Review TRENDS in Neurosciences Vol.29 No.7 July 2006

INMED/TINS special issue

Early patterns of electrical activity in the developing cerebral cortex of humans and rodents

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During prenatal and early postnatal development, the cerebral cortex exhibits synchronized oscillatory network activity that is believed to be essential for the generation of neuronal cortical circuits. The nature and functional role of these early activity patterns are of central interest in neuroscience. Much of the research is performed in rodents and *in vitro*, but how closely do these model systems relate to the human fetal brain? In this review, we compare observations in humans with *in vivo* and *in vitro* rodent data, focusing on particular oscillatory activity patterns that share many common features: delta brushes, spindle bursts and spindle-like oscillations. There is considerable evidence that the basic functional properties of immature cortical networks are conserved through mammalian evolution, making the neonatal rodent an excellent model for studying early cortical activity and associated plasticity during the developmental period corresponding to the human fetal stage. 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/).

Introduction

During development, about a trillion cortical neurons establish specific synaptic connections to produce highly organized functional cortical networks. There are many genetic determinants of early cortical connections [1], but spontaneous and sensory-driven activity is equally important for cortical development. Early electrical activity controls several developmental processes, including neuronal differentiation, migration, synaptogenesis, neurotransmitter specification and synaptic plasticity (for reviews, see Refs [2–9]). As in adults, early cortical activity is organized in distinct spatiotemporal patterns. However, the patterns of cortical activity during early developmental stages are remarkably different from those in adults. A variety of activity patterns has been described in the developing cortex of humans and in numerous animal models using various *in vivo* and *in vitro* preparations, experimental conditions and recording techniques. Many of these patterns share common features and probably reflect the same phenomena. In this paper, we will briefly review the various early cortical patterns, focusing on: (i) the oscillatory activity known as 'delta brush', identified in electroencephalographic recordings from human premature babies; (ii) recently described oscillatory patters of spindle bursts in the neonatal rat neocortex *in vivo* [10]; and (iii) ACh-dependent alpha–beta and beta–gamma oscillations in the neonatal rat and mouse cerebral cortex *in vitro* [11]. Remarkable similarities between these three patterns of activity suggest that the basic functional properties of immature cortical networks are conserved through mammalian evolution, making the neonatal rodent an excellent model for studying early cortical activity and associated plasticity during the developmental period corresponding to the fetal stage in humans.

Premature human neocortical patterns: delta brushes

Two remarkable features characterize the early human electroencephalogram (EEG): (i) a highly discontinuous temporal organization and (ii) certain patterns of activity that disappear with maturation. The first notion of the discontinuous nature of the early cortical activity came from studies of human premature neonates using surface electrographic recordings. Dreyfus-Brisac, Monod and their colleagues from INSERM Unit 29 (Port-Royal Hospital, Paris) analyzed EEGs from neonates during the second half of gestation (human gestation lasts for ~40 weeks) [12]. They noted that the cortical EEG is organized in intermittent bursts that are separated by periods of virtually complete suppression of activity that could last for minutes. This temporal organization was named *tracé discontinu*. With maturation, suppression of activity between the bursts becomes less pronounced and, starting from ~30 weeks post-conception, *tracé discontinu* evolves to *tracé alternant*. At full-term, some discontinuity is still evident [13,14]. *Tracé discontinu* was also observed in recordings from fetal macaque hippocampal slices *in vitro* during the second half of gestation [15]. A discontinuous organization of the EEG to

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Available online 19 May 2006

 0166-2236/$ - see front matter doi:10.1016/j.tins.2006.05.007

the extent seen in premature neonates would be considered as abnormal and indicative of brain pathology in adults.

