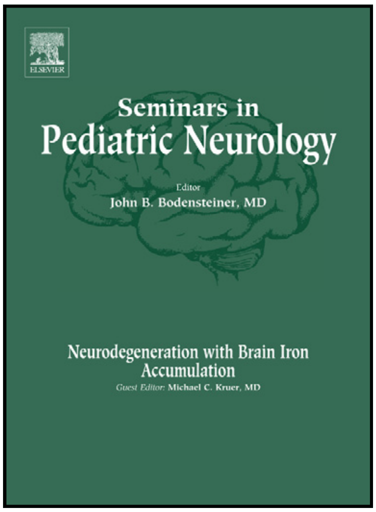

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ABSTRACT

Neuromodulation in the bioelectrical domain is an attractive option for the remediation of functionally-based deficits. Most of the interest to date has focused on exogenous methods such as repetitive transcranial magnetic stimulation (rTMS), transient DC Stimulation (tDCS), vagus nerve stimulation (VNS), and deep brain stimulation (DBS). Much less attention has been given to endogenous methods of exploiting latent brain plasticity. These have reached a level of sophistication and maturity that invites attention. Over the last seven years the domain of infra-low frequencies has been exploited productively for the enhancement of neuroregulation. The principal mechanism is putatively the re-normalization of functional connectivity of our resting state networks. The endogeneous techniques are particularly attractive for the pediatric population, where they can be utilized before dysfunctional patterns of brain behavior become consolidated and further elaborated into clinical syndromes.

INTRODUCTION

Endogenous neuromodulation refers to therapeutic methods in which recovery depends solely on information being provided to the brain on its own state of function. Currently this approach is being utilized in feedback applications of fMRI and EEG (e.g., Tan et al., 2009; deCharms et al., 2005; Chapin et al., 2012). In exploratory studies of fMRI feedback it has been shown that very specific functions or dysfunctions can be affected by challenging participants to alter the activity level in specific brain regions using real-time imagery. Even single-session training effects have been reported (Harmelech et al., 2013; Ros et al., 2013). In this manner, specific hubs of our primary regulatory networks can be directly targeted (e.g., Zhang et al., 2013; Van De Ville et al., 2012). Within-session alterations of local activation have the effect of altering network dynamics with lingering effects. A degree of learning obviously occurs. Over a number of sessions, these changes are then consolidated for more enduring benefit (e.g., Scheinost et al., 2013).

The practical exploitation and broad application of these scientific findings is handicapped, however, by the sheer expense and complexity of fMRI-based neurofeedback. It is of interest, therefore, to inquire whether feedback on the EEG may be configured to the same purpose. In principle, all of the requisite information on the activation of our core networks should also be available at the scalp EEG (e.g., Knyazev et al., 2011). But it is significant that resting state networks were not identified in the EEG prior to their discovery in fMRI. The complexity and dynamics of EEG activity obscured these basic patterns of correlation. The latter were only identified after it became clear what should be looked for.

EEG feedback on spectral band activity has shown itself useful in the training of self-regulation. In fact, EEG feedback has a history going back some forty years (Sterman & Friar, 1972; Roth et al., 1967, Nowlis & Kamiya, 1970). Research interest has been revived recently in this area as well. Presumably similar mechanisms of recovery are being engaged here. The question being addressed in this paper is whether a direct analog of fMRI training can be devised using information derived solely from the scalp EEG.

For this purpose, it is necessary to investigate the realm of infra-low frequencies, i.e. below 0.1 Hz, which corresponds to the range over which fMRI correlation data are analyzed. This frequency range is typically eliminated from the standard EEG, and thus has slipped outside of the awareness of modern electroencephalographers (e.g., Acunzo et al., 2012). Interest is being revived now because of the impetus provided from fMRI imagery. Below 0.1 Hz we see local cortical activation represented directly in the surface potential observable at the scalp (Mantini et al., 2007; He & Raichle, 2009; Ko et al., 2011; Bridwell et al., 2013; Yuan et al., 2013). If the fluctuations reflect the activation of our core networks, then in principle the objectives of fMRI neurofeedback can be pursued economically with the infra-low-frequency EEG.

Just as in the case of fMRI neurofeedback, the immediate engagement is with the activation-relaxation dynamics of specific regulatory networks. The essential difference in the case of EEG feedback is the focus on the relationship between two sites, by virtue of the use of bipolar montage. This makes the targeting much more specific with regard to the principal network being engaged. However, the effects are, if anything, even more system-wide. If the functional connectivity of key resting state networks is being affected, it is to be expected that all functions being subserved by these networks are potentially impacted. And if one key control network is altered in its functional organization, its interaction with other control networks is likewise affected (Lee et al., 2012).

These matters are best understood by regarding the brain at the system level as a hierarchical, highly integrated entity functioning with an essentially unitary, syntonic, homeodynamic quality from moment to moment. Any information back to the brain bearing on the quality of regulation affects the whole. That appears to be particularly the case when the information relates to the behavior of our core control networks, reaching deep into the hierarchy of regulation. The observable for the brain is the time course of activation. In first instance this allows the brain to recognize its connection with the signal. And then the signal quite naturally becomes the object of control by the brain. An external feedback loop becomes established, and is effectively internalized. The resulting regulatory challenge is the endogenous mechanism by which the brain enhances its own capacity for self-regulation (Othmer et al., 2011).

This is essentially the same process by which the brain acquires its self-regulatory skills over the course of its development (e.g., Castellanos et al., 2013). Control is gradually refined by means of a variety of internal feedback pathways, to which a new regulatory pathway is now added. By giving the brain more salient information directly, the process of adaptation is disambiguated and vastly accelerated. And by suitable targeting, the process is directed toward those functions and competences that most need shoring up. In this pursuit, the regulatory hierarchy is taken into account. This hierarchy is largely specified for us through ontogeny. A systems perspective is once again helpful here. Progress at the foundational levels of regulation sets the stage for further improvement at higher levels. The recovery of function proceeds by scaffolding, essentially replicating the original developmental hierarchy (Khundrakpam et al., 2013; Supekar et al 2009).

