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Early NMDA receptor-driven waves of activity in the developing neocortex: physiological or pathological network oscillations?

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Several patterns of coherent activity have been described in developing cortical structures, thus providing a general framework for network maturation. A detailed timely description of network patterns at circuit and cell levels is essential for the understanding of pathogenic processes occurring during brain development. Disturbances in the expression timetable of this pattern sequence are very likely to affect network maturation. This review focuses on the maturation of coherent activity patterns in developing neocortical structures. It emphasizes the intrinsic and synaptic cellular properties that are unique to the immature neocortex and, in particular, the critical role played by extracellular glutamate in controlling network excitability and triggering synchronous network waves of activity.

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The immature brain is endowed with the ability to generate a variety of coherent activity patterns (O'Donovan *et al.* 1998; Roerig & Feller, 2000; Moody & Bosma, 2005; Khazipov & Luhmann, 2006; Ben-Ari *et al.* 2007). Several studies indicate that as development proceeds, synchronous neuronal activity displays changing dynamics and is controlled by distinct mechanisms (Syed *et al.* 2004; Khazipov & Luhmann, 2006; McCabe *et al.* 2006; Allene *et al.* 2008; Sibilla *et al.* 2009). These successive stages closely parallel the maturation of physiological and morphological cellular properties (Picken Bahrey & Moody, 2003; Moody & Bosma, 2005; Torborg & Feller, 2005; Guido, 2008; Sibilla *et al.* 2009). The neocortex is the structure for which probably the most compelling variety of network patterns have been described (Yuste *et al.* 1992; Kandler & Katz, 1998; Owens & Kriegstein, 1998; Garaschuk *et al.* 2000; Peinado, 2000; Voigt *et al.* 2001; Opitz *et al.* 2002; Corlew *et al.* 2004; Khazipov *et al.* 2004; Weissman *et al.* 2004; Adelsberger *et al.* 2005; Dupont *et al.* 2005; McCabe *et al.* 2006; Milh *et al.* 2007*b*). This variety not only reflects an endogenous developmental programme, but also the multiplicity of experimental approaches and animal models used to study network oscillations. Hence, network patterns which were named differently because they were measured in different experimental conditions (e.g. *in vivo*

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vs. in vitro, calcium imaging *vs.* electrophysiology, etc.) may actually refer to the same biological phenomenon. In an attempt to assign a function to each synchronous neuronal activity pattern it is therefore essential to review and compare their different mechanisms and conditions of observation. Cortical early network oscillations (cENOs) are large-scale oscillatory calcium waves occurring immediately after birth at low frequency and providing most of the coherent activity during the first postnatal week in the developing rodent neocortex (Garaschuk *et al.* 2000). These were described both *in vitro* and *in vivo* using imaging techniques (Garaschuk *et al.* 2000; Adelsberger *et al.* 2005) and more recently using electrophysiological approaches (Allene *et al.* 2008; Yang *et al.* 2009). Many developmental network patterns are mediated by GABAergic transmission given its early excitatory actions and advanced maturation compared to glutamatergic synapses (Ben-Ari *et al.* 2007). Remarkably, cENOs were shown to be generated by the activation of NMDA receptors (NMDA-Rs) and are critically dependent on extracellular glutamate concentration (Garaschuk *et al.* 2000; Allene *et al.* 2008; Yang *et al.* 2009). This feature imparts to the immature cerebral cortex a critical sensitivity to pathological transmitter accumulations. It also confers on glutamate a critical role in early cortical development. Furthermore, cENOs are preferentially observed under specific conditions such as mild anoxia. This observation questions the physiological relevance of cENOs. In this review, we will discuss the mechanisms, developmental profile and dynamics specific to cENOs in order to propose a relevant function for this network pattern and NMDA-R-driven oscillations in general during brain maturation.

