Neurobiology of Disease 124 (2019) 396–407

Contents lists available at ScienceDirect

Neurobiology of Disease

journal homepage: www.elsevier.com/locate/ynbdi

Review

High-frequency oscillations and focal seizures in epileptic rodents

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ARTICLE INFO

Keywords:
High-frequency oscillations
Ripples
Fast ripples
Low-voltage fast onset seizures
Hypersynchronous-onset seizures
Animal models

ABSTRACT

High-pass filtering (> 80 Hz) of EEG signals has enabled neuroscientists to analyze high-frequency oscillations (HFOs; *i.e.*, ripples: 80–200 Hz and fast ripples: 250–500 Hz) in epileptic patients presenting with focal seizures and in animal models mimicking this condition. Evidence obtained from these studies indicate that HFOs mirror pathological network activity that may initiate and sustain ictogenesis and epileptogenesis. HFOs are observed in temporal lobe regions of epileptic animals during interictal periods but they also occur before seizure onset and during the ictal period, suggesting that they can pinpoint to the mechanisms of seizure generation. Accordingly, ripples and fast ripples predominate during two specific seizure onset patterns termed low-voltage fast and hypersynchronous, respectively. In this review we will: (i) summarize these experimental studies; (ii) consider the evolution of HFOs over time during epileptogenesis; (iii) address data obtained with optogenetic stimulating procedures both *in vitro* and *in vivo*, and (iv) take into account the impact of anti-epileptic drugs on HFOs. We expect these findings to contribute to understanding the neuronal mechanisms leading to ictogenesis and epileptogenesis thus leading to the development of mechanistically targeted anti-epileptic strategies.

1. Background

Mesial temporal lobe epilepsy (MTLE) represents the most common type of adult, refractory focal epilepsy (Engel, 1996; Gloor, 1997). MTLE is characterized by recurrent seizures that arise from temporal lobe areas such as the hippocampus and the rhinal cortices, and start occurring many years following an initial brain insult such as *status epilepticus,* traumatic brain injury, encephalitis or febrile convulsions (French et al., 1993; Mathern et al., 1995). These seizures are often resistant to anti-epileptic drugs (AEDs), making surgical resection of the epileptogenic tissue one of the few therapeutic alternatives (Engel et al., 2012; Blume and Parrent, 2006). Surgery is however costly and at times impracticable, and can lead to transient or permanent complications (Hader et al., 2013). It is therefore crucial to understand the mechanisms involved in seizure generation in MTLE to develop more effective, mechanism-targeted therapeutic interventions. To this end, several animal models of MTLE have been developed over the last few decades. Among them, the kainic acid (Ben-Ari and Lagowska, 1978; Lévesque and Avoli, 2013) and the pilocarpine model (Curia et al., 2008; Turski et al., 1983) have been extensively used because of their high level of similarity with human MTLE.

Both models rest on the topical or systemic administration of a chemoconvulsant in rodents to induce a *status epilepticus* that is followed by recurrent, focal temporal lobe seizures that are resistant to AEDs, as observed in epileptic patients (Löscher, 2013). Moreover, both in animal models and epileptic patients, neuronal damage takes place in hippocampal, extra-hippocampal and extra-temporal networks (Lévesque et al., 2015a; Moran et al., 2001). Finally, animal models appear to reproduce the latent period observed in epileptic patients, which is defined as the seizure-free period between the initial brain insult and the occurrence of the first spontaneous seizure. The latent period is thought to be associated to neuronal changes that will lead to the development of a chronic epileptic condition (Goldberg and Coulter, 2013); however, this notion is currently debated since epileptogenesis may also involve continuing and progressive changes in brain functions that extend to the chronic condition (Maguire, 2016).

Cell loss and reorganization of neuronal circuits following *status epilepticus* are likely to lead to disruptions of normal oscillatory activities in the brain. For instance, a complete disappearance of the theta rhythm and increased gamma activity was observed in the hippocampus ipsilateral to the site of injection in kainic acid-treated rodents (Dugladze et al., 2007; Lothman et al., 1981; Medvedev et al., 2000; Riban et al., 2002), and a decrease in theta power and frequency occurs in the pilocarpine model during both the latent (Chauvière et al., 2009; Karunakaran et al., 2016; Marcelin et al., 2009) and chronic epileptic period (Lee et al., 2017). Oscillations in higher frequency ranges,

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https://doi.org/10.1016/j.nbd.2018.12.016
Received 12 October 2018; Received in revised form 26 November 2018; Accepted 22 December 2018
Available online 24 December 2018
0969-9961/

referred to as ripples (80–200 Hz) and fast ripples (250–500 Hz), are also observed in MTLE patients (Jacobs et al., 2008; Zijlmans et al., 2011; Zijlmans et al., 2009) and in rodent models during the interictal phase (Bragin et al., 2007; Bragin et al., 2004; Bragin et al., 1999a; Lévesque et al., 2011; Salami et al., 2014); these high frequency oscillations (HFOs) are believed to reflect the activity of dysfunctional neuronal networks (Jefferys et al., 2012).

HFOs are also observed during seizures and interestingly, show a different distribution depending on the pattern of onset, suggesting that they could also be used to understand the pathophysiological mechanisms sustaining ictogenesis. In animal models of MTLE, ripples and fast ripples are preferentially associated to low-voltage fast-onset seizures (LVF) (Lévesque et al., 2012) and hypersynchronous-onset seizures (HYP) (Bragin et al., 2005; Lévesque et al., 2012), respectively. LVF and HYP seizures have been recorded in both humans and epileptic animals, and evidence obtained so far suggest that they could be generated by distinct neuronal networks (Avoli et al., 2016).

In this review we will address recent findings on HFOs that are recorded before as well as during HYP and LVF seizures in epileptic rodents, their distribution in hippocampal and extra-hippocampal regions, and their evolution over time during epileptogenesis. We will also consider the impact of AEDs on HFOs in animal models of MTLE. Finally, we will analyze the contribution provided by optogenetics to understanding the role of excitatory and inhibitory neuronal networks in ictogenesis.

2. High frequency (80–500 Hz) oscillations under physiological conditions

Various oscillatory rhythms, ranging from low frequency (around 0.5 Hz) to ultra fast (500 Hz) oscillations, characterise the EEG of rodents (Buzsáki and Draguhn, 2004). While slow oscillations can be visible on the EEG, HFOs such as ripples (80–200 Hz) and fast ripples (250–500 Hz) are only visible after the signal has been filtered in specific frequency ranges. It must however be noted that the categorization in ripples and fast ripples, which is solely based on frequency, is subjective. In fact, although distinct cellular mechanisms have been proposed to sustain ripple and fast ripple activity, both HFO subtypes may share common cellular and pharmacological mechanisms (Jefferys et al., 2012)

Ripples were originally recorded from the pyramidal cell layer of the hippocampal CA1 region in immobile or sleeping animals (Buzsáki et al., 1983) but, in subsequent studies, they have also been observed to occur in other regions such as the subiculum, entorhinal cortex, amygdala and associative cortex of rodents (Buzsaki et al., 1992; Khodagholy et al., 2017; Ponomarenko, 2003; Ylinen et al., 1995). They are often recorded in association with sharp waves, to form what is known as sharp wave-ripples (Buzsaki et al., 1992; Buzsáki, 2015). Numerous studies suggest that ripples support memory consolidation (Eschenko et al., 2008; Girardeau et al., 2017; Girardeau et al., 2009; Khodagholy et al., 2017; Girardeau et al., 2017; Ponomarenko et al., 2008) by re-activating, during sleep, cell assembly patterns that were active during learning (Dragoi and Tonegawa, 2011; Dupret et al., 2010; O'Neill et al., 2010; van de Ven et al., 2016). As proposed by Chrobak and Buzsáki (1996), ripples are generated from action potential discharges of highly interconnected neuronal networks in the CA3 region of the hippocampus, that would induce excitatory postsynaptic potentials on pyramidal cells and interneurons located in the CA1 area; the massive depolarization of CA1 interneurons should lead to sustained firing from basket cells and chandelier cells (Ylinen et al., 1995) thus producing inhibitory postsynaptic potentials in CA1 pyramidal cells; these inhibitory postsynaptic potentials would then summate spatially and temporally to produce an oscillation at approximately 200 Hz in the field potential (Buzsaki et al., 1992; Ylinen et al., 1995).

