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Mechanisms of physiological and epileptic HFO generation

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ABSTRACT

High frequency oscillations (HFO) have a variety of characteristics: band-limited or broad-band, transient burst-like phenomenon or steady-state. HFOs may be encountered under physiological or under pathological conditions (pHFO). Here we review the underlying mechanisms of oscillations, at the level of cells and networks, investigated in a variety of experimental *in vitro* and *in vivo* models. Diverse mechanisms are described, from intrinsic membrane oscillations to network processes involving different types of synaptic interactions, gap junctions and ephaptic coupling. HFOs with similar frequency ranges can differ considerably in their physiological mechanisms. The fact that in most cases the combination of intrinsic neuronal membrane oscillations and synaptic circuits are necessary to sustain network oscillations is emphasized. Evidence for pathological HFOs, particularly fast ripples, in experimental models of epilepsy and in human epileptic patients is scrutinized. The underlying mechanisms of fast ripples are examined both in the light of animal observations, *in vivo* and *in vitro*, and in epileptic patients, with emphasis on single cell dynamics. Experimental observations and computational modeling have led to hypotheses for these mechanisms, several of which are considered here, namely the role of out-of-phase firing in neuronal clusters, the importance of strong excitatory AMPA-synaptic currents and recurrent inhibitory connectivity in combination with the fast time scales of IPSPs, ephaptic coupling and the contribution of interneuronal coupling through gap junctions. The statistical behaviour of fast ripple events can provide useful information on the underlying mechanism and can help to further improve classification of the diverse forms of HFOs.

Contents

Abbreviations: α, alpha (rhythm or oscillation); AMPA, 2-amino-3-(5-methyl-3-oxo-1,2- oxazol-4-yl)propanoic acid, a subtype of ionotropic glutamate receptors; AP, action potential; β, beta (oscillation); CA, cellular automata; ECoG, electrocorticogram; EEG, electroencephalogram; GABA, gamma amino butyric acid; $GABA_A$, ionotropic gamma amino butyric acid receptor; γ, gamma (oscillation); HFO, High Frequency Oscillation; Hz, Hertz (cycles per second); I_h, the h-current, a depolarizing, cationic current activated by hyperpolarization; IPSC, inhibitory postsynaptic current; IPSP, inhibitory postsynaptic potential; KA, kainic acid; LFP, local field potential; MEG, magnetoencephalogram; mGluR, metabotropic glutamate receptor; μ, mu (oscillation); NMDA, *N*-methyl *D*-aspartate, a subtype of ionotropic glutamate receptor; pHFO, pathological high frequency oscillation; SPWR, sharp-wave ripples; TLE, temporal lobe epilepsy.

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1. Introduction

High frequency oscillations (HFOs) constitute a novel trend in neurophysiology that is fascinating neuroscientists in general, and epileptologists in particular. But what are HFOs? What is the frequency range of HFOs? Are there different types of HFOs, physiological and pathological? How are HFOs generated? Can HFOs represent temporal codes for cognitive processes? These questions are pressing, to which this review paper attempts to give constructive answers. In these introductory remarks we will consider the most basic question: what are HFOs and how should these be designated? To deal with this question it is useful to consider briefly how neurophysiologists have characterized neuronal oscillations in general, as reflected in local field potentials and therefore in EEG and MEG signals.

Since the early days of human neurophysiology scientists have been fascinated by the variety of oscillations that may be recorded from the scalp and directly from within the brain. Empirically a classification of these oscillations in a series of frequency bands emerged, which were designated by Greek letters ($\delta, \theta, \alpha/\mu, \beta, \gamma$) a classification that was supported by multivariate statistical analysis of EEG spectral values in the seventies (Lopes da Silva, 2011). Nonetheless the limits of the EEG frequency bands are fuzzy. Ultra-slow (near-DC) oscillations (Aladjalova, 1957; Vanhatalo et al., 2004) and ultra-fast frequency components have also been described. Here we concentrate primarily on the fast frequency components.

In the early descriptions of EEG the issue of frequency components higher than about 30 Hz was an unchartered continent. Two main factors changed this picture in the last three decades: (i) the rise of broad-band digital EEG, which made possible recording of signals beyond the traditional low-pass filtered EEG at 70 Hz, extended the recordings to frequencies as high as 500 Hz and beyond; (ii) novel findings in animal neurophysiology showing the existence of oscillations at frequencies in the γ band range of 38–100 Hz in several cortical and subcortical brain areas (for early literature on this subject see Bressler and Freeman (1980)). Currently, while there is some disagreement on whether the term HFO includes the γ frequency range, perhaps the most general usage is γ for frequency components between 30 and 100 Hz, and HFOs for frequencies beyond 100 Hz. However, we will review some aspects of γ oscillations, partly because they shed some light on HFO mechanisms, and partly because there can be overlap between γ and "ripples", a transient hippocampal HFO in the 100 Hz to 200–250 Hz band. Functionally γ and ripples can coexist under physiological conditions and share mechanisms (Sullivan et al., 2011), or can be linked under the term fast γ (90–150 Hz, with slow γ at 30–50 Hz and mid γ 50–90 Hz) (Belluscio et al., 2012), while other authors call oscillations from ~60 to 200–250 Hz "high γ" (Crone et al., 2006; Edwards et al., 2005).

Among physiological HFOs a number of specific phenomena attracted particular attention: γ oscillations around 40 Hz in the visual cortex associated with visual perception (reviewed in Singer and Gray (1995)), and in the sensorimotor cortex related to motor activity (Murthy and Fetz, 1996). The former were proposed to form the mechanism by which various features of a visual scene may be bound together into a percept—the "binding hypothesis". Beyond this observation, it was also shown that γ oscillations may operate as a general mechanism that is capable of binding together, by a process of phase synchronization, not only the firing of neurons at the local level, but also neural activities of spatially separate cortical areas (Roelfsema et al., 1997). Furthermore, the discovery of hippocampal ripples during behavioral immobility, consummatory behaviors and slow-wave sleep (Buzsáki et al., 1992), kindled the interest for understanding the functional significance of HFOs in the process of memory consolidation. The subsequent finding that similar short transient oscillations, named "fast ripples", can be observed in the local field potential recorded from the hippocampus and the temporal cortex of epileptic humans and rodents (Bragin et al., 1999b) stimulated the interest for these oscillatory phenomena as possible biomarkers of epileptogenic neural networks. These high frequency components recorded in local field potentials (LFPs), electrocorticograms (ECoG) and EEG/MEG signals received, collectively, the designation of HFOs.

We should note, however, that these terms are purely descriptive and do not have a precise definition. The term HFO can mean phenomena with a variety of characteristics: HFOs may be band-limited or broad-band, transient (burst-like) phenomenon or steady-state, event-related or not. Furthermore, HFOs may be encountered under physiological or under pathological conditions; for the latter the symbol pHFO has been used. This, however, is a secondary characterization that depends on the demonstration that this kind of HFO is significantly associated with a pathological brain condition such as epileptogenicity. One proposal distinguishes these pHFOs from physiological kinds of HFOs according to frequency content ("fast ripples" *vs* "ripples") (Bragin et al., 1999b), and is currently a matter of intense experimental scrutiny.

In order to promote clarity regarding the phenomenon under consideration it may be useful to take into consideration the following items in characterizing HFOs: (i) frequency range of the HFOs indicated between brackets, similarly to what is used in protein biochemistry to indicate a sequence of constitutive amino-acids: for example, HFO (80–150 Hz); (ii) whether the HFOs are phase-locked to a stimulus or event-related but not phase-locked to the precise timing of the event; (iii) whether HFOs are a transient (burst-like) or continuous (steady-state) phenomenon; (iv) location within the brain.

A better understanding of the significance of HFOs depends on a deeper analysis of the mechanisms of generation of different kinds of HFOs that typically are at the crossroads between intrinsic membrane properties and synaptic interactions. The complexity of these processes makes the development of relevant computational models most compelling.

