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The dark side of high-frequency oscillations in the developing brain

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Adult brain networks generate a wide range of oscillations. Some of these are behaviourally relevant, whereas others occur during seizures and other pathological conditions. This raises the question of how physiological oscillations differ from pathogenic ones. In this review, this issue is discussed from a developmental standpoint. Indeed, both epileptic and physiological high-frequency oscillations (HFOs) appear progressively during maturation, and it is therefore possible to determine how this program corresponds to maturation of the neuronal populations that generate these oscillations. We review here important differences in the development of neuronal populations that might contribute to their different oscillatory properties. In particular, at an early stage, the density of glutamatergic synapses is too low for physiological HFOs but an additional drive can be provided by excitatory GABA, triggering epileptic HFOs and the cascades involved in long-lasting epileptogenic transformations. This review is part of the INMED/TINS special issue *Nature and nurture in brain development and neurological disorders*, based on presentations at the annual INMED/TINS symposium (<http://inmednet.com/>).

Adult networks oscillations: for better and for worse

In the adult brain, high-frequency oscillations (HFOs; > 40 Hz) can be divided in two categories [1]. First, HFOs have a central role in various normal functions [2], including sensory binding [3], temporal regulation of neuronal activity during synaptic plasticity [4,5], memory processing [6] and large-scale integration [7–9]. Second, HFOs are also the hallmark of focal epilepsy: they are highly localized in the seizure onset zone and are thought to have a causal role in the initiation of seizures [10–16] or in epileptogenesis [17].

What are the differences between physiological and epileptic HFOs? Several have been proposed. The first possible difference is related to frequency. As reported in human studies of seizure onset patterns (Box 1), epileptic HFOs are mostly included in the high gamma-frequency band (60–120 Hz). Another class of HFOs are the fast ripples; these are recorded in limited areas of epileptogenic limbic structures and are of 250–500 Hz [10]. These

frequencies are actually higher than those classically associated with cognitive gamma oscillations (30–70 Hz) [3] or ripple activity (140–200 Hz) [18]. Nevertheless, cognitive HFOs have also been reported in humans with spectral frequencies up to 200 Hz in the visual cortex [19] and even up to 600 Hz in somatosensory cortex [20], suggesting that it is difficult to determine cut-off frequencies between physiological and pathological patterns in adults.

The second possible difference between the two categories of HFO is that epileptic HFOs are often encountered in cerebral structures that do not normally generate this type of activity. For example, pathological ripples recorded on the dentate gyrus of epileptic rats were not found in normal animals [11]. It has been speculated that these patterns are generated by seizure-triggered synaptic reorganization within affected neural networks, liberating local circuits from the inhibitory control [10,11,21]. However, it is still unknown which network alterations are necessary or sufficient for the occurrence of epileptic HFOs.

The third potential difference between epileptogenic and non-epileptogenic HFOs relates to cellular mechanisms underlying their induction and expression. As known from *in vitro* hippocampal models of these rhythms [22–24], physiological HFOs in the gamma range are controlled by recurrent feedback loops between GABAergic interneurons and pyramidal cells [25,26]. In addition, normal hippocampal ripples are hypothesized to be the summed inhibitory postsynaptic potentials of pyramidal cells receiving sustained rhythmic input from GABAergic interneurons [27]. *In vivo* studies confirmed that certain interneurons fire phase-synchronized fast series of action potentials during ripples [28]. The mechanisms underlying their epileptic counterparts remain controversial. *In vitro* reports suggest that recurrent excitatory synaptic transmission [29] and pyramidal axo-axonic gap junctions [13,30] might be important for very fast HFOs (>100 Hz) observed at seizure onset. Indeed, epileptic HFOs in the very high frequency range can be generated in adult hippocampal slices even in the absence of GABA_A receptors [11,31,32]. However, other *in vitro* evidences suggested that GABAergic interneurons might be involved in the patterning of both neocortical pathological ripples [33] and epileptic HFOs in the gamma range [12,34,35]. Even without

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Box 1. Clinical relevance of high-frequency oscillations in adults

Using intracranial electroencephalographic (iEEG) recording, it was shown that partial seizures in patients with temporal and extra-temporal epilepsy can begin with low-amplitude high-frequency oscillations (HFOs) and that the HFOs associated with epileptic seizures can localize to the epileptogenic zone. The reported frequencies on iEEG recordings varied but most were within the high gamma-frequency band: 20–80 Hz [82], 40–120 Hz [83], 60–100 Hz [84], 70–90 Hz [13], 80–110 Hz [85] and 60–150 Hz [86] (Figure 1a,b). Furthermore, it has been shown that surgical removal of the onset zone from which HFOs were localized in iEEG resulted in good seizure control for localization-related epilepsy patients [82,86]. Additionally, HFOs recorded from iEEG [84] or

microelectrodes (oscillations 250–500 Hz, termed ‘fast ripples’) [87] were also intermittently present in epileptic foci throughout the interictal (between-seizure) period (Figure 1c,d). Surprisingly, a significant increase in interictal HFOs was reported several minutes before onset of an epileptic seizure [84], suggesting that HFOs within the seizure onset zone are useful for identifying periods of increased predisposition to clinical seizures [86]. The presence of a reliable seizure precursors would open a therapeutic window, possibly enabling interruption of ictogenesis and prevention of seizures [88]. Better localization of the seizure onset zone by mapping HFOs in focal epilepsy might lead to better techniques for surgically disrupting the epileptic network in these patients.

