Review

Oscillations in the dentate gyrus as a tool for the performance of the hippocampal functions: Healthy and epileptic brain

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Highlight

- Oscillations in the activity of dentate gyrus play an important role in cognition
- Theta, beta and gamma rhythms involved in information processing performed by dentate neurons
- Impairment of cognitive functions during epileptogenesis associated with changes in dentate structure and activity
- Alterations in theta oscillations and theta rhythm coherence are signs of seizure pathology
- Disturbances of oscillations in the dentate gyrus can be used as a diagnostic marker in the treatment of epilepsy

Abstract: The dentate gyrus (DG) is part of the hippocampal formation and is essential for important cognitive processes such as navigation and memory. The oscillatory activity of the DG network is believed to play a critical role in cognition. DG circuits generate three main rhythms: theta, beta, and gamma, which participate in the specific information processing performed by DG neurons. In the temporal lobe epilepsy (TLE), cognitive abilities are impaired, which may be due to drastic alterations in the DG structure and network activity during epileptogenesis. The theta rhythm and theta coherence are especially vulnerable in dentate circuits; disturbances in DG theta oscillations and their coherence may be responsible for general cognitive impairments observed during epileptogenesis. Some researchers suggested that the vulnerability of DG mossy cells is a key factor in the genesis of TLE, but others did not support this hypothesis.

The aim of the review is not only to present the current state of the art in this field of research but to help pave the way for future investigations by highlighting the gaps in our knowledge to completely

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appreciate the role of DG rhythms in brain functions. Disturbances in oscillatory activity of the DG during TLE development are described in detail that may be a diagnostic marker in the treatment of this disease.

Keywords: oscillations, theta rhythm, gamma rhythm, coherence, temporal lobe epilepsy

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Introduction

The dentate gyrus (DG) is an evolutionary late substructure of the hippocampal formation (Papp et al., 2007; Kempermann, 2012; Stridter, 2016). This region is largely enigmatic because of its special properties and the complexity of investigation. Among the subregions of the hippocampal formation, the DG is the main target for sensory inputs from neocortical structures (putative "store" of information) and subcortical areas, which carry new signals to the hippocampus. Being an internal relay of the hippocampus, the DG is necessary for the implementation of such cognitive functions as novelty detection (Vinogradova, 2001; Hunsaker et al., 2008; Aggleton et al., 2013), pattern separation (Rolls 2016), information encoding (Treves, Rolls, 1994; Rolls, 2018), spatial working memory (Sasaki et al., 2018), and memory consolidation (Nakashiba et al., 2008; Kitamura et al., 2014; Park et al., 2016; Sasaki et al., 2018). The oscillatory activity of the DG network and dentate selective neurons is believed to play an important role in these functions.

The hippocampal formation generates many types of oscillations, which are involved in higher cognitive processes, such as memory and navigation (Eichenbaum et al., 1999; Vinogradova, 1995, 2001; Burgess et al., 2002; Nakazawa et al., 2004). Four main types of rhythms: theta, beta, gamma, and ripple oscillations are usually recorded in the CA1-CA3 hippocampal fields and DG. These rhythms differ in frequency, have behavioral correlates in several species, including rodents and humans, and are thought to perform particular functions in information and memory processing (Bragin et al., 1995a; Kopell et al., 2000; Pinto et al., 2003; Buzsáki, 2006; 2010; Colgin et al., 2016).

Thus far, most studies of hippocampal oscillatory activity have focused on CA1-CA3 fields. The nature and functions of various rhythms in the DG may differ from those in the hippocampus proper due the specific features of the DG, but this issue is yet poorly understood.

The mechanisms of temporal lobe epilepsy (TLE, a disease in which the main lesions occur in the hippocampus) have been studied for a long time, but there are still many ambiguities in this aspect. Studies of pathological tissues show that the DG is a common site of neuronal loss in this pathology (Margerison and Corsellis, 1966). How this loss affects the oscillatory activity of the DG and the

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hippocampus is not yet fully elucidated. A detailed analysis of alterations of rhythms in the epileptic brain, in particular in the DG, can contribute to understanding the mechanisms of development of the seizure disease.

The present review summarizes the data on oscillations in the DG of the healthy brain, as well as their changes in TLE; these data are based on materials from patients suffering from TLE and on animal models of this pathology. The mechanisms of generation of DG rhythms and their disturbances in the epileptic brain are also considered here, but only in general terms. A short description of the structural and morphological features of DG in the healthy and epileptic brains is also presented.

A detailed analysis carried out in this review may shed light on probable links between the damage to the DG network and rhythmopaties in the epileptic hippocampus and help in a search for new approaches to the early diagnosis of TLE, thereby contributing to the finding of new drugs for its treatment.

Dentate gyrus as a special part of the hippocampal formation

Structural, morphological, and biochemical features of the DG

The main structural components of the DG are a layer of granule cells, which forms two blades, and the hilus located between them. The DG is the only region of the hippocampus that contains two distinct glutamatergic cell types: numerous densely packed granule cells, located mostly in the granular layer, and relatively few mossy cells scattered in the hilus (Amaral, 1978; Amaral et al., 1990; Amaral et al., 2007) (**Fig. 1A**). A characteristic feature of mossy cells is the presence of several “thorny excrescences” on the bodies of neurons and proximal dendritic areas (Amaral, 1978; Ribak et al., 1985; Frotscher et al., 1991; Sharfman, 2016). The axons of DG granule neurons (mossy fibers) form very large (“giant”) synapses on mossy cells of the DG and CA3 pyramidal cells and interneurons. In addition to glutamate, these synapses contain vesicular zinc (Cole et al., 1999). It has been shown that zinc modulates the general excitability of the hippocampal network, affecting the release of glutamate; in the absence of vesicular zinc, exocytosis slows down (Lavoie et al., 2011).

Outside the granular layer, small subsets of granule cells are located. These are *semilunar* granule cells situated next to the granular layer (Williams et al., 2007; Larimer and Strowbridge, 2010) and *ectopic* granule cells located at the hilus (Scharfman et al., 2007). Semilunar granule neurons have a connection with mossy cells, due to which these neurons can activate mossy cells, bringing them to what is called a hilar upstate (Williams et al., 2007; Larimer and Strowbridge, 2010). The main postsynaptic targets of mossy cells are the dendrites of granule neurons (Blasco-Ibáñez, Freund, 1997; Scharfman and Myers, 2012). It is important that granule and mossy cells also form synaptic contacts

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with various *interneurons* located in all DG layers; their main characteristics and functions are similar to those of the hippocampus proper (Freund, Buzsáki, 1996).

It is interesting that the GABAergic phenotype of glutamatergic granule cells/mossy fiber terminals is observed in the brain of developing rodents (Ramirez and Gutiérrez, 2001; Gutiérrez, 2003, 2009; Maqueda et al., 2003; Safiulina et al., 2006) as well as of adult animals and humans (Sandler and Smith, 1991; Sloviter et al., 1996; Lehmann et al., 1996; Bergersen et al., 2003; Zander et al., 2010). However, there exists also evidence against the release of GABA from glutamatergic mossy fibers in the hippocampus (Xiong et al., 2012; Uchigashima et al., 2007). The reasons for this discrepancy are expected to be elucidated in future experiments.

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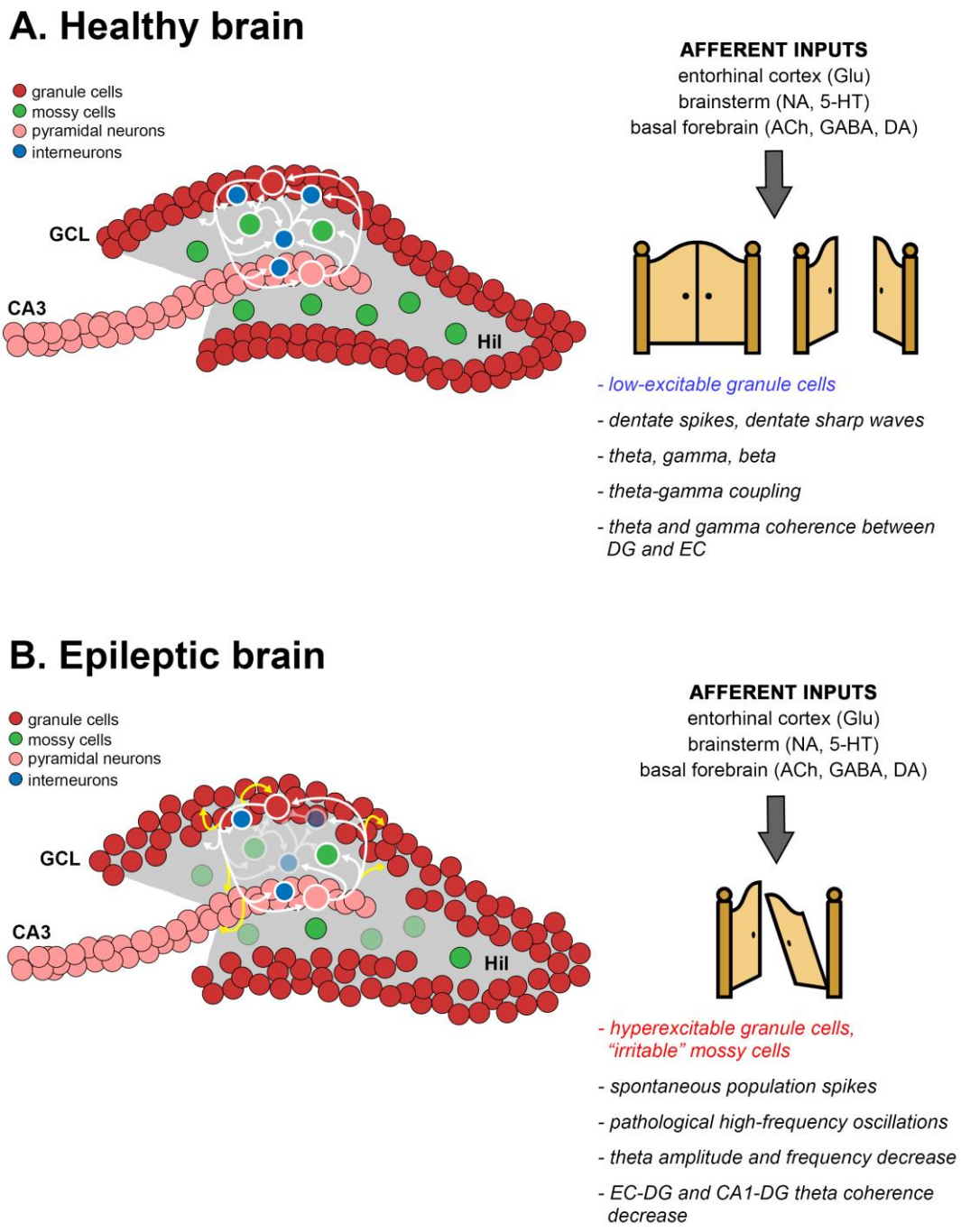

Fig. 1. **The dentate gyrus (DG) in healthy and epileptic brain.**
(A) *Left:* schematic of the DG with simplified connections between the dentate cell types and between DG and CA3 neurons. *Right:* the "gate" function of the DG. A phenomenon called "dentate gating" (Lothman et al., 1992) controls the propagation of excitatory signals from the neocortex to the hippocampus. The sources of major afferent inputs and normal DG activity are indicated.
(B). Alteration in DG structure and network activity during epileptogenesis. Damage/death of neurons and their projections is marked as ghost images; yellow lines represent formation of new recurrent exciting terminals. Impairment of DG "gate" function is considered to be a potential mechanism for generating ictal and interictal events in humans and animals.

5-HT, serotonin; ACh, acetylcholine; DA, dopamine; EC, entorhinal cortex; GCL, granule cell layer; Hil, hilus of the DG; NA, noradrenaline.

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Afferents to the DG come from many sources. The main cortical input to the DG is a glutamatergic projection pathway from layer II of the entorhinal cortex (the perforant path) to the dendrites of granule cells in the outer molecular layer (OML, input from the lateral entorhinal cortex) and in the medial molecular layer (MML, from the medial entorhinal cortex) of the DG (Steward and Scoville, 1976; Amaral et al., 2007; Witter, 2007) (**Fig. 1A**). The OML and MML also receive inputs from the brainstem (including noradrenergic and serotoninergic inputs) and from cholinergic and GABAergic neurons of the basal forebrain; another pathway is formed by the commissural projection system. The hilus receives various inputs, including the axons of granule cells, GABAergic DG neurons, mossy cells, and CA3 pyramidal cells, as well as neuromodulatory inputs from the brainstem (such as noradrenaline, serotonin, and dopamine neurons) and cholinergic cells of the basal forebrain (Amaral, Campbell, 1986; Swanson et al., 1987; Leranth, Frotscher, 1987; Nyakas et al., 1987; Leranth, Hajszan, 2005; Brown et al., 2005; Etter, Krezel, 2014; Hashimotodani et al., 2018; Salib et al., 2019). The outputs of the DG are formed by mossy fibers (axons of granule neurons) that project to the CA3 hippocampal field. A large projection of mossy cells (known as a 'distant' projection) terminates away from the cell body in both the ipsilateral and contralateral DG (Zimmer, 1971; Berger et al., 1981; Ribak et al., 1985; Frotscher et al., 1991; Buckmaster et al., 1996; Amaral et al., 2007; Scharfman, Myers, 2012). Thus, the DG is an exclusively internal relay of the hippocampus: the axons of DG cells do not extend beyond its contralateral region (Raisman et al., 1965; Blackstad, et al., 1970; Amaral, 1978; Ribak et al., 1985).