Therefore, at least in the CA1 region of the hippocampus, ripples should mirror summated Cl^- dependent, inhibitory postsynaptic potentials mainly generated by the soma of pyramidal cells in response to GABA released from interneurons, suggesting that they mainly rest on GABAergic transmission, and specifically on $GABA_A$ receptor signaling (Buzsaki et al., 1992; Chrobak and Buzsáki, 1996; Klausberger et al., 2004; Klausberger and Somogyi, 2008; Ylinen et al., 1995). In line with this evidence, a recent study has shown that fast, GABA-receptor mediated inhibition of pyramidal cells is a critical condition for the generation of ripples (Stark et al., 2014). However, it should be noted that HFOs in the ripple band have been recorded *in vitro* from the dentate gyrus during application of $GABA_A$-receptor antagonist picrotoxin (D'Antuono et al., 2005). Recent findings also suggest that ripples could mirror changes in extracellular Ca^{2+}, since in the *in vitro* hippocampal slice preparation, application of medium containing decreased $[Ca^{2+}]$ induces the appearance of ripple activity (Aivar et al., 2014). Gap junctions may also be involved in the generation of ripples since they are suppressed by gap junction blockers in *in vitro* preparations (Behrens et al., 2011; Draguhn et al., 1998), although ripples that are not dependent on gap junctions have also been observed *in vitro* (D'Antuono et al., 2005).

Physiological fast ripples are observed in the somatosensory cortex of animals, during sleep spindles, and the firing of pyramidal cells and interneurons is strongly phase-locked to these neocortical oscillations (Kandel and Buszaki, 1997). In humans, physiological fast ripples (400–600 Hz) have also been observed during the N20 evoked potentials recorded from the primary somatosensory cortex (Curio et al., 1994). The mechanisms that sustain the generation of physiological fast ripples is so far unclear but recent evidence suggest that the early component of fast ripples would reflect activity from thalamocortical projections whereas the late part would mirror the activity of fast-spiking interneurons that provide feedforward inhibition on pyramidal cells (Hashimoto et al., 1996; Ozaki and Hashimoto, 2011).

3. High frequency (80–500 Hz) oscillations in animal models of epilepsy

In epileptic animals, ripples occur either alone (Fig. 1A) or in association with interictal discharges (Fig. 1B) (Behr et al., 2015; Bragin et al., 1999a; Lévesque et al., 2011; Li et al., 2018; Salami et al., 2014; Xu et al., 2016), mainly during the spike component (Lévesque et al., 2011). Ripples have been observed in both the kainic acid (Bragin et al., 1999a) and pilocarpine models (Lévesque et al., 2011; Salami et al., 2014), and they are believed to mirror abnormal network activity (Bragin et al., 2004; Lévesque et al., 2011). In epileptic animals, they were first observed in hippocampal and para-hippocampal regions of kainic acid-treated animals in regions adjacent to the site of injection as well as in the dentate gyrus and entorhinal cortex ipsilateral to the injected hippocampus (Bragin et al., 1999a). They were later found in the temporal lobe of rodents following systemic injections of pilocarpine (Lévesque et al., 2011).

Fast ripples as well can occur either alone (Fig. 1C) or in association with interictal spikes (Fig. 1D) in epileptic animals after *status epilepticus* (Behr et al., 2015; Lévesque et al., 2011; Salami et al., 2014). However, compared to ripples, fast ripples are more tightly linked to the development of a chronic epileptic condition, since they were observed during the latent period only in animals that developed seizures several months later (Bragin et al., 2000). They are also believed to depend less on interneuron activity compared to ripples, since they are still observed after inhibitory transmission is blocked (Bragin et al., 2002). Fast ripples would therefore mirror the synchronous firing of principal (glutamatergic) cells due to a collapse of perisomatic inhibition (Gulyás and Freund, 2015). It has also been proposed that fast ripples reflect hypersynchronized action potentials generated by clusters of principal cells firing “in-phase” or “out-of-phase” (Bragin et al., 2011; Bragin et al., 2007; Bragin et al., 2002; Bragin et al., 1999a; Dzhala and Staley, 2004; Foffani et al., 2007; Gulyás and Freund, 2015; Ibarz et al., 2010). Changes in extracellular $[Ca^{2+}]$ concentrations

