CHAPTER

8

Neonatal Cortical Rhythms

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OUTLINE

Nomenclature

AMPA α-Amino-3-hydroxyl-5-methyl-4-isoxazole-propionate
DC Direct coupled
EEG Electroencephalography
ENO Early network oscillations
GABA γ-Aminobutyric acid
GDP Giant depolarizing potential
LGN Lateral geniculate nucleus
MEG Magnetoencephalography
NMDA *N*-Methyl-D-aspartic acid
ODCs Ocular dominance columns
P Postnatal day
R Receptor
S1 Primary somatosensory cortex
SAT Slow activity transient
STDP Spike-time-dependent plasticity
V1 Primary visual cortex
μV Microvolt

8.1 INTRODUCTION

The fetal period in humans is characterized by a number of fundamental events in the construction of the nervous system, such that at birth, many of the primary circuits already have been formed and display remarkable functional performance, although development evidently continues after birth until full maturity is reached at around age 30. Considerable evidence indicates that electrical activity expressed in the human fetal brain – and in lower mammals at corresponding developmental stages – controls a number of developmental processes, including neuronal differentiation, migration, synaptogenesis, and synaptic plasticity (for review, see Ben-Ari et al., 1997; Blankenship and Feller, 2010; Feldman et al., 1999; Feller and Scanziani, 2005; Fox, 2002; Henley and Poo, 2004; Katz and Crowley, 2002; Katz and Shatz, 1996; Rakic and Komuro, 1995; and Zhou and Poo, 2004a). Probably the most thoroughly elaborated evidence has been generated by studying sensory cortices, in which development of sensory maps is critically influenced by activity from the sensory periphery. However, the physiology of the fetal central nervous system, and notably the electrical patterns of organized neuronal activity that underlie map formation, has remained obscure for a long time. This is mainly a result of technical limitations in recording electrical activity from the fetal brain in utero. An important and almost paradoxical aspect of the problem is that the fetus develops

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in utero under conditions of virtually complete sensory deprivation. Knowing the importance of input from the sensory periphery for development of the nervous system raises an important question: What are the mechanisms that provide sensory stimulation to the developing sensory systems *in utero*? This question is accompanied by a number of related issues. For example, how are the early sensory inputs processed in developing circuits, and what are the specific activity patterns associated with the activity-dependent formation of the cortical maps? How are these early activity patterns generated, and how are they transformed to the mature mode of sensory processing necessary to support behavioral function?

In this chapter, we attempt to answer these questions by reviewing experimental evidence obtained in the premature human neonate and in the postnatal rodent, which seems to be an excellent model for studying the processes that occur during the human fetal development. In both systems, endogenous mechanisms for the activation of sensory pathways exist in two developing sensory systems: the somatosensory and the visual. In the somatosensory system, sensory input is generated by sensory feedback resulting from spontaneous movements. In the visual system, it is provided by spontaneous retinal waves generated in the initially light-insensitive retina. In both systems, this endogenously activated "sensory" input drives oscillatory bursts in thalamocortical networks. These central oscillations occur in a topographic manner and thus provide binding between the aligned elements of sensory circuits to create conditions for the activity-dependent formation of cortical maps. The generation of the early oscillatory patterns, which primarily include oscillations in alpha–beta and gamma frequency ranges, involves glutamatergic synapses including an input from the thalamus. The fast rhythmic components of early activities are generated primarily by α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) receptors at glutamatergic synapses, whereas *N*-methyl-D-aspartic acid (NMDA) receptors, also activated during the early oscillatory bursts due to summation of rhythmic input, provide conditions for NMDA-R-dependent synaptic plasticity. The local nature of early activity is generated as a result of the topographic organization of the thalamic input. Spread of early activity is limited by the delayed maturation of the long-range horizontal connections in the cortex and by surround inhibition provided by GABAergic interneurons even at a very early age. We propose a model in which the early oscillatory patterns shape early circuits according to spike-time-dependent plasticity (STDP) in localized regions.

We will finally discuss how early cortical activity patterns are related to the development of sensory signal processing and explorative functions. The main function of our brain consists of the online processing of the input from the external world and the body and the generation of an output according to previous experience and prediction. Although the early oscillatory bursts are reliably activated by endogenous mechanisms, these activity patterns are poorly suited for the exploration of the environment. Early in development, external sensory stimuli evoke all-or-none oscillatory bursts similar to those triggered by endogenously activated sensory input; however, this paradigm enables only a primitive form of sensation, not the high-frequency graded sensory processing required for explorative functions. With maturation, early oscillatory bursts disappear in association with a rapid developmental switch in the mode of sensory processing from bursting to "acuity." In the visual system, this switch occurs shortly before the onset of patterned sensory input – birth in the human and eye opening in the rat – in association with an emergence of the active cortical state. A similar switch also occurs in the somatosensory whisker-related rat barrel cortex just before the onset of active whisking. Thus, the early bursting mode of sensory signal processing is related to the development of the sensory cortex, but not to the exploration of the external world. This suggests an inside-out development of the sensory cortex, which initially is tuned to the internally generated activity at the sensory interface and serves to embed it into topographically organized sensory cortical maps and, once this is achieved and the maps are well tuned, switches to the exploration mode, enabling reliable high-frequency processing of sensory signals from the environment.