In this overview we primarily consider cortical (including hippocampal) oscillations under normal and epileptic conditions, but we should note that subcortical HFOs exist, for instance in the basal ganglia where they are faster (~300 Hz) in Parkinson's Disease patients than in patients with other conditions (~200 Hz) (Danish et al., 2007; Foffani et al., 2003). We will first address general mechanisms of oscillations, at the level of cells and networks, and an account of experimental *in vitro* and *in vivo* models being used to investigate HFOs; this is followed by a section where the focus lies on the role of HFOs in experimental and clinical epilepsy and the underlying mechanisms; in the final part the contribution of computational modeling is reviewed.

2. Cells and networks for oscillations

The fundamental idea that brain activity is associated with oscillations has a long history, back to the α and β oscillations of Berger (1929) and perhaps the earliest account of HFOs by Adrian (1935). A key question is whether oscillations depend on the intrinsic properties of individual neurons or on the collective properties of networks of neurons.

2.1. Cellular oscillators

Individual neurons clearly can sustain oscillations and action potential bursts at a range of frequencies. Pacemaker neurons have long been known (Jahnsen and Llinas, 1984; Kandel and Spencer, 1961; Leresche et al., 1991; Llinas, 1988), and such properties are important in generating epileptic activity (Traub et al., 1993). Perhaps the most dramatic demonstrations that single neurons can generate oscillations come from freshly dissociated neurons *in vitro* where synaptic networks are absent (Swensen and Bean, 2003), although structural disruption during dissociation, particularly loss of dendrites, does impact on intrinsic properties (Destexhe et al., 1996). In general these oscillations depend on a voltage-gated inward current, of Na^+ and Ca^{2+} ions, and outward currents of one or more of the many kinds of K^+ channels. Perhaps the most straightforward conceptually is an oscillation where Ca^{2+} influx activates a Ca^{2+}-dependent K^+ conductance that mediates a relatively slow afterhyperpolarization (Hotson and Prince, 1980; Jahnsen and Llinas, 1984; Kandel and Spencer, 1961; Leresche et al., 1991; Llinas, 1988; Traub et al., 1993; Wong and Prince, 1978). Dendritic P/Q type calcium channels can generate intrinsic oscillations *in vitro* of relatively high frequencies (20–80 Hz) (Pedroarena and Llinas, 1997). However, neuronal mechanisms of oscillations and resonances are diverse and complex (Hutcheon and Yarom, 2000). All biological membranes act as low-pass filters because of their capacitive properties, but neurons have a plethora of voltage-gated channels that can add a high-pass filtering property producing a tuned frequency response resembling a band-pass or notch filter. Examples of such currents include delayed-rectifier type K^+ currents and the inwardly rectifying current I_h (Hutcheon and Yarom, 2000). Resonance is amplified, and can produce an oscillation when a depolarizing current is also present, such as the persistent Na^+ current, Ca^{2+} currents or NMDA receptors at glutamatergic synapses (Hutcheon and Yarom, 2000; Traub et al., 1993). The particular ion channels involved in oscillations vary greatly between neurons, perhaps not surprisingly given that particular classes of neurons may have homeostatic capabilities that maintain their overall electrophysiological characteristics using a range of combinations of specific ion currents (Marder and Goaillard, 2006; Marder and Taylor, 2011; Swensen and Bean, 2005).

2.2. Network oscillators

Single neurons can sustain oscillations but cannot generate EEG oscillations on their own. At the very least the oscillating neurons have to be linked functionally, through chemical synapses and/or gap junctions (electrical synapses), electric field (ephaptic) coupling or in the case of the slowest oscillations, fluctuations in the extracellular concentrations of ions such as K^+ (Jefferys, 1995). It may be that the oscillatory properties of individual neurons are not necessary for collective network oscillations. One example is the γ-band activity produced in hippocampal slices depolarized by metabotropic glutamate receptors, where networks of inhibitory neurons synchronize their IPSPs to carve out a coherent γ oscillation from the rapid trains of action potentials that would be produced in fast spiking interneurons in the absence of synaptic connections (Whittington et al., 1995). The frequency of these oscillations proved to be modulated by experimental manipulations of the size and duration of the IPSPs as predicted by computer simulations (Whittington et al., 1995). Inhibitory neurons also play a key role in pacing faster physiological activity, in the ripple band 80–250 Hz, as shown by unit recordings *in vivo* (Ylinen et al., 1995): as mentioned above the distinction between γ and ripples is less clear that it once seemed (Belluscio et al., 2012; Crone et al., 2006; Edwards et al., 2005; Sullivan et al., 2011). However, prolonged high-frequency oscillations based exclusively on synaptic mechanisms are unlikely because neurotransmitter depletion will lead to a strong synaptic depression and thus to termination of these oscillations (Zucker and Regehr, 2002).

Subsequent investigations suggested that gap junction coupling between interneurons (Galarreta and Hestrin, 2001) helps "sharpen" the tuning of γ oscillations, presumably by helping synchronize interneuronal action potentials as the IPSPs wane (Beierlein et al., 2000; Fukuda and Kosaka, 2000; Tamas et al., 2000; Traub et al., 2001a). Fast spiking interneurons do not seem to sustain subthreshold resonance, so intrinsic properties are unlikely to contribute to these kinds of coherent γ oscillation, which argues for a synaptic mechanism (Zemankovics et al., 2010). This study, however, also revealed an I_h-dependent subthreshold resonance in other kinds of interneuron and in pyramidal cells at θ or slower frequencies (Zemankovics et al., 2010).

2.3. Combined cellular and network oscillators

In many cases both intrinsic and synaptic properties will be necessary to sustain network oscillations. One of the earliest examples is the role of inhibition in controlling the phasing of spontaneous thalamocortical spindles at around 10 Hz, which depended on "post-anodal exaltation" or rebound excitation (Andersen et al., 1964; Andersen and Sears, 1964), which more recently has been attributed to low threshold Ca^{2+} currents (Deschenes et al., 1982; Dreyfus et al., 2010; Huguenard and McCormick, 2007; Jahnsen and Llinás, 1984; Steriade et al., 1993).

Similar interactions between neuronal oscillators or resonators and synaptic networks can be found in a variety of conditions, including acute epileptic activity in hippocampal slices (Traub et al., 1993) and in neocortex *in vivo* (Timofeev et al., 2002a).

3. Experimental models *in vitro* and *in vivo*

3.1. Preparations and physiological oscillations

Experimental models are essential to investigating basic neuronal mechanisms in the brain, certainly at the cellular and local network levels, which are our primary concerns here. Models need to be accessible to the measurements and experimental interventions needed to unravel those mechanisms, here mainly microelectrode and other invasive recordings, while embodying key aspects of the phenomena to be studied. *In vitro* methods, particularly brain slices, have played a crucial role in discovering physiological properties of components of neuronal function, including ion channels, synaptic transmission and intracellular signalling. They have important advantages of stability, visualization of anatomy including of individual neurons, and easy chemical and other manipulation. Brain slices usually are relatively inactive, a point that was recognized from the earliest studies by biochemists (Field, 1948; Warburg, 1930) and physiologists (Gibson and McIlwain, 1965). The lack of the rest of the brain and of blood supply obviously has a major impact, and indeed reduced activity can be an advantage for reductionist studies of the properties of single neurons and synaptic connections. However, the low levels of activity mean that population activities including coherent oscillations usually (but not always, Pietersen et al., 2009) need sustained chemical or other stimulation, such as mGluR agonists, kainic acid or carbachol (Bartos et al., 2007; Fisahn et al., 1998; Whittington et al., 1995). Such models, combined with computational models *in silico* (see Section 6 below), have told us much on how neuronal networks can sustain coherent oscillations, and especially on the important roles of inhibitory interneurons in γ oscillations (Bartos et al., 2007). However, considerable caution should be exercized in relating these *in vitro* models to oscillations *in vivo* and to behavioural functions (Lu et al., 2011). To reiterate a key point made in the Introduction, the fact that oscillations have similar frequencies does not guarantee that they are the same phenomenon.

In vivo investigations of physiological oscillations in anaesthetized and unanaesthetized experimental animals are perhaps the most realistic models for these oscillations in humans. The perfect "model" is the real phenomenon of the brain activity during identified behaviours, but recording methods are constrained; for instance, intracellular recordings may be difficult in behaving animals. In rodents the use of techniques such as tetrode recordings has provided considerable insights, particularly on the roles of inhibitory neurons (Buzsáki et al., 1992; Csicsvari et al., 1999; Ylinen et al., 1995). In the case of humans, recordings are either limited to scalp EEGs under conditions that promote γ and faster oscillations (Rodriguez et al., 1999), or the relatively small number of cases where intracranial recording is required for clinical reasons (Maris et al., 2011).

