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Theta-associated high-frequency oscillations (110–160 Hz) in the hippocampus and neocortex

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ABSTRACT

We review recent evidence for a novel type of fast cortical oscillatory activity that occurs circumscribed between 110 and 160 Hz, which we refer to as high-frequency oscillations (HFOs). HFOs characteristically occur modulated by theta phase in the hippocampus and neocortex. HFOs can co-occur with gamma oscillations nested in the same theta cycle, in which case they typically peak at different theta phases. Despite the overlapping frequency ranges, HFOs differ from hippocampal ripple oscillations in some key characteristics, including amplitude, region of occurrence, associated behavioral state, and activity time-course (sustained vs intermittent). Recent in vitro evidence suggests that HFOs depend on fast GABAergic transmission and may also depend on axonal gap junctions. The functional role of HFOs is currently unclear. Both hippocampal and neocortical theta-HFO coupling increase during REM sleep, suggesting a role for HFOs in memory processing.

Contents

1. Introduction

The activity of cortical networks as reflected in local field potentials (LFPs) is often oscillatory (Buzsáki, 2006). Previously described, behavior-dependent bands of cortical network activity include delta (1–4 Hz), theta (4–12 Hz), alpha (8–12 Hz), high-voltage spindle (7–12 Hz), beta (12–30 Hz), gamma (30–100 Hz), and sharp wave-associated ripple (100–250 Hz) oscillations (Buzsáki and Draguhn, 2004; Buzsáki, 2006; Wang, 2010). In addition to these well-characterized rhythms, a novel type of

Abbreviations: CFC, cross-frequency coupling; EC, entorhinal cortex; HFOs, high-frequency oscillations; HG, high-gamma; HVS, high-voltage spindle; LFP, local field potential; LG, low-gamma; MI, modulation index; PAC, phase-amplitude coupling; PSD, power spectral density; REM, rapid eye movement sleep; SLHFO, spike-leaked high-frequency oscillations; SWS, slow-wave sleep.

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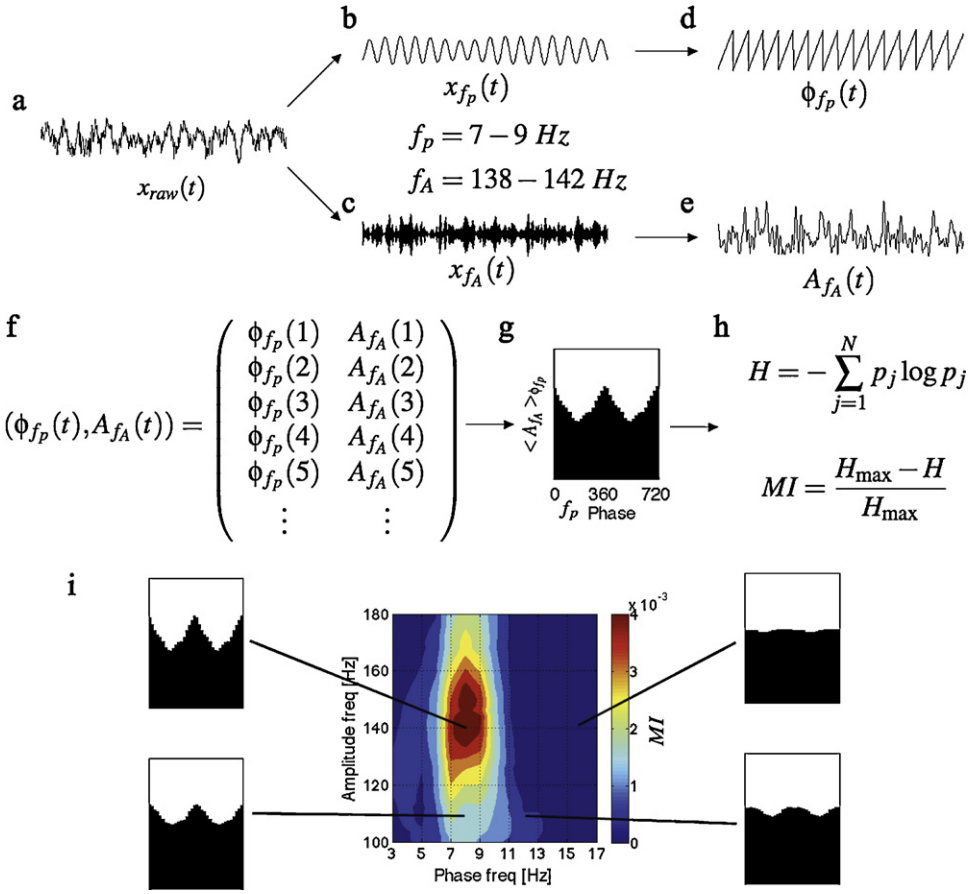

Fig. 1. Cross-frequency coupling analyses reveal the existence of theta-associated HFOs. Panels a–i show the steps required for computing the comodulation map. The local field potential (a, "raw") is independently filtered twice to obtain a slow (b, "f_p") and a fast (c, "f_A") frequency range of interest. The phase (d, ϕ) and amplitude (e, A) time series are subsequently obtained from the slow and fast filtered signals, respectively. The joint time series composed of the instantaneous phase vs amplitude values (f) is used to compute the mean amplitude of f_A at each phase bin (g). A modulation index (h, MI) is then computed to measure the strength of phase-amplitude coupling between f_p and f_A; the MI is based on the divergence of the distribution-like function shown in g from the uniform distribution (see Tort et al., 2010b for details). Finally, the comodulation map is obtained by repeating this framework to multiple frequency pairs, and expressing the associated MI values as a heat map in a bidimensional plot (i). Reproduced with permission from Tort et al. (2008).

cortical oscillatory activity in the 110–160 Hz range has been recently described (Scheffer-Teixeira et al., 2012; Tort et al., 2008). For reasons we explain below, in this work we denote this rhythm as high-frequency oscillations (HFOs), but we note that this same pattern of oscillatory activity has also been referred to as "fast gamma" (Jackson et al., 2011; Scheffzük et al., 2011). The HFOs have been detected in LFP recordings from the hippocampus (Jackson et al., 2011; Scheffer-Teixeira et al., 2012; Tort et al., 2008) and neocortex (Scheffzük et al., 2011; see also Sirota et al., 2008). In contrast to hippocampal ripples, they characteristically occur superimposed on theta activity and are modulated by the phase of this slower rhythm. Hence we also refer to this rhythm as theta-associated HFOs.

In this review we summarize the current evidence for theta-associated HFOs, as well as present previously unpublished data. We also point to several gaps in our current knowledge about this novel rhythm and suggest future research directions that will help to elucidate its network mechanisms and potential functions.

2. Identifying HFOs by cross-frequency coupling

The recent discovery of theta-associated HFOs was mainly due to the development of computational tools for analyzing phase-amplitude coupling (PAC) between LFP oscillations of different frequencies[1] (Canolty et al., 2006; Cohen, 2008; Onslow et al., 2011; Penny et al., 2008; Tort et al., 2010b). PAC is a ubiquitous phenomenon in the brain and constitutes a particular type of cross-frequency coupling (CFC) in which the amplitude of a fast oscillation depends on the phase of a slower rhythm (Canolty and Knight, 2010; Tort et al., 2010b). A now classical example of PAC is the coupling between theta and gamma oscillations in the hippocampus (Soltesz and Deschenes, 1993; Tort et al., 2009), but this type of coupling can also occur among other frequency ranges (e.g., He et al., 2010; Lakatos et al., 2005; Miller et al., 2010; Monto et al., 2008; Osipova et al., 2008; van der Meij et al., 2012; Voytek et al., 2010).

An important tool for identification of theta-associated HFOs is the comodulation map or "comodulogram" (Fig. 1). To obtain the comodulogram, first the level of coupling between multiple frequency pairs, each pair composed by one slow and one fast oscillation, is assessed by a measure called the modulation index (MI). The MI values are then expressed in a color-coded bidimensional map, in which one dimension represents the "phase frequencies" (the slower oscillations which provide the instantaneous phase) and the other dimension represents the "amplitude frequencies" (the faster oscillations which provide the amplitude envelope). A warm color in a given comodulogram entry means that there exists PAC between the corresponding frequency pair.

[1] Matlab codes for assessing PAC are available in the supplementary material of Kramer et al. (2008) and upon request from the corresponding author.

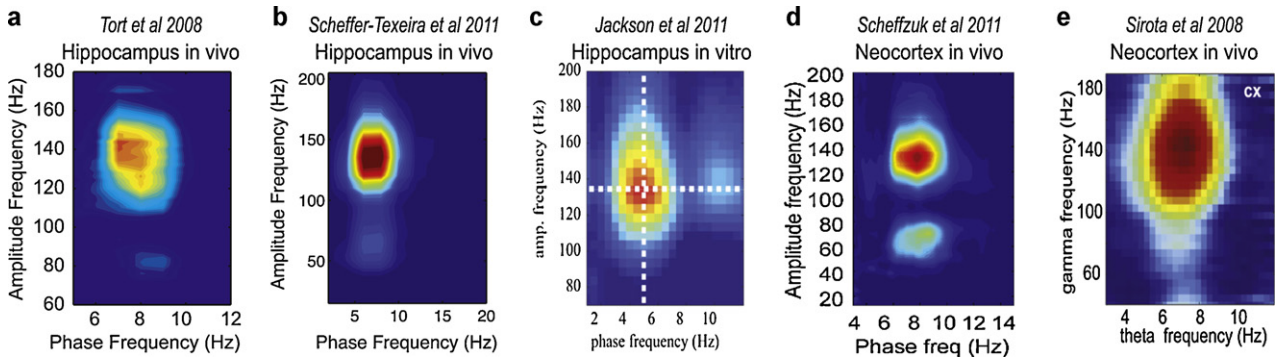

Fig. 2. Evidence for theta-associated HFOs obtained from different labs.
Reproduced with permission from Tort et al. (2008) (a), Scheffer-Teixeira et al. (2012) (b), Jackson et al. (2011) (c), Scheffzük et al. (2011) (d), and Sirota et al. (2008) (e).

