NeuroRegulation

# Infra-slow Fluctuation Training in Clinical Practice: A Technical History

*Mark Llewellyn Smith*[1*], *Thomas F. Collura*[2,3], *John Ferrera*[4], *Jacqueline de Vries*[5]

[1]Neurofeedback Services of New York, New York, USA
[2]BrainMaster Technologies, Inc., Bedford, Ohio, USA
[3]The Brain Enrichment Center, Bedford, Ohio, USA
[4]Private Practice, New York, New York, USA
[5]Crossroads Center of New Jersey, Ridgewood, New Jersey, USA

***Address correspondence to:** Mark Llewellyn Smith, Neurofeedback Services of New York, 140 West 79th Street, #2B, New York, NY, 10024. Email: neurofeedbackservicesny@gmail.com



## Abstract

Infra-slow Fluctuation (ISF) electroencephalogram (EEG) biofeedback is a recent development in neurofeedback training. This form of training is focused on the lowest energy the brain produces (< 0.1 Hz). The intervention is performed with a Direct Current (DC) coupled neurofeedback amplifier. It is distinct from Slow Cortical Potential (SCP) training and Infra-Low Frequency (ILF) training. It shares a similar optimization process with ILF that focuses on emergent state shifts within sessions. These state shifts require frequency adjustments that optimize client response to the training in real time. Due to the technical difficulties inherent in recording these frequencies, EEG investigators largely neglected this low energy until recently. As DC amplifiers improved, the slow frequencies became a signal of increasing interest to researchers. Research has demonstrated an important role for the infra-slow oscillations in clinical work. Positive clinical case outcomes suggest that a larger controlled study is warranted. The technical, clinical, and equipment requirements of the intervention make this form of neurofeedback unique in the pantheon of EEG biofeedback interventions.

***Keywords***: neurofeedback, biofeedback; infra-slow fluctuation; infra-slow oscillation; direct current

## History

The traditional method of recording the electroencephalogram (EEG) with an Alternating Current (AC) amplifier and a “corner” or cutoff frequency of approximately 0.5 Hz is more than half a century old (Collura, 1993). These AC amplifiers produced attenuated signals that allowed researchers to focus on the faster oscillations, considered the most salient features in the human EEG at that time. Before that time, attempts to record slow events produced electrode drifts that tended to saturate the amplifiers and so hastened the advent of the built-in high-pass filters on all amplifiers. The consequence of the ubiquitous initiation of high-pass filtering was a loss of all infra-slow dynamics, whether artifactual or physiological.

The first human DC recordings became possible with the introduction of chopper-stabilized amplifiers in the 1950s. A lack of stable electrodes and the need to manually cancel offset voltages prevented the widespread use of the technology (Tallgren, 2006). As DC equipment improved, researchers began to describe the observed phenomena at frequencies below the conventional limits. One definition proposed that EEG in the frequency range below 0.5 Hz consists of a standing potential (SP) and a slowly changing potential (SCP) (Manaka & Sano, 1979).

In the following decades DC coupled amplifiers became more common. The terms changed from standing potential to "DC potential shifts" and slowly changing potential to "slow cortical potentials" (Birbaumer, Elbert, Canavan, & Rockstroh, 1990; Elbert, Rockstroh, Lutzenberger, & Birbaumer, 1980). DC potential shifts are non-oscillatory fluctuations in amplitude measured in millivolts (Collura, 2009). This rise and fall of the large amplitude of the DC potential shift is frequent and impacts the smaller energy of the frequency domain measured in microvolts.

Slow Cortical Potentials (SCP) are changes of cortical polarization lasting several hundred milliseconds to several seconds. SCPs are related to the excitability level of underlying cortical regions. Negative SCP shifts reflect higher cortical excitability while positive shifts reflect reduced excitability or even inhibition.

SCP training has been employed, largely in Europe, for more than 30 years (Elbert et al., 1980). It has been used to train Epilepsy (Birbaumer et al., 1994), Brain-Computer Interface (Wolpaw, Birbaumer, McFarland, Pfurtscheller, & Vaughan, 2002), and ADHD (Birbaumer & Cohen, 2007; Heinrich, Gevensleben, Freisleder, Moll, & Rothenberger, 2004). SCP training is a "one size fits all protocol" with the majority of the training done at the vertex. As first developed, the client attempted to produce cortical excitation, a negative DC shift, in the case of ADHD; or cortical inhibition, a positive DC shift, in the case of Epilepsy over the course of many short trials (Birbaumer, 1999; Birbaumer et al., 1994). More recently SCP training has evolved to train in both negative and positive cortical shifts in the same session with proportions of negative and positive trials dependent on client presentation (Strehl et al., 2006).

Infra-slow Fluctuation (ISF) training is frequency-based training. These slow rhythms are influenced by changes in amplitude and polarization of the DC signal, but ISF neurofeedback is not SCP training.

ISF training owes its lineage to the early Beta/SMR training of Susan Othmer and EEG Spectrum (Kaiser & Othmer, 2000). That intervention was done with a single channel of EEG and an intra-hemispheric bipolar montage on the motor strip and temporal lobes. The starting frequency was in the 12–18 Hz range depending on the targeted hemisphere. The Othmers and others (Putman, Othmer, Othmer, & Pollock, 2005; Stokes & Lappin, 2010), modified this technique to include inter-hemispheric placements beginning on the temporal lobes. Instead of set reward bands, a 3 Hz window was shifted up or down contingent upon client response. The intervention produced immediate state shifts in the client. The trainer targeted state regulation in real time by discovering an optimum frequency through trial and error for each client. Success was defined by the immediate improvement in affect and arousal regulation in session and ultimately by generalized improvements in behavioral and state regulation in life. Over time, it became apparent that the vast majority of clients were finding an optimum clinical response at lower and lower frequencies until 2007, when the beginning frequency was established at 0–3 Hz.

It was at that time that a bifurcation in the field took place with one group of practitioners opting for an AC amplifier and another group, including the lead author, choosing a DC coupled encoder. Both groups continued the downward ramp of frequency optimization, narrowing the training window to less than 3 Hz.

As the optimum frequencies trained descended below 0.1 Hz, it became apparent to the DC amplifier users that optimum response was more readily achieved when training was executed with the amplifier in DC mode. The integration of the lower (DC) and higher (AC) energies produced enough "bounce" in the low alternating current domain to filter and to train the Ultradian Rhythms (< 0.01 Hz) (Palva & Palva, 2012) with more clarity and less noise in the signal.

## The ISF Signal

Amplifier limitations that led to the elimination of lower frequencies in routine EEG determined the scope of brain research. As commercial DC coupled amplifiers became available, researchers began to address frequencies outside the traditional bandwidth of 0.5–50 Hz. Evidence increased that salient spontaneous EEG activity in human brain activity related to physiological and pathological behavior were being ignored. A group of researchers, largely in Europe, began to investigate this low phenomena. Their process became known as DC-EEG or FB-EEG (Full-band EEG). FB-EEG research suggests that the infra-slow is endogenously driven neuronal activity that is crucial in shaping brain network connectivity (Vanhatalo, Voipio, & Kaila, 2005).

For two decades researchers have proposed that neurons, glial cells, and blood may be regarded as compound generators of these infra-slow bioelectrical phenomena (Hughes, Lőrincz, Parri, & Crunelli, 2011; Zschocke & Speckmann, 1993). Thalamocortical neurons have been observed to exhibit robust infra-slow oscillations (ISOs), in vitro, at approximately 0.005–0.1 Hz (Lőrincz, Geall, Bao, Crunelli, & Hughes, 2009). After a reappraisal of *in vivo* and *in vitro* evidence, Crunelli and Hughes (2010) have proposed a three cardinal oscillator model that identifies one cortical and two thalamic sources of infra-slow frequencies. Astrocytes have recently been identified by Hughes et al. (2011) as a source of ISOs in the 0.003–0.1 frequency range. These researchers observed neurons in cat Thalamus succumbing to a cyclic inhibitory influence that they proposed was generated in the slow regime by Thalamocortical astrocytes.

