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Changes in Spontaneous Brain Bioelectrical Activity During Transcranial Electrical and Electromagnetic Stimulation

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The systems responses of the brain to therapeutic transcranial electrical and electromagnetic stimulation were studied and the neurophysiological criteria for assessing the efficacy of this treatment were identified using comparative clinical and experimental studies with analysis of spontaneous bioelectrical activity, along with assessment of behavioral and clinical measures. Study groups consisted of six patients with chronic post-traumatic unconscious states during courses of transcranial electrical stimulation and 17 intact Wistar rats subjected to transcranial electromagnetic stimulation. A relationship was found between the effects of transcranial stimulation and the initial level of intercenter interactions of brain bioelectrical activity assessed in terms of coherence. Hypersynchronization of biopotentials, identified as a major element in the reactivity to this type of stimulation, may be of the greatest value in the recovery of patients with cerebral pathology in cases with initially reduced levels of intercenter interactions in the absence of pathologically increased functional connections in the brain.

KEY WORDS: transcranial electrical and electromagnetic stimulation, intercenter coherence relationships.

Transcranial electrical and electromagnetic and, more recently, magnetic stimulation has received increasing use as a therapeutic approach in cases of CNS pathology [4, 8, 15, 20]. Data have been obtained demonstrating the efficacy of this type of stimulation in the treatment of mental disorders (schizophrenia, manic states, depression) [9], depressed consciousness [4, 20], motor and speech disorders after cerebral infarcts [1], etc. Data in the literature emphasize the similarity of the physical mechanisms of these types of stimulation (passage of an electric current through a nerve cell membrane induces its depolarization and alters its excitability – with the appearance and propagation of an action potential) [9] and the activatory nature of its influence. However, the systems responses of the brain to these stimulations have received insufficient study [17]; the indications for the use of therapeutic electromagnetic stimulation and the criteria for assessing outcomes are unclearly defined.

The aim of the present work was to study and compare changes in spontaneous brain bioelectrical activity during low-frequency transcranial electrical and electromagnetic stimulation to clarify the neurophysiological criteria for the efficacy of these treatments.

METHODS

Data from our own clinical and experimental studies in humans and animals were analyzed.

Dynamic studies were performed using six patients aged 18–53 years after severe craniocerebral trauma with prolonged (9–14 days) coma and, at the time of the first EEG study, in a long-term post-comatose unconscious state. Therapeutic transcranial electrical stimulation (TES) was performed 1.5–5.5 months after craniocerebral trauma and, according to histories given by relatives, in the absence of

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clear positive effects from other treatments [13]. Square-wave direct-current impulses at 30 Hz and strength 3–5 mA were passed from a special apparatus developed at the Gor'kii Research Institute of Traumatology and Orthopedics via electrodes placed on the frontal (negative pole) and mastoid (positive pole) areas. Stimulation sessions lasted 30 min and courses consisted of 10–20 sessions.

It should be emphasized that this electrode positioning, in which the role of the primary "target" of stimulation is the frontal regions of the hemispheres, is in accord with our previous data demonstrating a correlation between the level of functional activity of the frontal lobes of the hemispheres and the success of mental rehabilitation of patients with severe cerebral pathology [12], and is also in accord with the view of Grindel' that the uncoupled state of the hemispheres, particularly their frontal areas, provides one of the neurophysiological mechanisms of the chronic unconscious state [16].

Studies in patients included assessment of changes in clinical condition and mental and bioelectrical activity during the process of therapeutic electrical stimulation. EEG recordings were made from symmetrical occipital, central, frontal, and temporal cortical areas before and 1 h after the first session, in the middle of courses of TES, and after courses. In four cases, clinical and electrophysiological observations were continued over periods of 1.5–3 years after trauma.

Animal studies were performed using 17 intact male Wistar rats (obtained from the Stolbovaya animal supplier, Russian Academy of Medical Sciences) aged 3–6 months, which were subjected to stimulation using an Infita electromagnetic physiotherapy apparatus (sourced in Russia) [7], with daily 3-min sessions for seven days (stimulation conditions were adapted to the clinical, with corrections for animal size and lifetime). The probe was placed over the animal's head in the frontal area at a distance of about 1 cm, using a field strength of 1–2 V/cm. The stimulation frequency was 60–70 Hz, 1) because it was a multiple of the adaptive frequencies of the electrical activity in the brains of rats surviving and recovering successfully from local stem lesions (6–7 Hz) [14], and 2) with consideration o data obtained by Lebedev [8] on the positive influences of TES at 70 Hz in various types of human and animal pathology.