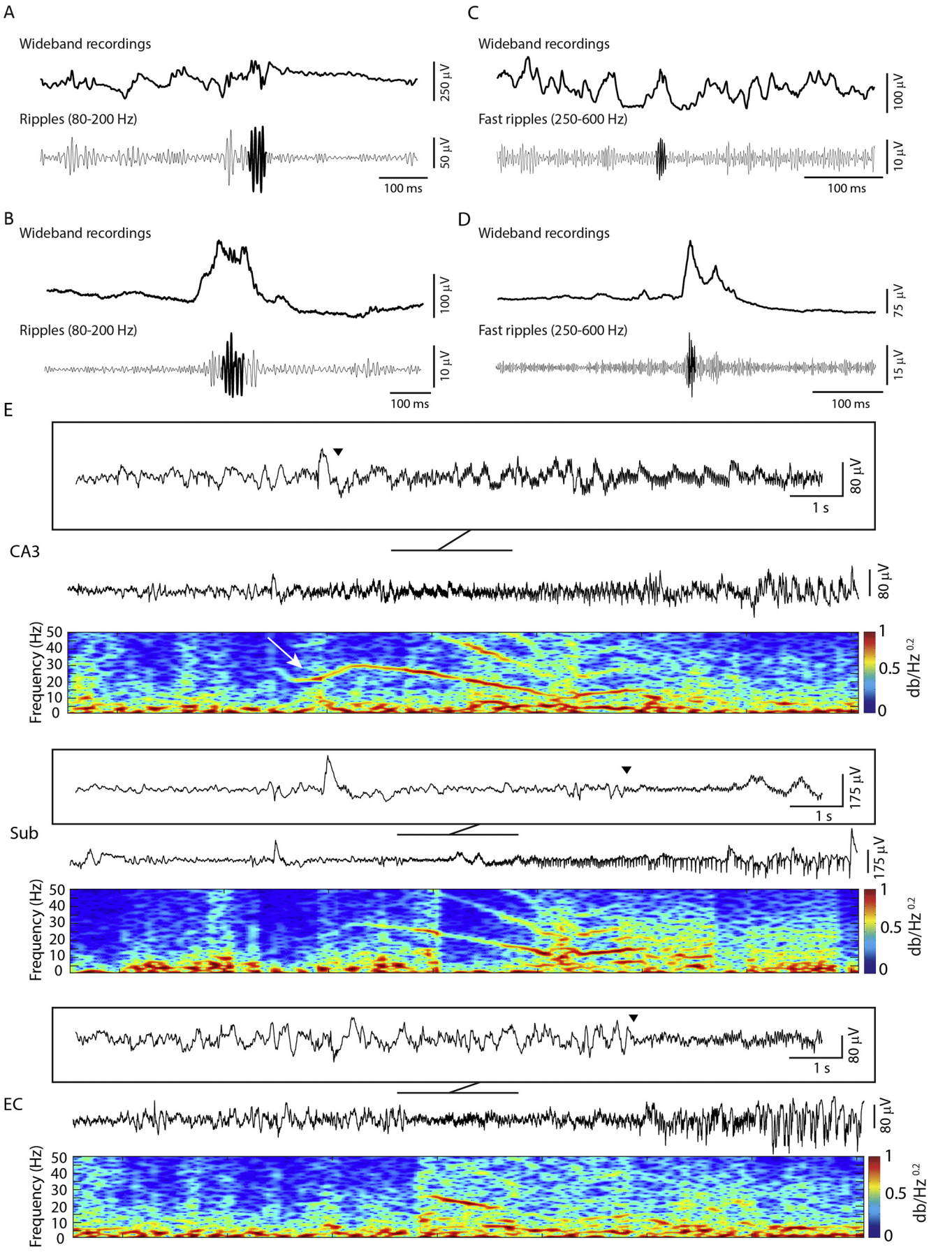

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Fig. 1. A and B: Representative examples of a ripple occurring independently of interictal spikes (A) and of a ripple occurring in association with an interictal spike (B) in a pilocarpine-treated epileptic animal. C and D: Representative examples of a fast ripple occurring alone (A) and of a fast ripple occurring in association with an interictal spike in a different pilocarpine-treated animal. E: Example of a LVF seizure recorded in a pilocarpine-treated animal. The onset of this seizure was located in the CA3 region (arrowhead). The low-voltage fast activity is visible in the power spectrogram (white arrow) and is mainly observed in the CA3 region of the hippocampus. An increase in the frequency of the field oscillations, followed by a gradual decrease, is often observed at the onset of LVF seizures. Data were obtained from the experiments published in Levesque et al. (2012). CA3 = CA3 region of the hippocampus, EC = entorhinal cortex, Sub = subiculum.

could also be responsible for the disruption of cell firing patterns and the generation of pathological fast ripples since, in the *in vitro* hippocampal slice preparation, treatment with medium containing decreased [Ca^{2+}] results in the emergence of fast ripples (Aivar et al., 2014). Serotonin may also play a modulatory effect on fast ripples in epileptic animals (Pardo-Pena et al., 2014; Garcia-Barba et al., 2016) while gap junctions are also believed to contribute to their generation since fast ripples are inhibited by halothane *in vitro* and can be generated *in silico* from networks of neurons connected through gap-junctions (Simon et al., 2014; Staba et al., 2004).

The administration of kainic acid or pilocarpine are known to cause neuropathological changes in animals that underwent a *status epilepticus*. In both models, neuronal loss is first observed in the hippocampus within 48 h after the injection, followed by cell layer dispersion in the dentate gyrus, mossy fiber sprouting and neuronal damage in extra-hippocampal regions (Ben-Ari et al., 1980; Cavalheiro et al., 1996; Covolan and Mello, 2000; Drexel et al., 2012; Sharma et al., 2007; Sloviter and Damiano, 1981; Sperk et al., 1983; Strain and Tasker, 1991; Turski et al., 1983). It is unknown how these changes affect the expression of HFOs; nonetheless, some studies have suggested that cell loss induces a decrease in ripple occurrence while favoring the expression of fast ripples both in epileptic animals (Foffani et al., 2007) and in patients (Staba et al., 2007). It was therefore hypothesized that ripples could rely on the activity of widespread neuronal networks and that following *status epilepticus*, their expression or generation is diminished as the result of a decrease in neuronal densities (Staba et al., 2007). On the other hand, fast ripples - which rely on the activity of small clusters of principal cells (Bragin et al., 2011, Bragin et al., 2007, Bragin et al., 2002, 1999a; Dzhala and Staley, 2004; Foffani et al., 2007; Gulyás and Freund, 2015; Ibarz et al., 2010) - would therefore emerge and predominate over ripples in epileptic animals and patients. Further studies are however needed in order to understand whether and how specific neuropathological changes modulate the expression of ripples and fast ripples overtime during epileptogenesis.

4. High frequency (80–500 Hz) oscillations and seizure onset patterns

It is well established that spontaneous seizures recorded with depth electrodes in MTLE patients can be classified according to their pattern of onset. LVF seizures, which are often characterized by an initial (sentinel) spike and on-going low-amplitude, fast frequency activity, are the most common pattern of ictal discharge initiation in MTLE patients (Lee et al., 2000; Perucca et al., 2013). They are also observed in other types of focal epileptic disorders (Perucca et al., 2013; Singh et al., 2015). Patients with LVF seizures tend to show widespread neuronal loss and a more extensive seizure onset zone (Ogren et al., 2009; Spencer et al., 1992; Velasco et al., 2000). Similar findings have been obtained in kainic acid-treated epileptic rodents (Bragin et al., 1999a, 1999b) as well as in the pilocarpine model, in which LVF seizures can present with onset zones located in the hippocampus (Fig. 1E) or in extra-hippocampal regions such as the entorhinal cortex (Behr et al., 2017; Lévesque et al., 2012).

The analysis of HFOs during seizures has revealed that ripples can occur during the pre-ictal phase of LVF seizures - which can coincide with the occurrence of a sentinel spike (Fig. 2A) - as well as during the overt ictal phase (Fig. 2B). When comparing the occurrence of ripples and fast ripples in pilocarpine-treated animals, LVF seizures are associated to high rates of ripples during the pre-ictal phase in seizure onset zones (Fig. 2C) (Lévesque et al., 2012). In addition, during the ictal phase, both seizure onset zones and regions of secondary spread show rates of ripples that are higher than those of fast ripples (Fig. 2C and D) (Lévesque et al., 2012). Since ripples are believed to rely on the activity of interneurons and GABAergic transmission (Buzsaki et al., 1992; Chrobak and Buzsáki, 1996; Klausberger et al., 2004; Klausberger and Somogyi, 2008; Ylinen et al., 1995), these findings support the hypothesis that the initiation and maintenance of LVF seizures should mainly rest on the involvement, and presumptive hyperactivity, of GABAergic interneuron networks (Avoli et al., 2016; de Curtis and Avoli, 2016).

This conclusion is in keeping with results obtained in several *in vitro* preparations. Accordingly, LVF ictal discharges that are induced by the K^+ channel blocker 4-aminopyridine are associated to high rates of ripples (Avoli et al., 2013; Panuccio et al., 2012; Uva et al., 2017) while interneurons increase their firing rates before LVF ictal discharges (Figure 2Ea) and show significant phase-locking relationships with LVF activity at onset (Figure 2Eb), with a tendency to fire close to the trough of field oscillations, between 90 and 150 degrees (Figure 2Ec) (De Curtis and Gnatkovsky, 2009; Gnatkovsky et al., 2008; Lévesque et al., 2016). Increased firing rates from interneurons have also been reported *in vivo* before LVF seizures in kainic-acid-treated epileptic animals (Grasse et al., 2013). Finally, intracranial pre-surgical recordings obtained with microelectrodes from patients with pharmacoresistant focal epilepsy have revealed that interneurons located in the seizure onset zone increase their firing rate at the start of focal seizure activity presenting with LVF electrographic features (Elahian et al., 2018).