This lower frequency band is embedded in DC potential shifts in amplitude. A spectral display (Figure 1) clearly images the correspondence of the ISOs and DC standing potential shifts. As DC fluctuates on the mV scale, the frequency domain responds in the lower regime and at much higher frequencies as well. These cross frequency correlations are well documented (Keković, Sekulić, Podgorac, Mihaljev-Martinov, & Gebauer-Bukurov, 2012; Nir et al., 2008; Pfurtscheller, Daly, Bauernfeind, & Müller-Putz, 2012; Vanhatalo et al., 2004; Zschocke & Speckmann, 1993). It is the interaction of frequency and DC potential shift that drove the choice of the designation ISF training. The DC fluctuations were observed to drive the microvolt changes in the slow frequency regime and offer a target for feedback.
In Figure 1, the morphology of the two signals are shown compared to the damped average of each signal. DC is measured in millivolts, while ISF is rendered in microvolts. It is this

recurrent amplitude change in the ISF signal, sometimes only a fraction of a microvolt, which is the focus of reinforcement, not the return of the slow oscillation itself.

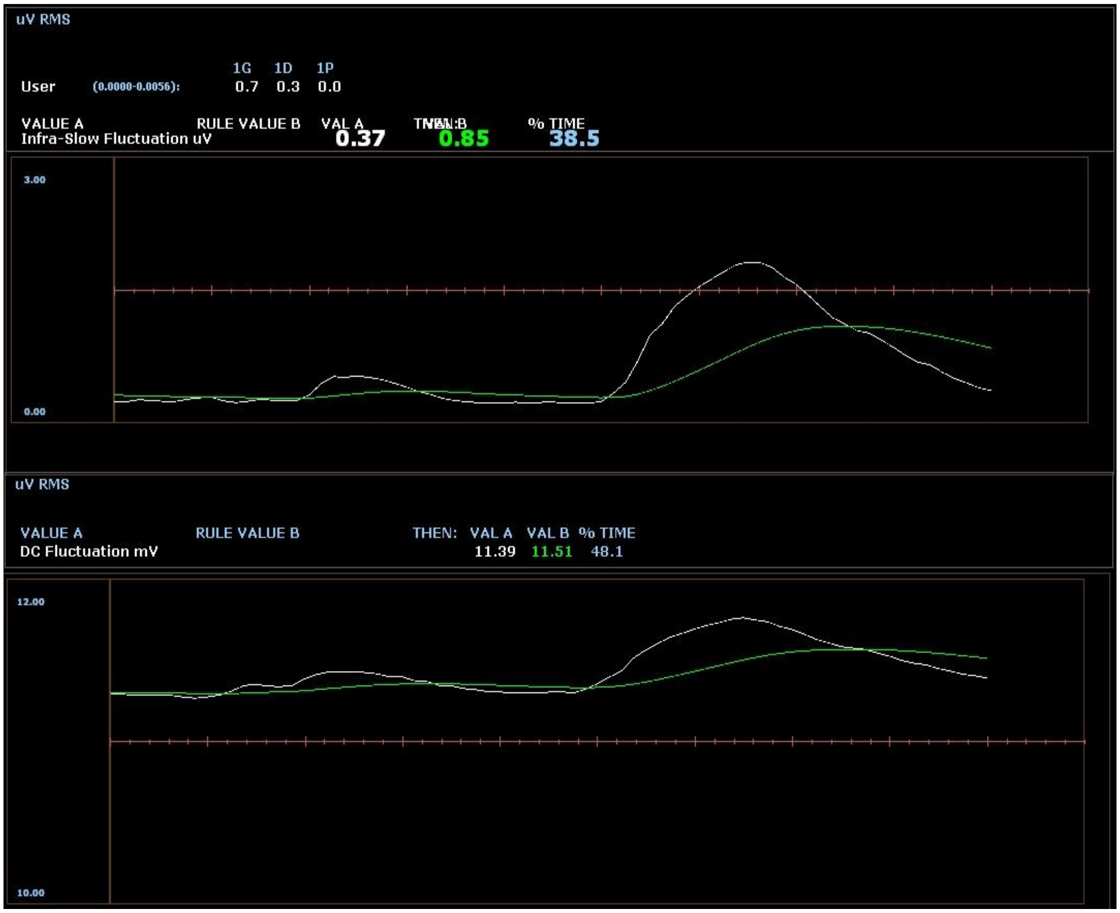


**Figure 1**. Top graph labeled: Infra-slow Fluctuation uV. Images the Alternating Current ISF signal in microvolts, the white line, with the damped average of the signal, the green line. Bottom graph labeled: DC Fluctuation mV. Images the amplitude fluctuations of Direct current measured in milivolts, the white line, with the damped average of the signal, the green line. Notice the similarity between the rise and fall in amplitudes of the two signals.

It is important to note that when working with very slow signals, although it is possible to quantify the system response as a frequency, it may be equivalently considered as a time-constant. In linear systems theory, it can be shown that for any filter there is a direct trade-off between frequency response and time-response, and that time and frequency can be considered as equivalent, alternative ways to view the system. The following figure (Figure 2) from Collura (1995) illustrates the relationship between the low-cutoff frequency and the time-constant.

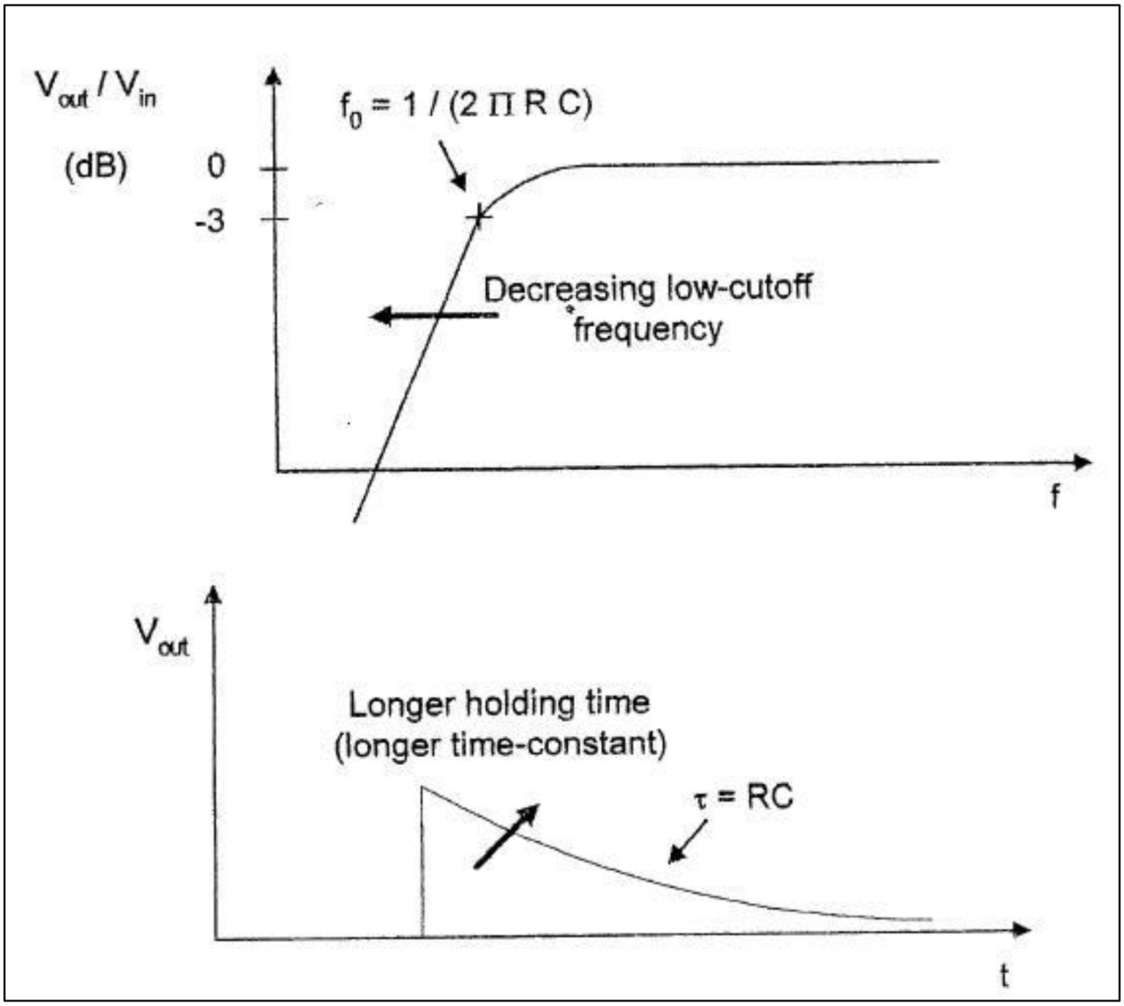


**Figure 2**. Relationship between cutoff frequency (top) and holding time-constant (bottom). A lower cutoff frequency is associated with a longer time-constant. These are shown for a first-order filter, but are representative of any order filter. Specifically, for a first-order filter, the time-constant is defined (approximately) as: t = 1 / 2 * PI * fc . For example, a low-cut frequency of 0.3 Hz would have a time constant of 1 / 2 * PI * 0.3 = 0.53 seconds. The following Figure 3, of a vintage Grass amplifier, shows how this relationship is implicit in an amplifier. The selector for the low-frequency cutoff, with settings of 0.15, 0.3, 1, 3, and 10 Hz, is shown with a second set of indicators beneath, designating, for this amplifier, time-constants of 0.45, 0.24, 0.1, 0.04, and 0.015 seconds.