That is, warm colors in (*x*,*y*) mean that the phase of the corresponding frequency in the *x*-axis modulates the amplitude of the frequency represented in the *y*-axis. An important feature of this kind of analysis is that it does not depend on the absolute amplitude of neither oscillation in the frequency pair; it only depends on the relative changes of the envelope of the amplitude-modulated oscillation as a function of the phase of the slower oscillation (see Tort et al., 2010b for details). In other words, the comodulation map corrects for the 1/*f* power distribution, and therefore allows for a good assessment of the upper spectrum, which is often overlooked in standard power analysis.

In Tort et al. (2008), the framework of comodulation was applied to hippocampal LFPs recorded from the CA1 region of rats while they performed a T-maze task. In addition to theta-gamma coupling, the comodulation maps revealed the existence of PAC between theta phase and the amplitude of a different kind of fast oscillations, which were remarkably circumscribed between 110 and 160 Hz (Fig. 2a); these oscillations were referred to as HFOs (Tort et al., 2008). Recent work carried out in an independent laboratory corroborated the existence of HFOs in CA1 (Fig. 2b) (Scheffer-Teixeira et al., 2012), and similar theta-associated HFOs were also found in CA3 in vivo (Tort, Komorowski, Kopell, Eichenbaum, unpublished observations). In addition, Jackson et al. (2011) have recently shown that the isolated rat hippocampus produces theta-associated HFOs (Fig. 2c). Theta-associated HFOs were also found in the parietal cortex of mice (Fig. 2d) (Scheffzük et al., 2011) and parietal/visual cortex of rats (Tal'nov and Brankačk, unpublished observations); we note, however, that a seemingly identical neocortical oscillation – namely, centered at ~140 Hz, modulated by theta phase and bounded between 100 and 170 Hz – had already been reported in Sirota et al. (2008) (Fig. 2e).

Therefore, to the best of our knowledge, in the past few years the study of CFC revealed the existence of theta-associated HFOs in LFPs collected in at least seven independent laboratories: Graybiel's at MIT (Tort et al., 2008), Eichenbaum's at BU (unpublished observations), Tort's at UFRN (Scheffer-Teixeira et al., 2012), Draguhn's at Heidelberg University (Scheffzük et al., 2011), Buzsáki's at Rutgers University (Sirota et al., 2008), Tal'nov's at the National Academy of Sciences of Ukraine (unpublished observations), and Williams' at McGill University (Jackson et al., 2011).

3. HFOs in the raw signal and power spectrum

Although HFOs were first identified in vivo by means of CFC tools, the existence of a sustained network rhythm in the HFO range could also be subsequently demonstrated by standard power spectral density (PSD) analysis. Namely, Scheffzük et al. (2011) and Scheffer-Teixeira et al. (2012) identified a clear PSD peak in the HFO range during behavioral states associated with theta oscillations (active waking and REM sleep) (Fig. 3a and b). Importantly, the HFO power peak reported in these studies cannot be attributed to the activity of ripple oscillations, since the latter occurs during other complementary behavioral states, such as immobility and slow-wave sleep (Buzsáki et al., 1992, 2003; Nguyen et al., 2009; Ylinen et al., 1995). Recently, HFO power peaks were also found in the parietal/visual cortex of rats (Tal'nov and Brankačk, unpublished observations) and in an in vitro preparation (Jackson et al., 2011; see Fig. 11a). It is unclear why Tort et al. (2008) found HFOs only in a CFC analysis but not directly in the PSD level[2]. We suspect this could be related to differences in the electrodes employed: while Tort et al. (2008) recorded from tetrode wires with 12.5 μm diameter, much thicker single wire electrodes were used in the subsequent studies. It may be that thinner electrodes, although appropriate for detecting spiking activity, are not well suited for detecting HFOs possibly because of wide-band "contamination" of genuine high-frequency LFP oscillations with multiunit spiking activity (more on this in Section 9), specially if their coating significantly lowers the impedance (Keefer et al., 2008).

In addition to appearing in CFC and power spectral analyses, the HFOs can also be directly observed by visual inspection of unfiltered LFP traces (see Fig. 3c and d for examples). As it happens with gamma and theta oscillations (Buzsáki, 2002; Csicsvari et al., 2003; Winson, 1974), the phase of HFOs reverses from superficial to deep hippocampal layers (Tort et al., 2008), suggesting that the HFOs are generated locally within the hippocampus (see also Jackson et al., 2011). Of note, phase reversal of oscillations of similar frequencies has been reported before (e.g., Csicsvari et al., 1999; Sullivan et al., 2011; but see Belluscio et al., 2012), but it is not clear whether these oscillations correspond to HFOs or a different rhythm.

4. HFOs vs low- and high-gamma oscillations

Theta-associated HFOs can co-occur with field oscillations in the traditional gamma range (30–100 Hz) (Scheffer-Teixeira et al., 2012; Tort et al., 2008). As mentioned in the introduction, some studies have referred to the HFOs as "fast gamma" oscillations (Jackson et al., 2011; Scheffzük et al., 2011; see also Sirota et al., 2008). We prefer not to employ such terminology, however, because the existence of at least two different hippocampal gamma oscillators with peak frequency below 100 Hz has already been

[2] We note that a similar phenomenon has been reported for gamma oscillations, in which a clear coupling to theta phase can sometimes be observed in the comodulation map without a clear PSD peak in the gamma range (see Scheffer-Teixeira et al., 2012).

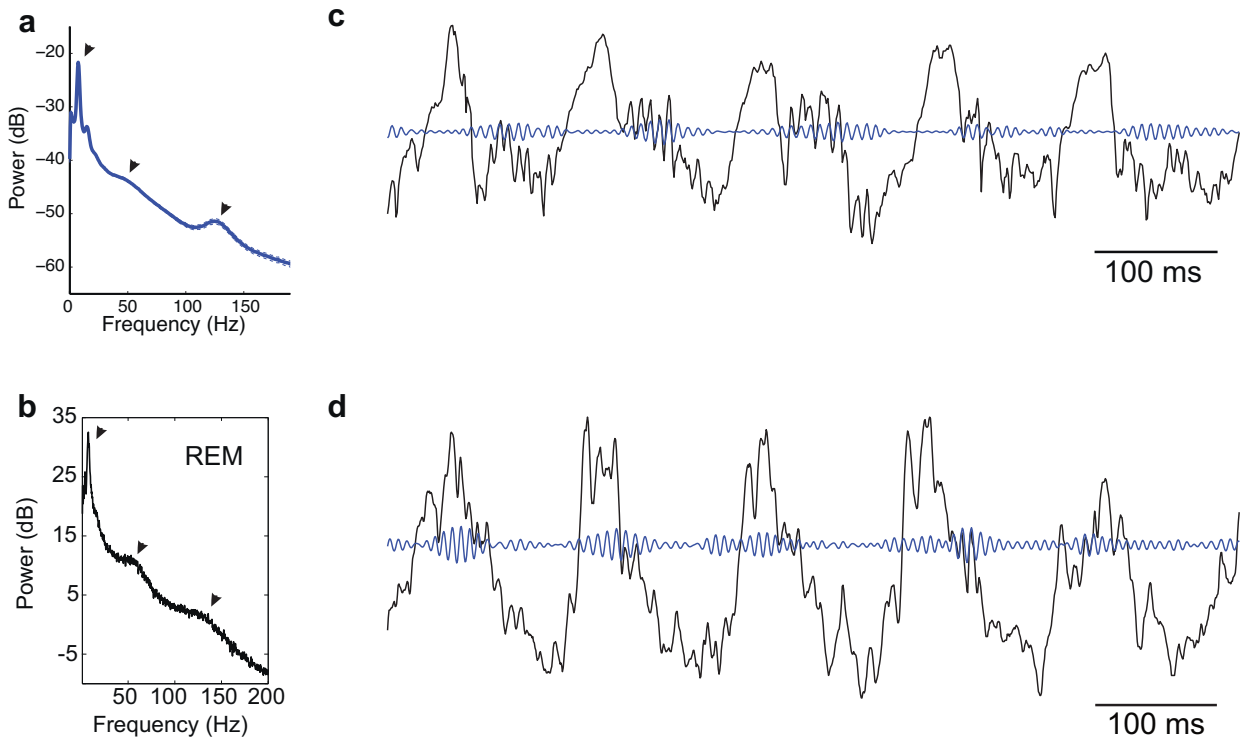

Fig. 3. HFOs in the raw signal and power spectrum. Arrowheads in a and b point to power peaks in the theta, gamma and HFO range. The HFO-filtered signal is shown in blue in c and d.
Adapted, with permission, from Scheffer-Teixeira et al. (2012) (a and c) and Scheffzük et al. (2011) (b and d).

demonstrated (Fig. 4) (Belluscio et al., 2012; Tort et al., 2008, 2010b; see also Colgin et al., 2009). In CA3, for instance, theta phase was found to modulate field oscillations with peak frequencies of ~30–60 Hz (Tort et al., 2009, 2010b), whereas in CA1 theta phase typically modulates a faster gamma oscillation with peak frequency ~60–100 Hz (Bragin et al., 1995; Chen et al., 2011; Scheffer-Teixeira et al., 2012; Tort et al., 2008, 2010b). At the same time, the slower gamma oscillation can also couple to theta in CA1 (Fig. 4b–d; Belluscio et al., 2012; Colgin et al., 2009; see also Fig. S3 in Tort et al., 2008). It is currently believed that the ~60–100 Hz component corresponds to medial entorhinal cortex (mEC) inputs to CA1 (Bragin et al., 1995; Colgin et al., 2009; Scheffer-Teixeira et al., 2012), whereas the ~30–60 Hz oscillation would be associated with CA3 inputs (Bragin et al., 1995; Colgin et al., 2009). Of note, the contribution of CA3 and mEC to the generation of CA1 HFOs is currently unknown.