A general sequence for the maturation of coherent activity patterns in cortical structures

Most developing peripheral and central neurons are spontaneously active. In the cortex, neuronal activity is associated with an intracellular calcium rise that can either be produced by a membrane potential depolarization measurable with electrophysiological approaches or be produced intracellularly without any electrical signature, although measurable with optical approaches (see Fig. 1). Spontaneous activity is further subdivided into uncorrelated and coherent activity patterns (see Fig. 1). Coherent electrical activity patterns progressively emerge during cortical development.

Calcium activity at embryonic stages consists of either uncorrelated membrane potential spikes (Komuro & Rakic, 1996; Crépel *et al.* 2007; Allene *et al.* 2008; Bortone & Polleux, 2009) or synchronous 'non-electrical' calcium rises (Owens & Kriegstein, 1998; Weissman *et al.* 2004; see Fig. 1). Embryonic calcium activity in cortical structures has been suggested to play a role in the regulation of neurogenesis (Owens & Kriegstein, 1998; Weissman *et al.* 2004) in neuronal differentiation and migration (Komuro & Rakic, 1996; Bortone & Polleux, 2009). Primitive forms of activity in embryonic cortical structures are mostly uncorrelated calcium rises that participate in the maturation of intrinsic neuronal properties.

Around birth in rodents, neuronal activity becomes coherent in cortical structures. Several patterns of synchronous neuronal activity have been described (see Figs 1 and 2). With the exception of cortical domains (Yuste *et al.* 1992; Kandler & Katz, 1998), all of them are associated with electrical activity (see Fig. 1). There is a robust timetable in the mechanisms responsible for the synchronization of neuronal activity: population coherence first relies on gap-junction coupling and on the activation of intrinsic voltage-dependent conductances before becoming mostly synapse-driven (see Fig. 1). We have recently established in both the neocortex (Allene *et al.* 2008) and the hippocampus (Crépel *et al.* 2007) that the earliest coherent electrical activity pattern emerges at birth in the form of synchronous plateau assemblies (SPAs), so named because of their characteristic spatial–temporal dynamics: SPAs involve small groups of neurons producing synchronous calcium plateaus. Each calcium plateau is associated with sustained intrinsic membrane potential oscillations. SPAs are therefore a step of coherent electrical activity common to hippocampal and neocortical networks that precedes the emergence of synapse-driven network oscillations (Fig. 2).

At early postnatal stages, two spontaneous synapse-driven network patterns have been extensively described in developing neocortical slices: giant depolarizing potentials (GDPs) driven by GABAergic transmission (Ben-Ari *et al.* 1989; Garaschuk *et al.* 1998; Crépel *et al.* 2007; Allene *et al.* 2008; Rheims *et al.* 2008*a*) and cortical early network oscillations (cENOs) driven by glutamatergic transmission (Garaschuk *et al.* 2000; Corlew *et al.* 2004; McCabe *et al.* 2006; Allene *et al.* 2008). Relying on the apparent similarities between these patterns, cENOs were initially thought to be the neocortical counterpart of hippocampal GDPs. However, we have recently found that NMDA-R-driven ENOs and $GABA_A$R-driven GDPs are indeed two distinct patterns in the neocortex, characterized by different spatiotemporal dynamics both in electrical and optical recordings. Whereas cENOs are low-frequency oscillations (0.01 Hz) displaying slow kinetics that gradually involve the entire network, cGDPs are recurrent oscillations (0.1 Hz) that repetitively synchronize localized neuronal assemblies. Moreover, ENOs and cGDPs are sequentially expressed in the immature neocortex since cENOs precede cGDPs. Interestingly, a recent *in vivo* study describing the maturation of coordinated electrical activity patterns in

the rat somatosensory cortex has reported two patterns of oscillatory activity, 'spindle bursts' and 'long oscillations', with dynamics very similar to cGDPs and cENOs, respectively (Yang *et al.* 2009). It is therefore very likely that the sequence established *in vitro* will also apply *in vivo* (Golshani *et al.* 2009).

