Changes in Theta and Gamma Network Oscillations during the Development of Neurodegenerative Disorders (Review)

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Theta and gamma oscillations registered in the hippocampus and neocortex are necessary for cognitive processes in the brain; their alterations are revealed in many neurological and psychiatric diseases. The most common forms of neurodegenerative disorders, Alzheimer's disease (AD) and temporal lobe epilepsy (TLE) are characterized by the loss of cells and progressive violations of cognitive functions, such as memory. Early diagnosis of diseases is very important for their successful treatment. Many efforts have been done for defining early signs of these diseases. Significant advances have been made in the searching of some AD and TLE reliable biomarkers with using biochemical and imaging approaches. However, there is a great need for the biomarkers that would reflect changes of brain activity within few milliseconds to obtain information about cognitive disturbances.

In the present review, the data of recent literature specifying that the coherent analysis of the theta and gamma oscillations can be used in early diagnostics of TLE and AD are considered. These data show that in a brain with the developing neurodegenerative disorder the specific violations of the theta and gamma interaction are observed. We summarize here the data on the alterations of the theta and gamma coherence based on examples from TLE and AD and from models of these diseases. The specific disturbances in interactions of theta–gamma oscillations in hippocampal, hippocampal–entorhinal, hippocampal–prefrontal, and hippocampal–septal networks were revealed in the epileptic brain. In the AD models, marked changes were observed in the theta–gamma coupling in the subiculum, an output region of the hippocampus. In addition, a decreased theta–gamma interaction between the hippocampus and the parietal cortex as well as between the hippocampus and the prefrontal cortex was also shown.

Key words: Alzheimer's disease; temporal lobe epilepsy; memory; oscillatory activity; coherent analysis; early diagnostics.

Introduction

Theta and gamma oscillations are the events related to cognitive processes. The theta rhythm (4 to 12 Hz) is usually recorded in the hippocampus and surrounding limbic structures during waking and rapid eye movement sleep [1–3]. Theta oscillations have also been registered in the neocortical [4–8] and subcortical structures [9–13]. The theta rhythm is important in the formation and retrieval of episodic and spatial memory [14]. The gamma rhythm (low frequency gamma, 25–45 Hz, and high frequency gamma, 50–120 Hz) usually occurs contemporary with the theta rhythm in the hippocampus [15–17]. In the neocortex, gamma oscillations mostly recorded in the frontal and parietal areas [18, 19]. The gamma rhythm is believed to play a role in attention [20, 21] and in the maintenance of relevant information in memory [22, 23]. Recent data indicating that the coupling between the phase of slow oscillations (in particular, theta) and the amplitude of fast oscillations (gamma) may be involved in information processing [24–26].

An important component of the neuronal processing underlying cognition is interaction between brain structures [27–30]. Multiple evidence point to brain rhythms as a basic mechanism of dynamical communication between brain areas; this is proved by task- and state-dependent changes in the coherence of local field potentials (LFPs) [31–37] and cross-correlated unit activity [29, 30, 38]. Synchronized activities of brain fields exert distinct effects on their ability to interact with each other [34], and provide a mechanism for the formation of cell ensembles and their coordination [30, 39–42]. The oscillations can be also considered as rhythmical changes in neuronal excitability [43, 44].

The hypothesis "communication through coherence" proposed by Pascal Fries in 2005 [44] is now widely accepted [30, 36, 45–51]. This hypothesis assumes that anatomic communications can be effective or ineffective depending on presence or lack of rhythmic synchronization [44, 52].

It is known that interaction of brain structures and oscillatory activity in them can disturb in psychiatric and neurological disorders [42, 53–57]. However, despite decades of research, the violations in the coherence of rhythms in pathologies, such as Alzheimer's disease (AD) and temporal lobe epilepsy (TLE) remain unclear.

This review summarizes the data on the changes of the theta and gamma coherence based on examples from TLE and AD and from models of these diseases. In addition, we provided the information on some similarities and differences in these disorders, mainly in

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the alterations of specific types of memory, parameters of theta and gamma rhythms and their coherence. These analyses may help to design new approaches to early diagnostics of pathologies.

