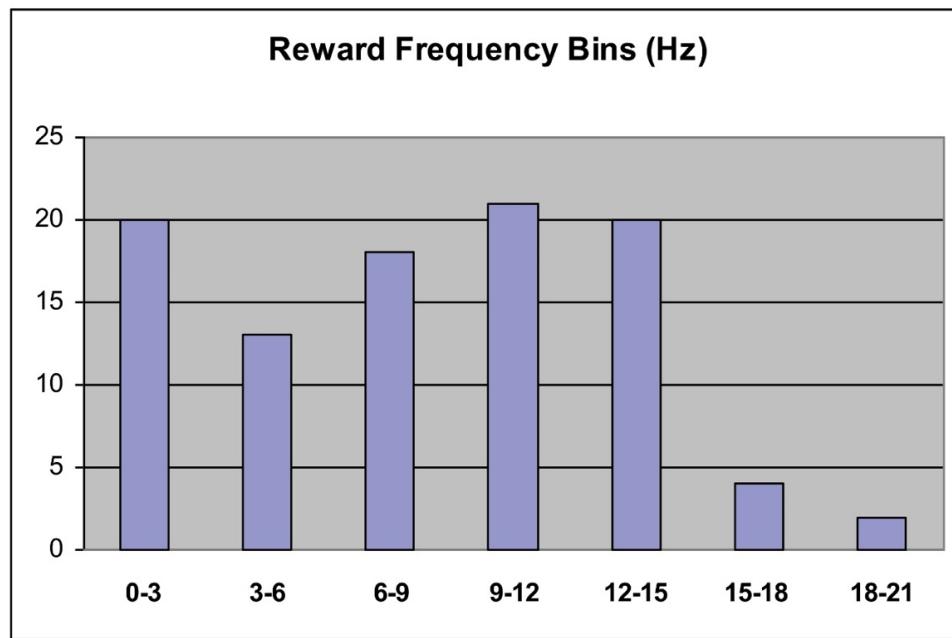


Figure 7. Distribution of Optimal Training Frequencies over six months in 2005. The predominance of frequencies below our prior standard training bands is evident. The 0-3-Hz band contains only one frequency, centered on 1.5 Hz, rather than the three for all the other bands. Had the data been plotted with 1-Hz bins, the dominance of the lowest frequency would have been evident.

Observe also that with frequency optimization, the 15-18 Hz training band subsided in relative importance. This had been our primary training protocol during the early years. It follows that the brain makes the best use of any relevant information that we provide. Training at the ORF is advantageous, but not usually obligatory, particularly

in the EEG range. Unsurprisingly, brain instabilities are the most sensitive to frequency. In the ILF regime, training at the ORF became ever more critical at lower frequencies.

With the march to lower frequencies in temporary stasis, attention turned to the spatial domain, and from 2004-2006 Sue Othmer explored the implications of working entirely with inter-hemispheric placements, as shown in Figure 8. All homotopic site pairs in the 10-20 model were evaluated as clinical opportunity presented itself. Each had its particular role to play, but three placements were found to carry the major burden: {T3 - T4}, {P3 - P4}, and {Fp1 - Fp2}, and they did so in that order. Most noteworthy in this hierarchy is the displacement of {C3 - C4} by {T3 - T4}, as indeed C3 and C4 were by far the most popular training sites in neurofeedback at the time (due in large part to the thousands of clinicians we had trained in those protocols over the years). Further, {C3 - C4} had been the only inter-hemispheric placement to find its way into the literature up to this time. Doug Quirk had been using it to great effect with violent offenders at the Ontario Correctional Facility. Indeed, this was the only protocol he ever used. It was his own independent insight to make inter-hemispheric coordination the principal objective in the training (Quirk, 1995).