Experiments on cats and monkeys have extended detailed investigation of HFOs to more highly developed mammals (Grenier et al., 2001; Skaggs et al., 2007). Recordings from cats demonstrated that HFOs with ripple frequency occur during active network states and when the membrane potential of cortical neurons is depolarized. However, the level of the membrane potential is not the sole factor; in normal behavioural conditions the maximal power of cortical ripples occurs during active "UP" phases of slow-wave sleep, smaller during passive wakefulness and REM sleep and lowest (virtually absent) during silent "DOWN" phases of slow wave sleep (Grenier et al., 2001). In hippocampus of both rats and monkeys, ripples are typically recorded during inactive, drowsy or sleeping behavioral states, all of which are associated with increased hippocampal pyramidal cell activity (Skaggs et al., 2007; Ylinen et al., 1995).

3.2. Epilepsy models

HFOs are prominent features of epilepsy in human and in other animals. Thus it is important to consider experimental models of epilepsy where such phenomena were found and are being actively studied as further described particularly in Sections 4 and 5. Basic research on epilepsy relies heavily on animal models because of the complex and varied histories of clinical cases and ethical and practical constraints on many of the measurements required for research. Many models exist and have been described in some detail in recent years (Pitkänen et al., 2005; Schwartzkroin, 2009; Soltesz and Staley, 2008). Here we will briefly review some of the key points with a particular focus on those mentioned elsewhere in this paper.

3.2.1. Acute models of epilepsy

Convulsant drugs and changes in extracellular ion concentrations readily produce recognizably epileptic activity in normal brain tissues, both *in vivo* and *in vitro*. These models usually relate to symptomatic seizures in clinical practice. The acute models mentioned elsewhere in this review use slices of hippocampus and other forebrain structures maintained *in vitro* (Jefferys, 2007) or *in vivo* (Prince, 1972; Qian et al., 2011; Stafstrom et al., 2009; Tabashidze and Mares, 2011). Many of them rely on blocking $GABA_A$ receptor mediated inhibition with drugs such as picrotoxin, bicuculline or penicillin (Dingledine and Gjerstad, 1979; Schwartzkroin and Prince, 1978). Convulsant treatments which do not block inhibition include 4-aminopyridine (Avoli et al., 1996; D'Antuono et al., 2002; Rutecki et al., 1987), elevated K^+ (Jiruska et al., 2010a; Rutecki et al., 1985; Traub and Dingledine, 1990) and low Mg^{2+} (Anderson et al., 1986; Derchansky et al., 2008). Another acute and realistic model *in vivo* is brain trauma, which leads to electrographic seizures in the majority of animals (Topolnik et al., 2003). In cats, even simple prolonged maintenance under ketamine-xylazine anaesthesia leads to seizure activity in 30% of animals (Boucetta et al., 2008). These models led to the recognition that both intrinsic properties such as voltage-gated Ca^{2+} currents (Schwartzkroin and Slawsky, 1977), pathologically large EPSPs (Johnston and Brown, 1981), recurrent excitatory networks (Traub et al., 1993, 1995; Traub and Wong, 1982), and depolarizing IPSPs and other currents (Timofeev, 2010) contribute to epileptic activity.

The role of IPSPs in promoting epileptic activity is surprising for a potential called inhibitory (Timofeev, 2010). Hyperpolarizing IPSPs can contribute to rhythmic synchronization by driving a kind of rebound excitation, for instance due to the low-threshold Ca^{2+} current (Andersen and Sears, 1964; Dreyfus et al., 2010; Huguenard and McCormick, 2007). However, the postsynaptic effect of GABA binding to the $GABA_A$ receptor depends on the Cl^- and HCO_3^- gradients across the membrane. Acutely the Cl^- gradient can run down with excessive use(Alger and Nicoll, 1979; Bracci et al., 1999; Fujiwara-Tsukamoto et al., 2003; Id Bihi et al., 2005; Kaila et al., 1997; Köhling et al., 2000; Perreault and Avoli, 1992; Staley et al., 1995) usually with superimposed ephaptically synchronized pyramidal cell discharges. GABA also can produce depolarizing potentials without repetitive activation, particularly in epileptic tissue (Huberfeld et al., 2007; Köhling et al., 1998).

Reducing extracellular Ca^{2+} close to zero results in a seizure-like activity lasting tens of seconds despite the absence of chemical synaptic transmission (Jefferys and Haas, 1982; Jiruska et al., 2010a). In this situation the prolonged bursts are primarily

synchronized on a slow time scale by transient increases in extracellular K^+ (Bikson et al., 2003b; Yaari et al., 1983) and on a faster time scale by ephaptic or field effect interactions (Frohlich and McCormick, 2010; Jefferys, 1995). The latter occur when the electrical currents generated by neuronal activity cause a transmembrane depolarization sufficient to nudge neighbouring neurons to threshold; this effect is relatively weak (Jefferys, 1981), but under conditions of heightened excitability, such as in low-Ca^{2+}media or during epileptic discharges, neurons are close enough to threshold for this effect to impact on spike timing.

3.2.2. Chronic models of epilepsy

Chronic models better represent the real clinical condition of epilepsy. Most of the models considered in this review are of temporal lobe epilepsy (TLE) and depend on some induction procedure. Perhaps the most commonly used chronic models of TLE rely on a period of *status epilepticus* lasting over 40 min (typically 1–2 h) with may be induced, in rat or in some cases in mouse, by one of kainic acid (KA, intrahippocampal or intraperitoneal) (Ben-Ari et al., 1980; Cavalheiro et al., 1982; Dudek et al., 2006), pilocarpine (intraperitoneal) (Cavalheiro et al., 2006; Curia et al., 2008) or electrical stimulation (intracerebral) (Gorter et al., 2001; Walker et al., 1999). In each of these models the induced *status epilepticus* is followed by a latent period of days to a couple of weeks before spontaneous seizures start, and then recur for the rest of the lifetime of the animal (Bortel et al., 2010; Lévesque et al., 2011; Williams et al., 2009). The latent period is not silent, as originally thought, but rather is characterized by progressive electrographic abnormalities that culminate in seizures (Bortel et al., 2010; Bragin et al., 1999b; White et al., 2010). The prolonged hyperactivity of *status epilepticus* causes substantial neuronal loss, which can be seen as a form of epileptogenic lesion.

Intrahippocampal tetanus toxin produces a non-lesional model of TLE (Jefferys and Walker, 2006). As with the *status* models injection is followed by a latent period of a week or two before seizures start, after which they recur spontaneously for several weeks (Hawkins and Mellanby, 1987). Over 70% of rats gain seizure remission after 6–8 weeks, but a minority do not, and they all retain permanent behavioural and physiological abnormalities (Brace et al., 1985; Vreugdenhil et al., 2002). The other popular model of chronic epileptogenesis is the cortical undercut. In this model, undercutting cortical white matter results in partial cortical deafferentation that leads to acute seizures lasting 3–8 h (Topolnik et al., 2003). Thereafter spontaneous electrographic paroxysmal activity reappears several days after the undercut, progressively expands into larger cortical territories and after 1.5–4 months leads to spontaneous behavioural seizures (Nita et al., 2007; Timofeev et al., 2010).

