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Chapter 5

Effect of Infra-Low Frequency Neurofeedback on Infra-Slow EEG Fluctuations

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Abstract

Infra-low frequency neurofeedback (ILF NF) has been proposed as an alternative or complementary treatment method. Previous studies have reported a good effect of ILF training on the subjective perception of positive psychological changes after training. Here we study whether the objective physiological parameters reflecting the brain function also change under the influence of ILF NF. Eight participants 21–50 years of age with no history of neurological or psychiatric diseases, but reporting about some physiological or psychological complaints, performed 20 sessions of infra-low frequency neurofeedback training. EEG in visual Go/NoGo test was recorded before the course of Neurofeedback and after its completion. The spectral power of slow EEG oscillations in the post-training recording was compared with the pretraining baseline. Along with remission of the clinical complaints, significant increase of spectral power in 0–0.5 Hz frequency band was observed in all eight participants in the post-training EEG patterns compared to the pretraining EEG, which may be linked to the improvement in the metabolic balance in the brain tissue and increasing efficiency of compensatory mechanisms in the stress regulation systems.

Keywords: neurofeedback, post-training effects, infra-low frequency, slow EEG oscillations, stress regulation

1. Introduction

The utilization of adjunctive, alternative or complementary treatment methods (CAM) has been growing in recent decades, driven by demand. Based on the report published by the

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National Institute of Mental Health (NIMH), there is a problem of burgeoning "off-label" medication prescription [1] and overrated effectiveness of pharmacological treatment for some conditions. Additionally, it has been found that best outcomes often depend on a combination of treatment strategies, including psychotherapy [2–6].

According to the definition proposed by the National Institute of Health (NIH), complementary medicine (CAM) constitutes a broad domain of healing resources that lie outside those intrinsic to the politically dominant health care system of a society [7]. Inevitably, CAM will include technologies that are in the preliminary stages of mainstream acceptance. Such a technology is neurofeedback, which typically utilizes specific frequencies of the EEG in feedback configuration in order to promote cerebral self-regulatory competence. Despite its origins in well-grounded animal research in the 1960s [8], and subsequent studies in application to epilepsy and attention deficit hyperactivity disorder (ADHD) in the 1970s and 1980s [9, 10], neurofeedback was not adopted into standard medical practice at the time.

Originally discovered in 1956 by Kamiya, what came to be called EEG biofeedback found its first clinical application to anxiety [11], but that finding was not welcomed by the mental health disciplines either. Nevertheless, neurofeedback has matured as a type of CAM over the last several decades, with some 2700 citations in PubMed for neurofeedback, EEG biofeedback, and neurotherapy. With refinements derived on the basis of "practice-based evidence," neurofeedback is now belatedly entering the mainstream.

Neurofeedback belongs in the class of brain computer interface technologies, in that it allows the user to react to his own brain electrophysiological signals in real time [12]. These are registered from surface electrodes, subjected to frequency-selective signal processing, and rendered observable in the form of visual, auditory and tactile feedback. In its dominant realization, the feedback is based on frequencies within the conventional EEG spectrum of 0.5–40 Hz.

In infra-low frequency (ILF) neurofeedback, the modulation target is the brain rhythmic activity that lies below 0.5 Hz [13, 14]. Despite a multidecadal history of research, the organization and functional role of this low-frequency rhythmic activity remains unspecified, and this topic is currently garnering renewed research interest after a considerable hiatus.

The term ILF was introduced by a Soviet Union neurophysiologist Aladjalova in 1956 in her paper "Infra-slow rhythmic changes of the brain electrical potential" [15]. In this paper, she described brain oscillations in the ILF region and suggested a possible physiological basis for these phenomena. Since that time, a vast amount of empirical knowledge has been obtained in studies by Russian scientists in animal research and in studies on human subjects, through reliance on nonpolarizable electrodes to achieve low drift characteristics [16, 17]. The authors found two types of infra-slow oscillations with periods of 10s and 30–90s, respectively. In the United States, similar work was pursued by Kamiya et al. [18]. The ILF domain has also been studied in Austria and Germany [19–24].