It is helpful not to over-estimate the magnitude of the task at hand. Many problems in medicine seemed intractable until the proper remedy was brought to bear. Much of psychopathology and many neurophysiological deficits can be seen as the consolidation of dysfunction through the mechanisms of brain plasticity, also called negative or maladaptive neuroplasticity (e.g., Watson & Rayner, 1920; Scharfman, 2002). Endogenous mechanisms of regulatory adaptation suffice to walk many patients back from their particular pathological *cul de sac*. And yet with feedback it is not even required to specify the path of recovery. It is necessary merely to provide the requisite state-related information to the brain. The clinician's burden is firstly site selection on the basis of an appraisal of the essential character of the core dysregulation at issue. Secondly, it is to judge the outcome in order to steer the process into its most propitious course by way of an ongoing optimization procedure (Othmer SF, 2013).

Advantage is taken of the fact that brain states in the neighborhood of the prevailing state are always accessible, and by virtue of brain plasticity the access to such states can be facilitated and consolidated through repetition. Typically in rehabilitation the brain is challenged to perform in various ways, which expands the space for the exploitation of brain plasticity. On the other hand, when the concern is the re-organization of our resting states, the therapeutic opportunity appears to be in the direction of unburdening the brain, of unloading and de-stressing it (e.g., Travis et al., 2010; Pagnoni, 2012; Taylor et al., 2013; Sliz et al., 2012). The best-regulated, least-challenged state is the most propitious for further progress. In this perspective, any overt engagement by the brain is to be seen as a constraint on the conformation of the neural networks. Such constraints militate against the reorganization of resting state networks that needs to take place. The concern here is not just about externally imposed constraints. The brain may equally well be constrained by internal disruptors. These may block the path to spontaneous self-recovery. In a highly dysregulated system, the pathway to recovery may be constrained in a variety of ways (e.g., Vaidya & Gordon, 2013). Every such case presents a unique clinical challenge.

Awareness of the therapeutic potential of moving the person toward calm states dates back to early times and is exploited in the present day in various non-medical disciplines (e.g., Benson, 1975). Most commonly this is done under the rubric of meditation, relaxation training, or mindfulness exercise. The earliest discoveries along these lines were often incorporated into ritualized spiritual practice: chanting, rhythmic breathing, healing touch, the monastic life, vows of silence, and forty days in the desert (e.g., Muesse, 2011). The impetus was spiritual practice rather than health, but mastery of brain function was the key to both. Most of these techniques are passive, however, in that they merely arrange for the therapeutic opportunity that comes with being internally engaged while residing in calm states.

With feedback on resting state activity, the process becomes an active one in which the brain seeks its best operating point while being minimally constrained. This both accelerates and refines the process, a welcome development. In application to highly dysregulated systems, this may represent the only practical therapeutic option for recovery (e.g., traumatic brain injury, dementia, chronic pain). The rapidity of response can be understood in terms of a model termed ‘dynamic network connectivity,’ which relates mechanisms of neuronal plasticity to the rapid re-configuration of control networks. (Arnsten et al., 2010)

The clinical exploration of the domain of endogenous neuromodulation is facilitated by its accessibility. The entry into infra-low frequency training was first undertaken in 2006. It was quickly rewarded with clinical results that were comparable in promptness and in responsiveness to those that have been seen in fMRI feedback, as for example in chronic pain (Jensen et al., 2007; deCharms, 2005). The low barrier to entry then also led to rapid diffusion of this technology, and to its application to the whole spectrum of psychopathology and functional neurophysiological deficits. Far more infra-low frequency neurofeedback is currently being done by mental health professionals than all of the exogenous neuromodulation techniques combined. It is time to bring this work to the attention of the larger neurology community.

THE CLINICAL METHOD

The clinical approach is based entirely on inviting the brain to engage with information derived from the low-frequency EEG. Typically the signal is presented in the form of a video display, often accompanied by tactile feedback. A bipolar montage is used exclusively. This informs the brain as to the time course of the differential activation at two cortical sites (e.g. ACNS, 2006). It also serves the usual purpose of suppressing common-mode signals, such as non-neuronal influences on the signal (Voipio, 2003). The spectral response is shaped in signal processing to pass only the low frequencies of interest. In order to attract the brain's attentions to the low-frequency components of the EEG, the higher-frequency components have to be suppressed.

Engagement with the signal leads to shifts in the person's state of arousal, of vigilance, of emotional ambiance, and of autonomic balance that are readily noticeable by the trainee and observable to the clinician. This immediate responsiveness is then used to guide the training toward its optimal course. This level of parametric sensitivity (on both electrode placement and target frequency) requires that a personalized optimization procedure must be adopted in order to extract full value from the exercise in first instance, and secondarily to avoid descent into dysfunctional states (Othmer SF, 2013).

As this process depends entirely on observations of change during the training process, the usual research paradigm of a blinded procedure is foreclosed. Moreover, it is not possible to reduce the protocol to a standard procedure. Additionally the method does not orient toward any particular diagnosis over others, and consequently it does not call for any specific assessment tool. Progress in the clinical realm simply has to be made one client at a time, and assessed comprehensively. This suits the clinical realm, although it presents a challenge to standard research design.

On the other hand, the training process amounts to the implementation of the most refined clinical research paradigm in every case, namely the A/B design using a within-subject control. By the very nature of the process, the clinician is continually confronted with clinical choices with respect to target frequency and placement. The rapidity and specificity of the response allow cause-and-effect relationships to be confirmed through the repetition of A/B comparisons, sometimes even within a single session. Incrementally the clinician and the client increase their understanding of the strengths, limitations, and vulnerabilities of the particular nervous system. Throughout the process the client becomes a better reporter on the subtle effects of the training and the clinician becomes a better judge of the implications for protocol going forward. The process calls upon the disparate skills of clinical observation, of hypothesis-testing, and of consolidating a therapeutic alliance with the client.