4. Evidence for HFOs in experimental and clinical epilepsy

Pathological HFOs were first described in the intrahippocampal KA model of chronic epilepsy (Bragin et al., 1999b). These oscillations, in the frequency band 250–500 Hz, were observed in the dentate gyrus and they were considered as pathological because in the dentate gyrus of normal rats the maximum frequency of recorded electrical activity was up to 100 Hz (Bragin et al., 1995, 2004; Buzsáki, 1986). These fast ripples or pHFOs provided a marker for epileptogenesis because they were seen selectively in the injected hippocampi of those rats that would go on to develop chronic epilepsy. Long-term recordings in the pilocarpine model have also shown a tight link between regions that generate spontaneous seizures and fast ripple activity (Lévesque et al., 2011). Increased fast ripple rates in the seizure onset zone were more specifically indicative of periods of high susceptibility to seizure occurrence, suggesting a role of HFOs in epileptogenesis. However, contrary to what was reported by (Bragin et al., 2004) with the intrahippocampal injection of kainic acid, fast ripples were not observed in all pilocarpine treated animals, even though they all showed spontaneous seizures; of course it is not possible to exclude the possibility that fast ripples occurred in tissue away from the recording sites. The presence of fast ripple pHFOs in models induced by *status epilepticus* led to the suggestion that they were associated with neuronal loss (Bragin et al., 1999c), but such pHFOs are found reliably in chronic foci without neuronal loss, and not induced by status epilepticus, in the intrahippocampal tetanus toxin model (Jiruska et al., 2010b) where they occur preferentially in regions that generate spontaneous seizures. The pHFOs in these different models fell within the same frequency bands, shared broadly similar appearance, and importantly all showed close associations with epileptic tissue, whether lesional or non-lesional, but as stated above this does not necessarily mean they share identical mechanisms—that is for future research to determine.

A major motivation for much of the work on the relationship between pHFOs and epileptic tissue is to contribute to the identification of the epileptogenic zone (Rosenow and Luders, 2001) to guide epilepsy surgery (Jiruska et al., 2008; Zijlmans et al., 2012). In this context it does not matter if pHFOs are an epiphenomenon, for instance a biomarker for enhanced excitability of a population of neurons. However, the possibility remains that pHFOs have a causal role in, for instance, ictogenesis, which would have conceptual importance and could have an impact in developing improved treatments. The progressive expansion of the spatial extent of HFO clusters before low-Ca^{2+} seizure like events (Jiruska et al., 2010a) suggests that a causal role is conceivable.

Analysis of voltage depth profiles of pathological HFOs in the kainic acid model showed that the maximum of their amplitude (Bragin et al., 2007) and the location of their sinks-sources (Ibarz et al., 2010) were in the cellular layers of the dentate gyrus or of CA1 area of hippocampus. Discharges of identified granular (Bragin et al., 2011) and pyramidal (Foffani et al., 2007) cells are phase locked with troughs of locally recorded pathological HFOs. The shape and voltage depth profiles of pathological HFOs recorded in the dentate gyrus were similar to the shape and voltage depth profiles of population spikes evoked by perforant path stimulation (Bragin et al., 2007). On the basis of these and other data it was hypothesized that pathological HFOs reflect spontaneous bursts of population spikes as a result of synchronous discharges of principal cells each of which fires at a lower frequency than the ensemble (Bikson et al., 2003a; Bragin et al., 2002a, 2007; Foffani et al., 2007; Ibarz et al., 2010; Jiruska et al., 2010a). Areas generating pathological HFOs are not homogeneously distributed within brain areas and, on the basis of animal studies, a hypothesis was suggested that pathological HFOs are generated by pathologically interconnected neuron clusters or PIN clusters (Bragin et al., 2000, 2002a).

Similar pathological HFOs were observed also in epileptic patients. Initially they were described in hippocampus and entorhinal cortex of patients with TLE (Bragin et al., 1999a, 2002b; Staba et al., 2002, 2004) using microelectrode recordings. Later they were observed using clinical depth and grid electrodes in patients with temporal lobe epilepsy as well in patients with different types of neocortical epilepsy (Bagshaw et al., 2009; Jacobs et al., 2008; Jirsch et al., 2006; Worrell et al., 2004, 2008). Whether mechanisms of pathological HFOs observed in the hippocampus of epileptic animals and those observed in the neocortex of epileptic patients are the same or different remains unclear. Local field potential recordings from cat neocortex suggest, however, that the frequency of normal and pathological ripples is similar (between 80 and 200 Hz), but that the power of ripples dramatically increases at the onset and during seizures (Grenier et al., 2003b).

HFOs also can be reproduced in brain slices *in vitro*. Very small HFOs can be recorded in the normal CA1 region in the absence of convulsant treatments, and have been attributed to non-synaptic mechanisms, possibly involving synchronization through gap junctions (Draguhn et al., 1998). The interictal discharges produced in normal brain slices by convulsant treatments (see Section 3.2.1 above) often have HFOs superimposed, typically in the ripple band (Foffani et al., 2007). Whether HFOs induced acutely in brain tissue model epilepsy-related pHFO or physiological sharp wave ripples is an open question (Taxidis et al., 2011; Ylinen et al., 1995). Evidence from the dentate gyrus exposed to the convulsant drug picrotoxin (D'Antuono et al., 2005), argues against a role for inhibitory synapses which contrasts with the evidence for physiological ripples in the same area *in vivo* (Ylinen et al., 1995) and reinforces the point that oscillations in the same frequency band are not necessarily the same phenomenon. In some studies loss of inhibition resulted in a transformation of sharp wave ripples, with HFO in the ripple band, to epileptiform discharges, with superimposed fast ripples, suggesting a role of inhibition in ripples and not fast ripples (Behrens et al., 2007). Evidence on roles for gap junctions in HFOs is both negative (D'Antuono et al., 2005) and positive (Nimmrich et al., 2005). A study of CA3 in elevated extracellular K^+ argues for a role for intrinsic burst firing characteristic of CA3 pyramidal cells (Dzhala and Staley, 2004). Seizure-like events, or "field bursts", in the low-Ca^{2+} model start with HFOs extending into the fast ripple band, which represent the collective activity of multiple clusters of neurons firing at lower frequencies (Bikson et al., 2003a; Jiruska et al., 2010a) (see Section 5.3 below). A common theme from all these studies *in vitro* is that HFOs arise when neuronal networks are hyperexcitable, but they can do so through several distinct mechanisms.

5. Mechanisms of epileptic HFOs

5.1. Cellular sources of local EEG activity

In order to understand the mechanisms underlying the generation of pathological HFOs one has to deal with a challenge task to dissect and interpret the signals contributing to the local field potentials. While in the normal brain the slower synaptic currents are the major components of the local EEG (Nunez and Srinivasan, 2006), several lines of evidence suggest basic differences between normal and epileptic brain, *e.g.* (Bragin et al., 1999b; Grenier et al., 2003b, 2001) and reviewed in (Menendez de la Prida and Trevelyan, 2011). First, a requirement for firing precision of the order of milliseconds for synchronous action potentials to become visible at the local EEG is rarely met for the activity in the normal brain but becomes critical in the epileptic tissue due to its enhanced excitability. Hence, clinical data on evoked potentials from epileptic patients is thought to represent a mixture of postsynaptic currents and population spikes (Rutecki et al., 1989; Valentin et al., 2002; Wilson et al., 1990). These population spikes represent precise synchronous action potentials of pools of parallel-oriented principal neurons (Andersen et al., 1971; Kloosterman et al., 2001). Second, the depolarizing shifts of $GABA_A$ receptor reversal potentials that can occur in the human epileptic hippocampal formation (Cohen et al., 2002; Huberfeld et al., 2007) might impact on the visibility and the signs of voltage deflections recorded extracellularly in a way we still do not fully understand (Menendez de la Prida and Trevelyan, 2011). This may affect inhibitory synaptic currents during HFO in the 40–100 Hz range, making them either invisible, due to a zero net current flow for those neurons operating at the equilibrium potential of the chloride currents, or extracellularly reversed due to a depolarizing action of chloride ions (Payne et al., 2003). Other pro-epileptic changes including interneuronal cell loss and disinhibition of large populations of pyramidal cells (Esclapez and Houser, 1999; Kobayashi and Buckmaster, 2003; Nadler et al., 1980; Shao and Dudek, 2005) also have an indirect impact in the nature of the extracellular signals by promoting hyperexcitability and favouring the generation of pathological large excitatory potentials (Ayala et al., 1973). Finally, local circuit reorganization and glutamatergic cell loss affecting the normal pattern of input lamination have an impact in the shape of many extracellular events, which can even change polarity (Bragin et al., 2007; Fabo et al., 2008; Lopes da Silva et al., 1982; Wadman et al., 1983).

