Toward a Theory of Infra-Low Frequency Neurofeedback

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Abstract

In Infra-Low Frequency Neurofeedback one is gifted with a cornucopia of compelling clinical data, along with a paucity of quantifiability and sparseness of theory for their interpretation. The real-time signal is meaningful only to the brain that produces it, and for the real-time response one is dependent on client report. The training process is entirely self-referential, i.e. endogenous, operating at the limit of subtlety at which good neuro-regulation must necessarily take place. Nevertheless, clear patterns of responding have been observed. Two primary failure modes have been identified and linked to two principal protocols that are broadly impactful for the clinical population. Precision is available to us in the frequency domain, and that has yielded a basis for understanding how the different brain regions coordinate in the frequency domain. The identified pattern holds over the entire range of frequencies of therapeutic relevance. Infra-Low Frequency Neurofeedback engages with a slow control system that was first identified in animal research. This takes us to the foundations of the developmental hierarchy, and as such facilitates recovery from early childhood trauma at any time in life, as well as enabling the re-direction of developmental trajectories in infancy and early childhood.

3.1 Introduction

Infra-low frequency neurofeedback is not readily subjected to formal evaluation by way of group studies in the classic mode. Not only does the procedure have to be individualized to a degree that is likely unprecedented in clinical practice, but the training procedure has to remain adaptive throughout the training process. The multi-dimensional discovery process involved here could only flourish in the clinical realm, and ILF training will likely remain a clinical frontier. Undoubtedly, we are only at the beginning of the exploitation of this new modality.[1]

At the same time, any arbitrary threshold of validity can be met even in this context by the principle of Bayesian inference, without resort to group studies. The body of knowledge reflected in this book testifies to that. The clinical model evolves incrementally in a manner similar to the growth of the conventional lava flow at Mount Kilauea: plasticity at the frontier of clinical practice, but leaving a trail of progressive solidity behind. Such plasticity is rare and precious in the sciences that bear on human health. ILF Neurofeedback also offers intrinsic tests of validity, by virtue of its parametric specificity in the frequency domain. And finally, supportive evidence is starting to be furnished by more basic studies.

The more intractable barrier to acceptance is at the theoretical level. The scientific mind resists being asked to take seriously data for which there is no agreed upon operative model.

The frontier of ILF NF has at times challenged our own belief systems, because the clinical findings were so startling that they pushed the limits of our own credulity. Clients respond rapidly and consistently to a relatively featureless low-frequency waveform. How is this to be explained? In consequence, we have only the greatest sympathy for critics outside of the field. If we hadn't been confronted with our own ineluctable case data, and if we had not had a chance to see systematic patterns emerge over the years, we would have been right among them. Our challenge in this chapter, then, is to shape the data into a compelling narrative, and to present a credible theoretical model.

3.2 Principal Categories of Brain Dysfunction

The top-level criterion for a clinical practice on the path to becoming an accepted discipline is that of systemization. Can the basic facts of a field be categorized, systematized, and manualized? In this regard, we face the challenge of working at the bottom of the regulatory hierarchy, intervening with the lowest frequencies at which brain function is dynamically regulated in a frequency-based manner. There are no established terms of discourse for this problem. There are no measures that track the approach to this objective. We are thrust back upon the self-report of clients with respect to their own self-regulatory status. We are reduced to the client's own 'observables,' by and large. The best we can do, therefore, is to rely on the terminology that is used with clients. In addition, we also take advantage of indices of autonomic function from physiological measures, and whatever we can discern from trends in the EEG. Over the longer term, we can track improvements in cognitive function with formal tests.

We begin by regarding the brain as a generic control system, one that has to satisfy the requirements of any self-regulatory control system. Thinking of the brain in such holistic terms takes us back to the very beginnings of the neurosciences. The neurologist Hughlings Jackson originally propounded the concept of a "cerebral global function" that governs the susceptibility to seizures. The fundamental burden of the brain is to assure its own categorical stability, sufficient to sustain basic functionality. Macro-instabilities violating this criterion include seizures, migraines, panic attacks, asthmatic episodes, and narcoleptic events. These instabilities constitute the primary objective of a training strategy toward functional normalization, as in their presence all subtlety of regulation is lost.

At the second level, the burden is to maintain setpoints of activation with respect to various functional domains. The most global variable in this category is central arousal. This concept also traces back to the origins of the neurosciences. As far back as 1895, Freud and Breuer asserted that "a certain measure of arousal exists in the conductive pathways of the resting, waking, engagement-capable brain." This whole-brain property of necessity could serve only a heuristic function then, and the same holds true now. Central arousal, in turn, modulates sympathetic arousal of the autonomic nervous system, and vigilance, which comprises the alertness of the attentional system, engagement of the executive function domain, and the poise of motor system. None of these can be readily quantified. We are therefore compelled to operate clinically with what is termed "ipsative trend analysis," the discernment of change

induced via the training process in correlates of the categories of interest. In the absence of measures, we are compelled to live with how the client interprets terms bearing on arousal, vigilance, and excitability that the clinician brings into the discussion. In addition, there are terms characterizing the affective state, the state of the autonomic nervous system, the quality of sleep, and the status with respect to drives such as hunger, pain, and cravings.

This unsettling lack of quantifiability notwithstanding, one may still ask the question: Just how we are thinking about terms such as arousal and vigilance? In the early years of our work, we understood the term arousal in the Yerkes-Dodson sense. Central arousal is whatever is under the management of the reticular activating system. (Even Yerkes-Dodson referred to motivation before it became arousal in their famous plot!) That view is coming into some question with the descent into the extreme low-frequency regime. The time constants of responsiveness of the reticular activating system are fairly short—seconds to minutes. Something else seems to be in a controlling role at the longer time constants, and with respect to our clinical agenda, that appears to be the most relevant aspect. One can think of the fast response of the reticular activating system as being precipitated by interactions with the outside world. For our purposes, the more salient issue is the maintenance of the internal milieu, our ambient or so-called resting state, where the time constants are typically longer.

Our clinical experience can be distilled into a primary concern with brain instability and with arousal dysregulation. These two categories are foundational to the whole enterprise of neural regulation, and both benefit from being readily describable by most clients. They map into our two primary protocols for the initiation of the clinical work. This is possible because the entire class of brain instabilities is responsive to the same protocol, or at least to the same class of protocols. Similarly, arousal dysregulation primarily responds to a single protocol.

The context out of which brain instabilities arise tends to be one of neuronal hyper-excitability. The roots of this concept also go back to Freud, who as early as 1894 referred to the “sum of excitation,” which he saw as relevant to psychopathologies such as hysteria and hallucinatory psychoses. As we now conceptualize the issue, there is a cellular (synaptic or other membrane) aspect to hyper-excitability, one that is typically addressed by anti-epileptic drugs, and there is a network aspect. The ILF training impinges on the network aspect in first instance, and over time appears to also affect the setpoints of excitability at the cellular level. That proposition is testified to by the observation that often levels of anti-convulsants can be reduced or even eliminated through the course of neurofeedback training.

The context out of which arousal dysregulation arises tends to be trauma-based, where this term is to be regarded in its most encompassing scope. Trauma does not have to be life-threatening (or its equivalent) in order to wreak havoc with the course of early neuronal development or to result in its dysregulation in maturity. The loss of a sense of safety, of personal security, or even of status at any level tends to move the nervous system to a state of over-arousal. This may become so well established as the new ambient that it is not perceived as such. A new comfort zone develops such that a return to calm states may even give rise to a sense of insecurity and loss of safety.

Physical injury such as concussions and other minor head injuries also disturb the integrity of neuronal network relations, which likely constitutes their primary failure mode. Commonly these are also observed to heighten neuronal excitability, particularly among those with that vulnerability. Our greatest clinical challenges are those for whom both arousal dysregulation and neuronal excitability prevail. In the case of the latter, we are typically dealing with a genetically-mediated propensity. Brain instabilities such as migraines tend to run in families, but they may not be evoked until triggered by a minor brain injury or other trauma. That is also the case for seizures, where the vulnerability may well remain latent in the absence of compounding events.

As over-arousal conditions tend to be trauma-related, they are typically environmental in causation. With affect dysregulation and the fear response as mediators, some considerable commonality in the neuronal failure modes is not unexpected. This may in turn account for the fact that a standard protocol goes a long way to resolving these issues. Already noted is that brain instabilities also tend to respond favorably to a single protocol, despite all of the variety in which they manifest, and that likewise suggests a common failure mode.

