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Rhythmic Activity in the Hippocampus and Entorhinal Cortex Is Impaired in a Model of Kainate Neurotoxicity in Rats in Free Behavior

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The hippocampus and medial entorhinal cortex (MEC) interact by means of bidirectional connections and play an important role in the processing, memorization, and reproduction of information. Data obtained in healthy animals show that the θ and γ oscillations are critical activities necessary for the interaction of the hippocampus and the MEC in signal processing. At the same time, these structures are among the most vulnerable parts of the brain to hyperactivation leading to excitotoxic damage and neuron death. In the present study toxicity was provoked by systemic administration of kainic acid (KA), inducing the development of status epilepticus. In control rats given physiological saline and rats given injections of KA, local field potentials were recorded simultaneously in hippocampal field CA1 and the MEC during exploratory behavior in an open field. A clearly apparent θ rhythm (4–10 Hz) was observed, along with a slow γ rhythm (25–50 Hz) and a fast γ rhythm (55–100 Hz) in the hippocampus and MEC of animals of both groups. Movement of control animals to the center of the open field was accompanied by an increase in the frequency of the θ rhythm and a decrease in the frequency of the fast γ rhythm in the hippocampus; the MEC showed a decrease in the power of the slow γ rhythm. This was not seen in rats given KA. This group also showed impairment to the phase-amplitude modulation of MEC activity by the hippocampal θ rhythm: changes in this modulation on movement of animals from the peripheral zones to the center of the open field were significantly less marked than in controls. There was also a significant increase in θ coherence between the hippocampus and MEC for all locations of the animal in the open field. Changes in the characteristics of rhythms in hippocampus-entorhinal interactions are potential biomarkers for impairments to the coding of spatial information and its retrieval from memory due to status epilepticus and often leading to the development of a convulsive focus in the temporal structures of the brain.

Keywords: open field, free behavior, exploratory activity, hippocampus, medial entorhinal cortex, oscillation, θ rhythm, γ rhythm, phase-amplitude modulation, intrafrequency coherence, kainate neurotoxicity.

The hippocampus and entorhinal cortex, which form the navigation system of the brain [Buzsáki and Moser, 2013], interact with each other via bidirectional connections [Steward, 1976; Kloosterman et al., 2003]. The medial part of the entorhinal cortex (MEC), like the hippocampus, contains neurons whose activity depends on the animal's location in space; these two areas of the brain are critical for orientation in the environment and spatial memory [O'Keefe, 1976; O'Keefe and Nadel, 1978; Hafting et al., 2005, 2008; Steffenach et al., 2005; Buzsáki and Moser, 2013; Zheng et al., 2016; Tan et al., 2017]. The activity of "space" neurons, on which the ability to orient to place (place cells in the hippocampus, head rotation cells, boundary cells, and grid cells in the MEC) depends, is coordinated and modulated by oscillations or brain rhythms [Buzsáki and Moser, 2013].

The main types of rhythmic field activity generated in the hippocampus and entorhinal cortex are θ and γ oscilla-

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tions. These rhythms are seen in humans and primates, as well as in lower mammals [Buzsáki, 2006]. The θ rhythm (4–12 Hz) is the highest-amplitude sinusoidal field potential recorded during exploratory behavior (particularly during sniffing), as well as during paradoxical sleep [Green and Arduini, 1952; Vanderwolf, 1969; Livanov et al., 1977; Bland, 1986; Vinogradova, 1995; Vinogradova et al., 2000; Buzsáki, 2002; Colgin, 2013]. γ oscillations (25–100 Hz), which are generally recorded along with the θ rhythm in the hippocampus and neocortex, are seen the most clearly on execution of cognitive tasks [Bouyer et al., 1981; Bragin et al., 1995; Strogatz, 2003; Montgomery et al., 2008; Benhanane, 2010].

The mechanisms of generation of the θ and γ rhythms are different. The literature develops the view that the θ rhythm, although generated in the hippocampus, depends on septal and entorhinal inputs [Petsche and Stumpf, 1962; Stumpf et al., 1962; Vinogradova, 1995; Buzsáki, 2002, 2006], while the γ rhythm has an intrahippocampal origin and does not depend on afferent inputs arising as a result of local interneuronal interactions [Buzsáki and Wang, 2012; Buzsáki, 2015]. It has been suggested that the mechanisms forming slow (25–50 Hz) and fast (55–100 Hz) γ oscillations differ in terms of the involvement of different types of hippocampal interneurons at different modulatory inputs to the hippocampus [Sutherland et al., 1983; Brun et al., 2002; Steffenach et al., 2022; Bastos et al., 2007; Belluscio et al., 2010; Kemere et al., 2013; Schomburg et al., 2014; Colgin, 2015]. The θ and γ rhythms are required for many cognitive processes, in which they perform different functions. The θ rhythm is believed to be important for active receipt and processing of sensory signals and selects them by comparison with information stored in memory [Vinogradova, 1995, 2001; Buszáki, 2006; Colgin, 2013]; it has also been suggested that the θ rhythm is a critical mechanism for binding the different attributes of an event into a single conceptual unit, both in humans [Fell et al., 2001; Lega et al., 2012; Fell and Axmacher, 2011] and rodents [Inostroza et al., 2012]. The main function of the γ rhythm is in selecting significant stimuli [Fries, 2009].

External or internal events can lead to synchronization of rhythms generated in different parts of the brain, as well as to formation of more complex functional manifestations known as phase coupling or phase coherence [Fell et al., 2008; Cavanagh et al., 2009; Canolty and Knight, 2010]. Standard phase coherence is the relative constancy of phase differences between two oscillations at the same frequency, i.e., intrafrequency coherence [Rodriguez et al., 1999; Hurtado et al., 2004]. Phase coherence has been shown to reflect different cognitive processes in humans [Canolty et al., 2006; Axmacher et al., 2010], monkeys [Canolty et al., 2010], rats [Montgomery et al., 2008; Tort et al., 2008, 2009; Nàcher et al., 2013], and mice [Wulff et al., 2009].