8.2 NEOCORTICAL PATTERNS IN PREMATURE HUMAN NEONATES

Determining the patterns of activity expressed in the fetal brain is a challenging task. While the standard way to characterize electrical brain activity is to record the electrical signals from the head surface using scalp electroencephalography (EEG), such recordings cannot be performed in the fetus (although some attempts have been made to record the EEG and the magnetoencephalograph (MEG) through the mother's abdomen). At present, the main approach to fetal brain activity consists of scalp EEG recordings from premature neonates. In this group of patients surveyed in specialized intensive care units, neurophysiological monitoring is a part of the standard patient examination. Evidently, as the environment is very different and the functions of many systems (cardiovascular, respiratory, and digestive) undergo significant development after birth, a question could be raised as to whether cortical activity in premature neonates is the same as in the fetus. For the most part, the answer is 'yes,' because EEG development is largely age-dependent, and the EEG patterns expressed in premature neonates match the gestational age, but not the

actual postnatal age. Moreover, studies using magnetoencephalography in the fetus *in utero* document a remarkable similarity with the temporal organization of activity and electrographic patterns observed in the gestational age-matching premature neonates. Therefore, scalp EEG from premature neonates is today considered a reliable approach to measuring fetal brain function.

Characteristic adult EEG patterns emerge essentially during the postnatal period and undergo pronounced changes in the amplitude and distribution of oscillations in different frequency bands until age 30 (Niedermeyer and Da Silva, 2005; Uhlhaas et al., 2010). Thus, the premature infant EEG displays a number of unique activity patterns. These include a number of distinct transient periods of rhythmic activity and intermittent sharp events that are expressed during certain periods of development (Anderson et al., 1985; Lamblin et al., 1999; Scher, 2006; Stockard-Pope et al., 1992). At mid-gestation, activity is dominated by intermittent delta waves from 0.3 to 2 Hz. By the 7th month, slow oscillations become intermixed with rapid rhythms. During the second half of gestation, the dominant EEG pattern in central, temporal, and rostral regions is the delta-brush (Anderson et al., 1985; Lamblin et al., 1999; Scher, 2006; Stockard-Pope et al., 1992) (Figure 8.1). Different terms have also been used in the literature to describe this pattern including spindle-shaped bursts of fast activity (Ellingson, 1958), rapid rhythm (Dreyfus-Brisac, 1962; Nolte et al., 1969; Parmelee et al., 1969), rapid bursts (Dreyfus-Brisac, 1962), spindle-like fast (Watanabe and Iwase, 1972), fast activity at 14–24 Hz (Goldie et al., 1971), and ripples of prematurity (Engel, 1975). A delta-brush consists of 8–25 Hz spindle-like, rhythmic activity superimposed on a delta wave. Often, delta-brushes occur in a sequence, and these grouped delta-brush activities may stay for up to 10 s, giving rise to so-called slow activity transients, or SATs, that, in direct coupled (DC) recordings, attain unusually large amplitudes of up to 800 μV (Vanhatalo et al., 2002, 2005). Such DC shifts are filtered and therefore not observed using conventional high-pass (>0.5–1 Hz) EEG recordings. Delta brushes are expressed in all cortical areas and fade near term. While resembling sleep spindles in some ways, delta brushes and sleep spindles appear to be distinct patterns. Sleep spindles emerge only during the second postnatal month.

Besides delta-brushes, other patterns expressed in the premature brain include the neonatal 'delta crest' (isolated frontopolar delta waves with superimposed fast activity), midline frontal theta–alpha burst, EEG spikes and sharp transients, anterior slow dysrhythmia, and temporal sawtooth or temporal theta bursts (Anderson et al., 1985; Lamblin et al., 1999; Scher, 2006; Stockard-Pope et al., 1992). Because nearly all information about the earliest cortical patterns in humans derives from scalp-recorded EEGs of premature infants, these observations alone do not inform us whether they represent pathological activity of the immature brain or the normal physiological patterns of developing neuronal networks. Addressing these issues requires simultaneous recording of neuronal spiking and EEG activity in intact developing tissue.