Spontaneous and evoked local field potentials were observed in various cortical and subcortical regions of patients in whom cortical and subcortical electrodes had been implanted for purposes of characterization, diagnosis, deep brain stimulation, or lesioning [25]. The cortical electrical potentials were found to be correlated with infra-slow metabolic oscillations such as fluctuations of local oxygen levels. It was also demonstrated that spectral characteristics of infra-slow oscillations of the human brain remained stable over days and weeks [25, 26]. Recently, ILF potentials have found increased interest in the international scientific community, especially with the growing scientific evidence for a significant role of infra-slow potential fluctuations in modulating the level of cortical excitability and thus regulating brain dynamical activity [27–32].

Infra-low frequency training, developed by Susan and Siegfried Othmer, extended the conventional frequency-based training to the lower frequency range. Feedback is then a matter of observing the slowly undulating signal. The technique has been described in a paper titled Clinical Neurofeedback: Training Brain Behavior [33]. The first reported clinical application was to Post-Traumatic Stress Disorder among military veterans [34]. The second dealt with cases of epilepsy [13]. The method came to be applied broadly to mental health concerns, with a range of application that was even larger than that of EEG-based training. The method has demonstrated dramatically positive outcomes for a variety of mental conditions, including different forms of anxiety, depression, sleep disturbances, ADHD, the autism spectrum, developmental trauma, migraines and other headaches, and traumatic brain injury [35, 36].

A surprising observation with respect to ILF training is the rapidity with which results are sometimes achieved even with challenging clinical presentations. The tonic slow cortical potential appears to be an exquisite reflection of the dynamics of cortical excitability. When the signal is derived in bipolar montage, network relations are revealed, and thus the training impinges on functional connectivity. By operating in the ILF regime, the training preferentially accesses the functional connectivity of the intrinsic connectivity networks that were originally identified with fMRI [29]. These low frequencies also give preferential access to the glial role in the regulation of the glial-neuronal system [37].

In consequence, the ILF training impinges on the ultradian cyclic fluctuation of physiological arousal and related autonomic nervous system regulation [26, 38]. For example, in anxiety disorders, the disruption of autonomic stress regulation system results in a range of symptoms [39]. Indeed, the data of Smith and colleagues support the hypothesis that ILF training preferentially influences autonomic nervous system regulation and thus improves the emotional equilibrium of patients, which in turn positively influences attention and working memory [36]. Further evidence along those lines was recently documented in a large-scale compilation of pre-post continuous performance test data on a clinical population [40]. Improvement in performance was consistently observed, irrespective of the conditions being targeted in the training.

The previous studies showed that ILF patterns of both electrical and nonelectrical phenomena remained quite stable over time. The goal of the present study is to demonstrate that the ILF training procedure induces persistent changes in the amplitude distribution within the ILF spectral range.

2. Material and methods

2.1. Participants

Eight individuals (mean age 33.1; range 21–50) participated in our study: five males (mean age 36.2; range 23–50) and three females (mean age 28.0; range 21–35). All of them had normal mental and physical development, no history of head injury, convulsions or neurological diseases, and were not currently taking any medication or drugs. Despite the absence of any medical diagnosis, participants still reported physical or mental complaints. Some of them experienced fatigue, depressed mood, symptoms of anxiety or mood swings; others had headaches and sleep problems. Most subjects were not satisfied with their concentration and memory function, or with their high reactivity to stress factors. The investigation was carried out in accordance with the Declaration of Helsinki. All subjects gave informed consent after the procedures had been fully explained to them.

2.2. EEG investigation

EEG was recorded using a Mitsar 21 channel EEG system (Mitsar, Ltd). Nineteen silver-chloride electrodes were applied according to the International 10–20 system. The input signals referenced to linked ears were filtered between 0 and 50 Hz and digitized at a rate of 250 Hz. The ground electrode was placed on the forehead. All electrode impedances were kept below 5kOhm. EEG was recorded during performance of the visual cued GO/NOGO task that uses pictures of 20 different animals, 20 different plants, and 20 different humans (together with a distracting beep tone) as stimuli [41].

One trial consisted of the sequential presentation of two pictures (prime and target), presented for 100 ms each, with an ISI of 1000 ms (SOA = 1100 ms). Trials were separated by 1500 ms. Patients were instructed to press the left button of the computer mouse as quickly as possible when an animal was followed by an animal (Go-condition) and not to respond when an animal was followed by a plant (NoGo-condition), or when a plant was followed by a plant or a human (distractor condition). The response interval lasted from 100 to 1000 ms.