What would be the main function carried by this precise sequence for the maturation of cortical networks? Given

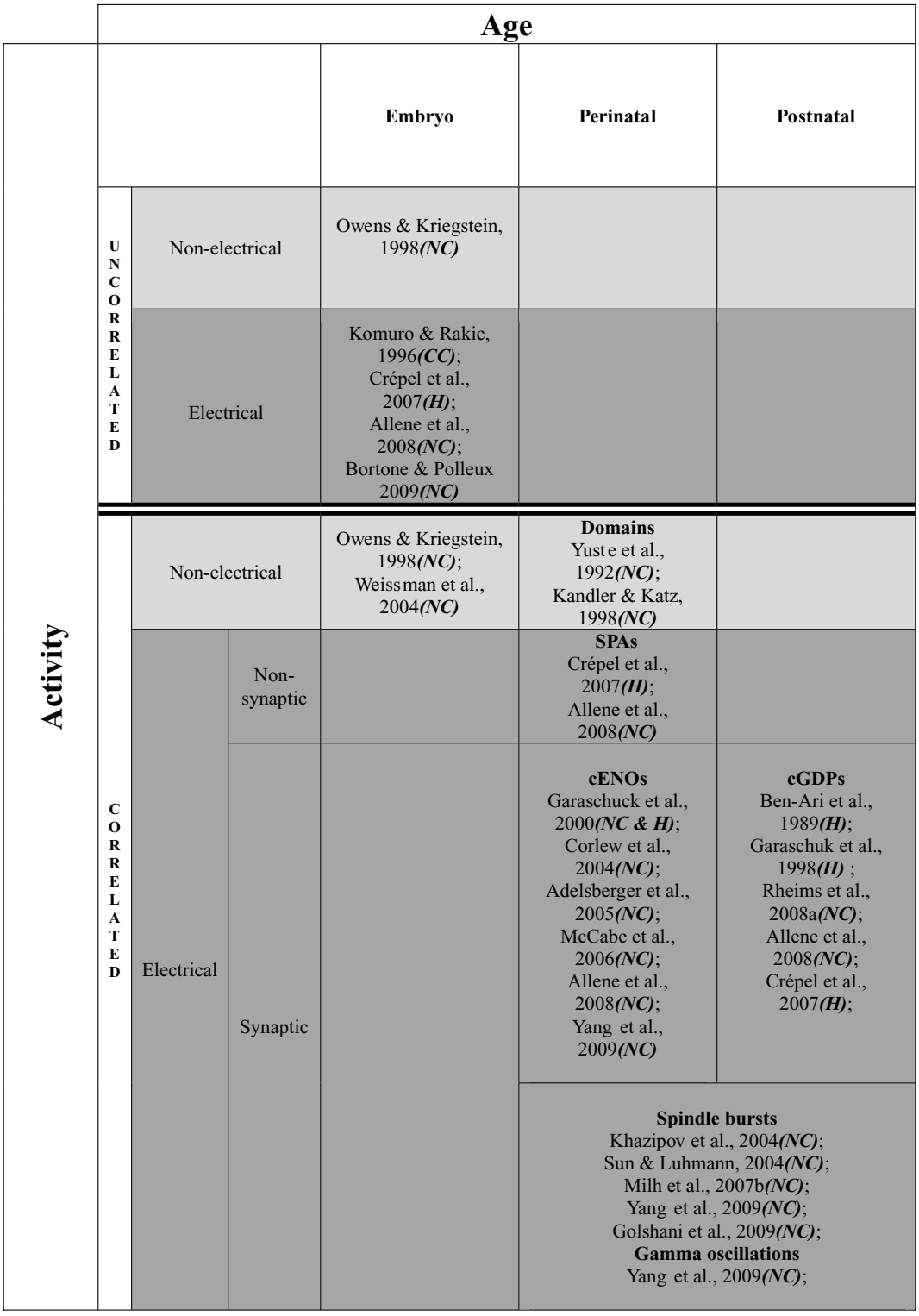


Figure 1. Spontaneous activity patterns in the developing rodent cortex
NC: neocortex; CC: cerebellar cortex; H: hippocampus.

the largely documented role of activity in the maturation of cortical neurons (Moody & Bosma, 2005; Cancedda *et al.* 2007; Lin *et al.* 2008; Wang & Kriegstein, 2008) and circuits (Katz & Shatz, 1996; Huang, 2009; Pfeffer *et al.* 2009), it is easy to speculate that the robust timetable for the maturation of network patterns is not merely the emergent expression of a precise sequence in the development of individual neuronal properties but something that also participates in proper cell maturation. In other words, activity itself would create a feedback loop that triggers the changes in neuronal and circuit properties that serve to terminate one network pattern and start the next. Experiments selectively preventing the expression of a given network pattern within a precise sequence indirectly support this hypothesis.

