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Cross-Correlation and Coherence Analysis of Electrocortigrams in Rats Subjected to Craniocerebral Trauma

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Craniocerebral trauma (CCT) is one of the leading causes of death and long-term loss of work capacity among the young population of both the Russian Federation and other countries. The development of adequate and reproducible models of CCT in laboratory animals and objective methods for assessing the extent of neurological impairments gives cause for optimism in seeking and studying new and effective neurorehabilitation approaches. The aim of the present work was to carry out a comparative cross-correlation and coherence analysis of electrocorticograms from presumptively healthy rats and animals subjected to CCT. After initial trepanning, open penetrating CCT was modeled by controlled cortical impacts applied to the motor cortex of the left hemisphere. Nichrome corticographic recording electrodes were implanted bilaterally in the primary and secondary motor cortex and in the primary somatosensory cortex (above the hippocampus). Electrocorticograms were recorded on days 3 and 7 after surgery in the home cage and in the resting state. Cross-correlation analysis consisted of computing the cross-correlation coefficient, the mean frequency, and the maximum span in the cross-correlation function. Mean coherence power levels for the δ, θ, α, and β rhythms were computed for pairs of leads. Unilateral traumatic damage to the motor cortex and underlying structures led to impairment to the operation of interhemisphere and intrahemisphere connections and these changes were seen not only in the impact area, but also in distant parts of the cortex on post-trauma days 3 and 7. These changes in ECoG cross-correlation and coherence parameters occurring in rats as a result of CCT were similar to those seen in patients in clinical practice, so it can be suggested that this experimental model can be used for neurophysiological and pharmacological research.

Keywords: craniocerebral trauma, controlled cortical impact, electrocorticogram, cross-correlation analysis, coherence analysis.

Craniocerebral trauma (CCT) has long been one of the most frequent CNS pathologies and affects the most socially active part of society – young and middle-aged people, leading to loss of work capacity, disability, and death [1]. Medication therapy in severe CCT during the acute phase is directed to settling cerebral edema and intracranial hypertension and preventing the development of early convulsive seizures. Diuretics, glucocorticoids, and anticonvulsant medications are used successfully for these complications and are the standard in clinical guidelines [2]. However, neurological disorders, among which, for example, motor disorders and/or degradation of cognitive functions are common, are not particularly susceptible to drug treatment. Drugs with neuroleptic (cerebroprotective) actions directed at reducing the severity of neurological deficit are rarely included in existing standard treatment because of the lack of evidence for clinical effects [3]. Thus, the search for new substances able to increase neuron survival after CCT, thus improving patient's functional status, is an important task in neuropharmacology. The successful search and study of new potential neuroprotective substances requires adequate experimental models of

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CCT and other CNS pathologies with pathogenetic similarity with real clinical situations. Furthermore, it is important to have methods and criteria for objective assessment of the efficacy of one or another drug in experimental conditions.

The severity of neurological impairments in experimental animals and the efficacy of one or another neuroprotector can be assessed using behavioral/functional tests [4–6] and biochemical [4, 7] and histological [8] methods. These are widely used in neuropharmacological research, though each approach has its drawbacks. For example, behavioral/functional tests are often subjective, and depend to a large extent on external factors, such that the results are difficult to interpret. Biochemical and histological studies require expensive apparatus and consumables, and it is generally the case that the animals used can only be studied once.

In clinical practice, a very important factor in the management of patients with CCT is complete and accurate diagnosis, in relation to both neuroimaging methods (MRI scans, CT scans, PET scans) and neurophysiological (electroencephalography (EEG) and event-related potentials) methods [9]. The EEG allows detection of impairments in mild CCT, when morphological changes are minor, predicts the outcome for patients in coma, and can be used in children [10]. This method is simple and noninvasive and provides for assessment of the course of illness at follow-up. More widely used in experimental studies in laboratory animals is the method of recording brain biological activity directly from the cortex, i.e., electrocorticography (ECoG) [11–13].