Using optogenetics *in vitro*, three groups have shown that ictal discharges with a LVF onset pattern can be triggered in the entorhinal cortex by activating GABAergic interneurons during perfusion with 4-aminopyridine (Chang et al., 2018; Shiri et al., 2016; Shiri et al., 2015b) (Fig. 3A). It is noteworthy that LVF ictal discharges triggered with parvalbumin-positive interneuron stimulation were found in one of these studies to be associated to high rates of ripples (Fig. 3B). Such findings have however not been so far reproduced *in vivo*. We therefore recently attempted to perform long-term stimulation of parvalbumin-positive interneurons in the pilocarpine model, in order to trigger ictal discharges in epileptic rodents. PV-ChR2 and PV-Cre mice that were treated with pilocarpine received continuous (24/7) unilateral optogenetic stimulation (450 nm, 50 mA, 20 ms pulse duration delivered at 8 Hz for 30 s every 2 min) of CA3 parvalbumin-positive interneurons, starting 3 h after the onset of *status epilepticus* to 14 days after. Although preliminary, findings obtained to date indicate that LVF seizures in PV-ChR2 animals can be triggered by optogenetically activating CA3 parvalbumin-positive interneurons (Fig. 3C).

HYP seizures are focal ictal discharges that are observed from hippocampal structures in MTLE patients (Perucca et al., 2013; Singh et al., 2015; Spencer et al., 1992; Velasco et al., 2000), and appear to be related to the presence of mesial temporal atrophy or sclerosis (Ogren et al., 2009; Perucca et al., 2013; Singh et al., 2015; Velasco et al., 2000). They are also observed in kainic-acid treated animals and, consistent with what is observed in epileptic patients, HYP seizures are mostly restricted to the hippocampus, and are not associated with severe behavioral symptoms unless they transition into another EEG pattern and/or become generalised (Bragin et al., 1999a, 1999b). We have also found in the pilocarpine animal model that HYP seizures (Fig. 4) initiate most often from the CA3 region of the hippocampus

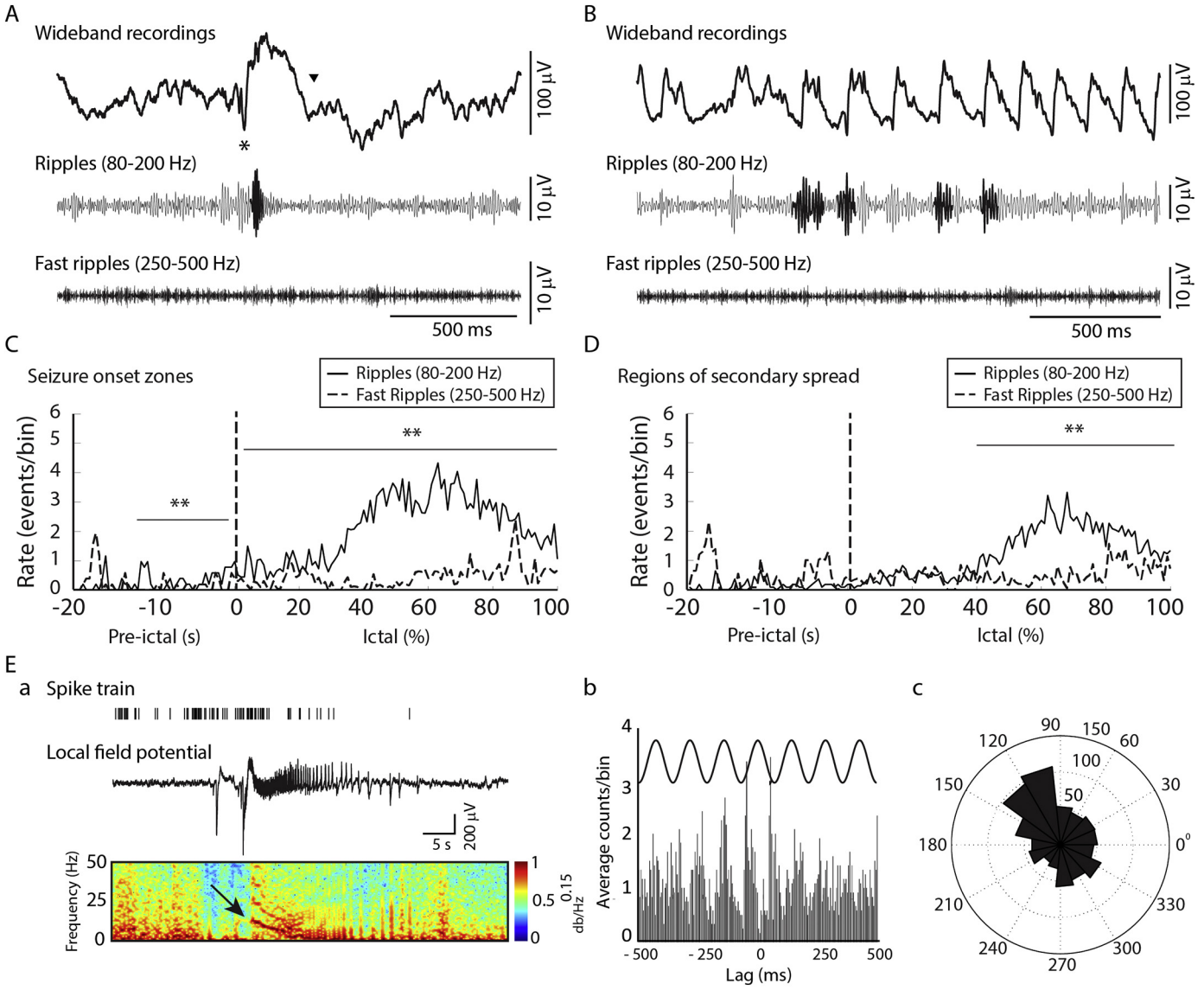

Fig. 2. A: Representative recording showing the sentinel spike of a LVF seizure (asterisk) that is followed by a LVF onset seizure (arrowhead) in a pilocarpine-treated animal. Note that the sentinel spike is associated to a ripple (black trace). B: Example of ripples (black trace) occurring during the ictal phase of the same LVF seizure shown in A. C and D: Distribution of ripples and fast ripples during the pre-ictal and ictal phase in seizure onset zones (C) and in regions of secondary spread (D) of LVF seizures occurring in pilocarpine-treated animals. Note that ripples significantly increased before ictal onset in seizure onset zones and during seizures in both seizures onset zones and regions of secondary spread (** $p < .01$). E: In a, spike train of a putative interneuron recorded *in vitro* with tetrode wires in the entorhinal cortex under 4-aminopyridine treatment during a LVF ictal discharge; the LVF activity during the tonic phase is indicated by the arrow in the spectrogram. In b, interneurons show a phase-locked relationship with LVF activity (5–15 Hz) occurring during the tonic phase of LVF ictal discharges. In c, interneurons tend to fire closed to the trough of field oscillations, between 90 and 150 degrees, as illustrated in the polar plot. Data were obtained from the experiments published in Levesque et al. (2012, 2016).

(Behr et al., 2017; Lévesque et al., 2012) and that they are significantly shorter in duration compared to LVF seizures (Lévesque et al., 2012). Similar findings were obtained *in vitro* by comparing ictal discharges with electrographic features resembling LVF and HYP seizures during bath application of the K^+ channel blocker 4-aminopyridine (Lopantsev and Avoli, 1998a, 1998b). However, no difference in duration between the two patterns of seizure onset has been reported to occur in kainic acid-treated animals (Bragin et al., 2005).

