DOI 10.1007/s11055-018-0631-3
Neuroscience and Behavioral Physiology, Vol. 48, No. 7, September, 2018

The Acute Post-Traumatic Period in Rats Is Accompanied by an Anxiety State and a Decrease in the Proportion of REM Sleep

I. G. Komol'tsev, I. P. Levshina, M. R. Novikova, A. O. Tishkina, M. Yu. Stepanichev, and N. V. Gulyaeva

UDC 612.821

Translated from Zhurnal Vysshei Nervnoi Deyatel'nosti imeni I. P. Pavlova, Vol. 67, No. 2, pp. 231–245, March–April, 2017. Original article submitted November 1, 2016. Accepted December 8, 2016.

The sequelae of craniocerebral trauma (CCT) were studied using a model based on severe (3–4 atm) lateral hydrodynamic percussion (liquid-percussive brain injury) in male Sprague–Dawley rats. With the aim of detecting the symptoms of anxiety states, the rats' behavior was assessed in the dark-light box and the elevated plus maze test; sleep impairments were detected by recording the electrocorticogram (ECoG) before trauma and during the first week after trauma. The results provided evidence of the post-CCT development of signs of an anxiety state, accompanied by decreases in the proportion of REM sleep and decreases in the amplitude and frequency of the ECoG during this phase.

Keywords: craniocerebral trauma, behavior, EEG, REM sleep, anxiety.

The sequelae of craniocerebral trauma (CCT) are among the most important problems in contemporary medicine. Most patients subsequently develop neurological and psychiatric impairments [Konovalov et al., 2002]. Severe CCT produces decreased consciousness in the acute phase, along with convulsive seizures and neurological deficit; the longer-term period includes the development of symptoms of an anxious-depressive state, sleep disturbances, cognitive impairments, apathy, and disordered coordination in space. Some 20% of patients with severe CCT develop symptomatic epilepsy in the late period. Despite the obvious importance of identifying risk factors for predicting the subsequent development of the sequelae of CCT, there are virtually no reports of experimental studies of the early behavioral and neurophysiological precursors of the development of post-traumatic pathology.

The mechanisms of post-traumatic pathologies can obviously be studied with success only in experiments. The productivity of translational studies depends on the validity of the models of pathological states used. The best approximation to CCT in humans is the lateral hydrodynamic percussion (liquid percussive brain trauma) model, which has been well developed in laboratory rats [McIntosh et al., 1989]. It is important to identify the sequelae of the development of pathological changes, which subsequently determine the set of pathogenetically defined treatment. Post-traumatic impairments are often accompanied by the development of an anxious-depressive state [Jorge and Arciniegas, 2014]. During this period, behavioral disorders can be expected, along with sleep disturbances and the appearance of epileptiform activity on the EEG. In the present study, these indicators were assessed by recording the electrocorticogram (ECoG) and 24-h video recording of behavior in the home cage and on testing.

We present here our results from assessment of the psychophysiological and neurological status of rats and the electrophysiological sequelae during the acute phase of CCT.

Methods. Animals experiments were performed in compliance with the requirements of European Parliament and Council Directives 2010/63/EU the "Regulations for laboratory practice," approved by decree of the Ministry of Health and Social Development of the Russian Federation

Laboratory for the Functional Biochemistry of the Nervous System, Institute of Higher Nervous Activity and Neurophysiology, Russian Academy of Sciences, Moscow, Russia; e-mail: komoltsev.ilia@gmail.com.

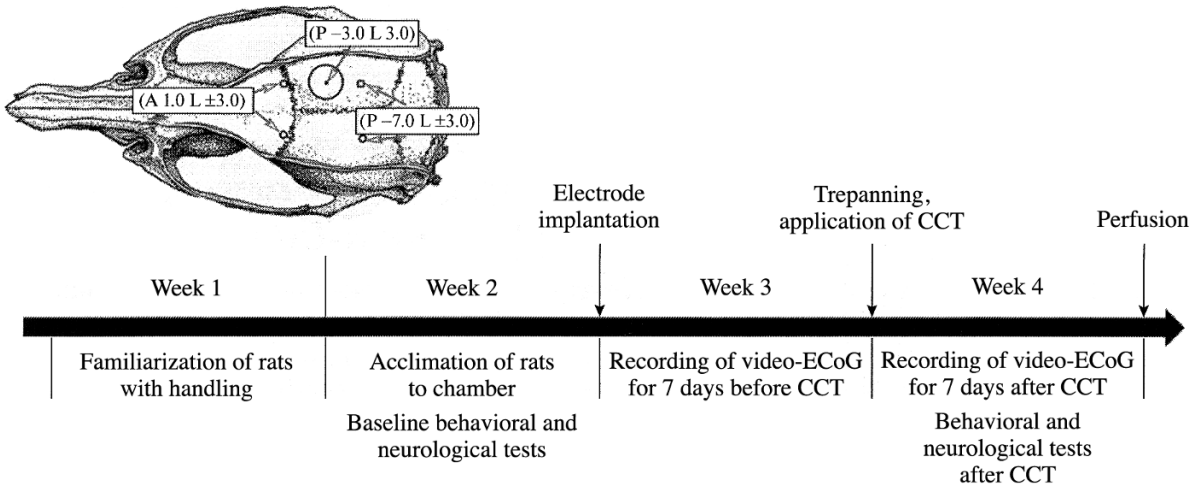

Fig. 1. Experimental design.

(No. 708n of August 23, 2010). The experimental protocol was approved by the Ethics Committee of the Institute of Higher Nervous Activity and Neurophysiology, Russian Academy of Sciences (protocol No. 10 of December 10, 2012). All measures to reduce the number of animals used and to minimize suffering were taken.

Experiments were performed on 17 male Sprague–Dawley rats aged about six months (weight 450–550 g) from the laboratory animal supplier Pushchino. The group of rats with CCT consisted of 10 animals, while the sham operated (SO) group consisted of seven animals.

The experimental protocol is shown in Fig. 1. Rats were familiarized with handling during the first week. Electrodes were implanted at the end of the second week, and trepanning and application of CCT were performed at the end of the third week of the experiment. The rats' behavior in baseline conditions was tested 1–2 days before electrode implantation (week 2) and 1–2 days before perfusion (week 4); in both cases, neurological symptomatology was assessed of the first day using a points scale in 10 tests [Hunterat et al., 2000] and a Rotarod balance test; animals were tested in the light/dark box (LDB) and the elevated plus maze (EPM) on day 2. The interval between tests performed on the same day was 4 h. ECoG and behavior were recorded on video during weeks 3 and 4. ECoG was recorded in individual chambers with free access to water and food in conditions of natural illumination. Rats lost no more than 10% of body weight during the experiments.

Animals anesthetized with chloral hydrate (450 mg/kg) were harvested from experiments by intracardiac perfusion with 4% paraformaldehyde solution in 0.1 M phosphate buffer pH 7.4.

Behavioral testing. The nature of motor functions and the endurance of the rats of the CCT and SO groups were studied by placing the animals on the bar of a Panlab LE8500 Rotarod rotating at 30–35 rpm. Rats were replaced on the bar if they fell off. As a rule, rats were placed on the apparatus three times, after which they acquired the skill of remaining confidently on the rotating bar for 180 sec.