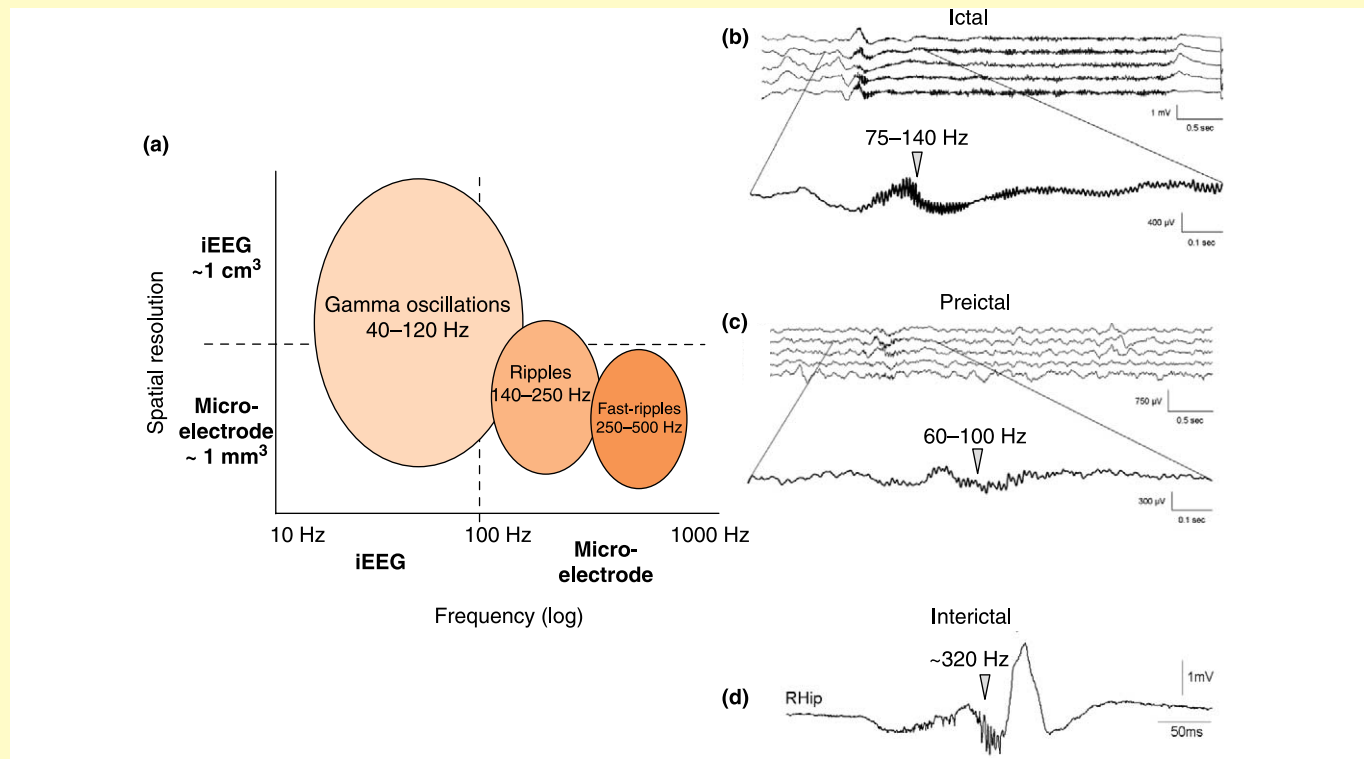


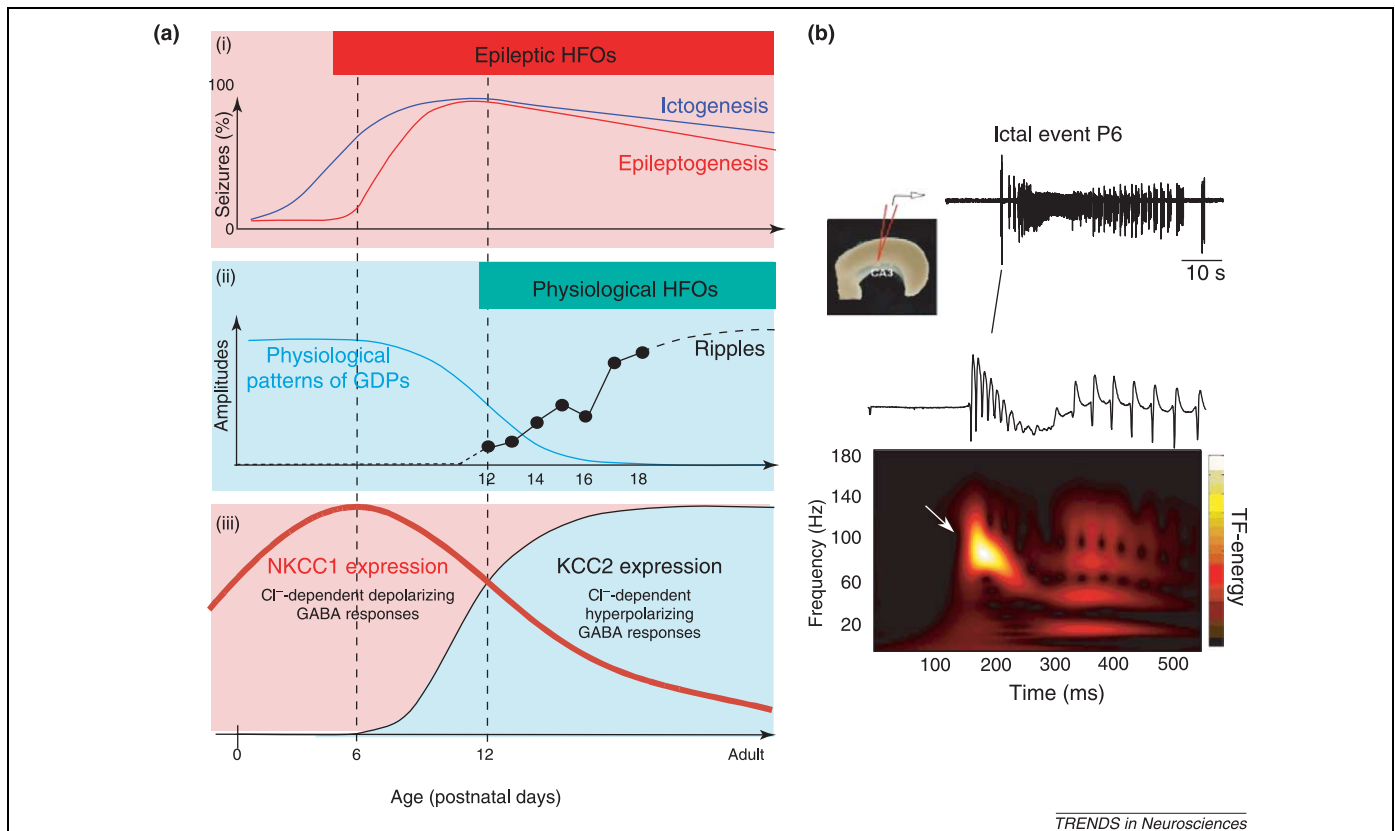
Figure 1. Most clinical invasive research carried out in epilepsy surgery centres makes use of iEEG recording using stereotactically implanted depth electrodes or subdural strip electrodes. (a) A sampling rate of 400 Hz or more can provide good descriptions of oscillatory signals at frequencies up to 150 Hz. (b,c) Examples of HFOs recorded using subdural electrodes in the left fronto-temporal cortices of an adolescent patient with epileptic spasms. It is also possible to attach microwires to standard depth electrodes for recording of field potentials. Using these micro-electrodes, HFOs from 250–500 Hz, called fast ripples, have been described in seizure-generating limbic areas, notably the right hippocampus (RHip) (d). Panels (b,c) adapted from Ref. [86]; (d) adapted from Ref. [89] © (2004) American Neurological Society.

excitatory synaptic transmission, the GABAergic network can be recruited into an epileptic rhythmic activity [36]. Clearly, the exact roles of glutamate-mediated and GABA-mediated transmission remain to be clarified, and it is difficult to claim conclusive differences between physiological and pathological oscillations in adults.

In this review, we discuss new arguments for possible differences between physiological and pathological HFOs, based on recent developmental studies in the rat limbic system. Addressing these issues in the context of brain development is particularly relevant because the developing brain – immediately postnatal in rodents – is more susceptible to seizures than the adult one and, in addition, immature brains already contain a dense functional network GABAergic interneurons [37,38], which are known to be central for the control of HFOs in the adult brain [39,40].

Glutamatergic synapses and physiological HFOs take their time to mature