In both the kainic acid and pilocarpine model, HYP and LVF seizures can be recorded in the same animal (Behr et al., 2017; Bragin et al., 1999b; Lévesque et al., 2012), indicating that a seizure onset zone can generate both patterns of ictal onset (Bragin et al., 1999b). Changes in onset patterns during a seizure recorded from one electrode were also observed in animals in which kainic acid was topically injected in the hippocampus. Bragin et al. (1999b) have indeed reported that in epileptic animals, 27% of HYP seizures could transform into LVF seizures and that 22% of LVF seizures could transform into HYP seizures. These data further suggest that LVF and HYP onset patterns are determined by distinct seizure generation mechanisms rather than by the anatomical location of the recording electrode. In line with this hypothesis, Salami et al. (2015) have shown that LVF seizures can be induced in rodents by systemic injection of 4-aminopyridine, which enhances both glutamatergic and GABAergic transmission (Perreault and Avoli, 1989; Rutecki et al., 1987), while injection of the $GABA_A$ receptor antagonist picrotoxin makes HYP seizures occur.

Fast ripples exhibit significant relationships with HYP seizures in both the kainic acid (Bragin et al., 2005) and the pilocarpine model (Behr et al., 2017; Lévesque et al., 2012); they can be observed during the pre-ictal phase of HYP seizures, sometimes in coincidence with the pre-ictal spikes preceding the onset of fast activity (Fig. 5A), and during

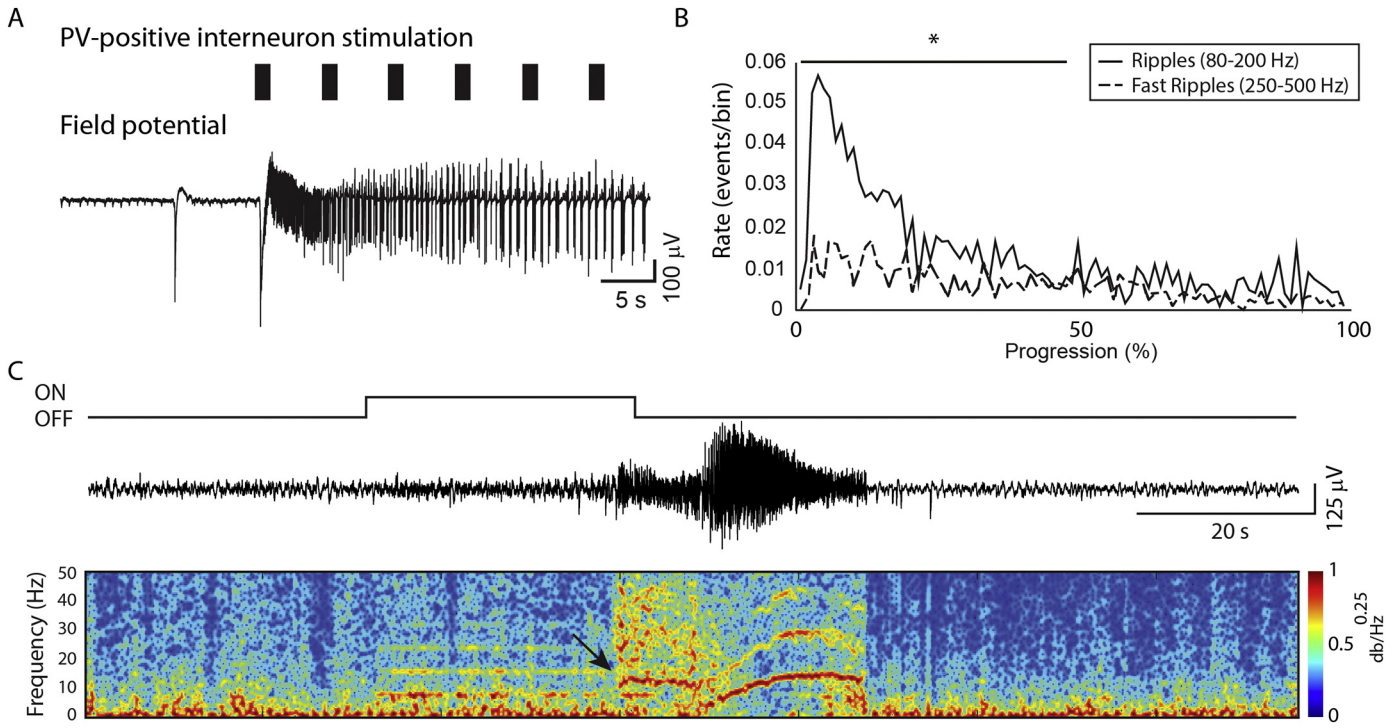

Fig. 3. A: Example of a LVF ictal discharge recorded *in vitro* during optogenetic stimulation of parvalbumin-positive interneurons in the entorhinal cortex during bath application of 4-aminopyridine. B: Distribution of ripples and fast ripples during LVF ictal discharges triggered by the optogenetic stimulation of parvalbumin-positive interneurons in the entorhinal cortex during bath application of 4-aminopyridine. Note that ripples occur at higher rates than fast ripples, a finding that is similar to what is observed during spontaneous LVF seizures in pilocarpine-treated epileptic animals (* $p < .05$). C: Optogenetic stimulation of parvalbumin-positive interneurons in a pilocarpine-treated PV-ChR2 animal triggers an LVF seizure. Note the presence of low-voltage fast activity in the spectrogram (arrow) (unpublished data). Data shown in A and B were obtained from experiments from published in Shiri et al. (2016).

the ictal phase (Fig. 5B). They predominate over ripples during the pre-ictal and ictal phase of HYP seizures, in both seizure onset zones and regions of secondary spread (Fig. 5C and D). *In vitro*, the optogenetic activation of CamKII-positive principal cells in the entorhinal cortex triggers HYP ictal discharges that are associated to high rates of fast ripples (Fig. 5E and F) (Shiri et al., 2016). It was also reported by Köhling et al. (2016) that HYP onset ictal discharges in the rat perirhinal cortex are caused by progressive weakening of $GABA_A$ receptor signaling, that is mirrored by transient elevations in $[K^+]_o$ that reach the highest values shortly before the onset of the electrographic tonic ictal activity. Overall, these findings suggest that, whereas LVF seizures are initiated by the synchronous activity of inhibitory interneuron networks, HYP seizures mostly rely on the involvement of glutamatergic principal cells (Avoli et al. 2016).

5. Overtime evolution of seizure onset patterns and high frequency (80–500 Hz) oscillations

Studies using animal models have often restricted their analysis to specific time-periods after the induction of the initial *status epilepticus* (Bragin et al., 2005; Lévesque et al., 2012). We have however recently studied two groups of animals recorded at different time-points, from day 3 to day 20 after *status epilepticus* (early stage) and from day 27 to day 53 after *status epilepticus* (late stage) (Behr et al., 2017). It was found in these experiments that seizure onset patterns presented with significant changes over time; HYP seizures predominated in the "early stage" group while LVF seizures were more frequent in the "late stage" group (Fig. 6A). We have also found that a significantly higher proportion of LVF seizures initiated from a widespread network in the "late stage" group compared to the "early stage" group (Fig. 6B). These changes in "ictogenetic modalities" were associated with time-dependent alterations in neuronal loss; specifically, rodents in the "late stage" group showed significant cell loss in the CA3 region of the hippocampus and granule cell layer dispersion compared to the "early stage" group (Fig. 6C). Therefore, the over time evolution of seizure onset patterns might reflect changes in neuronal network re-organization during disease progression and, as suggested by Ogren et al. (2009) in their study that was performed in patients with focal epilepsy, LVF seizures might result from extensive neuronal damage due to a long-term exposure to seizures (Tasch et al., 1999).