THE HIERARCHY OF REGULATION

If the brain is regarded as a control system, its fundamental responsibility is to assure its own unconditional stability (Fingelkurts & Fingelkurts, 2004; Werner, 2007). This is a particular challenge because in order to function in a real-time environment, the brain is also constrained to work in a critical state, poised for rapid, macroscopic state change (Beggs and Plenz, 2003, Kitzbichler et al, 2009). This maintains the brain far from an equilibrium state. This implies a narrow parameter space for both optimum responsiveness and stability in the vulnerable brain. Ultimately we have no choice but to rely on the brain's endogenous mechanisms to manage stability. Our best remedy, therefore, is to enhance those endogenous mechanisms by whatever means, and to whatever extent, is possible.

The secondary obligation of the brain is to manage set points of regulatory function, i.e. homeodynamic balance. The regulation of tonic arousal is foundational in this hierarchy of regulation (e.g., Halász, 1998; Sforza et al., 2000). Intimately connected with arousal regulation is affect regulation, which in turn is highly correlated with autonomic regulation, which in turn is dependent on good regulation of interoceptive function, our sense of the state of the body and of its safety within the environment. This is the foundational regulatory arc on which the integrity of brain function depends, and it is asymmetrically the principal burden of the right hemisphere (cf. Schore, 1994). This regulatory arc has priority in our developmental trajectory. The left hemisphere takes primary responsibility for the organization of goal-directed behavior, of executive function and the hierarchy of motor control, that mature later (Kaller et al., 2011; Schore, 1997; Southgate et al., 2013).

At the highest level, the brain must manage its dynamic interaction with the environment. However, the issues that arise in this domain are less likely to manifest themselves as disorders that require medical attention. Our concern is largely with the issue of stability and of the management of set points of central arousal and of specific network activation. Our primary observables in this project relate to the state of arousal, of affect regulation, and of autonomic regulation. Yet we suffer the handicap of not having an absolute measure of any of these. The clinical mandate then becomes clear: since it is impossible to specify what we cannot even reliably measure, the objective must be to train the brain in the capacity to self-regulate in generality, and to do so without specifying the end point in these terms. On the other hand, success with respect to state regulation will also be reflected sensitively in cognitive challenges that lend themselves readily to quantification. (Mueller et al, 2010)

THE PROTOCOLS IN THE SPATIAL DOMAIN

Protocol development has proceeded largely empirically, informed at all times by considerations of functional neuroanatomy. The critical drivers in this development were instability and severe dysregulation. A broad generalization has been consolidated over the years that brain stability is best promoted with inter-hemispheric placements (Othmer S, 2007; Putman et al., 2005). The placement offering the strongest effects and greatest breadth of clinical impact is T3-T4. The most severe cases of dysregulation observed in clinical practice tend to be those whose path of development was disrupted early in childhood due to physical trauma, emotional trauma, or neurological disease. In such cases the most effective pathway to restoration of function is the physical calming that comes with training at T4-P4. Emotional regulation is most effectively promoted with the placement T4-Fp2. Right-sided training is often balanced with left-sided training, and right-parietal training is often balanced with left-frontal training at T3-Fp1. These constitute the principal set of starting protocols, by analogy to the opening moves of a chess match. Subsequent moves are determined entirely by the response of the brain to the first initiative.

As the training goes on, subsidiary placements are added in order to address specific neurophysiological deficits. All of the standard 19 electrode sites in the 10-20 system have their unique role to play in the refinement of regulatory capacity. As a practical matter, however, most patients will experience no more than the above four principal placements during their course of training.

THE PROTOCOLS IN THE FREQUENCY DOMAIN

The unstable brain is the most sensitive to the parameters of the training, in particular the target frequency. Because of the extreme sensitivity to target frequency, the right-hemisphere issues drove the agenda for the deepening penetration of the infra-low frequency region. The most difficult and intractable cases tended to require the lowest target frequencies. Whereas the initial thrust into the lowest frequency region was mandated by our most challenging clients, by now it is clear that nearly everyone trains comfortably somewhere within the range of 0.1mHz to 2mHz. This range has become default in the *Ansatz* to the optimization procedure, even though many could train effectively also at higher frequencies.

Given such a narrow range for the optimum response, particularly for the instabilities, it is natural to think in terms of a resonant system organization (Othmer S, 2008). Seen in terms of such a model, we are dealing with a Q of 10. (Q is a figure of merit for resonant systems, referring to the ratio of the center frequency to the width of the resonance curve.) At higher frequencies, the Q can be greater than 50. A high Q in a self-regulating system is suggestive of an active mechanism that sustains the resonance. The resonance is dynamically maintained, and thus can be seen as a constraint on overall system dynamics. We are dealing with a persistent pattern in EEG organization that to our knowledge has not been identified previously in the conventional EEG spectrum.

At low frequencies, persistent spectral peaks have been observed in the ILF range down to 0.01 Hz. (Damuele et al, 2007). (See **Figure 1**) Narrow peaks are revealed in the linear plot, whereas the nulls shown in the logarithmic plot testify to a high degree of stability in the recorded spectrum over the data acquisition window of several hundred seconds. If there were any migration of the spectral properties over that interval the nulls would not be so distinct. These low-frequency oscillations are behaviorally relevant, being correlated with intra-individual fluctuations in cognitive performance (Sonuga-Barke EJ & Castellanos, 2007; Helps et al.,2008, Palva et al, 2013). It is quite possible that this peaked structure extends over the entire range of the ILF training, i.e. down to 0.1mHz. One may conjecture that the optimum target frequencies correspond to the peaks within such a distribution. On the basis of a resonant systems interpretation, the response of the system would be favorable at the resonant frequency, but potentially problematic in its vicinity. That conforms to our clinical experience.

