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Responses of the Nervous System to Low Frequency Stimulation and EEG Rhythms: Clinical Implications

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SALANSKY, N., A. FEDOTCHEV AND A. BONDAR. *Responses of the nervous system to low frequency stimulation and EEG rhythms: clinical implications*. NEUROSCI BIOBEHAV REV **22**(3) 395–409, 1998.—The present paper reviews literature data on the role of the non-specific central nervous system response mechanisms on the therapeutic effects of relatively weak external stimulations used in clinical practice. The factors affecting the stimulation efficiency and increased sensitiveness of living things to extra-low-frequency periodic stimulations (in the range of from less than 1 Hz to tens of Hz) are discussed. Among the factors determining such effects, the non-specific response mechanisms of the nervous system, the resonance phenomena in different organism systems, and the interaction of external stimulation with endogenous rhythmic processes are analyzed. Most attention is given to endogenous rhythms of the electrical brain activity reflected in the EEG rhythms. A high resolution EEG processing approach that is used to reveal the intrinsic oscillators in the individual EEG spectrum is described. Synchronization of sensory stimulation parameters with the frequencies of intrinsic EEG oscillators is supposed to be an appropriate way to enhance the therapeutic effects of various sensory stimulation treatments. Specific methods for utilizing resonance therapy via sensory stimulation with intrinsic EEG frequencies, and for automatic modulation of stimulation parameters by endogenous organism rhythms are delineated; some preliminary results are described. © 1998 Published by Elsevier Science Ltd. All rights reserved.

Central nervous system   Resonance phenomena   Endogenous organism rhythms   External rhythmical stimulation   Individual EEG oscillators

INTRODUCTION

THE CENTRAL nervous system (CNS) reacts to external stimulation through a complex series of specific and non-specific responses. The specific responses are determined by the physical nature of the stimulation, while the non-specific responses depend upon the intrinsic features of organism systems and are to a large extent determined by common mechanisms of the CNS adaptation to any stimulation.

Although basic studies are directed mainly toward specific mechanisms of CNS reactivity to various environmental stimuli, in recent years the analysis of non-specific CNS reactions to different natural stimulations has attracted attention. Such analysis allows for the opportunity to study CNS regulatory mechanisms and to develop new therapeutic methods based on sensory stimulation.

Non-specific CNS reactivity mechanisms play an extremely important role when rhythmically organized, relatively low-intensity sensory stimuli are used for treatment in different areas of medicine. There are several kinds of electrostimulation such as electronarcosis, electroacupuncture, transcranial or transcutaneous electric nerve stimulation (TENS), etc., which are known to be used for anesthesia (74,77,131), for treatment of steady pathological brain states (12) and for correction of cardiac pathologies (71). Light and/or sound stimulations are well known to be used for treatment of depression (151), migraine (4), endodontic anxiety (96) and sleep disorders (25). Different therapeutic and diagnostic procedures based on infrasound (5), laser (46,128) or magnetic stimulation (29) have been developed. Knowledge of non-specific mechanisms of CNS adaptation to different periodic stimulations is expected to provide sensory treatment effectiveness enhancement.

Data published in recent literature show that various low frequency sensory stimulations could, under some conditions, induce pronounced physiological effects. One of the most important conditions for observing therapeutic effects seems to be the concordance between stimulation parameters and individual characteristics of the central regulatory organism systems. Since the effects of intermittent

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stimulation are shown to be highly influenced by individual parameter selection (97,104,140), utilization of variable stimulation frequency (4,154) or the stimulation frequency coinciding with the organism's own rhythms (12,110,114), the importance of individual treatment alignment is now becoming more clear (49,113). The specific methods for selecting the stimulation for a particular patient are not widely discussed in the literature. This paper will analyze this particular subject, and will demonstrate that utilization of patients' EEG rhythms could help in selecting the specifics of the treatment modalities' alignment.

The current paper reviews literature data based on the roles of non-specific CNS reactivity mechanisms and intrinsic properties of organism functional systems on the therapeutic effects of relatively weak, rhythmically organized external stimulations. The factors determining stimulation efficiency, the increased sensitivity of living things to extra-low-frequency periodic stimulations (in the range from less than 1 Hz to tens of Hz) and CNS resonance phenomena are discussed. The role of endogenous rhythmic processes in organism interaction with the low-frequency sensory stimulation is analyzed. Most attention is given to endogenous brain electrical activity rhythms (EEG rhythms). Several new approaches to sensory stimulation efficiency enhancement via individual EEG oscillator's activity utilization are delineated and some preliminary results are described.

INCREASED SENSITIVITY OF HUMANS AND ANIMALS TO LOW-FREQUENCY PERIODIC STIMULATION

Humans and animals are particularly sensitive to low-frequency sensory stimulation and/or to low-frequency modulation of physical factors. Various sensory stimuli (e.g. light flashes, auditory signals, somatosensory impulses, etc.) have biological effects in the frequency range 3–30 Hz (103,134,138). Electrical states in the brain can be altered by light and EMFs with frequencies in the range 1–20 Hz (16).

The experimental data obtained from numerous studies demonstrate that different low intensity and sensory stimuli organized in time have the ability to induce enhanced effects. In some models of acute pain (26), interrupted electrical currents are known to be more analgesic than continuous currents. Lower level, chronically repeated environmental and proprioceptive stimuli may lead to sympathetic nervous system hyperfunction that is assumed to serve as a self-sustaining neurologic basis for stress-related diseases (37). Pronounced behavioral and biological effects may be obtained only under definite, resonant frequency parameters of electromagnetic field (EMF) modulation (52).

Many authors associate particular organism sensitivity to external low-frequency oscillations with specific evolutionary sensing mechanisms that were developed to derive valuable biological information from the normal magnetic field of the Earth (13) or to compensate for the effects of geological and meteorological EMFs (15). These EMFs are subjected to some amplification in the organism and are shown to affect different physiological systems (8,126,134).

Although the locus of EMF detection is unknown, there is evidence to suggest that this occurs in the nervous system (15,50). Similarly, the biophysical mechanisms of EMF detection are unknown. Various mechanisms have been proposed to explain the sensitivity to EMF. One of these mechanisms is based upon resonance interaction processes within the cell structures (16).

There are a variety of explanations provided for EMF detection mechanisms. One hypothesis is that EMFs may alter calcium-binding in membrane-bound glycoproteins, thereby affecting receptor–ligand interactions and resulting in transmission of a signal to the cell interior (2). The glycoprotein–EMF interaction appears to be maximal when the EMF frequency corresponds to a frequency of an ongoing physiological activity (1,2). Another possible mechanism assumes that the ionic permeability of membrane-channel proteins may be increased during the application of EMFs through ion resonance, thereby resulting in the initiation of second messengers that ultimately lead to biological effects (80). In this view, the strength of a static magnetic field, for a given ion species, and the frequency of a time-varying EMF determine whether resonance-mediated biological effects will occur. When these hypotheses are compared, the first (2) is considered to be more correct (45), since it is supported by recent experimental data (16).