The task consisted of 100 Go-trials, 100 NoGo trials, and 200 distractor trials. Trials were presented pseudo-randomly with equal probability. All trials were presented to the subject on a computer screen 1.5 m in front of them using the Psytask software (Mitsar Ltd.). The centrally presented stimuli subtended an approximate visual angle of 3°. Trials with omission and commission errors were excluded from analysis. Quantitative data were obtained using the WinEEG software.

The baseline investigation consisted of quantitative electroencephalogram (qEEG) in Visual Go/NoGo test, which took place 1–7 days before undertaking the course of NF training sessions. qEEG parameters were compared with the Human Brain Institute (HBI) normative Database. All the tests were repeated after 20 sessions in 1–7 days after the last session. The results of the second testing were compared with the pretreatment baseline.

The epochs with excessive amplitude of nonfiltered EEG and/or excessive high and slow frequency activity were automatically marked and excluded from further analysis. Eye blink artifacts were corrected by zeroing the activation curves corresponding to eye blinks. The method is similar to the one described in Vigario [42] and in Jung et al. [43].

Continuous artifact-free EEG epochs were selected manually for analysis. The duration of these epochs varied among the subjects from 550 to 1100 s.

The average spectral density in the 0–0.5 Hz frequency band was estimated for each electrode, each subject and each condition separately using the Thomson's multitaper method, and logarithmically transformed for normalization before further statistical analysis.

2.3. Neurofeedback

The instrument used for the clinical neurofeedback was the Cygnet system (bee Medic), consisting of the NeuroAmp II and Cygnet software, integrated with Somatic Vision video feedback and run on a Windows 7 operating system using a standard personal computer (PC) with a high-resolution monitor.

The Othmer Method utilizes evidence-based and well-established neurofeedback protocols, the implementation of which has been refined through empirical optimization procedures and A-B testing over a large number of neurofeedback clients referred for a variety of conditions. The method is protocol-based and is further characterized by the following essential features:

- It is a symptom-guided approach in which the symptom presentation from anamnesis is used to identify one of several basic patterns of dysregulation that are then targeted in a protocol-based manner;
- The training is process-oriented, involving the ongoing optimization of feedback parameters according to observed symptom changes during sessions and from session to session;
- The method utilizes bipolar EEG montages exclusively, and as such is oriented toward training the functional relationships between key cortical sites;
- The method involves continuous waveform-following for the low-frequency aspect of the training in combination with conventional discrete reinforcements for inhibit-based training;
- The inhibit-based training is triggered on transient anomalies observable within the conventional EEG spectrum;
- The method utilizes mainly audio-visual real-time animations in order to deliver the ILF feedback signal beneath conscious awareness.

The two parameters selectable by the clinician are:

a. position of the electrodes, according to symptom profile and symptom changes;

b. adjustment of the reward frequency according to patient feedback.

Until 2006, the signal processing was very similar to the classical beta-SMR scheme [44]. However, the reward frequency setting of a 3 Hz wide variable bandpass-filter was user-adjustable over the entire conventional EEG spectrum from 1.5 to 40 Hz in center frequency. For that purpose, a horizontal slider was implemented in the graphical user interface. The inhibits were comprised 10 separate filter blocks in fixed frequency steps in the range between 1 and 40 Hz. For both the reward and inhibit scheme, threshold setting was auto-corrected to maintain a chosen level of difficulty, the "percent success."

Specific design parameters in the signal-processing chain between initial EEG acquisition and ultimate feedback animation have always been assessed and optimized by means of an empirical approach based on qualitative evidence criteria. (A useful analogy to this process is the optimization of the suspension system of a car, where human factors come prominently into play.)

By expanding the underlying model of neurofeedback to incorporate the current understanding of the brain as a self-organizing dynamical system that interacts with itself by means of neurofeedback, improved approaches to signal processing and coupling to the feedback animations have been sought. This process got underway in 2001. In that regard, also slow cortical potentials were investigated. With the availability of greater computer power for additional signal processing as well as advanced signal acquisition technologies, it was found that the addition of such slow potentials appears to offer the brain a more direct and effective feedback interaction. It turned out that also with this scheme, tailoring of the parameter setting to the individual patient is beneficial or even necessary, just as was previously found for frequency-band training in the conventional EEG spectrum [45].