These considerations indicate that the field potential generators change dramatically under epileptic conditions in a very spatially inhomogeneous way. They also suggest that the cellular sources of HFO vary substantially in a wide band of frequencies, and even more, that different types of HFO might coexist and dynamically evolve over the course of epileptogenesis and ictogenesis. In this section we will review the most relevant experimental findings regarding the cellular basis of pathological HFO, covering a range from 100 Hz to very fast oscillations beyond 400 Hz.

5.2. Single cell dynamics during a wide range of HFO in epileptogenic regions

Activity of single-cells in epileptogenic regions was first recorded in the 1950s and 1960s using the chronic foci preparation in cats and monkeys (Calvin et al., 1968; Schmidt et al., 1959; Sypert and Ward, 1967). These early data clearly proved the existence of cells able to fire bursts of action potentials at high-frequencies (200–250 Hz). Other units recorded from the same electrode tracks exhibited a more normal pattern consisting of isolated single spikes or bursts at frequencies lower than 200 Hz (Colder et al., 1996; Wyler et al., 1975). Neocortical fast-spiking, presumed inhibitory, interneurons can discharge with frequency of up to 800 Hz (Timofeev et al., 2002b). During drowsy periods, both normal and abnormally bursting neurons were seen to fire together suggesting that they can be jointly activated by some common inputs (Wyler, 1974; Wyler et al., 1975; Wyler and Fetz, 1974).

In their earlier description of fast ripples (250–500 Hz), Bragin et al. (1999b, 2000) suggested that these HFO were generated by clusters of pathologically interconnected neurons producing powerful hypersynchronous bursts. Under this framework, abnormally bursting neurons able to fire at 200–300 Hz can become active together and create cycles of population spikes that are recorded in the field potential in the form of a short-lasting HFO of similar frequencies (Bragin et al., 1999b; Grenier et al., 2003a).

Using the *in vitro* high-K^+ model of population discharges, Dzhala and Staley (2004) carefully examined the relationship between burst firing precision at the single-cell level and the emergence of such pathological forms of HFO in the local field potentials of hippocampal slices from normal rats (Dzhala and Staley, 2004); see also (Spampanato and Mody, 2007). They found that the more precise the spiking activity between bursting cells the larger the amplitude of fast ripple oscillations, with their spectral peak reflecting the inter-spike frequency of individual neurons at 200–300 Hz. However, fast-ripples recorded *in situ* in the epileptic brain typically exhibit spectral components in a broad band from 250 to 800 Hz, well above the maximal firing frequency of most glutamatergic neurons. Also *in vitro*, hippocampal slices prepared from pilocarpine-treated epileptic rats are shown to generate spontaneous HFO >300 Hz with a more disorganized spectrum, but at roughly twice the frequency of the peak in the 200–300 Hz band (Foffani et al., 2007). Intriguingly, single pyramidal cells from these slices were found to fire similarly but less precisely than cells recorded from slices prepared from a normal animal, suggesting that less precise bursting correlate in

this case with faster and more disorganized HFO power spectra (Foffani et al., 2007). It was later shown that populations of bursting cells firing individually at 100–400 Hz can create fast ripples according to two main firing regimes: (1) in-phase synchronous firing resulting in fast ripples characterized by single spectral peaks that reflect single-cell behavior and (2) out-of-phase firing that results in emergent fast ripples at a broader frequency band (Ibarz et al., 2010) (see also Bikson et al., 2003a; Jiruska et al., 2010a). In this scenario, each fast ripple cycle reflects a population spike created by firing from individual neurons but not all neurons contribute to consecutive cycles similarly, hence the emergent character. Such conditions are met very locally so that fast ripples are shown to be confined to small areas of about 1 mm^3 (Bragin et al., 2002a; Crepon et al., 2010; Draguhn et al., 1998; Jiruska et al., 2010a). Thus, HFOs in the form of fast ripples (250–800 Hz) can be brought about locally by both precise and loose firing, which successfully explains the large range of frequencies recorded *in situ* in epileptic rodents and humans. Some authors have related the role of some forms of electric coupling with the synchronizing mechanisms required for very fast HFOs to emerge. Both gap junctions (Draguhn et al., 1998; Grenier et al., 2003b; Traub and Bibbig, 2000) and ephaptic interactions (Jefferys, 1995) may enhance synchronization and amplify high-frequency oscillations. Consequently, the cellular sources of these very fast HFO rely in the collective firing of bursting and non-bursting cells.

Earlier intracellular recordings from epileptogenic areas support the presence of structured and unstructured high-frequency bursting patterns (Atkinson and Ward, 1964; Prince and Futamachi, 1970), but they also suggest that pathological bursting can contribute to a slower range of pathological HFOs, in particular during seizures. While the entire paroxysmal bursts are shown to correlate with the spike component of the EEG recording (Ayala et al., 1973; Johnston and Brown, 1981), the hyperpolarization following the intracellular discharge is associated with the wave component, and a progressive depolarization leads to fast runs of EEG activity in the range of 10–15 Hz (Steriade et al., 1998). Participation of single cells is quite variable during these events, but a population of intrinsic bursting and fast-rhythmic bursting neurons fire more consistently than other neurons during fast runs (Boucetta et al., 2008). Thus, while the condition of millisecond synchronization required for fast ripples (250–800 Hz) to emerge is difficult to meet consistently in broader epileptogenic areas, coordination of rhythmic bursting in the 10–15 Hz frequency band is a more widespread phenomenon served by long-range excitatory connections (Timofeev et al., 1998).

Voltage-clamp recordings of synaptic currents also revealed high-frequency glutamatergic and GABAergic activity occurring in a broad range of frequencies from 50 to 400 Hz in association with population discharges (Marchionni and Maccaferri, 2009; Nyikos et al., 2003; Trevelyan et al., 2006). A poor correlation between these intracellular signals and the local field potential further suggests that they reflect convergent synaptic barrage that is poorly synchronized between cells, especially for frequencies >60 Hz (Lasztoczi et al., 2004; Trevelyan, 2009). In regions with relatively intact inhibition, chloride currents flowing into the cells through $GABA_A$ receptors could even become synchronous in many neurons due to the high connectivity ratio of some interneurons that contribute to generate field events (Glickfeld et al., 2009; Lasztoczi et al., 2004; Oren et al., 2010).

During the progressive recruitment to a seizure, before GABAergic inhibition weakens and an ever growing excitatory drive starts to dominate the firing dynamics (Dzhala and Staley, 2003; Huberfeld et al., 2011; Jiruska et al., 2010a; Timofeev and Steriade, 2004; Trevelyan et al., 2006), there is a major contribution of synchronous GABAergic potentials to HFO in the beta (20–30 Hz) and the gamma range (40–120 Hz) (Gnatkovsky et al., 2008; Köhling et al., 2000; Trevelyan et al., 2006; Trevelyan, 2009). Later on, this rhythmic GABAergic inhibition progressively decreases driven by the collapse of chloride gradients together with a desynchronization of interneuronal firing (Derchansky et al., 2008; Dzhala et al., 2010; Gnatkovsky et al., 2008; Lasztoczi et al., 2009; Timofeev et al., 2002b; Viitanen et al., 2010). Then, the local EEG is dominated by large changes in extracellular potassium and calcium that contribute to sustained potentials and slow down oscillatory activity (Amzica et al., 2002; Heinemann et al., 1977; Kaila et al., 1997). Thus, the major cellular generators contributing to the broad range of HFO could evolve dynamically as a seizure progresses and cannot be ascribed to a unique source.