The human body is constantly bombarded by energy generated by the sun, the universe, geomagnetic sources as well as from man-made sources (e.g. electricity and its resulting magnetic fields). Since all energies have a frequency and intensity and because light, sound, touch, smell, and taste function through the reaction to these frequencies, all human senses can be affected. All individuals are different and will react differently to environmental exposures, so specific frequencies must be accessed for helpful or harmful effects (113).

RESONANCE PHENOMENA IN THE NERVOUS SYSTEM

When a periodic signal of a characteristic frequency is applied to the system, a resonance response may be expected of underdamped systems. This response is characterized by a surprisingly large output amplitude for relatively small input amplitudes (i.e. the gain is large) (11). The so-called resonance phenomena in the central nervous system are manifestations of the activity of micro-oscillation circuits sequentially excited or inhibited in six layers of the brain cortex and macro-oscillation circuits of the brain (30).

Oscillations and resonance phenomena in the electrical activity of certain neuron sets in the brain and spinal cord are important factors in the organization of those connectivity properties that must be tuned by function (162). The complex dynamics of compound potentials and the resonance phenomena might play one of the most important roles in brain organization (9).

In the recent years, the importance of resonance phenomena in CNS regulatory processes has received wide acknowledgment. The resonance phenomena of the brain merit increasing consideration because of several new neurophysiological investigations at the cellular and electroencephalographic (EEG) levels and in magnetoencephalographic measurements (10).

Some authors have examined the relationships between CNS resonance properties and sensory stimulation. According to R. Miller, a collection of widely dispersed neurons throughout the cortical mantle may be set into a tonic state of elevated activation as a result of signals reaching the cortex via any of its sensory systems. The principle of co-operativity in this case should favor the strengthening of nerve communications that permit resonance (91).

Before sensory stimulation, the EEG oscillations and resonance phenomena are variable and have unstable frequencies and amplitudes. Following sensory stimulation, the frequency is stabilized and the amplitude is greatly enhanced. These responses are considered to be related to the coupling of neural oscillators and resonance of the nuclei. In the post stimulation period, there is a change to high coherency between brain structures in the inherent frequencies of their brain rhythms (161). Afferent information reaches different neuronal ensembles, they are considered to enter a coupled common mode of oscillation as if some kind of resonance takes place between the separate neuronal ensembles (162).

INTERACTION BETWEEN EXTERNAL SENSORY STIMULATION AND ENDOGENOUS ORGANISM RHYTHMS

Physiological functions are known to demonstrate spontaneous fluctuations of their parameters. Although the exact nature and the mechanisms of these intrinsic oscillations are still not well understood, they are currently being investigated by means of modern computer techniques and appear to play an important role in the regulatory processes of organisms. The utilization of fast fourier transform (FFT) for the analysis of low-frequency photoplethysmograph signals, that are usually treated as the noise of electronic equipment, has demonstrated their relation to blood pressure and temperature control mechanisms (61).

Different organism systems are characterized by their endogenous rhythms of spontaneous fluctuations. Some of the most important system-forming endogenous organism rhythms are respiratory rhythm, heart rate and EEG rhythms (109,129). These rhythms are known to demonstrate homeostatic auto-regulation and stability (170) and to play a stabilizing role in the central regulatory processes (116).

Spontaneous fluctuations and rhythms of physiological functions could be modulated by various external factors such as different physical agents, sensory stimulation, stressful events, etc. (18,22,107,136). Weak sensory stimuli are known to induce a phase sensitive bradycardia (64) and spontaneous K-complexes in the EEG (106). Weak low-frequency electromagnetic fields could lead to gene expression, RNA synthesis and enzyme modifications (155).

In certain conditions, the interaction between different external periodic influences and endogenous rhythmical processes leads to their synchronization and resonance (15,103,138) that could change the initial system state to a new one with corresponding metabolic transformation (109). The change from a random pattern of activity to an oscillatory mode, in a neuronal population, results from the interplay of intrinsic and network properties; oscillatory mechanisms have emerged as the mechanism of choice for a neural mass to switch between different behavioral modes (81).

Various brain structures depict spontaneous rhythmic activity in a wide frequency range between 1 and 1000 Hz. Without the application of external sensory stimulation, the spontaneous activity of a given brain structure can often show frequency-stable and high-magnitude electrical activity. If regular spontaneous oscillations can be detected in the electrical activity of a defined brain structure during a determined period, it is to be expected that upon external sensory stimulation, this structure will exhibit a susceptibility response within the same frequency range. The response susceptibility of a brain structure depends mostly on the susceptibility of its own ‘intrinsic rhythmic activity’ (10).

A particular role in the non-specific mechanisms of CNS reactivity to external stimulation is played by endogenous rhythmic processes in the electrical brain activity reflected in EEG rhythms.

EEG RHYTHMS AND ENDOGENOUS RHYTHMICAL PROCESSES

Spontaneous oscillatory activity of the brain is an example of organism endogenous rhythmic processes. EEG rhythms, as well as other endogenous organism rhythms, have close inter-relations with different physiological functions. A strong correlation has been established for EEG rhythms with electrical heart activity (95,120), respiratory activity (48), some behavioral (17) and sensorimotor characteristics (125).

In comparison with other endogenous rhythmic processes, EEG rhythms have a highly informative value and are widely used in practice. The role of EEG as a most important physiological signal of the central nervous system is now in re-appraisal (98). The state of the art in the EEG area will be discussed later in this paper.

Physiological Function Evaluation and Regulation Based on EEG Rhythms

The technology of EEG recording and analysis has recently been rapidly evolving. The results of this evolution promise a low cost, unobstructive functional brain imaging modality with an unsurpassed sub second temporal resolution and an useful degree of spatial resolution (44,54).

Despite the lack of comprehensive scientific proofs, the EEG generating mechanism points to the hypothesis that EEG signals stem from a periodic (or quasi-periodic) driven non-linear system. Neurons are highly non-linear elements. Moreover, multiple feedback loops exist in each of the hierarchic levels and in every ‘module’ of the central nervous system. Current understanding of the basic elements of this phenomenon suggests that EEG results from the excitatory post-synaptic potentials of the cortical pyramidal cells. Cortical neuronal activity is driven by the regularly appearing activity of thalamic nuclei that are under the influence of mesencephalo-reticulary activity (123).

EEG rhythms are expected to contain the most essential parameters of different functional organism systems and neuronal networks (81,146). Relevant EEG rhythmic patterns reflect the unique properties of thalamocortical circuits. These EEG patterns are topographically localized in relation to nervous system organization. Because of the interaction between specific and non-specific sensory mechanisms, cortical stimulation determines their frequency and cortical expression (147).

Predominance of different EEG frequency bands in humans is known to be associated with different brain functional states. For example, delta (0.5–3.5 Hz) EEG activity is known to be related to deep sleep (35) or opioid-induced brain states (78) and is supposed to be a sign of internal concentration during the performance of mental tasks (43,60). Theta (4–7 Hz) EEG waves are observed in the meditation state (65), during listening to pleasant music (72), in the state of situational awareness (164) or as a result of sleep deprivation (24,82,137). Synchronous EEG rhythms in the alpha range (8–13 Hz) indicate a demobilization of cortical processes that regulate neuromuscular processes which, in turn, eventuate in voluntary, purposeful, and defensive phasic and tonic movements (100).