In contrast to the classical concept of a rewarding experience that is controlled by the amplitude of the EEG in a given frequency band, the goal here is to present the brain with the most relevant representation of its slow cortical potential. For that purpose, derivations from the measured signal control various features in the feedback animation in a way that optimizes the brain's opportunity to engage with them.

For the purpose of continuity of the clinician's experience with the earlier era, the terminology of "reward frequency" was retained, as the rules for settings and for the optimization procedure carried over into the ILF region. However, the absence of discrete rewards in the ILF training meant that the traditional terminology of reward had lost its meaning. The unfolding of the continuous ILF signal allowed for no external reinforcers. Additionally, the slider that controlled the target frequency within the EEG regime was retained in the new design, but its function in the ILF regime must be understood differently. With the adopted

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signal-processing scheme, the slider influences the natural frequency of the control loop that the brain forms with the feedback system during neurofeedback on a continuous signal. It functions effectively as a kind of gain control.

Training was performed with bipolar placement of silver/silver chloride scalp electrodes applied using Ten20 conductive electrode paste at one or both of two initial placements, T4-P4 and T4-T3 (according to the standard 10–20 system). These are relied upon to characterize the response of the trainee and to guide further optimization. Subsequently, T4-Fp2 and T3-Fp1 are added to the protocol as needed. The "ground" electrode was placed at Fpz.

Each trainee received 20 separate 30–45 min neurofeedback sessions over 7–8 weeks. For each subject, the target frequency in the infra-low frequency region was optimized with each of the standard placements. The placement of electrodes was the standard one developed by Othmer [46] and adopted in the Othmer Method.

2.4. Statistical analysis

Two-way repeated measures ANOVA with factors condition (before-after) and location (19 electrode positions) was used to estimate the statistical significance of the training effect on the slow EEG oscillations. The Greenhouse-Geisser procedure was used to compensate for deviations from sphericity or circularity.

3. Results

After completion of 20 NFB sessions, all participants indicated improvement of their state. Most of them noticed a decrease of inner tension and reactivity to stressful factors. Further, they reported on stability of mood, improved body and space awareness, increase of energy level and of cognitive performance.

The post-training EEG patterns in all eight subjects revealed significant enhancement of spectral power in 0–0.5 Hz frequency band compared to the pre-training EEG. The locations of the most prominent changes were different: in some subjects, the dramatic ILF power increase was observed over the frontal-central region, in other cases over the posterior brain areas.

Figure 1 presents the EEG recordings before and after ILF NF course in one of the participants of our study.

Figure 2 demonstrates the increase of the level of infra-slow activity in 0.03–0.05 Hz range in the post-training EEG in this participant. This increase is most prominent over frontal region.

Two-way ANOVA revealed a significant main effect of the factor "Condition" for the slow activity in 0–0.5 Hz frequency band $F[1,7] = 18.4$, $p < 0.01$. This effect is illustrated in **Figure 3**.