This sequence is particularly well-documented in the maturing retina, a structure in which spontaneous retinal waves will develop in three stereotyped sequential steps characterized by different dynamics and mechanisms (Syed *et al.* 2004). While stage I waves are mostly mediated by gap-junction coupling, stage II and III rely on nicotinic and glutamatergic receptor activation, respectively (Syed *et al.* 2004; Torborg & Feller, 2005). Waves at a given stage could be restored to the previous stage by blocking their specific neurotransmission system (McLaughlin *et al.* 2003; Syed *et al.* 2004; Stacy *et al.* 2005; Blankenship *et al.* 2009). For example, mice lacking the enzyme that synthesizes acetylcholine will exhibit stage I gap junction-dependent retinal waves at a period of development normally dominated by stage II cholinergic waves (Stacy *et al.* 2005). Similarly, at the next stage of retinal activity pattern maturation, an absence of glutamatergic signalling in VGLUT1 KO mice was shown to delay the termination of stage II waves (Blankenship *et al.* 2009). Also, $\beta 2-/-$ mice lacking the nicotinic receptor subunits mediating stage II waves will not display nicotinic-dependent correlated activity while stage III glutamatergic waves will begin earlier (McLaughlin *et al.* 2003). A precisely timed handover of synchrony between different network activity patterns also applies to the developing hippocampus (Crépel *et al.* 2007). Indeed, we have shown in this structure that the occurrence of synapse-driven GDPs actively shuts off the expression of the earlier gap-junction mediated SPA oscillations.