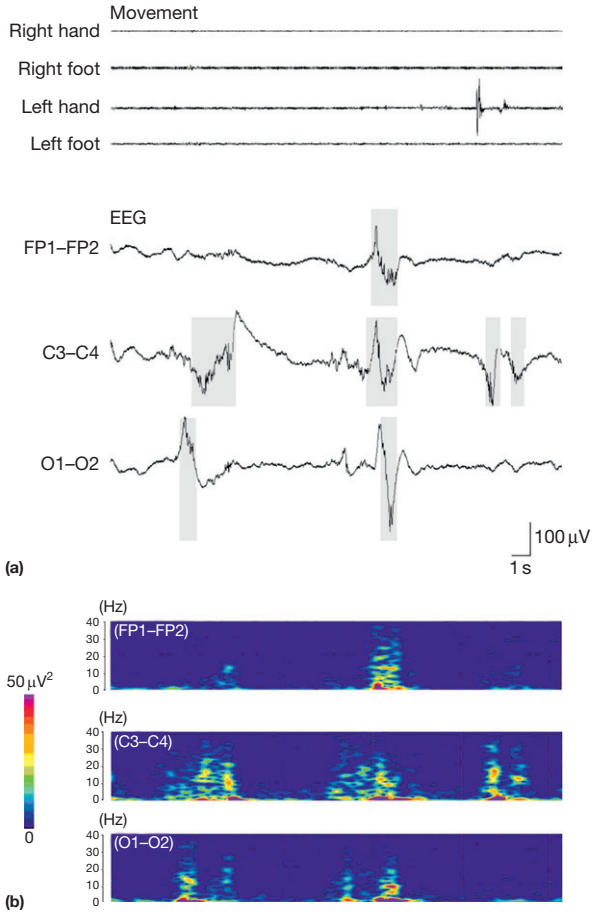

FIGURE 8.1 Delta-brushes in the human preterm neonate. (a) Representative example of three simultaneous EEG traces recorded in bipolar transversal montage (frontal FP1–FP2, central C3–C4, and occipital O1–O2) during quiet sleep in a 30-week, postconceptional-age neonate. Bursts of delta waves alternate with periods of hypoactivity. Delta-brushes are characterized by alpha–beta oscillations superimposed on delta waves (gray squares). Traces above show concomitant hand- and foot-movement recordings. (b) Wavelet analysis of bipolar EEG recordings shown in (a). *Adapted with permission from Milh M, Kaminska A, Huon C, Lapillonne A, Ben Ari Y, Khazipov R (2007) Rapid cortical oscillations and early motor activity in premature human neonate.* Cerebral Cortex *17: 1582–1594.*

8.3 THE FIRST ORGANIZED CORTICAL NETWORK PATTERNS IN THE NEONATAL RODENT

Offspring of rats and mice are altricial, that is, they are born in an immature state (Clancy et al., 2001). Although it is difficult to provide exact comparisons between

humans and rodents, the level of rat brain development at the day of birth (P0) can be roughly compared to the state of human cortex at mid-gestation, and term in humans roughly corresponds to the postnatal day P12 in the rat or mouse. Therefore, postnatal rodents could be an excellent model to study the developmental events that occur during the human fetal period. However, despite a rich repertoire of activity patterns observed in preterm human neonates during the second half of gestational age, until recently no organized brain activity had been reported during the first ten postnatal days in rodents. Based on EEG recordings, organized cortical activity in infant rodents was thought to commence with the emergence of delta waves, starting from P11 (Frank and Heller, 1997; Gramsbergen, 1976; Jouvet-Mounier et al., 1970). This stands in contrast with a number of patterns of correlated activity found in the neonatal cortical slices *in vitro* (for review, see Allene and Cossart, 2010). It should be noted that recording activity in neonatal rats is technically difficult because the skull is cartilaginous, making mechanically stable, movement-artifact-free recordings difficult to perform. This problem has been solved through the development of the technique of recordings from head-restrained animals with a dental cement-enforced head cup, first under anesthesia (Leinekugel et al., 2002) and later in the nonanesthetized (Khazipov et al., 2004b) and decerebrated rat pups (Karlsson and Blumberg, 2005). At present, this technique is widely used in neonatal rats to perform intracortical recordings of the local field potential and multiple units using electrode arrays, patch-clamp recordings from individual neurons, and imaging (Colonnese et al., 2010; Mohns and Blumberg, 2008; Sipila et al., 2006; Yang et al., 2009). Using this technique, several activity patterns had been described in neonatal rodents, revealing a remarkable similarity to the activities seen in human premature neonates and enabling investigation of their underlying mechanisms. These patterns so far have been thoroughly investigated in only the sensory cortices (notably somatosensory and visual areas) and the hippocampus.