We have previously referred to these two rhythms <100 Hz as low- (LG) and high-gamma (HG) oscillations (Tort et al., 2008, 2009, 2010b), and therefore employed another term – HFOs – to denote the ~110–160 Hz oscillation that we also found to be modulated by theta. However, we note that Belluscio et al. (2012) have recently introduced the terminology "slow" (30–50 Hz), "middle" (50–90 Hz) and "fast" (90–150 Hz) gamma to define frequency ranges similar to what we define as LG, HG and HFOs. Both terminologies are appropriate as long as it becomes clear that there are (at least) two other independent slower gamma oscillations <100 Hz in the hippocampus (in this convention, the slow gamma associated with CA3, and the middle gamma associated with mEC). Similar distinctions do possibly apply to neocortical areas such as the mEC (Middleton et al., 2008) and the auditory cortex (Ainsworth et al., 2011; see also Whittington et al., 2010). Calling HFOs "gamma oscillations" may be confusing because the latter term has been typically employed to denote an inhibition dependent rhythm (Whittington et al., 2000). These oscillations have been classically attributed either to the interplay between pyramidal cell excitation of local GABAergic interneurons followed by feedback inhibition (the so called pyramidal-interneuron-network-gamma – PING; Borgers et al., 2005; Fisahn et al., 1998; Kopell et al., 2010a), or to the activity of interconnected fast-spiking interneurons (interneuron-network-gamma – ING; Wang and Buzsáki, 1996; Whittington et al., 1995). The mechanisms underlying HFO generation, meanwhile, have yet to be better understood (see Section 11).

Theta-associated HFOs and lower-frequency gamma oscillations can occur simultaneously in different cortical regions or within the same region (Figs. 4d and 5; see also Sirota et al., 2008). Co-existence of theta-HFO and theta-gamma coupling in recordings from a single electrode has been found both in neocortex (Scheffzük et al., 2011) and hippocampus (Scheffer-Teixeira et al., 2012; Tort et al., 2008), in which case the amplitude of HFOs typically peaks a few degrees after gamma oscillations within the theta cycle. For instance, during active waking and REM sleep, gamma oscillations have maximal amplitude near the peak of the theta wave recorded at CA1 pyramidal layer or parietal cortex, whereas HFOs are maximal ~30° after, at the descending portion of the theta wave (Fig. 5). This finding suggests that HFOs and gamma oscillations arise from different biophysical processes.

5. Dependence of HFO activity on hippocampal layer

Besides having different theta phases of maximal amplitude, another characteristic distinguishing HFOs from gamma oscillations is their laminar profile in the hippocampus. Scheffer-Teixeira et al. (2012) have recently shown that theta-HFO coupling occurs mostly in superficial layers of the rat CA1 region (i.e., *stratum oriens-alveus*), whereas coupling between gamma and theta oscillations was found in the pyramidal layer and became strongest in *stratum lacunosum-moleculare* (Fig. 6a). Similar

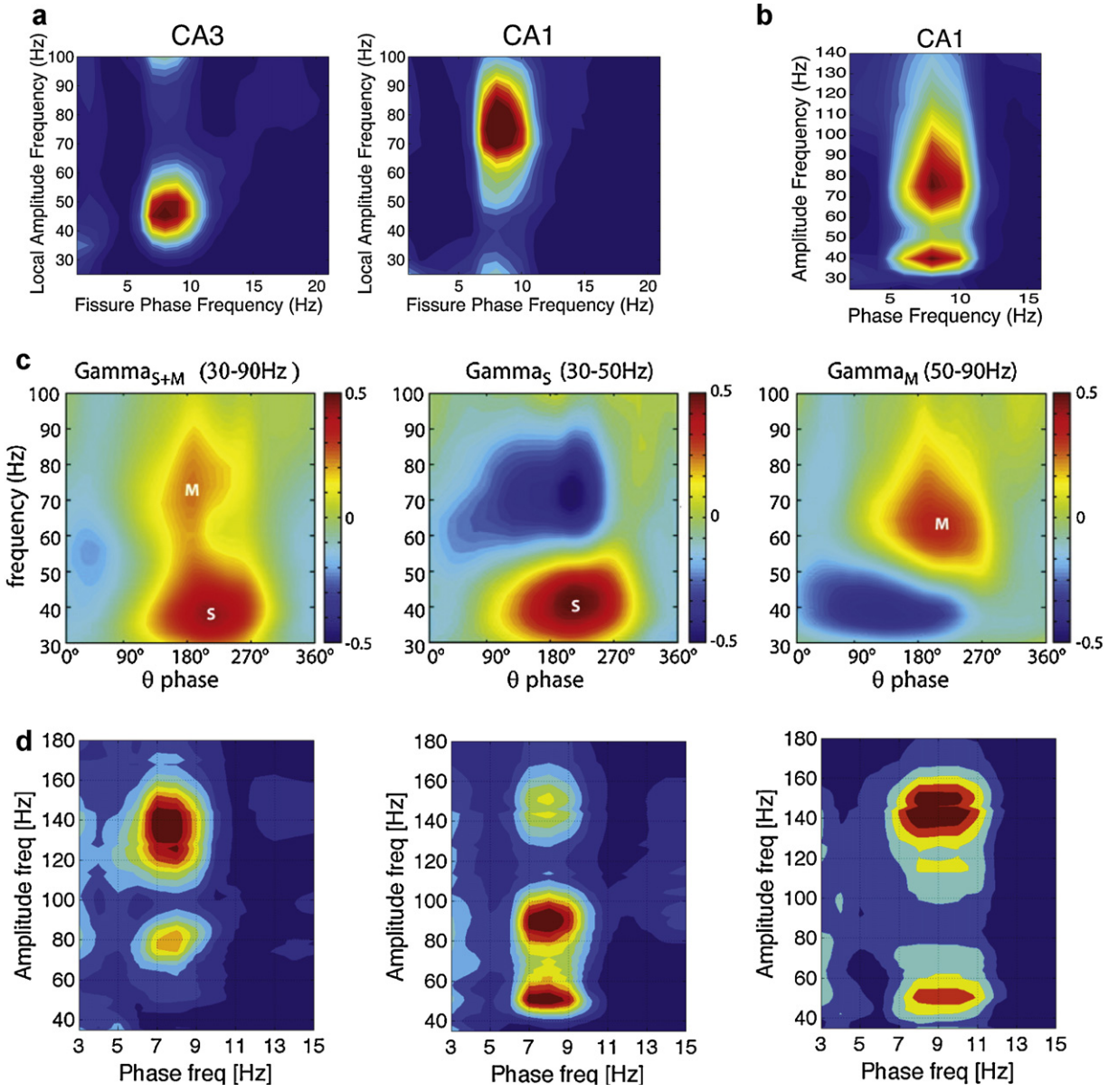

Fig. 4. Evidence for two types of hippocampal gamma oscillations with peak frequency below 100 Hz. (a) Comodulation maps of multisite hippocampal recordings evincing theta phase modulation of low-gamma oscillations in CA3 concurrent with theta modulation of high-gamma in CA1 (adapted, with permission, from Tort et al., 2010b; pyramidal layer recordings). (b and c) Simultaneous modulation of low- and high-gamma oscillations by theta phase in CA1 pyramidal layer (b, previously unpublished observations; c, reproduced with permission from Belluscio et al., 2012). (d) Coexistence of HFOs and gamma oscillations. Comodulation maps showing that theta phase can simultaneous couple to HFOs and either high-gamma (left), low-gamma (right) or both gamma-frequency oscillations (middle) in CA1 *s. oriens* (adapted, with permission, from Tort et al., 2008).

differences seem to be present in mice (Fig. 6b; Scheffzük et al., 2011). In contrast to rats, however, we did not observe exclusive theta-HFO coupling without any theta-gamma coupling in superficial CA1 electrodes in mice (Scheffzük, Tort, Draguhn, Brankačk, unpublished observations). This finding is consistent with the fact that mice have much more prominent gamma waves in the CA1 pyramidal layer than rats (Buzsáki et al., 2003).

It remains to be fully established whether the HFOs observed in *stratum oriens-alveus* of CA1 in vivo are locally generated or else volume-conducted from the overlying parietal cortex, where they also appear modulated by theta phase (Scheffzük et al., 2011; Sirota et al., 2008). There are three lines of evidence suggesting that theta-associated HFOs are generated locally in CA1: first, the level of phase coherence in the HFO range between the parietal cortex and the hippocampus is quite low (Scheffzük et al., 2011), arguing against volume conduction; second, the HFO phase reverses across the hippocampus (Tort et al., 2008; see also Sullivan et al., 2011), which suggests the existence of a hippocampal generator; third, the hippocampus in vitro is capable of producing HFOs when isolated from the parietal cortex (Jackson et al., 2011). In addition, we note that Belluscio et al. (2012) employing current source density analysis found "fast gamma" oscillations (90–150 Hz) arising within CA1, although these oscillations may not be the same as the HFOs (c.f. Section 9). Nevertheless, extended current source density studies performed across the parieto-hippocampal axis will be required to track the precise origin(s) of HFOs.