Interaction of the theta and gamma rhythms

The brain generates many types of oscillations at different frequencies. Low-frequency rhythms are dynamically involved across distant brain areas by cognitive tasks or sensory signals; at the same time, high-frequency brain activity reflects local cortical processing [42]. External or internal stimuli can lead to the synchronization of rhythms and thus evoke a complex functional phenomenon known as phase coherence or phase coupling. The classical phase coherence reveals the relative constancy of the phase difference between two oscillations of the same frequency, i.e. within-frequency synchrony (Figure 1) [59, 60]. It was shown that phase coupling reflects various cognitive processes in humans, monkeys, rats, and mice [25, 42, 61–66]. The within-frequency
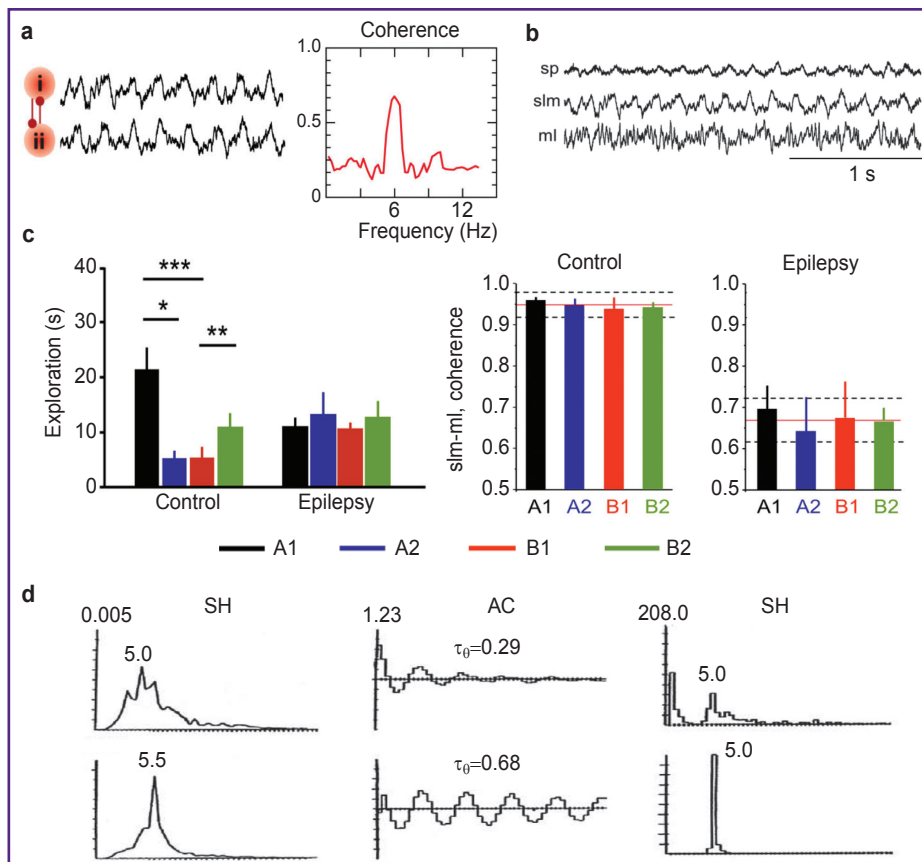

Figure 1. Changs of theta coherence between brain areas during epileptogenesis
(a) Phase–phase coupling of theta oscillations between two brain structures (i) and (ii). To the left: synthetic data used for theta rhythm illustration; to the right: coherence spectrum (or phase-specific measures) between two signals can determine the strength of theta phase coupling. (b) Representative hippocampal activity of an epileptic rat recorded in the stratum pyramidale (sp), lacunosum moleculare (slm), and moleculare (ml) during walking. (c) Behavioral data for rats during the performance of the episodic-like memory task; distribution of exploratory times per object in the test phase for the control and epileptic groups is shown. The objects shown in the task: A1 — old familiar stationary object, A2 — old familiar displaced, B1 — recent (i.e. shown 50 min later) familiar stationary, B2 — recent familiar displaced object; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.005$. Phase theta coherence between hippocampal layers (sml and ml) during exploration of each individual object in the episodic-like memory task; the mean values of theta coherence per object within the mean (*red line*) and standard deviation (*dashed line*) for the whole session in the control (*left*) and epileptic animals (*right*) are shown. It can be seen that theta coherence between hippocampal layers is high in the rat control group but significantly lower in the epileptic group. (d) Theta activity increases synchronously in the hippocampus and medial septal-diagonal band complex (MSDB) before seizures. From left to the right: spectral histograms (SH) for hippocampal local field potentials; autocorrelograms (AC) and SH for neuronal activity of MSDB; *above* — background, *below* — before seizures. On SH: the ordinate axis — spectral density (relative units); the abscissa axis — frequency, from 0.5 to 30 Hz; on AC: the ordinate axis — the value of the decay time constant of the rhythmic process (τ or rhythm index) (s); the abscissa axis — time, from 0 to 1 s. Adapted with permission from *Buzsáki, Watson, 2012* [42] (a); *Inostroza et al., 2013* [56] (b), (c); *Kitchigina, Butuzova, 2009* [58] (d)