8.3.1 Spindle- and Gamma-Bursts in Somatosensory Cortex

In the neonatal rat somatosensory cortex, formation of the body map representation occurs during the first postnatal week. Because modulation of sensory-driven experience strongly influences this process during this time, this period is also known as the critical period of the somatosensory map development. During this period, thalamocortical axons grow into the neocortex and form input-specific patterns of synapses with neocortical neurons (e.g., the whisker-specific-barrel pattern in the barrel cortex) (Erzurumlu and Jhaveri, 1990; Higashi et al., 2002; Molnar et al., 2003; Petersen, 2007; Price et al., 2006; Woolsey and Van Der Loos, 1970). Manipulations of the peripheral receptors, or of cortical activity, during this critical period can disrupt the formation of thalamocortical synapses (Cases et al., 1996; Catalano and Shatz, 1998; Feldman et al., 1999; Foeller and Feldman, 2004; Fox, 1992, 2002; Fox and Wong, 2005; Lu et al., 2006; O'Leary et al., 1994; Persico et al., 2001; Van der Loos and Woolsey, 1973; Woolsey and Wann, 1976). Pharmacological or genetic manipulations associated with a loss of function of NMDA-Rs result in malformations of barrel cortex development and functional deficits (Dagnew et al., 2003; Fox, 2002; Fox et al., 1996; Iwasato et al., 2000; Lee et al., 2005a,b; Schlaggar et al., 1993). During the critical period, thalamocortical synapses display an enhanced NMDA-R contribution and increased NMDA-R-dependent synaptic plasticity, including the conversion of 'silent' pure NMDA-R-based synapses to fully functional mixed AMPA/NMDA-R synapses, as well as switching to fast AMPA-receptor-mediated synaptic transmission from slow kainate-mediated transmission (Bannister et al., 2005; Barth and Malenka, 2001; Carmignoto and Vicini, 1992; Crair and Malenka, 1995; Daw et al., 2006; Feldman et al., 1998, 1999; Hestrin, 1992; Isaac et al., 1995, 1997; LoTurco et al., 1991; Monyer et al., 1994).

What are the patterns of cortical activity that underlie this activity-dependent plasticity during this critical period? Extracellular and patch-clamp recordings from rats during the first postnatal week revealed two predominant organized patterns of activity in the somatosensory neocortex: so-called spindle-bursts and gamma-bursts (Khazipov et al., 2004b; Marcano-Reik and Blumberg, 2008; Marcano-Reik et al., 2010; Minlebaev et al., 2007, 2009; Seelke and Blumberg, 2010; Yang et al., 2009) (Figure 8.2). Both are transient local oscillatory events, with a difference in the dominant frequency of oscillation and in the size of the recruited network. A spindle-burst is a transient burst of rhythmic, 5–25 Hz activity with a duration of approximately 1 s and a recruiting cortical zone of approximately a half millimeter. Gamma-bursts (40–50 Hz) are typically shorter in duration (150–300 ms) and are more local ($\sim$200 μm) events. Spindle bursts and gamma bursts may also intermingle. Recordings in the DC mode, without high-pass filtering of the signal, revealed that spindle bursts are associated with relatively large (up to hundreds of μV) negative delta waves. A tight temporal and quantitative correlation between the power of the alpha–beta oscillations and the time course and amplitude of the delta wave, a similar depth profile and location of the major current sinks in the dense cortical plate, and involvement (though differential, see below) of ionotropic glutamate receptors in the generation of