Accumulated data obtained in healthy animals shows that θ and γ oscillations are the main forms of activity required for interaction between the hippocampus and MEC in information processing, in particular spatial information. At the same time, these structures are susceptible to neurodegenerative diseases. The mechanisms of occurrence of many of these remain incompletely understood, so they are difficult to cure. The characteristics of the rhythmic activity in these structures in animals in free behavior and how these two areas of the brain interact in health and neurodegenerative pathology are questions which remain poorly investigated.

Our experiments using a kainate neurotoxicity model [Hellier et al., 1998; Bragin et al., 1999] and recording local field potentials (LFP) simultaneously in the hippocampus and MEC during exploratory behavior in rats in an open field yielded data on impairments to θ and γ oscillations in the temporal structures of the brain in neurodegenerative pathology.

Methods. Studies were carried out in compliance with the ethical principles formulated in the Helsinki Declaration for the Care and Use of Laboratory Animals and the Regulations of the European Parliament (86/609/EC).

Animals and surgery. Experiments were performed using young adult rats of the outbred Wistar strain (males, 150–250 g, n = 12) reared at the Experimental Animals Center, Institute of Theoretical and Experimental Biophysics, Russian Academy of Sciences (Pushchino. Russia). Animals were kept in pairs in control conditions (22–24°C, 12 h light/dark cycle) with ad libitum food and water. Animals were randomized to the experimental (kainate) and control groups. Animals in the kainate group (n = 6) received systemic injections of kainic acid (KA, 5 mg/kg, i.p.) to elicit status epilepticus. Control rats (same weight and age, n = 6) received analogous injections of physiological saline. Status epilepticus was evaluated on the Racine scale [Racine, 1972]; stages 4–5 (tonic-clonic seizures, circular movements with loss of posture and falling) lasting at least 1.5 h indicated the development of status epilepticus. If status epilepticus did not end by 2 h, rats (n = 2) were given i.m. diazepam. Before experiments, animals underwent surgery under general anesthesia (Zoletil 30 mg/kg and xylazine 12 mg/kg, i.m.) using a stereotaxic apparatus (Kopf Instruments). Body temperature was maintained using an electric heater and cardiopulmonary status was monitored during surgery using a pulsoximeter (Oxy9Vet Plus, Bionet, South Korea). Deep recording electrodes (insulated nichrome, diameter 0.05 mm) were implanted using a brain atlas [Paxinos and Watson, 1998] into the hippocampus (field CA1: AP = –3.8, ML = 2, DV = 3) and medial entorhinal cortex, layer III (MEC: AP = –8.5, ML = 4.5, DV = 6). The reference electrode was screwed into the occipital bone over the cerebellum. The whole complex was attached to the animal's head with acrylic cement. The animal then recovered for a week following surgery and acclimated to the experimental context.

Behavior in the open field. The apparatus (open field) consisted of a dimly illuminated square (110 × 110 × 60 cm);

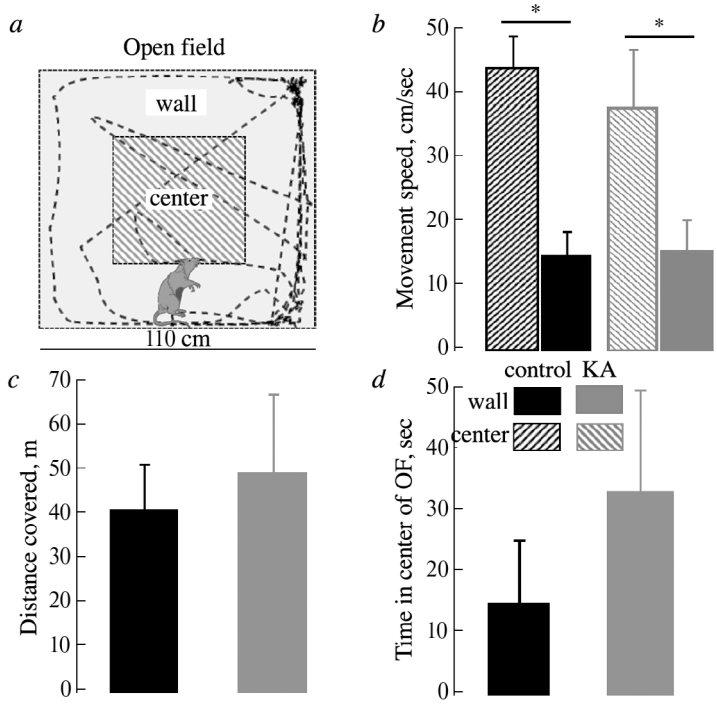

Fig. 1. Parameters of the movements of animals in the open field. *a*) Diagram of the layout of the open field and an example of an animal's track. *b*) Mean movement speed of animals in different zones of the open field; values in the center are shown by columns with diagonal shading and values in the periphery are shown as solid columns. *c*) Distance covered by rats throughout the experiment (10 min). *d*) Total time spent by the animal in the center of the open field (OF).

external sounds were masked with a white noise generator. Rats were always placed in the center of the field and their movements around the arena were monitored with a video camera located 180 cm above the center of the area using a computerized tacking system (Ethovision 1.90, Noldus IT). After manual handling, animals were familiarized with the new context (the open field) for one 10-min session per day for three days. During these sessions, animals generally barely left the center of the field, which was interpreted as an indicator of stress. After three rest days, the next 10-min session was taken as the test session. Two zones of interest were defined: the central zone (1/4 of the area of the open field) and the peripheral zone (the walls and the corners between them, 3/4 of the whole area). Movement activity was automatically recorded in these two zones (Fig. 1, *a*). As the animals explored the area, local field potentials (LFP) were recorded in hippocampal field CA1 and the MEC alongside video recordings. The apparatus was cleaned with 10% ethanol after each session.

Electrophysiological recording and analysis. One month after KA administration to rats, local field potentials (LFP) were recorded in hippocampal field CA1 and the MEC; recordings were made at the same time, between 17:00 and 21:00. Recording in animals of the epileptic group were made during periods between seizures. Recordings were made using a multichannel wireless system (Multichannel W-systems, Germany) with a sampling frequency of 5 kHz; experiments used recording in two channels. When experiments were complete, the animals' behavior and measures of oscillatory activity were analyzed offline using the programs Ethovision 1.90 and Igorpro v6.35). The coordinates of the animal in video clips of the experiment and ongoing movement speed were recorded at a frequency of 4 Hz (averaged for six frames) and compared with local field potentials. Data were automatically segmented into 1-sec epochs and episodes of movement and rest (speed <5 cm/sec) were identified. All epochs in which the animal was in the center of the field were used for analysis, along with epochs recorded in the periphery, of which there was an equivalent number in terms of the ratio of movement and rest epochs. Thus, 180 epochs were analyzed in the control group and 390 in the group given KA.