Characteristic EEG patterns of human premature neonates include transient periods of rhythmic activity and intermittent sharp events that are expressed during certain periods of fetal development [13,14,16,17]. At mid-gestation, the activity is dominated by delta waves of 0.3–2.0 Hz. Ultra-slow events associated with delta waves were recently detected using direct-current recordings [18]. By the seventh month of gestation, slow oscillations are intermixed with rapid rhythms. The dominant pattern of the rapid activity during this period is a delta-brush pattern [13,14,16,17] (Figure 1). Each delta brush consists of 8–25 Hz spindle-like, rhythmic activity superimposed on 0.3–1.5 Hz delta waves. Delta brushes are also known as spindle-shaped bursts of fast activity [19], rapid rhythm [20–22], rapid bursts [20], spindle-like fast [23], fast activity at 14–24 Hz [24] and ripples of prematurity [25]. Delta brushes are predominantly expressed in central areas before 28 weeks, and are then recorded in central, temporal and occipital areas from 28 weeks to near term [12–14,16,17]. Delta brushes often appear as spindle-shape events with a frequency of oscillations similar to that of adult sleep spindles. However, in contrast to synchronized sleep spindles, delta brushes are predominantly local events. Sleep spindles appear later in development, during the second postnatal month. Presence of delta brushes in EEG from preterm infants serves as a criterion of normal development, whereas their absence is indicative of brain pathology and poor prognosis [26]. In addition to delta brushes, several other patterns have been described in premature neonates, including delta crests, midline frontal theta and alpha bursts, frontal sharp transients, anterior slow dysrhythmia, temporal sawtooth and theta bursts. Detailed description of delta brushes and other premature patterns can be found in comprehensive reviews and books such as Refs [13,14,16,17].

Neonatal rodent neocortical patterns *in vivo*: spindle bursts

Until recently, state-of-the-art electrophysiological recordings could not be used in neonatal rodents owing to technical problems of mechanical stability. Solving these problems enabled extracellular field potential recordings, unit recordings and patch-clamp recordings in neonatal rats [10,27]. It was found that the two remarkable developmental features of the early cortical activity found in human premature neonates – its discontinuous temporal organization and particular 'immature' patterns of activity – are also present in neonatal rodents *in vivo*. Extracellular and patch-clamp recordings from the primary somatosensory (S1) cortex of postnatal day (P)1–P8 rat pups revealed that S1 activity is grouped in spindle-shaped bursts that are separated by periods of virtually complete electrical silence [10] (Figure 2a). A spindle burst is a transient spindle-shaped rhythmic activity at 5–25 Hz that typically lasts for $\sim$1 s, occurs at frequency of $\sim 5\,\mathrm{min}^{-1}$ and synchronizes most neuronal firing and synaptic activity. Three lines of evidence indicate that spindle bursts in neonatal rats are homologous to human premature delta brushes. First, both spindle-bursts and delta brushes are the dominant oscillatory patterns of cortical activity expressed during comparable developmental stages [28]. Second, both patterns are characterized by spindle-shaped rhythmic activity in a similar range of frequencies (5–25 Hz). The