Because the filter is removing low frequencies, the time-constant reflects the rate at which the output tends to “recover” to the baseline. The lower the corner frequency, the longer it takes to recover. Therefore, lower cutoff frequencies are associated with the ability to “hold” the baseline longer, hence reflect longer-term processes. The time-constant shows that the input does not have to be cyclic or repetitive, but can be viewed as a transient, or fleeting, event, that is passed by the filter only if it reaches a certain magnitude of displacement within a certain time. With a DC amplifier, the output time-constant is infinite, reflecting the fact that the low cutoff frequency is 0.0000 to an arbitrary precision.


**Figure 3**. Grass EEG amplifier showing combined “low frequency / time-constant” control, illustrating the interdependence of these two settings.

## Methods

### Amplification

ISF training uses Ag/AgCl electrodes and a DC coupled amplifier. As configured for ISF training, BrainMaster’s Atlantis amplifier uses first-order Butterworth filters utilizing quadrature methods with an implicit envelope detection method that provides information faster than conventional peak-to-peak detection processes. Depending on the low-cutoff frequency applied in the software, the resulting filter will also have a corresponding time-constant. For example, with a setting of 0.002 Hz as described in this report, the associated time-constant would be 175 seconds, or 2.92 minutes. This does not imply that the signal must oscillate with a period of 2.92 minutes, however. It simply indicates that when there is a shift in the baseline, the amplifier would require approximately 3 minutes to move the bulk of its recovery back to baseline. In other words, the amplifier “holds” onto the DC level of the value for a very long time, compared to the occurrences of each fluctuation or baseline shift.

### Feedback Parametrics

The optimum frequency is reflected back to the client with two reward sounds, a higher tone when the amplitude increases more than 15% and a lower tone when the amplitude decreases more than 15% compared to a damped average of the signal. There is no sustained reward criteria; the client is rewarded the instant the reward parameters are met and continues for the duration of the condition. In addition there is no refractory period between rewards. The reward structure allows for the rapid transmission of information to the client concerning minute changes in amplitude of the ISF signal.

The ISF reward band typically starts at a low band-pass filter setting of 0 to a high band-pass filter setting of 0.002 Hz, and ranges to a high band-pass filter setting of 0.012 Hz. Additionally, in the basic protocol, the EEG is inhibited from 1 to 40 Hz in small bands: 1–3, 4–7, 8–12, 12–15, 15–20, 20–30, and 30–40 Hz. Each band is inhibited 3% of the time with an auto-thresholding function. These inhibits are fed back to the client via dimming of a DVD or the playing of a video game. Advanced protocols render simultaneous bipolar and referential montages allowing for combinations of ISF and synchrony training and ISF and referential enhancement. These sophisticated protocols are applied based on in-training z-score monitoring and pre/post QEEG analysis.

### Optimizing Training

Clinical experience has made it clear that the best treatment response occurs when an Optimum Frequency (OF) is identified for each individual client. This process is undertaken for every client at either of two 10/20 sites: T4/P4 or T3/T4. The OF identification process may take place over several neurofeedback sessions and once identified rarely changes. Once the OF is known, frequency adjustments become necessary depending on the cortical area trained and the hemisphere involved. Some trainee outliers optimize above 0.012 and fewer still optimize below 0.002 with the vast majority between 0.002 and 0.012 Hz. The selection of cortical areas to be trained has traditionally been dictated by the relationship between client complaint and areas of cortical function. Recently the process of training site selection has been increasingly influenced by quantitative EEG (QEEG) assessments.

Optimization of frequency is achieved through a colloquy between therapist and client that leads to an optimum state of affect and arousal regulation in session. In addition, peripheral biofeedback measures such as heart rate, heart rate variability, Galvanic skin response, and skin temperature, are used to aid in the identification of autonomic balance and best response to the frequency parametrics.

## Clinical Rationale

Researchers in Russia first identified the infra-slow rhythm nearly 60 years ago (Aladjalova, 1957; Aladjalova, 1964). Scientists at the Institute of Biophysics in Moscow implanted electrodes in the brains of rabbits and observed two general rhythms: one in the 6–8 second, 0.6–0.8 Hz range; and the other slow periodic oscillation was identified in the 60–90 second, 0.023–0.0165 Hz range. Aladjalova labeled these rhythms “infra-slow” to distinguish them from the “slow wave” of the EEG.

The infra-slow band was observed to increase in amplitude and frequency when experimental animals were subjected to stress-producing stimuli. The Russian researchers observed that poisoning, asphyxia, and irritation of subcortical structures intensified ISOs.

They theorized that the increase in amplitude of the ISOs reflected the Hypothalamus's reparative, parasympathetic, response. Supporting a role in the function of the neuroendocrine system, Marshall (Marshall, Mölle, Fehm, & Born, 2000) discovered an association between ISOs and Hypothalamic-Pituitary secretory activity. An increase in the amplitude of infra-slow periodicities between 64 and 320 seconds was coupled with the onset of the pulse of the Luteinizing hormone. This hormone, released by the Hypothalamus, triggers ovulation and stimulates the production of testosterone.

ISOs' prominence during sleep has been established. However, the functional significance of ISOs for sleep physiology remains unclear. The low regime has been postulated to coordinate activity between cortico-cortical networks (Buzsaki, 2006). In this way, the infra-slow frequencies appear to organize a broad dissociation of cortical and sub-cortical activities during sleep (Picchioni et al., 2011) in areas that include the paramedian heteromodal cortices. Simultaneous positive associative correlations were established for the ISOs in the Cerebellum, Thalamus, Basil Ganglia, lateral neocortices, and Hippocampus. According to Picchioni, this suggests a role for ISOs in the organization of sleep-dependent neuroplastic processes generally and the consolidation of episodic memory specifically.

Recent research suggests that ISOs are embedded in and determinant of the excitability cycle of higher frequencies (Ko, Darvas, Poliakov, Ojemann, & Sorensen, 2011; Vanhatalo et al., 2004). Ko and workers revealed that the Default Mode Network (DMN) is characterized by high gamma band (65–110 Hz) coherence at infra-slow frequencies. This coherence, centered at 0.015 Hz, forms the neurophysiological basis of the DMN. Vanhatalo et al. (2004) established a role for the infra-slow frequencies in the control of gross cortical excitability. This research detected a close association between the ISOs and cyclic modulation of fast EEG activity. The phase of the ISO revealed a robust correlation with the amplitude of faster frequencies. Moreover, these low frequencies were observed to be tightly associated with K complexes, the largest event in the human EEG, and interictal epileptiform discharges: high amplitude paroxysmal activity. In fact, Vanhatalo became so convinced of the ISOs' centrality in cortex that he stated that any attempt to attenuate the signal eliminates the most salient features of the human EEG (Vanhatalo et al., 2005).

Pfurtscheller (1976) reported the first observations of embedded frequencies in the human EEG, and observed ISOs in the alpha (8–14 Hz) frequency band. Later studies expanded on this work identifying human fluctuations in the theta, alpha, and beta (14–30 Hz) frequency bands that were power law autocorrelated in time scales from tens to hundreds of seconds exhibiting scale free, fractal like dynamics across the infra-slow frequency band (Ko et al., 2011; Linkenkaer-Hansen, Nikouline, Palva, & Ilmoniemi, 2001). Direct cortical recordings in animals and humans observed the amplitudes and coherence of frequencies from delta to high gamma (100–150 Hz) exhibit robust ISOs and spectral power-law scaling (Ko et al., 2011).