The LDB was used to measure behavior in a conflict situation – the conflict between the orientational-exploratory motivation, which is directed to familiarization with the whole chamber, and the innate species-specific avoidance of light, as an anxiety factor, i.e., transfer to the preferred dark sector. The chamber, of height 27 cm, consisted of two sectors. The dark sector, of size 18 × 27 cm, was made of opaque black Plexiglas and the light chamber was a cube of size 27 × 27 cm made of white opaque Plexiglas. The size of the aperture between the dark and light sectors was 7 × 7 cm. The dark sector had a lid. Illumination of the light sector was at 108 Lx, compared with 8 Lx in the dark sector. After adaptation to the experimental room for 15 min, the animals were placed in the light sector of the chamber with the tail towards the aperture to the dark sector. Behavior was recorded on video for 300 sec. Processing of traces identified the duration of the time spent by the rats in the light sector before transfer to the dark sector (the latent period, LP) and the duration of time spent in the dark sector [Bourin et al., 2003]. The number of times the animals appeared at the aperture connecting the two halves of the chamber was determined, i.e., the number of glances by the rat from the light sector to the dark before transfer to the dark sector and from the dark sector to the light. The time spent exploring the light sector – a measure of exploratory activity – was determined; the number of glances from the dark sector to the light reflects the animal's anxiety [Lapin, 1999].

The EPM was initially developed to evaluate the anxiolytic and anxiogenic properties of drugs in experiments on rodents [Crawley and Goodwin, 1980]. Arm length in the maze was 50 cm and width was 10 cm; the central platform was 10 × 10 cm; wall height in the closed arms was 10 cm. The floor of each arm was divided into 10-cm sectors to

separate the arm into squares which were used to assess the length of the path followed by the rat. Bright illumination is known to increase aversiveness. The rats' movement activity started with illumination of 2.7–3.0 Lx in the open arms and the central platform and 1.7–1.8 Lx in the closed arms [Walf and Frye, 2007]. This illumination was selected to decrease the aversiveness of the EPM. The rat was placed in the central area of the EPM with the head towards an open arm. The time spent by the animal in the central platform (the latent period, LP) was measured, along with the time spent by the rat in selecting an arm each time it crossed the central platform, the number of times the central platform was crossed, and the number of squares crossed; these figures were used to compute the path length in the maze arms. In addition, the number of hangings from the ends of the arms and the numbers of outward and inward glances as the rat selected a "new" arm were determined. The number and duration of freezing reactions in the arms were determined, along with the number of times the rat returned to the "old arm" without crossing the central platform. The rat was taken to have left an arm (or the platform) when all four paws were outside the area concerned. The experimental lasted 300 sec. The experiment was analyzed on computer using video recordings.

Surgery was performed under inhalational anesthesia with 1–3% isoflurane. After scalping and removal of the temporal muscles, stainless steel epidural electrodes were implanted as shown in Fig. 1, preserving the area for subsequent craniotomy. The reference electrode was implanted into the midline of the caudal part of the occipital bone.

Hydrodynamic percussions were delivered by trepanning the skull. The diameter of the opening in the right parietal bone was 3 mm. The opening was positioned 3 mm caudal to the bregma and 3 mm lateral to the midline (Fig. 1). The head of a Luer-type injection needle was glued to the margins of the trepanned aperture with cyanoacrylate glue. One hour after craniotomy and recovery from anesthesia, CCT was applied to the rats during free behavior using a lateral hydrodynamic percussion at 3–4 atm. Responses to the percussion were evaluated using the Krushinskii scale [Krushinskii, 1960]. The only difference between rats of the SO group from those of the CCT group was the non-use of the hydrodynamic percussion.

ECoG recording. The ECoG was recorded continuously during weeks 3 and 4 (Fig. 1). Wireless eight-channel biopotentials amplifiers (Bio Recorded BR8V1) with an ADC resolution of 24 bits, an input range of up to 1200 mV, a digitization frequency of up to 1 kHz, and a sampling frequency of 250 Hz were used.

ECoG processing. Sleep structure was analyzed using continuous ECoG recordings by selecting 24-h fragments (containing both day- and nighttime periods) from three time points: baseline recording on day 5 after electrode implantation, in the first 24 h after delivery of the hydrodynamic percussion, and on post-trauma day 6. Traces were examined in EDF Browser 1.57 and processed with a Butterworth filter with a lower limit of 1 Hz and an upper limit of 30 Hz, and were divided into 20-sec epochs. Studies were run with time scans of 20 sec. Each epoch consisted of the following phases of the sleep–waking cycle: NREM sleep (the slow or slow-wave sleep phase), REM sleep (the rapid phase or paradoxical sleep), and the waking phase. Criteria for assigning the REM and walking phases were the appearance on the ECoG of waves in the broadened θ range of 4–12 Hz, including the frequency of the α range used in clinical studies; the REM phase and waking, which have similar EEG patterns, were discriminated using readings from an accelerometer responding to minimal movements in conscious animals, along with observations from video recordings. Furthermore, the obligatory sequence of changes in sleep phase was taken into consideration. Criteria for identifying the NREM sleep phase were the appearance of slow-wave high-amplitude activity in the δ range (1–4 Hz) and high-amplitude generalized spindle-shared bursts on the background of slow-wave activity at 7–14 Hz (sleep spindles). The proportions of the total time spent awake and in NREM and REM sleep were computed at each time point in rats with CCT and SO and also over time (baseline and post-trauma days 1 and 6) for each group.

The frequency and amplitude characteristics of the ECoG before trauma were compared by taking random segments of recordings on different days following electrode implantation and selecting 200–300 epochs containing the NREM sleep phase, 200–300 epochs containing the waking phase, and 60–120 epochs containing the REM sleep phase. After trauma, sets of 400–600 epochs with NREM sleep and waking and 120–240 epochs containing the REM sleep phase were also selected from random segments of recordings. Mean power spectra were computed for each phase of the sleep–waking cycle for ECoG segments from the right and left occipital leads. Plots of the averaged power spectrum were made for each of the phases and used to identify peaks. The frequencies and amplitudes of peaks on power spectrum plots were compared between and within the CCT and SO groups for each phase of the cycle and for each time point (baseline, after the percussion). These values were compared over time.

Statistical processing and analysis of test results were run in Statistica 10 (StatSoft Inc.). Effects in behavioral tests were identified using the Wilcoxon test (to assess within-group changes) and the Mann–Whitney test (for between-group comparisons); ECoG were compared by analysis of variance (ANOVA) for repeat measures. Post hoc analysis was performed using the Tukey HSD test. Fisher's exact test was used to evaluate differences in the numbers of animals showing concrete group-specific behavioral features. Data are presented as mean ± standard error of the mean.

Results. *Responses of rats after hydrodynamic percussion*. The first reaction of the rat after the percussion was a jump, which turned into a circular run in the anticlockwise