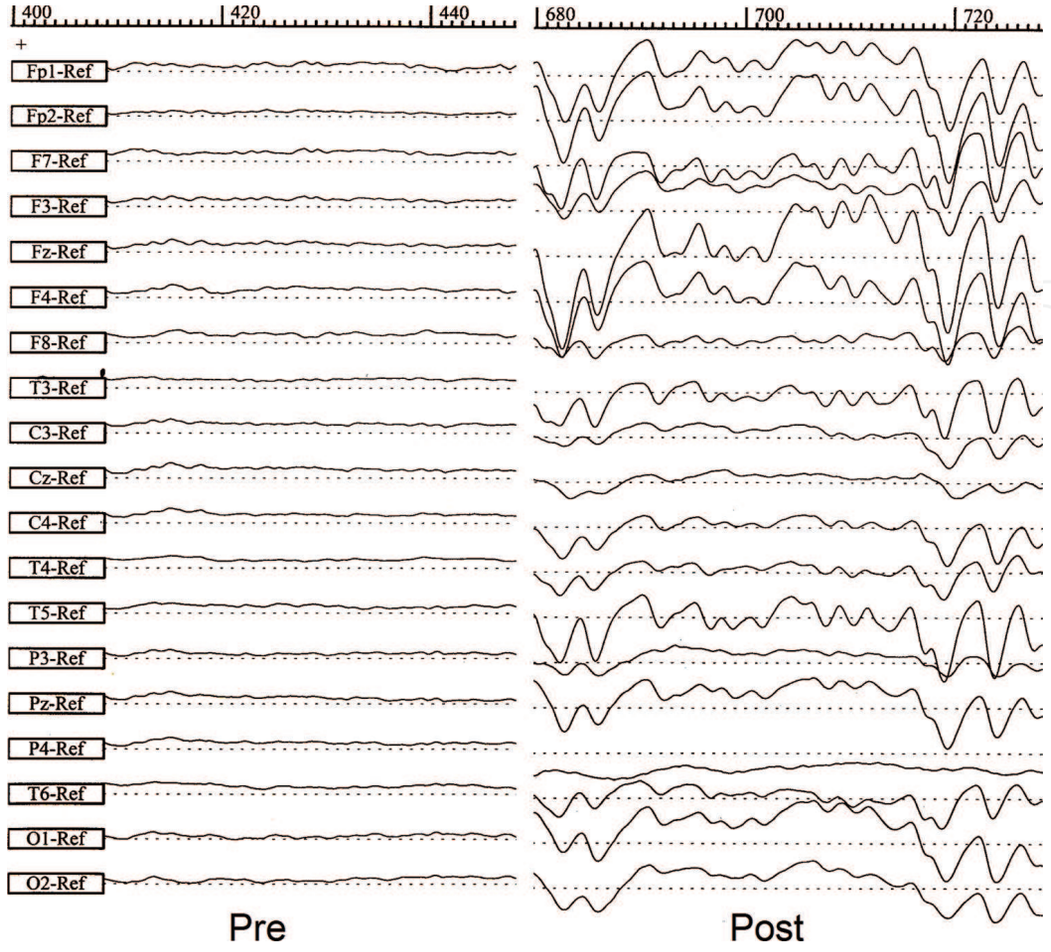


Figure 1. Pre-training (on the left) and post-training (on the right) EEG in the 43-year-old male subject. EEG recorded in the linked ear montage/reference during VCPT performance. Scale: 200uV/cm, speed–1.875 mm/s, time constant–10.0 s (0.016 Hz), low frequency filter–0.5 Hz.

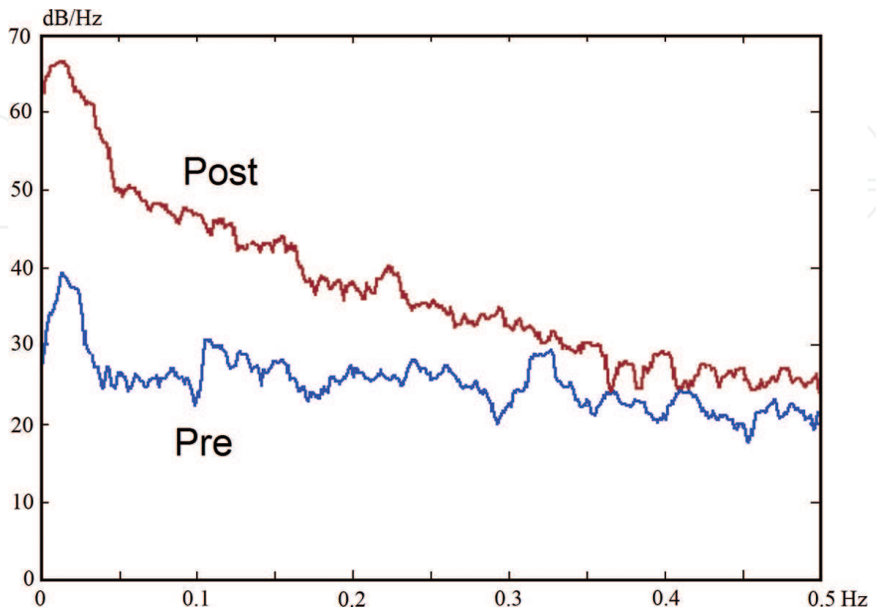


Figure 2. EEG power spectra at Fz in the 43-year-old male subject before and after training**.** Pre-training–Lower curve, post-training–Upper curve, X-axis–Frequency and Y-axis–Spectral power in logarithmic scale.