Transformation of the EEG signal into the frequency domain reveals the simultaneous, albeit weighted, contribution of the different temporal frequencies during all brain functional states (90). Such transformation provides the opportunity to characterize a wide spectrum of organism functional states via the specifics of the EEG patterns. Quantitative measures of rhythmical EEG components are considered the most reliable tool for evaluating sensory information processed by the brain (117) and for determining the extent and severity of cerebral pathology (31,157). EEG can provide a valid and objective index for mental effort and may reveal also task-related cognitive resource allocation, task mastery and task overload (148).

Rhythmic EEG characteristics are used efficiently for the following: common brain functional state evaluation in different states of wakefulness (36,86,94,158,168); brain state shift assessments during sleep (7,35,87), hypnosis (33), intensive therapy (142), anesthesia (55) and other therapies (19,96).

High information value of rhythmic EEG components has been demonstrated for the following: functional state evaluation under different stress influences (24,34,92), in extreme conditions of space flight (115), aircraft landing tasks (47) or strenuous operator activities (28,164). The EEG methodology permits one to quantitatively estimate the effects of functionally significant drugs (63) and to study the EEG profiles of physiologically active substances (70,78).

Heterogeneity and Polyfunctionality of the EEG Rhythms

Currently, spectral analysis has become increasingly popular for various kinds of EEG investigation. Most clinical studies apply spectral analysis to relatively long sections of background activity. EEG spectra are either averaged over time or split up into frequency bands. When the EEG spectra is averaged over time, the rapid dynamic changes in the EEG are lost. Similarly, the splitting of the EEG spectra into frequency bands conceals frequency changes commonly seen in the EEGs and can hide the presence of two or more rhythmic components with neighboring frequencies (62).

Usually, the whole EEG frequency spectrum is reduced in the common bands such as delta, theta, alpha and beta EEG rhythms to facilitate the data treatment. However, recent studies indicate the presence of inconsistencies in the traditional EEG frequency bands (83,144) and demonstrate a heterogeneity of conventional EEG rhythms (23,111,149,150). Sub-division of the spectrum into traditional bands lacks a theoretical basis (141) and may not be the optimal way to represent the functional relationship with cognitive states (168). Moreover, when certain conditions are applied, this procedure can modify the results (135), lead to their misinterpretation (3) or cause the loss of important information (163).

EEG changes induced by different treatments, tasks or drugs are shown to occur in certain narrow frequency bands within a given EEG rhythm while frequency neighboring spectral components of this rhythm could remain unchanged (51,78,150). Since even minimal frequency changes (i.e. 0.3 Hz) in clinical practice can be of importance (70), a more discrete evaluation of EEG components is needed for a better interpretation of brain electrical activity responses to different sensory treatment, drug or task influences. Improvements in specificity and sensitivity of the EEG method may be achieved by substituting broad band quantitative EEG analyses with their high resolution counterparts (150).

Some studies clearly indicate the advantages of using higher frequency resolution for spectral EEG analysis. In one of the studies (40), the authors were able to observe the greatest treatment-induced changes in the bandwidth 8.00–9.19 Hz and the least in the neighboring bandwidth 9.20–10.39 Hz when they sub-divided the single alpha EEG band into four equal frequency segments. Another study (66) show that after submitting the EEG data to very narrow band analysis, the power increase with work load occurred in a frequency range less than 1 Hz wide, typically between 3.8 and 4.2 Hz. These changes were severely obscured by dilution effects when averaged across the wide theta band (3.5–7.5 Hz).

EEG Oscillator's Frequency Resolution and EEG Pattern Dynamics

Cortical rhythms are the output of neuronal rhythm generators. It is suggested that the generation and features of these rhythms are the result of endogenous neuronal rhythmicity, reverberating circuits and non-linear dynamic factors, leading to deterministic chaos (81,114,146). Although the nature and essential features of brain generators (oscillators) are still not explicitly known, in recent years, they have been intensively studied by a number of investigators (21,85,90,145).

EEG generators appear to have narrow frequency tuning, since they demonstrate a high degree of frequency variability within different subjects (76,140,152,159) simultaneously with remarkable intra-subject stability (14,43,132,149). Some clinical results indicate that the abnormal electrical activity could be reflected in a very narrow frequency band (150).

The activity of multiple brain generators appears to have a dynamic nature. The occurrence of rhythmic activity may be rather fast; the characteristics of the input–output transfer of information through the neuronal network can change dramatically (81). Different EEG frequency components during a given EEG epoch are generated by neural populations in different brain locations (90). The EEG can show a great variety of patterns which are dynamically changing over time; one pattern may evolve into another and distinct patterns may simultaneously occur at different sites (62).

Multiple EEG oscillators appear to have resonant features. Some authors consider the EEG responses to external stimulation as being correlated with the brain's quasi-invariant resonant modes containing important brain frequency codes related to central nervous system function (9,10). In normal subjects, each of the response curves might be generated by a different dynamic system that responds to the external driving frequency with a different resonant frequency. Each of the EEG rhythms appears to have its own neuronal circuitry, resonant frequency and physiological correlates (114). Gradual build-up of EEG responses at the onset of intermittent stimulation and gradual decay after its cessation can exhibit a resonance phenomenon caused by a resonant filter (127).

Narrow frequency tuning, dynamics and resonant features of multiple EEG oscillators indicate that an appropriate way for better brain oscillatory activity evaluation is the utilization of fast fourier transform (FFT)-based modification of dynamic spectral analysis. This approach assumes that FFT will be performed for short-term time windows of the EEG with their successive overlapping intervals. When these short segment spectra are accumulated bit-by-bit for a given period, the resulting accumulated spectrum is based on a number of short-term ones. It has sufficient frequency resolution and contains reliable information about the most stable active EEG oscillators.

The approach described has some advantages compared with conventional FFT-based spectral EEG analysis. This method improves the EEG frequency resolution by avoiding the integration of spectral components, that are generally performed on the experimental data between the arbitrarily chosen frequency band boundaries (86). Successive epoch overlapping intervals provide an opportunity to trace the temporal dynamics of the EEG (62), to increase the statistical robustness of the analysis (53) and to improve the EEG frequency resolution (169). This dynamic approach appears to be an effective tool for the detailed investigation of endogenous rhythmic brain activity, since it permits one to observe the individual components of EEG spectrum that are shown to be stable for a given subject (42) and demonstrate significant correlation relationships with different somatic functions (41).