In the classic concept of the hippocampal network, DG granule cells are the first processing stage of the "trisynaptic loop'', which receives inputs from the entorhinal cortex (EC) and sends projections to the CA3 field of the hippocampus. Subsequently, a more complex circuitry was revealed, with the mossy cells forming both a disynaptic, recurrent processing loop within the DG and a disynaptic, feedback loop from the CA3 region to the DG granular layer (Scharfman, 1994, 2007; Myers and Scharfman, 2009). It should also be noted that, according to recent data, granule neurons, mossy cells, and local interneurons within the DG exhibit a complex pattern of feedback loops the strength of which changes during ontogenesis (Shi et al., 2019). Mossy cells innervating both glutamatergic and GABAergic neurons (Scharfman, Schwartzkroin, 1988; Buckmaster et al., 1996; Scharfman, Myers, 2012) are likely to be involved in the organization of complex network activity both in the DG itself and in the hippocampus. It is important that granule neurons and mossy cells can interact, and their interaction allows for the appropriate mixing of distal and local representations, enabling these cells to share both environmental contexts and remarkable local cues (Senzai, Buzsáki 2017).

The DG is a unique brain region, one of the few in adult mammals, including humans, where *neurogenesis* occurs (Eriksson et al., 1998; van Praag et al., 2002; Spalding et al., 2013). During a

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period of four to six weeks after birth, new granules are physiologically different from their mature counterparts. Several studies proposed that hippocampal neurogenesis may be necessary for cognitive flexibility, since it allows the avoidance of interference between novel and previously formed memories (Wiskott et al., 2006; Appleby Wiskott, 2009; Appleby et al., 2011; Rubin et al., 2014; Hvoslef-Eide and Oomen, 2016). Thus, the DG exhibits a unique form of neural plasticity by which newly born granule cells are integrated continuously into the DG neural network.

Characterization of DG neuronal activity

It is known that granule cells fire very sparsely during wakefulness and exhibit a higher frequency of discharges in the state of slow-wave sleep compared to the waking state. In contrast to them, mossy cells show a relatively high background firing rate and fire promiscuously in different animal locations and environment; they reveal a higher-frequency activity during wakefulness and a similar discharge frequency in the states of slow-wave sleep and waking. It is important that granule cells, which normally have low activity, limit the excitability of principal cells of the hippocampus under damaging conditions (Bragin et al., 1995a; Penttonen et al., 1997; GoodSmith et al., 2017; Henze and Buzsáki, 2007; Senzai, Buzsáki 2017).

Like the pyramidal neurons of the hippocampus, DG neurons are “place cells”. Granule neurons exhibit a single place field and reveal only humble changes in animals tested in different mazes in the same room (Senzai, Buzsáki 2017). In contrast, when tested in different rooms, they can have strong remapping; some neurons fire only in a single room (GoodSmith et al., 2017). Unlike granule neurons, mossy cells have multiple place fields and show a stronger remapping of place fields in response to changing the shapes of the testing apparatus in the same room (Senzai, Buzsáki 2017). Thus, as the authors suggest, granule neurons and mossy cells can be modulated separately. Nonetheless, these cells are likely to work in tandem, interacting with a high probability; these interactions are considered a key component of computations performed by the DG (Senzai, Buzsáki 2017).

Oscillations in the DG of a healthy brain

In the DG, as in the other regions of the hippocampus, low frequency theta (~4-10 Hz) and beta (~15-30 Hz) rhythms, as well as higher-frequency gamma oscillations (~30–150 Hz) were revealed. These rhythms are observed mainly in awake animals during exploratory behavior and are thought to be involved in learning and memory (Buzsáki et al., 1983, Buzsáki 2002, 2006, 2010; Bragin et al., 1995a; Igarashi et al., 2014; Rangel et al., 2015; Colgin et al., 2016).

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Theta oscillations

It was assumed that theta oscillations (~4-10 Hz) are important for the reception and processing of new sensory information (Vinogradova, 1995, 2001; Buzsáki, 2002, 2006; Colgin, 2013). In addition, the theta rhythm is thought to work as an internal mechanism for the on-line encoding of sensory input during learning and memory in awake animals and for the off-line processing of information during paradoxical (REM) sleep (Sejnowski and Destexhe, 2000; Montgomery et al., 2006).

Important results regarding the role of the DG theta rhythm in working memory were obtained in an early work by Givens (1996). The author examined the sensory-evoked reset of theta activity in the DG and questioned whether the phase shift occurs after all natural stimuli or only after signals that depend on active processing by the hippocampus during working memory. (**Fig. 2A**). In addition, it was suggested that the resetting of the theta rhythm by sensory stimuli permits the DG to use a wave of depolarization at the time a significant signal arrives from the EC. These and other data (Buzsáki et al., 1979; Tesche and Karhu, 2000; Vinogradova, 2001) allow one to conclude that the hippocampal theta rhythm as well as DG theta can be considered as a clock mechanism that brings together the activity of sensory- and memory-activated neurons in time, thereby affecting the behavioral output. Besides, rats that lost the theta rhythm in the DG and CA1 region (after blockade of the septal entrance to the hippocampus) showed impaired learning in the Morris water maze compared to the baseline level; the restoration of theta-like oscillations simultaneously restored learning to the initial high level (McNaughton et al., 2006).

During navigation in a novel space, an increase in theta power at most recorded DG and CA1 sites along the septotemporal (long) axis of the hippocampus in rats was revealed; moreover, during locomotion across a runway, the increase in theta power was independent of any alterations in the locomotor speed (Penley et al., 2013). Theta frequency also increased during navigational learning in all hippocampal circuits (including DG): on the last training day, theta oscillations were faster compared with the early stages of learning (Hernández-Pérez et al., 2016).

Gamma oscillations

The main function of the gamma rhythm (~25-100 Hz) is to select signals (Fries et al., 2007; Fries, 2009) and combine the activity of distributed neurons that process various parameters of stimuli, converting them into coherent perception (Gray et al., 1989; Pisarchik et al., 2019). It is assumed that the mechanisms of organization of slow (~25–50 Hz) and fast (~55–100 Hz) gamma oscillations in the hippocampal CA1 field are different since they are generated by different networks and show phase synchrony with CA3 field and the MEC, respectively (Colgin et al., 2009; Colgin, 2016; Mably and

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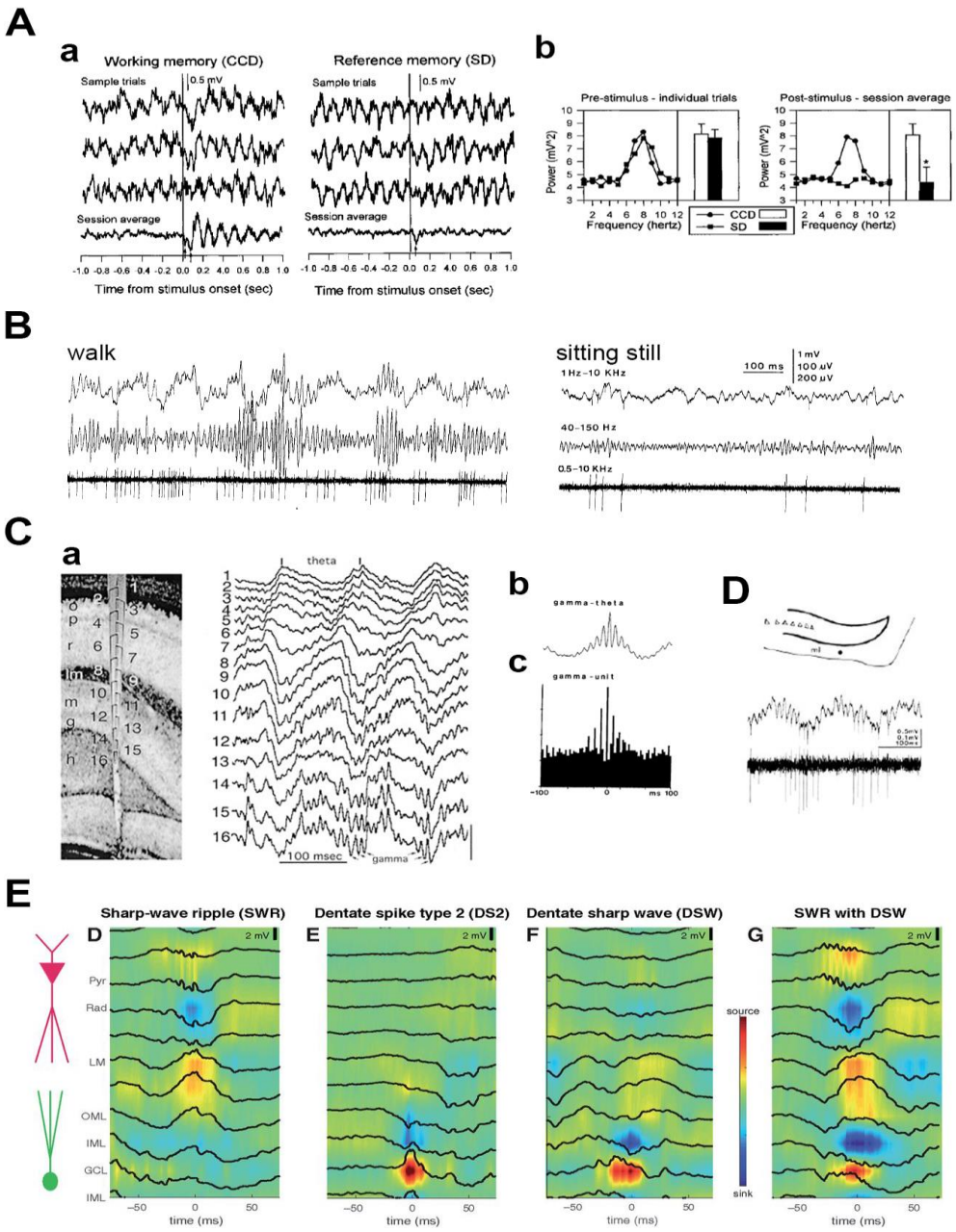

Fig. 2. Theta, gamma, and sharp wave-associated activity in the dentate gyrus (DG).

(**A**) Stimulus-evoked resetting of the dentate theta rhythm: relation to working memory. **a**, *Left*: Peristimulus EEG activity from the DG of a rat performing the continuous conditional discrimination (CCD) task. The individual traces (above) are taken from three sample trials. The stimuli (lights and tones) elicited an immediate negative potential during the first 100 ms (indicated by arrows), and a resetting of the rhythmic firing that was phase-locked to the onset of the stimulus, as is apparent in the average from the 180 trials in the session (below). *Right*: Peristimulus EEG activity from a rat performing the sensory discrimination (SD) task. Sample traces (above) reveal that theta was present before and after the stimulus. The average evoked response (below) from 173 trials, reveals an initial negative potential (arrow) and the absence of a resetting of theta activity. **b**, *Left*: Spectral density plot (left) and power in the theta frequency (right) for the prestimulus EEG data for each trial averaged across all rats in the CCD and SD groups. *Right*: Spectral density plot (left) and power in the theta frequency (right) for the post-stimulus EEG data for the averaged evoked potential from all rats in the CCD and SD groups. $*p < 0.05$.

(**B**) Activity in the hilar region. Microelectrode recording during exploratory walking and sitting motionless. Upper trace, wide band recording. Middle and lower truces, gamma activity (40-150 Hz) and unit firing (500 Hz to 5 kHz), respectively. Note theta- and gamma related modulation of the isolated neuron.

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(**C**) Theta-gamma activity in the hilar region. **a**, Voltage-versus-depth profile of theta oscillation in the rat. *Left:* A 16-site silicon probe in the CA1-dentate gyrus axis. Numbers indicate recording sites (100 μm spacing). o, str. oriens; p, pyramidal layer; r, str. radiatum; lm, str. lacunosum-moleculare; g, granule cell layer; h, hilus. *Right*: Theta waves recorded during exploration. Note gradual shift of theta phase from str. oriens to str. lacunosum-moleculare. Gamma waves superimposed on theta oscillation are marked by arrows. Vertical bar: 1 mV. **b**, Event related average of the wide band activity. The averager was triggered by the peaks of successive gamma waves. Note that the largest amplitude oscillation of gamma occurs on the positive portion of the averaged theta wave. **c**, Cross-correlogram of unit firing and peaks of the gamma waves. Note the relationship between averaged field (b) and unit discharges (c).
(D) Interneuronal activity in the DG in relation to local field potential (LFP) waves. The recording site in the molecular layer (ml) of the ventral leaf is indicated by a black dot. Wide band (above) and filtered unit (putative interneuron) activity (below). Note time locked firing of the cell to both theta and gamma waves. (**E**) Depth profile recordings using linear silicon probes during sleep. **a-d**, Examples of spontaneous characteristic depth profiles activity of the CA1-DG axes as current source density (CSD) plots with the LFP traces superimposed. Morphologic relationship to CA1 pyramidal neurons (magenta) and DG granule cells (green) is indicated on the left. The events shown were identified as follows: sharp-wave ripples (SWR) **(a)**, dentate spikes type 2 (DS2) **(b)**, a single dentate sharp wave (DSW) **(c)**, and a DSW coinciding with a SWR in CA1 **(d)**. Note that a DS2 shows a sink in the oriens-lacunisum moleculare (OLM), while a DSW shows a source in the outer molecular layer (OML). The DS2 further appears as a sharper potential in the CSD and LFP with shorter duration and larger slope. CSD and LFP scaling in a-d is identical; the examples shown refer to the same mouse.