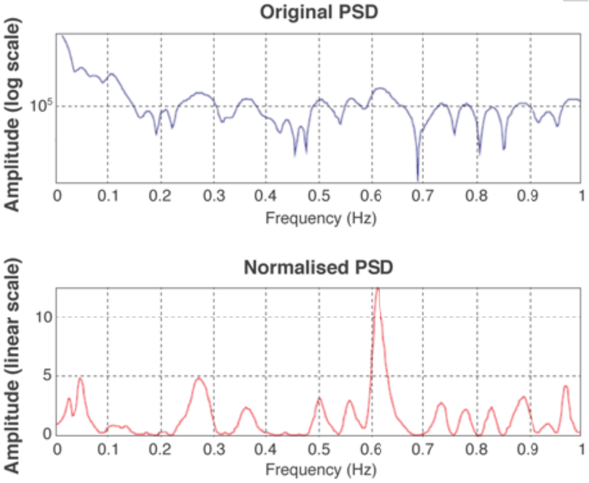

Figure 1. Power spectral density in the infra-low frequency region. Shown is the original data to logarithmic scale. The sharp nulls imply that the detected spectral pattern is at least short-term stable. The same data are also shown in a linear plot after correction for the secular 1/f-amplitude trend of SCP amplitudes in this spectral range. Narrowness of the peaks again indicates at least short-term stability of the spectral pattern.

It is in the frequency domain that we encounter our first hard scientific finding: over the entire infra-low frequency region the optimization frequencies for the left hemisphere placements are harmonically related to those on the right. They are related by a factor of two (Othmer SF, 2006). This relationship only breaks down in the conventional EEG spectrum, where the difference is given by an arithmetic rather than geometric relationship: the left hemisphere optimizes at two Hz higher than the right. These relationships are illustrated in **Figure 2**. Collectively, they hold over five orders of magnitude in frequency. The crossover is at 2 Hz for the right hemisphere.

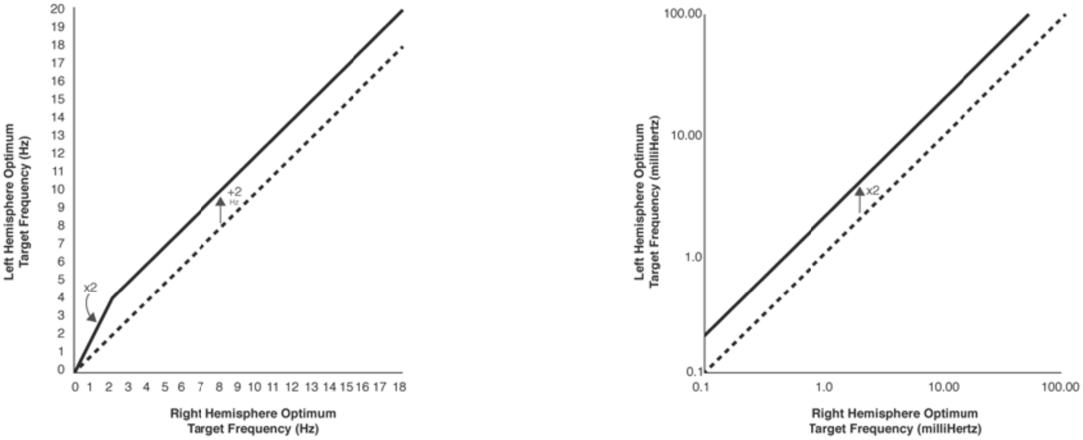

Figure 2. Universal relationship between optimum response frequency for left versus right hemisphere placements. The harmonic relationship applies over the entire infra-low frequency region. Hence the above relationship has been documented over five orders of magnitude of frequency, and for all right and left hemisphere placements that have been used to date.

ASSESSMENT

Assessment covers a broad range of observables that can capture the quality of system functioning and characterize the nature of the particular dysregulation at issue. Client history is extensively explored, with emphasis on early developmental issues. Brain stability and arousal regulation are probed with a continuous performance test with everyone capable of taking the test. The expectation for successful training is that the CPT measures normalize, or at least improve. The test tracks omission errors, commission errors, reaction time, and variability in a pressured choice reaction time test. Particularly significant for recovery from dysfunction are the discrete errors, omissions and commissions. For concreteness, comprehensive results for all clients who had been in significant deficit, who received infra-low frequency training at the EEG Institute in the 2009-2012 timeframe, and who were retested after twenty sessions, are shown in **Figure 3**. The QIKtest was used. It is modeled after the TOVA, an industry standard, so the same norms applied (Leark, 2000). Post-training results are shown with non-responders excluded. Substantial normalization of function is apparent among the responders, particularly for commission errors. This category is minimally impacted by organicity (5% non-responders). If a brain is capable of being impulsive, it generally has the capacity to function normally. By contrast, recovery in omission score is more constrained by organicity (26% non-responders at the 20-session juncture).

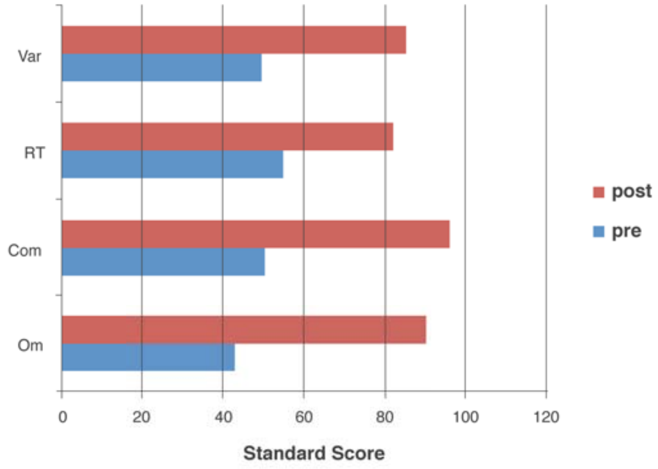

Figure 3. Shown are Pre-post QIKtest data on all 350 clients who underwent ILF training at the EEG Institute in the 2009-2012 timeframe for whom 20-session post-training data were available. Non-responders were not included. For the omission errors, non-responders were 26%; for commission errors, 5%; for reaction time, 27%; for variability, 20%.

THE THEORETICAL BASIS OF INFRA-LOW FREQUENCY TRAINING

Discrimination of the Slow Cortical Potential

It has been convenient to describe the brain's engagement with its own EEG in anthropomorphic terms. It is necessary to demonstrate, however, that translation of the simplistic model into a viable neurophysiological model is in prospect. An analogy may be helpful. The driver on a Los Angeles freeway is likely to have turned over the job of steering the car to his brain while his mind is engaged on higher matters. And even if his mind were to turn to thoughts of suicide, the brain would still not be diverted from its obligation to keep the car pointed properly. The brain is operating an independent control loop for which it has assumed responsibility.