Figure 1 summarizes cellular and synaptic mechanisms that have been linked so far with the generation of a wide range of pathological HFO. There is an intimate relationship between the temporal scales of intracellular activities and the frequency range of HFO recorded extracellularly in the local field potentials. The faster the HFO, the faster the intracellular associated events with synchronous burst of action potentials underlying fast ripple activity in a tight frequency range from 200 to up to 400 Hz. Beyond that level, HFO in the field recordings become independent on the firing rate of individual cells and all the field potential oscillations reflect emergent activity of slower discharging neurons. Factors such as osmolarity and acidosis that influence the level of electric coupling amongst cells are shown to boost extracellular HFO. These interactions occur at localized spatial scale (<1 mm^3) so that our ability to detect them is strongly related with the type of probes used for recordings, typically microelectrodes. The slower the HFO the highest the contribution of synaptic potentials, with GABAergic currents playing a major role not only at the gamma (30–100 Hz) but also at the beta range (20–30 Hz). All these actions are spatially constrained to the territories defined by the surviving local circuit interneurons that are activated by principal cells. Therefore they can be detected across multiple cortical regions and with larger electrodes. It is still unclear how changes of the chloride reversal potential do affect the expression of HFO in the gamma range, but they would necessarily modulate

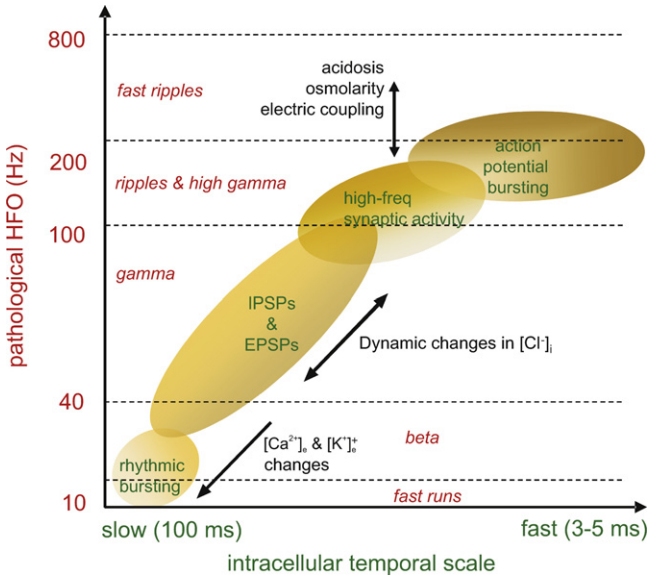

Fig. 1. Cellular mechanisms underlying pathological HFOs.
The *x* and *y* axes respectively represent the intracellular and the extracellular temporal scales of the underlying cellular processes running from slow to fast. The common classes of HFOs appear in red, while the associated cellular processes are illustrated in green. Modulatory factors including: changes in intracellular and extracellular ion concentrations, acidosis, osmolarity and electric coupling are represented in black. The associated arrows indicate the direction of their modulatory effect.

the frequency of the events detected extracellularly depending on a depolarizing or a shunting effect. This becomes critical during seizure progression when a failure of inhibition leads to fast runs of activity (10–15 Hz) generated by cyclic intracellular bursting of projecting pyramidal cells. Such a rhythm spans to larger neuronal territories aided by long-range excitatory projections. Seizure-associated changes in the extracellular Ca^{2+} and K^+ concentration are shown to slow down the intraburst frequency and to ultimately flatten the EEG oscillations.

5.3. Fast ripples and the epileptic hippocampus: the out-of-phase cluster hypothesis

From all the range of frequencies encompassed by HFO activity, fast ripples (250–600 Hz) are probably the most clinically relevant nowadays. The close relationship between hippocampal fast ripples and individual cell bursting is now widely accepted in the field (Bikson et al., 2003a; Engel et al., 2009; Köhling and Staley, 2011). A major reason to focus at their mechanisms is linked with their potential diagnostic value: if fast ripples are biomarkers of abnormal and enhanced forms of neuronal synchronization, then their detection can be used to closely delineate the epileptogenic territories and to eventually identify candidate areas for resection in combinations with other clinical variables (Jacobs et al., 2010; Zijlmans et al., 2012).

Direct evidence that fast ripples reflect some level of synchronous firing came from simultaneous recordings of single cells and field potentials in anesthetized epileptic rats and mice. Juxtacellular recordings revealed bursts of action potentials aligned with individual fast ripple cycles (Ibarz et al., 2010) and with large population spikes (Bragin et al., 2011). However, a poor correlation between the firing frequency of individual cells and the dominant spectral peak in the local EEG confirms that fast ripples emerge as a network phenomenon and that single cells rarely fire faster than 400 Hz. This leads to the out-of-phase cluster hypothesis that suggest that independent pools of cells fire in concert but out-of-phase with each other thus contributing to the higher frequency of fast ripples (Bikson et al., 2003a; D'Antuono et al., 2005; Foffani et al., 2007; Ibarz et al., 2010; Jiruska et al., 2010a).

The mechanisms for the phase differences can be directly related with the way in which population spikes are created in the extracellular field from the complex spatiotemporal interactions of several current dipoles (Andersen et al., 1971; Nicholson and Llinas, 1971). In the hippocampus, the individual action potential sinks at the pyramidal layer are followed by a current source and a delayed dendritic propagated sink (Deans et al., 2007; Jefferys, 1979; Kloosterman et al., 2001; Varona et al., 2000). Therefore, when a pool of neighbouring cells are jointly activated those cells firing closely will align their individual sinks together but those other cells firing at longer lags will not easily contribute to the same cycle because their current sinks are affected by the interaction with the previous dipole and its delayed dendritic propagation (Varona et al., 2000). Heterogeneity in the bursting pattern caused by the presence of normal and abnormally bursting cells contribute to the generation of the different clusters (Wyler, 1974; Wyler et al., 1975; Wyler and Fetz, 1974). As such, realistic computer simulations show that neurons firing each other with lags shorter than about 2 ms would contribute together to the same population spike, whereas those firing more separately would tend to generate an independent cycle (Ibarz et al., 2010). This generates functional clustering shaped by the preference phase alignment of neighbouring cells (Fig. 2A). Such effect probably explains why non-synaptic mechanisms can be also sufficient for the formation of similar functional clusters presumably coordinated by electric interactions (Bikson et al., 2003a; Draguhn et al., 1998; Jiruska et al., 2010a) (Fig. 2B). This would cause some jitter of the precise action potential timing with respect to the dominant frequency and the spectral components of the local EEG would reflect that fluctuations (Foffani et al., 2007; Ibarz et al., 2010; Netoff and Schiff, 2002).

Another possibility is the existence of network heterogeneities caused by different recurrent connectivity between pools of neurons or by different recruitment delays (Fig. 2C). Recordings and simulations indicate that the enrolment of cells into population discharges proceed after an explosive buildup period that is controlled by the topology of synaptic connections (Menendez de la Prida et al., 2006; Ibarz et al., 2010; Miles et al., 1988; Miles and Wong, 1987). Some cells acting as neuronal hubs might form heterogeneous connectivity maps (Morgan and Soltesz, 2008), which would probably explain the ability of some but not all individual neurons to trigger population discharges (Menendez de la Prida et al., 2006; Miles and Wong, 1983; Wittner and Miles, 2007). In the epileptic circuits, synaptic reorganization in the form of local sprouting and other pro-epileptogenic changes should be also affecting the connectivity pattern (Esclapez et al., 1999; Nadler et al., 1980; Shao and Dudek, 2004). Under this scenario, the different topological clusters are recruited out-of-phase each other at particular lags (Ibarz et al., 2010) (Fig. 2C).