According to researchers,(Dong et al., 2012; Mairena et al., 2012; Monto, Palva, Voipio, & Palva, 2008) human behavioral performance is correlated with the ISFs in ongoing brain activity. Monto detected a strong correlation between a subject's ability to detect a sensory stimuli and the phase of the low frequency signal. Mairena and co-workers posited that the ISO is nested in six frequency bands and is related to fluctuations in sensory detection.

More broadly, ISO has been associated with the DMN of the human cerebral cortex (Liu, Fukunaga, de Zwart, & Duyn, 2010) and appears to be related to ADHD symptom status (Helps et al., 2010; Tye et al., 2012). Supporting this correlation, Broyd (Broyd, Helps, &

Sonuga-Barke, 2011) found attention-induced deactivations of the ISF signal do not occur in Default Mode areas of cortex in subjects with ADHD, suggesting that they get "stuck" in self-referential processing and are unable to turn off areas of cortex when appropriate. This resting brain network is anti-correlated with a task-positive network. The ISF reflects a toggling mechanism that switches between the DMN, the network of introspective and self-referential thought, and the task positive network that responds to extrospective stimuli.

The ISO becomes intensified by agents that elicit a defense reaction similar to the response to "stress." Although the detailed physiological mechanisms underlying these Ultradian Rhythms have yet to be determined, some of the earliest research may provide data from which we can speculate on a precise mechanism of action of ISF training. In addition to its role in organizing neuronal networks, Aladjalova's research (Aladjalova, 1957, 1964) suggests the efficacy of ISF training may lie in the impact on the Hypothalamus.

The Hypothalamus is situated within the limbic system in the temporal lobes and plays an integral role in affective response as well as a vital role in maintaining homeostasis. It is the control center for many autonomic functions of the peripheral nervous system.

Hypothalamic hormones control pituitary hormone secretion, which in turn manages adrenal secretion of epinephrine and norepinephrine, the hormones that organize sympathetic nervous system response. Known as the Hypothalamic–Pituitary–Adrenal (HPA) Axis, this organ system has feedback loops that promote reparative, parasympathetic nervous system, response as well.

ISF training places an electrode on the temporal lobes as one of two bipolar placements on the scalp. The other placement may be any of the other nineteen 10/20 sites. It is proposed that this configuration may explain the behavioral data of calming, arousal reduction, and attention promotion observed among trainees. Our clinical data suggest that a bipolar electrode configuration and an optimum frequency promote the normalization of activation, as well as the communication between and within neuronal networks. So theoretically it regulates the activation of brain areas linked in chronic autonomic stress and normalizes the communication between the hypothalamic and limbic areas, separating the non-temporal area from the HPA distress signal.

Palva and Palva (2012) make a demarcation between the infra-slow (0.01–0.1 Hz) and the Ultradian rhythm (< 0.01 Hz) and refer to the former as ISFs. They point out in their research that the blood oxygenation-level dependent (BOLD) signals are correlated with constellations of brain regions that are very similar to networks that are correlated with the ISF signal. They note the direct association between ISFs in amplitude and behavioral performance with ISFs in the BOLD signal. The researchers concluded that ISFs arise from local cellular level mechanisms, as well as blood, and reflect the same underlying physiological phenomena: a superstructure of interrelating ISFs that regulates the integration within and decoupling between active neuronal networks.

We propose that ISF neurofeedback addresses this superstructure of interrelating neuronal networks. We submit that our pre-post QEEGs reveal changes in activation measures but especially in network dynamics as reflected by the coherence metric. The modification of information sharing between cortical areas produced by ISF training is consistent with research that demonstrates a role for the ISF in the regulation of neuronal networks. Addressing the integration of networks responsible for memory, affective response, autonomic regulation, and attention—to mention a few—may account for the reduction in symptom severity among our clients.

Our pre-post behavioral data is consistent with the theory that ISF regulates autonomic function. Appropriate affective behavior in a school setting was the general outcome for special needs children trained in this form of neurofeedback. ASD and emotionally disturbed children demonstrated improvements on the Child Behavior Checklist related to tantrums and aggressive behavior. Moreover, the ability to attend was improved as was social functioning. The pre-post training QEEG data is consistent with the ISO research in demonstrating an interaction with the phase relationships between cortical areas. In addition to improvements in absolute power, our data demonstrates substantial change in coherence relationships between cortical regions. The remediation of coherence values is resonant with the research that suggests a central role for the ISO in functional network communication (See the following case studies).

## Clinical Data

What follows are clinical examples of ISF training. First we present pre-post ISF training behavioral data on a group of special needs children trained in a school setting. Two individual cases with pre-post QEEGs are then offered to demonstrate the remediation of network communication and absolute power distribution that results from ISF training.

### Results of a School-Based Program

ISF neurofeedback was used as an intervention for a group of school-aged children in New York City. The population consisted of children with varying degrees of learning and developmental disabilities, including some who met criteria for high-functioning autism, others who met criteria for Asperger's syndrome, and still others with disorders of anxiety. All of the children also had sensory processing issues, some more severe than others. In addition, all of the participants were having significant difficulties meeting the demands of their school environment, despite being placed in supportive, specialized academic settings and receiving the services indicated on their Individual Education Plan (IEP). More information about each participant is included below. Admission to the neurofeedback program was based on parent or teacher referral, and students were excluded if they displayed signs of psychosis, uncontrolled seizures, recent traumatic brain injury, or if their medication regimen was too complex and/or unstable.

In total, 17 students were enrolled in the program, ranging in age from 6 to 15 years. In order to help conceptualize the experimental group and the effects of treatment, students were grouped into two broad clinical categories, Emotional Disorders (ED) or Pervasive Developmental Disorders (PDD). Participants in the ED group included students with a primary diagnosis of anxiety or another mood-related disorder, while those in the PDD group included children who were diagnosed to be on the autistic spectrum. Regardless of clinical category, all of the participants were having trouble meeting the academic and/or social demands of their school environment. In the most extreme cases, students were at serious risk of a forced transfer to a different school. Therefore, in addition to being grouped by their main diagnostic category, participants were also grouped according to the amount of difficulty they were having at school (i.e., high, moderate, or low risk) as shown in Table 1.

**Table 1**
*Participants Grouped by Clinical Categories and School Risk*

<table>
<tr><th colspan="3">Main Group</th></tr>
<tr><td colspan="2">ED (n = 7)<br>Participants from the ED group (7 total) included three students with a combination of social and generalized anxiety, three students with reactive attachment disorder, and one student with an atypical form of bipolar depression.</td><td>PDD (n = 10)<br>Participants from the PDD group (10 total) included children diagnosed to be on the autistic spectrum. The group included students with High Functioning Autism (HFA) and Asperger’s syndrome.</td></tr>
<tr><th colspan="3">Subgroups</th></tr>
<tr><td>Low Risk<br>Student is making adequate academic and social progress.</td><td>Moderate Risk<br>Student exhibits emotional and/or behavioral difficulties that hinder academic progress and/or leads to behavioral outbursts during school. Student at moderate risk of a forced transfer to a different school.</td><td>High Risk<br>Exhibits significant emotional and/or behavioral difficulties, including disruptive classroom behavior, that cause student to miss a significant amount of instructional time. Student at serious risk of forced transfer to another school as a result of disruptive classroom behavior and lack of adequate academic and/or social development.</td></tr>
</table>

Participants from the ED group (7 total) included those with a primary presentation of anxiety and/or depression. This group included three students with a combination of social and generalized anxiety, three students with reactive attachment disorder, and one student with an atypical form of bipolar depression. The three students with social and/or generalized anxiety were having difficulty initiating and completing tasks at school, which was causing them to underperform and become socially isolated. Regarding sensory issues, these students were hypersensitive, meaning they had a tendency to overreact to seemingly innocuous stimuli (i.e., touch, noises). The remaining four students in this group had difficulty regulating their emotional response to academic difficulties and/or social challenges, which led to serious behavioral disruptions and ultimately to removal from the classroom. Regarding sensory issues, these students were hyposensitive, meaning they were under-aroused and had a tendency to seek out excessive amounts of stimulation.