Matters are no different if the signal the brain is tracking happens to be the time course of the slow cortical potential. All that is required is for the brain to discover its agency with respect to the signal. Then it automatically follows that the brain will exploit that signal for its information content and assume responsibility for its further trajectory. This is a process of ongoing prediction in which the brain seeks to bring closure between the predicted and the actual trajectory. The brain will not relax its vigilance with respect to the signal any more than it will do so in the case of steering the car.

On the other hand, we know that the brain's experience of the world is restricted to the mutual interaction of neural networks. The optimization of the path of the car is the result of a continual updating of a correlation of certain neural firing patterns. One of these patterns is established through our sensory networks, and the other is a pattern prevailing in our distributed circuitry of motor control. At the present state of knowledge it would be almost impossible for the astute neuroscientist to identify the subtle correlation that the brain is depending on in this instance, and that it appears to manage quite trivially in subroutine.

In the neurofeedback case the sensory systems are processing the signal that represents the time course of the slow cortical potential, and the correlation is with local activation somewhere in cortex. But the effect of the fluctuating electrochemical potential at that location is non-specific, affecting all of the neuronal assemblies active there and modulating their firing rates. The brain, in its role as correlation detector, will find that the correlation between the two signals is not subtle at all. It is in fact a robust signal. And that accounts for the fact that in actual practice the brain seems to come to recognize this signal exceedingly quickly, and it does so even when the signal appears to be relatively featureless, as has to be the case at very low frequency.

Recognition of the signal is not enough to account for what we observe, however. The correlation is sufficiently robust to track the subtle fluctuations in the differential signal, fluctuations so subtle that they are apparent only to the brain that authored the signal in the first place. In fact, such subtle fluctuations are detectable only because of the existence of the correlation. Otherwise they would be ignored, just as they are over-looked by the independent observer. The same thing happens to the brain driving the car. A passenger in the car watching the behavior might well judge that the frequent steering inputs are overkill---the car is doing fine. But the brain in charge is not only processing the visual feedback from the road but also the tactile feedback from the steering wheel. Another multi-modal correlation calculation is driving events. The brain in charge is processing a richer signal stream at a much higher level of complexity than the observer; hence the reaction to subtlety that is not apparent to anyone else in the car.

Mechanisms Basis for Electrode Placement

The operative model of the ILF training is that the primary placements interface with key hubs of our core control networks, in particular the Default Mode that plays such a central role in both our quiescent and engaged states (e.g., Fair et al. 2008). These placements take us as close as we can get to the dynamic management of the level of neural network excitability (local), which ties us in directly to network activation (non-local) and central arousal (global). The correlations among the key hubs of the Default Mode Network were characterized by Buckner (2008), as reproduced in **Figure 4**. The magnitude of the correlation in each linkage is indicated by the thickness of the connection. The linkage between the Left Lateral Temporal Cortex (L LTC) and the

Right (R LTC) is prominent. This corresponds to our T3-T4 placement, which is the key to nearly all of our work with brain instabilities. The other major nodes that are readily accessible at the cortical surface are the right and left inferior parietal lobule (R IPL and L IPL). T4-P4 corresponds to the linkage between the right lateral temporal cortex (Brodmann area 21) and the right inferior parietal lobule (Brodmann area 39 and part of 40). This has emerged as the most important single pairing in all of the work with ILF protocols for the most debilitating disorders.

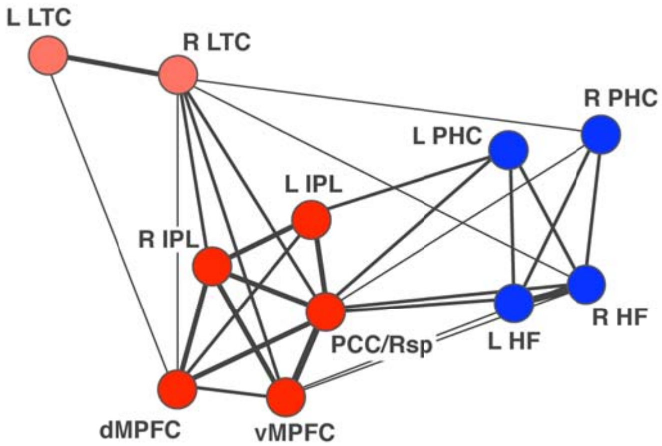

Figure 4. Principal hub connectivities of the Default Mode Network, according to Buckner. Relative coupling strengths are indicated by the thickness of the connecting lines. Strong coupling exists between the left lateral temporal cortex and the right (L LTC and R LTC), which corresponds to T3-T4. Direct coupling also exists between the R LTC and the Right Inferior Parietal Lobule (R IPL), which corresponds to the second principal starting placement, T4-P4. HF refers to Hippocampal formation; PHC refers to Parahippocampal cortex; PCC refers to Posterior Cingulate Cortex; Rsp refers to Retrosplenial cortex; dMPFC and vMPFC refer to the dorsomedial and ventromedial Pre-Frontal Cortex.

The right lateral temporal cortex is much more intimately connected with the various hubs of the DMN than the left, as shown in the Figure, and this is reflected in the fact that T4 plays a much larger role in the training than T3. T3 and T4 are involved in all lateralized linkages used in training, so it can be said equivalently that right-side training is more crucial for restoring foundational regulatory capacities than left-side training. A bias favoring the right hemisphere in this role also finds support in the work of Menon and Uddin, which posits that the Salience Network (SN) mediates the relationship between the Default Mode and the Central Executive Networks (CEN) (Menon 2010, Uddin et al., 2013). Although the salience network is represented symmetrically in both hemispheres, the right SN plays a preponderant role. Specifically it is the right anterior insula that governs the switching between task-negative and task-positive status of the control networks (Sridharan et al., 2008).