OBSERVATION OF INDIVIDUAL EEG OSCILLATORS VIA HIGH RESOLUTION EEG PROCESSING APPROACH

The dynamic modification of high resolution spectral EEG analysis has been developed to study individually-specific narrow-frequency EEG structure components (130). It uses FFT for 4-s intervals of the EEG with an overlapping succession of 25–75%. To determine the

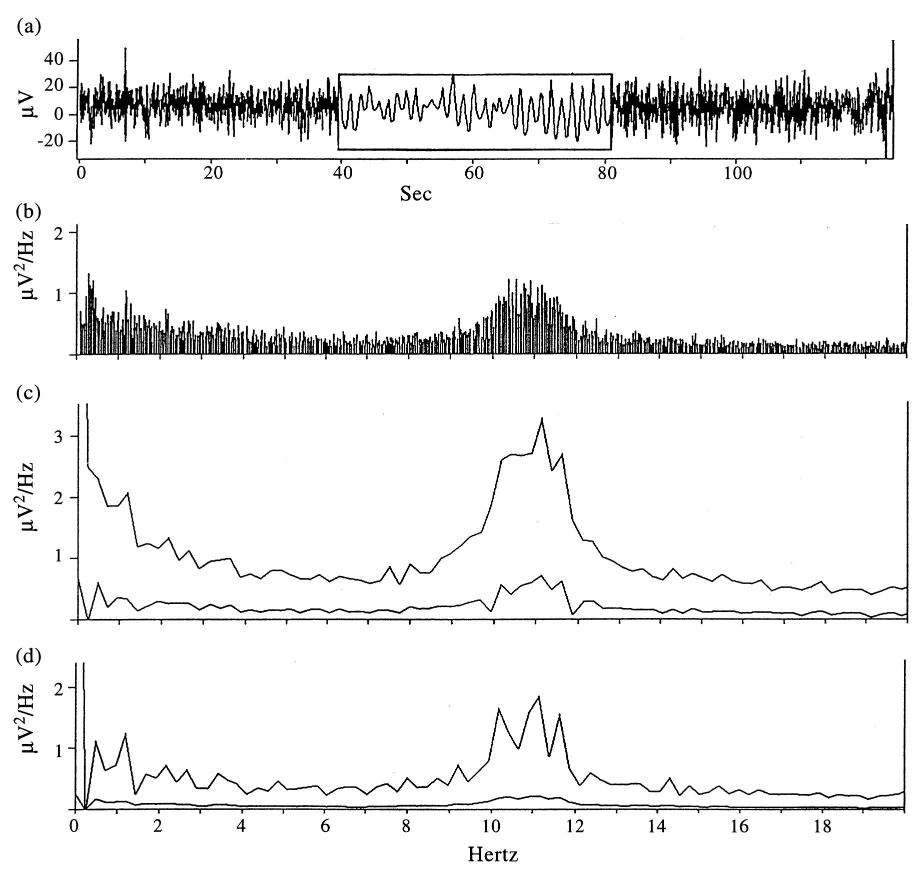

FIG. 1. Two minute fragment of the EEG (A), processed by three different FFT-based techniques (B–D). (B) FFT is applied to the whole EEG recording. (C) FFT is applied to successive 4 s EEG segments with data averaging. (D) FFT is applied to successive 4 s EEG segments with overlapping and prior selection of peaks from short-segment spectra before accumulation.

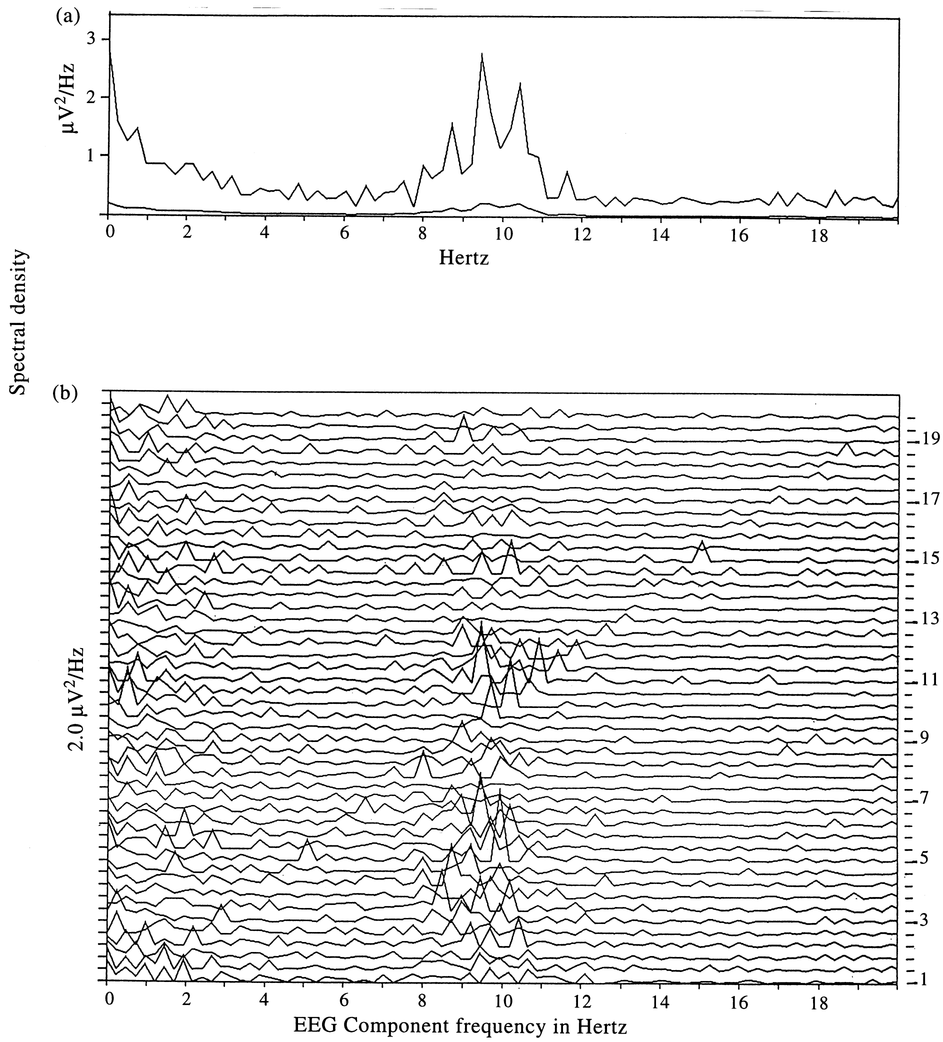

FIG. 2. Accumulated EEG spectra for rest (A) and photic stimulation (B) with different constant frequencies gradually increasing from 1.0 to 19.8 Hz in 0.4 Hz steps.

indices of background or reactive EEG, these short-term spectra are accumulated bit-by-bit for a given period of time, provided that only the main spectral peaks are accumulated and simultaneously the noise level is suppressed.

The advantages of this developed approach are demonstrated on Fig. 1, which shows the results of different EEG processing technique applications to the same EEG fragment (Fig. 1(A), compressed 2 min EEG recording with a window in the center exhibiting the real EEG signal).