phase coherence between oscillations in different brain areas (Figure 1 (a)) was studied extensively because of its proposed role in the regulation of inter-structural communications [34, 67–70].

Besides, the correlation between the amplitude envelopes of two brain waves at different frequencies, called cross-frequency amplitude–amplitude coupling, is also an oscillatory characteristic [71, 72]; this type of coupling was observed by some authors [71–74], but despite correlations with behavior, its functional role remains poorly understood.

The phase coupling between theta and gamma oscillations, namely, the phase–amplitude cross-frequency coupling (CFC) [7, 15, 22, 25, 64, 66, 75–83] and the phase–phase CFC in which several gamma cycles are entrained within one cycle of theta [84–88] are the most studied phenomena of phase coherence. The phase–amplitude CFC describes the dependence between the phase of the low-frequency rhythm and the amplitude of the high-frequency oscillations [24] (Figure 2). Thus, it reflects the interrelations between local microscale [49, 90] and system-level macroscale neuronal networks [24, 78, 91].

The case when the phase of slower oscillations modulates the amplitude of a faster rhythm (or rhythms) is probably the most prominent 'law' underlying the hierarchy of the system of brain oscillators [15, 92, 93]. Thus, phase–amplitude CFC can be used as an index of cortical excitability and network interactions [94–96]. In non-epileptogenic hippocampi of neurosurgical patients and in a healthy brain of rodents, the degree of theta–gamma phase–amplitude coupling increases with learning [25, 64, 97]. In the hippocampus, gamma and theta oscillations normally show a marked phase–amplitude CFC considered to be central to hippocampal functions [25, 64, 98]. Thus, during spatial learning, the strength of hippocampal theta–gamma coupling usually directly correlated with the increase in correct performance of a cognitive task [25].

At the same time, phase–phase CFC provides, as believed, a physiological mechanism for the linkage of the activity generated at significantly different rates. Since gamma oscillations are faster than theta ones, numerous cycles of gamma arise during a single cycle of theta (Figure 2 (a), (b)). The phenomenon of phase–phase theta–gamma coupling means that gamma waves always begin at the same phase of theta waves. Phase–phase CFC was hypothesized to take part in cognitive processes, such as attention and memory [22, 71, 78, 99, 100]. An influential model in which theta and gamma oscillations would interact to produce a neural code ("7±2 short-term memories"), in which several gamma cycles are entrained within one cycle of theta has been proposed a decade ago [78]. Latest findings show that this mechanism indeed is used by the hippocampus [85–88]. It is assumed that the temporal coordination of neuronal spikes by phase–phase theta–gamma coupling may improve transferring

information as well as spike-timing-dependent plasticity [100–102]. Desynchronization of these rhythms could be altered in certain neurodegenerative pathologies.

Disturbances of theta–gamma coherence are typical for Alzheimer's disease and temporal lobe epilepsy

Alterations in rhythm coherence in the epileptic brain. Epilepsy, a disorder associated with increased network excitability and neuron loss, is usually accompanied by rewiring in the brain (for review, see [103]). TLE is the most common and pharmacologically resistant type of adult focal epilepsy. In patients with TLE, selective and marked degradation of episodic (autobiographic) memory was shown, in which specific memory items are placed within temporal context during encoding and retrieval [104]. Animals with TLE also exhibited a highly specific impairment of the episodic-like memory while mostly preserving other forms of hippocampal-dependent memories [105–107].