The placement that ranks second only to T4-P4 among right-hemisphere linkages is T4-Fp2, which links to the Central Executive Network pre-frontally and to the temporal region, where it is sensitive to the local activation in which the anterior insula plays such a ‘salient’ role. Collectively, this line of argument supports the centrality of right-side training in the remediation of the most debilitating of psychopathologies. Up to now a distinction has been drawn between the targeting of brain instabilities and of state regulation. In reality, of course, these are intimately coupled as well. The dysregulated brain is less stable. In fact, behavioral variability is a key feature of most psychopathologies (e.g., Lin et al., 2013). Whereas brain instability is the first priority in training, state regulation may have to be pursued as the means to get there. When physical calming is the first priority in pursuit of brain stability, this can be seen as yet another argument in favor of the proposition that the core issue in endogenous neuromodulation is the quality of functioning of the Default Mode. It is apparently most productive to challenge this organization in its most persistent states. Supportive of this proposition is a systematic review of DMN dysregulation in mental disorders (Broyd et al., 2009).

THE HISTORICAL DEVELOPMENT OF INFRA-LOW FREQUENCY TRAINING

Feedback on spectral properties of the EEG

The roots of frequency-based neurofeedback go back to animal research performed in the 1960's. In the course of sleep research on cats a bursting rhythm was identified in sensorimotor cortex while the cats were motorically idle (Roth et al., 1967). Termed the sensorimotor rhythm (SMR), the spindle-bursts occurred at the same frequency as the sleep spindle, and thus were identified with it. Operant conditioning to promote the appearance of SMR-bursts altered both the waking and sleep behavior of the cats. (Sterman et al., 1970; Wywricka & Sterman, 1968. When the same cohort of experimental animals was later subjected to a toxic challenge to induce seizures, the SMR-trained cats showed much greater latency to seizure onset. Research with monkeys followed (Sterman et al. 1978; Wyler, 1977a; 1977b), leading to initial human trials (Sterman, 1973; Sterman & Friar, 1972). The method was formally researched for a number of years, but NIH-funding dried up by 1985. A review of the research history was conducted by M. Barry Sterman (2000), and covered 24 studies, 13 of which had competent controls, and collectively included 243 participants. Overall some 82% of subjects showed at least 30% improvement in seizure incidence, with an average improvement of 50%. All subjects had been medically refractory patients in stable condition. More recently a meta-analysis has brought matters up to date, coming to the conclusion that efficacy of SMR-training in seizure management has adequate scientific support (Tan et al., 2009).

The identical method was applied successfully to the problem of hyperkinesis, now attention hyperactivity disorder (ADHD). (Lubar & Lubar, 1984; Shouse & Lubar, 1976). This likewise led to a number of research studies over the years. A recent meta-analysis determined that efficacy of the training procedure in this application had been demonstrated (Arns et al., 2009).

An offshoot of the focus on seizure control was a clinical thrust to remediate residual symptoms of minor traumatic brain injury (mTBI) and stroke. Since the symptoms of mTBI relate to various regulatory subsystems, this work gave rise to the supposition that neurofeedback could be effective with those same symptoms in other contexts. Training in the SMR-band and in the beta1 band (15-18Hz) came to be used to address a broad variety of what could be labeled as disorders of cerebral dysregulation: the anxiety-depression spectrum, pain syndromes, and sleep disorders (Hauri et al., 1982; Sime, 2004). This thrust was given impetus in the early nineties with the availability of competent computerized instrumentation.

Feedback on the Slow Cortical Potential

Feedback on the slow cortical potential has a long and well-established research history in Europe (Strehl et al., 2005; Kotchoubey et al., 2001). The challenge presented to the trainee was to alter the ambient SCP by some 4 microvolts in the target direction, either up or down, within a time window of 8 seconds. Even if the baseline voltage was dominated by non-neuronal factors, the change in the signal certainly implicated neuronal mechanisms. Over time, the ability to control the SCP could be acquired by a large majority of trainees, and this capacity had behavioral consequences. Training was always done at Cz, where the contingent negative variation (CNV) was known to be maximized (Birbaumer, 2006).

Application areas of SCP training overlapped largely with work in the United States using frequency-based feedback: primary application was to ADHD and seizure management (Strehl et al., 2006a; 2006b), but research also extended to cover migraines (Siniatchkin et al., 2000) and even schizophrenia (Gruzelier, 2000; Gruzelier et al., 1999; Schneider, et al., 1992). In fact, Gruzelier was the first to report feedback on the SCP using inter-hemispheric placements (Gruzelier et al, 1999). Clinical claims for SCP training met a critical reception in Europe just as SMR/beta neurofeedback had in the US. More recently, research has been conducted comparing the two approaches in application to ADHD. The methods were found to be broadly equivalent (Gevensleben, 2009).

The Emergence of Infra-Low Frequency Training

The foundations for the emergence of infra-low frequency training were laid entirely within the realm of traditional frequency-based neurofeedback. By virtue of their sensitivity to reward frequency, brain instabilities became the driver toward precision in the reward frequency, while the right-hemisphere issues became the impetus toward ever lower reward frequencies. The initial migration below the standard SMR and beta1 frequency took place in 1999 with the adoption of inter-hemispheric placement for the instabilities. Progressively lower frequencies were clinically explored over the next ten years. The initial exploration of the ILF regime took place in 2006. Below 1 Hz, standard threshold-based amplitude training became impractical, and waveform-following was adopted, along with the abandonment of thresholding. The range was extended to 0.01 Hz in 2008, to 1mHz late in 2008, and to 0.1mHz in 2010 (Othmer et al., 2011).

In each case, the clinical reach was extended to cases that had previously been intractable. Qualitatively, however, there was complete continuity with the prior methods. The primary placements had already been identified in the higher-frequency region, and remained the same. The clinical strategies merely underwent tactical refinements. The ILF capability opened the door to the remediation of deficits related to early childhood emotional and physical trauma, which shifted the emphasis to a strategy of calming the nervous system as a first priority from a prior emphasis on brain instabilities.