Several observations suggest that spontaneous HFOs are not present in developing networks. In humans, electroencephalographic (EEG) investigation of infant brain function demonstrated that the first cognitive HFOs can be detected after eight months of age, consistent with the development of higher information processing [41]. In rat pups, physiological ripple oscillations >140 Hz are observed *in vivo* in the hippocampus after the end of the second postnatal week [42] (Figure 1a). In keeping with this, *in vitro* various HFO-generating procedures or agents – such as bath application of the ACh receptor agonist carbachol to the intact cerebral cortex of newborn rats (postnatal days P0–P7 [43]), or high-frequency stimulation of CA1 afferents in rat hippocampal slices



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Figure 1. Developmental switches and postnatal development of physiological and epileptic HFOs. **(a)** (i) Age dependence of ictogenesis (the generation of seizures) and epileptogenesis (the permanent transformation by seizures of a naïve network into an epileptic one) in rat hippocampus [46]. Epileptogenesis can be observed only from P6 onwards, suggesting that sufficient maturation of GABAergic and glutamatergic synapses is required to trigger long-term epileptic alterations. (ii) Energy of hippocampal physiological HFOs (ripples, 140–200 Hz) expressed *in vivo* in rat pups from P12–P20 [42]. Note that the HFOs do not begin until the second week of life and that the developmental time course of these HFOs parallels the switch of GABA from excitation to inhibition at P13–P15. This developmental switch also coincides with the end of the physiological pattern of the giant depolarizing potentials (GDPs) [46]. (iii) In neonatal animals, neurons accumulate Cl⁻ through the Na⁺-K⁺-2Cl⁻ cotransporter NKCC1, resulting in a depolarized E_{Cl} and the excitatory action of GABA. Later in development, increased expression of the neuron-specific K⁺-Cl⁻ cotransporter KCC2 results in Cl⁻ extrusion and a negative shift in the Cl⁻ equilibrium across the cell membrane, leading to the inhibitory action of GABA [46,80]. **(b)** A spontaneous ictal-like event recorded extracellularly in the CA3 area of a P6 rat intact immature hippocampus (that had been rendered chronically epileptic after several applications of kainate) started with HFOs in the gamma range (60–100 Hz), as shown by a time–frequency (TF) representation that illustrates the dominant frequency during an ictal episode [31].