Native traces were filtered for the ranges of interest (4–10 Hz for the θ rhythm, 25–50 Hz for the slow γ rhythm, and 55–100 Hz for the fast γ rhythm). Analysis of LFP used a Fourier transform window (window width 1 sec, displacement 250 msec). Spectral density histograms were plotted for each time point and the leading frequency of each subrange (Hz) was computed, along with the peak and integral power levels (dB, mV^2/Hz) of these rhythms.

For assessment of anomalous activity, high-amplitude events (three times greater than the standard deviation of the baseline signal, >3SD) were extracted from the overall trace using a digital filter; signals were summed and then

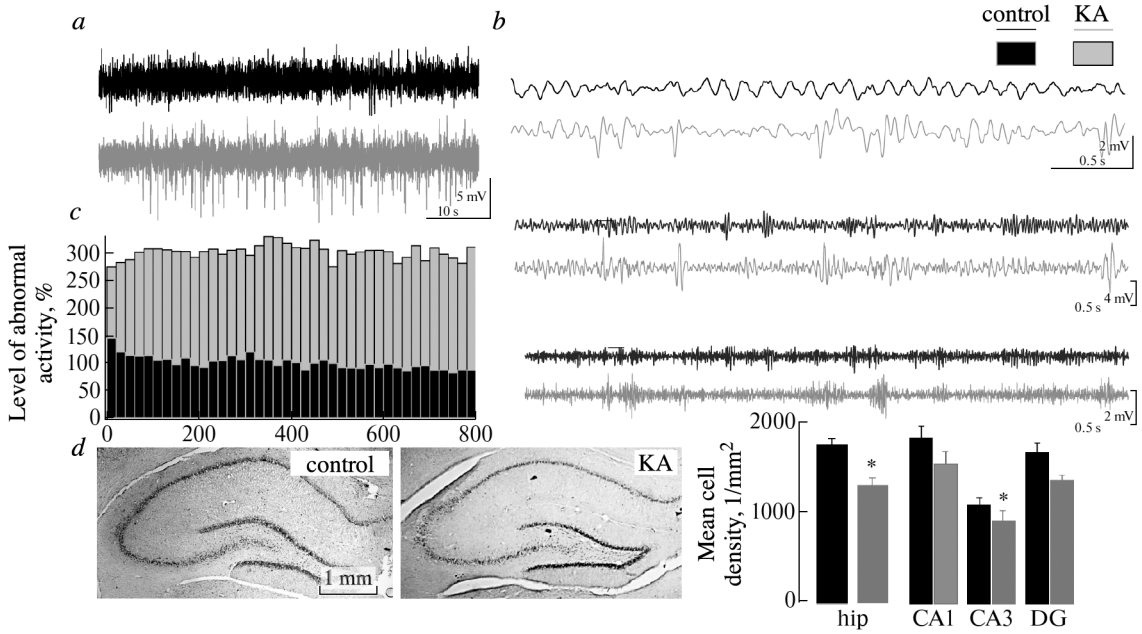

Fig. 2. Changes in the field activity and state of hippocampal tissues in the model of kainate neurotoxicity. *a*) Examples of recorded hippocampal LFP from healthy animals (controls) and in the model of kainate neurotoxicity (KA). Animals with the kainate neurotoxicity model displayed frequent high-amplitude paroxysmal events. *b*) Examples of LFP (same as in *a*) filtered in the θ (4–10 Hz, above), slow γ (25–50 Hz, middle), and fast γ (55–100 Hz, below) ranges. *c*) Total level of anomalous activity, all animals – integral of all high-amplitude (>3SD) events in hippocampal LFP. The level in controls was taken as 100%. *d*) Examples of frontal sections of the hippocampus stained by the Nissl method. Left: sections including all hippocampal fields and the dentate fascia in controls and after administration of kainic acid (KA); right: histogram showing mean cell density in the hippocampus as a whole (hip) and in separate parts of the hippocampus (CA1, CA3, DG); significant changes in cell numbers in field CA3 (*$p = 0.0483$).

the ratio of the signals to the average value in controls was determined.

Phase interactions were analyzed using a Gilbert transform. Phase-amplitude modulation was assessed by plotting histograms of the distribution of rhythmic events with amplitude greater than baseline (>3SD) in the filtered signal for each frequency range relative to the phase of the hippocampal θ wave. The measure of the extent of phase-amplitude modulation in different groups of animals was the Kullbak–Leibler distance.

Coherence of the two structures was assessed by plotting histograms of the distribution of phase differences between the hippocampus and entorhinal cortex for each of the frequency ranges selected. Levels of coherence were assessed using not only the maximum probability density, but also the coefficient of excess (steepness) of the distribution peak.

Histological monitoring. After completion of electrophysiological experiments, animals were prepared for tissue staining by the Nissl method to verify electrode positioning and to identify cell damage in the dorsal hippocampus (field CA3). This was carried out using a standard protocol as described in our previous reports [Malkov et al., 2018]. Neurons were counted on at least three sections at two rostrocaudal levels: AP = –3.5 mm and AP = –4.5 mm in each animal. Cells were quantitated by hand using the cell counter module of ImageJ (1.50i, USA). The presence of cell damage and reductions in cell numbers were evaluated as criteria for neurodegeneration.

Statistical analysis. Results are presented as mean ± ± standard deviation. All statistical tests were run using IgorPro (version 6.35, WaveMetrics, USA) and libraries of statistical online calculators https://www.socscistatistics.com/. Before the analysis, all initial data were tested for normality with the Kolmogorov–Smirnov test. Within-group comparisons (center-wall) were carried out using Student's *t* test. Statistical comparisons between the two groups were carried out using the unpaired *t* test or the Mann–Whitney U test. Nonparametric statistics were used to avoid assuming that dispersions were uniform and distributions normal; $p < 0.05$ was taken as the threshold for statistical significance.