These findings, however, have not been reported to occur in kainic acid-treated epileptic animals (Bragin et al., 1999b); it was found in this study that rodents recorded three to four months after *status epilepticus* showed a higher proportion of HYP seizures compared to LVF seizures. This discrepancy can be explained by differences in the methodological procedures employed to induce *status epilepticus*, since seizure onset patterns were analyzed after topical injections to the hippocampus of kainic acid (Bragin et al., 1999b, 2005) whereas in the pilocarpine model, systemic injections were used (Behr et al., 2017). It is known that the topical administration of a chemoconvulsant induces lesions that are more restricted compared to systemic administration (Lévesque and Avoli, 2013). Moreover, it is well established that pilocarpine induces more extensive lesions than kainic acid, since morphological changes are observed in extra-hippocampal structures such as the thalamus, substantia nigra, cerebral cortex, olfactory cortices and the amygdala (Rose Priel et al., 1996). LVF seizures, which are associated to widespread neuronal damage in hippocampal and extra-hippocampal regions, could therefore occur more frequently following the systemic administration of pilocarpine.

We have also investigated whether the relationships between HFOs and seizure onset patterns described above, could still be observed in epileptic animals recorded many weeks after a pilocarpine-induced *status epilepticus* (Behr et al., 2017). As shown in Fig. 6D, while in the early stage group ripples predominated during LVF seizures in the CA3

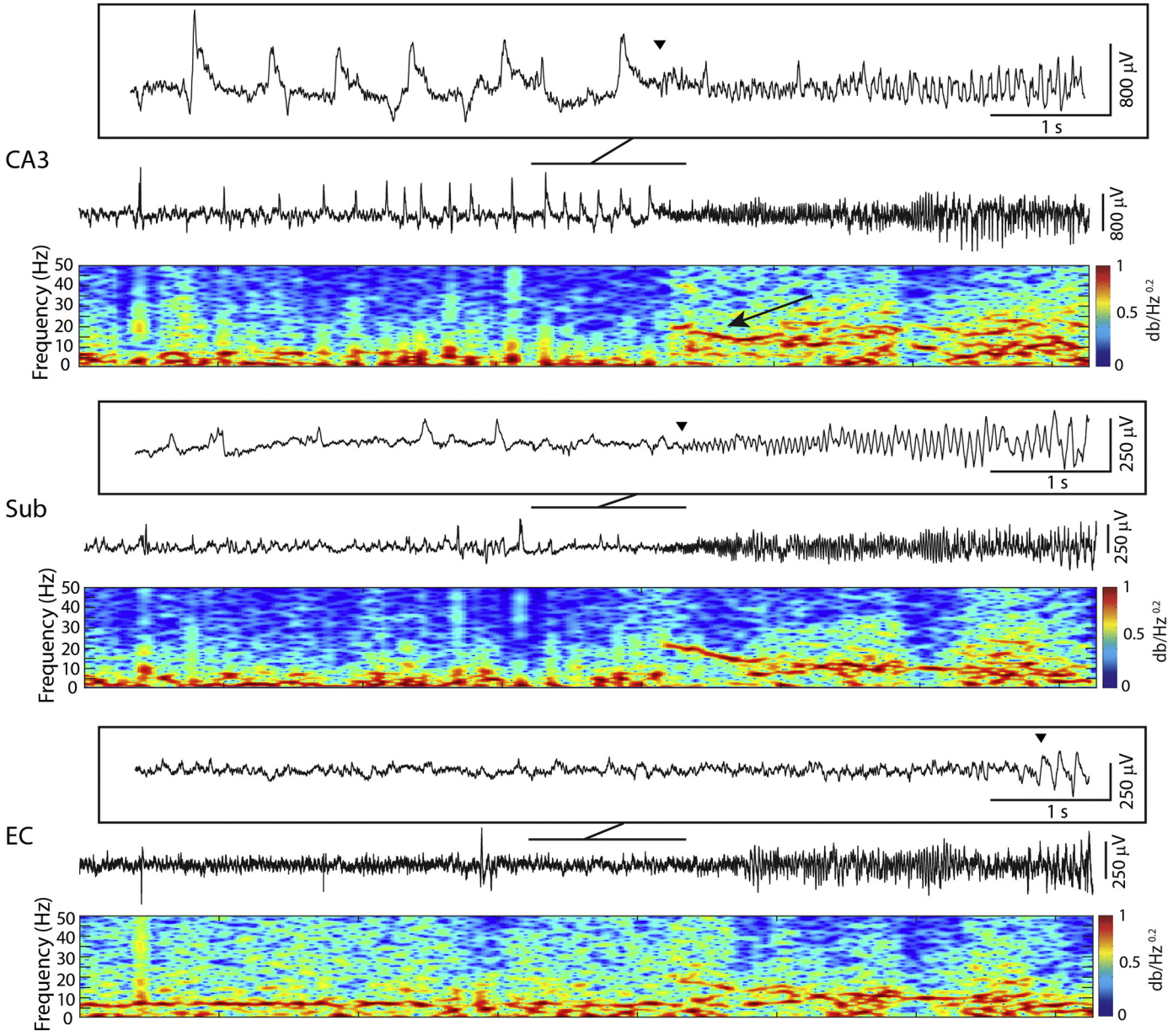

Fig. 4. A: Example of a HYP seizure recorded in a pilocarpine-treated epileptic animal. Note the onset in CA3 (arrowhead) that is characterized by the presence of oscillations between 10 and 20 Hz. Note also that in these epileptic animals, the CA3 region of the hippocampus always display pre-ictal spiking at approximately 2 Hz at the onset of HYP seizures; this spiking is then followed by high-frequency activity (arrow). Note also that similar initial spikes can also be observed in the subiculum. Data were obtained from the experiments published in Levesque et al. (2012).

hippocampal region (which is the most common seizure onset zone in this animal model), fast ripples occurred at higher rates during LVF seizures in the late stage group (Fig. 6E). Moreover, HYP seizures showed high rates of fast ripples in both the early (Fig. 6F) and late stage group (Fig. 6G). These results thus reveal that fast ripples predominate during spontaneous seizures, regardless of the onset pattern, several weeks after *status epilepticus* (Behr et al., 2017). These experimental findings are similar to those reported in MTLE patients, in which fast ripples predominate during HYP and LVF seizures (Perucca et al., 2013; Weiss et al., 2016).

The pathological reorganization of neuronal networks after a pilocarpine-induced *status epilepticus* could therefore lead to a predominance of fast ripples, which mirrors what is observed in epileptic patients who are recorded with depth electrodes several years after the onset of the disease (Perucca et al., 2013; Weiss et al., 2016). Indeed, it has been proposed that neuronal loss and morphological changes occurring after *status epilepticus* can split populations of synchronously firing principal cells into smaller neuronal assemblies and produce complex network interactions between disconnected neuronal populations oscillating at different frequencies; such condition would generate in field potential recordings the emergency of fast ripples presenting with frequencies at > 400 Hz (Foffani et al., 2007; Ibarz et al., 2010; Jiruska et al., 2017). Fast ripples are also correlated with hippocampal sclerosis in epileptic patients (Staba et al., 2007). However, it should be emphasized that they can also be observed in a non-lesional model of temporal lobe epilepsy that is induced by unilateral intrahippocampal injection of tetanus toxin (Jiruska et al., 2010) suggesting that neuronal loss is not a pre-requisite for fast ripple generation.