[44] – fail to generate normal gamma HFOs during the first postnatal week. Because physiological HFOs are driven largely by glutamate [25,26], these observations are consistent with the delayed maturation of glutama-

tergic synapses in a wide range of brain structures [37,38] (Box 2). As suggested previously [4] (Box 2), developing networks lack the critical density of functional glutamatergic synapses required for these oscillatory activities.

Box 2. Basic rules for the development of GABA-mediated and glutamate-mediated signalling

Development of cortical communication follows basic rules that have been uncovered in studies centred on *in utero* and postnatal recordings in hippocampal slices [45,71]:

(i) GABAergic synapses are formed before glutamatergic ones [90] in rodent and macaque hippocampal neurons *in utero* [91]. Although glutamatergic axons are present in the dendritic regions, synapses will not be formed until the pyramidal neurons have an extended apical dendrite. The first synapses are GABAergic and are targeted to the apical dendrites of pyramidal neurons.

(ii) GABAergic interneurons mature before pyramidal neurons and follow the same developmental sequence, with GABAergic synapses being established before glutamatergic ones upon interneurons [92]. Therefore, synapses between interneurons are formed at an early stage and interneuron networks are operative at a time when most pyramidal neurons are quiescent.

(iii) In all developing brain structures and animal species studied, the intracellular concentration of Cl⁻ progressively falls, leading to a shift of the actions of GABA from excitation to inhibition [92]. GABA in fact provides most of the excitatory drive at an early stage of brain development, a property that appears to have been kept throughout evolution.

(iv) Early in development, networks have a primitive network pattern of giant depolarizing potentials (GDPs) that is present in all developing brain structures and animal species studied [45]. This pattern disappears at the same time as the shift of GABA activity [46].

This programmed sequence ensures that GABA will provide the small excitatory drive needed for a level of Ca²⁺ influx that regulates growth and synapse formation but does not put the developing network at risk of excitotoxic damage, as could result from early uncontrolled glutamatergic excitation. Then, when the density of glutamatergic synapses is high, there is an abrupt shift of GABA activity, thanks to increased expression of KCC2, an efficient Cl⁻ transporter [66] that extrudes Cl⁻ rapidly and so reduces the intracellular concentration of Cl⁻. GDPs have little informative content (they are present in the retina at a time when the visual system is not operative) but they enable neurons, including very immature ones that have few synapses, to fire together. These potentials disappear when the networks are capable of generating more sophisticated and behaviourally relevant patterns. For example, macaque GDPs disappear a few weeks before birth [91].

Another key player in the expression of physiological HFOs is the establishment of GABA-mediated inhibition that is developmentally regulated by Cl^- transporters (Figure 1a): expression of the Cl^- -accumulating Na^+ - K^+ - 2Cl^- cotransporter (NKCC1) in cortical neurons is highest during the first postnatal week, and then decreases from P14 to the low levels found in adults. Expression of Cl^- extruders (e.g. KCC2) is minimal at birth, low during the first postnatal week and comparable with adult at P14–P15. Developmental upregulation of KCC2 expression is considered to promote the switch of GABA activity from excitatory to inhibitory [45]. Therefore, the developmental time course of these HFOs parallels the switch in the GABA_A receptor signaling from excitation to inhibition at P13–P15 [46], reflecting the crucial role of hyperpolarizing GABA (Figure 1a). Taken together, physiological HFOs are expressed only when inhibitory activity of GABA is combined with a sufficiently high density of operative glutamate synapses.

Excitatory GABAergic synapses are crucial in the early generation of pathogenic HFOs

Because GABAergic synapses are formed before glutamatergic ones in the hippocampus, GABA provides most of the excitatory drive in the first postnatal week [45] and is considered to contribute to epileptic hyperexcitability [46]. In the developing rat hippocampus, ictal activities can be generated during the early postnatal period from P2 [47] and chronic epileptogenic effects can be induced from P6 with a peak around P10–P12 [46,48] (Figure 1a). As early as P3, HFOs in the gamma range (40–120Hz, with an average peak ~80Hz) are superimposed on epileptiform bursts preceding transition to ictal activity in different regions of the hippocampus [31] (Figure 1b). This observation was originally made using repeated applications of kainate to an intact immature hippocampus [49,50], a preparation that is more relevant than hippocampal slices for studying network-driven activities during early development, because severing synaptic connections can have more drastic consequences at stages when the density of GABAergic synapses is already low [51]. Indeed, in hippocampal slices under epileptogenic conditions, ictal HFOs could not be elicited at all until the second postnatal week [12,52]. Very high frequency oscillations >140 Hz (in the ripples range 140–200 Hz or in the 'fast ripples' range 200–500 Hz) were not detected during the first postnatal week, suggesting that their maturation might be completed until that age [42]. Nevertheless, the immature hippocampus has already reached a sufficient level of organization to generate HFOs in the gamma-frequency range under epileptic but not control conditions.