Hippocampal network. The analysis of hippocampal LFPs in neurosurgical patients during the execution of episodic memory tasks revealed a sharp increase of gamma oscillations in non-epileptogenic hippocampi before successful item encoding. At the same time, the epileptogenic hippocampi exhibited a significant decrease in the gamma band power, which predicts successful item encoding [97, 108]. Thus, typical changes in the gamma band power during this process are reversed for human epileptogenic hippocampus [108]. Besides, it was shown in the TLE model [56] that kainate-treated rats with deficit of episodic-like memory exhibited reduction of hippocampal theta power and coherence along the CA1–dentate axis. In TLE animals, decreased theta coherence in the LFP signals was concentrated between the hippocampal stratum lacunosum-moleculare and moleculare of dentate gyrus (DG) (Figure 1 (b), (c)). Inostroza and colleagues [56] believe that these data point to discoordination of hippocampal inputs from layers III and II of the entorhinal cortex (EC) and from the contralateral hippocampus as a possible cause for dysfunction of episodic-like memory in TLE animals.

Hippocampal–entorhinal cortex network. It is known that a crucial mechanism of episodic memory is the coherence of neuronal activity in the hippocampal–entorhinal circuit; this mechanism is usually impaired in TLE [105]. An alteration of theta coherence between the EC and the DG was revealed in behaving kainate-injected epileptic mice during the interictal phase [54]. Indeed, in epileptic mice, the theta activity in the EC was delayed with respect to that of the DG, while the theta activity in healthy animals was synchronized between EC and DG, demonstrating the within-frequency phase coupling. On the basis of a computational neural mass model, the authors suggested that hippocampal cell loss destroyed the coupling of the subnetworks, which induced the EC–DG shift [54].
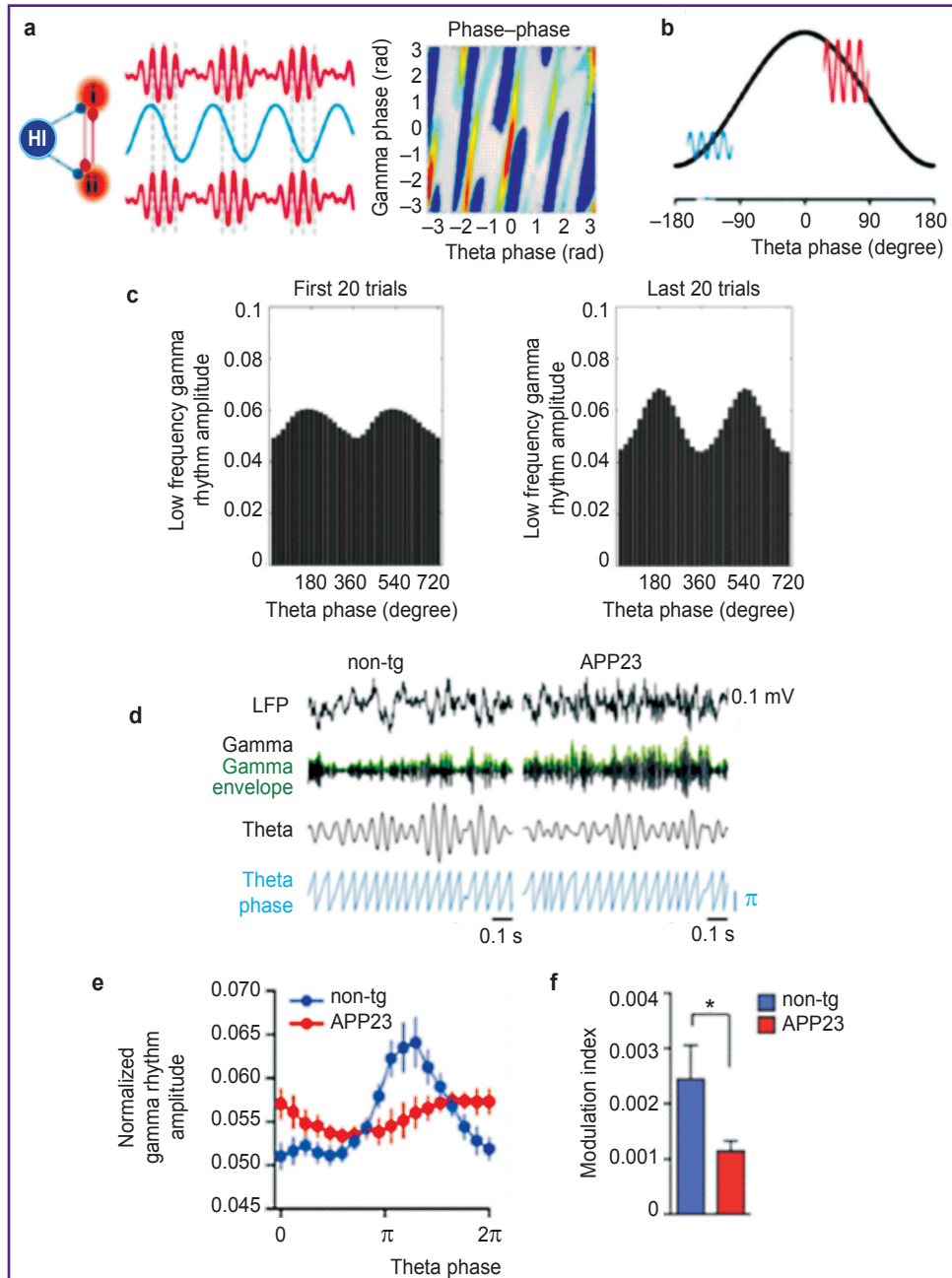
Figure 2. Theta–gamma cross-frequency coherence and its alteration in a rat Alzheimer's model