(A) Adapted with permission from Givens, 1996 (A); Bragin et al., 1995a (B-D); Meier et al., 2020 (E).

Colgin, 2018). Some authors also distinguish “high” (>100 Hz; epsilon) gamma oscillations (Csicsvari et al., 1999a,b; Canolty et al., 2006; Belluscio et al., 2012).

Like theta activity, gamma oscillations are easily recorded in the DG and other hippocampal areas during waking and REM sleep. Compared to the theta rhythm, gamma oscillations have a much lower amplitude and a high frequency variability (Bragin et al., 1995a; Colgin et al., 2009), which complicates their measurement in behaving animals. Recently, the recording of local field potentials (LFP) in the DG of freely moving mice showed that wide-band gamma activity (30–150 Hz) occurs in bursts, which are very heterogeneous in their spatial extensions, ranging from focal to global coherent events; this indicates that synchronized neuronal gamma activity can engage the whole network or exclusively a spatially clustered group of cells (Strüber et al., 2017).

The measurements of gamma oscillations (40–100 Hz) in the hilus of the DG of waking rats showed that they have a higher amplitude in comparison with the CA1 field and depend on the input from the EC: after its surgical removal, the power of dentate gamma rhythm sharply decreases, whereas in the CA1 field it increases (Bragin et al., 1995a). Later, in the study of gamma oscillation currents in the hippocampus, two gamma generators were identified, one in the DG and the other in CA3-CA1 fields; it was also shown that the gamma rhythm in the CA3-CA1 regions does not require external inputs, in contrast to DG oscillations (Csicsvari et al., 2003). Subsequently, the detailed analysis of

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slow (~ 25–55 Hz) and fast (~ 60–100 Hz) gamma rhythms recorded from the DG and CA3 in freely moving rats showed that slow gamma oscillations, as opposed to the fast gamma rhythm, are particularly prominent in the DG and have a higher amplitude compared to the CA3 (Hsiao et al., 2016). The authors investigated directional interactions between DG and CA3 using the Granger causality analysis and found that slow gamma oscillations in the DG influence those in the CA3 field. Thus, based on the results obtained in the above mentioned studies (Bragin et al., 1995a; Csicsvari et al., 2003; Hsiao et al. 2016), one can assume that the two hippocampal gamma generators are relatively independent and counteract each other, and that the DG is a subregion of the hippocampus critical for the origination of slow gamma oscillations.

As mentioned above, the power and frequency of the gamma rhythm in the hilus of the DG strongly decreased with the damage to/inactivation of the EC (Bragin et al., 1995a; Pernía-Andrade et al., 2014). It is not surprising, therefore, that, during free animal behavior with a pronounced theta rhythm, theta and gamma oscillations in the DG were associated with theta and gamma oscillations in the EC (Chroback and Buzsáki, 1998). More recently, it was shown by Fernández-Ruiz et al. (2021) that, during spatial learning, fast gamma oscillations (100 to 150 Hz) synchronized the MEC and DG and entrained predominantly granule cells; during object learning, slow gamma oscillations (30 to 50 Hz) synchronized the LEC and DG and preferentially recruited mossy cells and CA3 pyramidal neurons. A selective disturbance of gamma rhythms in the MEC or LEC led to a decrease, respectively, in the fast and slow gamma rhythm in the DG, accompanied by impaired spatial or object learning (Fernández-Ruiz et al., 2021). The authors supposed that the communication between the EC and the DG through slow and fast gamma oscillations is critical for routing task-relevant information and supports specific aspects of learning.

Possible synaptic mechanisms of DG theta and gamma oscillations

The cellular mechanisms of the rhythmic activity of the DG were analyzed in detail by Pernía-Andrade and Jonas (2014). The authors tried to resolve the paradox in explaining the mechanisms of gamma oscillations in the DG: it is thought that gamma activity is primarily dependent on inhibition (Bartos et al., 2007) but is reduced due to damage to the EC, which mainly suppresses excitation (Bragin et al., 1995a). To address the synaptic mechanisms underlying theta-gamma network oscillations, DG granule cells were recorded by the patch-clamp method (Pernía-Andrade and Jonas, 2014). Is was shown that these cells are discharged at a low frequency by bursts synchronized in phase with network theta-gamma oscillations. Excitatory postsynaptic currents in these cells, mainly transmitted from the EC, were coherent with LFP in the theta frequency range, and inhibitory postsynaptic currents,

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presumably generated by local interneurons, were coherent with LFP in the gamma range. Two mechanistically distinct rhythmic signals were suggested by the authors to coexist in the DG, with theta activity mainly relayed from the EC via excitation, and gamma rhythm generated by local inhibition. At the same time, the inputs from the medial septum, cholinergic and GABAergic, were found to have only a modulating effect on the theta and gamma activity in the DG through the innervation of EC pyramidal neurons or DG interneurons (Pernía-Andrade and Jonas, 2014). On the other hand, the classical and some modern models of hippocampal theta rhythm generation propose a critical role of inputs from the medial septum/diagonal band (Freund and Antal, 1988; Stewart and Fox, 1990; Buzsáki, 2002; Nuñez and Buño, 2021; Mysin, 2021) with the participation of the intrinsic recurrent connectivity in the hippocampus (Kocsis et al., 1999). Thus, it is possible that theta oscillations in the hippocampus proper and the DG are generated by different mechanisms.

Afferent inputs from certain brain structures may influence rhythmic activity in the DG. A recent study (Billwiller et al., 2020) showed that, during REM sleep in mice, the power of theta and gamma rhythms in the DG can increase under the influence of optogenetic stimulation of the lateral region of the supramammilary nucleus (SuML). Besides, during slow-wave sleep, the activation of the SuML-DG pathway induced the awakening of mice, a switch from delta to theta activity, and an increase in gamma power. At the cellular level, it was revealed that SuML neurons corelease GABA and glutamate on dentate granule cells and increase the activity of a subset of DG granule neurons (Billwiller et al., 2020). Thus, GABA–glutamate supramammillary neurons may participate in the control of theta and gamma oscillations in the DG during REM and slow-wave sleep.

Rhythm coherence

It is known that external events usually lead to the synchronization of rhythms and thus give rise to a more complex functional phenomenon known as the phase coherence or phase coupling (Fell et al., 2008; Cavanagh et al., 2009; Canolty and Knight, 2010). The standard phase coherence reveals a relative constancy of the phase difference between two oscillations of the same frequency (Rodriguez et al., 1999; Hurtado et al., 2004). Oscillations of different frequency, e.g., theta and gamma oscillations, can interact with each other, so that the theta phase modulates the amplitude of gamma rhythms (Bragin et al. 1995a; Belluscio et al., 2012; Colgin, 2016), a phenomenon, known as the cross-frequency phase-amplitude coupling (Tort et al. 2010). The synchronization of neuronal rhythms has been suggested as a mechanism to coordinate the information flow between distant brain regions (Fries, 2005).

In the hippocampus, gamma oscillations show a covariance with theta activity (**Fig. 2B,C,D)**. During theta-associated behaviors, such as exploration, sniffing, and rearing as well as in the

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paradoxical phase of sleep, the amplitude of DG gamma activity is higher than during sitting still and other consummatory behaviors (Bragin et al., 1995a). In the DG of waking rats, the changes in the frequencies of gamma (40-150 Hz) and theta (5-10 Hz) waves positively correlated, i.e., the amplitude of gamma oscillations varied as a function of the theta cycle, and the largest power of gamma activity coincided with the ascending phase of theta waves derived from the hilus (**Fig. 2C)** (Bragin et al., 1995a). In the DG, as in the CA1 field, regardless of the animal behavior (for example, during run or REM sleep), the coherence at theta and gamma rhythms decreases along the septotemporal (long) axis of the hippocampus (Penley et al. 2012). Interestingly, an environmental change does not modify the decrease in the theta coherence in the DG but increases the theta coherence along the long axis of the CA1 field (Penley et al. 2013). Similarly, in spatial learning in an appetitive version of the Barnes maze, the power of DG theta and gamma rhythms, as well as the theta-gamma coherence, generally decreases, in contrast to the CA1 field. However, when an animal approaches the reward, a learning-dependent transient increase in theta-gamma coherence in the DG (but not in the CA1) was observed specifically in the vicinity of the target area (Bott et al., 2015) (**Fig. 3**); the authors proposed that these results point to the long-lasting involvement of DG networks in spatial reference memory.

A very important issue in understanding the functions of DG oscillations is the interregional inter- and cross-frequency coupling. The highly coherent theta and gamma activity in the DG hilus along the longitudinal axis of the hippocampus was observed. Besides, gamma waves were highly coherent along the axis of the DG hilus, but this coherence decreased toward the CA3 and CA1 fields (Bragin et al., 1995a). This can be explained by the fact that gamma oscillations in the CA3-CA1 network are a rarer event compared to the DG, as evidenced by the absence of a significant gamma dipole in the CA1 region and by low values of coherence between the DG and CA3-CA1 regions (Bragin et al., 1995a). However, a significant degree of phase coherence at slow gamma frequencies between the DG and CA1 was found during episodes of theta activity in awake head-fixed mice (Lasztóczi and Klausberger 2017). Slow gamma oscillations both in the DG and CA1 modulated neuronal activity in the DG, as well as in the CA1 field (although to a lesser extent) (see **Fig. 4**). The authors believe that slow gamma oscillations in the DG and CA1 in mice were not independent phenomena. This is not fully consistent with the results obtained earlier in rats (Bragin et al., 1995a; Csicsvari et al., 2003). What are the exact reasons for these discrepancies: either species differences or distinctions in experimental design, should be clarified in future studies.

Gamma coherence in the DG and CA3 is shown to vary in the awake state of experimental animals (Bragin et al., 1995a; Csicsvari et al., 2003). It was demonstrated that slow DG gamma influenced CA3 gamma, and spike activity of DG place cells was synchronized and phase-locked to slow CA3 gamma, consistent with the notion that slow gamma-modulated spiking of DG place cells entrains slow

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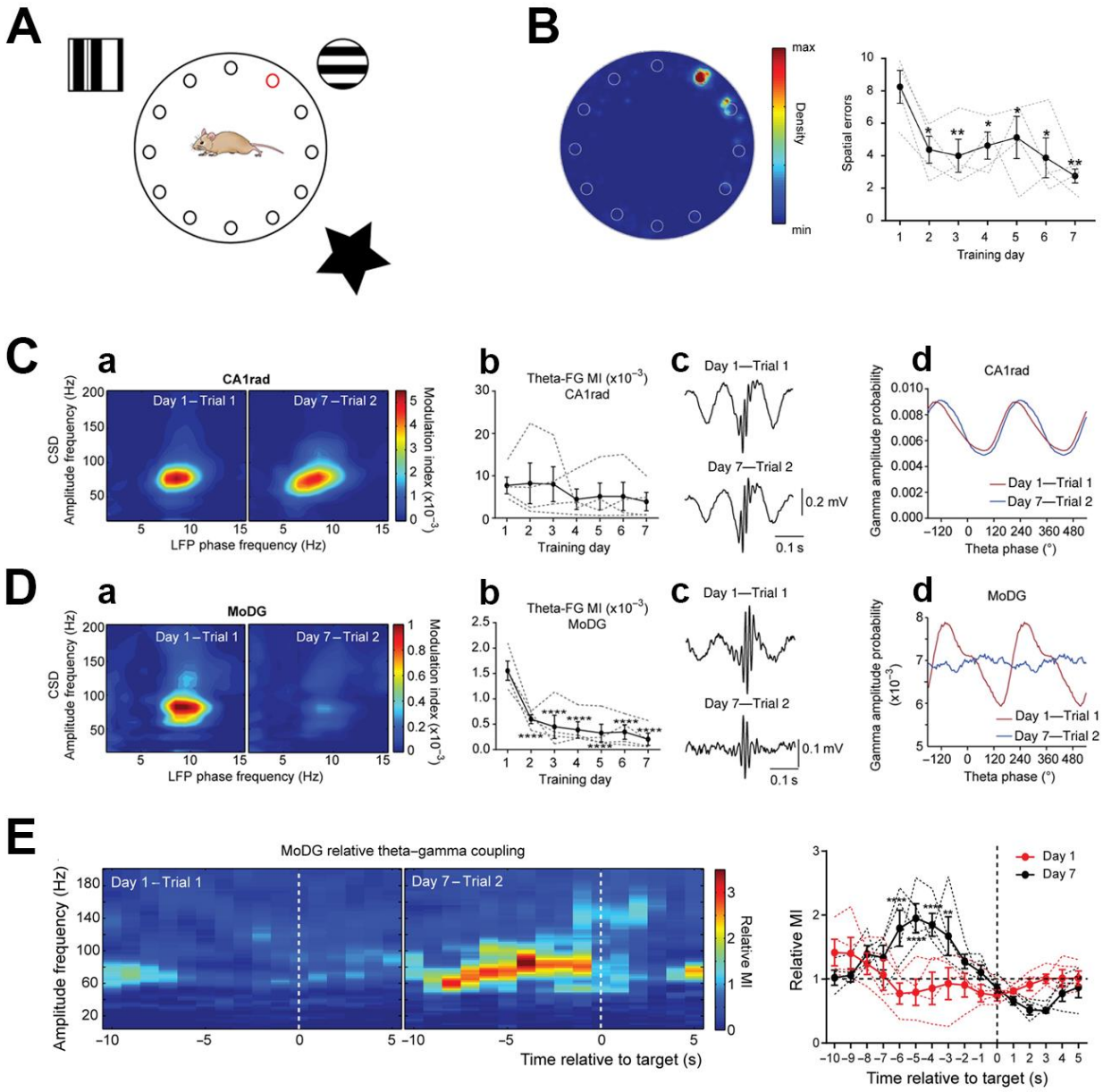

Fig. 3. Theta-gamma coupling in CA1 and DG across training in appetitive version of the Barnes maze.
(A) Schematic top view of the appetitive version of the Barnes maze. The red circle depicts the location of the goal during all training trials. Note that this location was stable in relation to distal cues dispersed in the testing room (represented by geometric symbols).
(B) Spatial learning in the modified version of the Barnes maze. *Left*: Density plot occupancy of the maze during the last trial of Day 7 for all mice. Note the time spent around the target cup. *Right*: The decreasing number of spatial errors (number of visits to non-target cup before the first visit to the target) was quantified across days of training (mean ±SEM, **P* < 0.05, and ***P* < 0.01, significantly different from Day 1). Dashed lines represent individual mice.
(C) Theta–fast gamma coupling across learning in CA1 stratum radiatum (CA1rad; whole trial). As shown in the comodulogram (a) and the quantification (b), there is no change of CA1rad theta–fast gamma coupling across learning. Average of the raw recordings based on current source density (CSD) fast gamma amplitude maximum on Day 1 and Day 7 (c). Note the presence of a theta wave following averaging during the first and last trial. Gamma amplitude modulation by theta phase was not changed during training, with the peak of gamma power being maximum near the trough of local theta oscillation (d).