3.3 The Trauma Model

The term trauma is at risk of becoming hackneyed and trivialized from over-generalization. It is particularly at risk when apparently minor traumas are discussed in the same context as major ones. But the fact is that even minor traumas can have major consequences. This holds true for both minor emotional traumas and minor brain injuries. The explanation is the obvious one. When even minor traumas afflict a vulnerable nervous system, it can be tipped into major dysfunction. When we look at personal histories in such cases, a consistent story can usually be told of a progressive vulnerability that finds its origins in early childhood. This means that minor traumas cannot be considered in isolation in the general case, or judged ‘on their own merits.’

This shifts our perspective from minor traumas, which are in fact ubiquitous in our upbringing, to the matter of recovery. What really matters here is the dispersion that exists in the distribution of recovery potential across the population. The wide variation in vulnerability, in the lack of resilience, compels us to see the connection among apparently disparate events. This process, in which a concatenation of apparently minor traumatic events can lead progressively to major dysfunction, we refer to as the “Dysregulation Cascade.” Tracing such a cascade to its causal origins commonly takes us back to a perilous environment for early upbringing.

Perhaps the best exemplar of a Dysregulation Cascade is a boxing match, in which the overt objective is the disruption of the neural integrity of the opponent. During the match, there is little opportunity for functional recovery, so injury is cumulative. Full functional recovery may eventuate, however, with nothing more than the tincture of time between matches. What matters most in accounting for attrition in the careers of boxers is not the

magnitude of the blows received but the variation in recovery capacity. This observation generalizes to the population at large.

This is such a critical issue that it bears further discussion. It has been found that even a single change in domicile in a 14-year-old teenager doubles the cumulative risk (to middle age) of attempted suicide. Roughly the same holds for the increased risk of substance abuse, violent offending, and of any psychiatric diagnosis. What appears to be a minor traumatic episode may in fact be quite significant in some children's lives. The only reasonable explanation is that this apparently 'minor' trauma has outsize consequences for a subset of the teenage population that is already at risk by virtue of prior history.[2]

What first brought this issue broadly into public awareness was the "Adverse Childhood Experiences (ACE) Study".[3] Here the focus was on overt traumatic experiences or contexts of living: psychological, physical, or sexual abuse, etc. Evaluation of some 9500 adult questionnaires yielded the finding that "Persons who had experienced four or more categories of childhood exposure had 4- to 12-fold increased health risks for alcoholism, drug abuse, depression, and suicide attempt." Even more surprising was the correlation with chronic medical disease: ischemic heart disease, cancer, lung disease, liver disease, and diabetes. With four or more ACE's the relative risk was elevated by about a factor of two.

Results were similar for a Scandinavian study that also evaluated the somatic health impact of psychological stress. In tracking the increased incidence of disability-related pensions post age 65, a dramatic correlation with early psychological stressors was brought to light. 3-7 stress factors yielded a doubling of the incidence of disability-related pension in the subsequent five years. 9-12 stress factors yielded a risk multiplier of four. Overall, "over a quarter of… disability pensions granted for somatic diagnoses could be attributed to psychological distress." Even more concerning, "…even mild psychological distress was associated with later onset of long-term disability".[4]

Our first solid indication of the relationship between early development and general health was furnished by the so-called Grant study on 256 Harvard students that began in the late 1940's.[5] Some fifty years later, the remaining 160 were evaluated for the usual diseases of aging. If the person had grown up in a positive emotional environment, the incidence of such diseases was 25%. If they had grown up in an adverse emotional climate, the incidence was 89%. The risk multiplier was an astounding 3.6. This is a more reliable figure than that furnished by the ACE study, where the more severely impacted may already have attritioned out of the population by the time it was questioned.

The Harvard study, on the other hand, has different limitations. It is representative of the segment of the population that was not in economic straits. Socio-economic status is known to be the largest single risk factor with respect to overall health and mortality. So, a more inclusive view would assign even higher import to emotional wellbeing than is implied in the Harvard study. A later study found that those with "six or more ACE's died nearly twenty years earlier than those without ACE's".[6]

The clear implication is that our general health status—mental and physical well-being—are closely correlated with early emotional upbringing. That brings us, then, to the question of mechanisms. We distinguish between event trauma and a steady-state adverse living environment. Event trauma transiently heightens memory function. The salience of an event renders it state-stamped rather than date-stamped. It is registered as a whole-body memory, with cognitive, affective, autonomic, and somatic responses fused into a unitary configuration, bound together with the historical memory of the event. Irrespective of whether the individual is personally at risk or is a mere witness, the event alters the setpoint of the threat response, and it does so relatively permanently. This may well be protective of the individual, but it comes at a cost to the physiology over the longer term. It has implications for the subsequent development of neural network relations, and of neuroimmune and neuroendocrine system activation.

In the matter of steady-state exposure to toxic living environments, we turn to the research of Martin Teicher and colleagues at Harvard. This group uses the term maltreatent trauma to characterize this population, which includes both overt mistreatment and abject neglect, physical as well as sexual and emotional abuse. The impact is so substantial that in the characterization of mental disorders, those with a maltreatment history may well constitute a distinct ecophenotype.[7]

Evidence for altered brain development is now coming into view.[8] Of particular interest to us is evidence for altered functional connectivity, as illustrated in Figure 3.1. The evidence is compelling that in unexposed brains one sees a healthy network under the aegis of the left anterior cingulate, directing a confident interaction with the outside world. By contrast, in the exposed case the well-elaborated network emanates instead from the right precuneus, which has primary responsibility for securing safety, in collaboration with the right anterior insula. At the same time, the frontal circuitry is impoverished in comparison with the unexposed individuals. The trauma history, irrespective of its nature, has fundamentally altered how the brain engages with the outside world and manages its internal regulatory regime.[9]

What about the 25% of the remaining Harvard students who suffered chronic disease but had a benign emotional upbringing? If neural network dysregulation, and dysregulation more generally (e.g, autonomic), lies prominently within the causal chain of chronic disease, has something been overlooked? Indeed. It is minor traumatic brain injury, which is an equal opportunity immiserator, afflicting the rich and poor alike. Minor traumatic brain injury has been just as much neglected in research as minor emotional trauma. Originally, the study of traumatic brain injury was largely a military matter, and those who did not have a bullet in their brain or a skull fracture were assigned to the category of minor traumatic brain injury (mTBI).