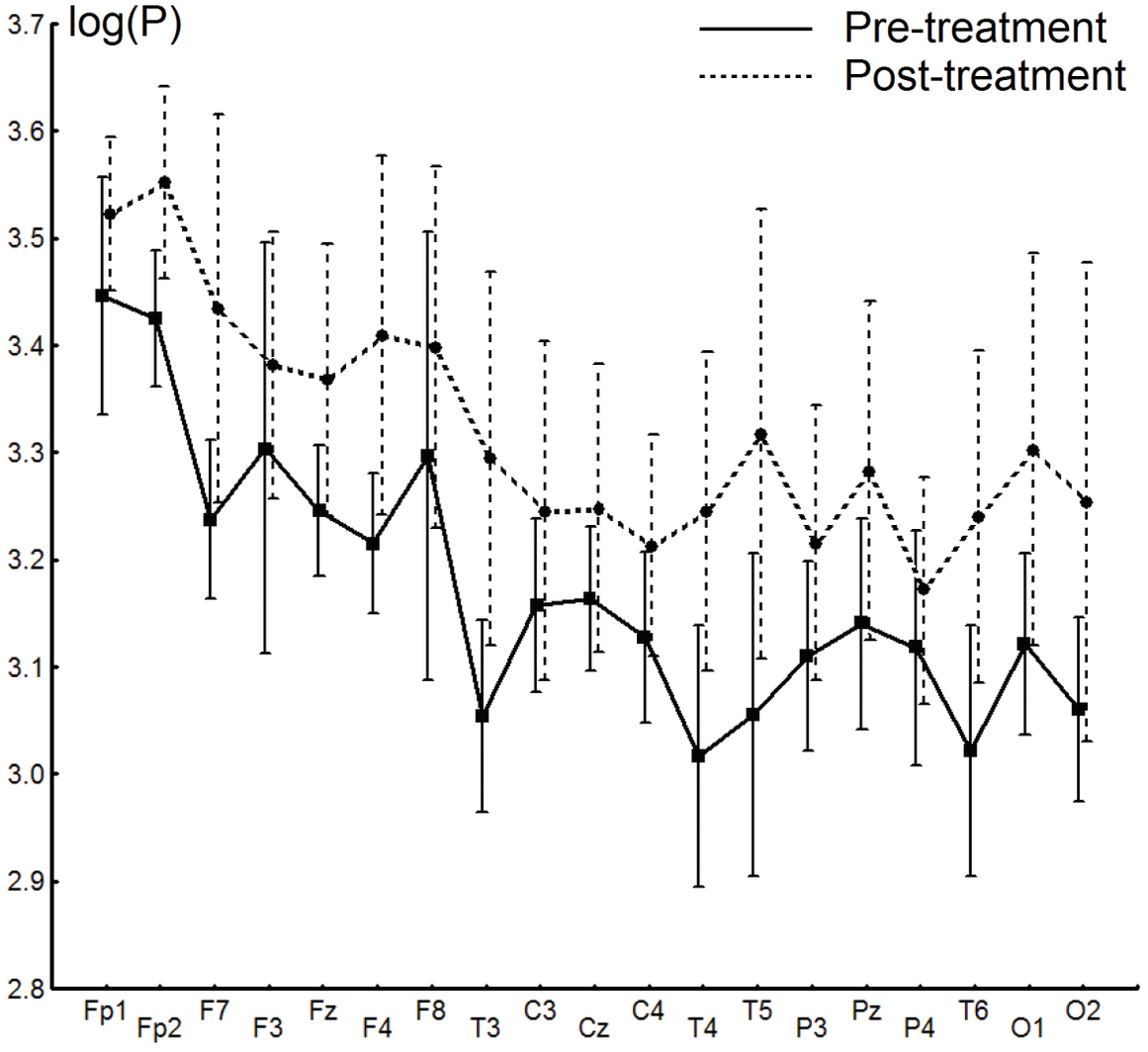


Figure 3. Influence of the ILF NF on the power of EEG activity in 0–0.5 Hz frequency band. X-axis–Electrodes localizations; Y-axis–Logarithmic scale of ILF (0–0.5 Hz) power. Whiskers represent a 95% confidence interval.

An increase of the logarithmical power averaged in eight subjects in 0–0.5 Hz band is seen in all 19 electrodes localizations.

4. Discussion

All participants had normal mental and physical development and had no history of any neurological abnormalities. However, most of them reported some form of self-perceived psychological and physiological issues such as fatigue, depressed mood, symptoms of inner tension, mood swings, headache, and sleep problems. These were accompanied by cognitive concerns such as diminished attention or poor working memory.