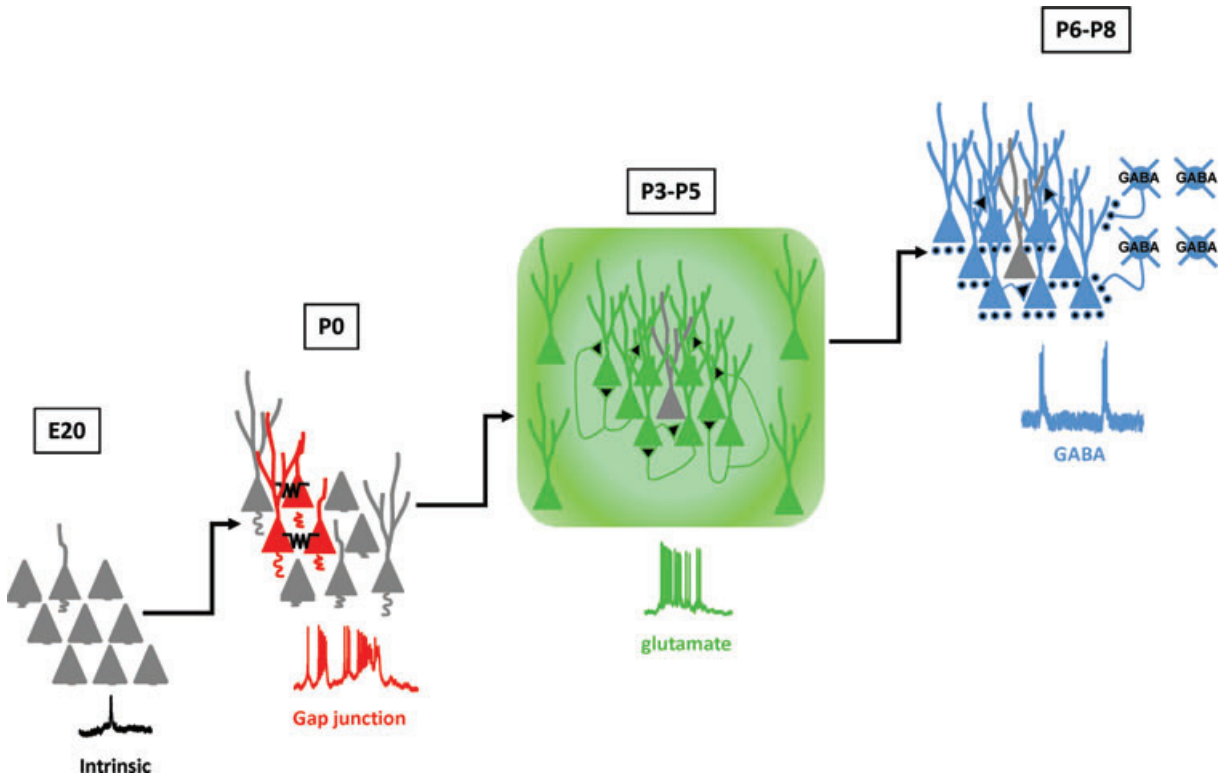


Figure 2. A general sequence for the maturation of coherent electrical activity patterns
Schematic representation of the sequential maturation of synchronized electrical activity patterns from late embryonic stages to the end of the first postnatal week in neocortical rodent slices (Allene *et al.* 2008). At embryonic stages electrical activity is uncorrelated. At birth it becomes synchronized through gap junctions and is supported by the activation of voltage-gated intrinsic conductances (SPAs). Later, network patterns are synapse-driven by glutamatergic (ENOs) or GABAergic (GDPs) transmission. Note that extrasynaptic glutamate receptors are also likely to be involved in the generation of ENOs. With the exception of ENOs, the same sequence was found in the developing hippocampus (Crépel *et al.* 2007).

Moreover these two patterns are mutually exclusive within the same network and blocking GDPs will restore SPAs during the first postnatal week (Crépel *et al.* 2007). It is possible that the activation of NMDA-Rs occurring during GDPs (Leinekugel *et al.* 1997) could produce a long-term down-regulation of connexin expression (Arumugam *et al.* 2005) that would silence SPAs. The handover of synchrony and direct interaction between SPAs, ENOs and GDPs has not yet been investigated in the neocortex. It is therefore at present difficult to claim whether a similar direct interaction between co-existing patterns also applies to the neocortex.

If such a precise timetable for synchronous neuronal activity maturation applies to the neocortex, it implies that a proper maturation of cortical structures will be highly sensitive to environmental factors. Indeed, coherent activity patterns can be largely modulated by environmental factors. For example, both in the neocortex and hippocampus, the emergence of SPAs is determined by the hormone oxytocin, which is released by the mother during delivery (Crépel *et al.* 2007; Allene *et al.* 2008). The effect of oxytocin on SPAs directly results from the action of the hormone on GABAergic transmission (Tyzio *et al.* 2006) since SPAs were shown to be favoured by an inhibitory GABA polarity, for example produced by NKCC1 blockade (Crépel *et al.* 2007). Hence, the same environmental change (i.e. oxytocin release) will create conditions that favour the emergence of SPAs but prevent GDPs. Interestingly, it is worth mentioning that probably several other environmental factors, including stress (Shen *et al.* 2007) and energy supply (Rheims *et al.* 2008*b*), will also ultimately impact network activity patterns by their direct action on the GABAergic system. In fact, we have shown that an anoxic episode occurring in a given network