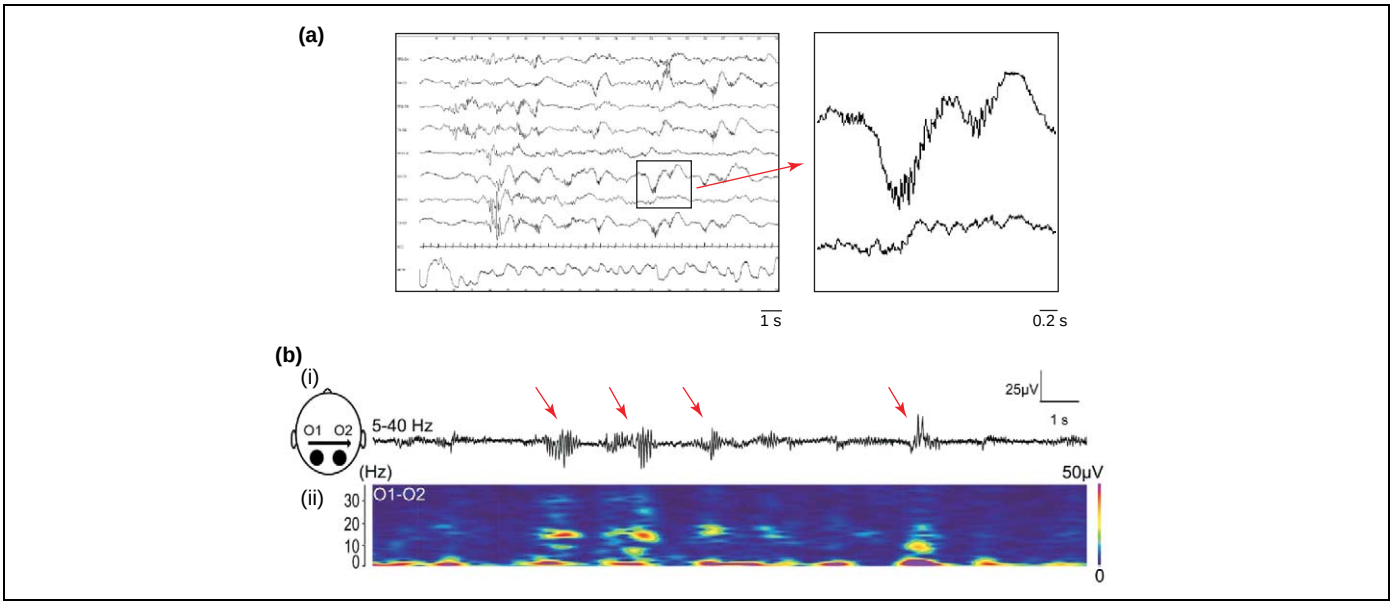

Figure 1. Hallmarks of the premature human electroencephalogram: *tracé discontinu* and delta brushes. **(a)** EEG recorded from a premature human neonate aged 33 weeks postconception during quiet sleep. Activity is characterized by discontinuous temporal organization (*tracé discontinu*), with the episodes of activity separated by the periods of silence. Typical patterns of activity are delta waves (1–3 Hz) in which are often nested high-frequency oscillations: delta brushes (an example delta brush is shown at an expanded timescale on the right). **(b)** (i) Bipolar occipital (O1–O2) recordings from the visual cortex of a premature neonate (filtered at bandpass 5–40 Hz). Note the intermittent rapid oscillations representing the rapid component of delta brushes (marked by red arrows). (ii) Time frequency analysis of the trace in (i). Note that activity at low (delta) frequencies coincides with rapid oscillatory activity during delta brushes. Courtesy of A. Kaminska (a) and M. Milh (b).

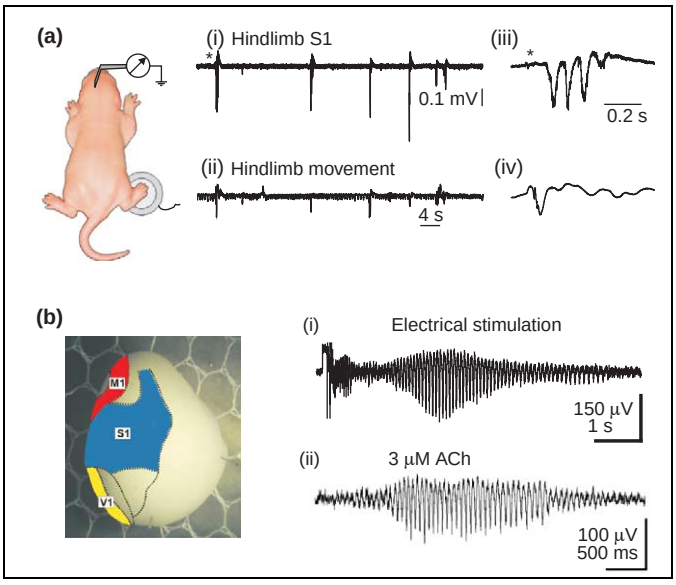

Figure 2. *Tracé discontinu* and early patterns of activity in the rat neocortex *in vivo* and *in vitro*. **(a)** Simultaneous recordings of (i) the intracortical field potential in the area representing the right foot in the P2 rat somatosensory (S1) cortex and (ii) the actual right-foot movements. Note discontinuous organization of the cortical activity and spindle bursts that are correlated with the movements. (iii) An example of a spindle burst marked by an asterisk in panel (i) that follows the foot movement. Note that the cortical event starts after the movement (iv). Reproduced from Ref. [10]. **(b)** A neonatal rat intact cortex preparation *in vitro*, with the S1, primary auditory (A1) and primary visual (V1) cortical areas indicated. Field-potential recordings from the neocortex reveal oscillations in response to (i) electrical stimulation and (ii) application of 3 μM ACh. Reproduced from Ref. [11].

delta component is more pronounced in human delta brushes; however, spindle bursts in rats are also often associated with a delta wave (Figure 2a; see also figure 4 from Ref. [10]). Third, both delta brushes and spindle bursts are local events that have a tendency to spread (see supplementary figures in Ref. [10]).

In neonatal rats, one feature of S1 spindle bursts is their tight correlation with spontaneous myoclonic twitches, which are a characteristic motor activity during the early developmental period. Myoclonic twitches are one of the most remarkable developmental phenomena in neonatal rats [29–31] and in human fetuses and premature neonates [32–35]. Such motor activity is expressed only during early developmental stages and it results from bursts of activity generated in the spinal cord. The delay between the movements and cortical spindle bursts, and the fact that spindle bursts can be triggered by direct sensory stimulation, indicates that spindle bursts are triggered by sensory feedback resulting from spontaneous movements. Spindle bursts persist after sensory deafferentation (spinal cord transection), although their frequency is reduced to about one third of normal. These results suggest that spindle bursts are endogenous oscillations that can be triggered by sensory feedback resulting from spontaneous movements. Besides the somatosensory cortex, events similar to spindle bursts were also found in the immature ferret visual cortex, where they could be evoked by light stimulation [36,37].