Another potential source of spatial inhomogeneity can be directly linked with the patchy neuronal loss known to affect epileptogenic regions (Fig. 2D). Fast ripples appear to correlate with reduced hippocampal volumes and neuronal loss both in

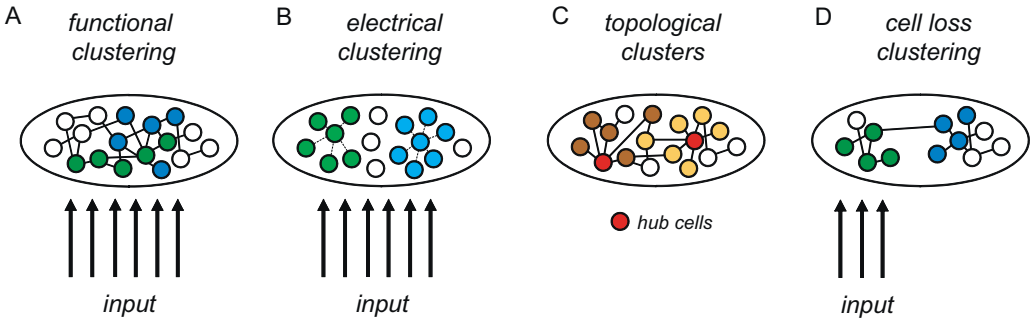

Fig. 2. Clustering of neuronal activity and pathological HFOs.
(A) Functional clustering of pools of active neurons in a network can emerge as a consequence of groups of neurons having similar firing delays in response to afferent input.
(B) Electrical or ephaptic coupling occurs when the firing of a neuron generates an electric field which tends to synchronize a cluster of neighbouring cells which already are close to threshold. This short range mechanism can strengthen clustering arising from synaptic or other mechanisms, but also can occur in the absence of synaptic transmission.
(C) Clusters also result from different connectivity patterns favoring the formation of hub cells each of which activates its particular pools of postsynaptic neurons within a short period. Axonal sprouting and other forms of synaptic reorganization can contribute to the generation of these topological clusters.
(D) Cell loss in epileptogenic regions can result in the generation of pathological clusters that remain densely connected.

human TLE (Ogren et al., 2009; Staba et al., 2007) and in experimental models (Bragin et al., 2002a; Foffani et al., 2007), but can occur in the absence of neuronal death (Jiruska et al., 2010b). Here too, different recruitment delays of several pools of neurons determine a sequential out-of-phase activation resulting in the emergent extracellular fast ripple oscillations.

The out-of-phase hypothesis thus provides a general phenomenological framework to understand the emergence of fast ripple oscillations in epileptogenic regions. Several factors including unreliable firing, synaptic noise, recruitment delays, non-random connectivity and neuronal loss would all play a role in out-of-phase firing clustering. They are not all necessary but sufficient to promote the clustering of activity that underlies fast ripples.

5.4. Spectral variability of fast ripples (250–800 Hz)

One consequence of the independence between the firing of individual neurons and the fast ripples recorded extracellularly is that these HFOs should carry large spectral variability from event to event. Because the interactions between the different cellular clusters should not proceed stereotypically due to the background noise, one should expect that the contribution of individual neurons and hence the appearance of fast ripple cycles varies substantially in a given region. Microelectrode recordings in humans have shown the coexistence of fast ripples with HFO in the physiological ripple band (Bragin et al., 1999b; Staba et al., 2002; Worrell et al., 2008), and the events themselves show spectral fluctuations being difficult to classify based only on frequency criteria (Blanco et al., 2010; Engel et al., 2009; Ibarz et al., 2010).

The frequency variability of fast ripples can be characterized by different spectral indices, including the spectral entropy, the band power and a fast ripple index (Foffani et al., 2007; Ibarz et al., 2010). Computer simulations of fast ripples emerging from reliable and unreliable neuronal bursting indicate a different statistical dynamics of these indices according to whether the events emerge from in-phase or out-of-phase neuronal firing below a particular frequency cut-off (Ibarz et al., 2010). The contribution and the evolution of different neuronal clusters, together with the firing organization within these groups will all determine the dominant frequencies of fast ripples at the local EEG. Therefore, the statistical behaviour of several fast ripple events can provide useful information on the underlying mechanism and can help to further improve classification of the diverse forms of HFOs.

6. *In silico* models of HFOs

6.1. The need for integrative approaches

As described in Section 5, a number of hypotheses were formulated regarding the mechanisms responsible for the generation of high frequencies oscillations that may exceed maximal neuronal firing rates. Among the mechanisms proposed we may note alterations in the timing of action potentials (APs) generated in neighbouring pyramidal cells (Foffani et al., 2007), enhanced recurrent excitatory synaptic transmission (Dzhala and Staley, 2004; Staley, 2007), unreliable firing of epileptic neurons in disorganized networks in conjunction with enhanced glutamatergic synaptic activity (Foffani et al., 2007), electrotonic coupling between pyramidal neurons (Draguhn et al., 1998; Traub et al., 2002), among others. The fact that the above mechanisms take place at various scales, sub-cellular (ion channels, neurotransmitter receptors), cellular (neurons) and network scales, is an indication of the complexity of the generation process of HFOs. Another source of complexity is that most of these mechanisms are nonlinear. Therefore, direct relations between variables across multiple levels of analysis cannot be readily obtained. This implies that a comprehensive interpretation of local field potentials in general, and HFOs in particular, could be dramatically improved by integrating structural, functional and dynamical properties of neural systems into a coherent framework. To some extent, the development of computational models, also referred to as '*in silico*', is intended to help achieving this goal.

6.2. Replication, prediction and validation

Any model is always an oversimplification of the real complex system under study. As described in Section 6.3, most of the computational models proposed to explain the mechanisms underlying HFOs were developed in close relationship with experimental and/or clinical data, whatever the considered level. A first requirement in the development of models is to reproduce the observed phenomena. In the present context the latter consist of neuronal activity recorded extracellularly, as local field potentials, that displays oscillations within a high frequency band. All HFO models proposed so far and reviewed hereafter can reproduce HFOs observed experimentally at the onset of epileptic seizures (70–120 Hz) or during ripples (150–250 Hz) or fast ripples (250–600 Hz). However, this capability to replicate observations is not sufficient to guarantee that the mechanisms embedded in the model are those actually occurring in real neuronal systems. In all cases, further model validation is always required. This is certainly a most difficult issue. It can be addressed using a so-called prediction-validation loop approach. The general idea is that our confidence in model-based interpretations of experimental findings can increase if model predictions can further be tested experimentally. If predictions are verified, models gain relevance and acceptance. Conversely, inconsistencies point towards the necessity of revising models. In any case, a combined theoretical/experimental approach is probably the ideal framework to elaborate valid models.

6.3. Computational models of HFOs

Over the past two decades, a number of computational models of local field potential HFOs have been developed. In this section, models are classified by the frequency range of oscillations under study.

6.3.1. HFOs at the onset of partial seizures (>70 Hz)

HFOs ranging from 70 to 120 Hz–the high end of the traditional gamma frequency band and beyond—are typically observed at the onset of partial seizures, and have been modeled using detailed compartmental models (Traub et al., 2001b, 2008, 2010), lumped-parameter models (Molaee-Ardekani et al., 2010) and cellular automata (Vladimirov et al., 2011).

6.3.1.1. Compartmental models. These consist of detailed modeling of the structure (dendrites, soma, axon) and the physiology of principal neurons and interneurons, including passive (leak currents) and active (voltage-dependent channels) properties of the membranes. In general the latter are implemented using Hodgkin and Huxley's formalism (Hodgkin and Huxley, 1952). To account for the generation of HFOs, Traub et al. (Traub et al., 2001b) designed several models consisting of pyramidal cells and interneurons interacting *via* synaptic and gap junctions, which suggested that the latter could play a crucial role in the generation of HFOs (>70 Hz) at the onset of focal seizures. Their simulations could replicate physiological recordings when axonal gap junctions between principal neurons were included and synaptic transmission was omitted. Unfortunately the lack of selective gap junction blockers makes rigorous experimental testing of the model difficult. These models have been central to theoretical

studies (Lewis and Rinzel, 2000; Munro and Bogers, 2010) aiming to analyze the role of electrical coupling among neurons in HFOs.

Lumped-parameter approach. In brief, the lumped-parameter approach consists in the simulation of a "neural mass", composed of sub-populations, for instance pyramidal cells and interneurons in the cortex interacting through synaptic connections.

A neural mass model was proposed to account for the generation of HFOs (>80 Hz) at the onset of neocortical seizures (Molaee-Ardekani et al., 2010). This simple model included one sub-population of pyramidal cells and one sub-population of interneurons targeting the perisomatic region of pyramidal cells where fast GABAergic currents are mediated. These authors could identify some necessary conditions for the model to reproduce the features of high-frequency, chirp-like signatures that were strikingly similar to those observed in real depth-EEG signals recorded in epileptic patients at seizure onset. Results indicated that (i) a high degree of interconnection within interneurons (mutual inhibition) is necessary in order to generate HFOs, and that (ii) the simulation of HFOs that fulfill the frequency/energy/bandwidth constraints (decreasing frequency, increasing energy and narrow bandwidth) can be only reproduced by a progressive decrease of average EPSP and IPSP amplitudes at the level of pyramidal cells. Interestingly, non-synaptic couplings were not explicitly represented in the model.