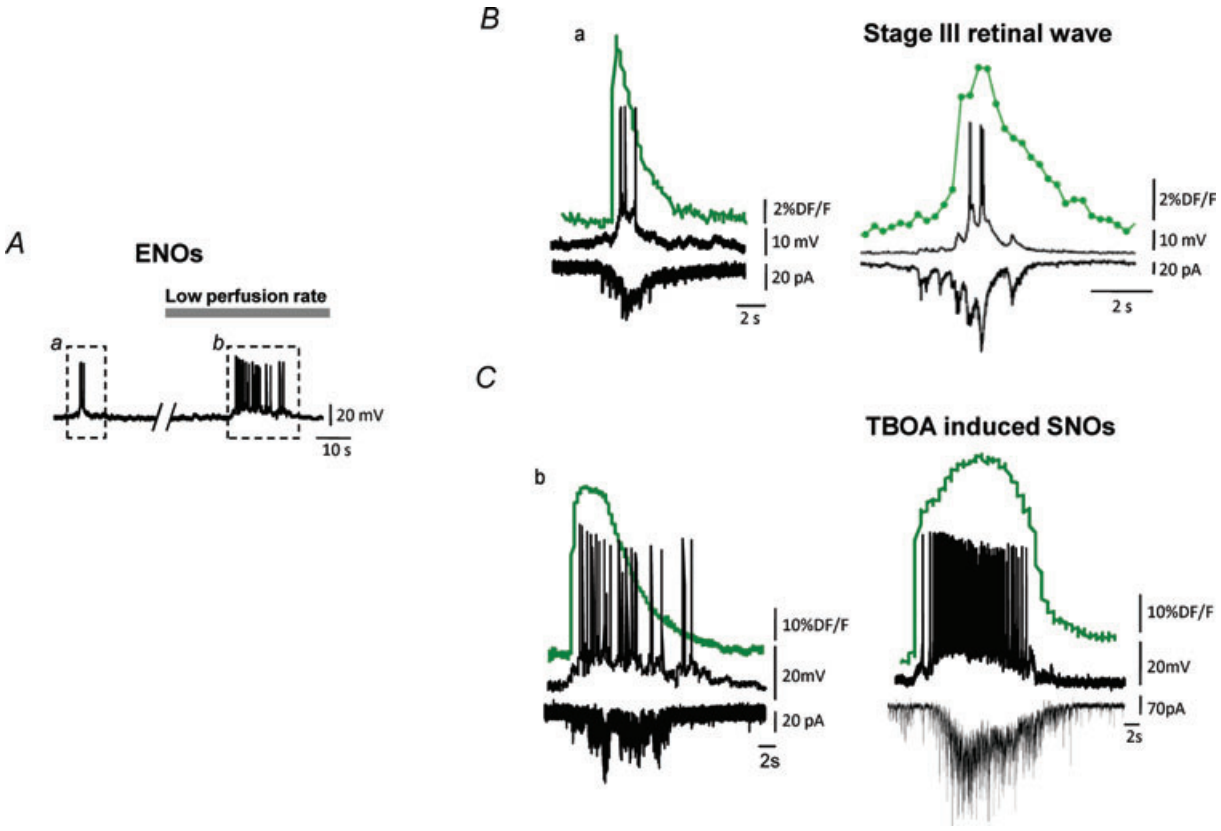


Figure 3. ENOs present striking similarities with both a physiological and a pathological network pattern

A, ENO-associated membrane potential depolarisations recorded in current clamp mode before (a) and after (b) decreasing the rate of the perfusion from 4 to 1 ml min^{-1} (data taken from Allene *et al.* 2008). Similar effects were found in anoxic/aglycaemic perfusion conditions (see Allene *et al.* 2008). *B*, comparison between the membrane potential depolarization (top black trace), the calcium fluorescence signal (green) and the spontaneous excitatory postsynaptic currents (sEPSCs, bottom black, $V_m = -60$ mV) associated with the spontaneous ENO illustrated in (*Aa*) and with a stage III retinal wave (reprinted from Blankenship *et al.* (2009) with permission from Elsevier). Note the similarity between the two patterns. *C*, same as in *B* but comparing ENOs produced by a mild anoxic condition occurring when decreasing the perfusion rate (*Ab*) with slow network oscillations (SNOs) induced by pharmacological EEAT blockade with DL-TBOA (unpublished data from L. Aniksztejn & A.A. Cattani).

will boost the occurrence of cENOs while preventing the emergence of GDPs, the later network oscillation (Fig. 3; Allene *et al.* 2008). This differential sensitivity of network patterns to environmental factors is directly determined by the cellular mechanism underlying their generation. In conclusion, the same environmental change can have different consequences on the network depending on which type of activity is dominant at the time it occurs.