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(**D**) Theta–fast gamma coupling across learning in the molecular layer of the dentate gyrus (MoDG) (whole trial). As shown in the comodulogram (a) and the quantification (b), there is a sharp decrease of MoDG theta–fast gamma coupling across learning (mean ±SEM, ****$P < 0.0001$, different from Day 1). Average of the raw recordings based on CSD fast gamma amplitude maximum on Day 1 and Day 7 (c). Note the presence of a theta wave following averaging during the first trial. In averaged traces from the last trial, theta oscillations are absent. Gamma amplitude modulation by theta phase is decreased in the MoDG during learning (d). Dashed lines represent individual mice.
(**E**) MoDG theta–gamma coupling across time at the vicinity of the target cup. Examples of relative theta–gamma coupling over time when the mouse reached the target for the first time on Day 1 and Day 7. *Left:* The theta–gamma comodulogram is shown and computed in 1-s bins. The modulation index (MI) was calculated as the coupling strength between theta and fast gamma. Note the specific increase in relative MI before time 0 at Day 7 (mean ± SEM, **$P < 0.01$ and ***$P < 0.001$, Day 7 vs. Day 1). Dashed lines represent individual mice.
Adapted with permission from Bott et al., 2015.

gamma activity in CA3 (Bragin et al., 1995a; Hsiao et al., 2016). Slow gamma coherence between DG and CA3 (as well as between CA3 and CA1) increases during novel object exploration, and the degree of this gamma synchrony positively correlates with subsequent performance of a memory test (Trimper et al., 2014). The increased coherence between these regions may reflect an increase in gamma DG input to the CA3 (Akam et al., 2012). Using optogenetic stimulation in hippocampal slices, Akam and colleagues showed that CA3 gamma oscillations can be entrained by periodic input from the DG over a wide frequency range (24-80 Hz).

Concerning fast gamma oscillations in the DG (75-150 Hz) and CA1 (92-150 Hz), it was shown that they were rather independent processes: they demonstrated low phase coherence and independence of the neuronal activity in the pyramidal CA1 layer from the fast gamma rhythm in the DG (Lasztóczi and Klausberger 2017). At the same time, it was found in another study on freely behaving rats that the amplitude of the DG fast gamma rhythm (> 60 Hz) depended on the phase of CA1 theta, but not vice versa *(*Nandi et al. 2019). Thus, further studies are needed to resolve these contradictions.

An analysis of the influence of *the running speed* on the relationship between the rhythms in the DG and CA1 in rats showed that, at moderate running speeds, gamma oscillations in CA1 mainly depend on the local theta rhythm, while the coupling of gamma oscillations in the DG with the gamma rhythm in the CA1 increases with increasing running speed (Sheremet et. al., 2020). In general, these data are consistent with the influential hypothesis of the theta-gamma interaction in the organization of the hippocampal LFP, where the theta rhythm plays the role of a global pacemaker in the entire hippocampal formation, while gamma rhythms are more local oscillations generated by spatially limited neural networks (Buszáki, Wang, 2012; Colgin, 2016).

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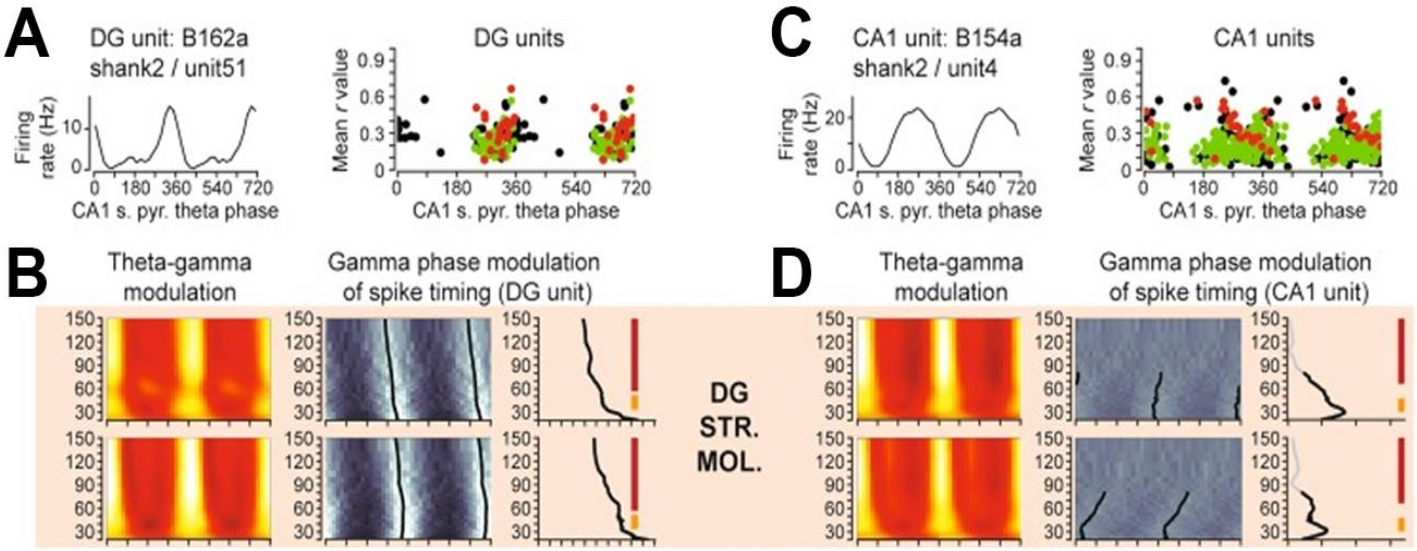

Fig. 4. **Phase modulation of spike-timing of units in the dentate gyrus (DG) and area CA1 by theta and different gamma oscillations.**

(A) *Left*: Theta phase histogram of firing of one unclassified unit, recorded from the DG. *Right*: Mean theta phase of firing (abscissa), and modulation strength (mean r value, ordinate) of all significantly modulated putative principal cells (green), putative interneurons (red), and unclassified units (black), recorded from the DG.

(B) Spike-timing modulation by gamma oscillations during theta oscillations of one unit, recorded from the DG (same unit as in A). *Left*: Amplitude modulation of gamma oscillations by theta oscillations, in current source density (CSD) traces from selected contacts in stratum moleculare of the DG. *Middle*: Spike density (greyscale-coded) of the unit, plotted as a function of CSD gamma phase and frequency for the same contacts. The mean phase values for the frequencies significantly phase-modulating the spike timing are plotted in black. *Right*: Modulation strength spectra (mean r values) for the unit, relative to gamma oscillations in different contacts (values at frequencies significantly modulating the spike-timing are plotted in black). Frequency ranges of the different gamma oscillations are displayed by colour-coded bars at the plots of most relevant contacts.

(C) Same as in A for units recorded from the CA1 area.

(D) Same as in B, for one unit recorded in the CA1 area (the same putative interneuron as in C).

Adapted with permission from Lasztyczi and Klausberger, 2017.

Thus, it can be finally assumed that theta and gamma oscillations as well as theta–gamma coupling are differentially modulated in specific hippocampal subfields by changes in environment and a particular moment of learning of the spatial task.

Beta and alpha oscillations

The beta rhythm (~10-30 Hz) has been hypothesized to assist in the coordination across brain structures and may be suitable for coordinating the flow of information from different input areas to specific parts of the brain (Kopell et al., 2000; Bibbig et al., 2002; Pinto et al., 2003). While theta and gamma oscillations in the DG and the hippocampus have been studied intensively, only a few works have been devoted to the study of the DG beta rhythm. In the 1990s, 15–30 Hz oscillations occurring

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simultaneously in the DG and olfactory bulb (OB) of freely moving rats (Vanderwolf, 1992) and in anesthetized rats were described (Heale and Vanderwolf, 1994). It was found that the beta rhythm was much more prominent in the DG than in CA1 field (Vanderwolf, 1992; Chapman et al., 1998). The authors demonstrated the co-occurrence of beta activity in the OB–DG circuit, but they did not study its features during cognitive loads due to technical limitations at the time. Later, the OB–DG coherence in the beta frequency range during odorant sampling in go/no-go tasks was shown (Martin et al., 2007). Original results on DG beta oscillations were then obtained in the study by Rangel and colleagues (2015), who analyzed the temporal interplay of theta and beta rhythms during the presentation of meaning cues. During LFP recordings in the DG, as rats performed different associative learning tasks, cue presentations elicited significant decrements in theta power and simultaneously an increase in the beta (15–30 Hz) amplitude. These changes persisted from the moment a cue was presented to the moment an animal received a reward and did not occur during similar behavior in the absence of relevant stimuli. Thus, the observed opposite changes in the amplitude of theta and beta oscillations may reflect a shift in the information processing that occurs when an animal under test encounters meaningful cues (Rangel et al., 2015). The authors also hypothesized that the observed oscillatory dynamics and a switch from the theta to beta rhythm in the DG indicate that the hippocampus is entering another processing state, with each rhythm operating through different neural mechanisms.

Recently, the features of beta oscillations in the DG, the hippocampus, and OB of rats anesthetized with urethane were characterized in more detail (Lockmann et al., 2018). The laminar voltage profile of beta in the hippocampus showed the maximum amplitude in the DG, which receives disynaptic olfactory input from the OB (Wilson and Steward, 1978; Yanovsky et al., 2014). All areas mentioned exhibited beta rhythms (10–20 Hz) that phase-lock across these areas and are believed to facilitate communication between them. It is important that DG beta not only was phase locked to simultaneously recorded OB beta but also was driven by it (Lockmann et al., 2018), which is consistent with the results of a previous study on nonanesthetized animals (Gourévitch et al., 2010). It is interesting that the respiration-coupled field potential rhythms (1–2 Hz), but not theta oscillations, modulated the beta amplitude in the DG and OB (Lockmann et al., 2018).

When animals were trained using the olfactory cues, short rhythmic bursts of beta-frequency waves were recorded in the DG and CA1 field during the selection of the odor, which was followed by the correct behavior of the animal. These beta bursts demonstrated phase coherence with beta oscillations in the OB and the LEC and correlated with the onset of learning and the formation of neural ensembles (Vanderwolf, 2001; Martin et al., 2007; Gourévitch et al., 2010; Rangel and Eichenbaum, 2014). In another study, in the DG, as well as in the CA3 field, the activity in the beta range increased during stationary behavior, and an increase in the beta coherence was observed

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between the DG and CA3 (Trimper et al., 2017). Overall, all these results support the hypothesis that beta activity mediates the communication between olfactory and hippocampal circuits in the brain of rodents.

Possibly, other types of oscillations can also take part in the functioning of the DG. Using intracellular recordings from DG neurons in mice running on a spherical treadmill, short-term oscillations of the membrane potential in the alpha frequency range were found. These alpha oscillations were associated with the onset of movements (Anderson and Strowbridge, 2014). Thus, alpha oscillations, being usually ignored, may participate in the regulation of DG spike timing during locomotion.

Dentate spikes and sharp waves

The largest-amplitude event in the DG is a ‘‘dentate spike’’ (DS), which is observed in rodents during immobile behavior and slow-wave sleep (**Fig. 2E**). This is a short-duration (<60 ms) and a large-amplitude (>0.5–2.5 mV) event, recorded from the hilus of the DG, which is characterized by a synchronous discharge of granule neurons, mossy cells, and interneurons (Bragin et al., 1995b; Penttonen et al., 1997). DSs are usually clearly distinguished from more prolonged hippocampal sharp waves (SPWs), which are associated with population bursts in the CA3-CA1 network; besides, DS and SPW rarely occur together in time within a 200-ms window around the DS (Bragin et al., 1995b). It was suggested that DS-associated synchronized bursts of hilar interneurons provide a suppressive effect on the excitability of the CA3-CA1 network in the intact brain. The elimination of the entorhinal input to the hippocampus reduces DSs but increases the occurrence of SPWs, suggesting that normally the entorhinal input to the hippocampus evokes DSs and suppresses SPWs (Bragin et al., 1995b).