Participants from the PDD group (10 total) included children with High Functioning Autism (HFA) or Asperger's syndrome. The presenting concern for many of these students was emotional reactivity, or the tendency to overreact in response to certain environmental stressors or challenges. For these students, hypersensitivity toward various environmental stressors led to disruptive outbursts, making it difficult for many of them to either remain in the classroom and/or to transition between different classes and activities. These students are often labeled inattentive; while this may be an accurate description of their classroom behavior, it is important to distinguish them from students with primary disorders of attention (i.e., ADHD). Students with a primary diagnosis of ADHD were not intentionally excluded from the experimental group; however, no students with this profile were enrolled into the program.

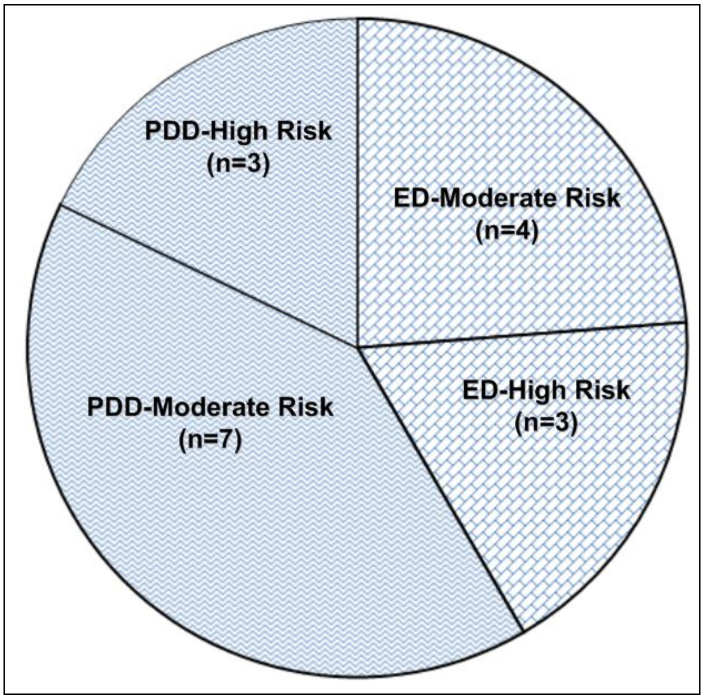


**Figure 4**. Pre-treatment breakdown of participants by diagnosis and presenting concern *ED = Emotional Disorder or **PDD = Pervasive Developmental Disorder. Results based on operationally defined construct (i.e., low, moderate, or high risk).

Fourteen of the 17 students had a definite positive response to ISF neurofeedback training that involved either: (1) a significant reduction of behavioral disruptions, (2) a reduction or elimination of psychotropic medication, and/or (3) improved ability to sustain attention during class and continued academic progress. Of the remaining two students, one had a positive response that is confounded by the initiation of an SSRI at the beginning of the program (a selectively mute child who saw a tremendous improvement in symptoms after about only one week on the SSRI and two weeks with neurofeedback). The other two students were determined to be at status quo at the completion of treatment.

**Table 2**
*Summary of Treatment Population*

| # | Group: (ED *or PDD**) DSM Diagnosis | Subgroup, Pre-treatment | Dependant Measure | 6-Month Follow-Up | Subgroup, Post-treatment |
|---|---|---|---|---|---|
| 1 | ED<br>Reactive attachment disorder | Moderate Risk | Ability to control behavioral outbursts at school and home. | Controls behavior at school, making continued academic progress | Low Risk |
| 2 | ED<br>Social anxiety | Moderate Risk | Avoidance of social activities, procrastination of HW | Increased capacity for social interaction; transferred to a more demanding academic environment and flourishing | Low Risk; now thriving in a mainstream school |
| 3 | ED<br>Selective mutism | Moderate Risk | Ability to express knowledge verbally and in writing | Now able to consistently express himself verbally and in writing; transferred to a more demanding environment and flourishing | Low Risk; now thriving in a mainstream school |
| 4 | PDD<br>HFA/Asperger's, SPD | High Risk | Behavioral outbursts, ability to remain in classroom | Making continued progress at same school | Low Risk |
| 5 | PDD<br>HFA/Asperger's | Moderate Risk | Ability to meet academic demands | Making continued progress at same school | Moderate Risk |
| 6 | PDD<br>High-functioning ability to meet demands of environment, Autism | Moderate Risk | Making continued progress at same school academic demands | Making continued progress at same school | Low Risk |
| 7 | PDD<br>High ability to meet demands of behavioral outbursts, functioning Autism/Asperger's, SPD | High Risk | Ability to remain in classroom | Status quo | Moderate Risk |
| 8 | PDD<br>HFA/Asperger's, SPD | High Risk | Disruptive behavior, ability to remain in classroom | No longer at risk of transfer, making progress | Moderate Risk |
| 9 | PDD<br>HFA/Asperger's, SPD | High Risk | Behavioral outbursts, ability to remain in classroom | No longer at risk of transfer, making progress | Moderate Risk |
| 10 | PDD<br>HFA, SPD | High Risk | Behavioral outbursts, ability to remain in classroom | No longer at risk of transfer, making progress | Low Risk |
| 11 | PDD<br>HFA, SPD | Moderate Risk | Ability to meet academic demands | Making continued progress at same school | Low Risk |

| # | Group: (ED *or PDD**) DSM Diagnosis | Subgroup, Pre-treatment | Dependant Measure | 6-Month Follow-Up | Subgroup, Post-treatment |
|---|---|---|---|---|---|
| 12 | PDD<br>HFA, SPD | Moderate Risk | Disruptive behavior, ability to meet academic demands | Making continued progress at same school | Low Risk |
| 13 | ED<br>Reactive attachment disorder | High Risk | Disruptive behavior, ability to remain in classroom | Controls behavior at school, no longer at risk of transfer | Moderate Risk; no longer disrupting classroom, better able to control outbursts |
| 14 | ED<br>Reactive attachment disorder | High Risk | Disruptive behavior, ability to remain in classroom | Controls behavior at school, no longer at risk of transfer | Moderate Risk; vulgar language during outbursts has disappeared |
| 15 | ED<br>Generalized anxiety | High Risk | Ability to meet academic demands | No longer at risk of transfer, making academic progress | Moderate Risk; maintained on a lower dose of stimulant medication, remains at school |
| 16 | ED<br>Depression, severe mood swings | Moderate Risk | Emotional lability, ability to remain in classroom | Status quo | Moderate Risk; No change in emotional lability |
| 17 | PDD<br>HFA, SPD | Moderate Risk | Ability to meet academic demands | Making continued progress at same school | Low Risk; promoted within same school |

**Teacher CBCL results.** Pre-post teacher CBCL data was available for 12 students. The Child Behavior Checklist (CBCL) is a standardized measure of emotional and behavioral functioning that is available in parent, teacher, and self-report forms. For the present group, pre-post teacher CBCL rating scales are available for 12 of the 17 participants. The teacher form consists of approximately 113 questions scored on a 3-point Likert scale (0 = absent, 1 = occurs sometimes, 2 = occurs often). Each CBCL item loads onto one or more clinical scales, including eight syndrome scales (i.e., anxious/depressed, depressed, somatic complaints, social problems, thought problems, attention problems, rule-breaking behavior, and aggressive behavior), and six DSM-oriented scales (i.e., affective problems, anxiety problems, somatic problems, ADHD, oppositional defiant problems, and conduct problems).

For 11 of the 12 students for which CBCL data was available, improvements of greater than one standard deviation on relevant clinical scales were demonstrated. Data from each of these students is plotted in Figure 5.