Mathematical analysis of the EEG/ECoG provides and assesses various electrophysiological parameters of the brain. One leading method consists of EEG correlation analysis, which was used for analysis of the earliest paper EEG traces, with calculations performed by hand. This approach includes autocorrelation (analysis of the interaction of parts of a single signal) and cross-correlation (analysis of the interaction of different signals) methods. The cross-correlation function reflects the extent of connections in processes at different points of the brain by extracting periodic components common to two EEG recordings. The extent of correlation is expressed as the correlation coefficient in the range –1 (antiphase EEG) to +1 (EEG traces identical) [14]. The development of computer technologies has a lowed correlation analysis to significantly displace coherence analysis, which allows the level of similarity of two oscillatory electrophysiological processes in two or more parts of the brain to be determined [15]. Correlation and coherence coefficients change values in various pathologies (for example, Alzheimer's disease, depression, CCT) and can indirectly characterize mental capacity [16]. This allows correlation and coherence analysis to be used for the diagnosis of CCT and prognostication of its course, and also for assessment of the influences of various medications on the course illness. We have suggested that correlation and coherence analysis in an experimental model of CCT in rats could be used to identify potential neuroprotective effects of novel drugs at the preclinical study stage. However, confirmation of this hypothesis requires initial determination of the extent to which measures of ECoG cross-correlation and coherence values provide evidence of organic brain lesions in rats with CCT. In addition, there is a need to evaluate whether these changes are analogous to those seen in patients in clinical practice.

Thus, the aim of the present work was to identify typical changes in electrocorticogram cross-correlation and coherence parameters in rats subjected to CCT as compared with presumptively healthy animals in a pilot experiment.

Methods. Studies were carried out in compliance with the principles of the Basel Declaration, Russian Federation Ministry of Health Order No. 199n of April 1, 2016, "Approval of Regulations for Good Laboratory Practice," and the recommendations of the Bioethics Committee of the St. Petersburg State Chemicopharmaceutical University, Russian Ministry of Health. Rats were kept in standard animal-house conditions on a standard diet with free access to water. All experimental and control animals were from a single batch and were quarantined for 14 days.

Experiments were carried out using 10 white mongrel male rats weighing 250–300 g obtained from the Rappolovo Laboratory Animal Supplier (Leningrad District). Each animal was given an identification number and was assigned to one of two groups – presumptively healthy (normal) and CCT – by randomization using random numbers. Each experimental group consisted of five animals.

Corticographic electrodes were made of nichrome wire of diameter 0.5 mm (for the recording and reference electrodes) and diameter 0.16 mm for the ground electrode. Insulation was with heatshrink tubing and the length of the recording (noninsulated) part was ≈1 mm. All electrodes were combined into a nest using a BLS-8 cable with a step of 2.54 mm.

For surgical manipulations, animals were first anesthetized with chloral hydrate (400 mg/kg). Before surgery, Opththagel (Santen OY, Finland) was placed in the eyes to prevent corneal drying. After preparation of the skull surface (removal of the muscular-fascial layer and periosteum, coagulation of bleeding points), openings of the appropriate diameters were drilled for the electrodes and fixing screws (screw insertion depth <1 mm). Heating of the brain was prevented by drilling with short intervals. Rats of the presumptively healthy group then underwent implantation of corticographic electrodes and insertion of fixing screws into the corresponding openings, while animals of the second group were first subjected to modeling of craniocerebral trauma as described previously [6, 17]. Animals underwent trepanning of the skull in the left frontal part over the zone of the sensorimotor cortex. The center of the trepanned opening was positioned 2.0 mm rostral and 1.5 mm medial to the bregma. After this a mobile steel piston of diameter 3 mm with a travel of 4 mm was placed in the trepanned opening and this was impacted from a height of 10 cm by a weight of mass 50 g sliding in a steel tube. The drilled