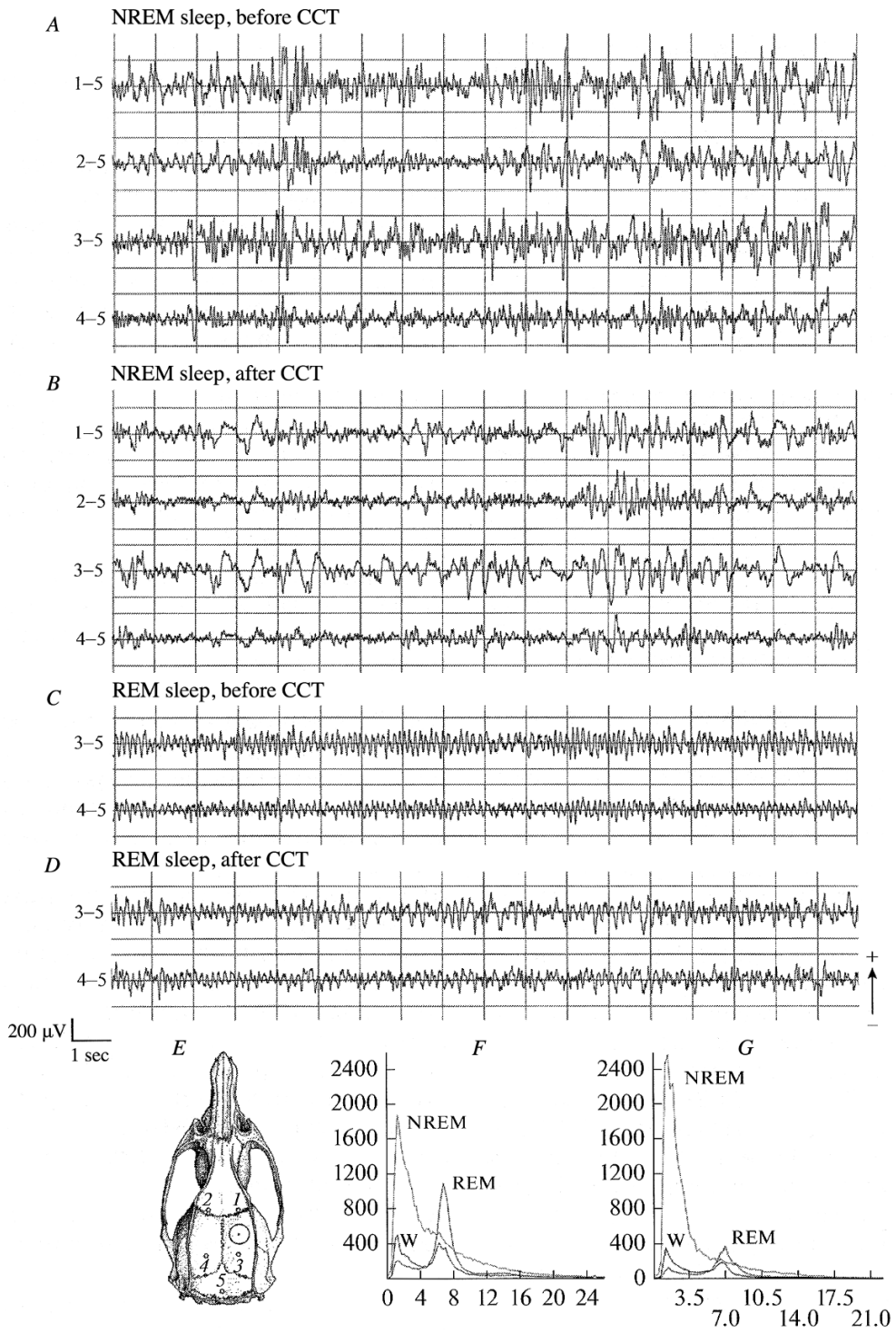

Fig. 2. Sequelae of CCT on ECoG. *A*, *B*) NREM sleep in rats before (*A*) and after (*B*) CCT. *C*, *D*) REM sleep in rats before (*C*) and after (*D*) CCT. All plots are presented for the evening before CCT and 6–8 h after CCT. For explanation see text. *E*) Electrode positions. *F*, *G*) Averaged power spectrum for each phase of the sleep–waking cycle for the ipsilateral hemisphere of one rat before (*F*) and after (*G*) CCT. REM – REM sleep; NREM – NREM sleep; W – waking. The abscissa shows spectral power frequency, Hz; the ordinate shows the amplitude of the power spectrum, μV^2.

direction. The run was replaced by falling onto the side, which was followed by clonic convulsions developing into clonic-tonic convulsions. This response was evaluated at 3–4 points on the Krushinskii scale. After convulsions, the rats remained immobile on their sides for 10–20 sec. Tachypnea and respiratory arrest were seen, which settled

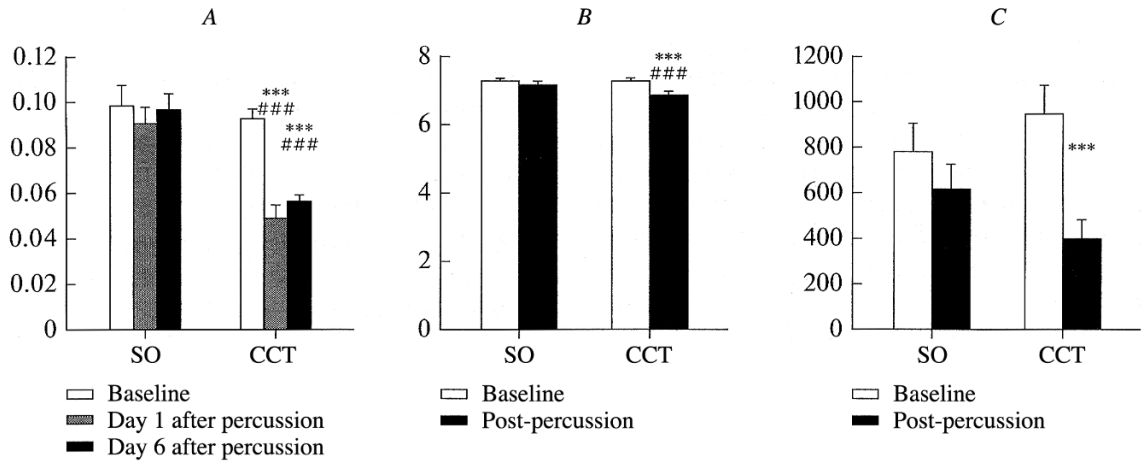

Fig. 3. Effects of CCT on the structure of REM sleep. *A*) Dynamics of changes in the proportion of REM sleep. After trauma, the proportion of REM sleep underwent a statistically significant decrease in the CCT group on days 1 and 6 as compared with the baseline value and that in the SO group on days 1 and 6 after sham operation. The ordinates show the proportion of total time, %. *B*) Dynamics of changes in the frequency of the spectral power peak for REM sleep. Peak power spectrum frequencies averaged for the first week after CCT in the CCT group after the percussion in comparison with the value before percussion and in comparison with the SO group after sham operation. Ordinates show spectral power peak frequency, Hz. *C*) Dynamics of changes in the amplitudes of power spectral peaks for REM sleep. Power spectrum peak amplitude averaged for the first week after CCT decreased in the CCT group after percussion as compared with the pre-percussion level. Ordinates show power spectrum peak amplitudes, μV^2. Data are presented for the ipsilateral hemisphere. $^{***}p < 0.001$ compared with baseline, $^{###}p < 0.001$ and $^{##}p < 0.01$ compared with the corresponding SO group.

either spontaneously or after assisted ventilation. Restoration of breathing did not occur in some rats, though their hearts continued to beat. A total of 32.5% of the rats died during the experiment.

Neurological tests and balance on the Rotarod did not identify any neurological derangement in either the SO group or the CCT group. In post-trauma tests, all animals coped with the task of remaining on the rotating bar throughout the initial 180 sec.

Behavior of rats in the LDB and EPM. Testing of rats of the SO group in the LDB showed that the LP of transfer from the light sector to the dark (6.4 ± 1.8 and 6.5 ± 2.0 sec, respectively) and the time spent in the dark sector (293.6 ± ± 1.8 and 293.5 ± 2.1 sec) did not change on comparison before and after the sham procedure (trepanning). Reductions in the numbers of glances out from the dark sector occurred at the level of a tendency (23.8 ± 2.9 and 14.2 ± 2.4 sec, $p < 0.07$). In the CCT group, measurements after the percussion revealed increases in LP for transfer to the dark sector (3.7 ± 1.1 and 12.9 ± 2.4 sec, $p < 0.01$) and, thus, a decrease in the time spent in the dark sector (296.3 ± 1.1 and 287.1 ± 2.4 sec, $p < 0.01$). In addition, there was a statistically significant increase in the number of glances out from the light sector into the dark before transfer into the dark sector (0.9 ± 0.3 and 2.2 ± 0.4 sec, $p < 0.01$). Comparison of results for this parameter from the two groups demonstrated statistically significant differences ($p < 0.02$). Before finally entering the dark sector, rats of the CCT group spent a long time sniffing the edges of the entrance aperture and peeping through it. Almost the whole of the extended body except the hind paws was often within the dark sector, though the animal returned to the light sector and only after manipulations finally entered the dark sector.