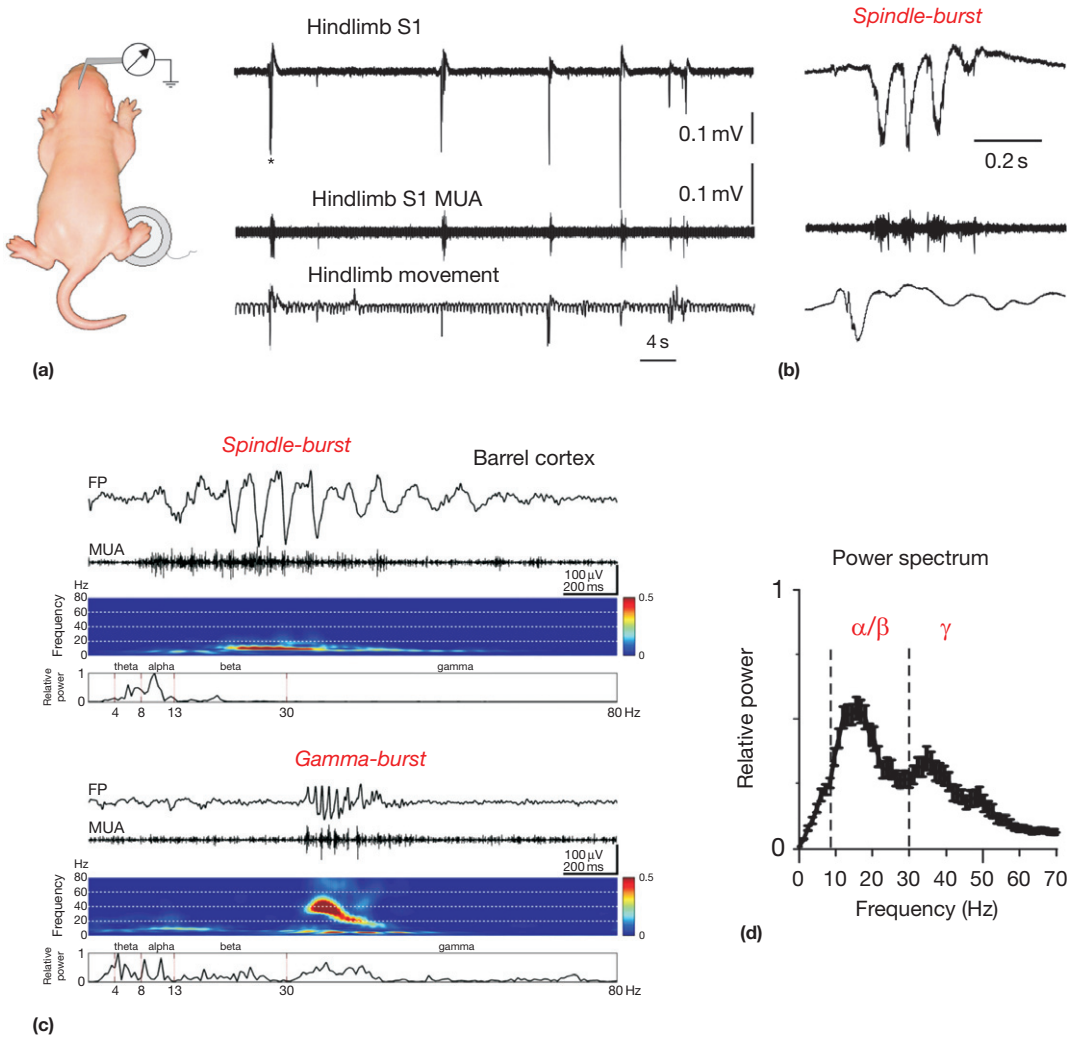

FIGURE 8.2 Spindle- and gamma-bursts in primary somatosensory cortex (S1) of the newborn rat. (a) Wide-band recordings of extracellular activity and filtered (0.3–5 kHz) MUA in S1 hindlimb area of a P2 rat. Positivity is up. Bottom, movement of the contralateral hindlimb. Continuous rhythm reflects respiration. Note that field events and synchronized unit bursts are associated with movements. The event marked by * is shown at an expanded time scale in (b). (c) Examples of spindle-bursts (top panel, P1) and gamma-bursts (bottom panel, P3) in the neonatal rat barrel cortex. Below the traces are shown color-coded wavelet spectra and relative powers in different frequency domains. (d) Average power spectrum of the bursts recorded in neonatal rat barrel cortex (pooled data from 14 P2–7 rates, total 499 bursts). Note two peaks at alpha–beta (8–30 Hz; spindle-bursts) and gamma (30–80 Hz, gamma-bursts) frequency ranges. *Adapted with permission from (a, b): Khazipov R, Sirota A, Leinekugel X, Holmes GL, Ben Ari Y, Buzsaki G (2004b) Early motor activity drives spindle bursts in the developing somatosensory cortex.* Nature *432: 758–761; (c) Yang JW, Hanganu-Opatz IL, Sun JJ, Luhmann HJ (2009) Three patterns of oscillatory activity differentially synchronize developing neocortical networks* in vivo. Journal of Neuroscience *29: 9011–9025; and (d) Minlebaev M, Ben-Ari Y, Khazipov R (2007) Network mechanisms of spindle-burst oscillations in the neonatal rat barrel cortex* in vivo. Journal of Neurophysiology *97: 692–700.*

both components, indicate that the high-frequency oscillations and the delta waves are two components of a single activity (Minlebaev et al., 2009). The identification of the slow component of spindle-bursts supports their homology with the human electrographic pattern of delta brushes, which are also expressed in somatosensory cortical areas of human premature neonates during the second half of gestation. The remarkable similarities between these two patterns indicate that they are the same physiological phenomenon (Khazipov and Luhmann, 2006). This also confirms that the neonatal rodent can be a useful model for studying the mechanism and physiological roles of this activity pattern in cortical development.