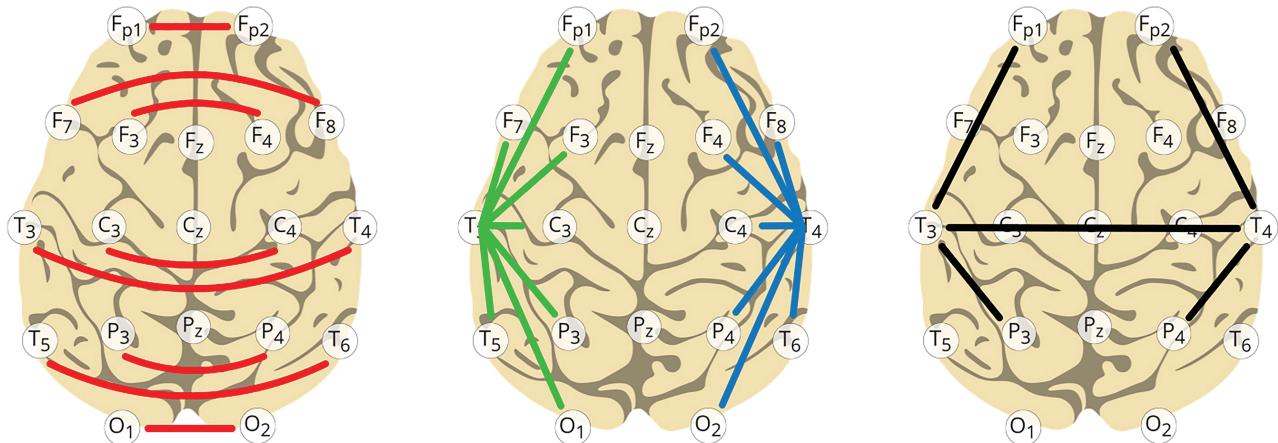


Figure 8. Represented here are the inter-hemispheric placements and lateralized placements that were systematically evaluated in the 2004-2006 time frame. Also shown are the principal placements that are conventionally utilized in Sue Othmer's protocol schema.

The historical pre-occupation with the central sites C3 and C4 can be ascribed to three principal factors. First of all, training on the motor strip is generally very well tolerated. Secondly, training the sensorimotor cortex is appropriate when targeting executive function, vigilance, and attention, which can be regarded as the highest levels

of the regulatory arc that governs motor function. And third, C3 and C4 are at the nexus of the sensory and motor realms, as the somatosensory and somatomotor domains are thoroughly interleaved. Finally, it may also be relevant to observe that the somatosensory faculty has primacy among our principal sensory modalities. As the late Oliver Sacks has observed, loss of this faculty can eventuate in the loss of identity and sense of self. Freud put it this way: Our self is in essence a body self. And Sherrington observed that 'The motor act is the cradle of the mind.'

With the migration to T3 and T4 priority that paralleled the migration to ever lower training frequencies, attention shifted from the engaged brain toward the resting brain. This shift was mainly taking place at the conceptual level, with the aid of new understandings emerging on the intrinsic connectivity networks (ICNs) from fMRI. The clinical reality had been there all along: Even with training on the central strip, we had been training the tonic regulation of central arousal, which is under the management of our task-negative network, the Default Mode. And the standard placements, {C3 - T3} and {C4 - T4}, that had been bequeathed to us from Sterman and Ayers for the SMR/beta training, already included the temporal sites.

With the inter-hemispheric placements characterized, the next challenge was to ascertain whether there were situations in which lateralized placements would be substantially additive. These lateralized placements now all had either T3 or T4 as a common site (See Figure 8). Preference for the lateralized placements that we had been using earlier was confirmed: {T4 - P4} and {T4 - Fp2}, and their left-side homologs. The distinguishing feature of the preferred sites is that they were the multi-modal association areas. These are the loci of the highest integration of the sensory modalities. They are also deemed to be highest in neural plasticity. In the newly emerging model of ICNs, the principal lateralized training sites were those in which the Default Mode was accessible to us at the cortical surface. Collectively, these placements constituted the principal basis set for the ILF training, as also shown in Figure 8.

It was in early 2006 that one of the practitioners in our network, Carl Shames, used his neurofeedback instrument to increment the training frequency downward in 0.1-Hz steps from the starting value of 1.5 Hz. Clear differences were noted at each step. Carl was ecstatic. This then refocused our attentions on a more serious exploration of the lower frequency range. For this purpose, we recruited BioExplorer software, which extended our range to a corner frequency of 0.1Hz, for a nominally 0.05 Hz center frequency. The training frequencies were now so low that the use of discrete rewards for threshold crossings no longer made sense.

The process became one of waveform-following: We had entered the realm of endogenous neuromodulation, in which the brain simply interacts with its own slowly evolving signal. It became clear very quickly that the brain didn't need to be nudged at all. The brain carried on as before. The conventional inhibit scheme was carried forward, but it could not bear the burden of explaining what we were witnessing. Besides, the process was exquisitely frequency-specific, which had nothing to do with the inhibits. We were now on entirely new terrain. Operating space in terms of frequency had now expanded considerably. One could reasonably anticipate that with training somewhere in frequency space we could substantially alleviate someone's complaints with respect to functional brain disorders.