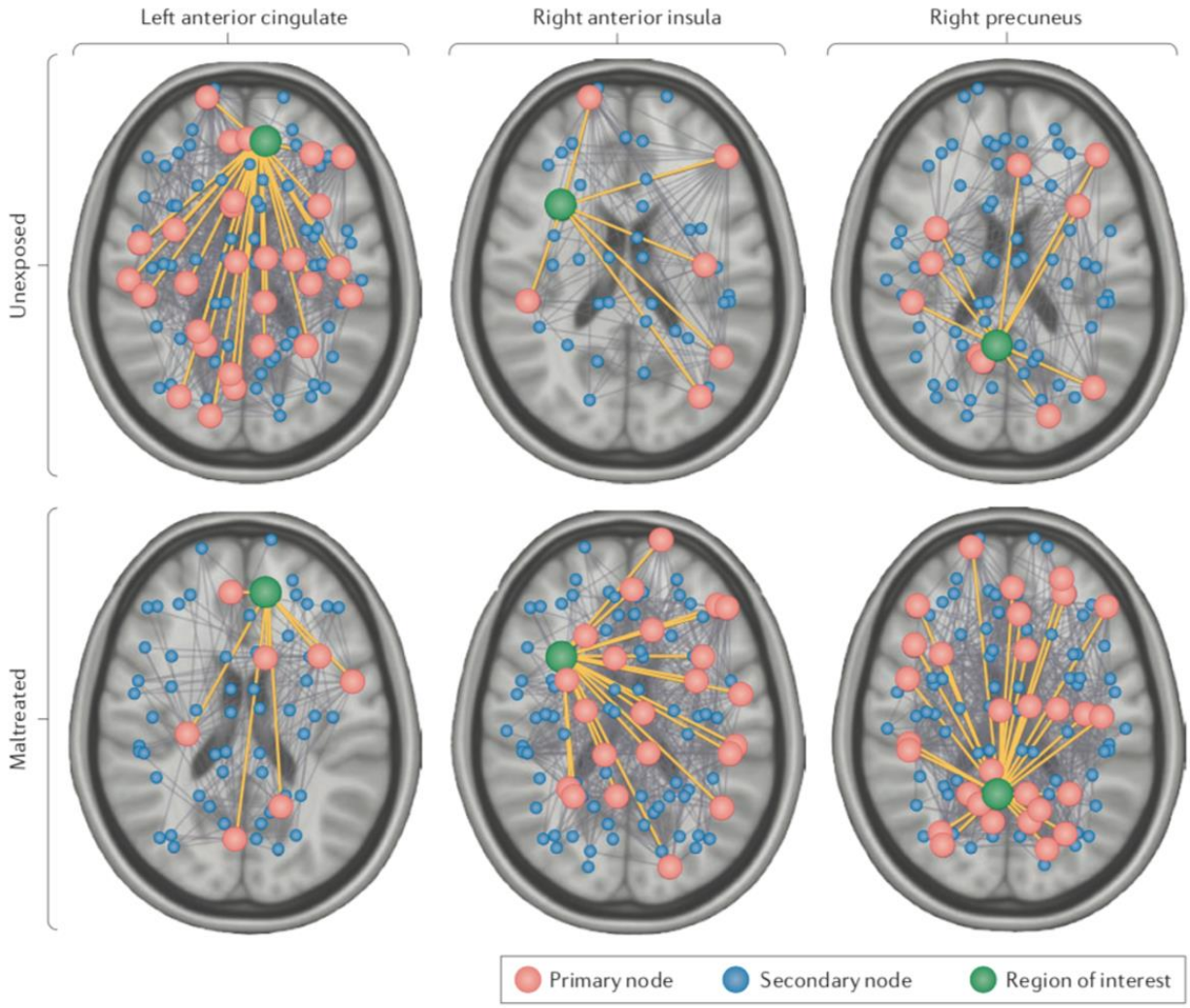

Figure 3.1. Network differences are identified for maltreated versus unexposed young adults. The green dots indicate regions of interest for the left anterior cingulate cortex, the right anterior insula, and the right precuneus. Connectivity analysis yielded the primary nodes that were common within each cohort. These are nodes with direct connections to the region of interest (shown as salmon-colored dots). Secondary nodes (blue dots) are linked to the region of interest only via the primary nodes. Jointly these linkages determine the 'centrality,' the relative importance, of the three regions of interest for the two cohorts. (Source: Teicher, M.D., Samson, J.A., et al, 2016; Original source: Teicher, M.H., Anderson, C.M., 2014.)

This tragically misrepresented the clinical realities. mTBI has been a stealth condition that has contributed to declining health status largely by the same mechanism of neural network dysregulation. Symptoms often get worse over the first six months post-insult, which means that—just as in the case of emotional trauma—the endogenous remedies that serve a short-term purpose may exact a longer-term penalty, a process referred to as maladaptive plasticity. Symptoms also get worse through cumulative insults, confirming the hypothesis of the Dysregulation Cascade. It is finally being recognized that sub-concussive injury must be taken seriously as well, particularly if it is part of a repetitious pattern, as in soccer play or football.[10] None of these events need to rise to the level of creating organic injury within the

brain, as that term is ordinarily understood (i.e., neuronal shearing, etc.). They may not even rise to the level of detectable symptoms. The primary mechanism of injury lies in the functional domain. This proposition is attested to by the finding of a tendency toward hyper-connectivity in mTBI.[11] Rapid recovery effected through neurofeedback training is also persuasive on this point.

3.3.1 ILF Neurofeedback: Rescue Remedy for the Trauma Response

The trend to lower training frequency that has been underway since around the turn of the century has, to all appearances, been driven by the imperatives of working with the traumatized population, which presents the greatest clinical challenge to the neurofeedback clinician. And in this project success has largely been achieved. Whereas there have always been clients who could not be helped with these protocols, that has become largely a non-issue with the available palette of training options, the extension into the deep ILF regime in particular. But a larger reality has also been uncovered. It is not only those who bear the scars of trauma that benefit from the two starting protocols. It is nearly everyone who comes for training.

One must conclude that these protocols are redressing failure modes that our species largely has in common. The tendency is for a challenged nervous system to move toward over-arousal, with hyper-excitability an additional consequence if that is a vulnerability. When that status cannot be sustained, the system may slide into under-arousal or crater into functional collapse. The languor and effort fatigue that we associate with mTBI is a case in point. The time courses seen in the anxiety-depression spectrum are another. Cratering is often masked by the kindling of a disease process, being then naturally associated with the latter rather than with its antecedent.

The prominence of early childhood adverse events in the life history of our most challenging clients implies that neural network development is affected in its earliest stages. By working at extremely low frequencies, we are addressing the foundations of the regulatory hierarchy in three aspects: 1) the developmental hierarchy; 2) the functional hierarchy (from the more general to the more specific; from the more distributed to the more localized); and 3) the hierarchy in the frequency domain. In the latter, the lower frequencies set the context for the dynamics unfolding at higher frequencies, and this hierarchy extends into the gamma range of frequencies. These three constructs jointly inform the therapeutic hierarchy. The implication of our clinical success is that even the intrinsic connectivity networks are sufficiently plastic so that re-normalization of function can be mediated by way of ILF Neurofeedback.

Moreover, this appears to be possible at any age. The clinical agenda has become one of re-normalization of the regulatory hierarchy from the bottom up with every client. It appears that the residue of challenges to our early development resides in all of us at some level, and that the mature nervous system can aid its own cause of functional enhancement by way of ILF neurofeedback at these extremely low frequencies. Higher training frequencies then attend to other levels in the hierarchy, to which the entire history of the neurofeedback field attests.

It may be helpful at this point to draw on a law of physics to elucidate the agenda: "The Law of Least Action." This is the principle that there should be minimal expenditure of energy consistent with the ends to be achieved. The most efficient operation of the human brain transpires at the levels of central arousal and of sub-system activation just sufficient for the demand, but no more. Experts in the martial arts, meditators, chess and Go players are likely well acquainted with this principle. Clients may become aware of it through the training process, as they experience higher levels of vigilance, of alertness and mental clarity, even as the nervous system is moved toward calmer states within a session.

3.4 Mechanisms of Regulation: Historical Roots of the Slow Cortical Potential

By 1935 the study of the EEG was substantially aided with the introduction of electronic (tube) amplifiers by Hubert Rohracher. This called for capacitive coupling, which blinded us to the slow potentials that lay beneath the cutoff frequency. In consequence, the world of EEG research went dark on the Slow Cortical Potential (SCP) for about three decades. There was a re-awakening in 1964 with the discovery by Grey Walter of the expectancy wave (Bereitschaftspotenzial), and the publication by Nina Aleksandrovna Aladjalova of her extensive animal studies on the tonic slow cortical potential in book form.[12] (Aladjalova, 1964). Soon followed the engagement with evoked potentials and contingent negative variation, all of which focused on the transient properties of the SCP. The tonic SCP was followed up by Joe Kamiya, Karl Pribram, and Juri Kropotov. Intimating its importance, Karl Pribram referred to the tonic SCP as "the second language of the brain."

Aladjalova's research has turned out to be of the greatest relevance to our present purposes. She studied the infra-slow rhythmic potential oscillations (ISPOs) at great length. "A single stimulation of the reticular formation immediately elicits an arousal reaction in the EEG of the cortex, but has no effect on infraslow activity," she writes. "This reaction is apparently regulated by the rapid regulatory system. Stimulation of the ventromedial part of the hypothalamus…intensifies infraslow cortical activity within 30-40 minutes. This reaction is presumably regulated by the slow regulatory system."

"…infraslow activity is intensified by certain actions after a long latency period, 30-100 and 120-200 minutes later. We conjectured that this phenomenon reflects the activity of the slow control system of the brain…not only to automatically adjust the system to keeping internal environment constant but actively to establish a new level of activity."

It does not take a great leap to connect our training in the deep infra-low frequency region with the slow control system Aladjalova identified. This system appears to be centrally regulated by the hypothalamus, known to govern our internal milieu—autonomic function, sleep-wake cycle, ultradian rhythms, etc. Thus, it makes sense that the ILF training extends down to the circadian frequency.

It should be mentioned in the interest of completeness that the electrical stimulation of yet other hypothalamic nuclei can also induce rapid state shift—even rapid de-activation—in

the same systems governed by the slow control system. For example, torpor could be suddenly induced in a cat with suitable stimulation. This was the work of Walter Rudolf Hess, published in 1954.[13]

ISPOs did not generate much interest again until fMRI imaging refocused attention through the discovery of the intrinsic connectivity networks, or resting state networks, around the turn of the century, some three decades later. They have been an intense area of study over the past fifteen years.[14,15,16] Raichle and He have illuminated the connection between the fMRI signal and the slow cortical potential.[17] It is these dynamics, predominantly in the range of 0.005 to 0.2 Hz, that are engaged in ILF neurofeedback. However, we impinge on this activity indirectly via the contribution the extremely low frequencies make to their generation.