The behavior of the rats in the EPM before trauma showed no differences between the SO and CCT groups. After trauma, rats of the CCT group showed an increase in the LP of excursions to the central platform (3.1 ± 0.5 and 5.2 ± 0.7 sec, $p < 0.03$). The time spent selecting the direction of movement after returning to the exit to the central platform was greater in rats of the CCT group than the SO group (137.7 ± 16.0 and 108.8 ± 10.5 sec, $p < 0.08$). There was a sharp increase in the time spent selecting an arm in rats of the CCT group after trauma (74.6 ± 9.0 and 137.7 ± ± 16.0 sec, $p < 0.01$). The number of crossings of the center, the latent period of departure from the central area after being placed in it, the number of hangings from the ends of the arms, and the number of glances before crossing the center showed no change after trauma.

In addition, post-trauma testing of rats of the CCT group revealed specific behavioral acts. Firstly, the animals did not leave the open arms and moved about only in the dark arms. This behavior was not associated with difficulties in moving, as path lengths before and after the percussion were no different: 70.8 ± 9.1 cm before trauma and 66.8 ± 9.1 cm after it. Secondly, behavioral features such as return to the closed arm after exploration of the center, rearing, and "not daring" to transfer into the other closed or open arm, appeared. The rats stopped and did not completely cross the central platform, adopting a position with the trunk straight (the stretched-attend position) and performing pendulum-type movements with the hindlimbs remaining in the initial arm. This behavior was not seen in the SO

group: all rats transferred into another arm after exploring the center. In the CCT group, the number of returning animals was greater (six vs. 0, $p < 0.02$). Thirdly, return to the initial arm frequently ended with freezing. Differences between the numbers of rats in the CCT and SO groups freezing in the arms after trauma were also statistically significant (10 and 1, $p < 0.01$).

Qualitative analysis of EEG. Overall electrical activity reflected the functional state of the brain in the rats. During the first hours after trauma, the ECoG was characterized by diffuse, irregular, slow-wave activity in the δ range and a decrease in signal amplitude – "flattening" of the ECoG – and impairment to discrimination between the phases of the sleep-waking cycle (the typical elements of phases were decreased and transfers between phases were smoothed out (Fig. 2, *A–D*). Restoration of the sleep–waking cycle occurred over the first 12–24 h after trauma. In the acute post-trauma period, sharp waves and polyspikes lasting up to several seconds were seen, while some animals showed spike-wave complexes. Epileptiform activity was recorded mainly during transfers from the waking phase to the NREM sleep phase, which coincided with twitching of the whiskers and chewing movements of the jaw which were not linked with eating food. Continuous video recordings of behavior did not document any developed convulsive seizures.

Analysis of the macro- and microarchitecture of sleep. Analysis of ECoG traces in baseline conditions showed that there were no differences in sleep structure between the CCT and SO groups: the waking phase accounted for 51.4 ± ± 1.1%, the NREM phase for 38.8 ± 1.0%, and the REM phase for 9.5 ± 0.4%.

After the hydrodynamic percussion, there were differences between the CCT and SO groups in terms of the proportion of REM sleep: $F(2,30) = 17.475$, $p < 0.01$. Post hoc analysis showed that the relative duration of REM sleep in rats of the CCT group decreased on the first day from 9.2 ± ± 0.4% to 4.9 ± 0.5% ($p < 0.01$); these changes persisted to day 6: 5.6 ± 0.3%, $p < 0.01$ compared with baseline. Sham operation had no effect in rats of the SO group: the proportion of REM sleep was 9.8 ± 0.9% at baseline, 9.0 ± 0.7% of day 1 after sham operation, and 9.6 ± 0.6% on day 6 (Fig. 3, *A*).

Comparison of the proportions of REM sleep in the CCT and SO groups demonstrated statistically significant differences between groups on post-trauma day 1 (4.9 ± 0.5% in the CCT group and 9.0 ± 0.7% in the SO group, $p < 0.01$) and day 6 (5.6 ± 0.3% and 9.6 ± 0.6%) ($p < 0.01$).

In the CCT group, there was a tendency to the proportion of NREM sleep to increase initially on post-trauma day 1 (48.3 ± 2.3% vs. 39.8 ± 1.3% before trauma), after which it decreased to baseline on day 6 (39.3 ± 3.9%).

Spectral analysis of baseline ECoG traces in the ipsilateral hemisphere of the brain in rats of the CCT and SO groups for each phase of the sleep–waking cycle identified the frequencies of peaks on power spectrum plots. There were two peak frequencies in waking: 6.5 ± 0.1 Hz, with a peak spectral amplitude of 342 ± 31 μV^2 and 1.4 ± 0.1 Hz with a peak spectral amplitude of 399 ± 34 μV^2; a peak for NREM sleep was seen at 1.5 ± 0.1 Hz with a peak spectral power amplitude of 1525 ± 158 μV^2; for REM sleep, a peak at 7.3 ± 0.1 Hz with a peak spectral power amplitude of 874 ± 90 μV^2 was seen.

Comparison of the frequency characteristics of the sleep phases after trauma showed that the CCT and SO groups were significantly different in terms of the frequencies of peaks on spectral power plots for REM sleep: $F(1,15) = 5.662$, $p < 0.04$. In the CCT group, the peak was displaced from 7.2 ± 0.1 to 6.8 ± 0.1 Hz for the ipsilateral hemisphere ($p < 0.01$) and from 7.2 ± 0.1 to 6.9 ± 0.1 Hz for the contralateral hemisphere ($p < 0.03$) (Fig. 3, *B*). The decreases in frequency for both hemispheres were by 4–5%. No between-hemisphere differences were seen in the frequencies of spectral power peaks. Significant differences in the frequencies of spectral power peaks were seen on comparison of rats of the CCT group after trauma with rats of the SO group after sham surgery: in the ipsilateral hemisphere, 6.8 ± 0.1 Hz in the CCT group vs. 7.2 ± 0.1 Hz in the SO group ($p < 0.02$), and for the contralateral hemisphere, 6.9 ± ± 0.1 Hz in the CCT group vs. 7.2 ± 0.1 Hz in the SO group ($p < 0.01$).

The CCT and SO groups differed significantly in terms of the peak amplitude on spectral power plots for REM sleep: $F(1,15) = 11.718$, $p < 0.01$. For the CCT group, the amplitude of the spectral power peak decreased after trauma: for the ipsilateral hemisphere, from 942 ± 128 to 399 ± ± 84 μV^2, $p < 0.01$, and for the contralateral hemisphere, from 755 ± 150 to 403 ± 83 μV^2, $p < 0.03$ (Fig. 3, *C*). The decrease in the amplitude of the power spectrum peak was by 58% in the ipsilateral hemisphere and by 46% in the contralateral hemisphere. Comparison of the peak spectral power amplitudes in the CCT group after trauma and the SO group after sham surgery revealed no statistically significant differences.

For the waking and NREM sleep phases, neither comparison of the two groups at each time point nor comparison within the CCT or SO groups revealed any significant differences in the frequencies of peaks on spectral power plots or the amplitudes of these peaks.