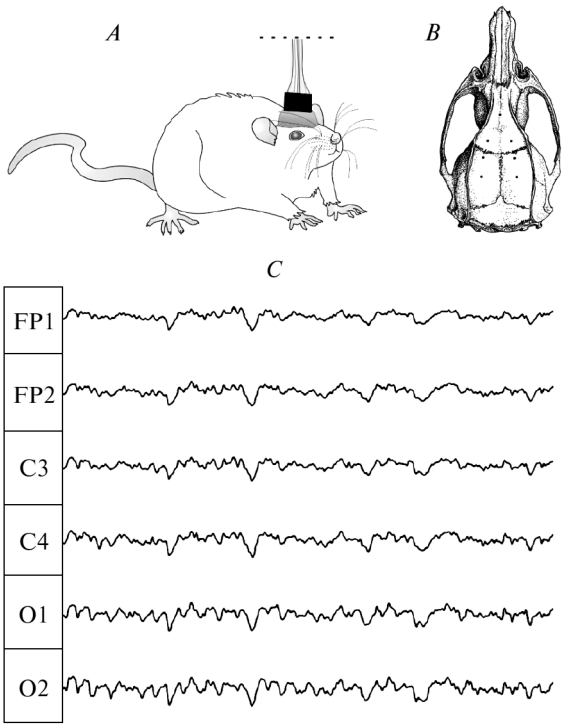

Fig. 1. *A*) External view of rat with implanted electrodes during ECoG traces. *B*) Diagram showing locations of recording (FP1, FP2, C3, C4, O1, and O2) and reference (Ref) electrodes. *C*) Example of an electrocorticogram recording from a healthy at in the resting state.

plate was returned to its position, the electrodes were implanted, and the fixing screws were inserted. The coordinates of the electrodes were determined using the Paxinos and Watson stereotaxic atlas of the rat brain [18]. Electrodes FP1 and FP2 were positioned in the area innervating the forelimb (secondary motor cortex, AP = +2.0, ML = 1.5, DV = 1.0), C3 and C4 were placed in the area innervating the hindlimbs (primary motor cortex, AP = –1.0, ML = 2.0, DV = 1.0), and O1 and O2 were placed over the hippocampus (primary somatosensory cortex, AP = –4.0, ML = 2.0, DV = 1.0) (Fig. 1, *B*). The selection of the specific recording points was due to the fact that we additionally recorded and analyzed somatosensory event-related potentials in these animals (electrodes FP1, FP2 and C3, C4 on stimulation of the median and sciatic nerves, respectively), as well as hippocampal activity during exploratory behavior (electrodes O1 and O2). The reference electrode was placed in the nasal bone and the ground electrode beneath the skin of the neck. Additional fixation of the construct to the skull was with Villacryl C dental cement (Zhermack, Italy). The skin incision was then sutured and the sutures and surrounding areas were treated with antiseptic.

After surgery, rats were kept in individual cages with free access to water and feed throughout the study period. Animals' status was followed immediately after recovery from anesthesia and then daily morning and evening and sutures were treated with iodine solution when necessary. To avoid dehydration, rats were given s.c. physiological saline during the first three days after surgery. We consciously avoided use of antibiotics, analgesics, and anti-inflammatories because most of these can to some extent or other influence the course of pathological processes in traumatic brain injury, thus distorting the study results.

Corticographic activity was recorded on post-operative days 3 and 7 using a Neiron-Spektr-1 eight-channel encephalograph (Neurosoft, Russia) with a bandpass of 0.5–35 Hz and a sampling frequency of 500 Hz. Selection of test time points was based on the need to assess the functional state of the brain in injured rats during the acute (day 3) and intermediate (day 7) post-CCT periods.

Trace segments were selected from 5-min corticograms on the basis that the test animal was in the calm waking state (absence of movement or exploratory activity, absence of grooming). Cross-correlation and coherence analysis was then run, after which the results from the two experimental groups were compared. Analysis epoch duration was 5 sec. Cross-correlation analysis consisted of computation of cross-correlation coefficients (C_{Cr}) for the electrode pairs FP1–C3, FP2–C4, C3–O1, C4–O2, FP1–FP2, C3–C4, and O1–O2, as well as the mean frequency (Hz) and maximum span of the cross-correlation function (CCF, μV). Mean coherence power levels in the δ (0.5–4.0 Hz), θ (4.0–8.0 Hz), α (8.0–14.0 Hz), and β (low-frequency (LF) 14.0–20.0 Hz; high-frequency (HF) 20.0–35.0 Hz) ranges were computed for the same pairs of leads.