Results. ***1. Electrophysiological experiments.*** The main aim of our experiments was to identify whether the θ and γ rhythms change when an animal changes its location in an arena. Analysis was based on selecting those periods of the LFP when the rat was either at the periphery or in the center of the field.

Oscillator activity in CA1 and the MEC while animals were in the open field was clearly apparent in both the θ and γ ranges (Fig. 2, *b*). Graphically, the spectral density of rhythmic power levels (SD) showed clear peaks in the θ (4–10 Hz), the slow γ (25–50 Hz), and the fast γ (55–100 Hz) ranges (Fig. 3), which were analogous to those in hippocampal field

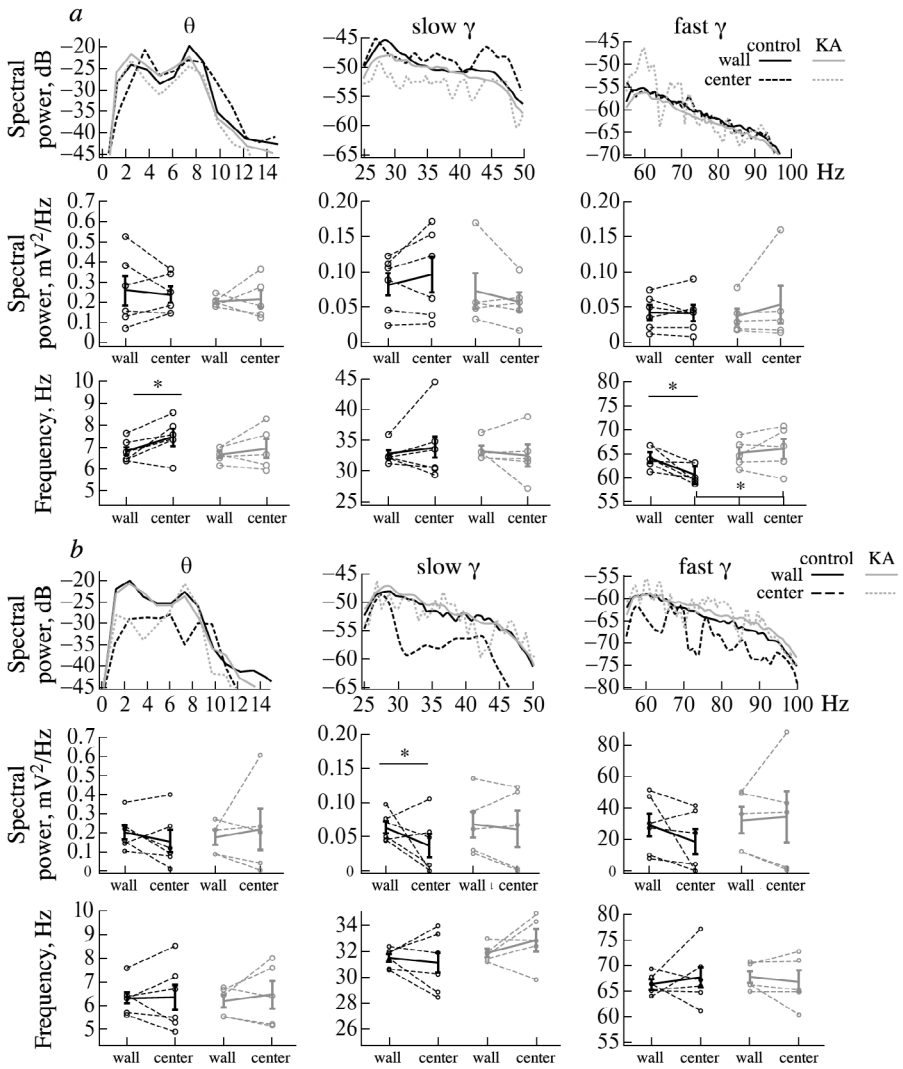

Fig. 3. Parameters of hippocampal and MEC LFP on movement of animals in the open field. *a*) Hippocampus; *b*) MEC. In *a* and *b*, parameters for the θ rhythm (left), the slow γ rhythm (middle), and the fast γ rhythm (right). The upper row shows plots of LFP spectral power for the corresponding frequency ranges. LFP spectrograms for when the animal is in the center of the open field are shown by dotted lines, those for the periphery as solid lines. The middle row shows changes in the integral power of rhythms (θ, slow γ, and fast γ rhythms) on movement of the animal from the periphery to the center. The lower row shows changes in the leading frequency of rhythms on movement of the rat from the periphery to the center. Circles show individual parameters for different animals; parameters from a given animal are shown in the center and periphery are connected by dotted lines. Mean values and standard errors are shown by solid lines.

CA1 described in earlier studies [Buzsaki, 2006; O'Keefe, 2007; Colgin, 2016].

1.1. Control group. Animals of this group sometimes moved from the peripheral zone (walls/corners) to the center of the field, but spent significantly more time at the periphery than in the center (in the 10 min of the experiment session the total time in the central zone averaged 14.5 ± ± 10.2 sec; Fig. 1). Movement speed in the center of the field was significantly greater than that at the periphery (0.43 ± 0.05 m/sec compared with 0.14 ± 0.04 m/sec; $F(1,10) = 106.51$, $p = 0.0005$); on average the animals covered 39.9 ± 10.8 m per session.

Recorded LFP showed that the θ rhythm was dominant in the hippocampus and MEC during tests (Fig. 3). Analysis of oscillation parameters in the hippocampus showed that movement of the rats from the periphery to the center of the field was accompanied by significant increases in the frequency of the θ rhythm (7.46 ± 0.4 Hz in the center vs. 6.81 ± 0.14 Hz at the periphery, $F(1,10) = 6.913$, $p = 0.0465$), and there was a tendency to a decrease in its peak power (0.237 ± 0.039 μV²/Hz vs. 0.257 ± 0.07 mV²/Hz, ($F(1,10) =$ $= 0.211$, $p = 0.664$). The fast γ rhythm also underwent significant changes: its frequency decreased significantly when the rats moved from the peripheral zones to the center of the field (from 64.0 ± 1.2 to 60.5 ± 1.85 Hz, $p < 0.05$, $F =$ $= 10.924$, $p = 0.02$); its power level did not change. The slow γ rhythm showed no significant changes as rats moved from the periphery to the center of the field.