Two types of DSs can be distinguished: dentate spike type 1 (DS1), an event initiated by LEC II inputs, and dentate spike type 2 (DS2), which is triggered by MEC II inputs (Bragin et al., 1995b; Dvorak et al., 2021). DS1 and DS2 have different voltage-versus-depth profiles and different spatial distribution of their current sinks; besides, DS1 appears usually as a brief oscillatory event, whereas DS2 is an isolated event followed by a longer negative field event (Bragin et al., 1995b). Moreover, the effects of DS2 on the DG-CA3-CA1 network differ from those of DS1: DS2 promotes slow gamma dominance and changes excitation-inhibition coordinated discharges in DG, CA3, and CA1, whereas DS1 does not. In addition, what is quite important, DS2 coordinates co-firing within DG, CA3, and CA1 networks and optimizes discharge timing between DG and CA1 for information transfer during memory recall (Dvorak et al., 2021).

In a recent work on sleeping mice, Meier and colleagues (Meier et al., 2020) showed a new type of network DG oscillations, called by them “dentate sharp waves” (DSWs), which occasionally were

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synchronous to sharp-waves ripples (SWRs) oscillations (see Bragin et al., 1995b) in the CA1 (**Fig 2D**). The current source density (CSD) signature of DSWs resembled that seen during SWRs in the CA1, but dentate DSWs usually occurred independently of CA1 SWRs. DSWs differed from DS by a current source in the molecular layer; besides, they displayed increased coupling to SWRs and increased occurrence rates after learning (Meier et al., 2020). It was therefore proposed that DSWs may be a sensitive indicator of hippocampus-dependent learning and complement locally detected CA1 SWRs in mice**.**

Although high-frequency network oscillations (~80–200 Hz) do not normally occur in the DG, in contrast to the CA1-CA3 hippocampal fields (Bragin et al., 2004; Buszáki, 2015), cell activity associated with SWRs was recorded recently in granule and mossy neurons (Swaminathan et al., 2018) and dentate interneurons (Szabo et al., 2017). As believed, this activity was generated through both feed-back DG activation and inhibition from CA3 and CA1 neurons: namely, through excitatory projections from CA3 to granule and mossy cells (Scharfman, 2007; Shi et al., 2019) and inhibitory interneuron projections from CA1 and CA3 to granule cells (Szabo et al., 2017). Interestingly, it was shown that granule cell activity is necessary for increased firing of CA3 neurons and SWR generation during specific periods of spatial learning, which, in turn, supports spatial working memory (Sasaki et al., 2018).

Neuronal rhythmicity

Oscillatory activity was also revealed in individual dentate neurons. Intracellular current clamp recordings from mossy cells of the dorsal DG in rats under ketamine-xylazine anesthesia showed oscillations in the membrane potential at low frequencies, which appeared to be phase-locked to the LFP theta rhythm (Soltesz et al., 1993). The frequency of the theta rhythmicity was independent of the membrane potential. However, the phase difference between intracellular and LFP theta rhythms as well as the amplitude of intracellular theta oscillations were voltage-dependent. At the resting membrane potential, mossy cells fired rarely (< 1 Hz), i.e., not in each cycle of the LFP theta rhythm. However, when they did fire they did so preferentially in phase with the peak positivity of the LFP theta rhythm. The reconstruction of two mossy cells with projections of axons into the inner molecular layer showed that the influence of these weakly firing mossy cells on other DG neurons during theta oscillations can extend to several millimeters in the septotemporal direction. These findings show that DG mossy cells in rats under ketamine-xylazine anesthesia participate in theta oscillations of the hippocampal formation during which their low-frequency firing may contribute to the phase-locking of a large number of spatially distributed neurons with postsynaptic sites in the inner molecular layer of the DG (Soltesz et al., 1993). Later, it was shown in a vivo study that granule cells fired in later

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phases of theta oscillations and earlier phases of gamma waves compared to mossy cells; also, granule cells were more strongly phase-modulated by both theta and gamma rhythms than mossy cells. Besides, granule cells were more effectively recruited to an LFP type 2 dentate spike (DS2, see below) than mossy cells (Senzai and Buzsáki, 2017). All these data point to the important role of theta and gamma oscillations in the fine tuning of the activity of the main cells in the DG, which, in turn, is considered necessary for the implementation of DG functions, such as pattern separation.

The recording of the activity of physiologically identified interneurons in the DG hilus during exploratory walking and immobile sitting of awake rats showed that such activity closely reflected changes in field potential (Bragin et al., 1995a). When animals explored their environment, DG putative interneurons fired rhythmically at gamma frequency by theta bursts (**Fig. 2B**, lower trace, and **Fig. 2C**) and were phase-locked to the ascending part of gamma waves recorded from the hilus **(Fig. 2C**, c). The phase locking of neuronal discharges became tighter with increasing amplitude of local gamma waves. Interspike intervals in discharges of hilar interneurons covaried with the frequency of locally derived gamma waves. During immobility, i.e., the non-theta behavior of animals, these units were discharged much more slowly than during active theta states (**Fig. 2B**, lower trace). The CSD analysis revealed large sinks and sources in the DG with the spatial distribution of currents similar to those of the dipoles evoked by the stimulation of the perforant path (Bragin et al., 1995a).

Generally, in rodents, the rhythmic activity in the DG is closely interrelated with that in the hippocampus. Nevertheless, the available data indicate that oscillatory processes in these structures can exhibit a certain degree of independence, which is possibly determined by differences in the mechanisms of their generation in the DG and hippocampal fields.

The role of neurogenesis in the activity of the DG network

Apparently, neurogenesis plays a special role in the regulation of the network activity of the DG. Several studies have provided evidence for the modulatory role of immature granule cells in regulating the neuronal activity of a larger population of mature neurons. Thus, to assess the effect of newborn cells on neuronal circuits in the DG, the generation of new DG neurons was eliminated by X-ray irradiation of the hippocampus, and the network activity of mice under urethane anesthesia was recorded (Lacefield et al., 2010). Paradoxically, it was revealed that the lack of more excitable young neurons increases spontaneous network activity in the DG; besides, dentate units tended to fire during LFP gamma bursts. Although this tendency was observed in both the control and X-irradiated groups, however, the discharges in the DG were more coupled to gamma bursts in X-irradiated animals: the cross-correlation analysis revealed a greater propensity to fire within a short period relative to gamma

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power peaks within each event in X-irradiated animals compared to the control group (**Fig. 5**). This result suggests that normally young neurons modulate the networks of mature cells in the DG. The authors supposed that, in the healthy brain, newborn DG neurons can reduce the excitation of mature granule neurons, firstly, via predominant activation of inhibitory interneurons, and, secondly, through competition with mature granules for the excitatory input. In any way, these data suggest that adult-born neurons have the ability to limit the network activity in the DG and coordinate cellular discharges in time through gamma oscillations (Lacefield et al., 2010).

Subsequently, the examination of how the modulation of the adult neurogenesis influences DG circuit activity and excitability was performed using fast voltage-sensitive dye imaging combined with laser photostimulation and electrical stimulation (Ikrar et al., 2013). An increase in the number of adult-born dentate granule neurons in mice was achieved by genetic engineering (Sahay et al., 2011), and the blockage of hippocampal neurogenesis was performed using targeted X-irradiation. It was shown that, in the DG of mice with increased number of adult-born neurons, the cell activation decreases and the propagation of excitation within the granular cell layer is more restricted, while the output from DG to CA3c field remains effective. By contrast, the inhibition of adult neurogenesis oppositely changed the excitability of DG neurons. The labeling of connectivity in mice with a greater number of newborn neurons revealed an increased number of excitatory synaptic contacts of young granule neurons with interneurons in the DG hilus (Ikrar et al., 2013). These data provided a new knowledge about DG functioning and the opportunity to develop new approaches to manage the activity of mature granule neurons.

In studies on survived slices, immature granule cells (about 40 days old) respond to a wider range of input signals (Marin-Burgin et al., 2012) and are thought to have increased excitability and plasticity, which distinguishes them from a less plastic and a relatively low-excitable population of mature granule neurons (60 days of age) (Espósito et al., 2005; Ge et al., 2007; Schmidt-Hieber et al., 2004; Mongiat et al., 2009). The high excitability of immature granule cells is probably due to the fact that they undergo a lesser synaptic inhibition compared to mature granular neurons (Dieni et al., 2015). This physiological state of newly born cells, different from adult granule neurons, suggests that immature granules play a unique role in the DG network: they reduce the excitability of neighboring mature granular neurons (Ikrar et al., 2013; Adlaf et al., 2017). An analysis of functional connectivity of adult-born granule neurons revealed synaptic connections with hilar mossy cells and interneurons (Toni et al., 2008); it can be assumed that these synaptic connections decrease the excitability of mature granule neurons due to a greater excitability of neighboring newly born cells. Thus, these findings are consistent with the results of the above mentioned more recent studies.

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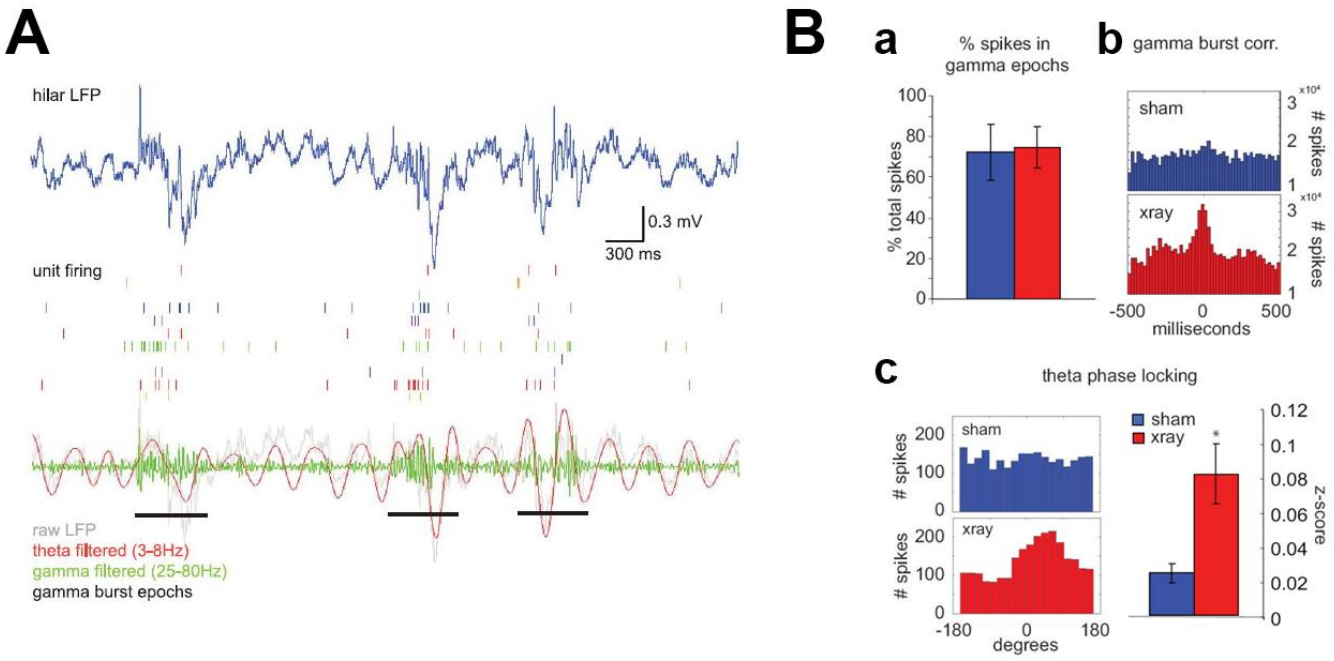

Fig. 5. Activity of neurons in the dentate gyrus (DG) of urethane-anesthetized mice.

(A) Dentate neurons tend to fire with gamma bursts. Raster plots of unit firing during gamma burst epochs show increases in firing rate during bursting events. *Top panel*: Raw local field potential (LFP) from probe contact located in the hilus. *Middle panel:* Raster plots from a selection of units recorded simultaneously with the above LFP. *Bottom panel:* LFP trace filtered for theta (3–8 Hz) (red) and gamma (25–80 Hz) (green). The raw trace is repeated in gray for comparison. Gamma burst epochs as identified by a gamma power algorithm are indicated in black.

(B) X-irradiation increases spike-LFP synchrony within gamma bursts. **a**, Percentage of spikes occurring during gamma bursts in sham (blue) and x-irradiated (red) animals. In both groups, most spikes occurred during gamma bursts. Mean ± SEM. **b**, Gamma-burst-triggered peri-event histograms of all spikes recorded from all animals in sham (blue) and X-irradiated (red) groups. Spikes in X-rayed animals occur preferentially at the peaks of gamma power during gamma bursts while sham animals show no such preference. Note the side peaks at 250- to 350-ms latency indicating prominent h-frequency modulation in the X-irradiated animals. **c**, *Left*: Theta-phase distribution histograms for spikes recorded from sham and x-irradiated animals; 100 spikes from each single unit were used (n = 34 units in X-irradiated animals, 25 units in sham animals). Theta phase was calculated from the LFP recorded in the hilus. *Right:* Mean Rayleigh's z-statistic (a measure of the strength of phase locking) from neurons recorded from sham and X-irradiated animals (P = 0.01, two-tailed Student's t-test on log transformed data).