Topological dependences of theta-HFO coupling have been also found in vitro. Working with a complete preparation of the isolated rat hippocampus that produces theta oscillations (Goutagny et al., 2009), Jackson et al. (2011) reported that HFOs (termed "fast gamma" in this study) and gamma oscillations ("slow gamma") are generated in different layers of the rat subiculum, with HFOs

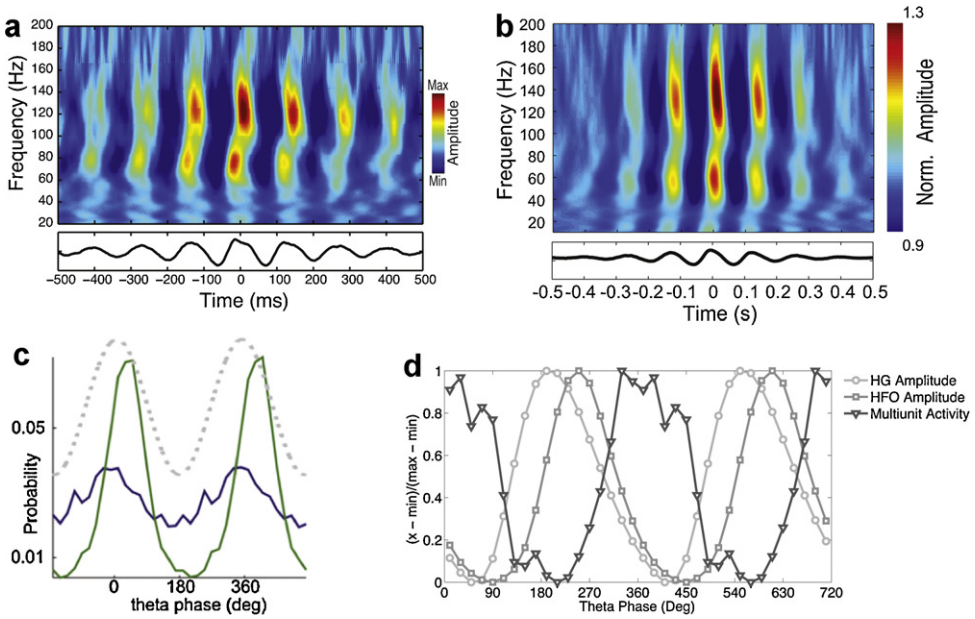

Fig. 5. HFOs and gamma oscillations peak at different theta phases. (a and b) Time-frequency distribution of the amplitude of fast oscillations time-locked to the peaks of theta oscillations in the rat hippocampus (a) and mouse parietal cortex (b). (c) Theta phase histogram of HFO (green) and gamma (blue) bursts. Gray dashed line represents reference theta cycle. (d) Normalized amplitude of HFO and gamma oscillations, along with normalized multiunit activity, as a function of theta phase (theta peak = 180°). Reproduced with permission from Scheffer-Teixeira et al. (2012) (a and d), Scheffzük et al. (2011) (b), and Sirota et al. (2008) (c).

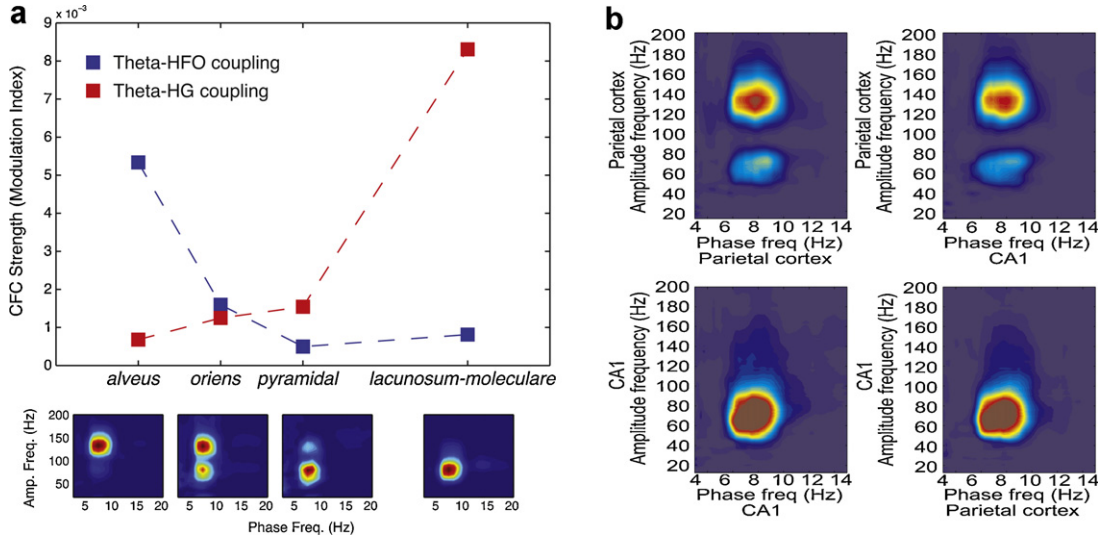

Fig. 6. Theta-HFO coupling strength depends on recording region. Theta-HFO coupling is strongest in superficial hippocampal layers (a) and parietal cortex (b), while theta-gamma coupling is strongest in deep hippocampal layers.
Reproduced with permission from Scheffer-Teixeira et al. (2012) (a; rat recordings) and Scheffzük et al. (2011) (b; mouse recordings).

appearing closer to the pyramidal layer, while gamma oscillations were mainly located in the molecular layer. Moreover, they also reported differences in the relative level of theta-HFO and theta-gamma coupling along the proximo-distal (from CA1) axis of the subiculum. Interestingly, and somewhat surprising, in this preparation neither HFOs nor gamma oscillations are modulated by theta in CA1 and CA3 (Jackson et al., 2011), suggesting that PAC in these regions may depend on external inputs.

6. HFOs vs ripple oscillations

Ripple oscillations are the best characterized pattern of fast oscillatory activity in the hippocampus. Ripple oscillations occur associated with synchronous discharges of CA1 pyramidal cells (Csicsvari et al., 1998), which have been implicated in the transfer of information from the hippocampus to the neocortex during memory consolidation (Buzsáki, 1989, 1996; Draguhn et al., 2000; Siapas and Wilson, 1998). Ripple network patterns in CA1 may vary in peak frequency, typically spanning a wide band from 100 to 250 Hz (Nguyen et al., 2009), encompassing therefore the HFO band. Based on this, it is reasonable to speculate that HFOs and ripple oscillations would be generated by similar network mechanisms. However, despite the overlapping frequency range, HFOs and ripple oscillations differ in key aspects: (1) in the hippocampus, HFOs are most prominent in *stratum oriens-alveus*, whereas ripple oscillations are confined to the *stratum pyramidale*; (2) HFOs couple to theta oscillations during REM and active waking behaviors, while ripples are associated with sharp waves in *stratum radiatum* that occur during slow-wave sleep and immobility periods; (3) HFOs have