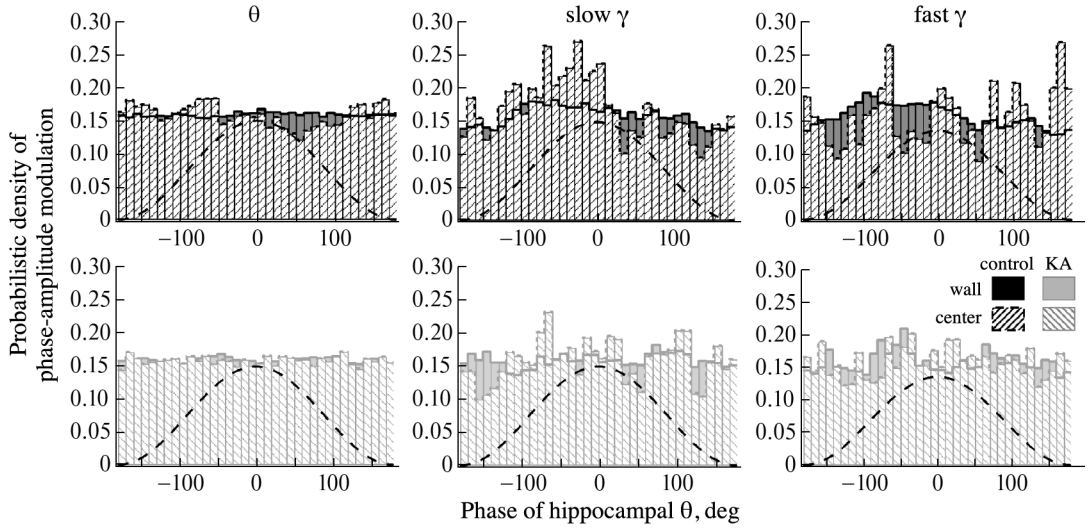

Fig. 4. Phase-amplitude modulation of MEC activity by the hippocampal θ rhythm. Distribution of θ-rhythm amplitudes (left), slow γ-rhythm amplitude (center), and fast γ amplitude (right) relative to the phase of the hippocampal θ rhythm. Averaged data for all animals. The center of the open field is shown by columns with diagonal shading and the periphery by solid columns. A single θ cycle is illustrated by dotted lines.

The MEC showed no significant changes in parameters of the θ or fast γ oscillations when rats changed their location by moving from the periphery to the center of the arena (Fig. 3, *b*). The low γ rhythm in the MEC, in contrast to that in the hippocampus, showed a significant (almost two-fold) decrease in power (0.036 ± 0.017 mV^2/Hz vs. 0.063 ± 0.009 mV^2/Hz, F(1,10) = 4.42, $p = 0.047$).

Phase-amplitude modulation of oscillations in the MEC by the hippocampal θ rhythm. The amplitude of rhythmic activity in the MEC when rats were in the center of the field was significantly modulated by the phase of the θ cycle in the hippocampus. The peak amplitude of modulation for the θ rhythm in the MEC was at the minimum of the θ cycle of the hippocampus (from 100° to –100°). The nature of the phase-amplitude modulation of the θ rhythm in the MEC by the hippocampal θ cycle did not change when the animals moved between zones in the arena (F(1,10) = 3.86, $p = 0.106$). The peak modulation for the slow and fast γ oscillations occurred at the ascending phase and peak of the θ rhythm (from –100° to 0°). On movement to the periphery, the distribution of the amplitudes of the θ, slow γ, and fast γ rhythms across the θ phase was more uniform and the measure of nonuniformity of the distribution was significantly different from its value at the center, for all rhythms (slow γ, F(1,10) = 11.5, $p = 0.019$); fast γ, F(1,10) = 10.85, $p = 0.022$) (Fig. 4).

Intra-frequency coherence of the hippocampus and MEC. Analysis of intra-frequency θ coherence between the hippocampus and MEC showed that in all animals in all locations in the field, the θ rhythm in the hippocampus was highly coherent with the entorhinal (probability density 0.255 ± 0.04 by the walls and 0.31 ± 0.06 in the center, F(1,10) = 2.92, $p = 0.148$); i.e., coherence showed a tendency to increase in the center of the field. The difference between θ phases in the hippocampus and the MEC was close to zero (–6.6 ± 15.8° at the periphery and –12 ± 18.5° in the center (Fig. 5). At the same time, γ oscillations in the hippocampus demonstrated relatively low coherence with those in the MEC with the rats in all locations (Fig. 5); the difference in phases had a wide spread and on average was close to zero. Thus, neither of the structures studied operated as the leading structure in control animals. As for the θ rhythm, movement from the periphery to the center produced a tendency to an increase in γ coherence (F(1,10) = 5.44, $p = 0.067$ for the slow γ rhythm and F(1,10) = 4.1, $p = 0.098$ for the fast γ rhythm).

Histological analysis. A total of 53 slices were tested. The mean neuron density in the hippocampus of control animals was 1742 ± 79 cells/mm^2 (Fig. 2, *d*). Cell density in hippocampal field CA3 was 1042 ± 82 cells/mm^2 and was somewhat lower than in CA1 and the dentate fascia, at 1770 ± ± 131 cells/mm^2 and 1619 ± 102 cells/mm^2, respectively.

1.2. The kainate group. We did not find any significant difference in movement speed in the open field in animals of this group as compared with control rats: as in the control group, movement speed in the center in animals given KA was significantly greater than at the periphery (Fig. 1, *b*). Animals of this group, like control rats, rarely moved from the walls/corners to the center of the field, though they showed a tendency to move to the center more often than control rats. We also found no significant differences between groups in the times spent by rats in the center or periphery; however, rats of the kainate group showed a tendency to spend more time in the center than controls (32.6 ± 16.9 sec compared with 14.5 ± 10.2 sec in controls, $p = 0.2$, U test) (Fig. 1, *d*).