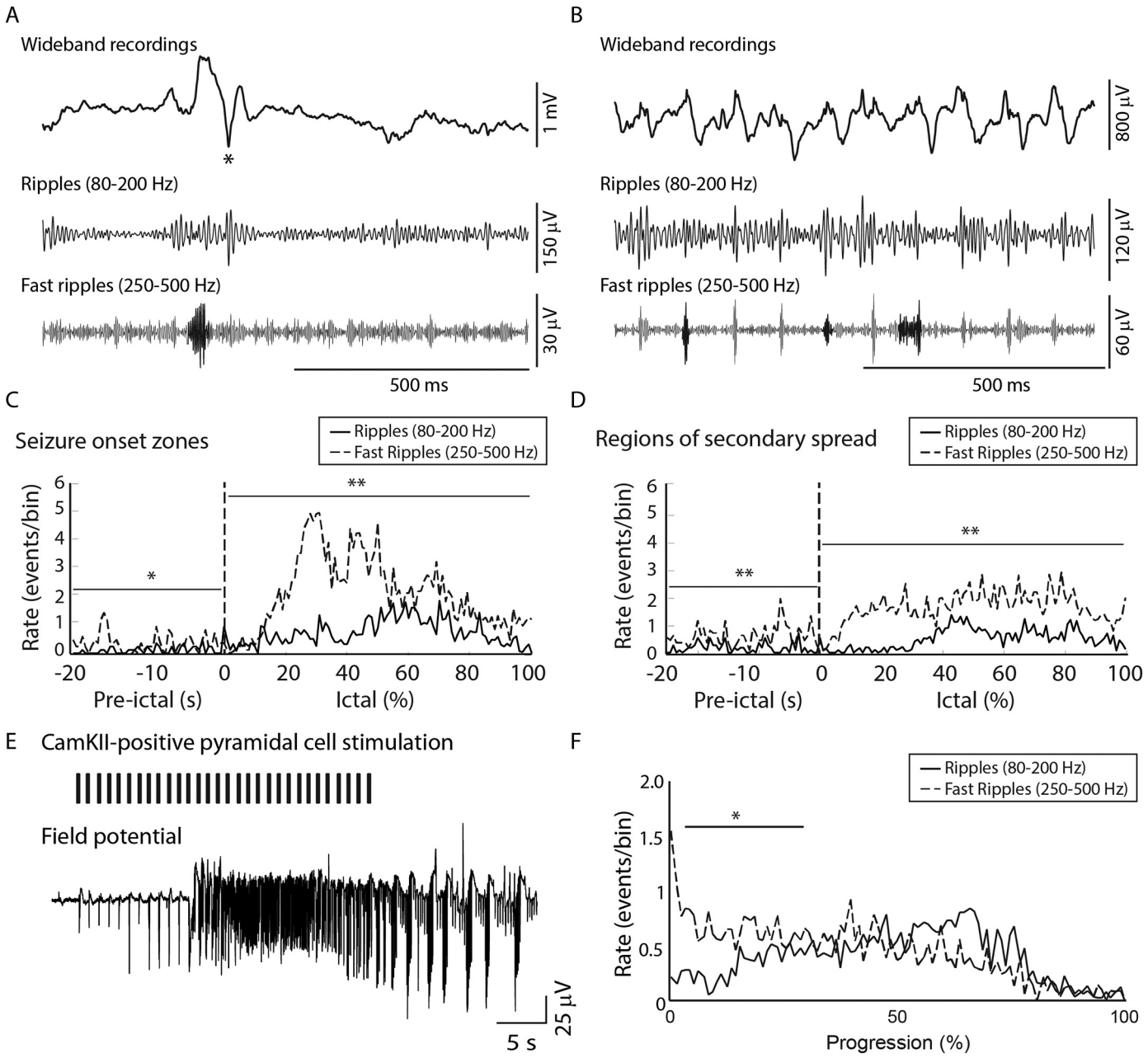

Fig. 5. A: Representative recording showing that fast ripples (black trace) can be observed during the spikes that precede the onset of fast activity during a HYP seizure in a pilocarpine-treated animal. B: Examples of fast ripples observed during the ictal phase of a HYP seizure. C and D: Distribution of ripples and fast ripples during the pre-ictal and ictal period of HYP seizures, in seizure onset zones (C) and in regions of secondary spread (D). Note that during HYP seizures, fast ripples predominate over ripples (* $p < .05$, ** $p < .01$). E: Optogenetic stimulation of CamKII-positive principal cells in the *in vitro* entorhinal cortex during application of 4-aminopyridine triggers HYP ictal discharges. F: These HYP ictal discharges are associated to high rates of fast ripples compared to ripples (* $p < .05$). Data were obtained from experiments published in Lévesque et al. (2012) and Shiri et al. (2016).

6. Effects of antiepileptic drugs on seizure onset patterns and high frequency (80–500 Hz) oscillations

The effects induced by AEDs on seizure onset patterns in animal models of MTLE have not been extensively studied but evidence obtained to date suggest that, even though seizure rates are significantly decreased by AEDs in the kainic acid and pilocarpine models (Behr et al., 2015; Duveau et al., 2016; Glien et al., 2002; Klein et al., 2015; Leite and Cavalheiro, 1995; Lévesque et al., 2015b), the proportions of HYP and LVF seizures are not significantly different in animals treated with AEDs and in non-treated animals (Lévesque et al., 2015b). AEDs might therefore decrease ictogenesis in animal models but no evidence suggest so far that they can target a specific cellular mechanism that underlies seizure onset patterns.

Moreover, few studies have addressed the effects of AEDs on HFOs in epileptic rodents. We have recently addressed this point using the second generation AED levetiracetam in pilocarpine-treated animals and found a significant decrease of interictal spikes with HFOs in treated animals compared to controls (Lévesque et al., 2015a, 2015b). Fast ripple activity was significantly lower in the hippocampus and subiculum, which are common seizure onset zones in this animal model (Lévesque et al., 2012; Toyoda et al., 2013). A significant decrease of fast ripples associated to interictal spikes was also found in pilocarpine-treated animals during treatment with the AED lacosamide, again in the hippocampus and subiculum (Behr et al., 2015). Fast ripples occurring outside of interictal spikes were also significantly lower in animals