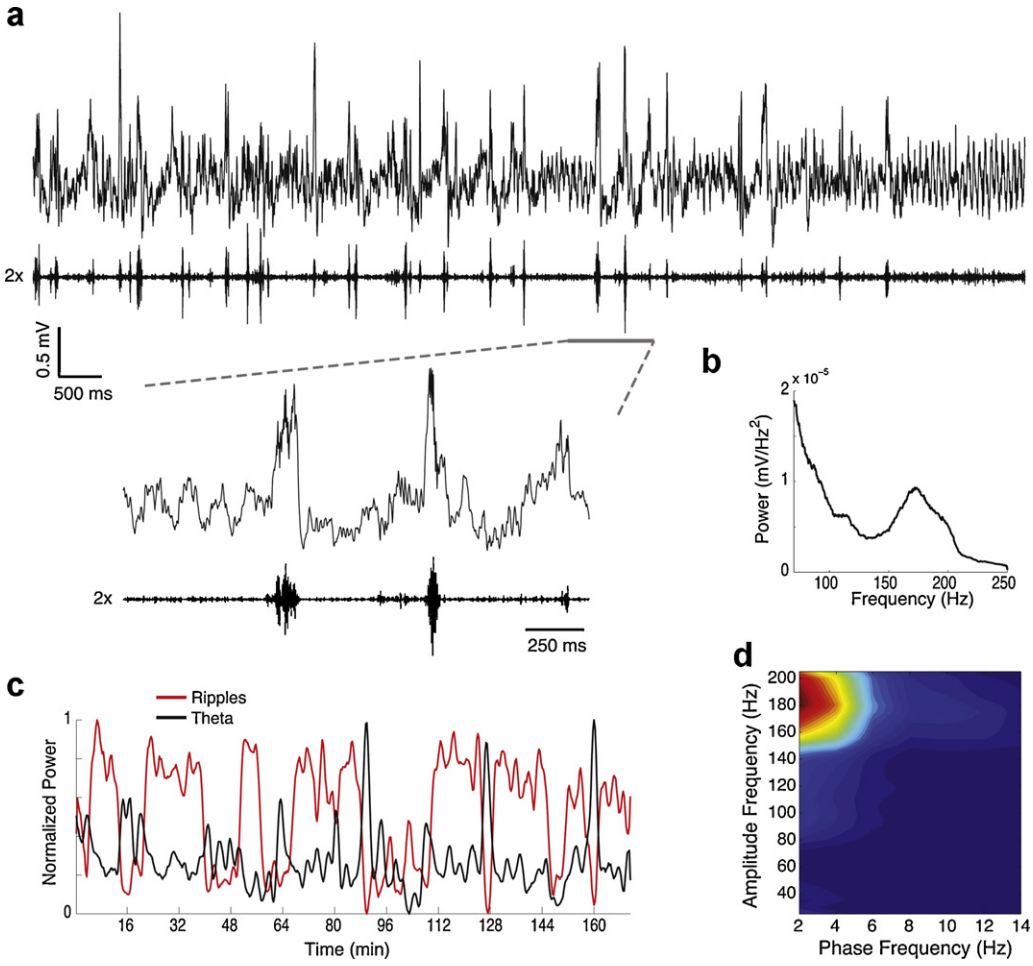

Fig. 7. Ripple oscillations differ from theta-associated HFOs in multiple aspects. (a) Unfiltered hippocampal LFP (top) and associated ripple-filtered signal (bottom). Notice emergence of theta oscillations at the end of the epoch along with disappearance of ripple bursts. (b) Power spectral density showing ripple peak activity at ~180 Hz. (c) Normalized theta and ripple power as a function of time (0 = min power value; 1 = max power value). Notice that epochs of high theta power are associated with low ripple power. (d) Comodulation map computed for an LFP epoch with prominent ripple activity (same epoch as in b).

lower amplitude than ripple oscillations; (4) HFOs are sustained oscillations, while ripples are intermittent, burst-like oscillations defined by large deviations of its amplitude envelope from the background mean. Finally, we show in Fig. 7 that the signature of sharp wave-associated ripples in the comodulation map is considerably different from that of HFOs (previously unpublished observations).

It should be noted that "exploration-associated" sharp wave/ripple activity (eSWR) has been described to occur within short pauses of or during theta oscillations (O'Neill et al., 2006; see also Cheng and Frank, 2008). Unfortunately, the fact that these previous studies have not assessed amplitude modulation by theta phase makes it difficult to conclude whether these network patterns are the same as the theta-associated HFOs. We suspect eSWRs may represent a different network activity from HFOs based on similar arguments as above; in particular, eSWRs were found in the pyramidal layer and described as burst-like oscillations defined by the crossing of an amplitude threshold, which contrasts with the lower amplitude and more persistent nature of HFOs. In addition, eSWRs have faster frequency (150–250 Hz) than theta-associated HFOs.

Taken together, there is strong evidence pointing to the existence of theta-associated HFOs as a novel type of oscillatory activity, different from classical hippocampal fast network patterns such as gamma and ripple oscillations.

7. Dependence of theta-HFO coupling on theta power

The strength of theta phase modulation of HFO amplitude is positively correlated with theta power; that is, periods in which theta oscillations have larger amplitude are associated with a greater level of theta-HFO coupling[3] (Scheffer-Teixeira et al., 2012; Scheffzük et al., 2011; Tort et al., 2008). A positive correlation between CFC and theta amplitude can be artificially generated by inclusion of data without measurable theta activity, yielding zero theta amplitude and zero coupling. However, the positive dependence of theta-HFO coupling on theta power also holds true when only considering LFP epochs containing theta oscillations. Note that this finding is not a direct consequence from the way PAC is defined; on the contrary, to compute PAC only the information about the phase of the theta rhythm is extracted, while its amplitude is not taken into account (Fig. 1).

Importantly, in simultaneous multi-site recordings, the strength of theta-HFO coupling across electrodes is not a function of their absolute level of theta power. That is, the dependence of theta-HFO coupling on theta power occurs within electrodes, and not across electrodes. In fact, CA1 theta power is strongest in *stratum lacunosum-moleculare*, while theta-HFO coupling is much

[3] A similar dependence on theta power exists for theta-gamma coupling; see Fig. S6b in Tort et al. (2008).

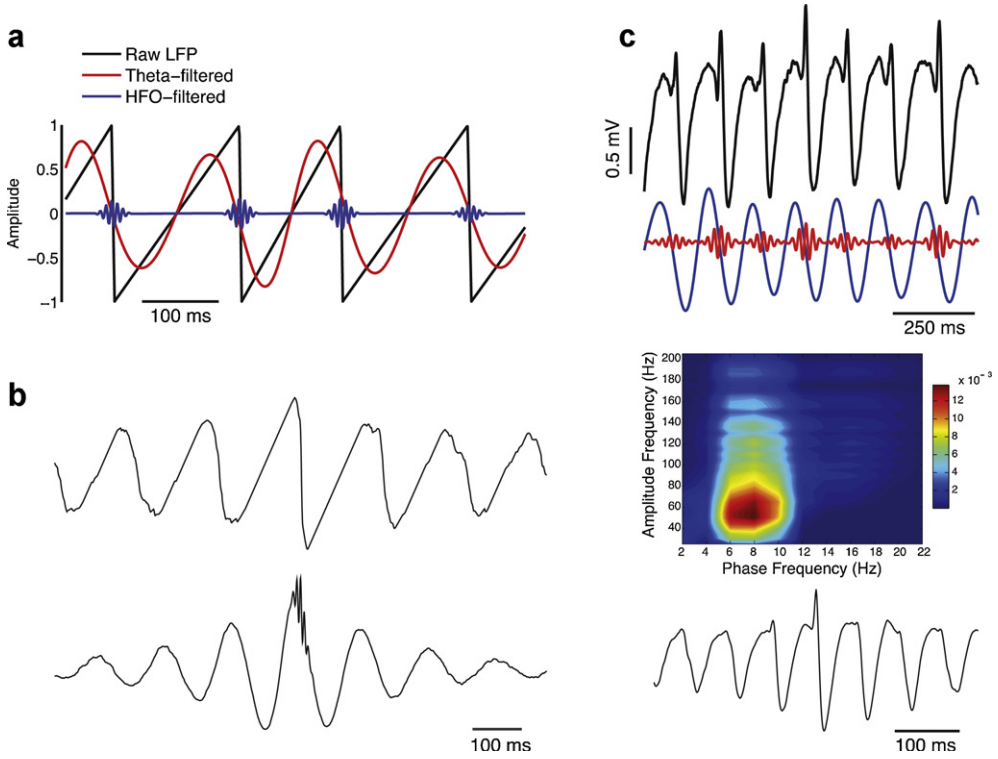

Fig. 8. Sharp signal deflections can lead to spurious cross-frequency coupling. (a) Illustrative example of a spurious phase-amplitude coupling originated from sharp edge effects. (b) Event-related average triggered by the peaks of the fast oscillation for the synthetic LFP in a (top) and for an actual LFP presenting theta-associated HFOs. Notice visible HFOs in the latter case. (c) Unfiltered LFP with prominent high-voltage spindle activity (black trace) and associated theta- (blue trace) and gamma-filtered (red trace) signals. Notice apparent coupling between the filtered signals. The associated comodulation map (middle) and event-related average triggered by the gamma peaks (bottom) are also shown. Notice absence of fast oscillations in the peak-triggered average.

weaker in this region than in more superficial layers where theta oscillations have lower amplitude (Fig. 6). For each individual electrode, however, theta-HFO coupling tends to increase with increases of theta power, irrespective of the absolute level of theta power. It should be noted that although theta-HFO coupling correlates with theta power, theta power alone is certainly not the only factor influencing CFC strength; for example, for the same levels of theta power, theta-HFO coupling is stronger during REM sleep than active waking (c.f. Section 10).

Theta-HFO coupling strength was also shown to depend on HFO and LG power, but not on HG power (see Fig. S7 in Tort et al., 2008). Together, these results suggest that the generators of theta, HFO and theta-HFO coupling are mechanistically related in the network level.

8. HFOs and sharp edge artifacts

CFC measures are prone to spurious results in the presence of sharp signal deflections, what we refer to as sharp edge artifacts (Kramer et al., 2008). In Fig. 8a we illustrate this phenomenon by means of a synthetic example (a sawtooth wave). Basically, the abrupt deflections of the periodic signal lead to higher frequency oscillations in the high-pass filtered version of the original signal (Fig. 8a). Although genuine high-frequency oscillations do not exist in the unfiltered signal, they appear in the spectral decomposition as a consequence of the non-sinusoidality of the original signal[4]; most importantly, the amplitude of the spurious oscillations couple to the slower rhythm, being largest at the particular phases where the sharp deflection occurs. Therefore, it is a reasonable concern to wonder whether the HFOs that appear phase-locked to the theta rhythm would be an artifact of the deviation of the theta waveform from a sinusoid.

Kramer et al. (2008) described some techniques to infer whether a detected PAC is genuine or due to sharp edge artifacts. Perhaps the most simple and important procedure is to visually inspect the unfiltered signal. Clearly, the presence of high-frequency oscillations observed at the raw signal level indicates that these oscillations are a genuine rhythm. Conversely, the absence of fast oscillations in the unfiltered signal would suggest the opposite. In this sense, the direct observation of HFOs in the unfiltered LFP (Fig. 3) rules out the possibility that these oscillations originate from sharp edge artifacts. In addition, we also note that the theta waveform is steepest in the rising phase (Belluscio et al., 2012), which is not the same phase where HFO amplitude is maximal (Fig. 5). Furthermore, theta oscillations are much sharper and larger in amplitude in CA1 *stratum lacunosum-moleculare*; were HFOs a consequence of abrupt deflections, theta-HFO coupling should be most prominent in this layer, which is not the case (Fig. 6).