What could be the underlying mechanism of these early epileptic HFOs? In the immature hippocampal formation, several arguments suggest that the excitatory action of GABA is instrumental in the generation of these oscillations. Patch-clamp recordings from identified interneurons, in conjunction with extracellular recordings, show that interneurons fired high-frequency bursts (~80 Hz) at seizure onset at the same frequency as field HFOs [31]. Furthermore, seizures generated by GABA

receptor antagonists in immature networks do not include HFOs; once GABA receptors are blocked, the network can generate recurrent activity at 10–20 Hz but not at higher frequencies [31]. Finally, in the presence of glutamate receptor antagonists [6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) and 2-amino-5-phosphonovalerate (APV)], electrical stimulations can induce in cells high-frequency bursts of action potentials in the gamma range that are totally blocked by GABA receptor antagonists [50]. These observations strongly suggest that HFOs result mainly from the synchronized firing of interneuron networks driven by excitatory GABA. Comparison with control tissues demonstrated that the excitatory actions of GABA are also increased after seizures [53] (Figure 2a), probably owing to downregulation of the KCC2 cotransporters [54].

Despite a central role of GABAergic synapses and interneuron networks, a certain degree of maturation of the glutamatergic circuitry is nevertheless also a prerequisite for HFOs to exert their epileptogenic actions fully (see next section). The first ictal HFOs can be detected as early as P3 but, before P6, they have a mean frequency of only 40–60Hz and do not lead to permanent epileptic alterations in naïve networks [31]. At this early stage, their excitatory drive is provided largely by GABAergic depolarization, and possibly promoted by electrical gap junctions between different interneuron populations – these have been reported in juvenile rodents, although not in neonatal ones [55] (Figure 2b). These observations are consistent with a developmental gradient of maturation of various interneurons types known to be instrumental for the generation of HFOs in adults [39,40]. The basket interneurons that are required for the generation of HFOs appear several days after birth [37]. In particular, fast-spiking parvalbumin-containing interneurons (a subpopulation of basket cells [56]) are detected in rat neocortex or hippocampus after P6 [57]. Furthermore, gap junctions are prevalent during the first postnatal days and their density drops dramatically within the ten days following birth [58]. Nevertheless, before P6 the network of interneurons is sufficiently mature to generate oscillations in the low gamma range, although the density of glutamatergic synapses is not sufficient for higher-frequency events (>60 Hz) [31] and epileptogenesis [50]. After P6, the maturation of GABAergic and glutamatergic synapses and particularly NMDA receptors reach a sufficient level of organization to drive pathogenic HFOs >60 Hz (Figure 2b). By contrast, more mature tissues that have a higher density of glutamatergic synapses can generate HFOs and the additional contribution of GABAergic synapses is not required for seizures to exert their pathogenic actions. Recurrent excitatory synaptic transmission [29] and pyramidal axo-axonic gap junctions [30] might thus be important for the very fast HFOs observed at seizure onset in the adult brain (Figure 2b).

Therefore, the maturation of physiogenic and pathogenic HFOs show important differences. In the normal developing brain, the excitatory drive supplied by glutamatergic synapses is not sufficient to generate physiological HFOs. Nevertheless, HFOs can be driven by GABA-mediated depolarization of interneuron networks, in