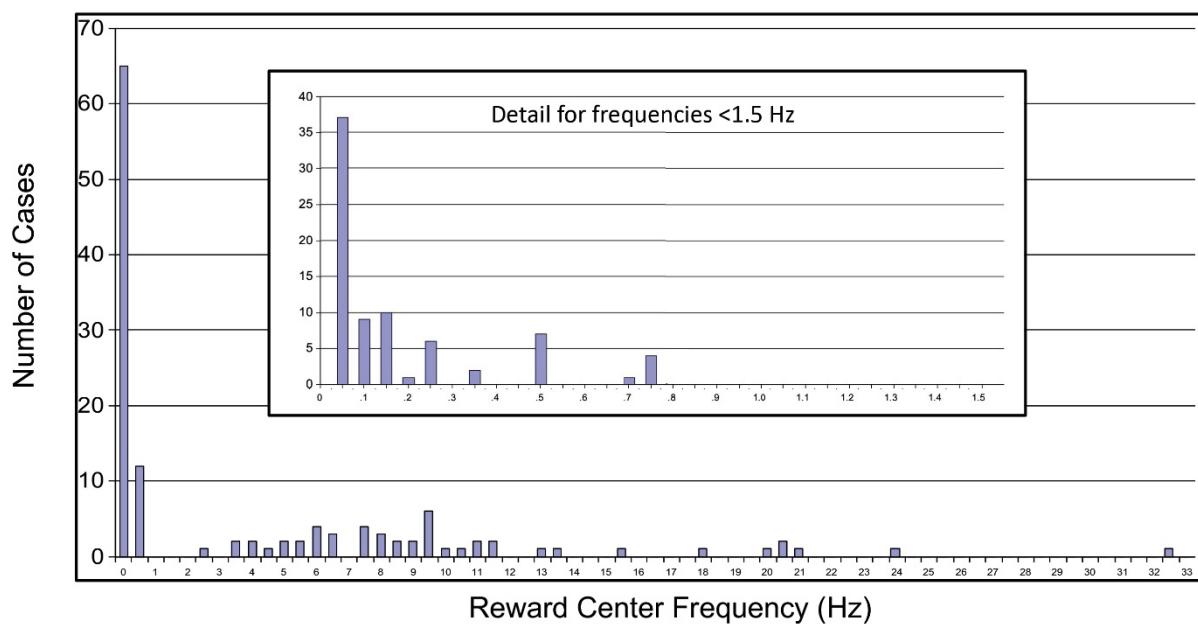


Figure 9. The distribution of optimal response frequencies are shown here for the second half of 2006. The frequencies were broadly distributed, but peaked strongly at the newly available lowest target frequency of 0.05 Hz and in its neighborhood, as shown in the insert.

By the end of 2006, it was once again clear that the lowest available training frequency was dominant. The data are shown in Figure 9. The case for moving to even lower frequencies was compelling. New software was needed, and that software, called Cygnet, became available to us by the end of 2007. It was in the hands of our practitioner network by early 2008. By the end of that year training had extended down to 1 mHz. The results are shown in Figure 10. Note, however, that training frequencies extended also to the upper regions of the EEG spectrum. Over the course of 2009 the need for pushing to even lower frequency consolidated.

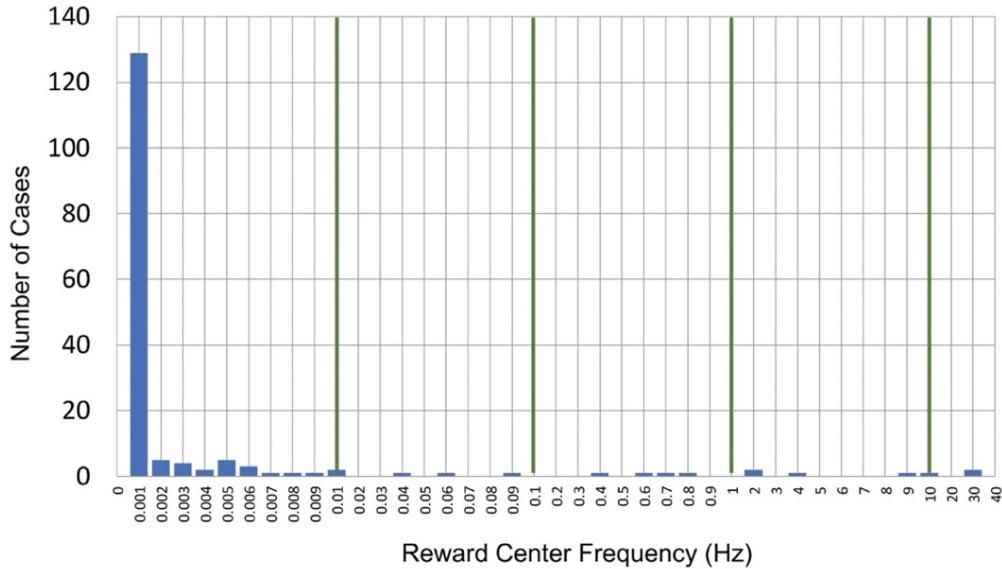


Figure 10. The distribution in optimal response frequencies observed in 2009. The distribution peaked strongly at the lowest available target frequency of 1mHz. Observe that the horizontal scale is linear within each decade, but logarithmic in decades.

The frequency range was extended in software to 0.1 mHz in early 2010. But we were reaching the limits of the architecture that had never been designed to operate at these low frequencies. We were operating far beyond the cutoff frequency of the high-pass filter, with marginal signal-to-noise ratio. New hardware design was called for. By 2013 the new hardware was operational with new software. By the end of the year, some two-thirds of all our clients had been training at the lowest frequency, 0.1 mHz, so the pattern shown in Figure 10 was essentially replicated at this lower frequency range.