Yet another technique to exclude sharp edge effects is to average the unfiltered LFP triggered by the peaks of the high-frequency oscillation (Kramer et al., 2008). Since sharp deflections lead to spurious fast oscillations in the filtered signal that are not present in the original trace, averaging the raw LFP signal around the peaks of the spurious oscillation will lead to no visible fast oscillations in the resultant trace; only the slower rhythm is evinced (see Fig. 8b top). True CFC, meanwhile, leads to visible oscillations in the averaged trace since these were present in the unfiltered LFP, and they appear nested in the slower rhythm (Kramer et al., 2008). Applying this technique to LFPs presenting theta-HFO coupling does indeed yield visible HFOs in the averaged trace (Fig. 8b bottom), corroborating once again their existence as

[4] Although not in the scope of the present review, we note that this kind of phenomenon can be particularly important when working with filtered versions of evoked responses. It is very dangerous to ascribe that a given oscillation occurs evoked by a given stimulus if the oscillation is not apparent in the unfiltered signal.

actual oscillations. Finally, a strong indication that theta-associated HFOs are not sharp edge artifacts comes from their appearance as genuine oscillatory activity in the PSD (Fig. 3). Accordingly, higher frequency harmonics occur with decreasing power at integer multiples of the basic frequency. In the case of a non-sinusoidal 8-Hz rhythm, harmonics are expected at 16, 24, 32, 40 Hz and so on, and not directly at the HFO band without harmonic peaks in between. Altogether, there is strong evidence to conclude that the HFOs are not an artifact of the shape of the theta wave.

Lastly, as a positive control, we show in Fig. 8c results obtained by the analysis of high-voltage spindles (HVS), also known as μ rhythms (Fontanini and Katz, 2005; Tort et al., 2010a; Wiest and Nicolelis, 2003). Although the comodulation map indicates coupling between the phase of 7–12 Hz oscillations and gamma amplitude (Fig. 8c middle), visual inspection of the raw signal (Fig. 8c top) and the peak-triggered average technique described above (Fig. 8c bottom) clearly show that PAC in this case is spurious, caused by the spike-and-wave shape of the 7–12 Hz rhythm; notice that there are no true gamma oscillations in the unfiltered LFP.

9. HFOs and spiking activity

We start this section by stressing the fact that we define theta-associated HFOs as a specific type of high-frequency activity that occurs in certain cortical regions bounded between 100 and 170 Hz, as inferred by CFC (Figs. 2 and 4–6) and power spectral analyses (Fig. 3). That said, we note that depending on the electrode location (see below), theta phase can be found to modulate a wide range of high-frequency oscillations that are not as circumscribed as the HFOs we have been describing. For reasons we explain below, we believe such unbounded activity is caused by the "spectral leakage" of the extracellular spike shape into several bands (see also Jackson et al., 2011 for a similar conclusion), and we therefore refer to this wide band of activity as spike-leaked high-frequency oscillations (SLHFO). In Fig. 9a we show an example of the coupling between theta and SLHFO, which was obtained from recordings from the CA1 pyramidal layer. Notice the clear difference from the typical HFO signature in the comodulation map.

The following observations led us to hypothesize that spiking activity causes SLHFO in the field potential: (1) similar high-frequency activity appears in the spike-triggered average of LFP time-frequency decompositions (Belluscio et al., 2012; Colgin et al., 2009; Peyrache et al., 2011); (2) recent studies have been suggesting that the power of oscillations in the SLHFO range correlates with spiking activity (Jia and Kohn, 2011; Ray et al., 2008; Ray and Maunsell, 2011); (3) the theta phase of maximal SLHFO amplitude coincides with the phase of maximal multiunit activity (Fig. 9b). Based on this, we believe theta modulation of SLHFO observed in some comodulation maps would be equivalent to theta modulation of spiking activity. In particular, when studying HFOs one should avoid computing comodulograms for channels where spikes are present.

As mentioned above, Belluscio et al. (2012) have recently defined slow, middle and fast gamma oscillations to represent frequency bands that roughly correspond to what we define as LG, HG and HFOs (Scheffer-Teixeira et al., 2012; Tort et al., 2008, 2010b). Despite the similar frequency, however, the fast gamma oscillations reported in Belluscio et al. peaked at a different theta phase from the HFOs: during active waking periods, Belluscio et al. found fast gamma amplitude to be maximal near the theta trough, the same phase of maximal spiking activity (see Figs. 5c and 9b). Moreover, in contrast to the stability of the preferred theta phase of HFOs across behavioral states (Scheffzük et al., 2011), the preferred phase of fast gamma oscillations shifted between awake and REM sleep, accompanying a phase shift also found for spikes (Belluscio et al., 2012). Finally, Belluscio et al. reported that their fast gamma oscillations were maximally modulated by theta in the pyramidal layer, which is another distinction from HFOs. Taken together, these findings indicate that the fast gamma oscillations investigated in Belluscio et al. (2012) were at least partially contaminated by SLHFO.

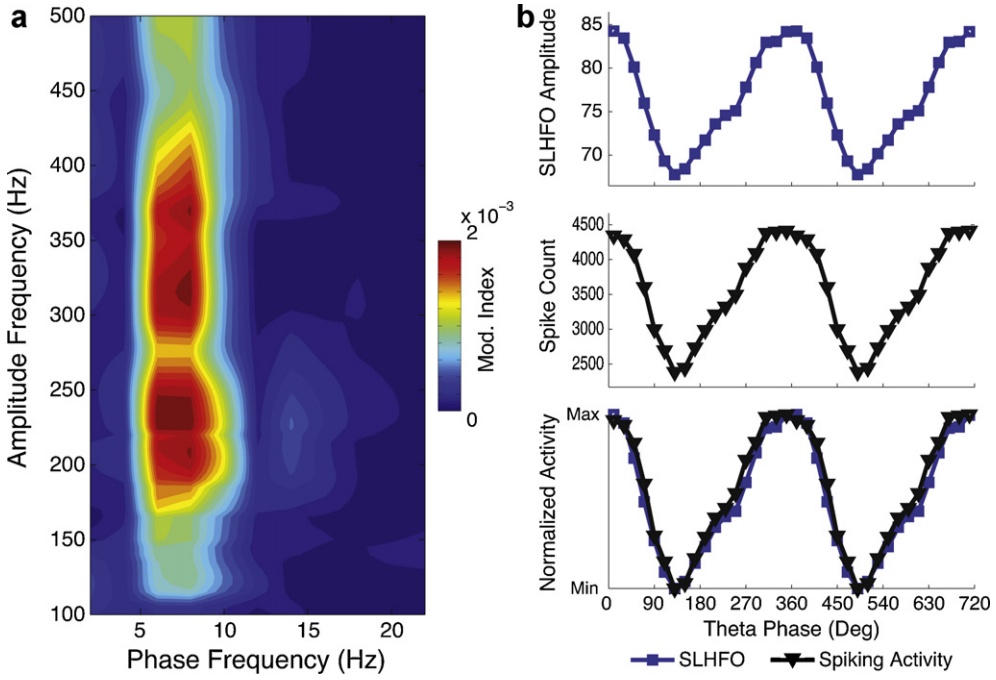

Fig. 9. Theta-SLHFO coupling reflects theta phase modulation of spiking activity. (a) Comodulation map showing coupling of theta phase and the amplitude of a wide band of very fast oscillations (defined as SLHFO; see text). (b) SLFHO amplitude and multiunit spiking activity as a function of theta phase (theta peak = 180°).

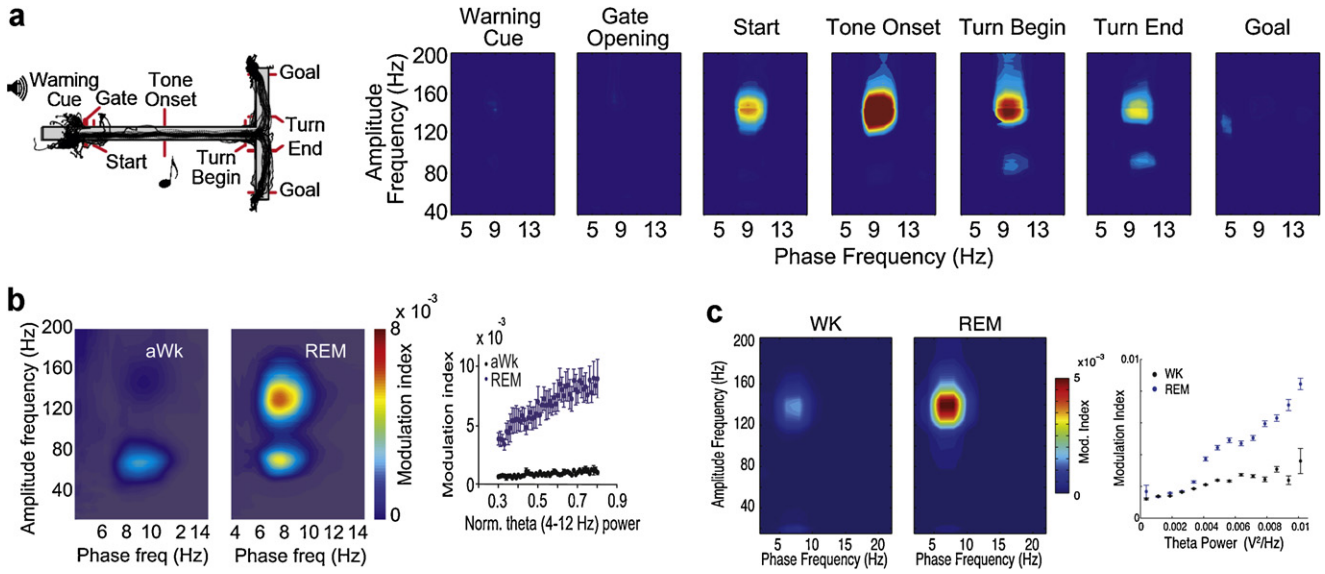

Fig. 10. Evidence for a possible cognitive role of theta-associated HFOs. (a) Comodulation maps showing increased theta-HFO coupling during the decision period of a T-maze task. (b and c) Theta-HFO coupling is strongest during REM sleep in both mice (b) and rats (c).
Reproduced with permission from Tort et al. (2008) (a) and Scheffzük et al. (2011) (b).