After 20 sessions of ILF training, the pattern of ILF activity at rest changed dramatically. The main difference was an increase in the amplitude of the ILF activity up to 0.3–1.0 mV in all recording sites.

These results indicate that ILF training modified the baseline brain state in each case. It is important to add here that the changes in brain dynamics were associated with improvement

in subjective perception of stress, fatigue, mood disturbances, and sleep problems after completion of 20 sessions of ILF training. Decreases in inner tension and in stress reactivity were reported. The psychological evaluation also reflects positive changes, including improved stability of mood, better body and space awareness, increase in energy level, and improved concentration and cognitive performance (e.g., working memory).

The effect of ILF training on the subjective perception of positive psychological changes was previously reported by a number of researchers and practitioners that utilize ILF training in their practice [35, 47]. Our analysis has both supported previous observations and established a link between the observed improvement in participants' condition with objective changes in physiological parameters that reflect the dynamics of the brain functional organization.

The previous studies have shown stability of the individual spectral characteristics of ILF brain potentials recorded both from scalp as well from intra-cortical and deep-brain electrodes [25, 26].

Consequently, the increase in the amplitude of the ILF activity found in the present study can be discussed in accordance with the mechanisms of the individual compensatory-adaptive brain-body regulation in response to stress factors [48]. In the present research, we assume that our participants had initial constraints in compensatory-adaptive brain reactions, which lead to the reduced brain tissue metabolic regulation followed by energy deficient state. The present study shows that ILF training outcomes are associated with an increase in amplitude of ILF. The increase in amplitude and regularity of ILF was previously described and discussed as a sign of improved tissue metabolic activity [48–50]. Therefore, the positive trend in ILF characteristics observed in our study may be linked to the increased compensatory mechanisms in the stress regulation systems.

It is important to mention that post-training enhancement of spectral power in the 0–0.5 Hz frequency band were the most prominent over the frontal-central and the posterior brain areas. The distribution of increased activity at infra low frequency is correlated with the principal hubs of the default mode network (DMN), located frontally and parietally on the midline. The DMN is by far the most dominant among our intrinsic connectivity networks (ICNs), typically accounting for more than 95% of the ambient activity of cortex. Among the ICNs, it bears the principal responsibility for the management of the tonic state of the brain. As such it can be thought of as setting the context for more specific functions such as cognitive and emotional control [51].

Previously published results discussed the possible involvement of ILF in the modulation of the internal organization of the DMN, which is associated with the brain homeostatic balance and is involved in the autonomic regulation [35, 36, 51]. These results support the hypothesis of the metabolic stress regulatory mechanisms [48] and raise the question on the role of DMN network in homeostatic balance and metabolic compensation in stress response.

At the same time, the disrupted connectivity within DMN was found in a number of diseases, especially related to faults in the stress-regulation system such as post-traumatic stress disorder [52], general anxiety disorder [53], major depressive disorder [54], and traumatic brain injuries [55].

Therefore, the positive effects of ILF feedback on the "renormalization of functional connectivity of resting-state networks" proposed by Othmer and colleagues can be linked with the normalization in the metabolic balance in the brain tissue as a specific effect of the ILF training [35].

The present research can be considered as the first step in uncovering the physiological basis of ILF training as the method that targets the balance within brain systems involved in metabolic regulation of brain and body. The role of ILF training on the DMN network regulation is a subject of future research, where the specific physiological effect of this practice in different brain diseases will be disclosed.

5. Conclusions

Our study has shown the changes in the amplitude distribution within the ILF spectral range in all participants that seems to be induced by the ILF training. In other words, the ILF training leads to the changes of the functional state of the brain. We suggest that the modification of the baseline ILF EEG pattern may reflect the normalization in the metabolic balance in the brain tissue and increasing efficiency of compensatory mechanisms in the stress regulation systems.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author contributions

VAG-Y recruited subjects, participated in experimental design, data acquisition, interpretation, and drafting of the manuscript. VAP performed statistical analysis and interpreted the data. BW developed the ILF NF technology. OK was involved in drafting of the manuscript. MG analyzed data. VAI participated in interpretation of data. JDK supervised the study and was involved in study design, interpretation of data and critical review of the manuscript.

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