In 2017 we became aware that Giovanni Piantoni, of Mass General Hospital, had identified slow brain rhythms of one to two-hour periodicity in extended recordings on epileptic patients using depth electrodes. He identified these with the Basic Rest and Activity Cycle (BRAC), a hypothesis that we entertained as well until we found it necessary to use even lower target frequencies, and were thus compelled to broaden our perspective. One hypothesis does not necessarily dispose of another. Over the entire ILF frequency range, we are no doubt engaging with a number of core regulatory mechanisms, including in particular the BRAC.

3.4.1 The Regulatory Hierarchy

Seen from the vantage point of our neurofeedback challenge, the regulatory hierarchy looks like what is shown in Figure 3.2. Early neurofeedback, including our own protocols, conformed to the interests of cognitive neuroscientists by engaging with the attentional and executive function domains, effectively the top of the regulatory hierarchy, as well as the motor system, which was also well characterized. Our adoption of an adaptive procedure for protocol refinement shifted the process from being prescriptive to being observational. That led ever so gradually to the brain guiding us to its own priorities, namely the bottom of the regulatory hierarchy, one client at a time, over the course of nearly two decades. This meant a progression to lower training frequencies, which took place at a pace of about one decade in frequency space per year for a number of years. This also meant a shift toward right-hemisphere rather than left-hemisphere priority, as right hemisphere function is the first to develop and has primary responsibility for personal safety as well as internal integrity and harmony.[18] It is also where the primary vulnerability to psychopathology is lodged.[19]

The sword-and-shield hypothesis is often invoked to concretize the above dichotomy. The sword is typically wielded by the right hand, governed by the left hemisphere, whereas the shield is borne by the left, governed by the right hemisphere. Left-handers most likely reverse this pattern. A less graphic version is the approach/withdrawal dichotomy. We bestride the world confidently with the left hemisphere in the lead, while the right is doing its best to keep us alive and healthy.

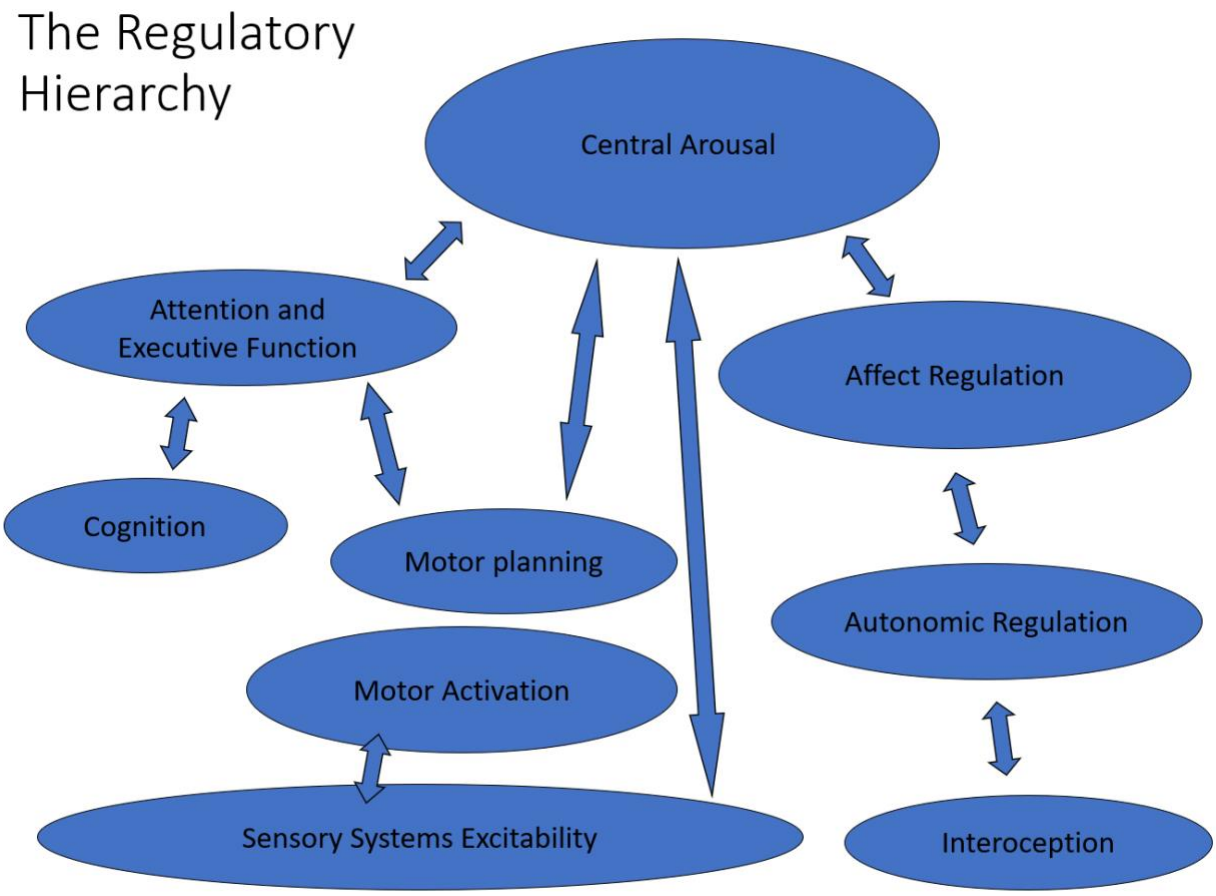

Figure 3. 2. The Hierarchy of Regulation as seen in the perspective of the neurofeedback therapist. Of primary interest is central arousal, which is intimately coupled to affective state, autonomic regulation, and interoception. All are seen as principally under the management of the right hemisphere, which therefore demands the earliest attentions. Executive function and cognition lie highest in the hierarchy, and are typically attended to later in the training, if that is still necessary.

Of course, this simple dichotomy has not gone without challenge, but we spare the reader a recitation of the counter-vailing evidence by reason of the following observation: In ILF neurofeedback hemispheric reversal has not been observed. This finding is consistent now over more than a decade, involving hundreds of thousands of clients, all being trained according to the identical schema. We are engaging with the core architecture, beneath the level where lateralized dominance—of eye, hand, and foot—is organized. In the early days of exclusively EEG-band training, reversals of right and left were observed with several sets of mirror image twins, as might well be expected. Since entering the ILF regime, however, we have not become aware of work with mirror image twins.

We may well observe a reversal of dominance with the training, and we understand this within the frame of birth trauma. Fetal thumb-sucking is the earliest indicator of laterality, and on that basis a substantial laterality shift with the natural delivery process has been documented (from ~95% right laterality to ~85% post-partum). That shift appears to be reversible with the training at any time in the person's life. The protocols with which that

laterality reversal is achieved, however, are themselves invariant with respect to laterality! The resolution of the conflicting data appears to lie in the supposition that whatever observables are relied upon to counter the universal assignment of core LH and RH control functions are themselves confounded by laterality issues.

With reference to Figure 3.2, the clinical priority in almost all cases is to train the regulatory arc of interoception, autonomic regulation, affect regulation, and central arousal. All of these are highly correlated, reflecting a high level of functional integration. This objective involves two protocols, targeting the posterior and the anterior aspect of the right hemisphere sequentially. The priority lies with the posterior aspect, by virtue of its coupling to the posterior hub of the Default Mode Network (DMN), which is the first to develop in infancy, and hence the first to bear the scars of a non-nurturing environment.[20] The anterior placement yields our most direct engagement with the Salience Network (SN) and the affective domain.[21]

The posterior placement is the primary site for calming over-arousal of the nervous system—of central arousal and of sympathetic activation. The latter should be demand-responsive, leaving one in the general case in a state of sympathetic-parasympathetic balance, or even of parasympathetic dominance—just as the lions of the veldt have modeled for us. If a steady state of sympathetic over-arousal prevails, it is costly to our physiology, and it is the right parietal placement that allows the system to de-escalate most efficiently and with the greatest persistence.

Brain stability has to be promoted concurrently whenever that issue arises. This calls for inter-hemispheric placement. Here the objective is good regulation, not merely the absence of overt instabilities. This is most readily observable in the autonomic nervous system. Thus, interhemispheric placement is called for not only to redress dysautonomia, or to tame asthmatic episodes (which can be thought of as parasympathetically mediated paroxysms), but to achieve good ambient autonomic regulation more generally. The subtle coordination between the hemispheres turns out to be key to the objective of a dynamic balance between the sympathetic and parasympathetic arms in the steady-state condition when the organism is not under overt challenge or duress.