Using fiber optics and Ca^{2+} imaging of large neuronal populations, Adelsberger *et al.* have recently described waves of synchronous rises of intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) over large cortical areas that propagated across the anatomical borders of the neonatal mouse neocortex [38]. Increase of $[Ca^{2+}]_i$ during these early network oscillations (ENOs) lasted for 1–4 s and occurred at ~10–20 s intervals; this is similar to the duration and occurrence of S1 spindle bursts [10]. Recorded in temporal cortex, ENOs occurred mainly in movement-free resting periods and it remains unknown whether ENOs in somatosensory cortex are associated with movements. In many aspects optical ENOs are similar to electrographic spindle bursts, including duration of events and inter-events intervals. Although the $[Ca^{2+}]_i$ increase during ENOs was smooth and no high-frequency component characteristic of delta brush was evident, this might have been due to the slow dynamics of $[Ca^{2+}]_i$ and the limited temporal resolution of Ca^{2+}-imaging techniques compared with electrophysiological recordings. Further experiments using simultaneous electrophysiological and imaging approaches are needed to determine whether spindle bursts are associated with Ca^{2+} ENOs.

Neonatal rodent neocortical patterns *in vitro*: synchronized oscillations

Numerous patterns of correlated activity have been described in postnatal rat neocortical slices *in vitro*, including neuronal domains synchronized via gap junctions [39–42], Ca^{2+} waves [43,44], ACh-dependent alpha–beta and beta–gamma oscillations [11] (Figure 2b), and early network oscillations driven by intracortical glutamatergic and excitatory GABAergic mechanisms [45]. Correlated neuronal activity was also observed in neonatal somatosensory cortex in intact-hemisphere preparations *in vitro* [11,46]. Although the complexity of neocortical *in vitro* patterns is probably explained by the diversity of experimental conditions and by age differences, the question arises: do any of these *in vitro* patterns resemble the *in vivo* spindle bursts? Comparing the spatiotemporal characteristics of the various patterns, the alpha–beta–gamma oscillations elicited by electrical stimulation or by activation of metabotropic glutamate or muscarinic ACh receptors resemble the *in vivo* spindle-bursts in many respects [11]. The spindle-shaped time course and the frequency of the transmitter-induced oscillations *in vitro* are very similar to the spindle bursts *in vivo*. Recently, spontaneous spindle-shaped oscillations were also recorded *in vitro* using an extracellular 60-channel recording system in control conditions, in absence of any drug that would enhance neuronal excitability (J-J. Sun and H.J. Luhmann, unpublished). Under these conditions, spindle-shaped oscillations were spatially confined, in the same way as the *in vivo* spindle-bursts [10]. These observations indicate that spindle-shaped oscillations are a self-organized activity pattern, generated by mechanisms that are intrinsic to the immature cerebral cortex. Such early cortical activity appears spontaneously, can be elicited by activation of metabotropic glutamate or muscarinic ACh receptors, and can also be triggered by stimulation of the afferent inputs [10,11,41,44].

Studies *in vitro* indicate that during the first postnatal week, the neonatal rodent cerebral cortex uses different neuronal circuits and mechanisms to generate

synchronized oscillatory activity, and that it switches from a subplate-driven, gap-junction-coupled syncytium to a cortical synaptic network acting mostly through NMDA receptors [11]. An important conclusion emerging from the *in vitro* studies is that the early patterns undergo profound developmental changes. Neurons and neuronal networks are already developing rudimentary forms of excitability during early embryogenesis. Voltage-dependent Ca^{2+} channel activity often develops before Na^{+} channel activity (reviewed in Ref. [8]), and small action potentials with slow kinetics can be elicited at perinatal stages [47]. At early stages, when chemical synapses are not yet formed or function rather unreliably, neurons are often coupled via electrical synapses that enable the fast co-activation of a local neuronal domain and the exchange of second messengers via gap junctions [48].