Analysis of hippocampal activity revealed significantly more frequent high-amplitude activity ("sharp" waves),

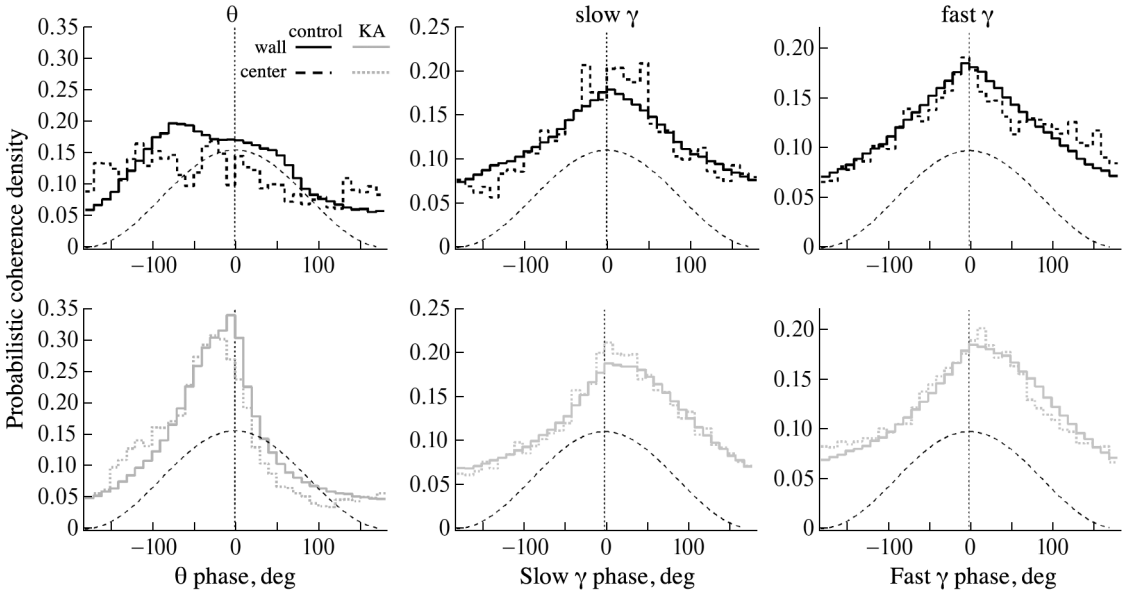

Fig. 5. Coherence of hippocampal and MEC activity in different frequency ranges. Distributions of phase differences in MEC relative to phase of the hippocampal rhythms in the corresponding frequency ranges (θ at left, slow γ in the middle, fast γ at right). The distribution in the center of the open field is shown by dotted lines and the distribution at the periphery by solid lines. A single θ cycle is illustrated by dotted lines.

at 296 ± 32% compared with controls, which were taken as 100%, U test, $p = 0.008$. In most cases, amplitude was significantly (2–3 times) greater than that in control rats (Fig. 2, *a*). However, as in control rats, recorded LFP showed dominance of the θ rhythm in the hippocampus and MEC (Fig. 3).

When the animals moved from the periphery to the center of the field, θ-rhythm power and frequency did not change in the hippocampus; there was also no significant change in slow and fast γ oscillations (the frequency of fast γ oscillations decreased in controls). However, it should be noted that in rats in the center of the field, fast γ oscillations had significantly higher frequency than those in healthy rats (66.0 ± 2.0 Hz vs. 60.5 ± 1.8 Hz, $F = 7.23$, $p = 0.025$) (Fig. 3). The frequency of the slow γ rhythm did not change when animals moved from the periphery to the center of the field, though controls showed a minor increase in frequency.

In the MEC, the parameters of θ and γ oscillations did not change when rats changed their location in the arena, and were not significantly different from those in the control group.

Phase-amplitude modulation of oscillations in the MEC by the hippocampal θ rhythm. Modulation of the amplitude of θ activity was weaker as compared with controls (U test: $p = 0.027$). For γ oscillations, changes in phase-amplitude modulation when animals moved from the periphery to the center were also less marked than in controls (the Kullbak–Leibler distance was significantly smaller; U test: slow γ, $p = 0.027$; fast γ, $p = 0.018$). It should, however, be noted that phase-amplitude modulation of the slow γ rhythm at the center of the field was significantly greater than that at the periphery ($F(1,10) = 14.37$, $p = 0.019$) (Fig. 4).

Intrafrequency coherence in the hippocampus and MEC. Coherence of θ activity in these two structures did not differ in the center and periphery of the open field ($F(1,10) = 3.19$, $p = 0.148$) but was significantly greater than in controls; differences were particularly marked when animals were located at the periphery (U test, $p = 0.042$ and $p = 0.027$ for the center and periphery, respectively). Intrafrequency phase relationships between the hippocampus and MEC in the slow and fast γ ranges did not differ from those in the control group (Fig. 5).

Histological analysis. Post mortem histological analysis in animals of this group identified damage in the hippocampus (fields CA1 and CA3) and the dentate fascia (Fig. 2, *d*). A total of 70 sections were examined. Mean neuron density throughout the hippocampus was significantly lower than in controls: 1291 ± 87 cells/mm^2 ($F(1,120) = 4.97$, $p = 0.037$, see Fig. 2, *d*). The decrease in the number of cells was observed in all areas analyzed (density in field CA1 was 1485 ± 141 cells/mm^2, that in the dentate fascia was 1319 ± 61 cells/mm^2; a significant difference in cell density was seen in field CA3: 873 ± 108 cells/mm^2 ($F(1,120) = 4.156$, $p = 0.0483$).

Discussion. This study presents evidence that one month after administration of KA and the resulting development of status epilepticus, θ and γ oscillations changed during exploratory activity in an open field. The interaction of the hippocampus and MEC and amplitude modulation of MEC rhythms by the phase of the hippocampal θ wave were also found to be impaired in animals with the kainate neurotoxicity model. It should be noted that status epilepticus generally leads to the development of chronic epilepsy, where there are repeating spontaneous convulsions [Lothman et

al., 1990; Hellier et al., 1998; Bragin et al., 1999]. We did not find any spontaneous convulsions, probably because one month is insufficient time for their clear development: published data indicate that they arise an average 2.5 months after KA-induced status epilepticus [Hellier et al., 1998]. On the other hand, the electrophysiological changes seen here can be used as early biological markers for neurodegenerative processes developing with epileptogenesis [Betjemann and Lowenstein, 2015; Lin et al., 2019].