The DMN must be seen as the primary target of ILF NF, in that it is our resting state (i.e., task-negative) network, which governs our level of function and bears our dysfunction.[22] The cortical resources it manages account for nearly all of the energy expended by the brain. The Salience Network is the secondary priority.[23] The Salience network mediates between the task-negative and the task-positive control network, the central executive.[24] It has a dual monitoring role, one in which the insula attends to our internal status (interoception), and the anterior cingulate portion tends to the interface with the external world. This activity is largely right-lateralized. [25]

This right-lateralization is most readily demonstrated in the description of Default Mode connectivity relationships by Buckner et al (2008) [26], as shown in Figure 3.3. Observe that the connectivities linked to the right lateral temporal cortex, in the immediate neighborhood of the

right insula, are much more elaborated than those to the left. This is the essential point. The lateralized hubs of the DMN (T3 and T4 and P3 and P4) have been our primary training sites, but it should be noted that that has been the case since the late nineties, well before the DMN was first characterized.[27]

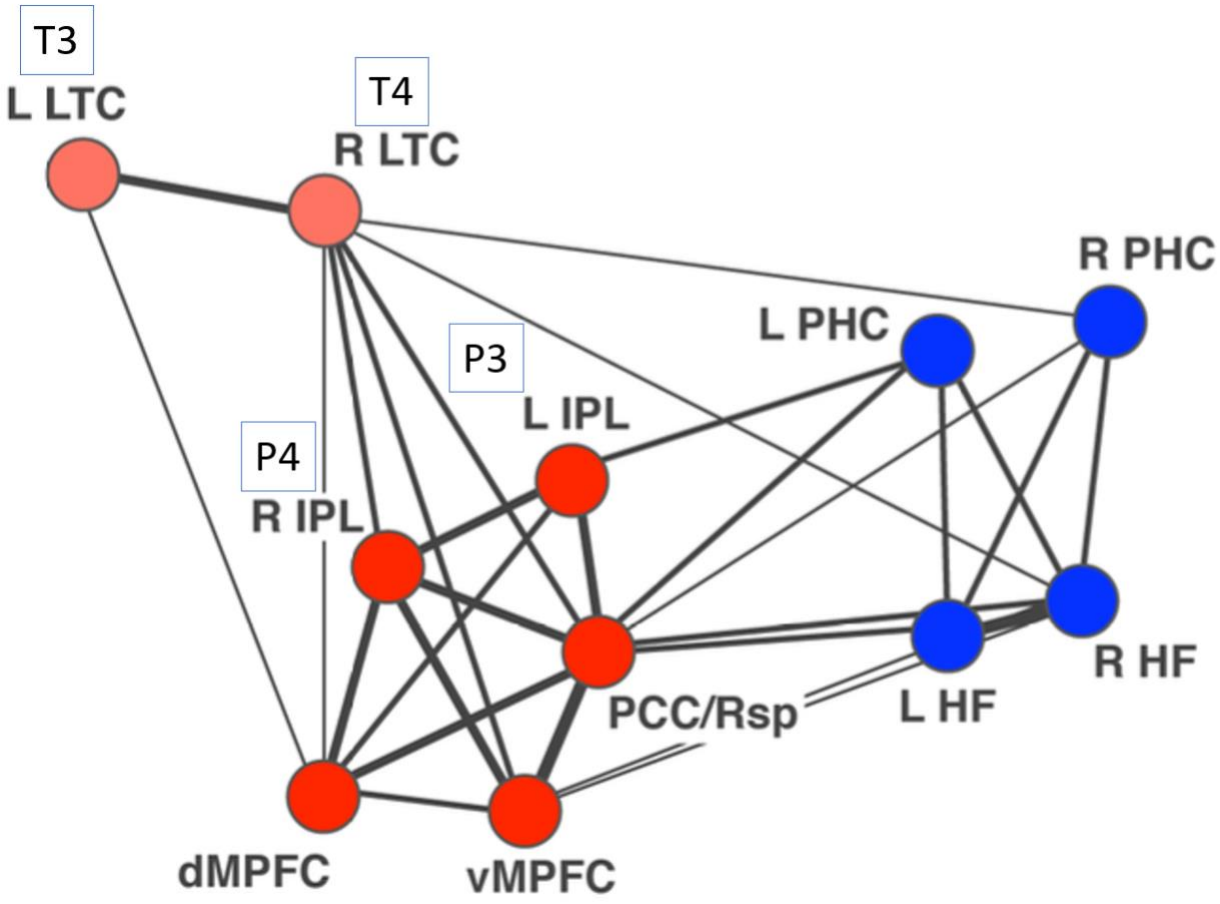

Figure 3.3 The principal hubs of the Default Mode Network are shown with their respective connectivities reflected in the thickness of the lines between them. The right lateral temporal cortex (R LTC) is shown to be more intimately connected to other hubs of the DMN than the left lateral temporal cortex (L LTC). These two sites are involved in all lateralized placements and thus constitute the primary training sites. The other primary training sites are the left and right inferior parietal lobules (L IPL and R IPL). The principal midline hubs of the DMN are the posterior cingulate and retrosplenial cortex (PCC/Rsp) and the ventromedial prefrontal cortex, along with the dorsomedial prefrontal cortex (vMPFC and dMPFC). HF refers to the hippocampal formation and PHC refers to the parahippocampal cortex. (Buckner, Andrews-Hanna, and Schacter, 2008)

Despite the major shift in our clinical priorities over the years, the specific placements have remained substantially invariant over that time. The shift from EEG-band priority to ILF-priority has involved mainly some shift from upper tier to lower tier sites, e.g. from central to temporal sites (C3 to T3, and C4 to T4). But in truth that shift may well have been more at the conceptual level than the practical. For example, the standard placement for Sterman's and Ayers' early work was C3-T3. So temporal placement has been in the picture since the beginning of research with human subjects. However, the Sterman model concerned itself with

the sensorimotor strip exclusively, whereas presently the model concerns itself primarily with the temporal sites, with T3 and T4 present in all lateralized placements.

The rationale for the shift to temporal priority emerged only after the clinical reality had been thoroughly established. The constellation of principal training sites lined up with the multi-modal association areas. This made sense since these areas are the most integrative in character, and they rank highest in terms of functional plasticity. For both reasons, they should therefore rank highest in training efficiency. This integrative character has been nicely demonstrated in a determination of connectivity gradient from the primary sensory areas to the multi-modal sites. [28] This is shown in Figure 3.4, which has been adapted from the original. The connectivity gradient is minimal in the primary sensory areas and maximizes in the multi-modal association areas. The loci of warmer colors identify our primary training sites: lateral temporal cortex (T3 and T4); angular gyrus (P3 and P4), and the inferior frontal gyrus (Fp1 and Fp2). At these sites, the Default Mode Network is accessible to us at the cortical surface for the purpose of lateralized training.