The behavioral effects of transcranial electromagnetic stimulation (TEMS) were analyzed by testing the animals in an open field before and one day after courses of stimulation. In the open field test, counts were made over 5 min of the numbers of squares crossed, vertical rearings, excursions, and crossings of the center of the open field, along with the numbers of urinations, defecations, and grooming reactions. Data were analyzed statistically using the non-parametric Wilcoxon test for linked pairs.

In six rats, chronic recordings of brain electrical activity (EA) were made from symmetrical orbitofrontal areas of the cortex, hippocampal field CA1, and the stem at the level of the lateral vestibular nucleus of Deiters. TEMS was started one week after implantation of electrodes, when the baseline pattern of EA had stabilized and rats showed no behavioral or neurological abnormalities. During the first and second stimulation sessions, the bioelectrical effects of TEMS were compared with the effects of a placebo (complete reproduction of the experimental conditions and application of the probe to the animal's forehead but without stimulation). Comparisons were made of EA in baseline conditions, during treatment, and 30 and 60 min after each treatment.

Animal experiments were performed in accord with humanitarian principles laid out in European Community Directive 86/609/EC and approved by the Ethics Committee of the Institute of Higher Nervous Activity and Neurophysiology of the Russian Academy of Sciences.

Visual and spectral coherence analysis of brain bioelectrical activity was performed in both series of studies using the Neirokartograf program from MBN (Russia). Coherence relationships were calculated from all combinations possible for the experiments concerned. Data were analyzed statistically using a program written by V. G. Voronov and O. M. Grindel' to perform the non-parametric Mann–Whitney test [3]. In patients with craniocerebral trauma, quantitative EEG characteristics before and after courses of stimulation were compared with the corresponding normative data (from a group of 53 healthy subjects).

RESULTS

Studies of the *clinical effects* of TES in severe craniocerebral trauma showed that treatment in five of the six patients produced positive changes. All patients showed the appearance of emotional reactions (changes in facial expressions in response to various external events, appearance of mimicry or vocalization) and fixation of gaze. Four patients also showed the recovery of verbal contact. The greatest clinical effects were seen 10–14 days after stimulation [13].

These changes in condition were accompanied by phasic *rearrangements of the EEG and its coherence*: there were sequential significant increases in relationships as compared with baseline – initially in the slow (delta-theta1) rhythms and in the anterior areas, then at higher (alpha-beta)family frequencies and in a generalized distribution (Fig. 1). The most clear and stable were increases in inter-hemisphere relationships (especially frontal) and relationships in the left hemisphere.

Stimulation in patients with initially subnormal levels of EEG coherence was the most successful. For example, TES transferred patient P, aged 23 years and experiencing coma for 12 days, from the vegetative state to mutism with increased orientation; by one month after stimulation she demonstrated emotional responses and followed simple instructions (Fig. 2).