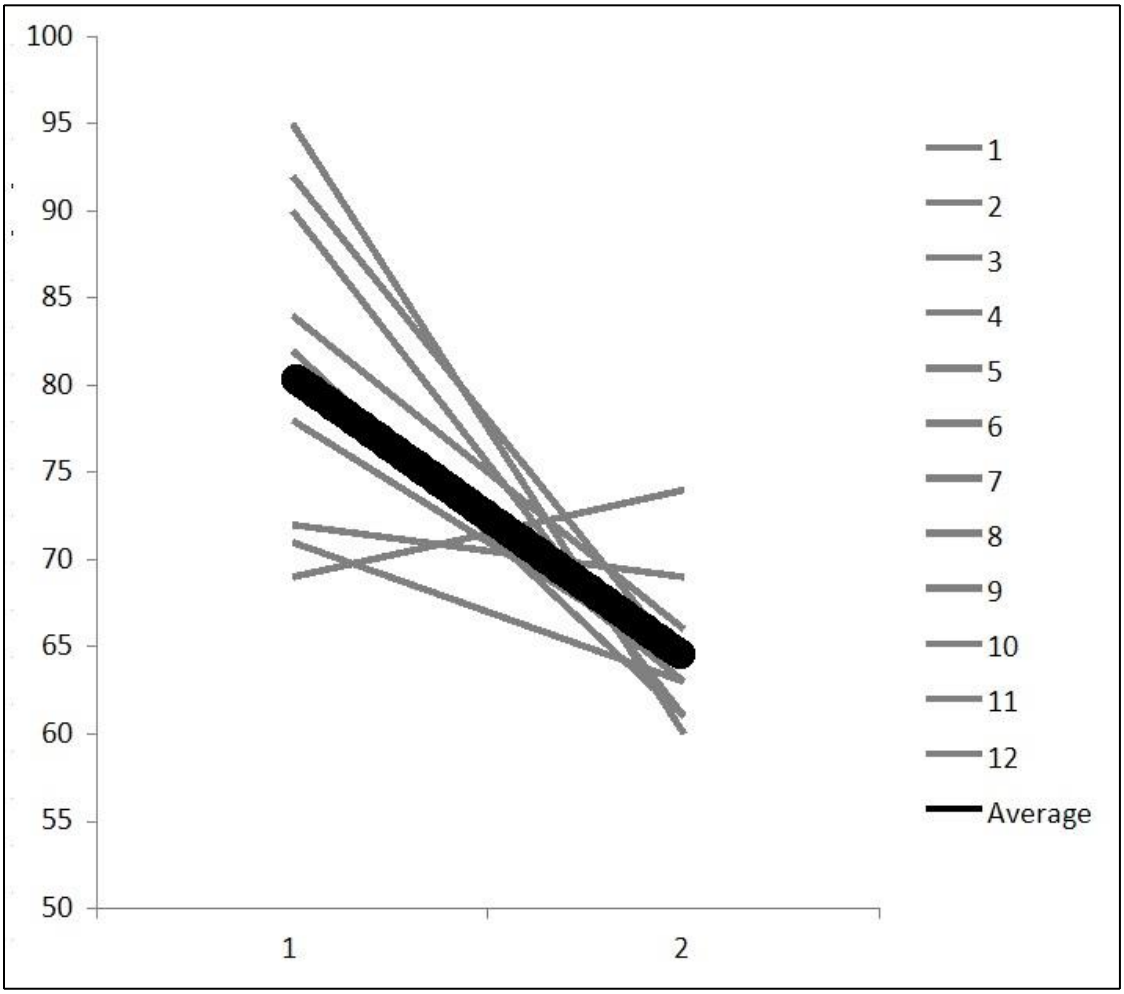


**Figure 5**. CBCL Results, Change on Marker of Primary Concern. CBCL results were available for 12 of the 17 students. The graph above plots the CBCL scaled score for each student's primary area of concern. There was an average improvement of 16 scaled score points, or 1.6 standard deviations of improvement.

**Case study 1.** The client, a 12-year-old male, was diagnosed with Autism after undergoing a developmental regression at 15 months old. He was relatively high functioning in his communication and had good eye contact when we started working with him in June 2010. He was 9 years old at the beginning of treatment. His presenting complaints – severe OCD, perseverative thinking, hyperactivity, and significant behavioral problems – prevented him from continuing in a mainstream school setting. He had recently been assigned to a school for children with behavioral problems and was learning at three grade levels below his age. Initial trials with ISF, then limited to a 3-decimal place optimal frequency adjustment, resulted in a hyperactive response.

Initially he received Z-score training, which provided positive results, albeit slowly. Both parents observed other children receiving ISF training and noted the rapid shifts in behavior. Several trials of ISF training were performed at their request, all resulting in short-term hyperactivity but with bigger positive gains following. In November 2010, 4-decimal places of optimal frequency adjustment were made available and the client was switched exclusively to ISF training with a suitable optimal frequency. He completed two ISF sessions each week and showed a rapid reduction in hyperactivity and behavioral issues. In March 2011 he received the "Student of the Month" award from his school for his exceptional behavior. Over the next year, ISF brain training reduced his level of OCD and perseverative thinking dramatically. At the end of 2012, his academic gap had closed; he tested between the 4th and 5th grade levels on the Structure of Intellect (SOI) rating scale and his OCD issues were resolved. His diagnosis has been changed to high-functioning Asperger's.

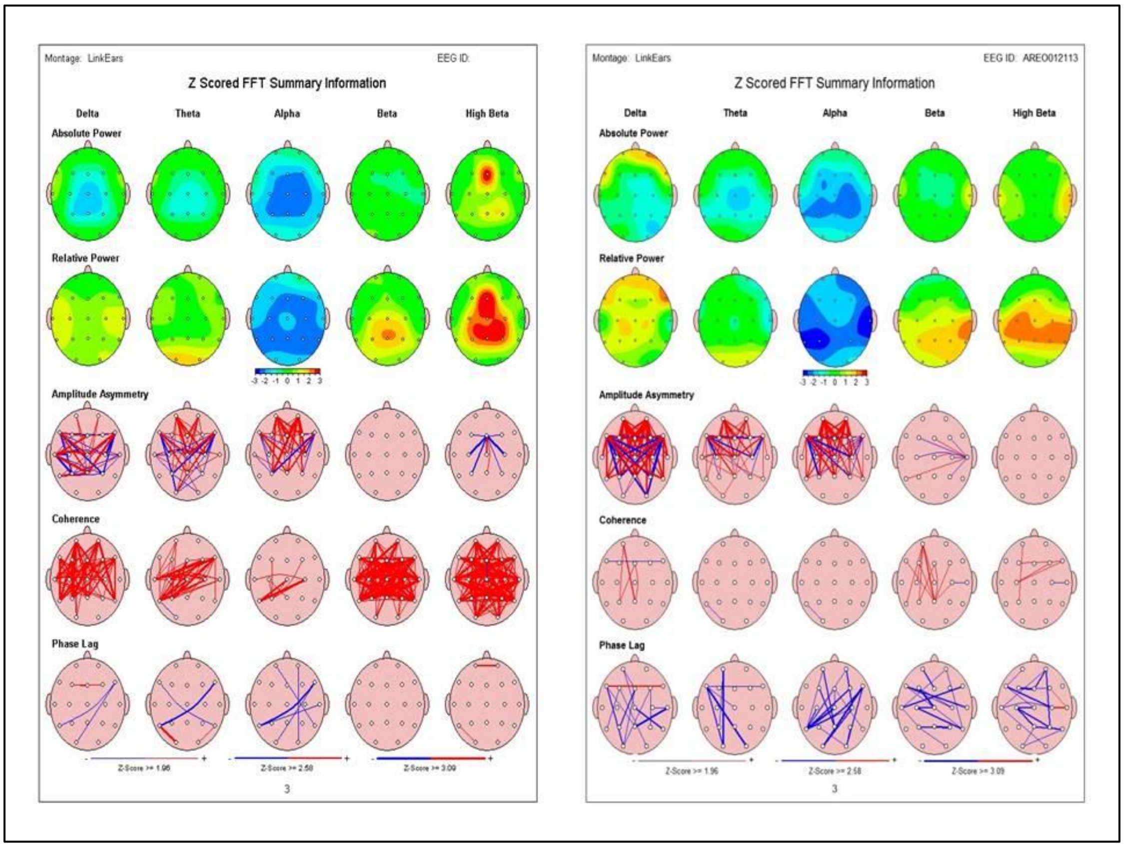


**Figure 6**. Pre/post QEEGs depicting near global remediation of coherence in all bands, with normalization of the deviant absolute power in the high beta band at the frontal midline.

**Case study 2.** The client, a 55-year-old African American male, presented with insomnia and PTSD. His early childhood was characterized by brutal, repetitive domestic violence between his parents. He witnessed his father's attempted murder of his mother. His father fractured his skull with a baseball bat. He was removed from the home by Child Services and placed in foster care at age eight. He was witness to beatings and gang rapes in group homes. The client was both shot and stabbed as an adult. He reported being a drug addict and alcoholic who had maintained abstinence for several years. At the beginning of training, he suffered with overwhelming anxiety, depression, and difficulty managing his anger. He reported sleeping with a rifle for protection. At the initiation of treatment, the client was extremely labile. His focus on fear and failure imagery had an obsessive quality that he felt powerless to control.