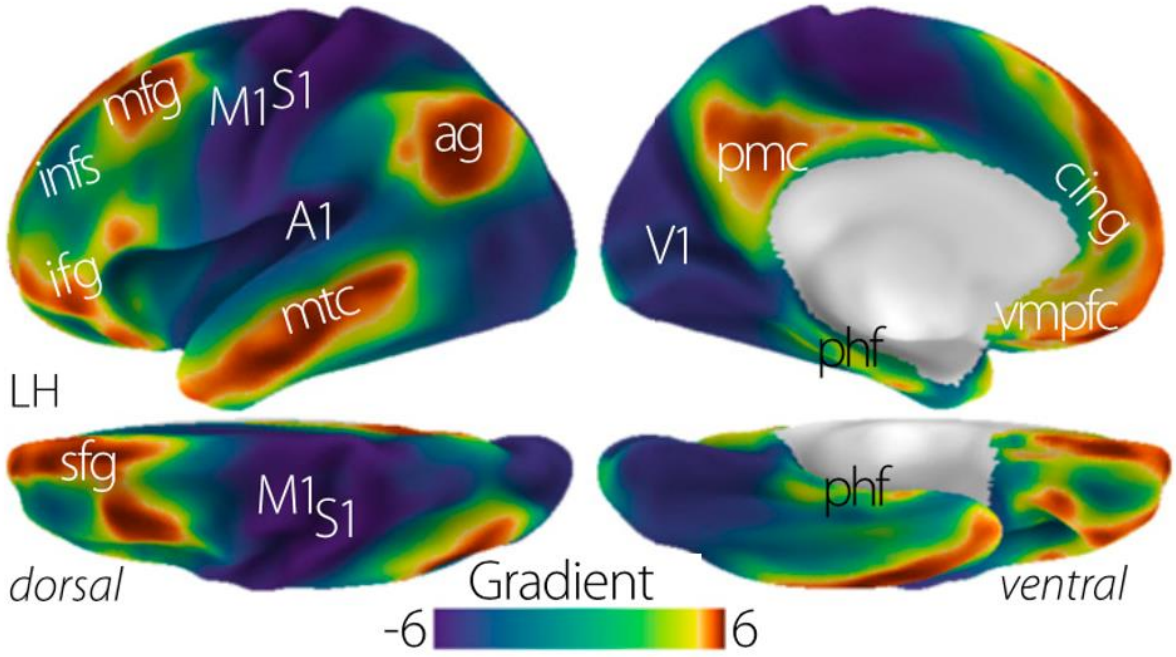

Figure 3.4. The gradient of connectivity exhibits a distribution that minimizes in the primary sensory areas of cortex (cool colors) and maximizes in the multi-modal association areas (warm colors). These connectivity maxima identify our primary training sites for lateralized training: medial temporal cortex (T3 and T4); angular gyrus (P3 and P4); inferior frontal gyrus (Fp1 and Fp2). They also correspond to the regions in which the Default Mode Network is accessible to us at the cortical surface for lateralized placements. A1, primary auditory cortex; S1 somatosensory cortex; M1, primary motor cortex; V1, primary visual cortex; mfg, medial frontal gyrus; infs, inferior frontal sulcus; sfg, superior frontal gyrus; phf, parahippocampal formation; pmc, posteromedial cortex; cing, cingulate; vmpfc, ventromedial prefrontal cortex. (Daniel S. Margulies et al, PNAS 2016: 133:44:12574-12579)

The Default Mode is accessible to us also at midline sites, and the primary linkage in the DMN, between the posterior and the anterior hubs (The PCC and MPFC in Figure 3), beckons for clinical attention. But this linkage turns out to train according to different rules. The differential training with bipolar montage, which was so clarifying in lateralized training, so unambiguous in its imperatives, turned out to be minimally productive when applied to midline sites. This repeatedly side-lined our attentions to this critical linkage for some years. Here the primary need is the enhancement of the coordination of the posterior and the anterior hubs of the DMN. Alpha band synchrony training, long popular within the field, may already have been serving this objective. To this agenda we have now added synchrony training in the ILF regime. In some of the most severe cases of early trauma, ILF synchrony training can be the keystone for functional restoration. In those cases where it is observed to be highly beneficial, it appears also to be indispensable.

In the extreme cases of early maltreatment and/or neglect, the intact core self does not have a chance to emerge because it is formed in relationship (the burden of the posterior hub) before it is consolidated in agency (the burden of the frontal hub). Neglect disrupts the orderly maturation of the posterior hub of the DMN in the first year of life, and the early phases of the coordination with the frontal hub. That state of maladaptation is then further consolidated over the course of development. Applying the ecophenotype model to this aspect, the mental health universe can be said to divide between those in whom the front-back axis of the DMN is profoundly dysregulated, and everyone else. Development takes us either on a boot-strapping path of repair and recovery, or of further consolidation of dysfunction. The reed bends as it lists, as it were. We end up with a bimodal distribution with little middle ground.

The Harvard group has looked at their bimodal distribution, distinguished as susceptible versus resilient, and perhaps surprisingly found the same array of brain abnormalities in both.[29] Reduced nodal efficiencies distinguished the resilient cohort, particularly with respect to the amygdala, and these were deemed to be neuroprotective. From our current vantage point, one is tempted to conjecture that the differences may show up more prominently in the dynamics than in static measures. Our clinical findings indicate that the remedy is to be found there as well, and that whatever brain abnormalities exist do not present a categorical barrier to recovery.

Some progress has recently been made in identifying a possible neurophysiological representation of the core self. This emerged out of extensive studies of sleep by Andreas Ioannides and colleagues in Japan.[30] A prominent characteristic of non-REM sleep is the high degree of variability associated with these states. They are not homogeneous in character. In that context, the stability and context-independence exhibited by two small regions attract attention. They are located anteriorly and posteriorly on the left side of the dorsal midline fissure, and are characterized by high levels of gamma-band activity. Curiously, this activity level increases progressively from awake state to light sleep to deep sleep, and maximizes finally in REM sleep.

Ioannides proposes that these two regions constitute the neural representation of the core self. They are identified as the Midline Self-Representational Core (MSRC1 and 2). Evidence for this is provided in the waking state, in which mental activities that are self-referential and autobiographical tend to evoke activity in the penumbra of the MSRC1 and 2. The Default Mode can therefore be characterized as a three-layer onion: The bulk is committed to managing the resting or baseline state of the brain, and is most active when the brain is in a non-engaged state; then there is the penumbra of the core self; and finally there is the core self. The penumbra mediates between the core and the bulk of the DMN. The core self, meanwhile, is preserved from ready alteration, particularly during the waking state.

It is during sleep states, in which the brain is largely non-engaged, that the opportunity maximizes for accommodation by the intrinsic self to new realities that have been assimilated during the waking state. Dreaming may be an essential part of this process. The inherent bias, however, remains one of stability and of resistance to ready alteration on the part of the core self. A threat to the survival or integrity of the self suffices, no doubt, to surmount this barrier to change.

3.5 ILF Neurofeedback in the Frequency Domain: The Frequency Rules

Whereas nearly all of the terms of discourse utilized in connection with ILF neurofeedback resist rigorous quantification, there is one singular exception, namely the relationships among the optimal response frequencies that prevail at the different training sites.[31] It is found that the ORFs for right-lateralized placements stand in harmonic relationship

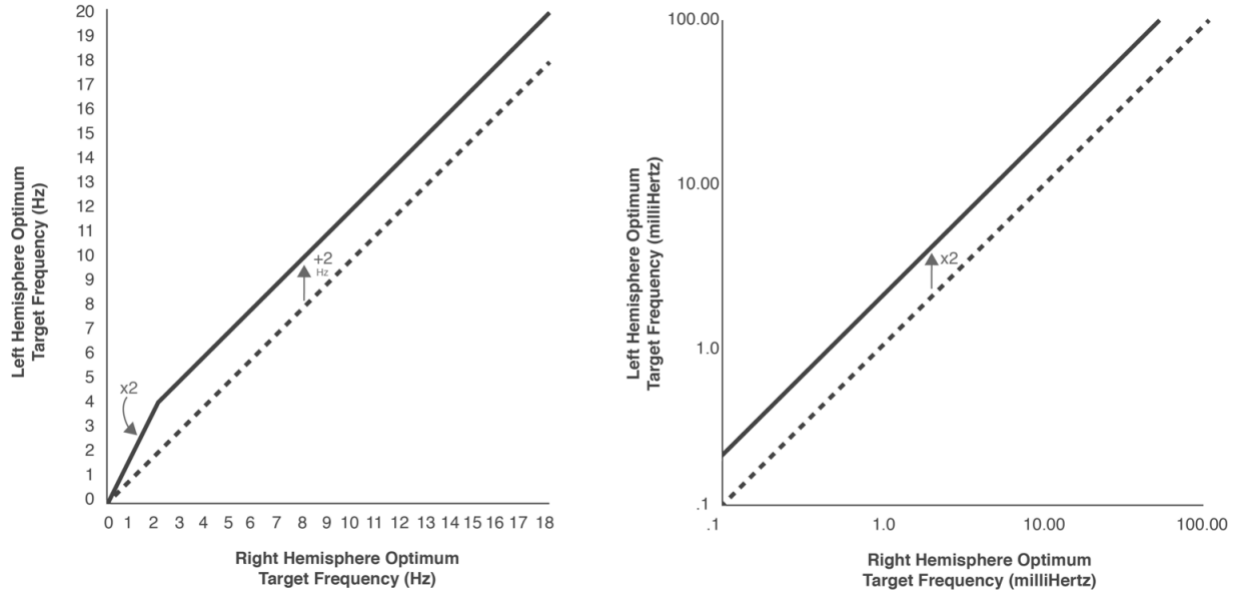

Figure 3. 5. The frequency rules governing lateralized training are shown here. A harmonic relationship prevails in the ILF region, whereas an arithmetic relationship applies in the EEG domain. The crossover is necessarily in the 2-4 Hz region of the delta band. Inter-hemispheric placement follows RH rules.

to the ORFs in left-lateralized placements. The ratio is universally a factor of two, with the left hemisphere at the higher frequency. This is found in the context that harmonic relationships are not commonplace in the EEG world. And indeed, a non-harmonic relationship for the ORFs prevails in the EEG range, where the left hemisphere optimizes at a frequency 2 Hz higher than the right. This is shown in Figure 3 5. Significantly, inter-hemispheric placements follow right-hemisphere rules.