Spindle bursts share some similar electrographic characteristics with adult sleep spindles (Steriade, 2001). However, in contrast to sleep spindles, neonatal spindle bursts are local events with a limited tendency to spread. Furthermore, spindle bursts are present in the waking pup even during walking and feeding and are typically triggered by myoclonic twitches of isolated muscles or whole-body startles. Myoclonic twitches are one of the

most remarkable developmental motor phenomena in the neonatal rat (Blumberg and Lucas, 1994; O'Donovan, 1999; Petersson et al., 2003), human fetus, and premature neonate (Cioni and Prechtl, 1990; de Vries et al., 1982; Hamburger, 1975; Prechtl, 1997; and is discussed extensively in Rubenstein and Rakic, 2013.). This particular type of motor activity results from the stochastic bursts of activity generated in the spinal cord under brainstem control (Blumberg and Lucas, 1994; Karlsson et al., 2005; Kreider and Blumberg, 2000). Delay between the movements and cortical spindle bursts, and the observation that spindle bursts can also be induced by direct sensory stimulation, indicated that spindle bursts are triggered by sensory feedback initiated by spontaneous movements (Figure 8.2(a)). At present, whether gamma bursts are initiated by sensory feedback is unknown, but both spindle bursts and gamma bursts are efficiently triggered by external stimulation (Khazipov et al., 2004b; Marcano-Reik and Blumberg, 2008; Marcano-Reik et al., 2010; Minlebaev et al., 2007; Yang et al., 2009). Importantly, spindle bursts and gamma bursts persist after sensory deafferentation (e.g., spinal cord transection or application of local anesthetics), although at a reduced frequency (Khazipov et al., 2004b; Yang et al., 2009). These results suggest that spindle bursts and gamma bursts are endogenous – probably thalamocortical or intracortical – oscillations. However, external stimuli brought about by the thalamocortical afferents can trigger these oscillations in the somatosensory cortex in a somatotopic manner.

In addition to gamma and spindle bursts, the somatosensory cortex of rodents during the first postnatal week also displays sharp wave transients (Khazipov et al., 2004b; Seelke and Blumberg, 2010) that may reflect sensory feedback events resulting from brief movements that failed to initiate oscillatory bursts. Long oscillations lasting for >40 s and reminiscent of SATs have also been described, although these events are rare in the somatosensory cortex (Yang et al., 2009).

8.3.2 Spindle Bursts and SATs in Visual Cortex

Despite the similarities between the functional organization of somatosensory and visual systems during the first postnatal week, there is an important difference. In the somatosensory system, sensory stimulation reliably evokes cortical responses starting from near birth – as soon as thalamic axons enter the cortex; in the visual system, however, the retina is insensitive to light during the first postnatal week. During this developmental period, when the visual cortical map is formed, the retina generates spontaneous waves of activity (see Rubenstein and Rakic, 2013). These waves are generated in the network of retinal ganglion and amacrine cells, and locally synchronize retinal activity local domains (Galli and Maffei, 1988; Meister et al., 1991; Torborg and Feller, 2005; Wong et al., 1993). Using an original *in vitro* preparation of the neonatal mouse intact retina – lateral geniculate nucleus (LGN) thalamic nucleus, it was demonstrated that spontaneous retinal activity is transmitted via the optic nerve to the LGN, where it drives bursts of activity (Mooney et al., 1996). Modulation of retinal waves during the first postnatal week results in alteration of retinal projections to their subcortical targets, suggesting an instructive role for retinal waves in the development of retinogeniculate connectivity (Chandrasekaran et al., 2005; Grubb et al., 2003; McLaughlin et al., 2003; Mrsic-Flogel et al., 2005; Muir-Robinson et al., 2002; Nicol et al., 2007; Penn et al., 1998; Shatz and Stryker, 1988; Stellwagen and Shatz, 2002). Evidence also exists for the contribution of retinal waves to cortical development. In monkeys, ocular dominance columns (ODCs) are formed already *in utero* before visual experience (Rakic, 1976). Although enucleation experiments suggest that retinal input may not be required for the formation of ODCs (Crowley and Katz, 1999), complete blockade of retinal activity can disturb segregation of thalamocortical connections in ODCs (Stryker and Harris, 1986). In neonatal mice, suppression of retinal waves during the first postnatal week also results in imprecise geniculocortical mapping (Cang et al., 2005). Furthermore, blockade of retinal waves in ferrets disrupts formation of ODCs. Together, these data show that spontaneous retinal waves are also involved in the development of thalamic connections to the visual cortex (Cang et al., 2005).