Discussion

1. The challenge of studying CCT-associated states in clinical practice and in animal models. In clinical practice, CCT is a mixed area including neurology and psychiatry and constitutes a major and distinct medical-social challenge [Zaitsev, 2011; Reilly, 2007]. Determination of the cause-effect relationships between states comorbid with CCT, such as anxious-depressive disorder and post-traumatic epilepsy, as well as sleep disturbances, remains an unresolved issue. In addition, the sequelae of severe craniocerebral trauma are difficult to prognosticate [Gekht et al., 2011]. Solution of these problems appears to require both clinical studies

and model experiments in animals. However, even the best models allow only some features of a disease to be studied, which leads to the problem of appropriate translation of data to clinical practice.

2. Localization of lesions and neurological deficit in rats after lateral hydrodynamic percussions. Behavioral impairments in rats after CCT are linked with traumatological processes developing in the brain. Our previous studies of a similar group of rats included histological analysis of the state of brain tissue one week after CCT [Komol'tsev et al., 2015]. This demonstrated the formation of two zones of different locations and morphologies in the hemisphere ipsilateral to the percussion. One zone was immediately beneath the trepanned aperture and appeared to be linked with compression of brain tissue due to the action of the hydrodynamic percussion; the second zone was due to displacement of the layers of brain tissue relative to each other. This explains the location of the second focus – the area of maximal damage was located caudal and lateral to the direct injury zone, i.e., on the boundary of the normal and "compressed" nervous tissue. It is interesting that areas distant to the injury showed marked changes accompanied by edema and later formation of foci of coagulation necrosis [Snesarev, 1946], as has been demonstrated in a hydrodynamic percussion model. The severity of histological damage depends on the strength of the percussion and is characterized by changes in neuron morphology and the formation of a uniform astroglial scar [Komol'tsev et al., 2015]. The absence of any differences in the results of neurological tests in the rats' behavior on the Rotarod before and after surgery in the present study appears to be associated with the location of the damage, as, despite the fact that the trepanned aperture was located over the sensorimotor area, the focus of remote damage, with more severe changes, was located in the projection zone of the whiskers in the sensorimotor cortex.

3. Detection of anxiety states in experimental models in animals. Behavior in the most commonly used tests (LDB, EPM) is determined by the ratio of the effectivenesses of two motivations – the investigative and the defensive – and these rapidly replace each other [Blanchard et al., 1993]. The LDB primarily addresses stress and the signs of anxiety behavior in rodents. Published data indicate that illumination of the light sector of the LDB plays a major role in the behavior of animals in this test. The usual level of illumination of the light sector varies in the he range 10–240 Lx; motor activity in rats is suppressed if it is greater than 300 Lx [Pereira et al., 2008]. In our experiments, illumination of the light sector was 107 Lx, so it was comfortable for the animals and did not increase the aversiveness of the chamber. In our studies, rats with CCT approached to aperture to the dark sector several times and glanced into it, and made the decision to transfer only after doing this. Glancing was often accompanied by stretching of the rats' trunks, where the anterior part was located in the dark part of the chamber and the rest of the body was in the light sector (the stretched attend posture). This behavior in the literature is interpreted as determined by the level of risk and assessment of the situation and the rat's preceding choice of location [Kathlee et al., 1982]. Difficulty in choosing is evidenced by increases in the latent period and the number of glances into the aperture on transfer from the light sector of the LDB to the dark, as demonstrated in the present study.

The EPM, as noted, was initially developed for assessment of the anxiolytic and anxiogenic properties of drugs in experiments on rodents [Pellow et al., 1985; Walf and Frye, 2007; Cole et al., 1995]. The behavioral features of animals with free choice of arm was assessed from the latent period of entry into the open arm, the total times spent in the closed and open arms, the numbers of excursions into the open and closed arms, and the numbers of rearings, hangings from the ends of the arms, defecations, and urinations. Increased levels of anxiety in the rodents were evidenced by avoidance of visiting the open arms and defecations, and adoption of the stretched attend posture. Freezing reactions were interpreted as manifestations of fear. The view that the EPM can be included in the list of tests for animals for identifying the signs of the anxious-emotional state is widely held [Hogg et al., 1996; Walf and Frye, 2007; Cole et al., 1995; Pinheiro et al., 2007, Varty et al., 2002; Gonzalez et al., 1997]. As in the LDB test, the behavior of rodents in the EPM depends on the illumination of the arms. The spread of the levels of illumination used in the open and closed arms of the EPM in published studies is quite large – from 0 to 900 Lx, and interpretation of effects on behavioral measures also has a wide spectrum: from confirmation that illumination has no relevance [Becker and Gresch, 1996; Beserra et al., 2005] to identification of a defining role [Bertoglio and Carobrez, 2002]. The responses of rats to different levels of illumination are defined in terms of how their behavior changes when given tranquillizers or antidepressants with known spectra of actions. Motor activity in rats started at an illumination level of at least 2.8 Lx [Walf and Frye, 2007; Varty et al., 2002]. Further increases in illumination to 100 Lx do not significantly affect the time spent by rats in the open arm [Gonzalez and File, 1997; Komada et al., 2008], though this was suppressed at illumination levels of 300 Lx and above. On the basis of the task before us and the features of the CCT used, we elected to illuminate the open arms at 2.7–3.0 Lx. At this level of illumination, rats of the CCT group placed in the central platform did not enter the open arms, but moved only in the closed arms. It is important to note that rats of this group showed no changes in measures such as path length, number of crossings of the center, number of hangings from the ends of the arms, or the number of peeps before crossing the center. However, the overall pattern of behavior in the EPM did show changes. After hydrodynamic percussion, rather than entering one of the three arms before the animal, the rats spent more or less long periods of time evaluating the situation. This evaluation apparent as stretching of the trunk, glancing into the arm, sniffing the

floor and walls, and lowering and raising the head – all this without leaving arm in which they were located, i.e., with the hindpaws still in the "old" arm. The rats quite often failed to make a choice and returned to the depth of the arm and froze for 20–30 sec. This behavior by the rats could also be seen in healthy, non-traumatized animals, but only as occasional, rare episodes. It is known from ethological studies that rats prefer closed passages. Rats, like other mammals leading the crepuscular lifestyle, make major use of the whiskers for orientation in space. It can be suggested that the rat also selected the maze arm by sensing the walls of the arm with the whiskers, though most investigators take the view that orientation in space involves many analyzers, a particular large contribution being made by the visual analyzer [Tolman, 1948; Rodgers and Cole, 1994]. Tolman considered his own results and an enormous amount of published data and came to the conclusion that "... incoming impulses are usually worked over and elaborated in the central control room into a tentative, cognitive-like map of the environment. And it is this tentative map, indicating routes and paths and environmental relationships, which finally determines what responses ... the animal will finally release" (cited in the [*Great Psychological Dictionary*]). These maps can be relatively narrow, covering a small part of the situation, or relatively wide, covering a larger field. In order to use the map, the rats must initially find a difference, to which it must pay attention. Rats identify differences in series of trials, which Tolman termed vicarious. The period during which the differences were identified was accompanied by the largest number of vicarious trials. Tolman assessed rats' behavior during this period as active choice. Success in choosing is determined by the width of the map, which depends primarily on the integrity of the brain. The more difficult it is to discriminate, the larger the number of trials will be. A large number of trials requires a large amount of time.

In our study, rats during the acute post-trauma period demonstrated symptoms of an anxiety disorder identified in the EPM and LDB tests. Testing in the LDB after trauma revealed no change in behavioral measures of animals of the SO group, though the behavior of rats of the CCT group changed after the percussion. Increases in the latent period and number of glances into the aperture on transfer from the light sector to the dark in the CCT group serve as measures of the difficulty of making a choice in the LDB, as compared with both baseline measurements and values in the SO group. The time spent by rats in selecting the EPM arm after CCT at the illumination level used here was greater than arm selection time at baseline.