At this low frequency, a single cycle takes 10,000 seconds. What does it mean to be training such a low frequency? It should be noted that as we went lower in frequency the training experience was not different for the client than it had been earlier at higher frequencies. Responses were just as prompt, and might make their appearance even more quickly because the training was now somewhat stronger, by and large, so its impact could be felt sooner. Nothing was slowing down, as might have been expected at lower training frequencies. That means the signal the brain was responding to couldn't be much slower either. The brain is engaging with the dynamics that are revealed in the signal, and these are not slowed down. They are merely attenuated by the filter. That reduces then to a question of signal-to-noise ratio. Quite evidently the brain has no difficulty on this score because the process is manifestly working—provided the clinician has arranged for a good, clean signal that is not dominated by electrode drift.

In the language of signal-processing, the target frequency functions effectively as a carrier frequency for the signal of interest. But this carrier frequency now lies beneath notice for the brain, which is able to discern only the modulations that reflect its role in brain regulation. Obviously, the target frequency must respond at the speed of life, or it would be irrelevant for purposes of dynamic state regulation. So, nothing is lost at the lower frequencies, but the signal-to-noise ratio does decline as one goes lower, presenting more of a practical challenge to the signal-processing.

## 4. Protocols, Tactics, and Mechanisms

As already noted, the principal protocols in use in ILF neurofeedback with bipolar montage are shown in Figure 8. All four quadrants of the cortical surface are given special attention. Only two placements are typically used as starting protocols: {T4 - P4} and {T3 - T4}. The third most common training site is {T4 - Fp2}, but it is usually only probed after the groundwork has been done with the starting protocols. Next is {T3 - Fp1} for executive function, and {T3 - P3} for the processing of detail.

The two starting protocols target the two principal failure modes that have been identified. {T4 - P4} is a highly efficient placement for training arousal disregulation. Early trauma and the vicissitudes of life tend to drive the system toward high arousal levels, which can be costly to the functionality of the system long-term. Quite commonly, training at {T4 - P4} takes such people to a state of calmness that lies outside of their prior experience. This calmness is the observable aspect of the protocol, what the client can readily report on. The impact of the training, of course, is much broader. The greater calmness indexes a more general improvement in functionality that only becomes apparent through the activities of life.

{T3 - T4} is a highly efficient placement for calming neuronal excitability and thus for raising the threshold for the kindling of brain instabilities. This is a large and heterogeneous category, which in addition to the conditions already mentioned earlier (migraines, seizures, asthmatic episodes, and panic attacks), include trigeminal neuralgia, vertigo, schizophrenia, Bipolar Disorder, narcolepsy, and most importantly, dysautonomia.

These conditions tend to involve a significant genetic contribution to the risk exposure, and organicity as well (e.g., trigeminal neuralgia, schizophrenia). Nevertheless, training toward better coordination between the two hemispheres can raise the instability threshold significantly. We benefit from the fact that as neural regulation is improved, the extremes in the behavioral continuum diminish the most

rapidly. So it may not actually take very much training to reduce the incidence of conditions that are typically rare in the first place (migraines, seizures) to *de facto* clinical irrelevance. In the case of epilepsy, one would obviously seek an optimal combination of anti-epileptic drugs with neurofeedback. The AEDs target neuronal excitability at the membrane level, while neurofeedback addresses it at the network level.

Dysautonomia deserves special mention. We are not dealing here just with the conditions that rise to the level of being labeled dysautonomia. Rather, the issue is the entire continuum of autonomic disregulation. This has been the almost exclusive preoccupation of the field of biofeedback over its entire existence. Unfortunately, the centrality of autonomic regulation in health status has never been appreciated in medical education. This has been a grievous oversight.

On the other hand, the various methods of peripheral biofeedback, including the training of hand temperature, galvanic skin response, electromyographic activity, and Heart Rate Variability (HRV), cannot readily avail themselves of the key relationship at issue here, which is the coordination of the two hemispheres. So ILF NF is making a unique contribution, particularly for the more severe presentations. Conversations about autonomic regulation tend to be cast in rather stark terms: either one is dealing with sympathetic dominance or parasympathetic. Realistically, of course, the regulatory dance exists on a continuum. Subtlety of regulation is the ideal. Both biofeedback and ILF NF operate at that more subtle level, and neither one displaces the other. At its best, training toward improved autonomic regulation takes advantage of multiple independent pathways/modalities, a lesson based on decades of experience in biofeedback.

The cardinal issues in core regulation, as seen in the perspective of the neurofeedback therapist, may be illustrated as in Figure 11. Training in the deep ILF region now completes the migration, over the course of 37 years, from an initial engagement with executive function, vigilance, and attention in ADHD to a primary concern with core regulation, which is the regulatory arc of interoception, autonomic regulation, affect regulation, and the tonic regulation of central arousal. Here the right hemisphere bears the primary burden, and the posterior region in particular. This accounts for the large clinical footprint of {T4 - P4}.