These findings suggested the hypothesis that retinal waves are transmitted to and trigger activity in the developing visual cortex. This hypothesis has been tested in neonatal rats (Colonnese and Khazipov, 2010; Hanganu et al., 2006). Using extracellular and whole-cell recordings from the visual cortex of neonatal rats *in vivo*, it was shown that, as in the somatosensory cortex, the dominant pattern of activity in the visual cortex during the first postnatal week is a spindle burst (Figure 8.3). Simultaneous recordings from the retina and the primary visual (V1) cortex revealed a strong correlation between spindle bursts in the visual cortex and spontaneous retinal waves. In addition, V1 spindle bursts could be reliably evoked by direct stimulation of the optic nerve. Pharmacological modulation of retinal activity affected the rate of occurrence of V1 spindle bursts; for instance, intraocular forskolin injection, known to increase the frequency and amplitude of retinal waves (Tsai et al., 1987), greatly increased the rate of occurrence of cortical spindle bursts in the contralateral V1 cortex. On the other hand, blocking the propagation of retinal activity with local application of tetrodotoxin or removing the retina resulted in a twofold reduction of V1 spindle-burst frequency, analogous to the reduction of somatosensory spindles after spinal cord transections.

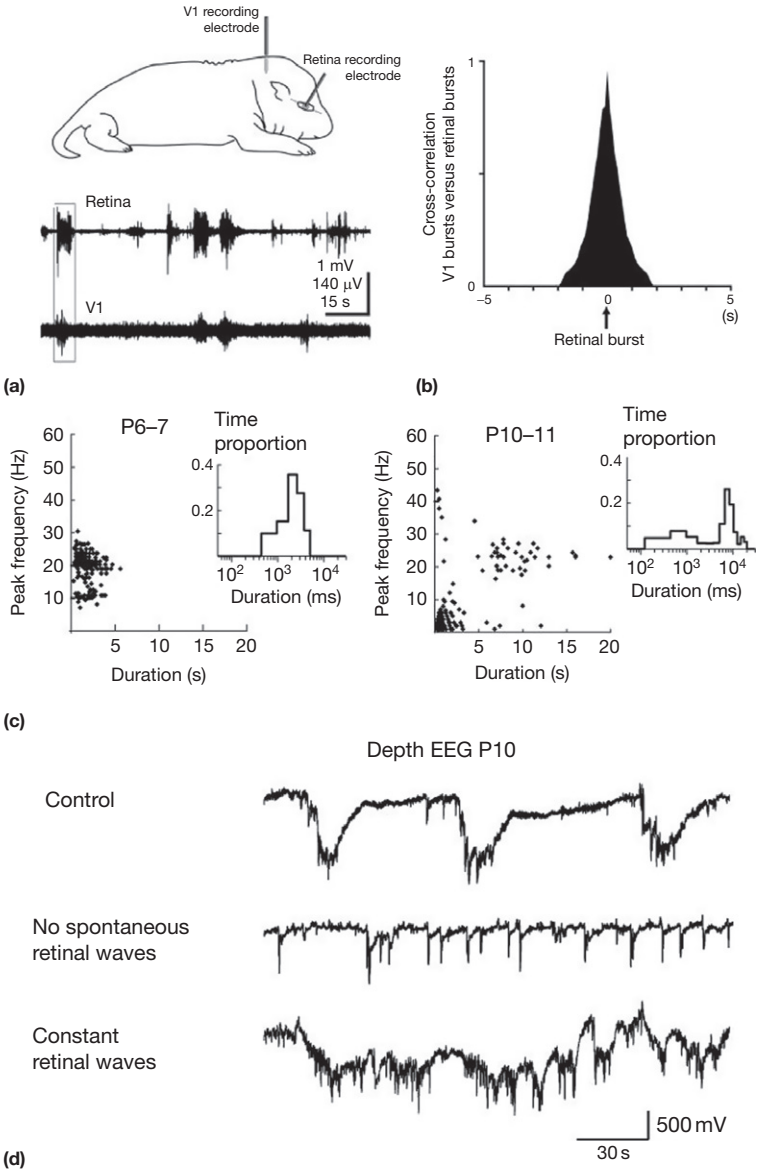

FIGURE 8.3 Retinal drive of visual cortex activity in neonatal rats. (a) Simultaneous recordings of retinal and cortical activity during the first postnatal week reveal synchrony of retinal bursts and cortical spindle-bursts. (b) Cross-correlation of cortical and retinal activity bursts. (c) Diversification of activity patterns during the second postnatal week. Spontaneous activity P6–7 forms a single distribution of duration and presence of rapid oscillations (spindles). By P10–11, elongation of bursts containing rapid oscillations (SATs) and the emergence of short-activity bursts with no oscillatory component lead to two clearly separable activity patterns. (d) Manipulation of spontaneous retinal waves specifically affects SATs, either eliminating them when retinal waves are blocked (enucleation or intra-ocular urethane injection) or increasing their occurrence when retinal activity is increased (retinal inhibition blockade). *Adapted with permission from Hanganu IL, Ben Ari Y, Khazipov R (2006) Retinal waves trigger spindle bursts in the neonatal rat visual cortex.* Journal of Neuroscience *26: 6728–6736 (a, b) and Colonnese MT and Khazipov R (2010) "Slow activity transients" in infant rat visual cortex: A spreading synchronous oscillation patterned by retinal waves.* Journal of Neuroscience *30: 4325–4337 (c, d).*