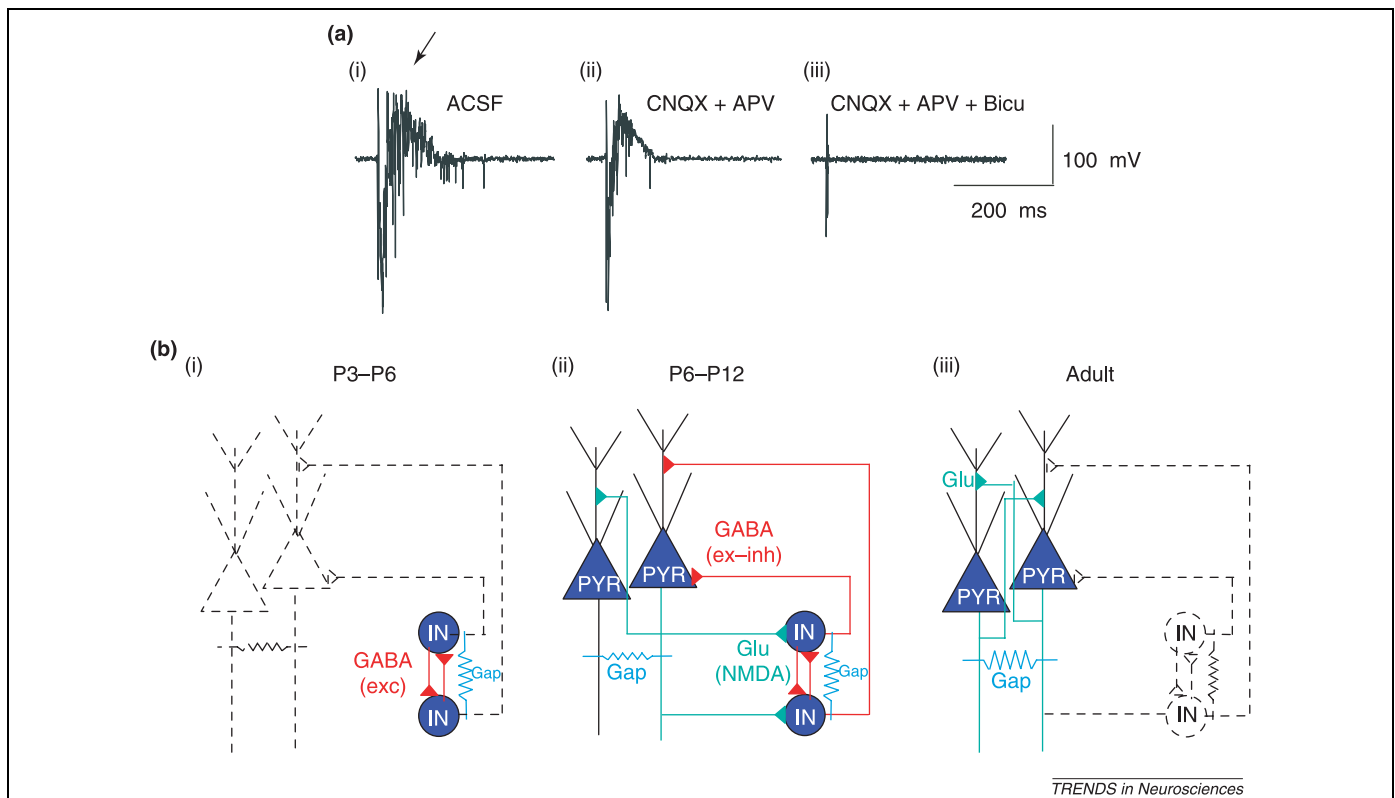


Figure 2. Excitatory action of GABA and the generation of epileptic HFOs. **(a)** In tissue from a focus of secondary epileptic activity in P7 rat brain, electrical stimulation can induce high-frequency bursts of action potentials in the gamma-frequency range in neurons (i, arrow; ACSF, artificial cerebrospinal fluid). A significant component of this burst persists during application of APV and CNQX (ii) but is totally blocked by bicuculline (iii, Bicu), confirming that it is generated mainly by the excitatory action of GABA [50]. **(b)** At P3–P6 (i), ictal HFOs are driven purely by interneuron populations interacting through excitatory actions of GABA (exc) and possibly electrical gap junctions. This network is sufficiently mature to generate oscillations in the low gamma range (40–60 Hz), but the density of glutamatergic synapses is not sufficient for high-frequency events and epileptogenesis. At P6–P12 (ii), the maturation of synapses using glutamate (Glu) has reached a sufficient level of organization to generate epileptogenic HFOs in the high gamma range (60–120 Hz) that can transform a naïve network into an epileptic one. At this age, GABA activity is shifting from being excitatory to being inhibitory (ex-inh). In more mature tissues (iii), purely glutamatergic pyramidal networks, through recurrent excitatory synaptic transmission and pyramidal axo-axonic gap junctions, are able to generate HFOs in the very high frequency range (> 140 Hz).

epileptic conditions but not in physiological ones at an earlier stage. These will trigger the cascades involved in epileptogenesis in the developing hippocampus.

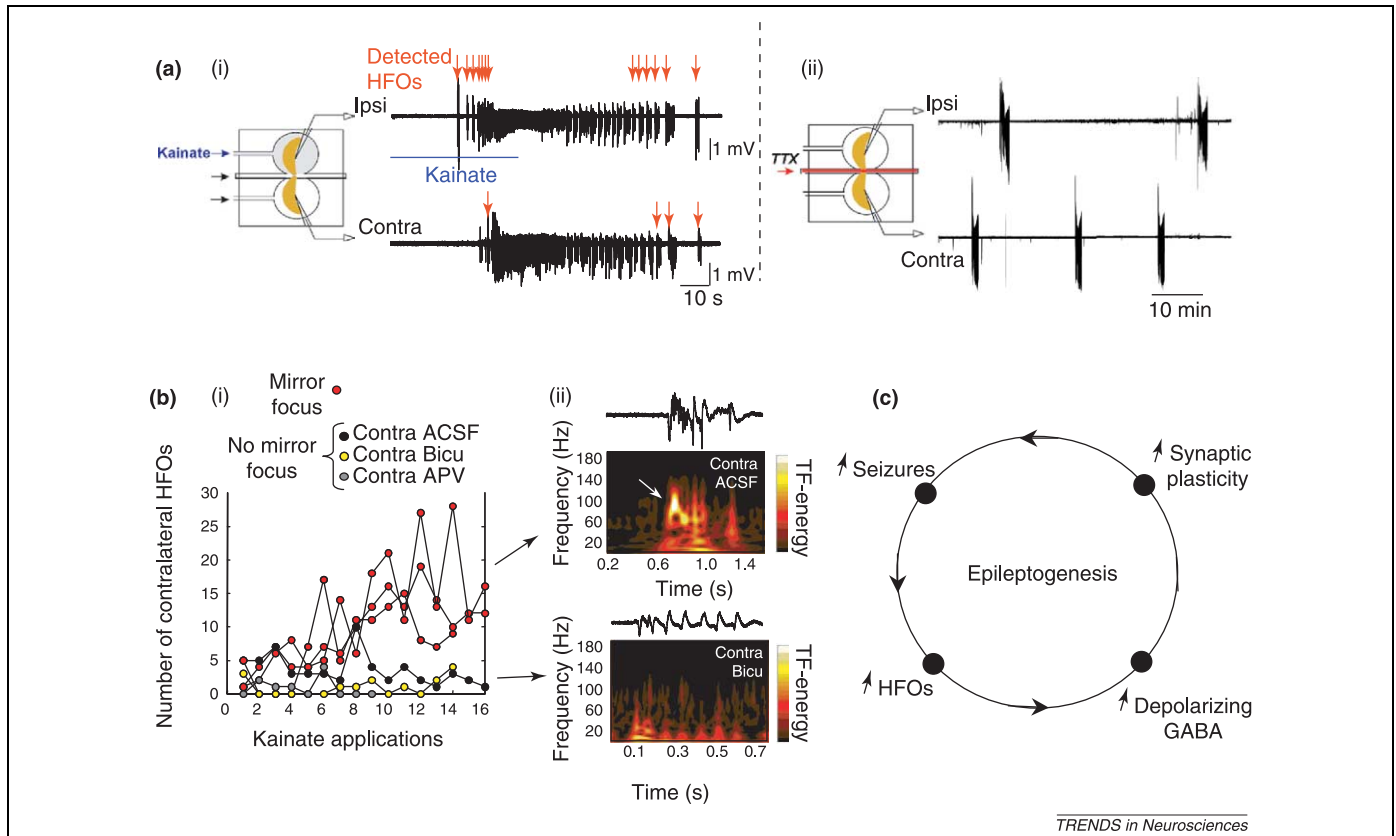
HFOs are required for seizures to beget seizures in the immature brain