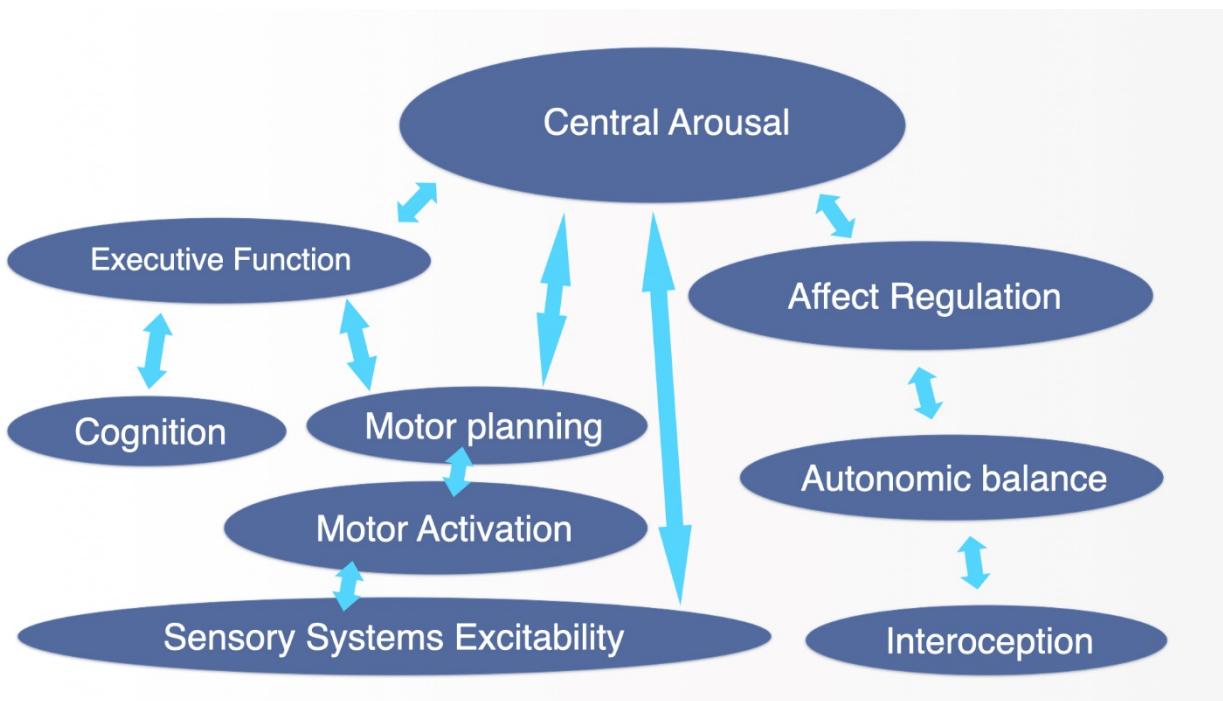


Figure 11. Shown here is a perspective on core regulation that is relevant to the neurofeedback project. Core regulation, the burden of the slow control system, involves the regulatory arc of interoception, autonomic regulation, affect regulation and tonic central arousal. This is the principal responsibility of the right hemisphere. This sets the ambient context for phasic arousal that governs executive function, the sensory systems, and the motor system—the primary burden of the left hemisphere.

The insula is the linchpin in this regulatory arc. As the key hub in the salience network, it integrates information from all bodily systems, as well as information from the environment bearing on status, safety and threat—interoception and exteroception. This informs autonomic and affect regulation, and modulates our feeling states. The insula comes closest to representing the entire individual. Thus Antonio Damasio refers to the insula as manifesting “the sentient self.” Reference here is mainly to the right insula. Despite intimate functional coupling between the two, the right insula has a very different life experience from that of the left.

Arousal disregulation is typically attributable to environmental causation, in particular to early childhood adverse events that predispose the neural networks to an acquired orientation to threat, or more generally to a lack of a sense of safety. This issue prevails broadly in our population. Cerebral instability and hyper-excitability are the other principal failures mode to which a large fraction of the population is heir, and {T3 - T4} is most likely the best recourse.

The clinical population segmented in our practice as follows: Some one-third of clients rely on {T4 - P4} as their starting protocol; some one-third rely entirely on

{T3 - T4} placement for entry into the training; and one-third require both placements right in the first session. Thus {T4 - P4} is called for in two-thirds of all starting sessions, and the same holds for {T3 - T4}. By the time clients graduate from their training, nearly all will have had the benefit of both starting placements. There are always a few who cannot tolerate one or the other.

By 2013, it had become apparent that the distributions of ORF's differed between the two starting placements. For {T4 - P4} the distribution tended to be weighted toward the lowest frequency, whereas for {T3 - T4} the ORFs were more widely distributed, without such a concentration at the lowest frequencies. This might have been problematic for those who needed both starting protocols, but that hasn't been the case. The sensitivity to training frequency was always greatest for the instabilities, so when both protocols are called for, the instabilities play the controlling role. In the hierarchy of regulation in all control systems, stability of the system is the paramount consideration.