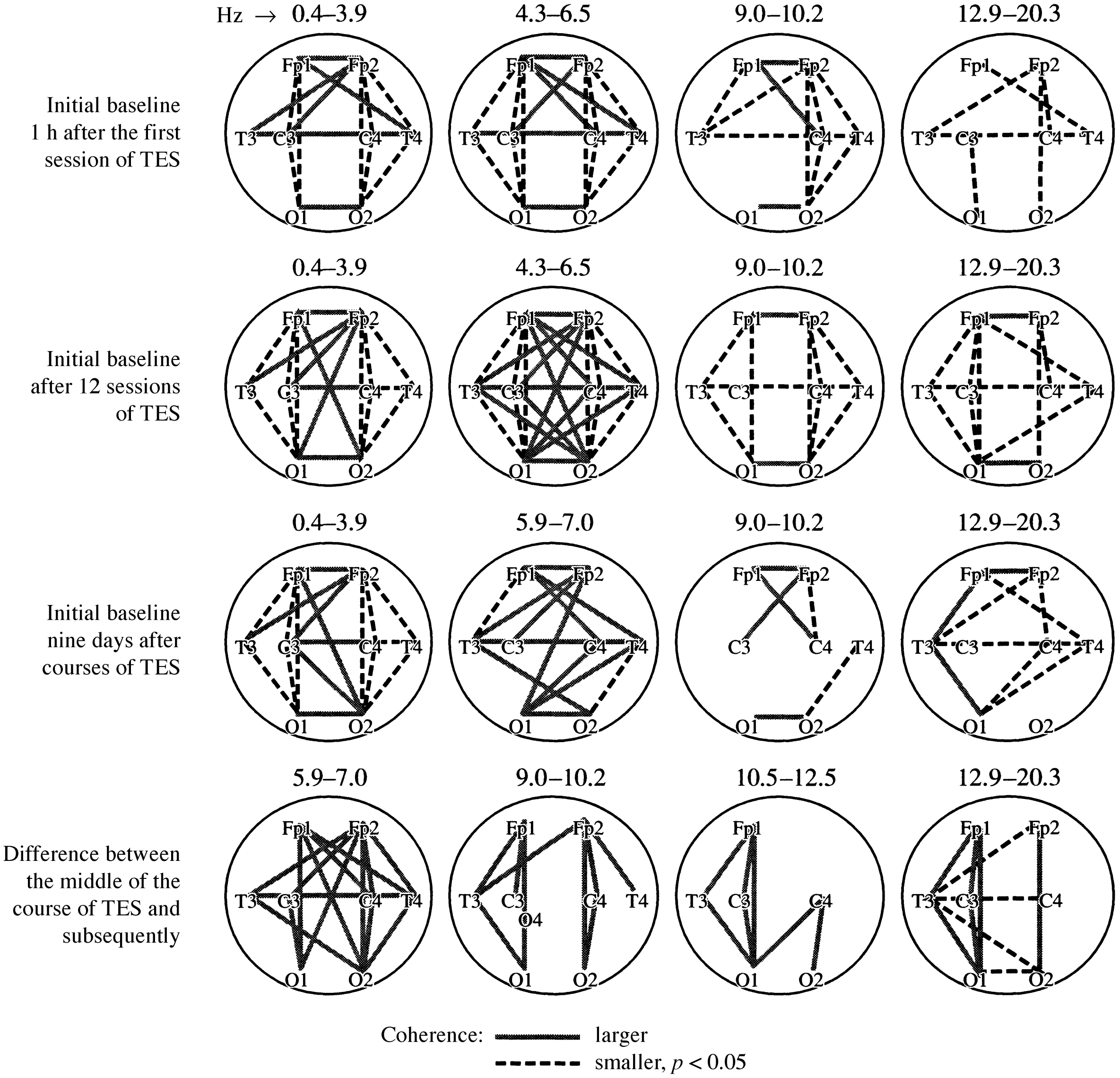

Fig. 1. Significant changes in EEG coherence in patients with post-traumatic unconscious states during and after courses of transcranial electrical stimulation.

While initial abnormalities in EEG coherence were in different directions, weakened relationships (usually interhemisphere) were strengthened and pathologically increased relationships either did not change or increased. This latter type of EEG response was seen in the single case in which TES was followed by a negative clinical effect. Differently directed shifts in weakened interhemisphere EEG relationships were seen 1 h after the first stimulation session, with clear increases in initially increased (mainly affecting the slow and beta1 rhythms) intrahemisphere coherence, particularly on the left. Clinically, this was accompanied by increases in convulsive myoclonic twitching which, over one day, became continuous; electrical stimulation was withdrawn.

In experimental behavioral studies on rats, courses of TEMS were followed by decreases in movement and investigative activity – most significantly ($p = 0.005$) for the number of vertical rearings in the open field. some rats also showed changes (increases) in emotionality.

These results, which were quite unexpected, received some explanation during the electrophysiological investigations.

The electrophysiological response of the rat brain to electromagnetic stimulation appeared in response to the first session of TEMS and consisted of a defined, sometimes phasic, rearrangement of the temporospatial organization of EA. Stimulation was followed by a significant increase in the power of biopotentials in most of the brain areas recorded,