Treatment consisted of 31 sessions of ISF training targeting anxiety and depression. Areas trained included right pre-frontal and right parietal regions, bilateral temporal, and left prefrontal areas. Four sessions of alpha two-channel sum training in parietal regions were implemented at the end of ISF training.

At the termination of treatment, Ct reported better affect regulation: significant relief from his crippling anxiety and sense of hopelessness. Unemployed at the beginning of treatment, he returned to work in the construction trades during the latter stages of training. His problematic relationships with his wife and child improved. He reported breaking his rifle down and storing it in a safe location so as not to endanger his son. Some symptoms of PTSD persisted.

Post treatment brain mapping (Figure 7) revealed improved network relations, as demonstrated by coherence values, in all bands but high beta. The source of the excess absolute power in the high beta band was identified as the Anterior Cingulate Gyrus by LORETA current source density analysis and may have been related to the obsessive quality of the client’s failure imagery. The question for further study is whether the appearance of less information sharing in anterior/posterior relations, as reflected by the coherence metric, and slowed rate of information transfer, as reflected by the increase in slowed phase lag, in the high beta band is related to the reduction in frontal high beta absolute power in the surface maps. If so, this may reflect a compensatory mechanism.

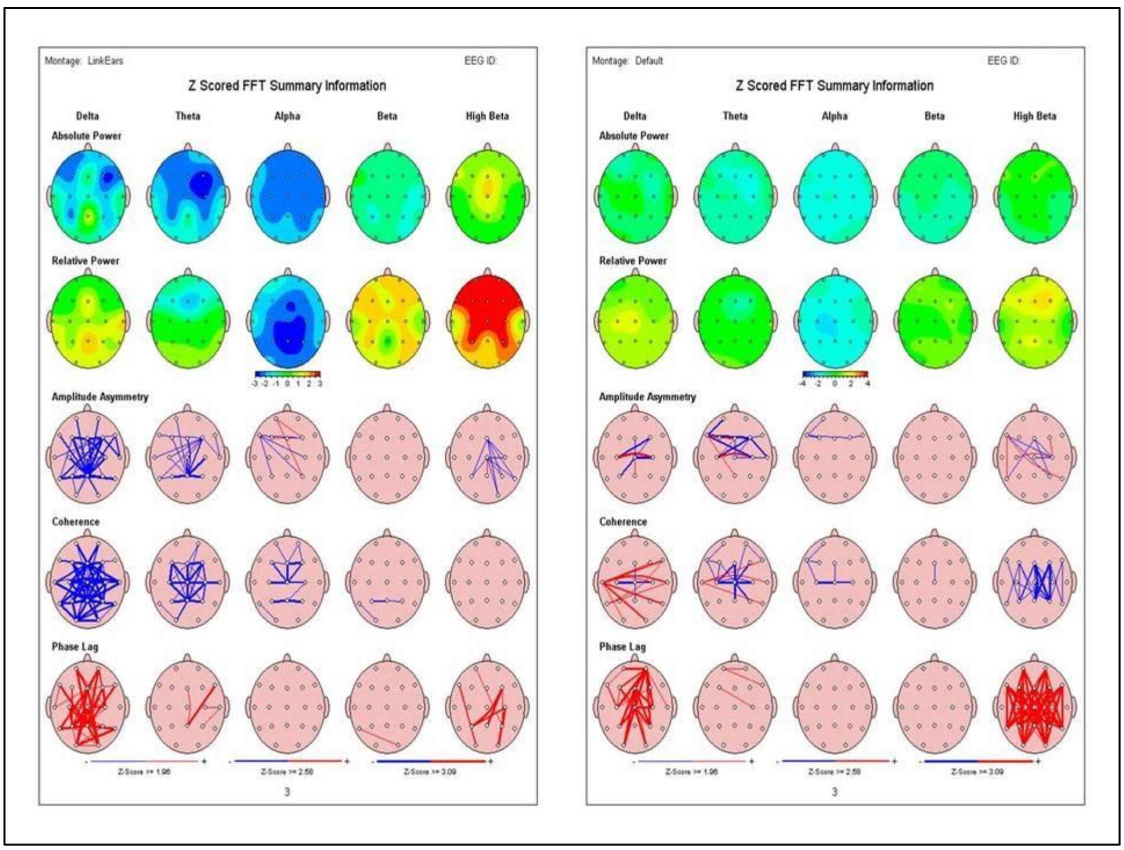


**Figure 7**. Pre-post training QEEGs. Complete resolution of Absolute Power abnormalities in all bands. Coherence indices improved in all bands but high beta.

## Conclusion

Progress in equipment has allowed for the imaging of EEG signals below the traditional limit. Research spanning the last 60 years has demonstrated a functional centrality for ISOs in human and animal behavior. Clinical outcomes in ISF training are consistent with the functional research and demonstrate significant behavioral changes as established by empirically based assessment instruments. Post-treatment QEEG results reveal remediation of excesses of power, insufficiencies of power, and especially in network communications in cortex. This data is suggestive of the clinical efficacy of ISF training. Based on this data, a larger controlled study is warranted.

## References

Aladjalova, N. A. (1957). Infra-slow rhythmic oscillations of the steady potential of the cerebral cortex. *Nature, 179*(4567), 957–959.

Aladjalova, N. A. (Ed.). (1964). *Slow electrical processes in the brain* (Vol. v. 7). Amsterdam, New York: Elsevier.

Birbaumer, N. (1999). Slow cortical potentials: Plasticity, operant control, and behavioral effects. *The Neuroscientist, 5*(2), 74–78.

Birbaumer, N., & Cohen, L. G. (2007). Brain-computer-Interfaces(BCI): Communication and restoration of movement in paralysis. *The Journal of Physiology, 579, 621-636.* http://dx.doi.org/10.1113/jphysiol.2006.125633

Birbaumer, N., Elbert, T., Canavan, A. G., & Rockstroh, B. (1990). Slow potentials of the cerebral cortex and behavior. *Physiological Reviews, 70*(1), 1–41.

Birbaumer, N., Rockstroh, B., Elbert, T., Wolf, P., Duchting-Roth, A., Reker, M., . . . Dichgans, J. (1994). Biofeedback of slow cortical potentials in epilepsy. In J. G. Carlson, A. R. Seifert, N. Birbaumer (Eds.), *Clinical applied psychophysiology* (pp. 29–42). New York, NY: Plenum Press.

Broyd, S. J., Helps, S. K., & Sonuga-Barke, E. J. S. (2011). Attention-induced deactivations in very low frequency EEG oscillations: Differential localisation according to ADHD symptom status. *PLoS ONE, 6*(3), e17325. http://dx.doi.org/10.1371%2Fjournal.pone.0017325

Buzsaki, G. (2006). *Rhythms of the brain*. New York, NY: Oxford University Press.

Collura, T. F. (1993). History of electroencephalographic instruments and techniques. *Journal of Clinical Neurophysiology, 10*(4), 476–504. http://www.brainmaster.com/tfc/index_files/Publications/535-027 theory and evolution of electroencephalographic.pdf

Collura, T. F. (1995). Basic electronics and physics, In: K. Levin, & H. Luders, (eds.) *Comprehensive Clinical Neurophysiology*. Amsterdam, Netherlands: Elsevier.

Collura, T. F. (2009). Practicing with multichannel EEG, DC, and slow cortical potentials. *NeuroConnections,* 35–39.