6.3.1.2. Cellular-automata (CA) approach. A cellular automaton is a discrete model consisting of a grid of cells in which each cell can have a finite number of states. Recently, this modeling approach was used to analyze the spatio-temporal features of waves of activity as recorded in electrocorticograms during HFOs (>80 Hz) at the onset of seizures (Traub et al., 2010). In order to predict wave propagation these authors designed a 2D network of excitable cells, each with only 3 states (resting, firing, refractory), with spatially constrained electrical coupling. Their rationale for using CA models is based on one main assumption that HFOs (>80 Hz) are generated by networks of axons coupled by gap junctions. Results showed that the model can reproduce spatio-temporal patterns of activity (referred to as "blobs") which appear during HFOs at seizure onset. The same group (Vladimirov et al., 2011) subsequently used the CA modeling approach to derive a mean field theory of wave propagation.

6.3.2. Ripples (150–250 Hz)

A first computational model for ripples was proposed fifteen years ago (Traub et al., 1999), following a study of HFOs (~200 Hz) in the hippocampus *in vitro* (Draguhn et al., 1998) which hypothesized the presence of axo-axonic gap junctions between pyramidal cells, for which there is now some evidence from dye coupling (Schmitz et al., 2001) and electron microscopy (Hamzei-Sichani et al., 2007), as discussed in Ben-Ari (2009). The model for ripples consisted of a network containing multi-compartment pyramidal cells with axo-axonic gap junctions. The model did not consider either synaptic interactions or ephaptic interactions produced by field effects. In this case, the network activity was found to be characterized by spikelets and partial spikes, as well as by full action potentials, in cell somata. In a second simulation phase, recurrent excitatory synapses were added to the model and led to a different shape of the network burst with slightly faster superimposed HFOs resembling a population spike component. These simulations suggested that sparsely distributed gap junctions among pyramidal cells could explain high-frequency neuronal population oscillations, without the participation of chemical synapses. The model was then extended to include inhibitory interneurons and synaptic interactions (Traub and Bibbig, 2000), again suggesting that ripple oscillations are primarily due to gap junctional interconnections, but when inhibitory input from interneurons onto pyramidal cells is powerful enough, gamma frequency activity is produced and can be modulated at a frequency determined by the time course of $GABA_A$ IPSCs. This group also constructed a single-column thalamocortical network model comprising several types of neurons connected by chemical synapses and electrical coupling between dendrites of interneurons and between the axons of some cortical pyramidal cells (Traub et al., 2005b). As with previous models of the same group, this work argued that axo-axonic electrical coupling was necessary for gamma oscillations and HFOs (>100 Hz).

More recently, Taxidis et al. (2011) proposed a model representing the CA3 and CA1 hippocampal subfields without gap junctions. Both areas were represented by one-dimensional arrays containing pyramidal cells and inhibitory interneurons and were connected in a feed-forward fashion by excitatory connections mimicking Schaffer collaterals. Only fast AMPA and $GABA_A$-mediated synaptic interactions were considered. The full CA3–CA1 model predicted that quasi-synchronous population bursts in CA3 can evoke responses in CA1 sharing numerous characteristic features observed in real hippocampal sharp-wave ripples (SPWRs, 200 Hz). In addition, strong excitatory AMPA-synaptic currents and strong recurrent inhibitory connectivity in combination with the fast time scales of IPSPs were found to be important parameters for the sharp wave and ripple components, respectively. Interestingly, this model led to alternative hypotheses regarding the mechanism of ripple generation in SPWRs as it relies on inhibitory activity and solely on chemical synaptic interactions, in marked contrast with the models by Traub's group. Taxidis et al. (2011) propose that gap junctions are not a necessary driving component for the SPWRs, but these authors consider that gap junctions could be an additional mechanism that may contribute to ripple generation.

Regarding ripple oscillations, we should also quote several more theoretical studies showing (i) the contribution of intrinsic membrane dynamics to fast (200 Hz) network oscillations (Geisler et al., 2005), (ii) the influence of synaptic dynamics (excitation–inhibition balance) on the frequency of fast network (200 Hz) oscillations (Brunel and Wang, 2003) and iii) the influence of synaptic noise and physiological coupling in the generation of HFOs (100–200 Hz) (Stacey et al., 2009).

6.3.3. Fast ripples (250–600 Hz)

Very recently, three computational models were proposed to investigate the mechanisms underlying the generation of fast ripples (250–600 Hz) which are likely to be a signature of pathological processes, as distinct from ripples at slower frequencies which may be generated under physiological conditions.

One network model (Roopun et al., 2010) followed the network designed by Traub et al. (2005a). Using this model in conjunction with physiological measurements in human tissue resected from neocortical epileptic foci, *in vitro*, these authors argued for the importance of axo-axonic gap junctions in fast ripples.

The second model of fast ripples is that proposed by Ibarz et al. (2010) following a previous paper from the same group investigating the emergence of HFOs (>250 Hz) in the rat epileptic hippocampus (Foffani et al., 2007) (see also comment in Staley, 2007). The model had a similar design to Traub's but did not include gap junction coupling. Results suggested that one essential parameter for the emergence of oscillations in the fast ripples band was the spike timing of pyramidal cells as described above in Section 5.3. Two different regimes could be identified. Fast ripples can arise from "in-phase" firing (resulting from pathological synchronous bursting) that produces narrow-band oscillations (up to 300 Hz in CA1, and 400 Hz in the dentate gyrus). But fast ripples can also be produced by "out-of-phase" firing patterns in neuronal

clusters of slower-discharging cells, giving rise to LFP oscillations at higher frequency.

The third model (Demont-Guignard et al., 2012), was designed to analyze the hyperexcitability mechanisms at the origin of fast ripples and epileptic spikes. This detailed model was intended to mimic the hippocampus CA1 neuronal network and included both feedback and feedforward inhibition processes. The model was found to accurately reproduce both interictal epileptic spikes and fast ripples for quite specific parameter configurations. Results indicated that fast ripples and interictal spikes share certain common mechanisms (shifted $GABA_A$ reversal potential, altered synaptic transmission). However, critical differences could also be identified in terms of the number of pyramidal cells involved (small *vs.* large), the spatial distribution of hyperexcitable pyramidal cells (clustered *vs.* uniform) and the firing patterns (weakly *vs.* highly synchronized). Interestingly, some model predictions could be verified in experiments *in vitro* performed in hippocampal slice cultures: subtle changes in GABAergic and glutamatergic transmission favor the emergence of either fast ripples or interictal spikes. As in Ibarz's model, electrotonic couplings were not introduced in the model. The origin of fast ripples mainly stems from disrupted spike firing patterns of pyramidal cells. This issue is still a matter of debate.

In short, it appears that each of these different computational models may have value in accounting for the main properties of gamma oscillations, ripples and fast ripples, although they may be based on different physiological mechanisms. The latter, however, are not necessarily mutually exclusive and it is likely that combinations of such mechanisms may be operational to different degrees depending on the specific conditions. It is necessary to develop rigorous experimental validation tests that may provide independent assessment of the construction and predictive values of such models.

7. Conclusions

There are several kinds of gamma oscillations and HFOs, which can be distinguished on their dynamics (*e.g.* ripples, fast ripples, or steady-state rhythmic activity), spatial extent and distributions (*e.g.* recorded with micro or macroelectrodes, located in cortical or sub-cortical regions), neurocognitive correlates (sensory processing, motor programming, memory). In addition to occurring in the normal brain, certain types of HFOs are associated with pathological excitability states, particularly with epilepsies. Pathological HFOs can be biomarkers of epileptogenesis, and thus may have diagnostic and prognostic value particularly in progressive epilepsy disorders. They also can be biomarkers for the epileptogenic zone that may be amenable to surgical resection.

The search for physiological mechanisms underlying HFOs constitutes a challenging research topic that is being pursued not only *in vivo*, both in human and in animals, but also in brain slices *in vitro*, and using computational modeling "*in silico*". Very likely different kinds of mechanisms correspond to distinct types of HFOs, but much work remains before definitive conclusions can be drawn. This issue is the subject of vigorous experimental approaches and controversial discussions.

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