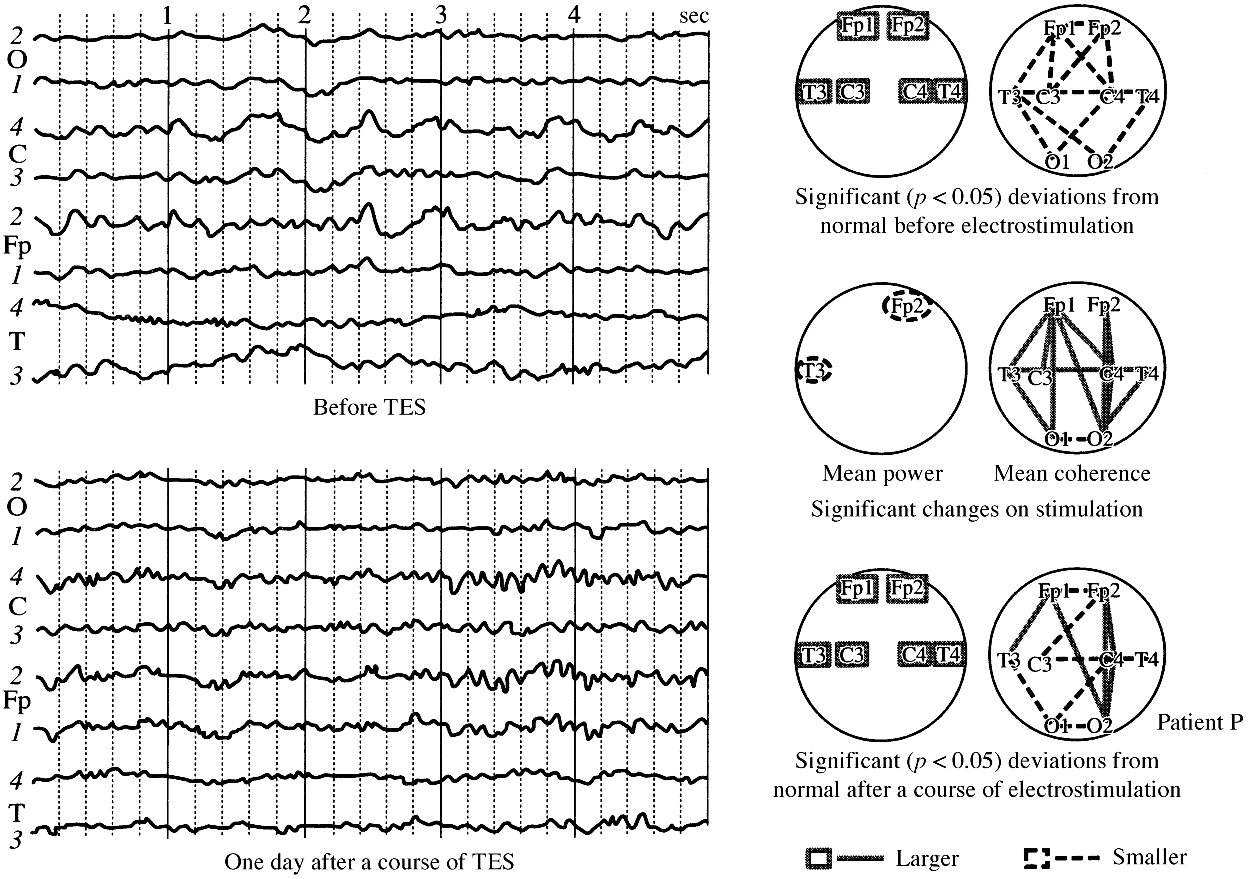

Fig. 2. EEG recordings are different points during a course of transcranial electrical stimulation in a case with positive changes in the state of a patient with severe craniocerebral trauma.

with synchronization of the major baseline EA rhythms – to the extent that bursts of exalted epileptiform activity appeared, maximally in the hippocampus (Fig. 3, *A*, *B*). This corresponds to a significant increase in interactions between the cerebral areas studied (in terms of the coherence of EA) of both symmetrical (at the level of the stem, hippocampus, and cortex) and unilateral (predominantly the stem-hippocampal) areas of the brain (Fig. 3, *B*). Significant EA differences between the effects of TEMS and placebo were seen not during treatment but were present 30–60 min after each type of treatment.

The tendency to a gradual increase in intercenter relationships with an increase in mean EA power persisted throughout the entire course of TEMS – to two or more weeks after the end of treatment, affecting both the slow (delta, theta) EA rhythms characteristic of the animals' initial state and the higher-frequency (alpha and particularly beta) rhythms (Fig. 4). The neurodynamic changes started to revert one week after courses of TEMS, with relative decreases in individual (mainly symmetrical stem) coherence relationships. The most stable tendency to increases in relationships (up to three weeks after stimulation) was characteristic for the symmetrical orbitofrontal areas over a wide range of frequencies, as well as for the left half of the brain. A clear similarity could be seen between the rearrangements in EA seen in rats treated with TEMS and EEG changes in patients treated with TES.