In addition to the two principal starting protocols, several other placements have played supporting roles within the ILF framework (Figure 8). The four quadrants of cortex particularize in their training requirements. Right pre-frontal training plays a large role in affect regulation. Left pre-frontal training targets the executive function domain. And left parietal deals with the discernment of details, and thus is relevant to both learning disabilities and fine motor control. The particulars may be found in Sue Othmer's Protocol Guide, which is now in its seventh edition (Othmer, 2019). The ILF protocols are then complemented, as appropriate, with more familiar protocols in the EEG range. Training in the EEG spectral range appears to be more productive if the ILF protocols are used first.

One of the most striking aspects of the existing protocol schema is the lack of reliance on midline sites. This is particularly odd since the primary hubs of the Default Mode are the frontal and parietal hubs, which are most accessible along the midline. Attempts were certainly made at various junctures to bring the critical relationship of the frontal and parietal hubs into more harmonious coordination, but success in that thrust was long in coming. In the resting state, the two hubs are highly correlated in their hemodynamics. Promotion of such correlation motivated the design of a synchrony training protocol for the ILF domain.

ILF synchrony training, with placement at {Fz + Pz}, had immediate and dramatic positive impact on two of our clients who were most severely impaired. This already became apparent after the very first session. These were charity cases that we had been training for a number of years (> 7y in one case; > 25y in the other). As protocols

evolved, they continued to benefit. With ILF synchrony, both benefited to the extent that neither of them is still being seen. Our understanding of these cases is that the front-back relationship never had a chance to develop properly due to early emotional trauma. Whenever that is the issue, repairing the front-back relationship is the clinical priority, in the absence of which normal function likely cannot be restored.

ILF synchrony in the range of 0.01 to 0.06 Hz can be profoundly helpful in reducing social anxiety. Those with crippling anxiety, preventing them from participating in life events, may even see their anxiety and fears subside substantially in a single session. Such single-session effects are then consolidated in subsequent sessions.

It is relevant in this context to draw attention to the recognition of Maltreatment Trauma as a distinct ecophenotype in psychiatry by Martin Teicher and his research group at Harvard (Teicher and Samson, 2013). Maltreatment trauma accounts for more of the variance in connectivity relationships than underlying diagnoses such as Bipolar Disorder and schizophrenia. Whatever one's genetic endowment may be, early emotional trauma is a compounding factor that renders mental dysfunctions much more intractable, and now endogenous neuromodulation is offering a path to recovery.

On the basis of the above, one may view the journey to ever lower frequencies as being largely driven by cases of early emotional trauma. Throughout our history, it tended to be those who failed conventional treatments that sought out neurofeedback. And within that cohort, the most challenging cases pushed the clinical frontier, and these were typically cases with a problematic early history. The earliest and most intractable traumas call for both ILF bipolar and synchrony training for restoration of core regulatory competence.

This training would then be complemented with synchrony training in the alpha and gamma bands, and by other neurotherapies such as the Alpha-Theta experience that facilitates psychological resolution. Jointly these constitute the principal elements of our program of restoring functional competence to the nervous system.

## **Theory and Foundational Studies**

Two book chapters have been written on the theory underlying ILF NF. One deals with the more general question of the frequency basis of neural organization (Othmer, 2017) and the other concerns itself more directly with the infra-low frequency domain (Othmer, 2020). This theory rests largely on the early work of Nina Aladjalova in identifying and characterizing the Slow Control System in the mammalian brain

(Aladjalova, 1964). Tonic regulation is under the explicit management of the right hemisphere, and phasic regulation is more directly managed by the left. This division of labor is so basic that we have yet to observe laterality reversals in our protocols in children who are not mirror-image twins.

Foundational studies have been published by two research organizations in the Russian Federation. The Institute of the Human Brain in St. Petersburg has observed macroscopic alteration of power spectral densities in the ILF regime upon twenty sessions of training in a non-clinical population. A systematic trend toward increased spectral power in the ILF regime was observed. The control group, which underwent conventional biofeedback training, showed smaller changes, and in either direction. The group differences were significant (Grin-Yatsenko et al, 2020). Further analysis of the slow oscillations in this population has just been published (Grin-Yatsenko et al, 2023).

Under the joint sponsorship of the International Institute of Psychosomatic Health in Moscow and the Treatment and Rehabilitation Center of the Russian Federation, a large-scale controlled study has also been performed that documented robust single-session changes in functional connectivity. These could readily be distinguished between veridical and sham training conditions (Dobrushina et al, 2020). This was not intended as an efficacy study, as efficacy was not in question. Rather, the intention was to characterize single-session effects according the several hypotheses.

## **Summary and Conclusion**

Endogenous Neuromodulation has emerged as an efficacious and efficient therapeutic method to redress functional cerebral deficits traceable to early developmental trauma, conditions that have been relatively intractable to date. It is applicable broadly to mental health concerns. In the absence of any overt challenge, the continuous feedback loop can operate at the limits of subtlety and refinement at which state regulation necessarily has to take place.