Another unique feature of HFOs recorded during the first postnatal week is their involvement in epileptogenesis. It has been known for a long time that some seizures can permanently transform a naïve network to an epileptic one [59,60], but the pathophysiological mechanism leading to these alterations *per se* is not clear. Several factors including neuronal loss, alterations in membrane transporters and synaptic reorganization have been implicated in the induction of epileptogenesis [61]. Seizures also generate an NMDA-receptor-dependent long-lasting increase of glutamatergic synaptic currents – an epileptic form of LTP [62] – that will facilitate the generation of further seizures. Furthermore, repeated brief high-frequency electrical stimulations (kindling) lead to the gradual development of a permanent epileptic condition [63,64]. Nevertheless, *in vivo* study of these changes is problematic owing to difficulties in studying serially how repeated seizures affect a distant naïve neuronal network. For the developing hippocampus, use of the newly developed triple chamber provides an unique possibility

to record from both hemispheres and determine the effects of various agents on the generation and propagation of activities from one hemisphere to the other [50] (Figure 3a). Use of this preparation recently provided direct evidence that the repeated propagation of ictal HFOs of 60–120 Hz was crucial for development of a secondary mirror focus [31]. In the cases where a mirror focus was generated, the number of HFOs gradually increased in the contralateral hippocampus with each ipsilateral kainate exposure (Figure 3b). In cases where a mirror focus failed to form, HFOs were either fully or largely absent, confirming the involvement of HFOs in the formation of a mirror focus.

GABA_A receptors are required for neonatal epileptogenesis

What could be the underlying mechanism of these long-lasting effects mediated by HFOs? Several lines of evidence indicate that, in the developing hippocampus, seizures beget seizures only if GABAergic synapses are functional [31]. For example, applications of the GABA_A receptor antagonist bicuculline to the contralateral side block the HFOs (only low-frequency bursts <20 Hz were recorded during ictal events) and also block the formation by seizures of an epileptogenic mirror focus (Figure 3b). Furthermore, seizures induced by application of



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Figure 3. Causal relationship between GABA, HFOs and formation of a mirror focus. (a) In a triple-chamber preparation that involves two intact hippocampi and their commissural connections, seizures generated by kainate application to one hippocampus propagate to the contralateral hippocampus (i). This transforms it into a chronic epileptic focus capable of generating seizures when disconnected by TTX from the kainate-treated side (ii). (b) In cases where a mirror focus was generated, the number of HFOs gradually increased in the contralateral hippocampus with repeated kainate applications (i). In experiments when a mirror focus failed to form, the number of HFOs remained low [31]. We then applied various agents to the contralateral hippocampus while applying kainate repeatedly to the stimulated hippocampus. Applications of APV or bicuculline (Bicu) to block respectively the NMDA and GABA receptors (only in the naïve hemisphere) prevented the increase of HFOs and the formation of a mirror focus. The presence or absence of HFOs in the contralateral compartment can be seen in the field potentials and in their corresponding time-frequency representations (ii). (c) Epileptogenesis in the immature brain involves a vicious feedback loop in which seizures generate HFOs that increase the excitatory activity of GABAergic synapses; this in turn promotes activity-induced neuronal plasticity, thus setting up a network prone to more seizures.

bicuculline generate HFOs and an epileptogenic focus in the naïve contralateral hippocampus, where GABAergic synapses are functional, but not locally, where they are not. Thus, purely glutamatergic seizures can occur recurrently without leading to long-lasting consequences because they do not include HFOs. These observations lead to the conclusion that activation of GABA_A receptors is required for the generation of HFOs and for secondary epileptogenesis in the immature hippocampus. Interestingly, a mirror focus cannot be generated before P6, suggesting that sufficient maturation of hippocampal networks, in particular those able to generate HFOs > 60 Hz, is required (see previous section). Other observations also suggest that seizures do not lead to long-lasting consequences before P6 [65].