The crossover between the two regions is necessarily where the two criteria converge, which is at a LH frequency of 4Hz and a RH frequency of 2 Hz. The 2-4 Hz range therefore represents a major transition region between the domains where the ILF rules and the EEG spectrum rules apply. The distinction has long been made between the delta band and the theta band, and 4 Hz has been broadly accepted as the dividing line. So, we now have reason to associate the delta band with the ILF regime in this critical respect.

The implications of the frequency relationships for model-building are likely profound, although they can only be intimated at the present state of knowledge. First of all, the fact that inter-hemispheric training follows RH rules confirms RH primacy in organizing the frequency hierarchy. It is therefore more foundational in the regulatory hierarchy. This is consistent with the observed dominance of our right-hemisphere placements with respect to the regulation of the resting state.

Frequency rules have also been discerned for inter-hemispheric placements at homotopic sites. With respect to the central strip sites of C3/C4 and T3/T4 that have garnered most of the clinical attention in the history of EEG neurofeedback, frontal and pre-frontal sites train at ORFs that are 2 Hz lower, and posterior sites train at frequencies that are 4 Hz lower. In the ILF range a harmonic relationship once again applies, as frontal sites train a factor of two lower than central, and posterior sites a factor of four lower. There has been little opportunity, however, to explore these relationships in the ILF regime. This is for two reasons. First of all, we have the historical circumstance that over most of the period of development of ILF NF, the lowest frequency available in the software ended up being the preferred frequency, rendering submultiples unavailable. The primary reason, however, is that most of the inter-hemispheric training has defaulted the T3-T4 placement, and there has been little incentive to date to explore other homotopic site pairs. This remains a task for the future.

The solidity of the findings with respect to frequency rules more than compensates for the manifest shortcoming of the ORF phenomenology, namely that the entire basis rests on the self-reports of clients. No other evidence in support of the model has ever been found. Nevertheless, the reproducibility of the ORF from session to session, the one just as blinded as the other, places the whole matter beyond dispute, unsatisfactory as that may be in the eye of the critical researcher. Typically, the ORF only undergoes subtle migration over the course of training. Moreover, one protocol has been found to alter the ORF slightly and, to all appearances, systematically.

The ORFs are dynamically regulated, and the ILF training clearly impinges on that process, subtly re-organizing the frequency-based properties of the neural networks. This constitutes the most rigorous proof of validity over the entire frequency regime, in that the observed frequency rules hold consistently over eight orders of magnitude, from 10^{-6} to 100 Hz. Is there anything that renders the unitary quality of our regulatory regime more obvious than this? When it comes to brain function, we are confronted with dynamics on all relevant temporal and spatial scales—a continuous modulation of activation, of successive affiliation and dissociation of neural assemblies—but certain relationships can be invariant and stable, and so they appear to be.

3.6 A Resonance Phenomenon

We first published the observation that the behavior of the training process in the vicinity of the ORF was reminiscent of a resonance phenomenon in 2008, so this model of the process has engaged us for a long time.[32] The usual handicap prevails, namely the limits on performing experiments in clinical settings. The standard resonance curve is shown in Fig. 6, showing only the real component. It reflects the major features of the clinical experience. The training appears to be more impactful at the center frequency, and also more unambiguously positive, than training at nearby frequencies.

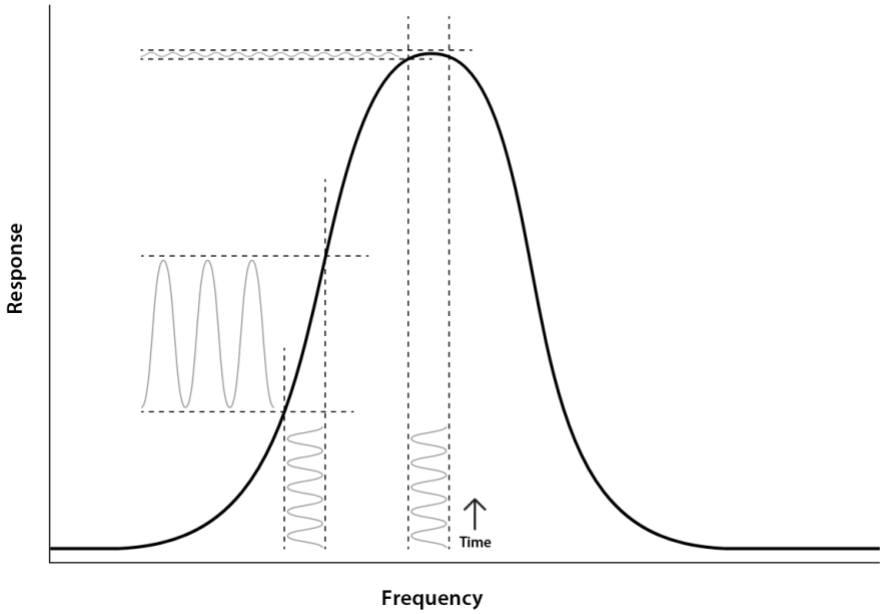

Figure 3.6. A standard resonance curve is shown to illustrate the dependence of the response on frequency with the assumption of an operative biological rhythm at the ORF. Shown also is the effect of perturbations, including in particular fluctuations in the ORF itself. If the spectral filter is mistuned with respect to the ORF, large errors can creep into the signal that the brain may then misinterpret. These error signals are much smaller when the filter is aligned with the ORF.

The approach to the ORF in actual practice can be analogized to a piece of music going from dissonance to resolution. In the immediate vicinity of the ORF, the training experience can be more complex, confounding, and even adverse. When this is encountered in a clinical

setting, the clinician feels obliged to find resolution in the ORF promptly. One does not linger to establish reproducibility of such a phenomenon. Clients are not research subjects. Once the ORF is found, it is not abandoned for the sake of scientific exploration. Hence the handicap. All of the observations along these lines remain singular events for which patterns of reproducibility could not be established.

The resonance phenomenon does not lend itself to ready evaluation in that it is not being studied in isolation, as would be the case for electronic apparatus, for example. The 'system under test', so to speak, is the client's brain in interaction with the signal. We are seeing the response of a control loop with a sentient being in a controlling role. Once signal acquisition occurs, in the sense that the brain has detected the correlation of the signal with its own internal state, the brain undertakes to refine and particularize its response to that signal, an essential part of the learning process. The control loop becomes a function of time, and repeatability is not available to us in any event. As the training proceeds to lower frequencies within the first session in the search for the ORF, a return to higher frequencies yields a different response than was observed before—even after just a few minutes. The process is so impactful that the caution of the Buddhist meditator prevails: "You never train the same brain twice."

Yet another confound is that the strongest responses to the training are observed with the most dysregulated brains which are on their own unpredictable journey—particularly under the provocation of the feedback loop. That is sufficient all by itself to obliterate any expectations of reproducibility. Matters become much more manageable, however, once the ORF is found, and a systematic path forward can usually be charted on the basis of ongoing client reports. This ORF may have to be targeted within five percent or even less.

What could account for such a degree of parametric specificity? It is the requirement to operate at the very top of the resonance curve, which is flat. Under these conditions the subtle modulations on which the training depends are least compromised by all the confounding factors that prevail in this experimental design. This is illustrated in Figure 6, in which an arbitrary perturbation of the system is shown as a sinusoidal excursion on the frequency axis. When the target frequency is mistuned to the skirts of the resonance curve, a large fluctuation is expected in the signal output. At the ORF, the fluctuation is much smaller. This can explain the much greater 'turbulence' that prevails when training on the slope of the curve near the peak. A related issue is that of phase, which varies strongly in the vicinity of the resonance peak. This phase combines with the phase shift induced by the filter to yield the phase of the loop response function. A narrow workspace in the frequency domain follows. The resonance curve giveth, and it taketh away—all within the scope of a few percent variation in the training frequency around the ORF.