For us it was important to emphasize the *duration of selection*, which reflects decision-taking difficulty, and this is one of the symptoms of depression in humans and involves the lack of the appropriate motivation to take the decision and avoid negative outcomes [Sonuga-Barke et al., 2016]. However, there are insufficient data to allow us to discuss depression in animals on the basis of the time taken to make a choice. Thus, the results provide evidence of the presence of signs of anxiety disorders in rats during the acute post-trauma period, which is also consistent with a number of animal studies [Jones et al., 2008].

These observations are particularly interesting in the light of the fact that anxiety and depression are highly comorbid states in humans. Anxiety states are often seen at the onset of depression [Beesdo et al., 2010; Adams et al., 2016], though this has not been convincingly demonstrated for depression due to CCT. Similar data on the onset of depression with elevated anxiety have been obtained in various other animal models [Warnick et al., 2009].

4. Structural characteristics of sleep in CCT. Sleep disturbances in CCT constitute a problem encountered in most patients in both the acute and long-term periods of trauma. These disturbances form a wide range of manifestations – insomnia, hypersomnia, daytime drowsiness, and parasomnias (behavioral impairments during the REM sleep stage), impairments to the daily rhythm, subjective decreases in sleep quality, etc. sleep disorders in CCT are linked with the symptoms of anxious-depressive disorders, cognitive impairments, and increased fatigue [Verma et al., 2007; Ponsford et al., 2012; Ouellet et al., 2015]. Polysomnographic studies of patients with CCT at different post-trauma time points demonstrated decreases in the effectiveness of sleep, with fragmentation, along with changes in sleep architecture – *decreases in the proportion and increases in the latent period of the REM sleep phase*, as well as an increase in the proportion of the NREM sleep phase [Shekleton et al., 2010; Ponsford et al., 2012, Grima et al., 2016]. Spectral analysis demonstrated a predominance of δ and lower β activity in REM sleep, while the α and β ranges were dominant in NREM sleep [Rao et al., 2011]. However, there are few animal studies in this area, and data on changes in sleep structure are contradictory [Willie et al., 2012; Skopin et al., 2015]. Various sleep impairments are also typical of patients with symptoms of anxious-depressive states not associated with CCT and are included among the diagnostic criteria of major depressive disorder. However, patients with depression have been shown to have other polysomnographic changes, such as sleep fragmentation, *increases in the proportion of REM sleep*, increases in the density of REM sleep, and *decreases in the latent period of REM sleep*, as well as reductions in NREM sleep [Medina et al., 2014; Wang et al., 2015]. However, there are few data showing that the proportion of REM sleep is decreased in patients with anxiety disorders as compared with patients with depressive disorders [Cox and Olatunji, 2016]. Changes in sleep in depression are largely opposite to those seen in patients after CCT. Data from several studies indicate that sleep impairments may be predictors of the appearance of clinical symptoms and the effectiveness of pharmacological treatments in depression [Palagini et al., 2013]. In addition, sleep and epilepsy spectrum disorders

have extensive mutual influences [Unterberger et al., 2015]. Sleep deprivation is a powerful provoker of convulsive seizures in patients [Shvarts and Chung, 2013] and decreases the threshold of excitability of cortical neurons in animals [Vyazovskiy et al., 2013]. Clinical studies have also demonstrated the reverse influence, i.e., of seizures on sleep structure, with *a decrease in the proportion of REM sleep* in patients after daily complex partial seizures [Bazil et al., 2000] and status epilepticus [Bazil and Anderson, 2001]. These data have been confirmed by only few experimental studies on animals [Moyanova and Riche, 1999; Raol and Meti, 1998]. It follows from these studies that changes in sleep structure after epileptic seizures are similar to those seen in patients after CCT but not in patients with major depressive disorder. The symptoms of anxious-depressive disorder are known to be associated with epilepsy and can precede the debut of this disease [Hesdorffer et al., 2000, 2012], i.e., can be present during the period of asymptomatic epileptogenesis. However, sleep structure in these patients has not been described. Investigations of changes in sleep architecture may play an important role in selecting treatments for patients with anxious-depressive disorder syndromes. Most antidepressants act on sleep phases: with rare exceptions, they decrease the duration of the REM phase and increase its latency [Winokur et al., 2001; Wang et al., 2015]. Use of antidepressants also produces increases in neurogenesis [Wainwright and Galea, 2013]. A number of antidepressants have proconvulsant activity [Cardamone et al., 2013; Kanner, 2013]. Antiepileptic drugs have different actions on sleep structure and the emotional domain. Some new-generation antiepileptic drugs, in contrast to antidepressants, increase the duration of REM sleep [Shvarts and Chung, 2013]. It should be noted that the approach to the differential diagnosis and treatment of anxious-depressive disorders based on objective polysomnographic data on sleep structure is not yet widely used in clinical practice.

Our study revealed changes in the sleep-waking cycle: in the CCT group these affected REM sleep and were expressed as decreases in the proportion, reductions in the peak frequency on the power spectrum, and decreases in the amplitude of the spectral peak in REM sleep.

Thus, detailed description of the nature of anxiety and/or depressive disorders after CCT may assist in selecting treatment and assessing treatment efficacy. We have obtained new data on behavioral features and changes in sleep structure during the acute period of CCT. However, the search for risk factors for the development of post-traumatic epilepsy requires long-term (months in animals and years in humans) observations to the point at which unprovoked epileptic seizures begin. The hydrodynamic percussion model in rodents is suitable for investigations of this type.

5. Characteristics of brain plasticity in CCT-associated diseases. Animal studies have demonstrated increases in hippocampal excitability after CCT, which is the pathogenetic element in the development of post-traumatic epilepsy [Pitkanen et al., 2014]. The hippocampus, where brain plasticity processes take place, is regarded as the central component in the pathogenesis of both post-traumatic epilepsy and depression [Gulyaeva, 2015], though levels of neurogenesis in the germinative zones of the hippocampus in these states are opposite: epileptogenesis is accompanied by increases in the level of neurogenesis [Gulyaeva, 2010], while the level of neurogenesis in the hippocampus in depression decreases [Aniol and Gulyaeva, 2015]. However, both processes are accompanied by cell death and lead to structural changes in the hippocampus [Malykhin et al., 2010; Malmgren and Thom, 2012], with impairments to its functions. Neurogenesis has not been studied in anxiety disorders at the onset of depression [Schoenfeld and Cameron, 2015]. It is unknown whether depression with a high level of neurogenesis, as seen in epileptogenesis and after CCT, differs from depression with a low level of neurogenesis, or whether such differences can be seen in terms of early behavioral and electrophysiological measures during disease modeling.

Processes occurring during REM sleep are important for normal plasticity to occur. Activation of the limbic zone in REM sleep has been demonstrated; this is required for normal learning and memory reconsolidation processes [Hobson and Pace-Schott, 2002; Gorgoni et al., 2013]. Deprivation of REM sleep is accompanied by decreases in neurogenesis [Guzman-Marin et al., 2008; Meerlo et al., 2009]. The role of neurogenesis in changes in REM sleep is not entirely clear, though existing patterns may be useful in both clinical and experimental studies.

We believe that the mechanisms of development of anxious-depressive states after CCT have as yet received insufficient study. Analysis of the literature suggests that some elements of the pathogenesis of post-traumatic anxious-depressive disorder differ from the pathogenesis of depression not associated with CCT, which requires further studies.

Conclusions

1. Damage induced by hydrodynamic percussions of 3–4 atm located in the cortical representation of the whiskers, muscle endurance, and movement coordination did not change in rats five days after CCT. No neurological deficit was seen.

2. Signs of anxiety behavior were seen during the first week after CCT.

3. ECoG studies in the first days after trauma were characterized by changes in the baseline rhythm and the presence of epileptiform activity.