(a) Schematic illustration of cross-frequency phase–phase coupling. Phases of theta and gamma oscillations are correlated, as shown on the right by the phase–phase plot of the two frequencies; (i) and (ii) — different brain areas, Hi — hippocampus. (b) A schematic model of cross-frequency phase–amplitude coupling. Gamma oscillations are large in the excitatory phase of theta wave (near to the top) and small in the inhibitory phase of theta wave (near to the trough). (c) Amplitude of gamma oscillations in the hippocampal CA3 field increases with learning; the distribution of gamma amplitudes is shown depending on the phase of the theta wave during the first twenty samples (*left*) and during the last twenty samples (*right*). (d) Top-down: original local field potentials (LFP), filtered theta (4–12 Hz) and gamma (25–100 Hz) oscillations, gamma-wave envelope, theta phase in APP23 (tg) and normal (non-tg) rats; representative signals from 5 animals of each genotype are presented. (e) Phase–amplitude plot (gamma amplitude modulation by theta wave phase) computed for hippocampal LFPs recorded in control and APP23 (tg) mice. (f) Modulation index computed for the phase–amplitude distributions shown in (e); * $p<0.05$. Adapted with permission from *Buzsáki, Watson, 2012* [42] (a); *Kirihara et al., 2012* [53] (b); *Tort et al., 2009* [25] (c); *Ittner et al., 2014* [89] (d)–(f)

In experiments with healthy rats, the inputs from the medial and lateral EC (via temporoammonic and perforant inputs) evoked a firing of hippocampal neurons, which reflects an integrated representation of spatial and temporal information [109–113] as well as new experience [114, 115]. This neuronal coding is precisely

organized within a time scale, which is controlled by ongoing oscillations, especially by the hippocampal theta and gamma rhythms [2, 14, 26, 116–119]. A careful measurement of the proximodistal coherence of the theta activity in the dorsal hippocampus of normal and epileptic animals showed that healthy rats exhibited a stronger coordination between the temporoammonic and perforant entorhinal inputs near CA3 field (at proximal locations), while epileptic rats showed stronger coordination near subiculum (at distal locations) [57]. This opposing trend in epileptic rats was associated with the connectivity constraint, which accompanies cell death in the hippocampus. Laurent et al. [57] also discovered that the appropriate timing between entorhinal inputs arriving over several theta cycles at the proximal and distal ends of the dorsal hippocampus was impaired in epileptic rats. It is important that the computational reconstruction of LFP signals predicted that timing variability has a major impact on repairing theta coherence. Thus, the proximodistal organization of entorhinal inputs plays an important role in temporal lobe physiology, and this organization alters during TLE [57].