NMDA-R driven early network oscillations: a role in synapse maturation?

As discussed above, ENOs are the dominant network pattern in neocortical slices at early postnatal stages. In contrast to most synapse-driven oscillations in other developing structures including the hippocampus, ENOs are mediated by the activation of NMDA-Rs rather than $GABA_A$-Rs (Garaschuk *et al.* 2000; Dupont *et al.* 2005; McCabe *et al.* 2006; Sun & Luhmann, 2007; Allene *et al.* 2008). Accordingly, oscillations recorded *in vivo* in the neonatal rat barrel cortex are also largely dependent on NMDA-R activation (Minlebaev *et al.* 2007; Yang *et al.* 2009). Therefore NMDA-Rs specifically have a major network function at early developmental stages in the neocortex. In contrast, in the hippocampus, GABAergic synapses are established before glutamatergic ones (Ben-Ari *et al.* 2004). Accordingly, the first synapse-driven network pattern in this region is the $GABA_A$-R-driven GDPs. The sequence of synapse maturation in the neocortex might be different even though GABAergic transmission also critically modulates neocortical activity through its complex excitatory/shunting action (Rheims *et al.* 2008*a*). Several observations indicate that NMDA-R signalling operates early in cortical development, notably to regulate the synaptic recruitment of AMPA-Rs (Feldmeyer & Cull-Candy, 1996; Zhu *et al.* 2000; Shi *et al.* 2001; Radnikow *et al.* 2002; Voigt *et al.* 2005; Brill & Huguenard, 2008; Wang & Kriegstein, 2008). A detailed morpho-functional description of the sequential maturation of GABAergic and glutamatergic synapses in the neocortex will undoubtedly be helpful to understand the differences between the neocortex and hippocampus.

It is important to stress that the network function of NMDA-Rs in the neocortex does not necessarily imply synaptic activation of these receptors. Indeed, we have recently shown that NMDA-Rs also contribute to neuronal excitability in the neocortex by mediating a tonic current that supports membrane potential depolarization (Allene *et al.* 2008). In the same study, we established the critical involvement of extracellular glutamate concentrations in the generation of cENOs. It is therefore possible that the generation of cENOs partly originates in the activation of extrasynaptic NMDA-Rs by ambient glutamate (Allene *et al.* 2008). The analogy between retinal and neocortical activity patterns is striking, in particular regarding the involvement of extrasynaptic glutamate receptors. Indeed, increases in ambient levels of glutamate were recently shown to be critically involved in generating stage III retinal waves (Blankenship *et al.* 2009). In addition, the dynamics underlying NMDA-R-driven stage III retinal waves is remarkably similar to cortical ENOs (Blankenship *et al.* 2009). The kinetics of both calcium and electrophysiological events associated with stage III retinal waves are as slow as those occurring during cENOs (Fig. 3). Interestingly, stage III retinal waves were shown to appear at a period when the glutamatergic synaptic system is not yet mature in the retina (Syed *et al.* 2004; Blankenship *et al.* 2009) supporting a role for extrasynaptic NMDA-R activation in the maturation of synaptic circuits.