DISCUSSION

The approach used here, consisting of comparison of clinical and behavioral features of the study state with the characteristics of the temporospatial organization of spontaneous brain bioelectrical activity, was productive in terms of identifying and assessing functional changes in transcranial stimulation of the brain. It should be noted that other studies in this direction have generally used such measures of brain functional activity as evoked potentials, particularly the P300 component of the acoustic evoked potential [4, 18], functional MRI [19], and psychological test results [1, 17]. Use of the EEG is particularly interesting in terms of its spectral characteristics [1, 4].

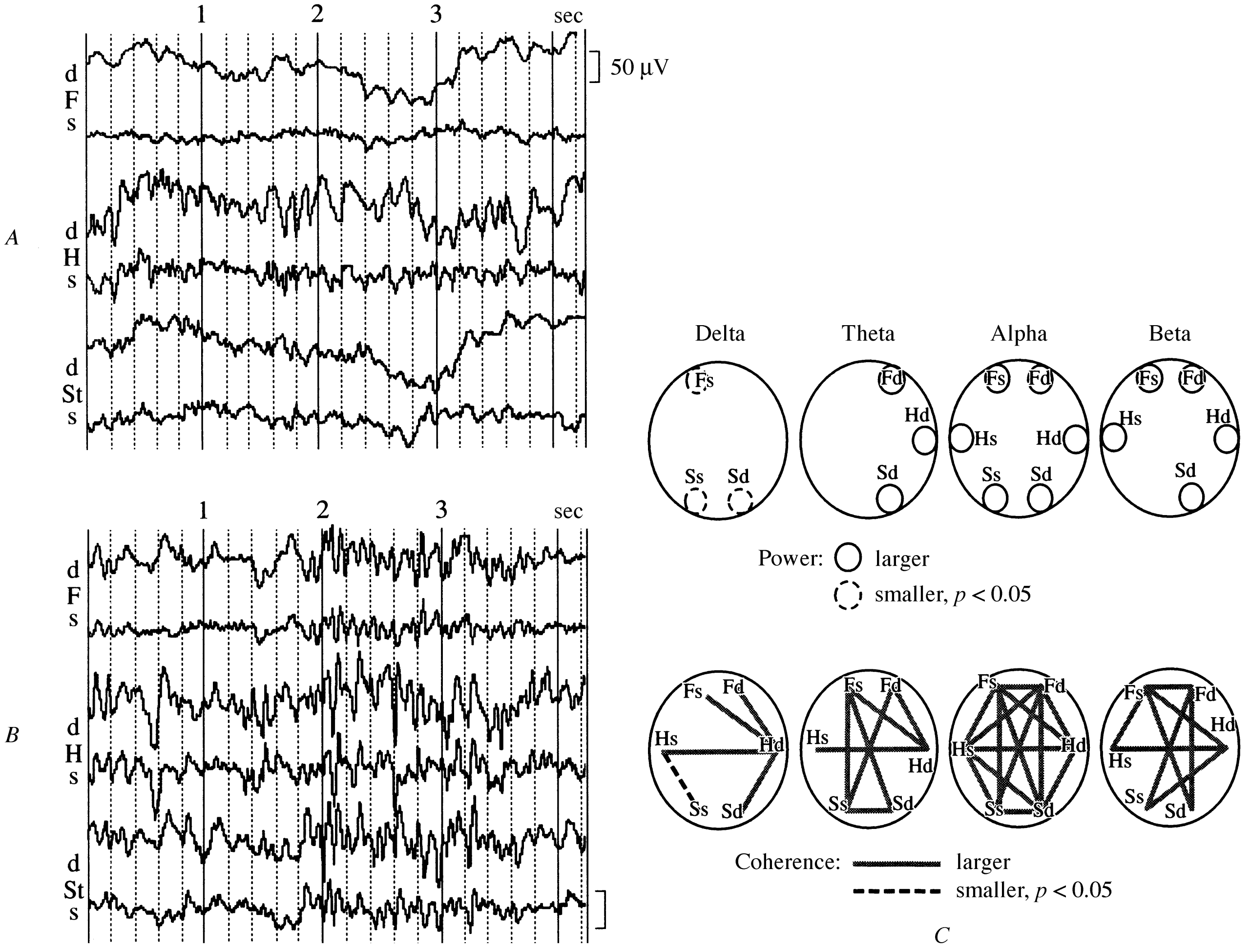

Fig. 3. Changes in brain electrical activity (EA) in an intact rat 60 min after the first session of TEMS. *A*) Baseline EA; *B*) EA 1 h after TEMS at a frequency of 60 Hz; *C*) spectral (upper plots) and coherence (lower plots) characteristics of EA showing significant ($p < 0.05$) changes from baseline at 1 h. EA recording zones: F is the orbitofrontal cortex, H is the hippocampus, St is the stem at the level of the lateral vestibular nuclei of Deiters. s = left, d = right.