On day 7, after all experiments were complete, animals were euthanased with CO_2. Extracted brains were fixed in 10% neutral formalin for 24 h. For histological studies, brains were dissected such that the vertical section passed through the middle of the focus of the traumatic lesion and the corresponding sectors of the contralateral hemisphere. Tissue samples were cut into plates of thickness 0.2–0.3 cm. The resulting tissue samples were prepared histologically and immersed and embedded in paraffin using standard methods. A rotary microtome was used to cut sections from paraffin blocks, loaded onto slides, and stained with hematoxylin and eosin, after which they were dehydrated and embedded under cover slips. Histological preparations were fully scanned in their entirety using a laboratory scanning system with Panoramic MIDI image processing software (3D Histech Kft, Hungary).

Data were analyzed statistically in GraphPad Prism 7.00. Data are presented as mean ± standard error of the mean. The classical version of cross-correlation analysis was used, based on computation of Pearson cross-correlation coefficients with subsequent averaging [19, 20] despite the fact that there are other approaches to this analysis [21]. Significant differences were identified using the nonparametric Mann–Whitney U test. Differences were regarded as significant at $p < 0.05$.

Results. These experiments showed that presumptively healthy rats displayed a relationship between rhythmic

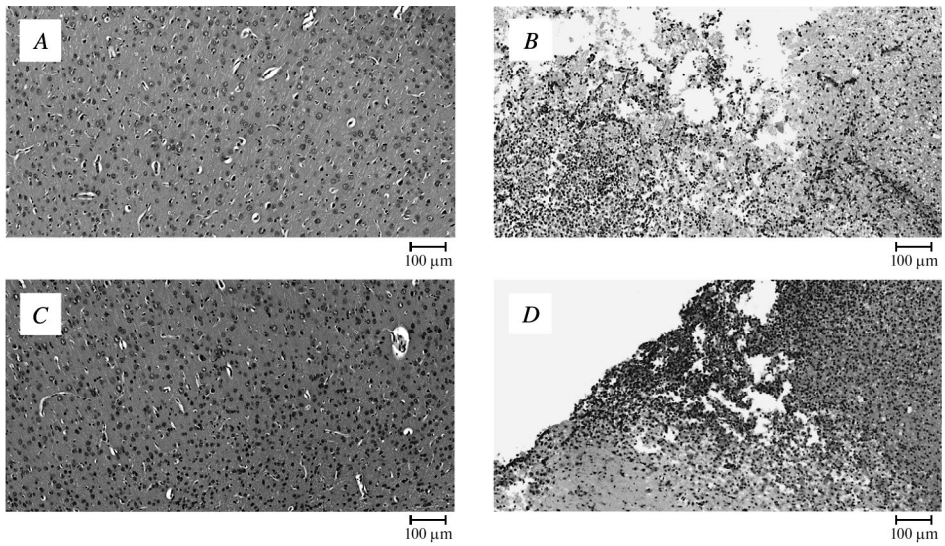

Fig. 2. Pathomorphological picture of lesion focus in rat brain on post-CCT days 3 and 7. *A*) Cortex of healthy hemisphere of an injured animal on post-trauma day 3; *B*) cortex of healthy hemisphere of an injured rat on post-trauma day 7; *C*) cortex of injured hemisphere of an injured rat on post-trauma day 3; *D*) cortex of injured hemisphere of an injured rat on post-trauma day 7. See text for explanation.