Nature and nurture

Immature neuronal networks might combine genetic information (i.e. nature) and environmental influences (i.e. nurture), through a prenatal learning process of electrical activity patterns followed by an early postnatal period of activity-dependent synaptic modifications based on Hebb-like learning rules ('cells that fire together, wire together; cells that don't, won't') [49] (Figure 3). The rules and mechanisms of the prenatal learning process are currently unknown, but mutual interactions between early electrical activity and gene expression patterns have been demonstrated in various immature neuronal circuits, and it has been suggested that the temporal dynamics of the electrical activity (e.g. frequency or duration of action potential bursts or $[Ca^{2+}]_i$ transients) might have distinct effects on different intracellular signaling pathways or transcription of specific genes (reviewed in Refs [50,51]). These genes can be considered as 'thermostats' that are turned up and down by intrinsic electrical activity. Although intrinsic electrical activity self-organizes into distinct temporal patterns [10], external signals such as environmental noxious factors might disturb these neuronal rhythms, thereby modifying gene transcription and generating pathological circuits.

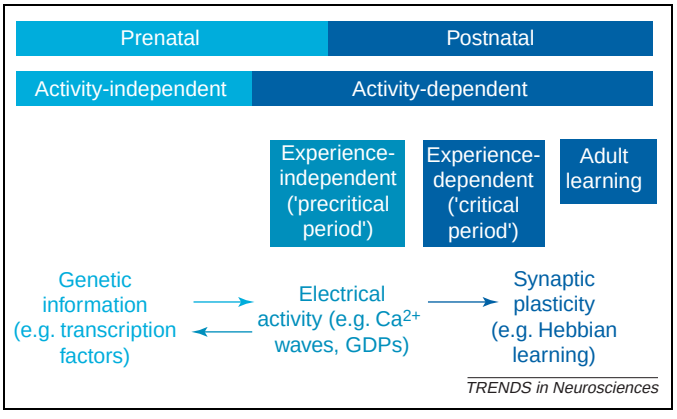

Figure 3. Formation of early neuronal networks relies on genetic information and on electrical activity. During embryonic development, immature neuronal circuits and crude topographic connections are established on the basis of genetic information. With the emergence of gap-junction coupling, voltage-dependent Ca^{2+} and Na^{+} channels and various neurotransmitter receptors during prenatal and early postnatal stages, neuronal circuits develop highly correlated spontaneous or transmitter-evoked electrical activity patterns, which often propagate over long distances within the network [e.g. retinal Ca^{2+} waves, hippocampal giant depolarizing potentials (GDPs) or widespread cortical oscillations]. During perinatal development (e.g. during 'precritical periods'), certain electrical activity patterns induce specific gene expression. During further postnatal development (e.g. during 'critical periods'), the network is modified in an experience-dependent manner based on Hebbian learning rules.

Many immature neuronal circuits incorporate NMDA receptors into their network activity during further development [7,11,45,46,52–54]. At perinatal stages in rodents, intrinsic correlated neuronal activity might act as a 'training partner' for sensory-evoked synaptic inputs when these signals from the environment are available for the first time (e.g. upon eye opening or upon arrival of the afferent sensory inputs). This activity-dependent, but experience-independent 'precritical period' might enable gross map formation, whereas map refinement takes place during the subsequent experience-dependent 'critical period' (reviewed in Ref. [6]).

Concluding remarks

Recent studies in neonatal rodents have revealed early patterns of synchronized cortical activity (spindle bursts *in vivo* and spindle-shaped oscillations *in vitro*) that share many features with the delta-brush pattern in the human premature neonate. Providing a platform for elaboration of hypotheses in neonatal rodents that could be followed by testing in premature human neonates or even human fetuses *in utero*, this opens wide perspectives for further research into the mechanisms and physiological roles of these early activity patterns. It will be of major interest to understand the link between spindle bursts and afferent inputs in systems other than the somatosensory system; for example, spontaneous retinal waves might have a role in triggering spindle bursts in the immature visual cortex. Particularly interesting is the question of whether spontaneous activity in afferent inputs drives delta brushes in various sensory cortical areas of human premature neonates. It would be also interesting to study whether the generation of delta brushes *in vivo* undergoes a similar developmental switch to that reported *in vitro* – that is, from a subplate-driven gap-junction-coupled syncytium to a cortical synaptic network utilizing NMDA receptors. Finally, perhaps the most important and challenging task would be to study the role of early cortical activity in developmental plasticity and in the activity-dependent formation of cortical circuits during 'precritical periods'.

Acknowledgements

We thank our co-workers whose data contributed to this review. This work was supported by INSERM, FRM, ANR and MNRT grants to R.K., and DFG grants to H.J.L.

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