The present study showed that changes in the dynamics of brain bioelectrical activity under the influence of TES and TEMS were in the same direction in both the clinical and the experimental investigations; stimulation led to marked changes in intercenter coherence relationships, most changes being increases.

Comparison of our data from the two series of experiments indicates that there is a relationship between the functional effects of transcranial stimulation and the initial level of intercenter interactions in brain bioelectrical activity. The positive clinical influences of TES in most patients, with increases in the extent of activity mainly in the emotional and motor spheres, were more marked in patients with initially subnormal levels of EEG coherence. TEMS in intact animals, which had an initially high levels of intercenter coherence relationships, led to further and inappropriate increases, which were accompanied by decreases in movement and investigative activity. These data are in agreement with the views of Rusinov and his adherents [2] that deviation from the individual optimum level of cerebral intercenter interactions in either direction is linked with suppression of the individual's local or overall functional activity.

These results support and develop Kholodov's conclusions on the influences of the initial functional state of the CNS on the outcome of magnetic stimulation [11]. We suggest that an objective criterion for assessing the initial state of the brain and its reactive shifts in response to different types of transcranial stimulation may be provided by the coherence of brain bioelectrical activity. Hypersynchronization of biopotentials, identified as an important non-specific neurophysiological element of reactivity to this type of stimulation, may facilitate the recovery of patients with cerebral pathology in cases with initially decreased levels of intercenter interactions in the absence of any pathologically increased functional relationships in the brain.