Several characteristics reviewed in the above sections distinguish HFOs from SLHFO, including preferred coupling phase (compare Figs. 5c and 9b). We therefore conclude that theta-associated HFOs are not trivially explained by spectral contamination of the LFP signal by somatic spikes. In all, these observations suggest that when studying fast oscillations in field potentials, one must pay special attention to possible influences of extracellular spikes. Conversely, recent papers conveyed the idea that high-frequency field oscillations are essentially due to spiking activity (Jia and Kohn, 2011; Ray et al., 2008; Ray and Maunsell, 2011), but the HFOs constitute a counterexample to this generalization. In all, these results add to others (e.g., Kopell et al., 2010b; Tort et al., 2010a) that recommend avoiding defining brain rhythms solely based on frequency ranges.

10. HFOs, cognitive function and REM sleep

The functional role of theta-associated HFOs, if any, remains to be better understood. Initial evidence comes from Tort et al. (2008), who showed that hippocampal theta-HFO coupling increases during the decision-making period of a T-maze task (Fig. 10a). Importantly, the changes in CFC strength within maze runs could not be entirely accounted for by variations in theta power and running speed (Tort et al., 2008). This is an important concern since PAC is positively correlated with theta power (cf. Section 7); therefore, variations in theta band power should always be taken into account when studying the potential roles of theta-HFO coupling.[5] This is not to say that increased theta-HFO coupling observed along with increased theta power would not be cognitively relevant; we actually think the opposite. We only remark that in this case it is difficult to dissociate which factor would be most important, if the power levels of the individual oscillations per se or if the strength of the oscillatory interaction. On the other hand, finding increased PAC with no changes in oscillatory power would suggest that theta-HFO coupling in itself plays a role in cognitive function.

[5] It goes without saying that we believe theta power should also be regarded as an important confounding factor when studying theta-gamma coupling as well as theta phase modulation of spiking activity.

More recently, Scheffzük et al. (2011) reported a striking increase in the magnitude of neocortical theta-HFO coupling during REM sleep in mice (Fig. 10b). Importantly, coupling strength was consistently stronger during REM sleep even after matching periods of active waking with equal levels of theta power (Fig. 10b). We have recently found a similar result in hippocampal recordings of rats, which also held true after controlling for differences in theta power between active waking and REM sleep (Fig. 10c, previously unpublished results). Given that REM sleep has been associated with mnemonic functions (Paller and Voss, 2004; Poe et al., 2000; Ribeiro et al., 1999, 2002), these results constitute indirect evidence for a possible role for HFOs in memory processing. It is important to notice that both types of fast oscillations, HFOs and sharp wave-associated ripples, occur during complementary behavioral states: sharp wave ripples are most prominent during slow-wave sleep and during awake immobility (Buzsáki et al., 1992; Ego-Stengel and Wilson, 2010; Ylinen et al., 1995), while HFOs are most prominent during active wakefulness and REM sleep (Scheffer-Teixeira et al., 2012; Scheffzük et al., 2011). REM and slow-wave sleep were proposed to play complementary functions in memory processing (Diekelmann and Born, 2010; Ribeiro et al., 2004; Ribeiro and Nicolelis, 2004). Further understanding the differences and similarities of complementary vigilance states should help understanding the function of the associated rhythms.

A deeper understanding of the role of CFC in brain computation should also help clarifying the function of theta-HFO coupling. It has been recently shown that CFC between theta and gamma rhythms in the hippocampus may be related to mnemonic functions in both rats (Tort et al., 2009) and humans (Axmacher et al., 2010). Oscillations are believed to represent changes in the excitability of neuronal networks, in a way of providing windows for optimal neuronal communication (Fries, 2005). Current theories propose that lower frequency rhythms, which are coherent over large distances, would be responsible for long-range communication, whereas fast oscillations would mainly represent local computations (see Canolty and Knight, 2010 for a recent review). The coupling between theta oscillations and HFOs could thus be a way of integrating information processed locally in multiple brain regions.

11. Possible cellular and network mechanisms underlying HFOs and theta-HFO coupling

Theta-associated HFOs are only starting to be recognized as a new type of cortical oscillations, and, given their infancy, the mechanisms underlying their generation are currently far from being understood. Jackson et al. (2011) have taken an important step forward by showing that the HFOs observed in vitro depend on fast GABAergic inhibition but not on NMDA nor AMPA/kainate glutamate receptors (Fig. 11a and b). Of note, in these same recordings gamma oscillations were sensitive to both $GABA_A$ and AMPA/kainate receptor blockade (Fig. 11b), which constitutes yet another piece of evidence supporting the independence of gamma and HFOs. The results reported in Jackson et al. (2011) suggest that HFOs can be generated without fast glutamatergic transmission, which argues against a PING-like model in which the HFOs would be generated by an interplay of excitation and feedback inhibition, as is believed to occur for gamma oscillations (Borgers et al., 2005; Fisahn et al., 1998; Whittington et al., 2000). Evidence for a role of $GABA_A$ receptors in generating HFOs is being currently obtained in vivo. Namely, systemic administration of the benzodiazepine diazepam to freely behaving mice reduces HFO peak frequency and power (Scheffzük, Draguhn, Tort, Brankačk, ongoing work).

A different set of experiments has shown that hippocampal fast oscillations >100 Hz can be generated in vitro (Draguhn et al., 1998; Traub et al., 2002, 2003). For instance, Traub et al. (2003) showed that bath application of kainate induces fast oscillations with peak activity ~150 Hz in a CA1 slice preparation in which *stratum oriens-alveus* was surgically separated from *stratum pyramidale* and *stratum radiatum* (Fig. 12a and b). Interestingly, the same pharmacological drive that generated the ~150 Hz rhythm in *stratum oriens* did not lead to any sort of oscillatory activity in *stratum pyramidale* and *radiatum* (Fig. 12c). The in vitro fast oscillations described by Traub et al. have several features similar to the HFOs: (i) peak frequency; (ii) location in *stratum oriens-alveus*; (iii) insensitivity to the blockade of fast glutamatergic currents; (iv) dependence on $GABA_A$ (but not $GABA_B$) receptors. Traub et al. (2003) hypothesized that the ~150 Hz oscillations are generated by the activity of ectopic spikes in an "axonal plexus" formed by pyramidal cell axons mutually connected by gap junctions (see also Munro and Borgers, 2010). The similarities between HFOs and the fast oscillations described in Traub et al. (2003) suggest that they may reflect the same biological process. However, in contrast to the whole hippocampus in vitro preparation investigated in Jackson et al. (2011), no theta oscillations, and therefore no theta-HFO coupling, were apparent in the slice study of Traub et al. (2003), which suggests that theta generation and theta phase coupling depend on network connections that are severed in slices. The absence of theta oscillations in Traub et al. (2003) also precludes the conclusion of their in vitro fast oscillations being the same as the theta-associated HFOs observed in vivo.

Further understanding the biophysical mechanisms underlying HFOs will likely shed light on what causes the coupling to theta phase. Nevertheless, there are standard network mechanisms that may account for PAC in general, and theta-HFO coupling in particular (Fig. 13). For instance, PAC could stem from pulses of inhibition paced at the slower frequency and targeted at the generators of the faster oscillation (Kopell et al., 2010a; Neymotin et al., 2011; Tort et al., 2007; Wulff et al., 2009). One concept on the mechanisms underlying HFOs postulates that rhythmic activity is generated within a plexus of electrically coupled axons (Traub