Hippocampal–medial prefrontal cortex network. As was mentioned above, experiments with healthy animals showed that theta and gamma oscillations are usually present and work in synchrony in the hippocampus and medial prefrontal cortex (mPFC) during the performance of cognitive tasks [19, 64]. Hippocampal theta oscillations are normally coupled to mPFC theta waves [19] and modulate hippocampal and mPFC gamma oscillations during cognitive behavior [64, 120, 121]. In a TLE model generated by perforant path stimulation, abnormal changes in the hippocampal–mPFC circuit were observed during the recording of mPFC and hippocampal LFPs in rats with spontaneous recurrent seizures [122]. Broggini and colleagues [122] showed that recurrent seizures weaken hippocampal theta rhythm while the hippocampal and mPFC theta coherence increases during a period preceding the onset of seizures. Simultaneously with the increase in theta synchrony a stronger coupling between hippocampal theta and mPFC gamma oscillations was observed. Using the Granger causality, it was shown that the increase in hippocampus–mPFC synchrony in the preictal phase was provoked by hippocampal networks. The data indicate that the increase in hippocampal–mPFC coherence may predict the seizure onset [122]. Besides, the too strong coupling of hippocampal theta and mPFC gamma oscillations may induce abnormal plasticity in mPFC communications [86].

Hippocampal–septal network. The registration of LFPs in the hippocampus and medial septal-diagonal band complex (MSDB) of rats and guinea pigs revealed that normally theta oscillations were relatively synchronous in these brain regions [10, 13, 36]. Usually, theta power in the MSDB was smaller compared to that in the hippocampus, but the frequency of theta oscillations, although it did not coincide in these structures, did not differ significantly. The theta coherence between the hippocampus and MSDB was relatively high: a phase analysis revealed no clear unidirectional shifts (<10 ms) in the hippocampal and MSDB theta phases in healthy animals [10, 13]. In chronic epileptic animals, a significant decrease of the theta power was revealed in the hippocampus [36, 123–126] and MSDB [13]. In addition, in a pilocarpine rat model of TLE, a dysfunctional and uncoupled septohippocampal network was revealed [127]. However, in the perforant path kindling model of TLE, some increase in synchronization between hippocampus and MSDB within the theta band was observed in waking guinea pigs during epileptogenesis [13]. Besides, in this model of TLE, a dramatic increase of the theta oscillations simultaneously in the rabbit hippocampus and MSDB before (within 20 s) the seizures was observed [58]. This phenomenon reminds the events in the hippocampal–mPFC network over time prior to seizure onset in rats in the same model of TLE [122]. Interestingly, in the perforant path kindling model of TLE in guinea pigs, the interactions between the hippocampus and MSDB changed for opposite during epileptogenesis: at the beginning of kindling, the MSDB was ahead in the theta phase, but after formation of the pathological focus, MSDB lagged the hippocampus [13]. In addition, the relationships between rhythmic bursts of septal neurons and the phases of the hippocampal theta waves during spontaneous seizures in rabbits with TLE model could reverse to almost opposite comparative to interictal ones [58], i.e, these relationships were not constants.

Alterations in the rhythm coherence in Alzheimer's disease and in the Alzheimer's disease models

Disturbances of theta and gamma rhythms in brain with AD pathology. AD is a progressive neurodegenerative disease associated with an irreversible deterioration of cognitive functions, especially memory. Although the etiology of AD remains unknown and now there is no reliable treatment, a consensus has emerged early in this century on the amyloid hypothesis [128, 129], which posits that the amyloid β (Aβ) peptide, a major constituent of amyloid plaques, is mostly responsible for the alteration of cognitive functions [129, 130]. In the last years, however, this hypothesis was challenged: a potential role of metabolism impairment of amyloid precursor protein (APP) and its progress through tau pathology were considered in the etiology of AD (for review, see [131]). Moreover, the recent data of experiments with wild-type and APP/PS1 transgenic mice indicate that amyloid plaques can possess capacity for binding additional Aβ [132].