When FFT is applied to the whole 2-min period of the EEG (Fig. 1(B)), only increased spectral density for delta (0–4 Hz) and alpha (8–13 Hz) components could be detected. FFT application to successive 4-s EEG epochs with their averaging (Fig. 1(C)) provides further details; however, the intrinsic EEG oscillators are poorly revealed after this conventional FFT-based analysis. For instance, it is difficult to differentiate between several narrow-band oscillators in the alpha (8–13 Hz) EEG range. When the FFT is performed for 4-s windows of the EEG with their successive overlapping intervals and prior selection of peaks from each spectra (Fig. 1(D)), the resulting accumulated spectrum is thus obtained from the analysis of hundreds of the short-term ones to increase signal-to-noise ratio for distinguishing between the neighbor-frequency spectral EEG components. It has sufficient frequency resolution (0.25 Hz) and contains highly reliable and statistically robust (see bottom curve reflecting the standard errors) individual characteristics of three narrow-frequency EEG oscillators within the alpha EEG band.

The spectra shown on Fig. 1 are obtained for resting EEG. Another way to examine the intrinsic EEG oscillators is the utilization of the recently developed resonance activation approach.

Under external sensory stimulation, a defined brain structure shows a corresponding response susceptibility in the same frequency channels where spontaneous oscillations can be detected (10,75,103). Visual stimulation at rates too fast to allow brain mechanisms to return to their resting levels (between flashes) produces steady-state visually evoked responses (VER) reaching maximum amplitudes in the occipital cortex. A VER is produced by entrainment or photic driving of the EEG at the frequency of the stimulus. Under this condition, the brain is presumed to have achieved a steady state of excitability (75). With an accurate and stable stimulus, the VER can be concentrated into very narrow frequency bands (112).

A periodic visual stimulus influences bulk brain activity not only by producing an averaged VER, but also by altering the background EEG (88). Gradual build-up of photic responses at the onset of intermittent photic stimulation and gradual decay after its cessation can exhibit a resonance phenomenon, that potentially may be caused by a resonant brain filter (127). Therefore, it seems that the response to photic stimulation driving is due to the resonance between spontaneous rhythms of the brain and visually evoked responses, as claimed in classical theories (101,166).

The photic driving response appears most likely to be an interaction or resonance between intrinsic rhythms and evoked rhythms generated by the periodic photic pulses (75). The system can actually be 'driven' at different rates, but is synchronized when it is 'tuned' at the 'resonant' frequency. Such resonant-like behavior, already reported in relation to the VER (118), could be described by a simple model. A collection of cyclically charged excitatory–inhibitory post-synaptic potentials, usually weakly correlated but featuring a common averaged repetition rate, is locked in phase by the resonant stimulation in the proximity of the end stations of the sensory pathways, leading to a potentiation of the global response (103).

The EEG response to rhythmic sensory stimulation is not limited to the visual modality: EEG response driven by somesthetic (102,103) and auditory (122) stimuli has been reported in humans. Since each EEG rhythm can be driven somewhat independently in normal subjects (114), scanning the frequency in the sensory stimulation range and observing the responses will allow one to identify and study the underlying oscillating circuitry. In the recent review (11), it is claimed that forced oscillations due to resonance phenomena or EEG responses can be analyzed by gradually increasing the frequency in a pre-selected range, the output amplitude relative to the input amplitude is measured as a function of frequency.

Although this approach reveals the natural frequencies of a system, only a small number of works have investigated the behavior of such an EEG response. Difficulties result from the requirement for evoked responses to reflect over at least two to three decades of stimulation frequencies (11).

One possible way to overcome these difficulties is the application of the above described EEG processing technique to the successive periods of the EEG, recorded under low-intensity LED photostimulation with the frequency gradually changing in the range of main EEG rhythms (i.e. 1–20 Hz).

An example of the application of this approach is demonstrated on Fig. 2. This diagram shows the EEG spectra accumulated for a 2 min rest period (Fig. 2(A)) and for successive 12 s periods of photic stimulation with the frequencies gradually (by 0.4 Hz) increasing from 1.0 to 19.8 Hz (Fig. 2(B)).

Several EEG oscillators are revealed in the background EEG activity by the application of peak selection and EEG epoch overlapping techniques (Fig. 2(A)). When short (1 ms) low-intensity (0.1 mW) LED flashes with the frequencies changing each 12 s from 1.0 to 19.8 Hz by 0.4 Hz steps are presented to the subject, the peaks of spectral density are observed at EEG frequencies coinciding with the stimulation frequency, thus reflecting the resonant activation of intrinsic EEG oscillators (Fig. 2(B)). For a number of photic stimulation frequencies, there is no response at all, and at the same time the amplitudes might be different for the frequencies where the responses are observed. For this given individual, resonance activation is observed for 3.0, 5.0, 6.6, 7.8, 9.0, 9.8, 10.2, 11.0–12.2, 15.0, and 18.6 Hz EEG components.

Thus, the improved frequency resolution of the EEG signals due to the modified dynamic spectral FFT analysis provides the experimenter with an opportunity to observe a more detailed EEG spectrum and to establish both the individual oscillator's distribution and their activation patterns.

SENSORY STIMULATION EFFICIENCY ENHANCEMENT DUE TO INDIVIDUAL EEG STRUCTURE UTILIZATION

The following conclusions may be inferred from the reviewed literature data.

1. Changes in organism functional state may be induced by the modifications of endogenous organism rhythms—respiratory rhythm, heart rate and the EEG rhythms. These changes are determined by several factors such as increased CNS sensitiveness to external low-frequency stimulation, non-specific CNS reactivity to rhythmic stimulation and resonance phenomena in different organism systems.
2. Some central regulatory processes are reflected in the spectral EEG parameters. The most precise and informative of these could be revealed by dynamic high resolution EEG structure analysis.

These statements clearly indicate that the maximal synchronization of the parameters for each organism's endogenous rhythms, and particularly with the frequencies of intrinsic EEG oscillators is an appropriate method to enhance the CNS response to sensory stimulation. Since rhythmic EEG components have close interrelations with different physiological organism systems (17,59,121) and are supposed to play an active organizational function within the brain (9,54), there are several possible ways to utilize the frequency characteristics of individual EEG oscillators for sensory stimulation and treatment efficiency improvement.

Resonance Biofeedback Training with Amplitude of EEG Oscillators as a Voluntary Feedback-Controlled Parameter

EEG rhythms are known to be widely used in biofeedback training as a parameter that is voluntarily self-regulated by the patient, in order to obtain particular healing effects. For example, slow cortical potential biofeedback may be used for seizure control in epileptic patients (20). Sensorimotor EEG rhythm is used for complex tic suppression (153) and attention-deficit/hyperactivity disorder treatment (84). Alpha EEG biofeedback is commonly used for correction of stress states or generalized anxiety disorders (56,108,119). Usually, the traditional EEG rhythm amplitude or even an amplitude of more wide frequency EEG bands is extracted from the subject's EEG in order to be transformed into sound or light feedback signal intensity (38,108).

The efficiency of existing EEG biofeedback training procedures is known to be not sufficient (84) and is limited by difficulties to differentially examine the full range of EEG frequency components (147). Commonly used EEG bandwidths are too wide and may contain a composition of several EEG oscillators with different functional properties. The EEG feedback signal composed in this manner may produce ambiguous responses and cause difficulties in the subject's efforts to voluntarily regulate it.