Adapted with permission from Lacefield et al., 2010.

Later, Park and colleagues (2015) investigated the role of neurogenesis in discriminating between similar kinds of memory. In experiments on normal and X-irradiated mice, they applied active place avoidance tasks to assess experience-dependent changes in the electrophysiological properties of the DG by measuring the response of granule cells to the neocortical input and dentate LFP. The authors showed that, in naive mice, which have no place avoidance training experience, the loss of neurogenesis resulted in reduced responsiveness of the dentate network to the neocortical input; a day after learning, synaptic responses to the neocortical input in the DG changed, but only in the presence,

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but not in the absence of adult-born neurons. Besides, in X-irradiated mice, during place avoidance, the excitation–inhibition coupled neural synchrony in dentate LFP was reduced, especially in the theta band, and the memory discrimination was impaired, in contrast to normal mice. The authors concluded that maturing adult-born neurons regulate dentate gyrus synaptic and spiking responses to the neocortical input rather than directly store information and, consequently, the contribution of adult neurogenesis to memory is indirect, through the regulation of dentate excitation–inhibition coupling mostly in the theta band (Park et al., 2015).

Changes in the DG of an epileptic brain

Many functions of brain structures and their specific activities become clearer during the development of certain diseases in humans or in their models in animals. For example, in the TLE brain, cognitive abilities are impaired, which indicates the important role of the hippocampal networks in the tuning of information processing.

TLE is the most common type of epilepsy in adults, which is associated with the localization of the seizure focus in the temporal lobe of the cortex, in particular, in the hippocampus (Engel et al., 2001; Toyoda et al., 2013). TLE is characterized by circuit pathologies in brain structures (Alexander et al., 2016) and memory-related cognitive deficits (Helmstaedter et al., 2003; Saling, 2009; Zhao et al., 2014). It is a drug-resistant disease (Stephen et al., 2002), and its treatment is recently mainly based on symptomatic strategies and surgery, both being focused on seizure suppression but not on epileptogenesis (Loscher and Schmidt, 2004). This indicates a low level of the understanding of the mechanisms of TLE development.

Does the DG play a specific role in the development of TLE, and if so, what exactly are the disturbances in it that are crucial? Solving these questions can help clarify the causes of TLE occurrence. In this part of the review, we will consider changes in the activity (in particular, in oscillations) and functioning of the DG in the TLE brain. In addition, the issues of structural reorganization of the DG and hippocampal networks during TLE will be touched upon.

Anatomical anomalies in the DG in temporal lobe epilepsy

The main histological marker of TLE is the loss of DG cells in both humans (Mathern et al., 1995; El Bahh et al., 1999; Blumcke et al., 1999; Loup et al., 2000) and experimental animals (Lowenstein et al., 1992; Toth, et al., 1997; Kotti et al., 1996; Arabadzisz and Freund, 1999; Sloviter,

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1991; Cavazos et al., 1994; Magloczky and Freund, 1995; Leite et al., 1996; Buckmaster and Jongen-Relo, 1999; Esclapez et al., 1999).

Damage to the DG structure is considered by some authors as a possible cause of the onset of TLE development (McNamara, 1994). In the DG neural network, mossy cells are most vulnerable to damage due to the specificity of GABA receptor composition (Tong et al., 2015) and the presence of excitatory inputs from granule neurons (Buckmaster, Schwartzkroin, 1994; Sloviter, 1994; Scharfman, 1999; Scharfman, Myers, 2012). It was suggested in some studies that it is precisely the vulnerability of mossy cells that is a key factor in the genesis of TLE: these neurons normally behave as protectors because they suppress the excitability of granule cells through GABAergic interneurons (Scharfman, 1995; Larimer, Strowbridge, 2008), and their death can break the safety of the dentate circuit (Buckmaster and Schwartzkroin, 1994). However, the study of Ratzliff et al. did not support the hypothesis that the loss of mossy cells after seizures or traumatic brain injury directly results in hyperexcitability (Ratzliff et al. 2004). An analysis of a hippocampal tissue taken from TLE patients (Blümcke et al., 1999; Houser, 1999) and epileptic animals (Cavazos et al., 1994; Buckmaster and Jongen-Relo, 1999) showed a loss of mossy cells, but some neurons remained intact (Seress et al., 2009); survived mossy cells became proepileptogenic due to an excessive increase in the activity of granule neurons projected onto them (Santhakumar et al., 2000; Ratzliff et al., 2002). The increased excitability of survived mossy cells formed the basis for the hypothesis of hypersensitive (“irritable”) mossy cells as a cause of the onset of epileptogenesis (Santhakumar et al., 2000).

In general, the most significant anatomical abnormalities found in the DG of patients with TLE and in animal models of this disease were the following:

(1) reactive sprouting of mossy fibers in the inner molecular layer and the hilus of the DG, so that, on the average, one granule neuron in epileptic rats projected 75% more axonal branches compared to control animals (Margerison and Corsellis, 1966; Sutula et al., 1989; Tauck and Nadler 1985; Houser, 1990; Buckmaster and Dudek 1999; Longo et al. 2003; Nadler 2003; Buckmaster 2012);

(2) an increase in the number of projections of recurrent axon collaterals of CA3 cells to granule neurons (Nadler et al., 1980; Sutula et al., 1989; Nadler, 2003; Sutula and Dudek, 2007; Scharfman and Myers, 2012) (**Fig. 1B**);

(3) a significant loss of mossy cells (Houser, 1999; Blümcke et al., 1999; Cavazos et al., 1994; Buckmaster and Jongen-Relo, 1999);

(4) the death of hilar interneurons (Sloviter, 1987; 1991; Cossart et al., 2001; Sun et al., 2007; Sloviter et al., 2012; Obenaus et al., 1993; Kobayashi and Buckmaster, 2003);

(5) proliferation of ectopic granule cells in the DG hilus (Houser, 1990; Harvey and Sloviter, 2005; Parent et al., 1997, 2006; Curia et al., 2008; da Costa Neves, 2012), which are abnormally

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integrated and become hyperexcitable (Scharfman et al., 2000; Dashtipour et al., 2001; Jung et al., 2004; Cameron et al., 2011; Scharfman and Pierce, 2012);

(6) alterations in GABA receptors (Brooks-Kayal et al., 1998; Coulter and Carlson, 2007);

(7) synaptic reorganization (Sloviter, 1999; Kienzler et al., 2009; Zhang et al., 2014);

(8) dispersion of granule cells (Houser, 1990; Mello et al., 1992; Lowenstein, 2001; Jessberger et al., 2005; Neves et al., 2012; Coras et al., 2014) (**Fig. 1B**).

The last two alterations may coincide in time with the onset of spontaneous seizures (late changes in the DG).

It is interesting that, after epileptic seizures, the markers of GABAergic phenotype of glutamatergic granular cell/mossy fiber terminals were clearly detected in the DG of adult rats (Gutiérrez and Heinemann, 2006), suggesting the colocalization of GABA and glutamate in granule cells of the normal adult brain. Thus, when this colocalization occurs, monosynaptic GABA receptor-mediated transmission emerges in mossy fiber synapses, which restrains excitation and mediates antiepileptic and neuroprotective actions.

During neurogenesis, adult-born granular cells that formed weeks before and after epileptogenic brain injury may be integrated abnormally with the DG network, potentially mediating epileptogenesis in the temporal lobe. It is also possible that the continuation of neurogenesis leads to an increase in the sprouting of mossy fibers, which is further enhanced by subsequent spontaneous seizures and causes increased excitability in the DG (Cameron et al., 1993; Parent et al., 1997; Bengzon et al., 1997; *but see* Zeng et al., 2009; Buckmaster and Lew, 2011). However, another study showed that reduced neurogenesis in adults exacerbates the effect of the neurotoxin kainic acid in the development of seizures (Iyengar et al., 2015). A recent work in mice demonstrated that the elimination of newly born granular cells, applied at a clinically significant time point after an epileptogenic stroke, may have modifying effects on the development of epilepsy (Hosford et al., 2016). At the same time, it was shown in transgenic mice using optogenetic methods that, despite the sprouting of mossy fibers of granule cells born after status epilepticus (SE), the synapses formed by them were not functionally active and could not cause recurrent excitation (Hendricks et al., 2017). The reasons for this discrepancy are expected to be elucidated in future experiments.

Alterations of theta oscillations

As was shown in freely moving rodents, the theta rhythm was preserved in the activity of the DG network in kainate-treated epileptic animals (Froriep et al., 2012; Inostroza et al., 2013; Kilias et al., 2018). The frequency of the theta peak was significantly higher during running than without

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movement in both epileptic and control animals (Kilias et al., 2018) (**Fig. 6)**. However, compared with healthy animals, there was a decrease in theta power (Froriep et al., 2012; Inostroza et al., 2013) and frequency (Inostroza et al., 2013; Kilias et al., 2018) in the DG of epileptic rodents (**Fig. 7**). The decreased theta power was associated with several histopathological changes in the TLE brain, namely, neuronal death (Froriep et al., 2012; Inostroza et al., 2013) and the dispersion of granule cells (Froriep et al., 2012). It was demonstrated recently in freely behaving epileptic mice that the theta frequency decreased in the ipsilateral and contralateral DG along the entire septo-temporal axis (Kilias et al., 2018) (**Fig. 6**). Besides, the reduction in the theta frequency in epileptic mice was independent of the behavioral state of animals, and, surprisingly, did not correlate with the progression of pathology and the degree of dispersion of granular cells (Kilias et al., 2018). This is not consistent with the proposed causative relationship between changes in theta rhythm parameters and the injury of cells in the DG and the hippocampus in TLE patients (Houser, 1999; Blümcke et al., 1999) and in animal models (Cavazos et al., 1994; Buckmaster and Jongen-Relo, 1999; Covolan et al., 2000; Riban et al., 2002; Arabadzisz et al., 2005; Dugladze et al., 2007; Inostroza et al., 2013). Kilias et al. (2018) argue that the maintenance of DG theta activity regardless of the degree of dispersion of granular cells is consistent with the integrity of the projection of the perforant path onto dispersed granule cells in epileptic mice (Froriep et al., 2012; Janz et al., 2017a). Thus, the decrease in DG theta frequency was possibly a consequence not of a local damage to the DG but of a global event affecting the hippocampal formation in its entirety (Kilias et al., 2018).

Alterations in theta rhythm coherence

In freely behaving kainate-injected epileptic mice, an alteration of theta coherence between the EC and the DG was revealed (Froriep et al., 2012). Indeed, the theta activity in the EC was delayed with respect to that in the DG, while the theta rhythm in healthy animals was synchronized between the EC and DG, demonstrating the within-frequency phase coupling (**Fig. 8**). Based on a computational neural mass model, the authors suggested that hippocampal cell loss disturbed the coupling of subnetworks, which induced an EC–DG shift (Froriep et al., 2012).

In a similar TLE rat model, a decrease in theta coherence in LFP signals between the molecular layer of the DG and stratum lacunosum-moleculare of the CA1 hippocampal field compared to the control group was revealed (Inostroza et al. 2013) (**Fig. 7E**). Besides, in this study, the impairment of the theta phase-locking value (a measure of theta phase synchronization) between these layers was also observed (**Fig. 7**).

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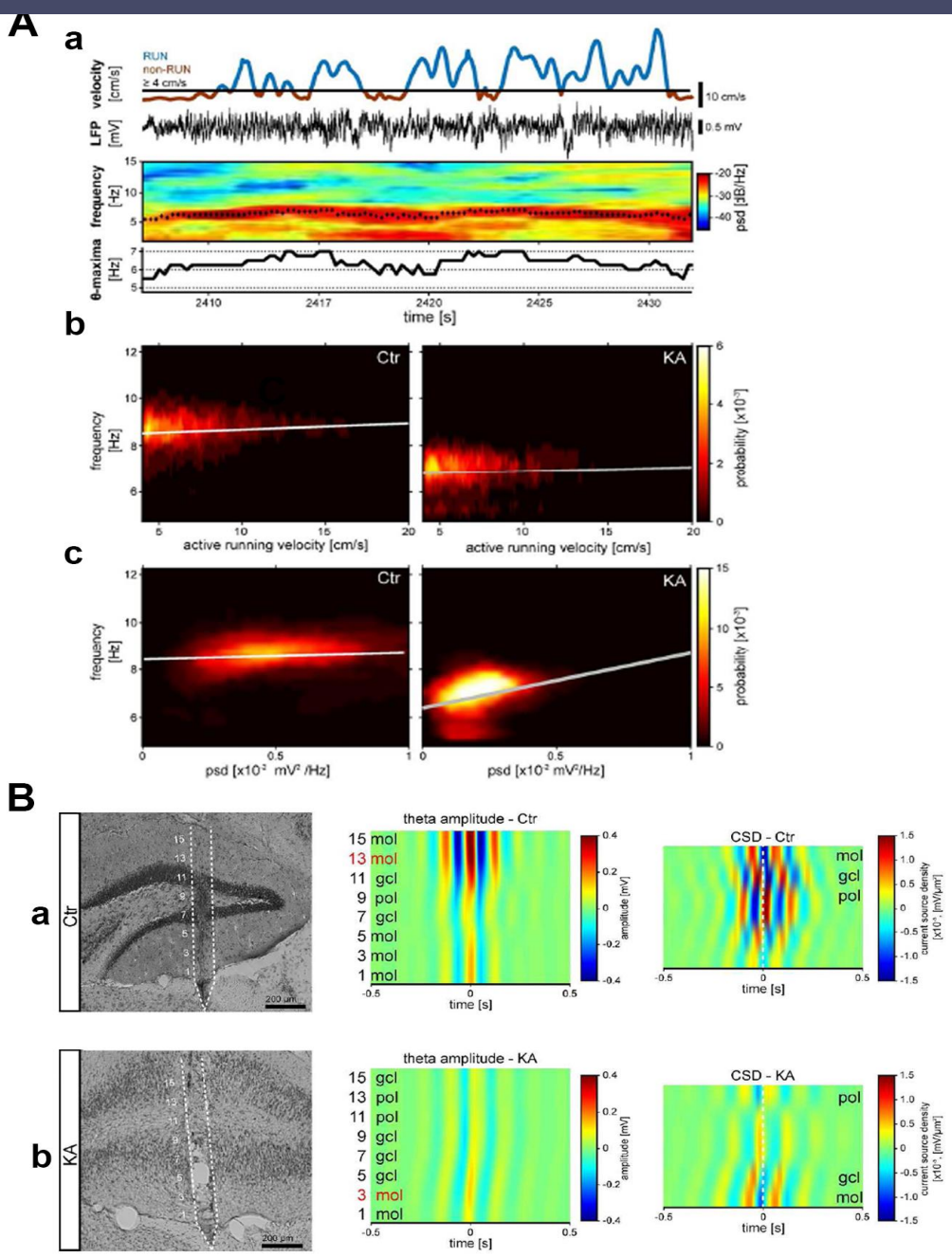

Fig. 6. Theta rhythm decreased in the dentate gyrus (DG) network activity in kainate-treated epileptic animals.