Crunelli, V., & Hughes, S. W. (2010). The slow (<1 Hz) rhythm of non-REM sleep: A dialogue between three cardinal oscillators. *Nature Neuroscience, 13*(1), 1–9. http://dx.doi.org/10.1038/nn.2445

Dong, Z.-Y., Liu, D.-Q., Wang, J., Qing, Z., Zang, Z.-X., Yan, C.-G., & Zang, Y.-F. (2012). Low-frequency fluctuation in continuous real-time feedback of finger force: A new paradigm for sustained attention. *Neuroscience Bulletin*, 1–12. http://link.springer.com/article/10.1007%2Fs12264-012-1254-2

Elbert, T., Rockstroh, B., Lutzenberger, W., & Birbaumer, N. (1980). Biofeedback of slow cortical potentials. *Electroencephalography and Clinical Neurophysiology, 48*(3), 293–301. http://dx.doi.org/10.1016/0013-4694(80)90265-5

Heinrich, H., Gevensleben, H., Freisleder, F. J., Moll, G. H., & Rothenberger, A. (2004). Training of slow cortical potentials in attention-deficit/hyperactivity disorder: Evidence for positive behavioral and neurophysiological effects. *Biological Psychiatry, 55*(7), 772–775. http://dx.doi.org/10.1016/j.biopsych.2003.11.013

Helps, S. K., Broyd, S. J., James, C. J., Karl, A., Chen, W., & Sonuga-Barke, E. J. S. (2010). Altered spontaneous low frequency brain activity in Attention Deficit/Hyperactivity Disorder. *Brain Research, 1322*, 134–143. http://www.sciencedirect.com/science/article/pii/S0006899310002118

Hughes, S. W., Lorincz, M. L., Parri, H. R.,& Crunelli,V. (2011). Infraslow (<0.1Hz) oscillations in thalamic relay nuclei: Basic mechanisms and significance to health and disease states. *Progress in Brain Research, 193*, 145–162. http://dx.doi.org/10.1016/B978-0-444-53839-0.00010-7

Kaiser, D. A., & Othmer, S. (2000). Effect of neurofeedback on variables of attention in a large multi-center trial. *Journal of Neurotherapy, 4*(1), 5–15. http://dx.doi.org/10.1300/J184v04n01_02

Keković, G., Sekulić, S., Podgorac, J., Mihaljev-Martinov, J., & Gebauer-Bukurov, K. (2012). The slow and infraslow oscillations of cortical neural network. *Neurology, Psychiatry and Brain Research, 18*(4), 175-180. http://dx.doi.org/10.1016/j.npbr.2012.04.003

Ko, A. L., Darvas, F., Poliakov, A., Ojemann, J., & Sorensen, L. B. (2011). Quasi-periodic fluctuations in default mode network electrophysiology. *The Journal of Neuroscience, 31*(32), 11728–11732. http://www.jneurosci.org/content/31/32/11728.abstract

Linkenkaer-Hansen, K., Nikouline, V. V., Palva, J. M., & Ilmoniemi, R. J. (2001). Long-range temporal correlations and scaling behavior in human brain oscillations. *The Journal of Neuroscience, 21*(4), 1370–1377. http://www.jneurosci.org/content/21/4/1370.abstract

Liu, Z., Fukunaga, M., de Zwart, J. A., & Duyn, J. H. (2010). Large-scale spontaneous fluctuations and correlations in brain electrical activity observed with magnetoencephalography. *Neuroimage, 51*(1), 102–111. http://www.sciencedirect.com/science/article/pii/S1053811910001151

Lőrincz, M. L., Geall, F., Bao, Y., Crunelli, V., & Hughes, S. W. (2009). ATP-dependent infra-slow (<0.1 Hz) oscillations in thalamic networks. *PLoS ONE, 4*(2), e4447. http://dx.doi.org/10.1371%2Fjournal.pone.0004447

Mairena, M., Martino, A., Domínguez-Martín, C., Gómez-Guerrero, L., Gioia, G., Petkova, E., & Castellanos, F. X. (2012). Low frequency oscillations of response time explain parent ratings of inattention and hyperactivity/impulsivity. *European Child & Adolescent Psychiatry, 21*(2), 101–109. http://dx.doi.org/10.1007/s00787-011-0237-6

Manaka, S., & Sano, K. (1979). Stationary potential of the brain: Part I. Basic studies. *Neurologia medico-chirurgica, 19*(7), 643–653.

Marshall, L., Mölle, M., Fehm, H. L., & Born, J. (2000). Changes in direct current (DC) potentials and infra-slow EEG oscillations at the onset of the luteinizing hormone (LH) pulse. *European Journal of Neuroscience, 12*(11), 3935–3943. http://dx.doi.org/10.1046/j.1460-9568.2000.00304.x

Monto, S., Palva, S., Voipio, J., & Palva, J. M. (2008). Very slow EEG fluctuations predict the dynamics of stimulus detection and oscillation amplitudes in humans. *The Journal of. Neuroscience, 28*(33), 8268–8272. http://dx.doi.org/10.1523/JNEUROSCI.1910-08.2008

Nir, Y., Mukamel, R., Dinstein, I., Privman, E., Harel, M., Fisch, L., . . . Malach, R. (2008). Interhemispheric correlations of slow spontaneous neuronal fluctuations revealed in human sensory cortex. *Nature neuroscience, 11*(9), 1100–1108. http://dx.doi.org/10.1038/nn.2177

Palva, J. M., & Palva, S. (2012). Infra-slow fluctuations in electrophysiological recordings, blood-oxygenation-level-dependent signals, and psychophysical time series. *Neuroimage, 62*(4), 2201–221. http://dx.doi.org/10.1016/j.neuroimage.2012.02.060

Pfurtscheller, G. (1976). Ultralangsame schwankungen innerhalb der rhythmischen aktivität im alpha-band und deren mögliche ursachen. *Pflügers Archiv, 367*(1), 55–66. http://dx.doi.org/10.1007/BF00583657

Pfurtscheller, G., Daly, I., Bauernfeind, G., & Müller-Putz, G. R. (2012). Coupling between intrinsic prefrontal HbO2 and central EEG beta power oscillations in the resting brain. *PLoS ONE, 7*(8), e43640. http://dx.doi.org/10.1371%2Fjournal.pone.0043640

Picchioni, D., Horovitz, S. G., Fukunaga, M., Carr, W. S., Meltzer, J. A., Balkin, T. J., Braun, A. R. (2011). Infraslow EEG oscillations organize large-scale cortical–subcortical interactions during sleep: A combined EEG/fMRI study. *Brain Research, 1374*(0), 63–72. http://www.sciencedirect.com/science/article/pii/S0006899310027009

Putman, J. A., Othmer, S. F., Othmer, S., & Pollock, V. E. (2005). TOVA results following inter-hemispheric bipolar EEG training. *Journal of Neurotherapy, 9*(1), 37–52. http://dx.doi.org/10.1300/J184v09n01_04

Stokes, D., & Lappin, M. (2010). Neurofeedback and biofeedback with 37 migraineurs: A clinical outcome study. *Behavior and Brain Functions, 6*. http://link.springer.com/article/10.1186%2F1744-9081-6-9

Strehl, U., Leins, U., Goth, G., Klinger, C., Hinterberger, T., & Birbaumer, N. (2006). Self-regulation of slow cortical potentials: A new treatment for children with attention-deficit/hyperactivity disorder. *Pediatrics, 118*(5), e1530–1540. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17060480

Tallgren, P. (2006). *DC-EEG for routine clinical use: Methods and clinical impact.* (PhD Dissertation), Helsinki Univesity of Technology, Helsinki. http://linkinghub.elsevier.com/retrieve/pii/S1388245704003906?showall=true

Tye, C., Rijsdijk, F., Greven, C. U., Kuntsi, J., Asherson, P., & McLoughlin, G. (2012). Shared genetic influences on ADHD symptoms and very low-frequency EEG activity: A twin study. *Journal of Child Psychology and Psychiatry, 53*(6), 706-715. http://dx.doi.org/10.1111/j.1469-7610.2011.02501.x

Vanhatalo, S., Palva, J. M., Holmes, M. D., Miller, J. W., Voipio, J., & Kaila, K. (2004). Infraslow oscillations modulate excitability and interictal epileptic activity in the human cortex during sleep. *Proceedings of the National Academy of Sciences of the USA, 101*(14), 5053–5057. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15044698

Vanhatalo, S., Voipio, J., & Kaila, K. (2005). Full-band EEG (FbEEG): An emerging standard in electroencephalography. *Clinical neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology, 116*(1), 1–8. http://linkinghub.elsevier.com/retrieve/pii/S1388245704003748?showall=true

Vanhatalo, S., Voipio, J., & Kaila, K. (2005). Infraslow EEG activity. In E. Neidermeyer & F. da Silva (Eds.), *Electroencephalography* (5th ed.). Baltimore, MD: Lippincott Williams & Wilkins.

Wolpaw, J. R., Birbaumer, N., McFarland, D. J., Pfurtscheller, G., & Vaughan, T. M. (2002). Brain-computer interfaces for communication and control. *Clinincal Neurophysiology, 113*(6), 767–791. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12048038

Zschocke, S., & Speckmann, E.J. (Eds.). (1993). *Basic mechanisms of the EEG*. New York, NY: Springer.