bioelectrical processes occurring in different areas of the cerebral cortex. The largest C_{Cr} values, this being the quantitative measure of the functional connection between any two leads, were seen between the following pairs of leads: FP1–FP2, C3–C4, O1–O2, FP1–C3, and FP2–C4. Mean values for these pairs ranged from 0.87 to 0.92 on both day 3 and day 7 after surgery. Somewhat smaller C_{Cr} values were recorded between electrode pairs C3–O1 and C3–O2, from 0.77 to 0.8 (Fig. 3, *B*). Mean coherence power levels in the δ, θ, α, and β rhythms also changed in a similar way – pairs with the smallest C_{Cr} values also had small coherence values. Pathomorphological changes in the injury zone (Fig. 2) on post-trauma day 3 consisted mainly of damage processes apparent as formation of zones of necrosis with severe perifocal edema, spreading exudative cellular reactions, and spreading glial reactions in brain tissue around focal injuries. On post-trauma day 7, significant decreases in the content of necrotic detritus were noted in the injury zone, with development of a marked exudative cellular reaction in this zone, decreases in edema, and formation of a perifocal zone of severe gliosis of brain tissue. Tissue in the contralateral hemisphere of the brain did not display structural changes.

Traumatic damage to the motor cortex and underlying areas in rats led to statistically significant decreases in C_{Cr} for electrode pairs FP1–FP2, C3–C4, and O1–O2 (interhemisphere connections) by a mean of 33% ($p < 0.05$ and $p < 0.01$) on day 3 and 19% ($p < 0.05$ and $p < 0.01$) on day 7. In addition, animals with CCT had a lower C_{Cr} in pair C4–O2 as compared with presumptively healthy animals: by 21% ($p < 0.01$) on day 3 and 23% ($p < 0.05$) on day 7 after trauma (Fig. 3, *A*, *B*). Mean CCF frequency was also different in rats with CCT: there was a mean one-third decrease in this value ($p < 0.05, p < 0.01$) for electrode pairs FP1–FP2, C3–O1, and C4–O2, with gradual restoration to the level in presumptively healthy animals by post-trauma day 7 (Fig. 3, *C*). Another indicator of cross-correlation which also changed in rats as a result of CCT was the maximum span of CCF. In traumatized animals, this value was smaller than in normal animals on day 3 (by a mean of 67% for all leads, $p < 0.05$ and $p < 0.01$, respectively) and day 7 (by 45% for all leads, $p < 0.05$ and $p < 0.01$, respectively) on day 7 (Fig. 3, *D*).

Craniocerebral trauma had similar effects on coherence in the rhythms of interest. For example, the CCT group on post-trauma day 3 showed statistically significant decreases in the mean amplitude of coherence power in the δ, θ, and α rhythms, by 12% ($p < 0.05, p < 0.01$) for lead pairs FP1–FP2, C3–C4, and O1–O2 (interhemisphere connections). Analogous changes in the operation of interhemisphere connections, though less marked in the trauma zone, were also detected in the β-LF and β-HF rhythms (Fig. 4). Mean coherence power in the rhythms characterizing intrahemisphere connections (FP1–C3, FP2–C4, C3–O12, and V4–O2) also decreased, the most marked changes being seen in the coherence of the δ rhythm (Fig. 4). These changes were recorded in traumatized rats on post-operative day 7, with a tendency to a slow spontaneous recovery of mean coherence power levels to normal values (Fig. 4).

Discussion. The CCT model used here produced damage to both the motor cortex and the underlying parts of the brain, particularly the striatum and corpus callosum [22]. At present there is no standard means of classifying injury severity in experimental models of CCT (mild, moderate, severe), though in clinical practice severe brain contusion (accompanied by disruption of brain tissue and meningeal tears) is taken as severe CCT [23]. In addition, previous studies have shown that rats with this model of trau-