Various forms of memory are disturbed in AD [133]. It has been assumed that navigation deficits can help to separate individuals at higher risk of developing AD from patients with other neurodegenerative diseases [134]. As it was revealed in some works, AD patients, as opposed to healthy age-matched control subjects, exhibit an increase in the relative power of slow oscillations (in particular, theta rhythm) and a decrease in the relative

power of fast oscillations (gamma rhythm) [135–139]. On the contrary, in other works, an increased gamma rhythm power and the lack of theta increase in AD patients were reported [140, 141]. Some authors noted that changes in EEG of resting AD patients might not be specific, and various types of dementia can also exhibit similar network disturbances [136]. Besides, contrary to the data on AD patients, a decrease of both theta and gamma bands was revealed in Tg5xFAD mice, a transgenic mouse model of AD; in this case, the decrease preceded alterations in learning performances in spatial task [142]. In addition, transgenic APP23 mice, another mouse model of AD, demonstrated the compromised spectral contributions of hippocampal theta and gamma oscillations, compared to nontransgenic controls: a markedly lower spectral power of theta oscillations (~10 Hz) and a higher power of gamma oscillations (25–50 Hz) [89], changes opposite to those in AD patients. Hence, a decrease or an increase in theta and gamma oscillations power per se may not be specific for this pathology [136].

Alterations in theta–gamma coherence are indicative for brain with AD pathology. Probably, most convincing evidence of rhythm disturbances in a pathological AD brain is alterations in the theta–gamma CFC. Thus, in humans with AD, an enhanced CFC between the gamma and low-frequency bands (in particular, theta) compared to healthy control was revealed [141]. During performance of working memory tasks, evidence for a relationship between altered theta–gamma coupling and working memory deficits in individuals with AD was obtained [143].

In the AD model (adult APP23 transgenic free-roaming mice), an impairment of cross-frequency gamma amplitude modulation by hippocampal theta rhythm was observed [89] (Figure 2 (c), (d)). It is important that these changes were observed before the onset of Aβ plaque pathology. Moreover, it was shown on TgCRND8 mice that a significant proportion of 1-month-old animals exhibited marked alterations in the theta–gamma coupling in the output region of the hippocampus, the subiculum. This uncoupling of rhythms arises before any histopathological abnormalities such as the presence of amyloid plaques [144]. In addition, it was shown that 1-month-old TgCRND8 mice expressed extremely low levels of Aβ compared to controls. Goutagny et al. [144] suggested that in animals (TgCRND8 mice) disturbed theta–gamma CFC in the subiculum may be the earliest detectable AD-related biomarker. This is in contrast with the existing hypothesis, which states that the beginning of hippocampal network alterations and memory deficits in animal models of AD are caused by the overproduction of soluble Aβ [129, 130, 145].

Interestingly, though APP is supposed to be critically involved in the pathophysiology of AD, APP-deficient mice exhibit cognitive deficits [146, 147]; this confirms that APP plays an important role in the functioning of neurons in the healthy brain. Recently, strongly diminished theta–gamma coupling in LFPs from the dorsal hippocampus and parietal cortex was revealed in APP knockout mice. Besides, cross-regional hippocampal–prefrontal CFC was largely disrupted in these knockout mice [148]. This effect may be of importance for the origination of cognitive deficits in APP-deficient animals. Thus, APP is important for the interaction of rhythms of different frequencies. The facts mentioned above possibly indicate, that there exists very thin frontier between functioning of APP in the healthy and pathological brains.

Quite recently, it has been tested whether a preclinical AD pathologic feature, tau aggregation in the EC, can disrupt the coordination of LFPs between its two efferent regions, the hippocampus and prelimbic mPFC [73]. Tanninen and colleagues [73] revealed strengthened phase–phase and amplitude–amplitude couplings of theta and gamma oscillations in these two regions during associative learning in healthy rats. In tau-expressing rats, the hippocampus and prefrontal cortex showed a significant attenuation of stimulus-evoked theta oscillations. In addition, despite normal memory acquisition, the learning-related oscillatory coupling between the hippocampus and the prefrontal cortex in these rats was diminished; at the same time, the entorhinal tau overexpression enhanced the stimulus-evoked theta–gamma phase–amplitude coupling within the mPFC. The authors suggested that the tau aggregation in the EC caused aberrant long-range circuit activity during associative learning, indicating the disturbances in neural oscillations of preclinical AD stages [73].