4. CCT led to decreases in the proportion of REM sleep. Displacement of peaks on spectral power plots to lower frequencies, with decreases in peak spectral amplitude, occurred during REM sleep. CCT was not found to have effects on other phases of the sleep–waking cycle.

This study was supported by the Russian Foundation for Basic Research (Grant No. 16-04-00855) (modeling of CCT, behavior, EEG), and the Russian Science Foundation (Grant No. 14-25-00-136) (studies of anxiety).

REFERENCES

Adams, G. C., Balbuena, L., Meng, X., and Asmundson, G. J., "When social anxiety and depression go together. A population study of comorbidity and associated consequences," *J. Affect. Disord.*, **206**, 48–54 (2016).

Aniol, V. A. and Gulyaeva, N. V., "Changes in postnatal neurogenesis in the germinative zone of the human hippocampus in depressive spectrum disorders," *Neirokhimiya*, **1**, 13–18 (2015).

Bazil, C. W. and Anderson, C. T., "Sleep structure following status epilepticus," *Sleep Med.*, **2**, No. 5, 447–449 (2001).

Bazil, C. W., Castro, L. H., and Walczak, T. S., "Reduction of rapid eye movement sleep by diurnal and nocturnal seizures in temporal lobe epilepsy," *Arch. Neurol.*, **57**, No. 3, 363–368 (2000).

Becker, A. and Grecksch, G., "Illumination has no effect on rats' behavior in the elevated plus-maze," *Physiol. Behav.*, **59**, No. 6, 1175–1177 (1996).

Beesdo, K., Pine, D. S., Lieb, R., and Wittchen, H. U., "Incidence and risk patterns of anxiety and depressive disorders and categorization of generalized anxiety disorder," *Arch. Gen. Psychiatry*, **67**, No. 1, 47–57 (2010).

Bertoglio, L. J. and Carobrez, A. P., "Behavioral profile of rats submitted to session 1-session 2 in the elevated plus-maze diurnal/nocturnal phases and under different illumination conditions," *Behav. Brain Res.*, **132**, No. 2, 135–143 (2002).

Beserra, A. M., Cardenas, F. P., and Morato, S., "Effects of different illumination on rats behavior in the elevated plus-maze," *Physiol. Behav.*, **85**, No. 1, 265–270 (2005).

Blanchard, R. J., Yudko, E. B., Rodgers R. J., and Blanchard, D. C., "Defense system psychopharmacology: an ethological approach to the pharmacology of fear and anxiety," *Behav. Brain Res.*, **58**, No. 1–2, 155–165 (1993).

Bourin, M. and Hascat, M., "The mouse light/dark box test," *Eur. J. Pharmacol.*, **463**, No. 1–3, 55–56 (2003).

Cardamone, L., Salzberg, M. R., O'Brien, T. J., and Jones, N. C., "Antidepressant therapy in epilepsy: can treating the comorbidities affect the underlying disorder?" *Br. J. Pharmacol.*, **168**, No. 7, 1531–1554 (2013).

Gekht, A. B., Gulyaeva, N. V., Krylov, et al., "Epilepsy in patients with stroke and craniocerebral trauma," in: *Current Epileptology*, ALKIPRO (2011), pp. 243–260.

Gonzalez, L. E. and File, S., "A five minute experience in the elevated plus-maze alters the state of benzodiazepine receptor in the dorsal raphe nucleus," *J. Neurosci.*, **17**, No. 4, 1505–1511 (1997).

Gorgoni, M., D'Atri, A., Lauri, et al., "Is sleep essential for neural plasticity in humans, and how does it affect motor and cognitive recovery?" *Neural Plast.*, **2013**, 103949 (2013).

Grima, N., Ponsford, J., Rajamtnam, et al., "Sleep disturbances in traumatic brain injury: A meta-analysis," *J. Clin. Sleep Med.*, **12**, No. 3, 419–428 (2016).

Gulyaeea, N. V., "'Aberrant' neurogenesis in the adult rat brain in epilepsy: compensatory or pathological?" *Neirokhimiya*, **27**, No. 2, 102–108 (2010).

Gulyaeva, N. V., "Neuroplasticity and epilepsy: current concepts and mechanisms of the comorbidity of epilepsy and depression," *Zh. Nevrol. Psikhiatr.*, **12**, 148–153 (2015).

Guzman-Marin, R., Suntsova, N., Bashir, et al., "Rapid eye movement sleep deprivation contributes to reduction of neurogenesis in the hippocampal dentate gyrus of the adult rat," *Sleep*, **31**, No. 2, 167–175 (2008).

Hesdorffer, D. C., Hauser, W. A., Annegers, J. F., and Cascino, G., "Major depression is a risk factor for seizures in older adults," *Ann. Neurol.*, **47**, No. 2, 246–249 (2000).

Hesdorffer, D. C., Ishihara, L., Mynepalli, L., et al., "Epilepsy, suicidality, and psychiatric disorders: a bidirectional association," *Ann. Neurol.*, **72**, No. 2, 184–191 (2012).

Hillmann, M., Seidelmann, D., Klewer, M., and Jones, G. H., "Effects of benzodiazepine receptor partial inverse agonists in the elevated plus maze test of anxiety in the rat," *Psychopharmacology (Berlin)*, **121**, No. 1, 118–126 (1995).

Hobson, J. A. and Pace-Schott, E. F., "The cognitive neuroscience of sleep: neuronal systems, consciousness and learning," *Nat. Rev. Neurosci.*, **3**, No. 9, 679–693 (2002).

Hogg, S., "A review of the validity and variability of the elevated plus-maze as animal model of anxiety," *Pharmacol. Biochem. Behav.*, **54**, No. 1, 21–30 (1996).

Hunter, A. J., Hatcher, J., Wirley, et al., "Functional assessments in mice and rats after focal stroke," *Neuropharmacology*, **39**, 806–816 (2000).

Jones, N. C., Cardamone, L., William, et al., "Experimental traumatic brain injury induces a pervasive hyperanxious phenotype in rats," *J. Neurotrauma*, **25**, No. 11, 1367–1374 (2008).

Jorge, R. E. and Arciniegas, D. B., "Mood disorders after TBI," *Psychiatr. Clin. North Am.*, **37**, No. 1, 13–29 (2014).

Kanner, A. M., "The treatment of depressive disorders in epilepsy: what all neurologists should know," *Epilepsia*, **54**, No. 1, 3–12 (2013).

Kathlee, R., Bailey, K. R., Jacqueline, N., and Crawley, J. N., "Anxiety-related behaviors in mice," in: *Methods of Behavior Analysis in Neuroscience*, Todd, D. (ed.), Gould (1985), pp. 77–103.

Komada, M., Takao, K., and Miyakawa, T., " Elevated plus maze for mice," *J. Vis. Exp.*, No. 22, 1088 (2008).

Komol'tsev, I. G., Levshina, I. L., Novikova, et al., "Changes in the cerebral cortex after dosed craniocerebral trauma in rats of different ages," *Morfologiya*, **5**, 14–20 (2015).

Konovalov, A. N., Likhterman, L. E., and Potapov, A. A., "*Clinical Guidelines for Craniocerebral Trauma*, Antidor, Moscow (2002).

Krushinskii, L. V., *Formation of Behavior in Animals in Health and Disease*, Moscow State University Press, Moscow (1960), pp. 121–122.

Lapin, I. P., "Decreases in the frequency of peeps from the dark sector – a unique measure of the effects of anxiogens on behavior in mice in the 'light-dark' chamber," *Zh. Vyssh. Nerv. Deyat.*, **49**, No. 3, 521–526 (1999).

Malmgren, K. and Thom, M., "Hippocampal sclerosis – origins and imaging," *Epilepsia*, **53**, No. 4, 19–33 (2012).