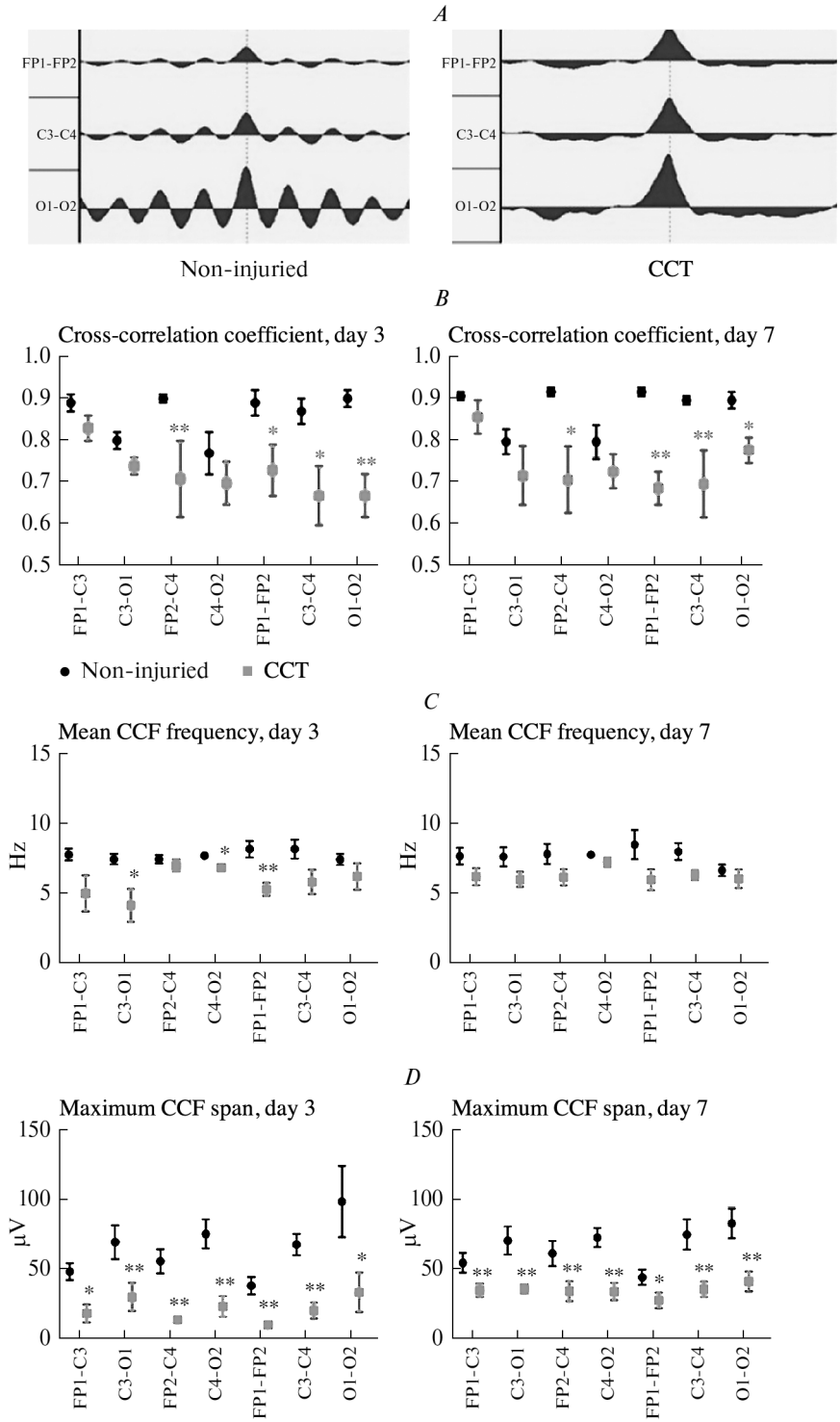

Fig. 3. Example plots of cross-correlation functions of electrode pairs FP1–FP2, C3–C4, and O1–O2, in presumptively healthy (normal) and injured (CCT) rats. *B*, *C*, *D*) Cross-correlation coefficients (C_{Cr}), mean CCF frequency, and maximum span of CCF for electrode pairs in rats of the presumptively healthy (normal) and injured (CCT) groups on post-operative days 3 and 7. $^{*}p < 0.05$, $^{**}p < 0.01$ – statistically significant differences compared with the presumptively healthy group.

ma produce severe neurological deficit, apparent as severe reductions in total movement and exploratory-investigative activity in the open field test on day 3 after injury [5, 6]. These animals also showed stable motor disorders, seen in the cylinder, beam walking, staircase, and paw placement tests on post-injury days 3 and 7 [4–6]. In addition, analysis