Different test requirements can be designed to selectively activate different functional pathways; with modern, computer-based EEG analysis methodology it is possible to achieve a refined evaluation of both the frequency and topography characteristics of response to such requirements (147). Recently published literature data (169) clearly indicate that higher frequency resolution of the EEG is needed for use in the EEG biofeedback training procedures.

In this study, human subjects learned to use two channels of bipolar alpha EEG activity to control two-dimensional movement of a cursor on a computer screen. Off-line higher-resolution (i.e. 1 Hz) analysis indicated that the EEG these subjects had learned to control fell in a narrow frequency range. The subject's control of vertical cursor movement was provided by a 10 Hz EEG component, while control of horizontal movement was provided by an 11 Hz component. The authors claimed that EEG-based communication might be substantially improved by increasing the frequency and topographic resolution of the on-line algorithm that converts the EEG into cursor movement (169).

To overcome the problem of frequency resolution in existing EEG biofeedback training paradigm, utilization of individual EEG oscillators appears to be useful. If an amplitude of single individual EEG oscillator is used as a feedback parameter, a patient will voluntarily regulate the activity of their narrow-band spectral EEG component having definite functional properties. Such biofeedback training paradigm is expected to be more effective than the existing ones in many fields of experimental and clinical biofeedback training application.

Resonance Therapy via Sensory Stimulation with Intrinsic EEG Frequencies

Synchronization of treatment parameters with endogenous organism rhythms is not a new concept. For example, alpha synchronized serial photic stimulation (6) and the alpha-contingent one (99) are shown to be effective tools for studying the integrity of visual pathways and for improving EEG data evaluation. Maximal synchronization of electrostimulation parameters with endogenous EEG rhythms is shown to be highly effective for the treatment of stable psychopathological disorders (12).

The described EEG-synchronized stimulation approach has substantial advantages compared with other sensory stimulation methods. However, since the traditional EEG rhythms are known to be highly heterogeneous (23,149,150), its efficiency is seriously limited. Using the whole band of the EEG rhythm as the synchronizing parameter, the experimenter fails to reach the maximal interaction between individually functionally significant, narrow frequency-tuned EEG oscillators and sensory stimulation.

Some literature data clearly confirm the above mentioned considerations. It is well known that there are a number of devices, such as the so-called 'Brain Wave Synchronizer', in which light or sound rhythmic stimuli with the frequencies of the main EEG rhythms are used for different therapeutic purposes (96). In the case of empirically chosen parameters, these techniques are shown either to have no success in inducing relaxation or alertness (139), or even to cause epileptic seizures (133). However, in the case of prior individual EEG alpha component evaluation and tuning the device by its frequency, the efficiency of the procedure to bring an individual into relaxed state or to overcome anxiety was recently evidenced (98).

For effective resonance interaction between sensory stimulation and intrinsic functional organism systems, the narrow-frequency individually-specific EEG components should be used as a parameter for EEG-synchronized sensory stimulation.

The above statement appears to be proven by our recent experimental data. To examine electrocortical, autonomic and subjective responses to different frequencies of photic stimulation, healthy subjects were exposed to a comfortably perceived bright (1.3 mW) rhythmical light stimulation with red LED pulse duration of 1 ms. The frequency of LED flashes was changed gradually, in 1 Hz steps, from 1 to 20 Hz. Step duration at a given frequency was 18 s. Simultaneous registration of the occipital EEG and some physiological characteristics (heart rate, blood volume pulse, breath rate and amplitude, skin conductivity, etc.) occurred.

During photostimulation both the resonance activation EEG effects and the shifts in somatic physiological characteristics varied as a function of stimulation frequency. An example of such changes can be seen on Fig. 3, which demonstrates the dynamics of compressed EEG and blood volume pulse (BVP) amplitudes for successive steps of gradual flash frequency changes. Real-time signals for two fragments (a and b) are shown in the windows at the bottom of Fig. 3. The compressed amplitudes of both signals exhibit dynamic shifts with successive steps of frequency changes, and this demonstrates some reciprocal interrelations. For example, during a 10 Hz stimulation (fragment a) the EEG shows the photic driving pattern with high amplitude of a 10 Hz wave, whereas the BVP signals are relatively small. In turn, during a 19 Hz stimulation (fragment b), the EEG amplitude is relatively small, whereas the BVP signal reaches its maximal value.

After such photic stimulation the subjects have often reported various subjective feelings they perceived during successive stimulation frequency steps. Objectively, it was expressed as an increase in both EEG and BVP variations during photostimulation compared with the initial base line.

Recent literature shows that exposure to bright light may be associated with enhanced subjective alertness (25). Intermittent photic stimulation at a repetition rate of 5–30 Hz could externally induce a more coherent state in the cortex, due to some kind of resonant filter or neuronal network underlying the augmentation of the EEG activity (127). Rhythmic audio-visual programs differing in the stimulation parameters could also induce altered states of consciousness (19,97). The frequency setting of 3 Hz is