Viewed in the perspective of classical research designs, the process is inherently sham-controlled. The brain has no impetus to respond to the signal unless and until it recognizes its significance. A prompt, strong physiological response therefore demonstrates that the salience of the signal has been recognized. The matter of sham-controlled training is therefore academic, in that the very existence of an optimal response frequency rules out a placebo model for ILF NF. The existence of the frequency rules, in turn, testifies to the validity, robustness and generality of the ORF concept.

A hierarchically organized, sequential process of improving self-regulatory competence is now in place. The training procedure is inherently controlled, in that protocol status is always a contingency in an A/B paradigm. In complex presentations—which all brains are at the level we get to engage them—trainees necessarily have to serve as their own controls. The method is not reducible to a ‘procedure’ that can be evaluated in conventional group designs. It is most parsimoniously regarded in the skill learning or mastery model. For this project, the brain is in need of information rather than instruction.

The clinical setting has proved ideal for this journey of ‘discovery science.’ We have been drawn forward ineluctably by compelling clinical observations that confounded all pre-conceived notions. Hypotheses necessarily followed from the data; they could not reasonably have been formulated in advance.

## References

- Aladjalova, N.A. (1964). Slow Electrical Processes in the Brain. Elsevier Publishing Company. Elsevier. Web. 2 Feb. 2019
- Beggs JM and Plenz D (2003). Neuronal avalanches in neocortical circuits. *J Neurosci* 23(35):11167-77.
- Birbaumer, N., Elbert, T., Canavan, A.G.M., Rockstroh, B. (1990) Slow Potentials of the Cerebral Cortex and Behavior, *Physiological Reviews*, 70(1), 1-41.
- Birbaumer, N. (1999). Slow cortical potentials: Plasticity, operant control, and behavioral effects. *The Neuroscientist*, 5, 74–78.
- Biswal B, Yetkin FZ, Haughton VM, Hyde JS (1995) Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magn Reson Med* 34: 537–541.
- Dobrushina OR, Vlasova RM, Rumshiskaya AD, Litvinova LD, Mershina EA, Sinitsyn VE, Pechenkova EV (2020), Modulation of Intrinsic Brain Connectivity by Implicit Electroencephalographic Neurofeedback, *Frontiers in Human Neuroscience* 14(192):1-13 doi:10.3389/fnhum.2020.00192
- Friston, K.J. (2009) Modalities, Modes, and Models in Functional Neuroimaging, *Science*, 326(5951), 399-403 DOI: 10.1126/science.1174521
- Gerge, A. (2020). A multifaceted case-vignette integrating neurofeedback and EMDR in the treatment of complex PTSD. *European Journal of Trauma & Dissociation*, 4(3), 100157 <https://doi.org/10.1016/j.ejtd.2020.100157>
- Greicius, M. D., Krasnow, B., Reiss, B. A., & Menon, V. (2003). Functional connectivity in the resting brain: A network analysis of the default mode hypothesis. *Proceedings of the National Academy of Sciences of the United States of America*, 100, 253–258.
- Grin-Yatsenko VA, Othmer S, Ponomarev V, Evdokimov S, Konoplev Y, Kropotov J (2018). Infra-Low Frequency Neurofeedback in Depression: Three case studies, *NeuroRegulation* 5(1): 30-42 DOI: 10.15540/nr.5.1.30

Grin-Yatsenko VA, Kara O, Evdokimov SA, Gregory M, Othmer S, Kropotov JD (2020). Infra-Low Frequency Neurofeedback Modulates Infra-Slow Oscillations of Brain Potentials: A Controlled Study, *J Biomed Eng Res* 4(104): 1-10

Grin-Yatsenko VA, Ponomarev VA, Kropotov JD (2023). The Changes of the Infra-Slow Fluctuations of the Brain Potentials under Influence of Infra-Low Frequency Neurofeedback, *Journal of Evolutionary Biochemistry and Physiology*, 59(3), 831-840

Gruzelier J, Hardman E, Wild J, et al (1999). Learned control of interhemispheric slow potential negativity in schizophrenia. *International Journal of Psychophysiology* 34:341-8.

He B.J. and Raichle M.E., (2009) The fMRI signal, slow cortical potential, and consciousness, *Trends in Cognitive Sciences* 13(7): 302-309 doi:10.1016/j.tics.2009.04.004

Jensen, M.P., Grierson, C., Tracy-Smith, V., Bacigalupi, S.C., Othmer, S. (2007). Neurofeedback treatment for pain associated with Complex Regional Pain Syndrome Type I, *Journal of Neurotherapy*, 11(1), pp 45-53

Kelson, C. (2013). The Impact of EEG Biofeedback on Veterans' Symptoms of Post-Traumatic Stress Disorder, Dissertation, Chicago School of Professional Psychology, unpublished.