(A) Theta band activity scales with running speed. **a**, Local field potential (LFP) oscillations (second panel) with a spectral peak in the theta band (third panel) recorded from dispersed granule cells (GCs) varied with running speed (top panel) during exploration. Frequency and power of the theta rhythm were estimated by windowed spectral peak detection (4 s windows, 5–12 Hz, black crosses: local theta power maxima per 4 s window). **b**, Probability to find a theta peak frequency at a certain running speed (all 4 s windows of all 10 sessions pooled) for representative epileptic and control mice. Theta frequency increased linearly with running speed in both examples (linear fit). **c**, Equivalent analysis and animals as in (b) for the theta frequency-power relationship. Theta frequency significantly scaled with theta power in the majority of animals. Correlation coefficient r = line width.

(**B**) Current source density (CSD) estimate across DG layers. *Left:* Positioning of the Si-probe within the DG of a control **(a)** and an epileptic mouse (**b**). Temporal evolution of the theta amplitudes (middle) and the resulting CSD (right) for all odd electrodes of a representative control and epileptic mouse. Electrodes numbers and layers used for theta peak detection are indicated in red. Theta frequency in epileptic animals was reduced compared with controls. *Adapted with permission from Kilias et al., 2018.*

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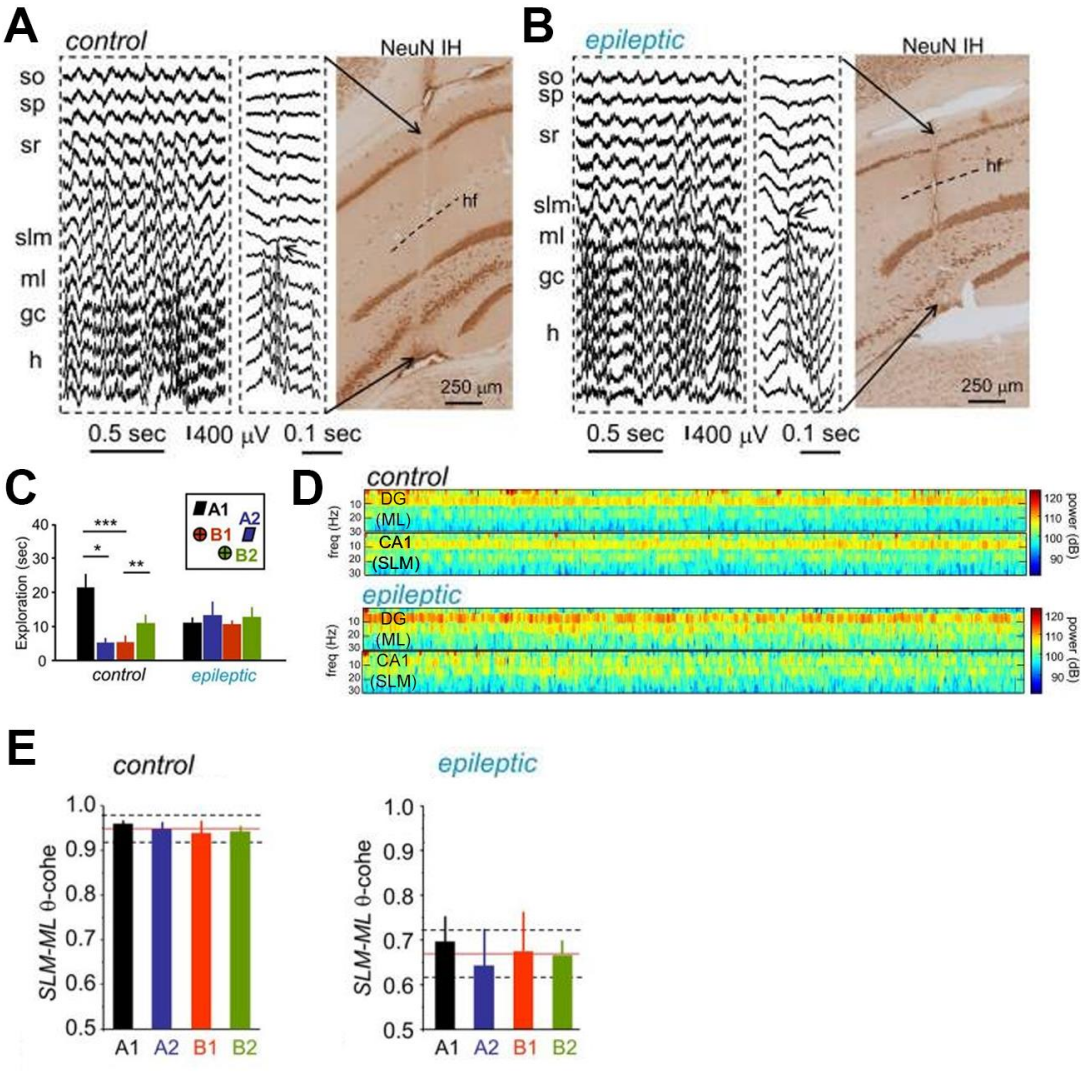

Fig. 7. Activity from the hippocampal CA1 field and dentate gyrus (DG) of healthy rats in compare to kainite-injected (KA) epileptic ones.

(A) *Left*: Typical theta activity recorded from the dorsal hippocampus of a normal rat during the episodic-like memory task with a 16-channel probe. Red arrows indicate the borders between recordings in the hippocampus and DG. Middle traces show a representative dentate spike (short black arrows), which changes polarity at the outer molecular layer of the DG. *Right:* Immunostaining for the neuronal marker NeuN provided further data for localization of hippocampal strata.

(**B**) Representative epochs of theta activity (left) and a dentate spike (middle) from an epileptic rat. NeuN immunostaining (right) was used in epileptic rats to reveal some histopathological features of temporal lobe epilepsy. Note neuronal loss and hippocampal atrophy, and the probe track (long black arrows). SO, stratum oriens; SP, stratum pyramidale; SR, stratum radiatum; SLM, stratum lacunosum moleculare; ML, molecular layer; GC, granule cell layer; h, hilus; hf, hippocampal fissure. Arrows indicate the probe track.

(C) Behavioral data for rats during the performance the episodic-like memory task. Distribution of exploratory times per object in the test phase for the control and epileptic groups. The inset represents the object configuration in the task. Data are represented as the mean ± SEM (n = 6 control, n = 9 epileptic). *P < 0.05, **P < 0.01, ***P < 0.005. (D) Specific alterations in hippocampal theta activity in temporal lobe epilepsy brain during object exploration in the episodic-like memory task; the time–frequency power spectrum of hippocampal field potentials in the SLM and the ML layers is shown for the 1–30 Hz frequency band. (E) Theta coherence between hippocampal SLM–ML layers 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 (discontinuous line) for the whole session in the control and epileptic animals are shown.

Adapted with permission from Inostroza et al., 2013.

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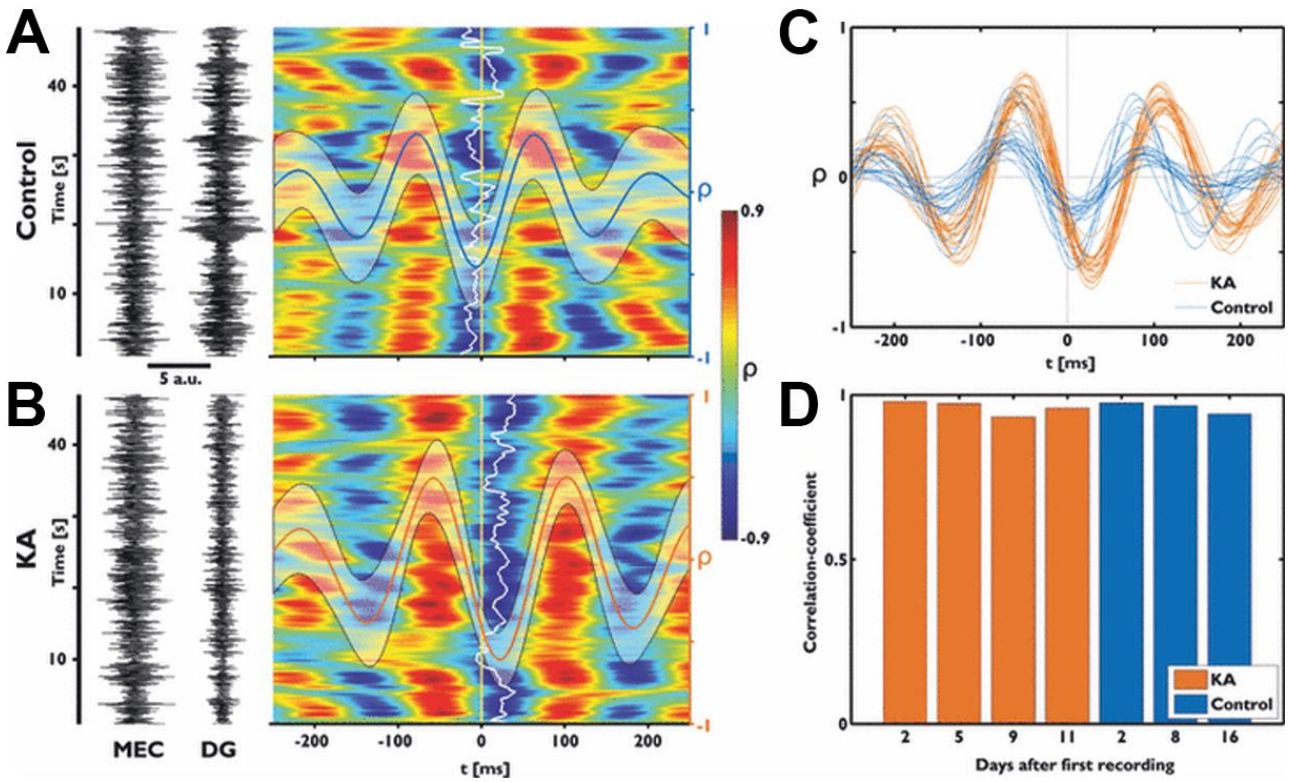

Fig. 8. Correlation analysis in theta band of kainate-injected mice (KA) shows a positive lag between medial entorhinal cortex (MEC) and dentate gyrus (DG) when compared to control data.

(**A**) *Left*: Example epoch with ongoing activity from MEC and DG electrodes in a healthy control mouse (S120) after filtering in theta band (4–8 Hz). *Right*: Time-resolved cross-correlation result (q: correlation-coefficient, t: lag) from this epoch (pseudo-color map, time axis is the same as for the traces) with the mean (blue line, right y-axis) and standard deviation (transparent surface) of q superimposed (right y-axis gives coefficient). Each horizontal line in the pseudo-color plot is the result from cross-correlating 2 s of the filtered MEC signal with the filtered DG signal. The evolution over time results from sliding these 2-s cutouts by 250 msec until maximum time of the epoch is reached. The vertical white line follows the maximal anti-correlation to estimate the jitter, the yellow line indicates t = 0 and thereby 0 msec lag. The mean of the correlation result displays its highest absolute q-value close to 0 msec lag (i.e., Δt_{peak} ~ 0 ms). (**B**) Same as A, but without epileptiform signals from a KA-injected mouse (K116) and the line representing the mean in red. The highest mean correlation is at Δt_{peak} ~ 23 ms. (**C**) Mean of the correlation results from all epochs from one recording session for K116 (orange, Δt_{peak} ~ 24 ms) and S120 (blue, Δt_{peak} ~ 0 ms). The Δt_{peak} ~ 23 ms values of KA and control persist over epochs. (**D**) Stability of the average cross-correlation results from all epochs from given recordings over weeks. The bars give the pairwise linear correlation of the mean correlation result of the first recording with following recordings as a measure of similarity in the two mice.

Adapted with permission from Froriep et al., 2012.