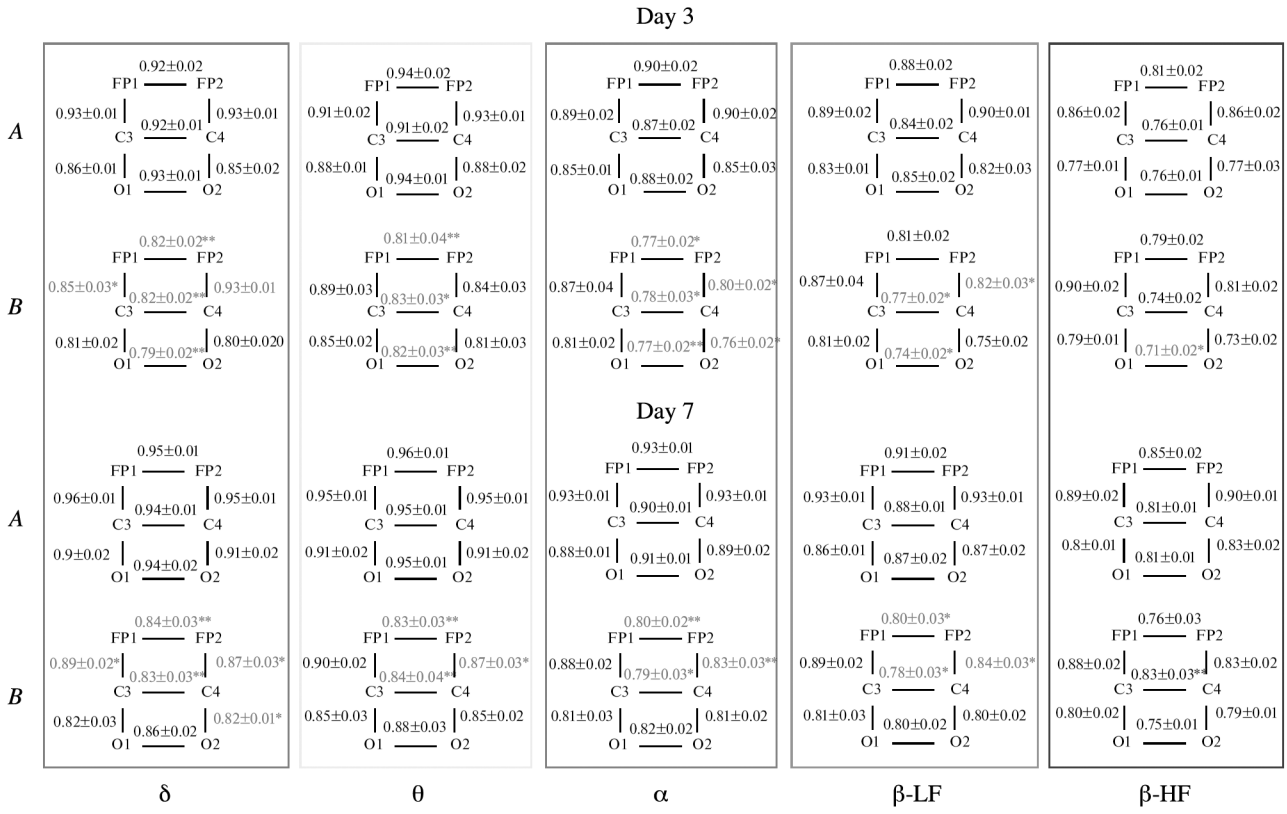

Fig. 4. Mean coherence power levels of electrode pairs in test animals (*A* – presumptively healthy group, *B* – CCT) on post-operative days 3 and 7. $^{*}p < 0.05$, $^{**}p < 0.01$ – statistically significant differences compared with the presumptively healthy group.

of total CSF protein showed that these animals displayed severe impairments to the barrier function of the blood-brain barrier [6]. Thus, previous studies lead to the conclusion that the present studies developed a model of severe CCT.