Cortical ENOs may support the conversion of 'silent' to 'active' synapses and regulate the recruitment of AMPA-Rs into functional synapses. Indeed this network pattern occurs just before the shift of 'silent' or 'labile' synapses to functional ones (Groc *et al.* 2006) and glutamate spillover was shown to be critical for the activation of 'silent synapses' (Balland *et al.* 2008). In agreement with this hypothesis, it was recently shown that $GABA_A$-R and NMDA-R synaptic currents can be recorded prior to AMPA-R EPSCs in the neocortex and jointly contribute to the development of AMPA-R mediated transmission (Wang & Kriegstein, 2008). Still, the regulation of AMPA-Rs by NMDA-R-driven ENOs is probably not so straightforward. Indeed, while some reports suggested that NMDA-R signalling early in development negatively regulates the recruitment of functional AMPA-Rs into synapses (Hall & Ghosh, 2008), others proposed a positive regulation of AMPA-Rs by NMDA-R-mediated transmission (Zhu *et al.* 2000; Shi *et al.* 2001; Voigt *et al.* 2005; Brill & Huguenard, 2008). In fact, this controversy belongs to a more general one, as other studies have indicated that the maturation of these two types of receptors might be independent (Meguro *et al.* 1992; Okabe *et al.* 1998; Zhu & Malinow, 2002; Colonnese *et al.* 2003). This debate underlies the complex role of NMDA-R signalling during development and makes it difficult to attribute a single function to early NMDA-R-driven oscillations.

The developing neocortex: a network in a 'critical state'?

ENO dynamics are characterized by a massive recruitment of neuronal populations throughout cortical subregions irrespective of anatomical boundaries (Garaschuk *et al.* 2000; Adelsberger *et al.* 2005; Yang *et al.* 2009). Interestingly, during a restricted developmental period of 1 or 2 days, these large synchronizations co-exist with local events in the form of GDPs (Allene *et al.* 2008). The

coexistence of these two network events with very different sizes could be the sign of an 'avalanche' mode of activity in developing neocortical slices (Plenz & Thiagarajan, 2007; Werner, 2007). The term 'neuronal avalanche' was recently introduced to describe the fact that the size of spontaneous neuronal synchronizations can follow a power-law distribution implying that both rare massive events and frequent local ones can occur in the same network (Plenz & Thiagarajan, 2007; Werner, 2007). An avalanche type of organization is the sign of a network in a critical state and was reported in immature organotypic cortical cultures (Stewart & Plenz, 2008).

By definition, a critical state is at the edge of stability, and any small perturbation would break it. Several observations could indeed indicate that network dynamics in the developing neocortex can rapidly switch to a pathological state. Maybe the most striking one is the fact that the neocortex is exceptionally prone to seizures at early developmental stages (Ben-Ari & Holmes, 2006; Bender & Baram, 2007; Holmes *et al.* 2007; Scantlebury *et al.* 2007). For example, it was recently shown that GDPs in that region rapidly evolve towards interictal and ictal-like seizures if synaptic activity levels are pharmacologically increased (Rheims *et al.* 2008*b*). Likewise, the blockade of excitatory amino acid transporters (EAAT) that remove glutamate from the extracellular space induces an epileptiform 'suppression burst' activity pattern (Demarque *et al.* 2004). These slow network oscillations (SNOs) induced by EAAT blockade share striking features with hypoxia-induced-ENOs (Allene *et al.* 2008) regarding their dynamics and mechanisms (Fig. 3). SNOs appear as an amplified form of ENOs in regard to individual event kinetics and network dynamics. Interestingly, hypoxic–ischaemic encephalopathy in human neonates is very often associated with discontinuous EEG patterns including 'suppression bursts', in which dynamics and suggested cellular mechanisms can also be intriguingly similar to cENOs (Biagioni *et al.* 1999; Ohtahara & Yamatogi, 2003; Milh *et al.* 2007*a*). Moreover, hypoxic conditions both facilitate ENOs (Allene *et al.* 2008) and impair glutamate transporter function (Dallas *et al.* 2007). Altogether, this would suggest that ENOs could be a network pattern critically close to a pathological state.

To conclude, we propose a robust sequence for the maturation of coherent activity patterns in cortical structures with the role of NMDA-R driven ENOs remaining an open question. Because of their resemblance to both physiological patterns like stage III retinal waves or neuronal avalanches, and pathological oscillations like the bursts induced by an impairment of EAAT, it is at present difficult to assign a definite developmental function to ENOs. Finding the *in vivo* electrical pattern corresponding to cENOs is a difficult task. It will require combining multineuron imaging with electrophysiological recordings but it will certainly help to address this issue.

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