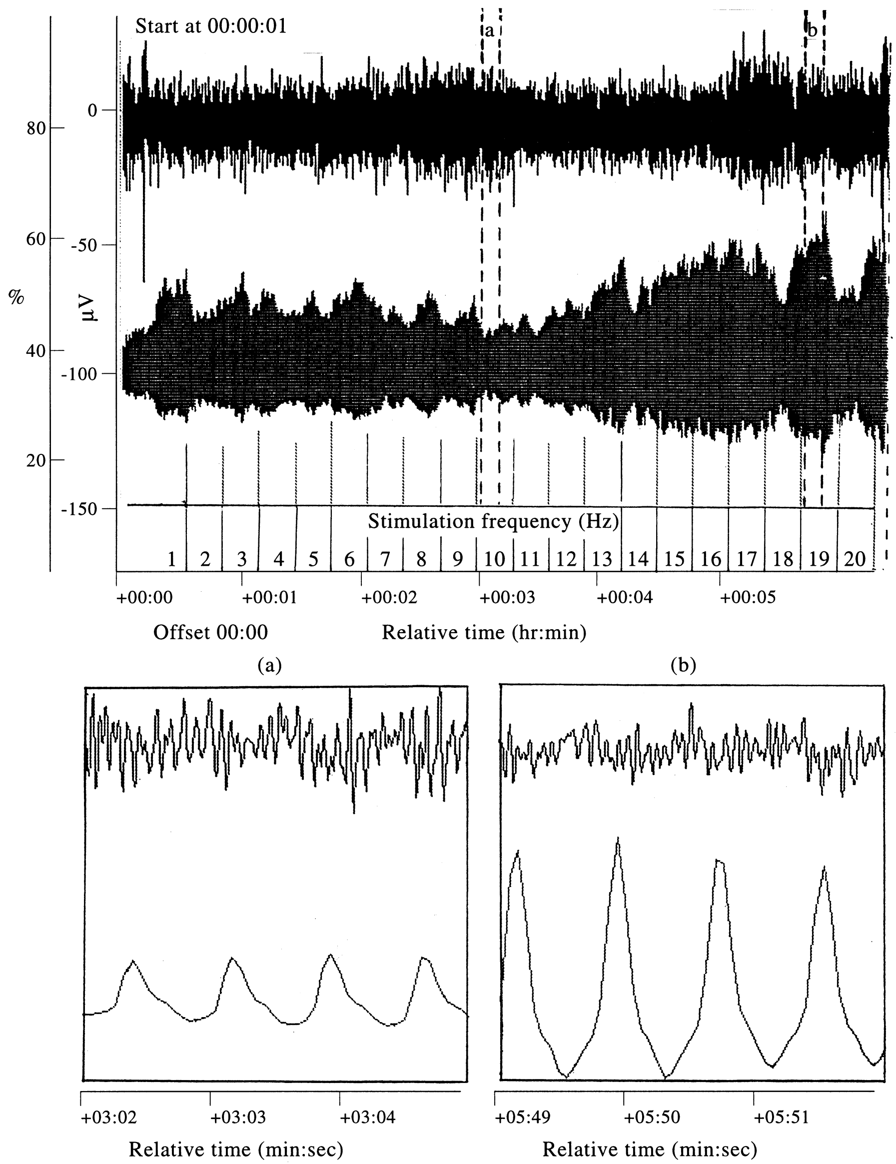

FIG. 3. Compressed dynamics of EEG and blood volume pulse amplitudes during the whole period of LED photostimulation with the frequencies gradually increasing from 1.0 to 20.0 Hz in 1.0 Hz steps.

designed to bring a person into a theta state and help that individual fall asleep, whereas a setting of near 10 Hz is purported to bring an individual into an alpha state and help that person become relaxed and overcome anxiety (97). Such a technique is proposed for overcoming anxiety associated with sports, public speaking, writing tests and various phobias (96).

The results obtained in our preliminary experiments clearly indicate that the resonance activation of discrete EEG oscillators via photic stimulation in the range 1–20 Hz could cause certain frequency-specific physiological effects and subjective responses. Although the mechanisms of such functional shifts and exact functional characteristics of discrete EEG oscillators are still not fully understood, the resonance activation approach, which is based on high resolution EEG structure analysis, seems to provide some new opportunities for quantitative evaluation and regulation of somatic functions.

Automatic Modulation of Stimulation Parameters by Endogenous Organism Rhythms

A possible way to reach an increased interaction between sensory stimulation and intrinsic physiological function properties appears to be the automatic modulation of stimulation parameters by the patient's own endogenous rhythms. This approach assumes the latter to be registered in a given patient and to be automatically sent as a feedback signal into the electrical circuit of the stimulating device. Such feedback provides direct stimulation of the organism's functional systems due to automatic concordance of stimulation parameters to the patient's CNS resonance properties. The efficiency of such an approach is expected to be based on multiple resonance effects which occur during the interaction of harmonic and sub-harmonic rhythmical stimulation components with organism intrinsic oscillatory systems.

An example of the efficiency of this approach was demonstrated by the study (171), in which a synchronized combination of EEG alpha feedback and photic driving equipment was shown to enhance the alpha rhythm (waxing and waning) without any effort from the subject.

In our preliminary experiments, the described approach has been tested using patient's respiratory rhythm as the modulating factor for rhythmical electrostimulation. Although breathing pattern (depth and frequency of breathing) is known to affect self-rated tension and state anxiety (32), pain reaction (105) and the EEG (48,143), respiration is supposed to be the most underrated variable in current psychophysiological research (93) and is rarely used in biofeedback studies (18).

To test the optimization of the electrostimulation parameters for effective stress reduction, the low-frequency (4 Hz) transcutaneous electric nerve stimulation (TENS) protocol was used in 12 patients with different etiology of stress. The amplitude of electrical stimuli was feedback-controlled by the patient's breath rate. Owing to such modulation, TENS was expected to acquire a resonant nature, its parameter changes being feedback matched to the patient's own endogenous rhythm (129).

Breath-controlled TENS has activated several low-frequency alpha EEG components in the range 8–10 Hz and caused a shift of the dominant EEG frequency to lower values. Positive changes after TENS were observed for several physiological characteristics: optimization of cardiovascular activity, growth of breath stability and amplitude, muscle relaxation and a decrease of galvanic skin response amplitude were registered as a result of breath-controlled TENS. Simultaneously, a reduction in the patient's self-ratings of stress (by 8.4%) after just one 15-min stimulation was obtained (129).

Described results are in agreement with the recent study (18), showing that breathing pattern may be used as a reliable index for the effectiveness of techniques applied for the regulation of mental states. Obtained experimental data demonstrate the advantages of breath feedback-controlled electrostimulation for the correction of physiological parameters and indicate that EEG rhythm structure analysis could be useful for further optimization of TENS parameters.

Utilization of EEG Data for Selection of Optimal TENS Parameters

Although TENS has become a popular modality in pain management over the past 20 years, there is still a debate over its mechanisms of action and efficacy. According to the literature, approximately 30% of patients either fail to respond or rapidly become tolerant to TENS (57,68). A possible cause of poor TENS efficacy seems to be insufficient activation or depletion of the endogenous opioid system, which is known to be involved in pain and stress mechanisms (67,73,89) and to be strongly implicated in responses to intense electrical stimulation (89,124,156,167).

To enhance the efficacy of TENS, some authors recommend the evaluation of the importance of electrical stimulation parameters such as pulse width and rate, and the establishment of the duration of pain relief (74). A recent study (154) has demonstrated that frequency dependence of TENS treatment is not a placebo effect. However, there is still a lack of definitive evidence for the selection of optimal TENS frequencies for pain management (165).

Some authors suppose TENS frequencies near 100 Hz to be optimal (58), but in most studies the efficacy of low-frequency electrical stimuli is claimed. The exact TENS frequency values could vary in a wide frequency range: 1–16 Hz (79), 5–20 Hz (160), 5–10 Hz (124,154,167). A recent study (27) has demonstrated that double modulation (15 and 500 Hz) of electrical stimuli causes a substantial reduction of pain even in patients not helped by conventional TENS devices. The randomized electrostimulation device 'Codetron' (131) with 4 Hz frequency of electrical pulses was shown to produce statistically significant pain reduction in 80% of patients with osteoarthritis (39).

In most studies, the optimal electrostimulation frequency coincides with the frequency range of the main EEG rhythms. Since individual variation in intrinsic cortical responsivity to external stimuli has been recently shown to determine a patient's response to TENS (69), individually adjusted stimulation frequencies within the range of the patient's own EEG oscillators could be expected to enhance the efficiency of TENS procedures.

In our preliminary study (129) with TENS modulated by the patient's breath rate, the activation of certain low-frequency alpha EEG components was induced by 4 Hz breath-controlled electrical currents. One might expect the low alpha (8–10 Hz) frequencies of TENS to produce even more pronounced resonant activation of certain TENS-sensitive brain oscillators. Since their activation is accompanied by relaxation and pain relief effects, an assumption of enhanced release of endogenous opioid peptides could be made to explain the observed TENS-induced phenomenon.