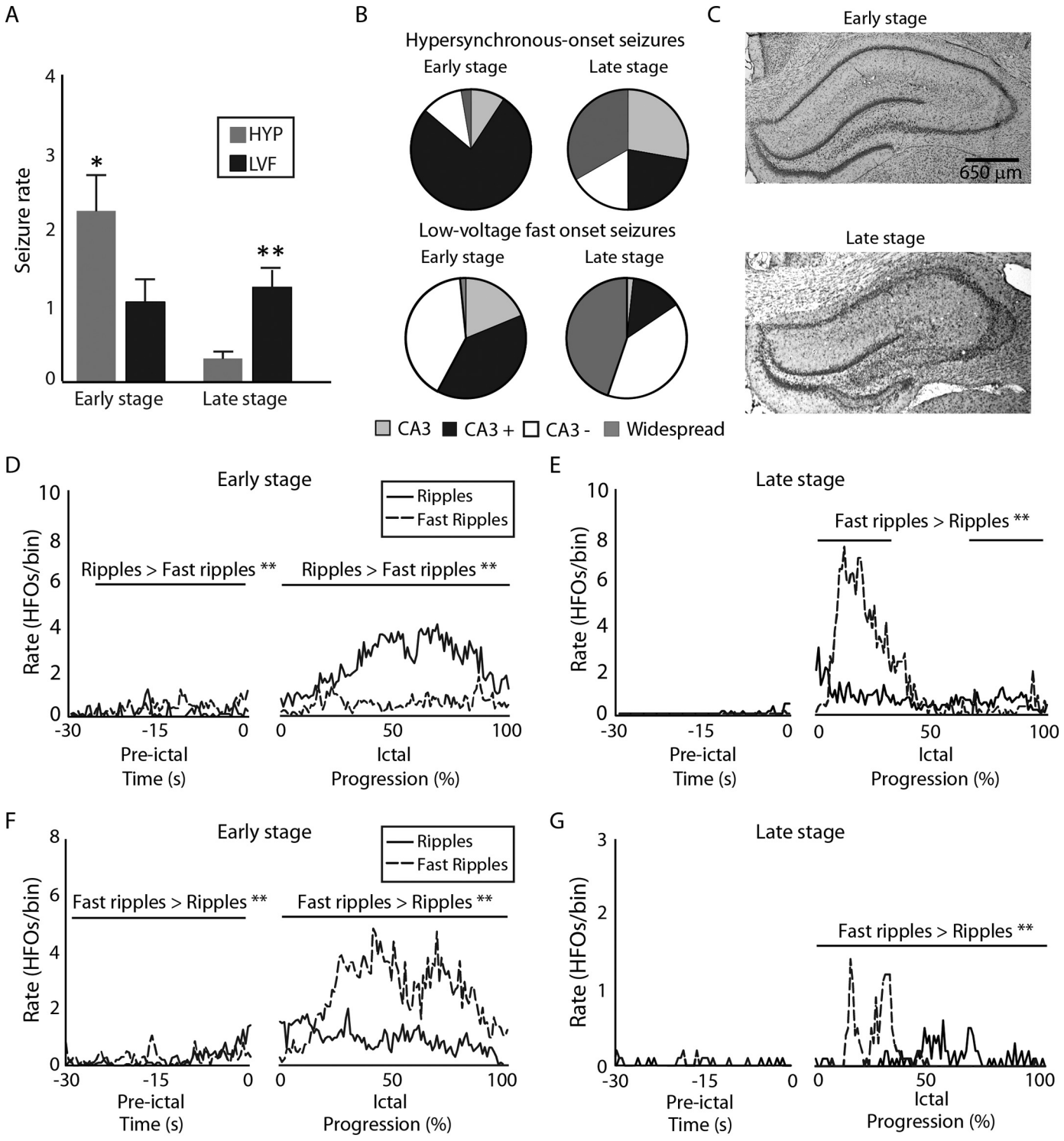

Fig. 6. A: Bar graph showing average seizure rates in animals recorded from day 3 to day 20 after a pilocarpine-induced *status epilepticus* (early stage) and in animals from day 27 to 53 after *status epilepticus* (late stage). Note that animals in the early stage group showed significantly higher rates of HYP seizures compared to LVF seizures whereas animals in the late stage group showed significantly higher rates of LVF seizures (** $p < .01$, * $p < .05$). B: Pie charts showing the distribution of seizure onset zones for HYP and LVF seizures in the early and late stage group. HYP seizures were significantly more likely to originate from the hippocampus than from a widespread network in the early stage group ($p < .01$) whereas no significant differences were observed in the late stage group. LVF seizures did not show any preferred region of onset in the early stage group but were significantly more likely to originate from a widespread network compared to an onset from the hippocampus ($p < .01$). Seizures initiating in the CA3 region were labeled "CA3"; seizures characterized by a simultaneous onset in CA3 and another region were labeled "CA3 +"; seizures initiating simultaneously in CA3, entorhinal cortex, subiculum and dentate gyrus were labeled as "widespread" and seizures that did not involve CA3 were labeled as "CA3–". C: Frontal sections of the hippocampus from epileptic animals in the early and late stage group. Extensive neuronal cell loss is observed in the late stage group, which appears to affect CA1 and CA3 pyramidal cells. Dispersion of granule cells in the dentate gyrus is also observed. D and E: Distribution of HFOs during the pre-ictal and ictal phase of LVF seizures in the early (D) and late stage group (E). Ripples predominated in the early stage group whereas higher rates of fast ripples were observed during LVF seizures in the late stage group. F and G: Distribution of HFOs during the pre-ictal and ictal phase of HYP seizures in the early (F) and late stage group (G). Fast ripples predominated during HYP seizures in both groups (** $p < .01$, * $p < .05$). Data were obtained from experiments published in Behr et al. (2017).

treated with this AED.

We have also investigated whether other molecules, such as neurosteroids, modulate interictal oscillations that include spikes or HFOs in pilocarpine-treated animals. In this study, allopregnanolone, which acts as a positive allosteric modulator of synaptic and extrasynaptic $GABA_A$ receptors (Carter and Reddy, 2013), was administered systemically for 14 continuous days after pilocarpine-induced *status epilepticus* (Lévesque et al., 2017). We found that the frequency of spontaneous seizures was significantly reduced and that animals not showing seizures had significantly lower rates of interictal spikes with fast ripples, but not of interictal spikes with ripples, in the CA3 region of the hippocampus compared to untreated ("control") epileptic subjects. Altogether, these findings suggest that neurosteroids have anti-epileptic properties (Reddy and Rogawski, 2012; Shiri et al., 2015a). However, no study has addressed so far whether AEDs or neurosteroids are capable of regulating the occurrence of HFOs during HYP and LVF seizures.

7. Concluding remarks

We have reviewed here the cellular and pharmacological mechanisms that underlie pathological neuronal network oscillations - which include interictal spikes, HFOs, and seizures - in epileptic rodents. We have also reviewed the occurrence of HFOs during ictogenesis in two animal models of MTLE. Findings obtained to date support the hypothesis that two main patterns of seizure onset are recorded in epileptic animals and in patients presenting with focal epileptic disorders, an specifically MTLE: (i) LVF seizures, which presumably reflect the preponderant involvement of GABAergic interneuron network activity, and (ii) HYP seizures, which appear to be associated to the hyperactivity of glutamatergic principal cells.

It is likely that these findings should contribute to the development of targeted therapeutic strategies in epileptic patients and help in elucidating the mechanisms that lead to seizure generation in MTLE. Further studies are however needed to further understand how neuronal loss after *status epilepticus* affects the relationship between seizure onset patterns and HFOs, since as reviewed above, the strength of the relationship between ripples and LVF seizures and between fast ripples and HYP seizures decreases with disease progression. This experimental evidence suggest that perhaps earlier, more aggressive surgical interventions could lead to better results in clinical practice (Engel et al., 2012; Engel, 2008; Engel, 1999; Sperling, 2004).

Future fundamental work should also investigate the effects exerted by AEDs on HFOs that are recorded during pharmacoresistant seizures; indeed, these studies may help in understanding how and why residual abnormal neuronal network synchronization during ictal activity occurs when proper anti-epileptic medication is given.

Acknowledgments

The original studies published in this review were supported by the Canadian Institutes of Health Research (MOP130328 and MOP8109) and the Savoy Foundation. We are grateful to Drs. Charles Behr, Jean Gotman, Shabnam Hamidi, Rochelle Herrington, Pariya Salami, Zahra Shiri and Ms. Li-Yuan Chen for contributing to the original experiments reviewed and illustrated here.

Conflicts of interest

None of the authors has any conflict of interest to disclose.

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