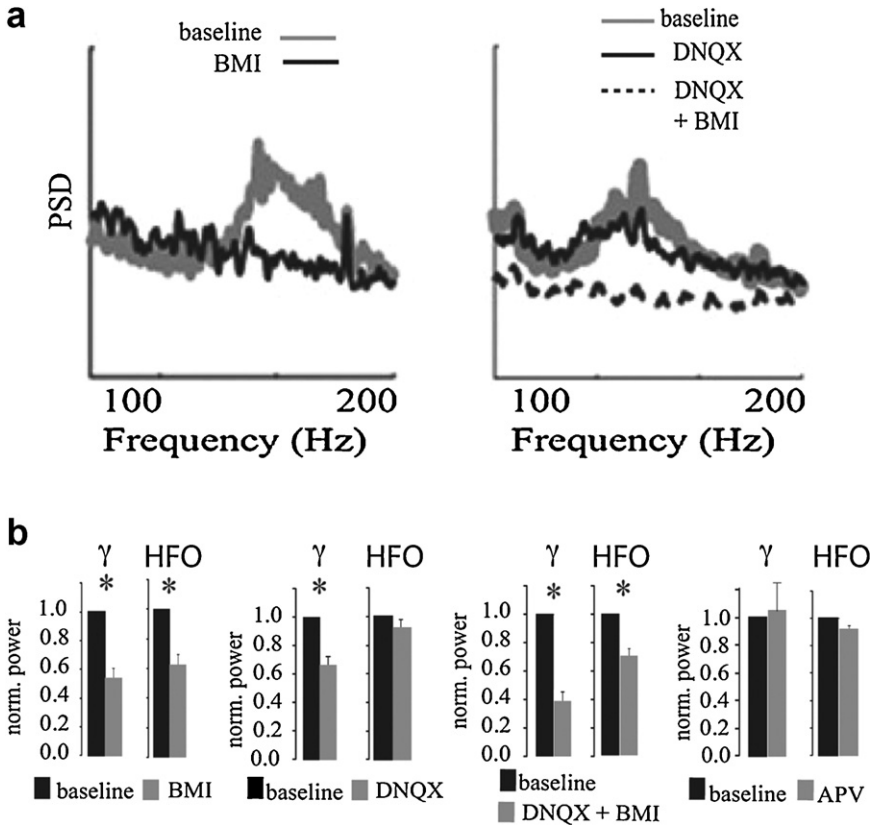

Fig. 11. HFOs depend on fast GABAergic but not glutamatergic transmission. (a) Representative power spectra showing that in vitro HFOs are sensitive to GABA-A receptor blockade by bicuculline (BMI) but not to AMPA/kainate receptor blockade by DNQX. (b) Group results of gamma and HFO power changes associated with pharmacological blockade of GABA-A or/and glutamate receptors in vitro.
Adapted, with permission, from Jackson et al. (2011).

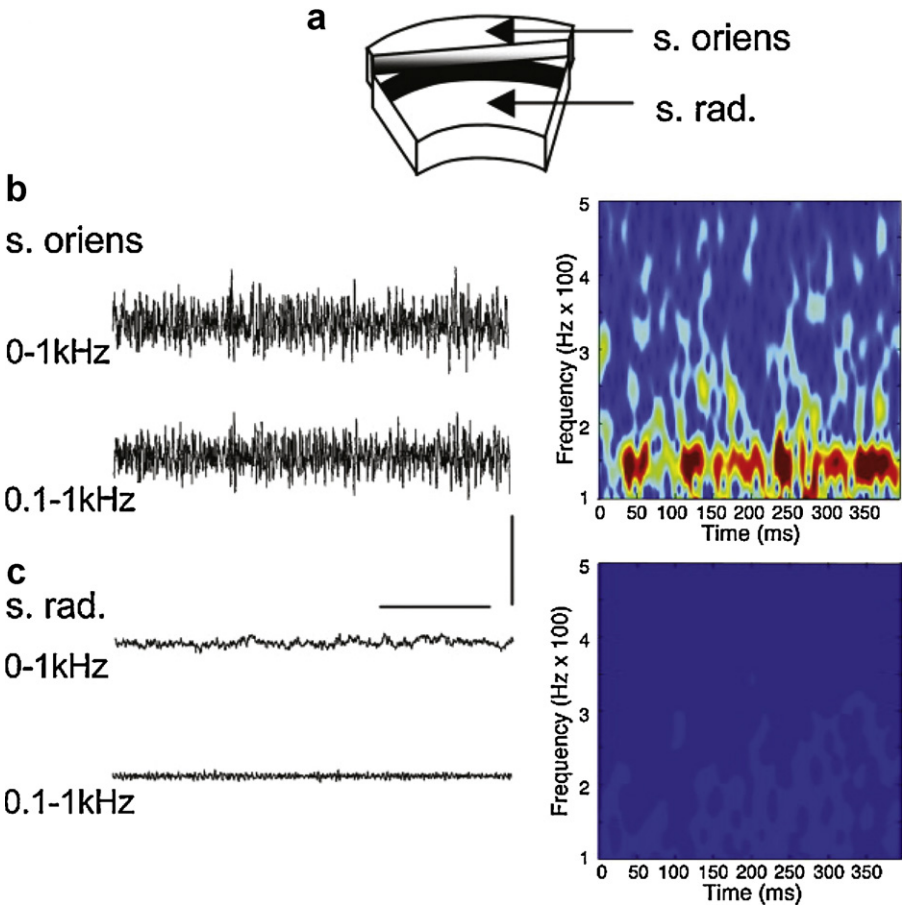

Fig. 12. In vitro evidence for the generation of HFOs in *stratum oriens-alveus*. (a) Schema representing a slice preparation in which the *stratum oriens-alveus* was surgically isolated from *stratum pyramidale* and *stratum radiatum*. (b) Left: recordings of the isolated *stratum oriens-alveus* in the presence of kainate exhibit persistent high-frequency oscillations. Right: spectrogram of the high-pass filtered signal revealing a peak ~150 Hz. (c) In this same preparation, no oscillatory activity was observed in *stratum radiatum* (scale bars: 100 ms/0.2 mV).
Reproduced with permission from Traub et al. (2003).

et al., 2002, 2003). In this case, coupling of fast oscillations to theta phase may result from theta-rhythmic inhibition of ectopic spikes. Likewise, if HFOs are the field effect of synchronous IPSPs from fast-spiking interneurons such as axo-axonic cells (Howard et al., 2005; Klausberger et al., 2003; see also Zhang et al., 2012), theta-rhythmic inhibition of these cells would also lead to theta-HFO coupling in the field potential (Fig. 13a). This latter model would also account for fast oscillations of different frequencies occurring at different theta phases: when theta-paced inhibition starts to wear off, the fast-spiking interneurons would start spiking at a lower frequency at first, and then at a higher spiking rate when the inhibition has completely worn off; therefore, this CFC model predicts that the lower frequency oscillation should precede the faster oscillation.

An alternative possibility is that PAC is caused by shunting inhibition. In this case, both the faster and slower field oscillations would arise from rhythmic trains of IPSPs at the respective frequencies. The inhibition associated with the slower rhythm would be much stronger and bring the postsynaptic membrane potential to the inhibitory reversal potential. Therefore, the faster IPSPs would have reduced amplitude during the periods of shunting inhibition, leading to an observable PAC in the LFP (Fig. 13b).

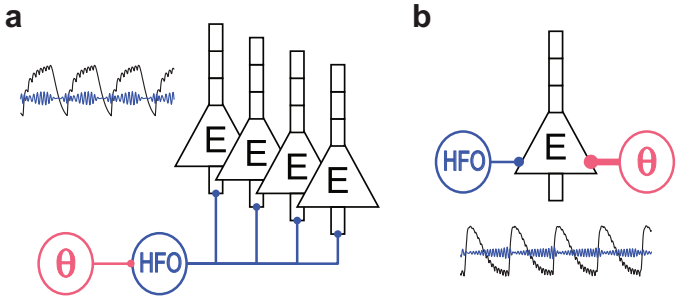

Fig. 13. Possible network mechanisms giving rise to theta-HFO coupling. (a and b) Theta-HFO coupling could result from theta-paced inhibition of cells that generate HFO (a), or from shunting inhibition in which theta-paced inhibition of principal cells is much stronger than HFO inhibition (b).

12. Conclusions and future directions

Theta-associated HFOs have been observed in different labs over the last 5 years. Above we summarized the current evidence pointing to their existence as an independent type of fast cortical activity, distinct from previously characterized rhythms such as gamma and ripple oscillations. Despite recent progress, however, several open questions remain to be addressed. Below we suggest some future directions that would help elucidating their mechanisms of generation and potential functions.

Firstly, the anatomical locations where the HFOs are generated remain to be fully established. To that end, studies using densely spaced multielectrodes will be needed for performing fine-grained current source density analysis that allow the mapping of the exact cortical regions that produce theta-associated HFOs. Multisite recordings will also allow the investigation of interregional HFO

coherence, which should further help to dissociate their origin; in particular, coherence between CA1 HFOs with CA3 and mEC has not yet been investigated. Further work is required to investigate whether the high-frequency oscillations observed in vitro in *stratum oriens* (Traub et al., 2003) correspond to the theta-associated HFOs observed in vivo in the same hippocampal layer (Scheffer-Teixeira et al., 2012). In particular, the possible role of electrical coupling in generating HFOs can be investigated by pharmacological blockade of gap junctions and/or by verifying whether animals knockout for gap junction proteins have altered HFOs. Similar strategies will also be valuable to disentangle other potential cellular and network mechanisms, and to further understand the role of excitation and inhibition in contributing to field HFOs. The advent of optogenetics (Boyden et al., 2005) along with the recent generation of PV-cre and SOM-cre mouse lines (Taniguchi et al., 2011) should allow studying the role of different interneuron populations in contributing to theta, HFOs and their phase-amplitude coupling. The proposal of a distinction between wide band high-frequency oscillations putatively attributed to spiking activity (SLHFO) and the more circumscribed nature of theta-associated HFOs would benefit from a thorough investigation by independent labs. Finally, much work has yet to be done to understand the implications of the increase in theta-HFO coupling during REM sleep and to investigate other possible functional roles for this rhythm. This could be accomplished by behavioral studies in combination with strategies to disrupt HFOs and/or their coupling to theta, although the latter should only be available after a better understanding of the mechanisms underlying HFO generation. In all, we hope this review helps including theta-associated HFOs in the research agenda of other groups worldwide.

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