One cause of the rhythm impairments seen in our experiments would appear to be damage to cells in the hippocampus, along with intense cell death: as demonstrated previously, hippocampal neurons play a decisive role in generating θ and γ oscillations [Buzsáki, 2002, 2006; Buzsáki and Wang, 2010].

The open field test is one of the most popular ethological tests for assessing anxiety and exploratory behavior in rodents [Broadhurst, 1957, 1958; Kiniishi et al., 2017]. Increases or decreases in movement frequencies in animals in the center of a limited space point to decreases or increases in anxiety, respectively [Prut and Belzung, 2003]. However, as our experiments included placing the rats in the open field for familiarization, their behavior during testing showed no marked agitation (there were no prolonged periods of sitting immobile in the corner). Thus, we suggest that their main motivation on being placed in the open field was to explore the environment.

Comparison of animals of the control and kainate groups did not identify any significant differences in the frequency of excursions to the center of the field or in the times spent by the rats at the periphery and center; this means that the emotional level and exploratory drive were almost identical in animals of both groups. The fact that rats given KA showed a tendency to move to the center somewhat earlier than healthy animals and to spend more time there may be evidence that they were more excitable [Prut and Belzung, 2003]. This is also evidenced by the fact that the field activity of the hippocampus showed sharp waves with almost threefold greater amplitude. The periodic occurrence of these paroxysms is seen in the normal hippocampus [Freund and Buzsáki, 1996]; however, sharp increases in their frequency and amplitude are evidence for formation of a convulsive focus [Mazarati et al., 2002; Chauviere et al., 2009]. Mazarati et al. [2002] found a statistically significant correlation between the frequency of sharp events (spikes) during status epilepticus and during the interictal period. The authors also noted that the "silent" period following status epilepticus, i.e., the absence of convulsions, was seen only in behavior, while the EEG showed paroxysmal activity [Mazarati et al., 2002].

Our main interest in this study was to detect changes in θ and γ oscillations in the rhythmic interactions between structures in the epileptic brain as compared with controls.

Experiments on control rats allowed us to identify significant hippocampal and MEC reactivity to changes in the animals' spatial location; there was an increase in the frequency of the θ rhythm and a decrease in the frequency of the fast γ rhythm in the hippocampus when the animals moved to the center. It was interesting that in the MEC, there was a significant weakening of the slow γ rhythm, while other types of oscillation remained relatively constant.

Changes in the location of the animals in the environment were regarded as accompanied by activation of attention and processing of spatial information; this is due in particular to activation of spatially modulated pyramidal cells in the hippocampus and MEC [O'Keefe et al., 1976; O'Keefe and Nadel, 1978; Hafting et al., 2005, 2008]. The θ and γ rhythms play an important role in these events [Jensen and Lisman, 2005; Caiger and Lisman, 2005; Colgin and Moser, 2010; Zheng et al., 2016]; our data are consistent with this view. The θ rhythm is known to undergo an increase in frequency as the influx of external information increases [Green and Arduini, 1954; Vinogradova, 1995; Buzsaki, 2002]; this is seen when animals move in the arena. In addition, it takes part in modulating the activity of space cells [O'Keefe et al., 1993; Hasselmo et al., 2014], and the increase in the frequency of this activity as rats move may be explained by the functional connection with the activity of these neurons. Thus, the increase in θ-rhythm frequency when the animals move from the periphery to the center of the area seen in our experiments is entirely explicable.

The fast γ rhythm in field CA1 is associated with the afferent input from layer III of the MEC [Colgin et al., 2009], which is a structure critical for information coding and spatial memory [Sutherland et al., 1983; Brun et al., 2002; Steffenach et al., 2002]. In the MEC, fast γ oscillations in our experiments did not change; nonetheless, spatially modulated neurons present in this part of the brain [Hafting et al., 2005; Taube et al., 1990] can alter their activity when the animal changes its location in the open field, thus influencing the parameters of the fast γ rhythm in the hippocampus. Specific changes in the activity of space cells, particularly grid cells, in the MEC when an animal changes its location in the environment [Hafting et al., 2005] may also explain the reduction in the power of slow γ oscillations in this structure seen in our studies.

Phase-amplitude modulation of oscillations in the MEC by the hippocampal θ rhythm. The hippocampus, which is the generator of θ oscillations, significantly modulates activity in structures connected to it. We have observed a significant relationship between phase-amplitude θ modulation of MEC activity in all frequency ranges and spatial location in rats. When the frequency of the hippocampal θ rhythm increases, the increase in phase-amplitude modulation of MEC activity when the animal moves from the periphery to the center of the open field may reflect an increase in attention and activation of coding processes and/or consolidation of spatial information [Colgin, 2015b, 2016].

Intrafrequency coherence of the hippocampus and MEC. Another interesting fact obtained in the present stud-

ies on healthy rats is that computation of intrafrequency θ coherence between the hippocampus and MEC in all animals and at all locations in the area showed that the θ rhythm in hippocampal field CA1 demonstrated a high level of coherence with the θ rhythm in layer III of the MEC, i.e., phase locking of θ activity in the two structures was strong. No leading structure was identified; the phase differences in different animals were somewhat different, which led to flattening of the probability density peak on the overall correlogram (Fig. 5). An earlier study in freely moving mice demonstrating high θ coherence between the dentate fascia of the hippocampus and the MEC: the phase difference, as in the present study, was close to zero [Froriep et al., 2012]. Thus, our data are consistent with results obtained in the study cited above, despite the fact that the experiments were performed in different rodent species and hippocampal activity was recorded at different positions. Our and the above-cited previous studies lead to the conclusion that θ oscillations in the hippocampus and MEC in healthy rodents moving in an open field are quite synchronous regardless of their locations in space. The high θ coherence between the hippocampus and MEC is evidence of a tight interaction between these structures in processing spatial information [Womelsdorf et al., 2006; Gregoriou et al., 2009; Siegel et al., 2009]. However, γ oscillations in the hippocampus demonstrated relatively low coherence with those in the MEC with animals in all locations, with a large range of phase differences. In contrast to our data, previous studies showed that fast γ oscillations in hippocampal field CA1 are coherent with those in the MEC [Colgin et al., 2009]. Later, multiple recordings of activity in all layers of field CA1 and along the proximal-dorsal axis of the dorsal hippocampus reported by Schumburg et al., [2014] were able to give accurate locations of the sources of different types of γ oscillations and demonstrated their independence. The analysis showed that γ oscillations in the MEC do not "behave" like γ oscillations in CA1; this led the authors to suggest that propagation of γ waves in the hippocampus is restricted. This may explain the differences in the results obtained by us and other authors.