Representative Clinical Results

Disorders of sleep regulation

Since the quality of sleep is a good index to the quality of arousal regulation, it is an appropriate starting point for a discussion of clinical effects (e.g., Scher et al., 2010). Remediation of insomnia was originally reported for SMR-training for cases involving an anxiety condition (Hauri, 1982). ILF training has been found to be more generally helpful with ordinary insomnia---delayed sleep onset, frequent waking, failure to return to sleep after early wakening, etc. The impacts are often felt after a single session. Given the high responsiveness of the dysregulated brain, training-induced changes in sleep quality are sensitive indicators for optimizing the training parameters. The quality of sleep is also a good indicator of whether training objectives have been achieved.

Nightmares are very responsive to the training, and can consequently also serve to guide the training. If nightmares persist, one may assume that the training has not been optimized. Bed-wetting commonly subsides quickly in children, or else is non-responsive. Night terrors and sleep-walking in childhood respond readily. Restless leg syndrome is responsive. We observe only occasional remediation of sleep apnea, and only occasional improvement in narcolepsy. Circadian rhythm disorders can now be helped, whereas we were previously unsuccessful in such cases with conventional frequency-based neurofeedback.

Brain Instabilities

Brain stability is the most critical issue in the systems perspective, and neurofeedback can be very helpful in this regard. Sudden descents into dysfunction are collectively labeled brain instabilities. This category encompasses seizures, migraines, panic attacks, asthma attacks, vertigo, and even bipolar excursions on any timescale. For all of these conditions inter-hemispheric placement is called for. What is being trained is the quality of functioning of the particularly brain, specifically the coordination between the hemispheres of the resting state networks. The reduction in risk of an episode testifies to the success in that effort.

The greatest experience base has been accumulated with migraines, and this is also where outcomes are the most predictable. Superb outcomes have recently been reported using conventional frequency-based neurofeedback (Walker, 2011). 71 migraineurs being managed with medication were offered complementary neurofeedback. Of the 46 who pursued the training, 90% reduced their migraine incidence by more than 50%, versus 9% for those who stayed on the medication-only track. Fully half saw their migraine incidence reduced to zero, versus none in the medication-only group. 68% of the latter saw no improvement in incidence at all. The follow-up period was one year. It is our clinical impression that ILF feedback yields comparable outcomes in general, but holds advantages when migraines are part of a more severe pattern of dysfunction.

The majority of migraineurs may expect to become substantially migraine-free. Some care may have to be taken with lifestyle factors and known triggers. Significantly, hormonally-mediated migraines tend to respond to the training as well. If someone enters the aura phase of the migraine, it can usually be aborted quickly with the training. If a trainee comes to the session with a migraine and is able to train, it is likely that the normal trajectory of the migraine will be interrupted, and set on a path to resolution. Even before the training has been fully consolidated, a client may report that a migraine prodrome self-aborted between sessions. The same has been seen with panic attacks.

With asthma much of the clinical experience is in connection with children training for ADHD. Parents routinely report that their children show less resort to medication. With regard to seizure susceptibility, clinical experience indicates that ILF feedback impacts incidence to a clinically significant degree in the majority of cases of medically refractory pediatric epilepsy (Legarda, 2011). Re-titration of AEDs is usually indicated. The need for polypharmacy may be reduced.

Deficits in State Regulation

Steady-state deficits in state regulation are discussed separately from the instabilities. The issue here is the failure to maintain set points of subsystem activation appropriate to the situational demand, which we observe for individuals complaining of anxiety, depression, or attention problems. These conditions are responsive to ILF training, and normalization of function is in prospect for the large majority of the affected population when the training is imbedded within a comprehensive treatment program. Neurofeedback complements both pharmacotherapy and/or psychotherapy in these applications. However, as is apparent, without neurofeedback such treatments often fall short for a significant number of these individuals.

Drug Dependence

Efficacy of traditional frequency-based neurofeedback in application to alcoholism and other drugs has been established in several controlled studies. In all such cases, the training was imbedded within a conventional treatment program. (Peniston, 1990; Scott, 2005) It was only occasionally observed, however, that the training eliminated craving.

The complementarity of ILF feedback and psychoactive medication therapy is particularly apparent in application to drug dependency. With ILF training we encounter cases of clients giving up smoking without ever having intended to. The craving for the drug of dependency simply subsides. The same is seen with alcohol. And when it comes to medical marijuana, it is quite common for clients to give it up completely as training objectives are met. ILF feedback can also be helpful in eliminating dependence on anxiolytics, pain and sleep medications.

Disorders of Dysregulation

Some disorders are characterized by such system-wide impacts that they practically define the category of Disorders of Dysregulation. Although various degrees of organicity may prevail in each case, the defining characteristic is disorder in the functional realm. These conditions are not substantially helped by either pharmacological interventions or psychotherapeutic techniques, yet they may yield readily to ILF training. Examples are Post-Traumatic Stress Disorder, minor Traumatic Brain Injury, the autistic spectrum, developmental trauma, and the severe eating disorders (e.g., Moritz et al., 2001; Koen & Stein, 2011; Ganz et al., 2010).

When it comes to minor traumatic brain injury, medical practice has largely relied upon endogenous mechanisms of recovery that may take as much as eighteen months to plateau. Neurofeedback training can place the patient on the path to substantial recovery of function. Systematic success of feedback-guided rehabilitation demonstrates that the factors impeding recovery lie largely in the functional domain and are accessible to remediation (Thornton, 2005). ILF training can likewise be used to accelerate and augment the recovery process in the general case. Training for functional recovery is typically begun after the acute symptoms of TBI (edema, etc.) have subsided. During the initial post-trauma phase, ILF feedback would be directed mainly toward symptom relief of headaches, nausea, blurry vision, etc., provided that the training is well-tolerated.

The above arguments extend also to stroke and the sequelae of brain surgery. Many of the symptoms of stroke are those of global system dysregulation, which can be remediated effectively with neurofeedback in general, and with ILF training in particular, quite independently of progress made with the specific losses attributed to the stroke.