In contrast to the data obtained by Froriep and colleagues (2012), it was shown later on a similar kainate model that, in epileptic mice, the theta oscillation coherence between the DG and the MEC, as well as across different parts of the DG was retained. However, as compared with healthy mice, a phase shift in the coupling of theta oscillations between the DG and MEC in the septal (but not the temporal) part of the DG occurred in these animals (Kilias et al., 2018).

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Gamma and low frequency oscillations in an epileptic brain

Regarding the gamma rhythm, Inostroza et al. (2013) showed that gamma oscillations in both control and epileptic rats were more prominent in the DG compared to CA1. Besides, the authors did not find any significant difference between control and epileptic animals in the spatial profile of gamma oscillations.

It was recently shown that specific low-frequency oscillations (LFOs) appear in the DG of epileptic rats in a model of prolonged perforant pathway stimulation (PPS); they arose during a seizure-free latent period at a rate of around one per second with a frequency of 13–17 Hz within a cycle. These events began following the 8-h PPS, and their frequency, duration, time of day were unpredictable. The oscillations often decreased in the hour preceding a spontaneous seizure (Meyer et al., 2016). The authors believe that LFOs recorded from the DG may be a reliable biomarker of hippocampal epileptogenesis. They hypothesize that a source of this pathological DG activity is granule cell dendrites, since the bilateral transection of the perforant path affects neither their incidence nor the latency in epilepsy emergence, nor hippocampal neuropathology (Meyer et al., 2016).

Pathological high-frequency oscillations and population spikes in an epileptic brain

It was shown during the preoperative assessment of the seizure focus in patients with TLE that in the DG there appear pathological high-frequency oscillations (pHFOs, 200-600 Hz), also called fast ripples (Bragin et al., 1999, 2011; Staba et al., 2002). It was also revealed during the recording of the hippocampal activity in human TLE epileptic brains that pHFOs were associated with the ascending phase (from trough to peak) of slow waves (Weiss et al., 2020). Since fast ripples are not recorded in the DG in healthy rodents, the appearance of oscillations at a frequency above 100 Hz in the DG of the brain with a TLE model was considered as a pathological epileptiform event, i.e., a marker of epileptogenesis (Csicsvari et al., 2003; Bragin et al., 2007, 2011; Engel et al., 2018). During pHFOs, the field potential represented population spikes consisting of the sum of neuronal spikes in the DG (Bragin et al., 2011). In the work by Bragin et al. (2011), the activity of identified granular cells and interneurons of the DG was registered simultaneously with pHFOs in anesthetized mice in a pilocarpine model of TLE. Granule cells fired by single population spikes predominantly synchronously with pHFOs, while in interneurons a reduced firing rate was registered in this time (Bragin et al., 2011) (**Fig. 9**). Interestingly, basket interneurons in the DG during pHFOs behaved differently than they did during ripple oscillations in the CA1 field of normal hippocampus: in the DG of epileptic animals, the firing rate decreased (Bragin et al., 2011), while in the CA1 of healthy rats the spike frequency increased, giving rise to oscillations (Ylinen et al., 1995). Recently, an in vivo study showed the involvement of CA3 back projection onto DG as a facilitator of a closed circuit

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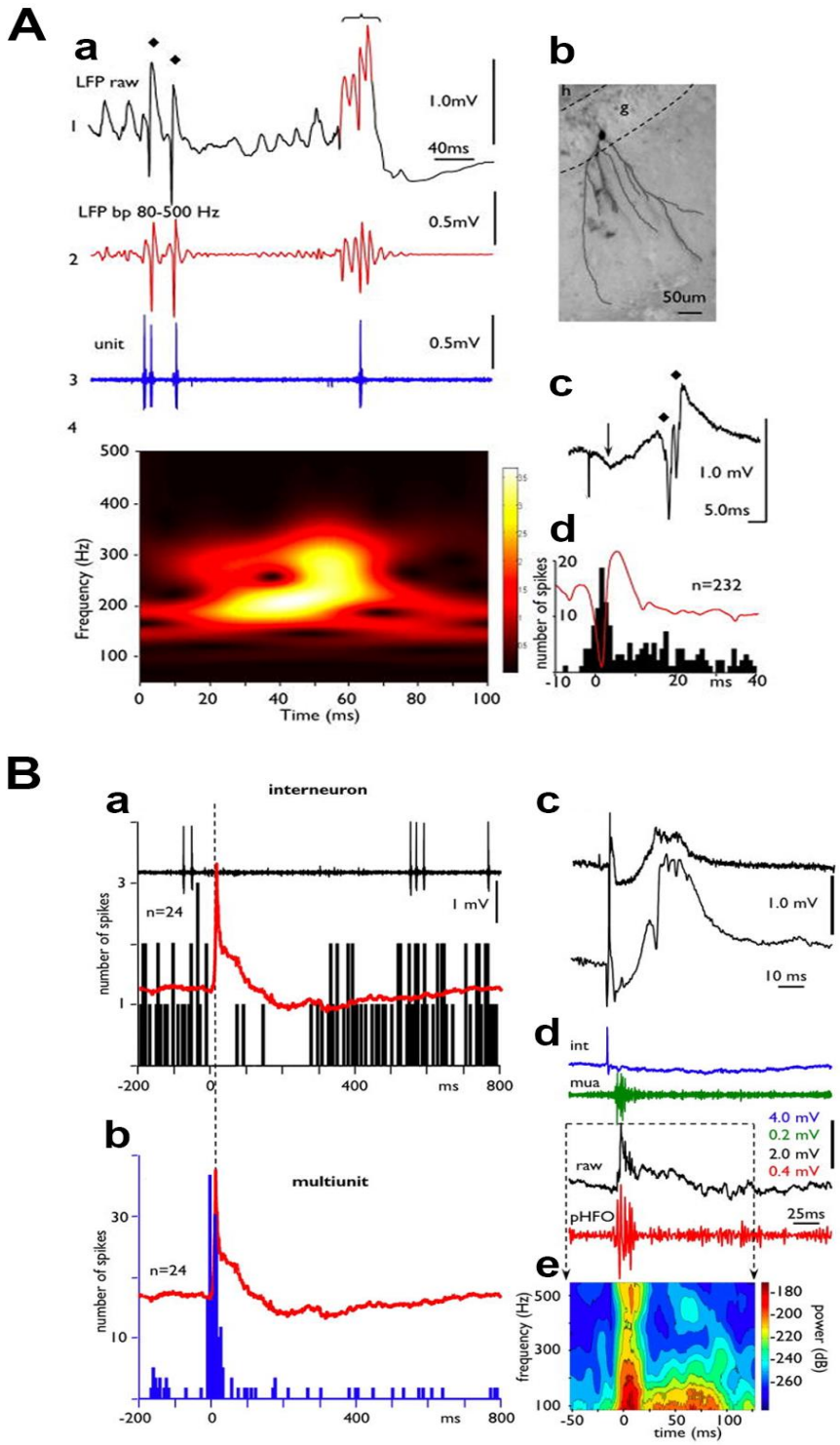

Fig. 9. Discharges of an identified dentate gyrus cells during single population spikes and pathological high frequency oscillations (pHFOs).

(A) An example of two single population spikes (diamonds) and pHFOs (bracket) accompanied by discharges of the granular cell. **a1,** Raw data recorded with 0.1 Hz-5.0 kHz frequency band. **a2**, The same data filtered with frequency band 200–500 Hz. **a3**, Discharges of the granular cell (labeled in b) recorded by the glass microelectrode with the tip located 200 μm from the tungsten microelectrode which recorded the field potentials in a1. **a4**, Color coded power spectrogram of the pHFO. Numbers on the color bar indicate energy in μV^2. **b**, the granular cell labeled by neurobiotin after the completion of the electrophysiological experiments. Some dendritic branches are enhanced with Photoshop. **c**, An evoked field potential in response to perforant path

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stimulation. The beginning of a population EPSP indicated by the arrow is followed by two population spikes (diamonds). **d**, Perievent histogram of the granular cell discharges during 232 population spikes (red) where "0" is the beginning of the population spike.
(B) Suppression of discharges of an identified interneuron (c) during pHFOs. **a,** Perievent histogram of the interneuron triggered at the peak of the local field potentials (n=24, dashed line). **b,** Perievent histogram of simultaneously recorded multiunit activity that predominantly represents discharges of granular cells. **c,** Example of DG interneuron. **d,** Examples of discharges of an interneuron (int) and multiunit activity (mua) during a single pHFO. **e,** Color coded map of the local field potentials power in the frequency band 100 Hz to 500 Hz.

Adapted with permission from Bragin et al., 2011.

among these regions, which prolonged the excitatory activity of CA3 (Núñez-Ochoa et al., 2021). The authors suggest that the loss of DG inhibitory drive in the epileptic hippocampus may result in the generation of fast ripples in CA1.

Another pathological marker in the DG electrical activity is the occurrence of spontaneous single population spikes (Bragin et al., 2011), which have never been revealed in the DG of healthy animals. These population spikes showed up both as single events and oscillations (**Fig. 9A**). During pHFOs and single population spikes, granule cells were discharged, whereas interneurons decreased their firing during this time. pHFOs and spontaneous single population spikes are thought to reflect similar neural mechanisms: both represent a high degree of synchronous activity in granule neurons (Bragin et al., 2011).

Conclusions

Thus, the DG, which has specific structural, morphological, and biochemical properties, as well as the capacity for adult neurogenesis, plays a significant role in the functioning of the hippocampus. It is assumed that DG oscillatory activities are important functional tools in the implementation of hippocampal functions, such as attention and memory.

Theta oscillations in the DG are critical to working memory. A sensory-evoked phase shift of the theta rhythm contributes to the encoding of stimulus information in this type of memory: this resetting of the theta rhythm permits the DG to use a wave of depolarization at the time a significant signal arrives from the EC. Beta oscillations are thought to mediate the communication between the olfactory and DG circuits, and a transformation from theta to beta rhythm in DG suggests that the hippocampus is switched to another state for the processing of information, with each rhythm driven by different neural mechanisms. DG gamma activity participates in the information processing and coding; both

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the gamma rhythm and the theta-gamma coherence play an important role in spatial reference memory. During free animal behavior, theta and gamma oscillations in the DG are associated with those rhythms in the EC. As supposed, two mechanistically distinct rhythmic signals coexist in the DG: theta activity is mainly relayed from the entorhinal cortex via excitation, and gamma rhythm is generated by local inhibition.

However, some questions about the oscillations in the DG and their role in the functioning of the hippocampus remain not resolved; thus, the significance of mossy cells in oscillatory processes has not been completely elucidated. The specific role of neurogenesis in rhythmic activities in the DG and other regions of the hippocampal formation in adult mammals and humans is also not fully clear. There is still a certain gap between research on the DG neural network and the study of DG-dependent behavior. Therefore, the main goal in the future regarding the functions of DG is expected to fill this gap.

Most of the published data indicate that the DG is a structure that normally performs a filtering ("gate") function, i.e., controls the propagation of excitatory signals from the neocortex to the hippocampus. Therefore, the hypothesis prevails that the damage to the DG structure (mainly to mossy cells) is a possible cause of the initial stage of TLE development. However, this hypothesis has not yet received final experimental support; there are doubts in this respect, and this problem will hopefully be resolved in the future.

The protective role of the DG in hippocampus functioning is supported by evidence for the colocalization of GABA and glutamate in granule cell/mossy fiber terminals. The coexistence of GABA and glutamate is especially evident after epileptic seizures, suggesting such a colocalization in granule cells in the DG of the normal brain. If this is true, monosynaptic GABA receptor-mediated transmission emerges in mossy fiber synapses, which restrains excitation and mediates antiepileptic and neuroprotective actions.

In the TLE brain, a clear pathological marker is the generation of spontaneous population spikes in the DG electrical activity, which appear as single events or oscillations. Besides, in the DG of epileptic rats, changes in the oscillatory activity are revealed: high-frequency oscillations (~80–200 Hz) are detected, while in the normal DG they are absent. In addition, in the DG of patients with TLE, fast ripple oscillations (~200-600 Hz) occur. Consequently, oscillations with a frequency above 100 Hz in the DG are regarded as epileptiform phenomena; i.e., their occurrence is a marker of epileptogenesis.

The theta rhythm, although present in the DG of the epileptic brain, is decreased in amplitude and frequency. Besides, the within-frequency theta phase coupling in the DG of epileptic animals is altered.

Typical for the epileptic brain is also disturbances in interstructural interactions of the DG with some other brain regions in the theta frequency range.

Several lines of evidence indicate that the theta rhythm and theta coherence are critically involved in memory processing, and they undergo dramatic changes in the TLE brain. Disturbances of DG theta oscillations and their coherence may be involved in general cognitive impairments observed during epileptogenesis.

It can be stated that, in the future, changes in the DG oscillatory activity would be regarded as an early biomarker of epileptogenesis. In turn, the possibility of detecting TLE at the initial stages of development would contribute to the creation of new approaches to its treatment.

Abbreviations: DG - dentate gyrus; DS – dentate spike; DSWs – dentate sharp waves; EC – entorhinal cortex; HFOs – high-frequency oscillations; LFPs – local field potentials; MEC – medial entorhinal cortex; LEC – lateral entorhinal cortex; OB – olfactory bulb; pHFOs – pathological high-frequency oscillations; SPWs – hippocampal sharp waves; SWRs – sharp-wave ripples; TLE – temporal lobe epilepsy.

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CONFLICT OF INTEREST
The authors declared no conflict of interest.

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