In animals given kainic acid, unlike controls, the hippocampus and MEC were less reactive when the animal moved from the periphery to the center. In the hippocampus, the power and frequency of the θ rhythm, in contrast to controls, did not change; there was also no significant change in fast γ oscillations, as occurred in healthy animals. This may reflect impairment to attention processes and the memorization of information, particularly spatial information [Tramoni-Negre et al., 2017; Lemesle et al., 2017]. No decrease in the frequency of the fast γ rhythm was seen, though such a reduction occurred in control animals when moving from the periphery to the center; as a result, γ oscillations on movement to the central part of the field had a significantly higher frequency than in controls. This change in the characteristics of the fast γ rhythm depending on the location of the animal in space may be linked with a change in the activity of the hippocampal interneurons involved in forming it [Freund and Buzsaki, 1996], or their death. This may also be induced by changes in the modulating influence of the MEC, as neurons in this structure also die after status epilepticus [Betjemann and Lowenstein, 2015; Lin et al., 2019]. In the MEC, unlike the situation in control rats, we also saw no changes in the extent of slow γ oscillations when animals moved in the open field, which may be due to impairments to cell activity and cell death in both the hippocampus, where this rhythm is generated, and the MEC.

Phase-amplitude modulation of oscillations in the MEC by the hippocampal θ rhythm. In animals given KA, changes in phase-amplitude modulation of movement to the center were significantly weaker than in controls. This may reflect a decrease in the level of attention and impairment to coding processes and/or the consolidation of spatial memory seen on changes in location in normal rats [Colgin, 2015b, 2016]. These impairments may explain the decrease in memory in neurodegenerative changes in the hippocampus.

Intrafrequency coherence in the hippocampus and MEC. Another notable change in the brains of animals given kainate as compared with healthy rats was the formation of hypersynchronous θ oscillations in the hippocampus-MEC network, apparent as an increase in their coherence. Field activity in the hippocampus and MEC in animals with the kainate model reacted to changes in spatial location less than controls. In addition, changes in phase-amplitude modulation on movement of rats to the center in animals of this group were significantly weaker than in healthy animals. These changes, especially the formation of hypersynchronous θ oscillations in the entorhinal-hippocampal network, probably make appropriate information processing impossible.

From the data on changes in γ rhythms in the brains of rats given KA obtained in the present study, it remains difficult to come to firm conclusions as to which consequences might follow these impairments. The functional role of different γ-oscillation frequency bands continues to be debated in the literature, though it is known that they take part in many aspects of the cognitive operation of the brain [Colgin, 2015a, 2015b, 2016]. As regards the functions of the fast γ rhythm, it has been suggested that it has a relationship with information coding [Newman et al., 2013; Zheng et al., 2016]; it can therefore be suggested that the absence of changes seen in these rats in our studies on moving from the periphery to the center, as seen in healthy animals, is linked with impairment to spatial coding. Turning to the functions of slow γ oscillations, these have been suggested to be linked to mediating the storage (retention) of information in memory and its extraction from memory [Treves and Rolos, 1992; Steffenach et al., 2002]. Thus, we can conclude that the changes in the characteristics of the fast and slow γ rhythms seen in rats with the kainate model is evidence for impairments to spatial information coding, its storage in, and its extraction from memory in neurodegenerative pa-

thology. It is important to emphasize that changes in the characteristics of oscillatory activity when an animal changes its location in the open field in rats given injections of KA were not induced by differences in movement speed, as there was no significant difference in movement speed in the center and periphery between rats of the two groups.

Thus, using the kainate model of neurodegenerative pathology, we provided the first observation in freely moving rats of impairments to the parameters of the θ and γ rhythms, hypersynchronization of the activity of the hippocampus and MEC, and impairments to the phase-amplitude modulation of MEC activity by the hippocampal θ rhythm. As all the types of oscillatory activity studied here are involved in cognitive functions, it can be suggested that the changes seen in our studies are part of the mechanism of cognitive impairments occurring as a result of neurodegenerative processes in the hippocampus [Dupont et al., 2000; Helmstaedter, 2002; Inostroza et al., 2013] and may be used as early biomarkers for this pathology.

Conclusions

1. In the open field test, control rats and rats given the neurotoxin kainic acid showed no difference in the frequency of movement from the peripheral zones to the center of the field or in the times spent in these zones. Clear θ (4–10 Hz) and fast (25–50 Hz) and slow (55–100 Hz) γ rhythms were seen in the hippocampus and MEC in animals of both groups.

2. In all control rats in all locations in the arena, the hippocampal θ rhythm was highly coherent with the θ rhythm in the MEC; significant variability was seen in the phase difference between the experimental animals. Animals with the model of kainate neurotoxicity showed greater coherence in the θ range with phase differences close to 0°.

3. In control animals, the θ rhythm was increased and the fast γ rhythm was decreased in frequency when rats moved from the peripheral zones to the center of the field. Slow γ oscillations decreased in power. Similar changes on movement of the animals were not seen in the model of neurotoxicity.

4. Phase-amplitude modulation of MEC activity by the hippocampal θ rhythm in control rats changed significantly depending on the spatial location of the animals; kainate rats showed a significant decrease in phase-amplitude modulation of MEC activity on making excursions to the center of the open field.

6. The changes in the characteristics of θ oscillations and the fast and slow γ rhythms seen in rats with the neurotoxicity model are possible biomarkers for the impairments to memorization of spatial information and its extraction from memory seen in neurodegeneration in the hippocampus.

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