The arguments also extend to the dementias, where worthwhile improvement in system function may be achievable. ILF training can also compensate for misdiagnoses of dementia through rather complete recovery of function. Similarly, the quality of system functioning can be broadly enhanced in the steady state after brain infections such as encephalitis.

The autism spectrum clearly manifests a mixture of organically-based and functionally-based deficits. Conventional neurofeedback has already been helpful here (Pineda, 2008), but ILF training offers distinct advantages in this application. Bringing the child’s nervous system to calmer states is a pre-condition to effective training of affect and arousal regulation, and with ILF training one can observe this process in real time. Because of organicity, ILF training for this population is opportunistic in character. It is the training itself that reveals how important a role it should play in the child’s therapeutic hierarchy. For a substantial minority of autistic children, the ILF training is life-altering, potentially involving the initiation of language and of emotional engagement with family members. For the majority of autistic children who are at elevated risk of seizure, ILF feedback can be helpful. Nearly all autistic children will likely experience worthwhile increments in functionality with the ILF training. For example, it is quite commonly the answer to constipation, a persistent problem for many autistic children.

Developmental trauma refers to the disruption of the normal developmental trajectory early in life due to persistent emotional duress. Under these conditions, there is a greater likelihood that adverse patterns of functional organization are consolidated. These are later particularly resistant to remediation (Najjar et al., 2008; Pearlman & Courtois, 2005). Affected individuals reveal themselves as treatment-resistant in a variety of health practices, as they migrate from one to another. Affected individuals lack resilience, likely leading to further dysregulation with the cumulative effect of additional minor brain insults. Somatic health status is adversely impacted as well. These people are unfortunately often categorized as somatizers. Somatization should be seen as the natural end stage of progressive, pervasive dysregulation (Arciniegas et al., 2005). The term is a vestige of our dualistic tradition (Babić et al., 2013).

Post-Traumatic Stress Disorder (PTSD)

PTSD is first and foremost a Disorder of Dysregulation (e.g., Weems & Carrión, 2009; Fairholme et al., 2013). It may have had a purely psychological origin, and it does indeed have psychological consequences. But it is not adequately described as a psychological condition, and it is by and large refractory to psychotherapeutic remedies (although these do have a legitimate role to play in the trajectory to comprehensive recovery) (Hamner et al., 2004; Nelson & Esty, 2012). The priority in the remediation of PTSD must be the pervasive physiological dysregulation that characterizes the condition. ILF training can effect recovery admirably, and often quite quickly. Initial success in treating combat-related PTSD has, already been demonstrated previously with Alpha-Theta training (Peniston&Kulkosky, 1992). In our experience recovery is more comprehensive with the ILF training.

It is for PTSD that we have the largest number of relevant case histories to draw upon for a single diagnostic category, including veterans of recent wars and even going back to the Vietnam era. Several thousand veterans have benefitted from infra-low frequency training to date. With this training, a quarter of veterans see their PTSD symptoms subside to clinical insignificance within 12 training sessions (median; range to 20). Half have their symptoms largely abated by 30 sessions (median; range of 20-40). The remaining cases require 40 or more sessions, with about 5% being treatment-resistant.

The identified symptoms of dysregulation have been systematically tracked for many individuals undergoing ILF training for PTSD. Some 65 symptom categories were commonly represented in this population. The category showing the greatest responsiveness to training was migraine, with 90% reporting substantial remediation (n>100). The least impacted category was tinnitus, with 50% indicating substantial relief (n>50). All other symptom categories fell within this range, although for some symptoms where our numbers were small, recovery was observed in all cases. These categories included suicidality, hypertension, chronic constipation, asthma, motion sickness, stomach pain, and joint pain.

Significantly, in 80% of cases in which depression had been rated above 6 out of a range of 0-10, depression scores were cut in half within less than eight sessions (n>100). Almost identical results were obtained for anxiety (n>100). 80% of cases of panic attacks responded, and flashbacks of trauma subsided in 75% (n>100).

An Appraisal and a Projection

Understanding and treating the brain in the perspective of its functioning as a dynamically regulated, hierarchical control system has turned out to be highly fruitful, and portends significant implications for clinical neurology and psychiatry, and for all the neurosciences. Stimulating and promoting endogenous mechanisms of recovery allows for a level of subtlety, refinement, and comprehensiveness in clinical practice that is not available with existing exogenous therapies.

The potential is particularly great in pediatric applications, where there is a reluctance to diagnose and to medicate prematurely (e.g., Cosgrove et al., 2013). The observation of a first seizure in a young child should lead to the supposition that the nervous system is marginally stable, which calls for bringing neurofeedback to bear. Taking this argument further, the observation of any sustained indication of a self-regulatory deficit on the part of a child should result in a trial of neurofeedback before other therapies are invoked. Persistent headache is the most obvious symptom of a brain in a state of dysregulation, and it calls for neurofeedback in preference to symptomatic relief. The same holds for sleep issues, and generally for pervasive, idiopathic distress in an infant. Successful training has been initiated as early as three weeks.

The symptoms of autism often reveal themselves quite early in childhood. A formal diagnosis is not needed in order to make neurofeedback advisable in such cases. One would clearly like to intervene as early as possible in order to redirect the developmental trajectory. The same arguments serve for children who suffer from developmental trauma, or who have been exposed early in life to abuse or neglect. Voluminous research now definitively ties later mental and somatic health outcomes to the quality of early childhood emotional experience (e.g., Rafferty et al., 2011; Black et al., 1994). The implication is that unremediated problems of dysregulation tend to progress toward becoming ever more obtrusive and intractable, eventuating in disturbances of somatic functioning. The latent effects of early trauma now appear accessible to us through ILF neurofeedback.

With a focus on the quality of self-regulation, the salience of a specific diagnosis is diminished. The training is entirely oriented toward the enhancement of functional competence. Dysfunction subsides as a consequence of the improved quality of regulation, and symptom severity serves as an index to the success of the procedure. Although every child can potentially benefit from this kind of brain exercise, it must first be a priority for those children suffering from brain-based medical afflictions. With the maturation of ILF training through clinical practice, an important new therapeutic method is being added to the medical arsenal.

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