We are closing in on a model in which dynamically-organized biological rhythms exist within the EEG and ILF realms that play key roles in organizing frequency-based relationships on the large spatial scale—interhemispheric and lateralized. In the ILF realm, they govern resting state dynamics on the longer time scales. Nevertheless, they must be responsive at the speed

of life. The resulting modulations are detectable if the brain itself is the detector, and they become meaningful as the brain assigns meaning. The feedback loop effectively becomes internalized, and thus makes possible the subtle refinement of resting state temporal organization 'within paradigm', i.e. entirely within the resting state framework.

This process is capable of refining the regulatory regime to the limit of subtlety at which it should ideally function. That cannot be accomplished via externalities such as reinforcers any more than one could hope to improve Hilary Hahn's violin playing by such means. This process is also an answer to Karl Friston's open-ended question back in 2009: Just how does one do experiments on resting state organization (i.e., without disrupting what one is trying to study).[33] The answer is to let the brain operate within paradigm, absent any external challenge, and just monitor the unfolding process. That is ILF neurofeedback.

3.7 Implications for Inter-hemispheric Coordination

The case has been made for the primacy of the right hemisphere in managing resting state activation and coordination. All along, however, there has been a latent concern that a shift to right hemisphere priority in the training, along with a shift from the EEG band to ILF, might entail the neglect of what had previously been our priority, namely the training of vigilance with left-central and left-frontal placements. That concern has been laid to rest. Continuous performance tests have been done throughout this period of protocol evolution, and they documented that no price was being paid with the shift in clinical priorities. The quality of resting state organization governs even those functions that we associated with the left hemisphere, and involve the engaged rather than the resting brain.

To illuminate the role of the left hemisphere, we turn to a seminal paper that looks at information flow among the principal hubs of the Default Mode Network. These were originally identified in the study of microstates by the Lehman group in Switzerland, well before there was any talk of resting state networks. [34] These are shown in Figure 3.7. Each of the microstates is identified with one of four hubs of the DMN, three in the posterior region and one with an anterior locus. Two are lateralized, and two lie along the midline.

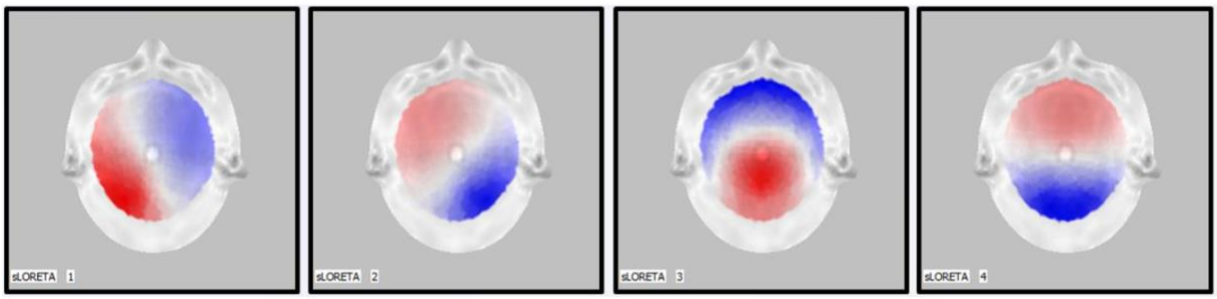

Figure 3.7. Shown schematically here are the four microstates that were originally identified by Lehman et al. Two are lateralized; two are on the midline; three are posteriorly centered; only one has a frontal bias. (Ignore polarities.) This tends to support the parietal bias in ILF neurofeedback. (Adapted from Lehman et al, 2014)

Information flow among these hubs was determined by means of a measure of directed coherence on the alpha and low beta bands, leading to the finding that information flow was dominant from the left hemisphere to the right, as well as from the left to the midline hub, relative to the flows the other way. The imbalance can be substantial. This is shown in Fig. 8. The clear implication is that with respect to the regulatory role of the lower EEG bands, the left hemisphere is in a commanding position with respect to the right hemisphere.

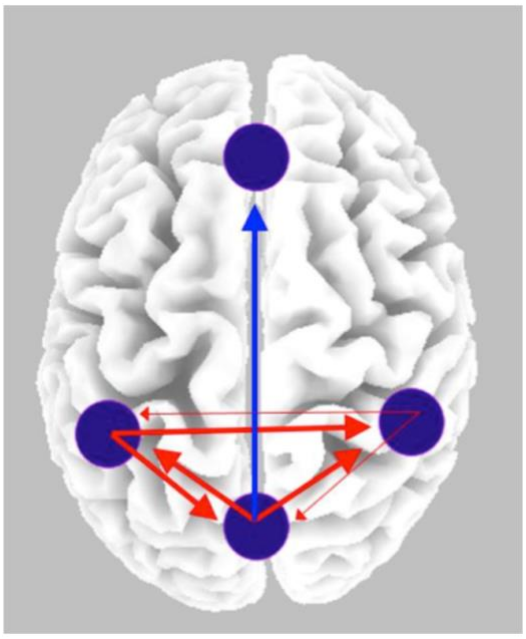

Figure 3.8. The relative magnitude of information flow between the posterior hubs is shown here. This is derived from calculations of directed coherence in the EEG bands of alpha and low beta. The information flow from left to right vastly exceeds that from right to left, which implies that in the EEG range the left hemisphere is playing the dominant role in organizing inter-hemispheric communication. (Adapted from Lehman et al, 2014).

A division of responsibilities is indicated. The right hemisphere bears the primary burden of organizing our resting states while the left hemisphere supervises our engagement with the outside world. The ILF regime plays a primary role in organizing the resting state configuration, whereas the EEG regime handles the complexity, coordination, and temporal precision required for our interface with the outside world. The delta band falls in the middle ground.

3.8 Foundational Research in Characterization of ILF Neurofeedback

ILF neurofeedback attracted the attentions of Dr. Olga Dobrushina of the International Institute of Psychosomatic Health in Moscow, and of the Treatment and Rehabilitation Center of the Russian Federation, also located in Moscow. Over the last several years they have collaborated on a large-scale study of ILF NF using functional magnetic resonance. The objective was to identify the networks engaged in this process of covert neurofeedback in a comparison of veridical with sham training. 52 healthy volunteers were recruited to a single session of ILF NF under uniform conditions, and resting state fMRI data were acquired immediately prior to and again following the session.[35]

Significant changes were observed in both groups, and there were systematic findings among the members of each group, despite their heterogeneity. In the veridical training group, "increased connectivity was observed through a network consisting of the right and left inferior lateral occipital cortex, right dorsolateral prefrontal cortex and striatum nuclei." The sham training group, by contrast, showed increased involvement of the salience network but not of the striatum. The authors proposed that whereas the salience network is responsible for the conscious perception of rewards, the striatum plays more of a role in reward that lies beneath consciousness.

This major study also contributes to the accreting body of evidence testifying to the proposition that sham neurofeedback is not to be considered a neutral process. In order for the control to be meaningful at all, the sham training group has to be given the same instructions as the veridical training cohort. Both enter the study under the assumption of undergoing an active process. In the search for persistent correlations that results, the brains in the veridical group experience closure and get to settle down to an actual feedback process, whereas the brains in the sham remain in a search status, one that is never graced with success. This can account for the greater role of the salience network in the sham group, which is expected to be largest when the salience question on the table cannot be satisfactorily resolved over an extended period of time.

The theoretical aspects of neurofeedback are also starting to attract academic attention.[36] Among the several models for neurofeedback, the skill learning model is also discussed.

3.9 Summary and Conclusion

The state of our current thinking with respect to the basic mechanisms underlying ILF neurofeedback has been presented in narrative fashion, appropriate to the state of knowledge derived largely from clinical practice, which does not lend itself to experimentation for ethical and other reasons. The basis has been laid for further fundamental studies of the ORF phenomenology using the ILF feedback scheme as a probe of resting state functional organization.

ILF neurofeedback is likely the most prominent exemplar of endogenous neuromodulation—i.e., covert and continuous neurofeedback—in clinical practice. Whereas in the ILF frequency domain there is no alternative, the advantages carry over to EEG-band training as well. After all, it was in the EEG range that the ORF principle was first discovered more than twenty years ago—also by way of covert, continuous feedback that was provided for within the then-standard operant conditioning design. This approach allows the brain to assume control through internalization of the process. Only endogenous neurofeedback can take the process to the limits of subtlety and refinement at which brain regulation must necessarily take place.

This skill learning modality, for which there is no known alternative, has import for the entire realm of human functioning that involves the nervous system. It holds the greatest significance for those contending with severe functional deficits acquired in the early stages of development. Moreover, it offers a remedy available at any age when a need for the training is identified, even down to early infancy. This is possible because the training imposes no cognitive demand and is not contingent on conscious awareness on the part of the trainee.

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