To study the temporal dynamics of electrostimulation effects, the visual evoked potentials (VEPs) were analyzed in our preliminary experiments at different stages of 4 Hz Codetron electrostimulation. The VEPs were recorded in subjects just before stimulation, during the 20 min procedure (at 5th and 20th minute of stimulation), and after its cessation (15 and 60 min later). The VEPs were produced by 2 Hz LED flashes with intensity 0.1 mW and presented to the subjects through the glasses.

The VEP amplitude varies as a function of Codetron electrostimulation time course. Before treatment (Fig. 4(1)) the VEP peak-to-peak amplitude is relatively weak. During treatment (Fig. 4(2)–Fig. 4(3)) it increases and reaches its maximal value 15 min after treatment (Fig. 4(4)). At this stage, the peak-to-peak VEP amplitude is significantly increased compared with the initial level. When the VEP measurements are made 60 min after treatment (Fig. 4(5)), the VEP pattern is similar to that observed before stimulation. In the case of placebo treatment, the VEP peak-to-peak amplitude does not show significant changes during the whole experiment, demonstrating the normal variability of the VEP patterns described in the literature (159).

The experimental data obtained support the hypothesis that the activation of brain structures, which control the release of endogenous opioid peptides under Codetron stimulation, has clear time dynamics, and the maximal activation is reached approximately 15–40 min after the start of Codetron administration. Therefore, the maximal effect in this case was observed after Codetron stimulation is finished.

The results clearly indicate that the developed EEG–CEP

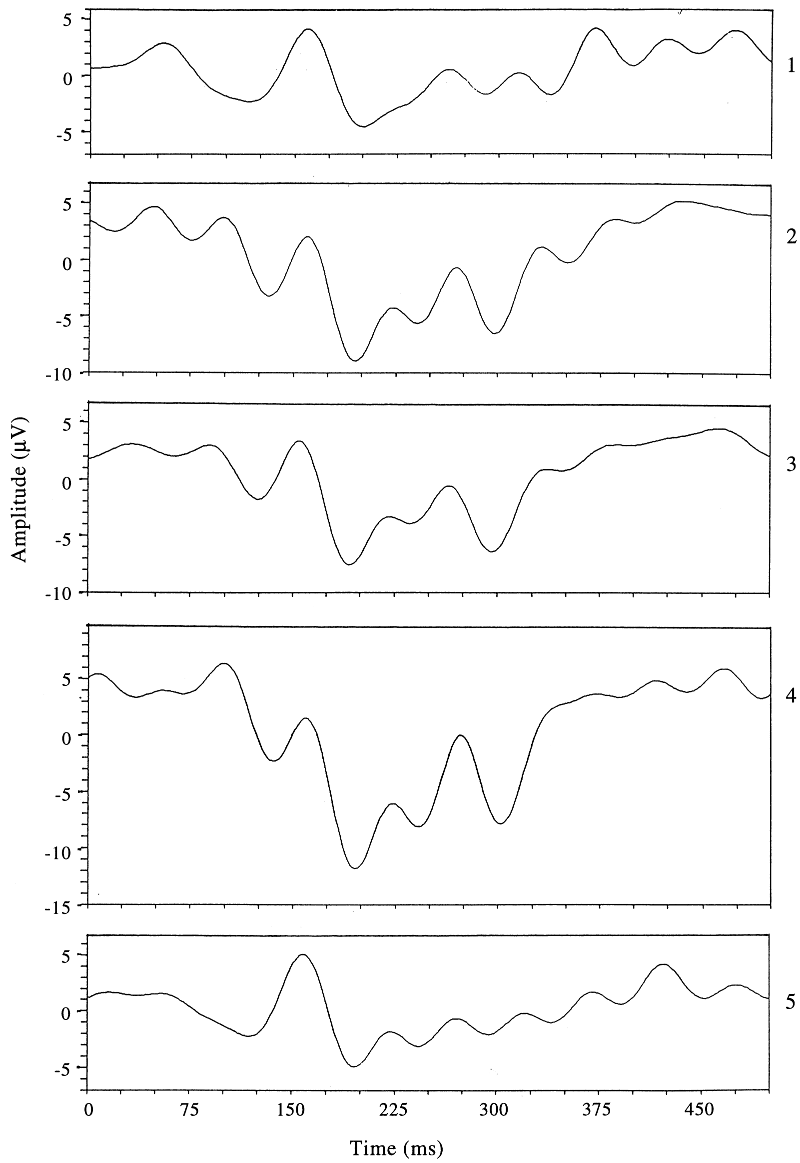

FIG. 4. The VEPs recorded at successive stages of Codetron treatment: (1) before Codetron stimulation; (2) during treatment, 5th minute; (3) during treatment, 20th minute; (4) 15 min after treatment; (5) 60 min after treatment.

processing technique is a powerful tool for the evaluation of central nervous system changes under different conditions. Based on the data obtained, we expect the developed EEG–CEP system to provide useful correlates for both the evaluation of stress-induced changes and the correction of stress-related organism states via Codetron stimulation.

CONCLUSION

Various physical agents and sensory stimuli can induce enhanced physiological effects. Humans and animals are particularly sensitive to low frequency sensory stimulation and/or to low frequency modulation of physical factors due to evolutionary developed non-specific CNS response mechanisms.

Different organism systems are characterized by their endogenous rhythms. These rhythms could be modulated by numerous external factors including low frequency sensory stimulation. Under certain circumstances, the interaction between different external periodic stimulation and the endogenous rhythmic processes leads to their synchronization, resonance and possible metabolic transformations.

A particular role in the non-specific mechanisms of CNS reactivity to low frequency external stimulation is played by the endogenous rhythmic processes in the spectral EEG parameters of electrical brain activity. The most precise and informative processes can be revealed by dynamic high resolution EEG structure analysis. This structural analysis provides the user with an opportunity to observe a more detailed EEG spectrum and to establish both the individual EEG oscillator's distribution and their resonance activation patterns.

It is hypothesized that the maximal synchronization of sensory stimulation parameters with the frequencies of intrinsic EEG oscillators is an appropriate way to enhance the patient's CNS response to external stimuli. Since rhythmic EEG components have close interrelations with different physiological systems, these components could be utilized for sensory stimulation and treatment efficiency enhancement.

The above hypothesis seems to be supported by our preliminary data on biofeedback training with the amplitude of EEG oscillators as a voluntary feedback-controlled parameter, resonance therapy via sensory stimulation with intrinsic EEG frequencies, and automatic modulation of stimulation parameters by endogenous organism rhythms. It was shown that the utilization of non-specific CNS reactivity mechanisms and resonance EEG-based stimulation methods provides the opportunity to use individually adjusted parameters for sensory stimulation and treatment efficiency enhancement. These parameters could be derived from the frequency characteristics of individual EEG oscillators revealed by individual resonance activation patterns, or might be defined by synchronization of feedback-controlled stimulation with patient's intrinsic rhythms.

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