Similarities and differences in brain disorders with neuropathologies peculiar for Alzheimer's disease and temporal lobe epilepsy

Similarities in the alterations of oscillatory activity in the AD/TLE brain (in particular, disturbances in theta–gamma coherence in hippocampal-neocortical networks) suggests that these diseases have some common properties and, probably, at least partially similar mechanisms of their development.

The potential relation between TLE and AD has been supported by experimental and clinical data. Thus, aging is a common and well-established risk factor for epilepsy and AD [149–153]. Besides, AD may be an important cause of epileptic disorders, as shown in elderly humans [149, 154–156] and in animals with AD models [153, 157]. Patients with AD have a five- to tenfold increased risk of the development of seizures or other forms of epileptiform activity [150]. Although seizure pathology was previously believed to be secondary to AD, it was found that neuronal activity can regulate regional vulnerability to Aβ [129, 158, 159]; in particular, enhanced neuronal excitability can increase Aβ generation [160]. Moreover, disturbed activity may

contribute to the development of cognitive violations: epileptiform and rhythmic abnormalities in the temporal regions (in particular in the hippocampus) can cause amnestic disorders, which were reduced by antiepileptic drug treatment [55, 161]. In patients with seizures in combination with AD, a case series from California with so-called vu/déjà vu phenomena was described [162], while another series from France [163] had some cases that were termed "epileptic prodromal AD". The authors believed that there is an epileptic version of AD, which usually starts with seizures as an initial symptom followed by cognitive deficit. Similar signs of cognitive and behavioral impairments in TLE and AD have been recently described by Chin and Scharfman [164].

Abundant clinical evidence indicates to increased comorbidity of seizure pathology in AD: it is becoming clear that AD is associated with neuronal hyperexcitability as well as network hypersynchronicity, which is the main reasons of epilepsy development [165–168]. Indeed, epileptic prodromal AD patients suffer from seizures sometimes even before developing clear cognitive disorders. The epileptiform activity may manifest itself in the early stages of AD more often than was previously proposed. Thus, seizures in patients with AD and amnestic mild cognitive impairment are associated with an earlier appearance of cognitive decline [150, 162, 169, 170].

At the same time, neurodegenerative processes peculiar to dementia can play a central role in the development of epilepsy in the patients predisposed to cognitive deficit. Adult-onset epilepsy of unknown cause could thus represent a risk factor for the ongoing neurodegenerative damage, even when epileptic manifestations and clinically recognized dementia are separated by long time [171].

In the hippocampus, one of the main foci of cell death in TLE and AD brains, the network hypersynchronicity and epileptiform activity can be the result of formation of extensive aberrant neuronal connections. This aberrant remodeling was revealed in epileptic rats and in APP transgenic mice [39, 129, 158, 172, 173]. The aberrant reconstruction can be a cause of alterations in the oscillatory activity and rhythm coherence in brains with TLE and AD pathologies.

Conclusions

The main difficulties in diagnosis of neurodegenerative diseases are the detection of neuronal abnormalities at early stages of their development. Now significant achievements have been made in the development of methods for the detection of some biomarkers of AD and TLE, including cerebrospinal fluid and plasma measurements and glucose positron emission tomography. However, there is an urgent need for biomarkers that would reflect changes in brain functioning within few milliseconds to obtain information about the progressing cognitive deficiency [174]. The application of

magnetoencephalography [175] in combination with the coherent analysis, in particular during cognitive loading, is a promising approach to early diagnosis of these diseases. Thus, the specific disturbances in interactions of theta–gamma oscillations in hippocampal, hippocampal–entorhinal, hippocampal–prefrontal, and hippocampal–septal networks were revealed in the epileptic brain. In the AD models, marked changes were observed in the theta–gamma coupling in the subiculum, an output region of the hippocampus. Besides, a decreased theta–gamma coupling between the hippocampus and the parietal cortex as well as between the hippocampus and the prefrontal cortex was also shown.

Possibly, in future, specific disturbances in theta–gamma coherence will serve as markers of particular cell damage and will allow one to direct therapeutic influences to certain neural loci at early stages of the development of the disease.

Conflicts of interest. The authors have no conflicts of interest to disclose.

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