Malykhin, N. V., Carter, R., Seres, P., and Coupland, N. J., "Structural changes in the hippocampus in major depressive disorder: contributions of disease and treatment," *J. Psychiatry Neurosci.*, **35**, No. 5, 337–343 (2010).

McIntosh, T. K., Vink, R., Noble, L., et al., "Traumatic brain injury in the rat: characterization of a lateral fluid-percussion model," *Neuroscience*, **28**, No. 1, 233–244 (1989).

Medina, A. B., Lechuga, D. A., Escandón, O. S., and Moctezuma, J. V., "Update of sleep alterations in depression," *Sleep Sci.*, **7**, No. 3, 165–169 (2014).

Meerlo, P., Mistiberger, R. E., Jacobs, et al., "New neurons in the adult brain: the role of sleep and consequences of sleep loss," *Sleep Med. Rev.*, **13**, No. 3, 187–194 (2009).

Mesherikov, B. G. and Zinchenko, V. P. (eds.), *Great Psychological Dictionary*, Praim-Evroznak, Moscow (2003).

Moyanova, S. and Riche, D., "Effect of kainic acid injected into raphe dorsal nucleus on sleep stages in cats," *Acta Neurobiol. Exp.*, **51**, No. 3–4, 107–114 (1991).

Ouellet, M. C., Beaulieu-Bonneau, S., and Morin, C. M., "Sleep-wake disturbances after traumatic brain injury," *Lancet Neurol.*, **14**, No. 7, 746–757 (2015).

Palagini, L., Baglioni, C., Ciapparelli, A., et al., "REM sleep dysregulation in depression: state of the art," *Sleep Med. Rev.*, **17**, No. 5, 377–390 (2013).

Pellow, S., Chopin, P., File, S. E., and Briley, M., "Validation of open:-closed arm entries in an elevated plus-maze as a measure of anxiety in the rat," *J. Neurosci. Meth.*, **14**, No. 3, 149–167 (1985).

Pereira, E., Gisele, M. C., Wehrmeister, T. D., and Geison, S. I., "Integrating the open field, elevated plus maze and light/dark box to assess differ-

ent types of emotional behaviors in one single trial," *Behav. Brain Res*., **193**, 277–288 (2008).

Pinheiro, S. H., Zangrossi, H., Jr., Del-Ben C., and Graeff, F. C., "Elevated mazes as animal models of anxiety: effects of serotonergic agents," *Ann. Braz. Acad. Sci*., **79**, No. 1, 71–85 (2007).

Pitkanen, A., Kemppainen, S., Ndode-Ekane, X. E., et al.., "Posttraumatic epilepsy – disease or comorbidity?" *Epilepsy Behav.*, **38**, 19–24 (2014).

Ponsford, J. L., Ziino, C., Parcell, D. L., et al., "Fatigue and sleep disturbance following traumatic brain injury – their nature, causes, and potential treatments," *J. Head Trauma Rehabil*., **27**, No. 3, 224–233 (2012).

Rao, V., Bergey, A., Hill, H., et al., "Sleep disturbance after mild traumatic brain injury: indicator of injury?" *J. Neuropsych. Clin. Neurosci*., **23**, No. 2, 201–205 (2011).

Raol, Y. H. and Meti, B. L., "Sleep-wakefulness alterations in amygdala-kindled rats," *Epilepsia*, **39**, No. 11, 1133–1137 (1998).

Reilly, R., "The impact of neurotrauma on society: an international perspective," *Prog. Brain Res*., **161**, 3–9 (2007).

Rodgers. R. J. and Cole, J. C., "The elevated plus-maze: pharmacology, methodology and ethology," in: *Ethology and Psychopharmacology*, Cooper, S. J. and Hendrie, C. A. (eds.), John Wiley & Son Ltd. (1994), pp. 9–44.

Schoenfeld, T. J. and Cameron, H. A., "Adult neurogenesis and mental illness," *Neuropsychopharmacology*, **40**, No. 1, 113–128 (2015).

Shekleton, J. A., Parcell, D. L., Redman, J. R., et al., "Sleep disturbance and melatonin levels following traumatic brain injury," *Neurology*, **74**, No. 21, 1732–1738 (2010).

Shvarts, V. and Chung, S., "Epilepsy, antiseizure therapy, and sleep cycle parameters," *Epilepsy Res. Treat*., **2013**, 670–682.

Skopin, M. D., Kabadi, S. V., Viechweg, S. S., et al., "Chronic decrease in wakefulness and disruption of sleep-wake behavior after experimental traumatic brain injury," *J. Neurotrauma*, **32**, No. 5, 289–296 (2015).

Snesarev, P. V., *General Histopathology of Cerebral Trauma*, Medgiz, Moscow (1946), pp. 21–34.

Sonuga-Barke, E. J., Cortese, S., Fairchild, G., and Stringaris, A., "Annual research review: Transdiagnostic neuroscience of child and adolescent mental disorders differentiating decision making in attention-deficit/hyperactivity disorder, conduct disorder, depression, and anxiety," *J. Child Psychol. Psychiatry*, **57**, No. 3, 321–349 (2016).

Tolman, E. C., "Cognitive maps in rats and men," *Psychol. Rev*., **55**, 189–208 (1948).

Tolmen, E., "Cognitive maps in rats and humans," *A Reader on the History of Psychology*, Moscow State University, Moscow (1980), pp. 63–69.

Unterberger I., Gabelia D., Prieschl, M., et al., "Sleep disorders and circadian rhythm in epilepsy revisited: a prospective controlled study," *Sleep Med*., **16**, No. 2, 237–242 (2015).

Varty, G. B., Morgan, C. A., Cohen-Williams, M. E., et al., "The gerbil elevated plus-maze. I. Behavioral characterization and pharmacological validation," *Neuropsychopharmacology*, **27**, No. 3, 357–370 (2002).

Verma, A., Anand V, and Verma, N. P., "Sleep disorders in chronic traumatic brain injury," *J. Clin. Sleep Med*., **3**, No. 4, 357–362 (2007).

Vyazovskiy, V. V., Olcese, U., Cirelli, C., and Tononi, G., "Prolonged wakefulness alters neuronal responsiveness to local electrical stimulation of the neocortex in awake rats," *J. Sleep Res*., **22**, No. 3, 239–250 (2013).

Wainwright, S. R. and Galea, L. A., "The neural plasticity theory of depression: assessing the roles of adult neurogenesis and PSA-NCAM within the hippocampus," *Neural Plast*., 805497 (2013).

Walf, A. and Frye, C., "The use of elevated plus-maze as an assay of anxiety-related behavior in rodents," *Nat. Protoc*., **2**, No. 2, 322–8 (2007).

Wang, Y. Q., Li, R., Zhang, M. Q., et al., "The neurobiological mechanisms and treatments of REM sleep disturbances in depression," *Curr. Neuropharmacol*., **13**, No. 4, 543–553 (2015).

Warnick, L. E., Huang, C. L., Acevedo, E. O., and Sufka, K. J., "Modelling the anxiety-depression continuum in chicks," *J. Psychopharmacol*., **23**, No. 2, 143–56

Willie, J. T., Lim, M. M., Bennett, R. E., et al., "Controlled cortical impact traumatic brain injury acutely disrupts wakefulness and extracellular orexin dynamics as determined by intracerebral microdialysis in mice," *J. Neurotrauma*, **29**, No. 10, 1908–1921 (2012).

Winokur, A., Gary, K. A., Rodner, S., et al., "Depression, sleep physiology, and antidepressant drugs," *Depress. Anxiety*, **14**, No. 1, 19–28 (2001).

Zaitsev, O. S., *The Psychopathology of Severe Craniocerebral Trauma*, Medpress-Inform, Moscow (2011).