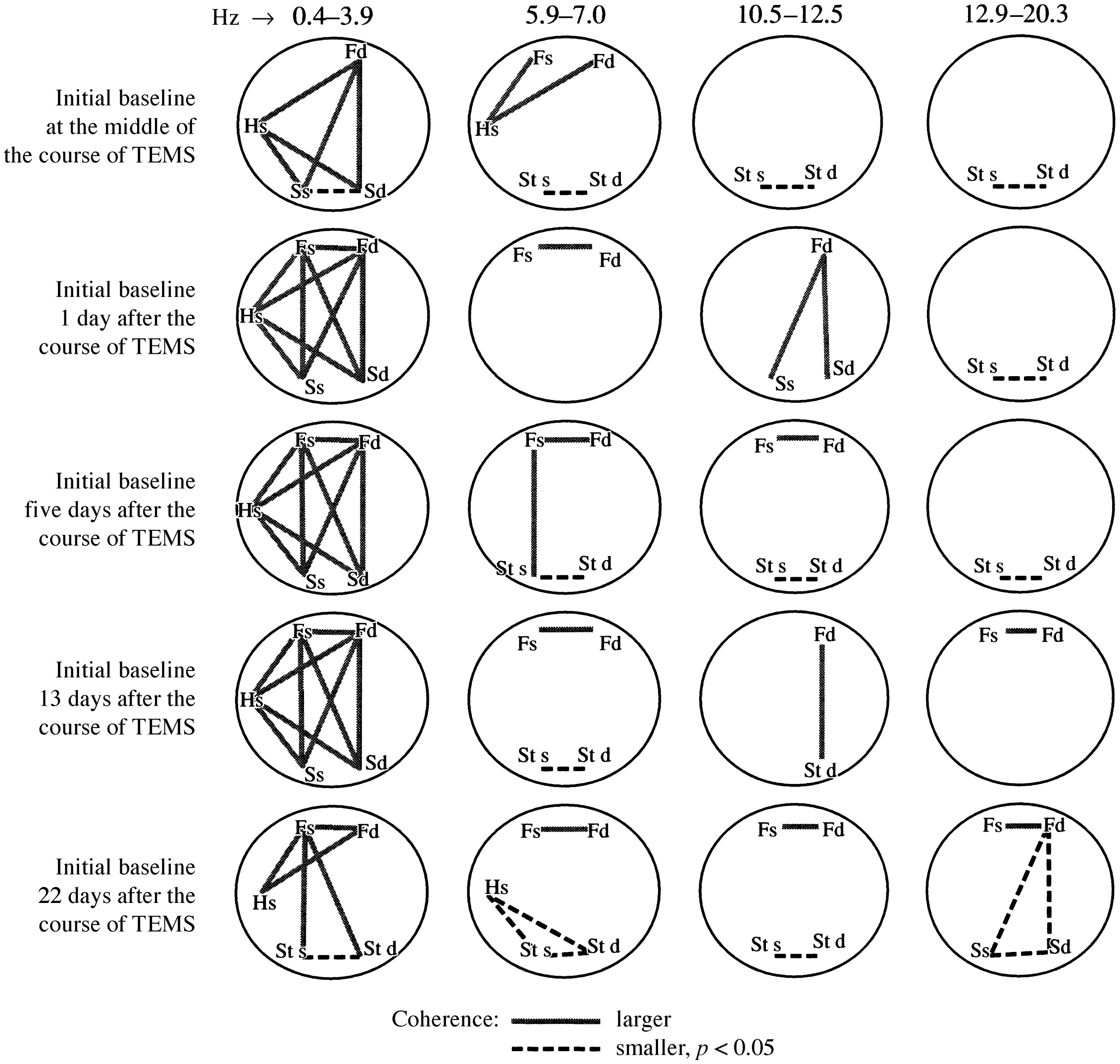

Fig. 4. Significant changes in the coherence of brain EA during and after a course of TEMS.

However, this is not to deny the relationship between the behavioral and clinical effects of electrical and magnetic stimulation and its frequency which have been noted in many studies [6, 9]. The frequencies used in our two sets of observations were different – 30 and 60 Hz. Lebedev's data on the analgesic and anti-stress effects of TES at 70–80 Hz [8] suggest that stimulation at 60–70 Hz is characterized by a more marked sedative influence.

What happens to the electrical activity of neurons in the brain during exposure to these types of stimulation? Although the models considered above do not allow this question to be addressed, we have obtained a partial answer to this question in experiments on neurons from the mollusks *Helix pomatia* and *Helix lucorum* [5, 10]. Pacemaker neurons in the these mollusks, which in normal conditions demonstrate rhythmic activity, were subjected to various types of treatment (electric shock, creation of a penicillin focus, or seasonal inactivation), and these were found to inactivate spike generation without altering the membrane potential. "Treatment" was performed by delivering intracellular impulses of depolarizing or hyperpolarizing current. The results of these experiments showed that the electrical activity of these neurons could be restored when the electrical stimulation satisfied the following criteria: 1) it had to be rhythmic (constant currents were ineffective, while a rhythmic electrical hyperpolarization current at 0.3–2 Hz was effective; a depolarizing current of the same frequency led to the generation of action potentials during impulse application, but this did not continue after stimulation ended); 2) the rhythmic hyperpolarizing current was particularly effective when *individually selected* stimulation parameters were used, including total duration of stimulation, stimulation frequency, individual impulse duration, and current strength. The following parameters for the rhythmic hyperpolarization electrical current were effective in the experiments: strength 0.45–8.5 nA, impulse duration 50–200 msec, and total stimulation duration 30 sec to 3 min. Hyperpolarizing rhythmic stimulation led to the restoration of the electrical activity of neurons, which persisted beyond the end of the "treatment."

The results obtained from studies on mollusks led to the suggestion that the therapeutic effect of electrical stimulation on brain macrostructures is associated with the restoration of the rhythmic activity of neurons with an endogenous generator. Triggering of the pacemaker activity of these generator neurons is responsible for the subsequent normalization of the electrical activity of the neurons associated with them.

CONCLUSIONS

1. Therapeutic transcranial electrical stimulation of the frontal lobes has positive influences on brain bioelectrical activity in patients in a post-traumatic vegetative state, with positive changes in the mental and motor spheres.

2. Studies of the reactions of the brain to low-frequency transcranial electromagnetic stimulation in clinical and experimental conditions provided evidence that the most important element of reactivity to this type of stimulation was the hypersynchronization of biopotentials.

3. A relationship between the neurophysiological and behavioral effects of transcranial stimulation and the initial level of intercenter relationships in brain bioelectrical activity assessed in terms of coherence was identified.

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