Within the framework of the present study, the status of the brain was assessed in injured rats in the acute (day 3) and intermediate (day 7) post-trauma periods after CCT. Clinically, the acute period is characterized by loss of brain functions, accompanied by deterioration of consciousness and reductions in mental activity. In addition, cerebral edema, formation of detritus, macro- and microfocal hemorrhages, as well as increases in autoimmune reactions – the typical pathomorphological picture of this period were seen [24].

The intermediate period is characterized by partial recovery of general brain functions, though changes such as motor and motor coordination impairments can still be seen. The injury focus contains focal and diffuse posttraumatic processes with differently directed changes in brain matter (regenerative processes/phagocytosis of dead tissue). Regression of cerebral edema also occurs [24].

The model used here is characterized by a decrease (to the point of the complete absence) of motor activity in injured areas on post-trauma day 3, with gradual recovery by day 7 [6]. The pathomorphological picture in the injury focus in these animals is characterized by a predominance of alteration processes with retention of necrotic detritus in the injury zone, severe perifocal edema, formation of moderate exudative and cellular reactions, and spreading perifocal glial reactions on day 3 and significant predominance of exudative cellular reactions, with elimination of necrotic detritus from the injury focus, decreased severity of edema, and formation of severe limited perifocal glial reactions on day 7 after CCT (Fig. 2). We did not analyze the extent of cerebral edema in this model, though data from other authors provide evidence that this develops in rats in the first two days, settling by days 5–7 [25]. Thus, the time points selected for testing in this model are taken as the acute and subacute periods following trauma.

The present study showed that unilateral traumatic injury to the motor cortex and underlying areas in rats leads to damage to interhemisphere and intrahemisphere functional connections both in the trauma area and distant parts of the brain. These adverse changes can be detected by cross-correlation and coherence analysis on post-CCT days 3 and 7. Cross-correlation analysis of the characteristic features of these impairments are reductions in cross-correlation and mean CCF frequency coefficients, as well as increases in the maximum span of CCF in pairs of leads. This latter parameter is the most sensitive to CCT, as it showed statistically significant changes in all pairs of leads. It should be noted that the mean CCF frequency analysis provides indirect evidence of the course of pathological processes occur-

ring in the brain following CCT, as on day 7 this parameter in injured rats approached that in healthy animals. Coherence analysis demonstrated that rats with CCT showed reductions in mean coherence power in the δ, θ, α, and β rhythms, coherence in the high-frequency β rhythm being the least sensitive to trauma.

Decreases in the extent of cross-correlation and mean coherence power levels in pairs of leads have repeatedly been seen, not only in people with CCT, but also in those with other focal organic brain lesions. Studies of EEG cross-correlation functions with foci in different locations showed that different pathological interactions between cortical areas arise, depending on the area of brain damage. Correlational links between zones of direct brain damage and other parts of the cortex are sharply decreased. At the same time, specific pathological correlations with other parts of the brain arise in the injury zone and establish pathological links between cortical zones distant from the focus and not subject to primary injury [26].

The studies reported by Sharova et al. showed that most coherence connections in the main EEG frequency ranges in people with post-coma unconsciousness following severe CCT were statistically significantly decreased from normal. The authors particularly emphasized the fact of a sharp reduction in interhemisphere interactions, varying from 30% to 80% relative to normal and connected this not only with direct damage to the frontal lobes and commissural tracts, but also with damage (dysfunction) of regulatory structures at different levels [19]. A similar study in patients, reported by Klimash et al., showed reductions in coherence in the α and β ranges [20].

Thus, the CCT model used here induced changes in electrocorticogram CCF and coherence parameters in rats similar to those seen in patients with focal brain injuries and in particular those with severe craniocerebral trauma. This suggests that assessment of CCF and coherence parameters in the CCT model in rats can be used as objective indicators of the efficacy of pharmacotherapy in studies of potential neuroprotector substances. However, as the study was a pilot investigation, the results obtained here cannot reliably be translated to large groups of animals or people. Validation of this model requires confirmatory experiments with larger numbers of rats in each group. Our data can be used to determine optimum cohort sizes for larger studies, for example, by power analysis or other methods based on preliminary results [27].

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The authors have no conflicts of interests.

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