Epileptic HFOs increase the excitatory action of GABAergic synapses

The main factor that controls HFOs at early developmental stages is the excitatory drive provided by depolarizing responses of GABAergic interneurons. One likely candidate to mediate these changes is the 'ionic plasticity' [66] – that is, short-term and long-term shifts in the concentration of Cl⁻ in postsynaptic neurons. Short-term ionic plasticity is caused by activity-dependent ionic

shifts, whereas long-term plasticity depends on changes in the expression of proteins such as the Cl⁻-extruding K⁺-Cl⁻ cotransporter KCC2 and cytosolic carbonic anhydrase isoform VII [66]. Therefore, recurrent HFOs under epileptogenic conditions might trigger a cascade of deleterious intracellular events, including trophic factors and second messenger cascades that directly downregulate the expression of KCC2 and finally permanently increase the excitatory action of GABAergic synapses [67]. In keeping with this, the HFOs in seizures produce a stable accumulation of Cl⁻ and a long-term transformation of the actions of GABA from inhibitory to excitatory in most of the recorded neurons [50]. This confirms that HFOs might be particularly powerful in triggering short-term depolarizing shifts [12,68] but also can induce a long-term alteration of the GABA system.

Epileptic HFOs induce a long-term synaptic plasticity

Generation of HFOs increases the excitatory action of GABAergic synapses that, in turn, promote activity-dependent long-term synaptic plasticity (Figure 3c). Several lines of evidences support the hypothesis that synaptic alterations are expressed at glutamatergic synapses. In keeping with this, the transformation of a naïve hippocampus into an epileptic one requires

functional NMDA receptors, and blocking NMDA receptors prevents the epileptic action of repetitive seizures [50,62]. This suggests that the epileptogenesis might be triggered by the GABA_A-NMDA synergy that is restricted to immature neurons when GABA exerts an excitatory action: the activation of GABA_A receptor signalling removes the voltage-dependent Mg²⁺ blockade of GABA receptors, thereby leading to activation of that channel and a Ca²⁺ influx that in turn participates in synaptic plasticity [69,70]. In addition, another factor that might affect the development of epileptic neuronal circuits is the long-term plasticity of early GABAergic synapses. Recent observations suggest that endogenous physiological oscillations (e.g. 'giant depolarizing potentials' [71]) or repeated high-frequency electrical stimulations of hippocampal slices can generate LTP or LTD of GABAergic synapses at early developmental stages [72]. Both are post synaptically triggered in a Ca²⁺-dependent manner and expressed by a presynaptic alteration of the release of GABA. However, in the neonatal hippocampus, LTP at GABAergic synapses is mediated by the opening of postsynaptic voltage-gated Ca²⁺ channels [73], whereas NMDA receptors are needed for LTD of GABAergic synapses [74], indicating that the GABA_A-NMDA synergy reduces rather than augments the efficacy of GABAergic synapses. This counterintuitive observation suggests that, although the persistent enhancement of excitability and induction seizures by HFOs are facilitated by GABA_A-NMDA synergy, HFOs also have a complex effect on GABA-mediated excitatory drive: a reduction of synaptic efficacy but an increase excitatory action by long-term augmentation of Cl⁻ levels [74]. Clearly more information, particularly on the role of KCC2 [75] and how it is affected by physiogenic and pathogenic HFOs, is required for full understanding of the long-term changes to GABAergic plasticity that underlie epileptogenesis.

Concluding remarks

The mechanisms that underlie pathological HFOs, and the differences between these and physiological HFOs, remain unknown in adults. One way to gain better understanding of these issues is to examine how these oscillations mature and become operative during brain development. GABAergic interneurons are central to the generation of oscillations in both adults and developing networks, but there are important differences due to the shift of GABA activity, which excites immature neurons but inhibits adult ones. As discussed in this review, it seems that pathological HFOs can be generated during the first postnatal week, in contrast to physiological HFOs, which are recorded only in more mature networks. The excitatory action of GABA is instrumental in the generation of pathological HFOs and, in synergy with NMDA receptors, can lead to the production of a persistent chronic epileptic condition.

These findings have major implications for treatment of neonatal epilepsy. Newborns are prone to frequent seizure in the first month of life [76] and these are difficult to treat [77]. Although the immature brain is more resistant to acute seizure-induced cell loss than the adult brain, both clinical [78] and experimental [79] studies have confirmed

that neonatal seizures lead to long-term impairments in brain development and functional abnormalities. If, in the developing brain, HFOs are required for seizures to beget seizures (epileptogenesis), then current anti-epileptic drugs that primarily block the process that triggers seizures (ictogenesis) might be replaced advantageously with agents that prevent epileptogenesis. A potential strategy for new anti-epileptogenic drugs is to target HFOs and the excitatory action of GABA. For example bumetanide, which is a potent NKCC1 blocker, has already shown some promise as an anti-epileptogenic drug [80]. This would represent a more refined approach than most traditional pharmacotherapy, which results in the undesirable side effects commonly seen with the use of anti-ictogenic agents in infants [77]. Furthermore HFOs provide a new electrographic clue for anticipating the deleterious consequences of seizures in neonates. Non-invasive scalp EEG with high sampling frequency [81] or surgical implantation of intracranial EEG electrodes with high spatial resolution (Box 1) can be used to record focal HFOs of seizures in neonatal epilepsies. This information might be useful as a guide to whether an aggressive anti-epileptic treatment is needed after seizures. If seizures lead to cognitive dysfunction – for instance when associated with HFOs – the risk–benefit balance rests on the side of stopping seizures. However, if the seizures are less detrimental to distal structures, it might seem more appropriate to avoid aggressive treatments, especially if the treatment involves drugs that have adverse side effects.

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