Kitzbichler MG, Smith ML, Christiansen SR, et al (2009). Broadband Criticality of Human Brain Network Synchronization. *PLOS Comput Biol* 5(3):e1000314. doi:10.1371/journal.pcbi.1000314

Kirk, HW, editor (2015, 2020). Restoring the Brain, Taylor and Francis, Boca Raton, FL

Kotchoubey B, Strehl U, Uhlmann C, et al (2001). Modification of slow cortical potentials in patients with refractory epilepsy: a controlled outcome study. *Epilepsia* 42:406-16.

Legarda, S. B., McMahon, D., Othmer, S., & Othmer, S. (2011). Clinical neurofeedback: Case studies, Proposed Mechanism, and Implications for Pediatric Neurology Practice. *Journal of Child Neurology*, 26, 1045–1051.

Othmer S, Othmer SF (2009), Post Traumatic Stress Disorder - The Neurofeedback Remedy Siegfried Othmer, PhD, and Susan F. Othmer, BA *Biofeedback Magazine*, Volume 37, Issue 1, pp. 24-31

Othmer, S. (2009) Neuromodulation Technologies: An Attempt at Classification. Chapter 1 in *Introduction to QEEG and Neurofeedback: Advanced Theory and Applications* (Second Edition), Thomas Budzynski, James R. Evans, and Andrew Abarbanel, Eds, Elsevier, pp. 3-26.

Othmer S, Othmer SF, Legarda SB (2011) Clinical Neurofeedback: Training Brain Behavior, Treatment Strategies - Pediatric Neurology and Psychiatry, 2(1):67-73

Othmer, S., Othmer, S.F., Kaiser, D.A., Putman, J. (2013). Endogenous Neuromodulation at Infra-Low Frequencies. *Seminars in Pediatric Neurology*, 20(4): 246-260.

Othmer, S., Othmer, S.F. (2017). Toward a Frequency-based Theory of Neurofeedback. Chapter 8 in *Rhythmic Stimulation Procedures in Neuromodulation*, James R. Evans and Robert A. Turner, Eds., Academic Press (London), 2017, pp. 254-307

Othmer, S F (2019) The Protocol Guide (Seventh Edition), EEGInfo Press, Woodland Hills, CA

Othmer, S., Editor (2022). Endogenous Neuromodulation in the Infra-Low Frequency Regime, *Frontiers of Human Neuroscience*, <https://www.frontiersin.org/research-topics/24349/endogenous-neuromodulation-in-the-infra-low-frequency-regime#articles>

Quirk, D. A. (1995). Composite biofeedback conditioning and dangerous offenders: III. Journal of Neurotherapy. 1 (2), 44-54.

Raichle ME, MacLeod AM, Snyder AZ, Power WJ, and Gusnard DA (2001), A default mode of brain function, Proc Nat Acad Sci 98(2): 676-682 DOI: 10.1073/pnas.98.2.676

Raichle, ME (2010 ) Two views of brain function, Trends in Cog Neurosci 14(4):180-190  
doi:10.1016/j.tics.2010.01.008

Raichle ME (2011) The Restless Brain, Brain Connectivity 1(1), 3 – 12  
DOI: 10.1089/brain.2011.0019

Rockstroh B, Elbert T, Canavan AG, Lutzenberger W, Birbaumer N. (1989). Slow Cortical Potentials and Behavior, Second ed. Baltimore: Urban & Schwarzenberg.

Rockstroh, B., Elbert, T., Birbaumer, N., Wolf, P., Duchtling-Roth, A., Reker, M., et al. (1993). Cortical self-regulation in patients with epilepsies. Epilepsy Research, 14, 63–72.

Schneider F, Rockstroh B, Heimann H, et al (1992). Self-regulation of slow cortical potentials in psychiatric patients: Schizophrenia. Biofeedback & Self-Regulation 17:277-92.

Schneider H, Alfred A, Wandernoth B, Blunck A. (2019), Therapeutic effect of Infra-Low-Frequency (ILF-) Neurofeedback training on Children and Adolescents with Attention Deficit (Hyperkinetic) Disorder, Clinical Neurophysiology 130(8):e125-e126 DOI: 10.1016/j.clinph.2019.04.619

Siniatchkin, M., Hierundar, A., Kropp, P., Kuhnert, R., Gerber,W. D., & Stephani, U. (2000). Self-regulation of slow cortical potentials in children with migraine: An exploratory study. Applied Psychophysiology & Biofeedback, 25, 13–32.

Strehl, U., Leins, U., Goth, G., Klinger, Ch., Hinterberger, Th., & Birbaumer, N. (2006). Self-regulation of slow cortical potentials—A new treatment for children with ADHD. Pediatrics, 118, 1530–1540.

Strehl, U. (2009). Slow Cortical Potentials Neurofeedback. Journal of Neurotherapy: 13(2): 117-126  
DOI: 10.1080/10874200902885936

Teicher, M. H. & Samson, J. A. (2013) Childhood maltreatment and psychopathology: a case for ecophenotypic variants as clinically and neurobiologically distinct subtypes. Am. J. Psychiatry 170, 1114–1133 (2013).