During the second postnatal week, when the retina becomes responsive to light, spontaneous activity in the visual cortex starts to diversify. Spindle bursts start to group in long-lasting events associated with large amplitude, slow (5–10 s long) DC shifts that are highly reminiscent of SATs in the human premature neonate (Figures 8.3 and 8.4). SATs in the rat are completely eliminated by enucleation. In addition, their main characteristics (duration, interevent intervals, and subburst structure) exactly match those of phase III retinal waves recorded *in vitro*. This indicates that SATs are also driven by retinal waves, as are spindle bursts during the first postnatal week. In parallel, starting from postnatal day P9 a separate class of events of short duration (200 ms) emerges, reminiscent of cortical up-states, which also start to be seen at around the same age in cortical slices *in vitro* (Allene et al., 2008; Rheims et al., 2008). Similarly, in postnatal day P22–39 ferrets, V1 multiple unit activity is organized in bursts with about 10-Hz intraburst multi-unit activity (MUA). Studied with multielectrode arrays, this bursting activity exhibited a patchy structure that reflects ODCs in the visual cortex (Chiu and Weliky, 2001, 2002).

In parallel with the electrophysiological discovery of the early oscillatory patterns, a related pattern, termed early network oscillations (ENOs), has been described using calcium imaging of large neuronal populations *in vivo* (Adelsberger et al., 2005). ENOs are characterized by synchronous intracellular calcium increases that last for about 1 s and recur at about 10-s intervals in P3–4 rats, similar to spindle-bursts. Recorded in the temporal cortex, ENOs mainly occurred during movement-free

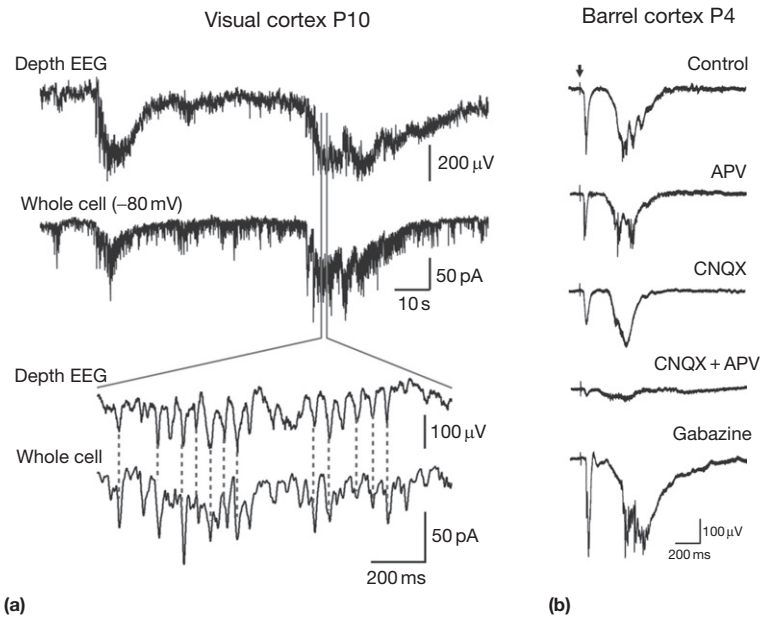

FIGURE 8.4 The mechanisms of the early oscillatory bursts. (a) Simultaneous depth EEG (field-potential, top trace) and whole-cell (400 μm depth, bottom trace) recordings from P10 rat visual cortex show that the infra-slow wave of SATs is composed of a similar long-duration depolarizing current. At expanded time base, rapid oscillations in the field potential are closely correlated with excitatory synaptic currents. (b) Pharmacological analysis of spindle-bursts evoked by electrical whisker pad stimulation in the P4 rat barrel cortex. Note that rapid oscillatory component (brush) is suppressed by the cortical application of the AMPA/kainate receptors (CNQX), whereas the delta-component is blockaded by combined application of AMPA/kainate and NMDA-receptor antagonists (CNQX and APV). Blockade of GABA(A) receptors with gabazine enhances the response. *Adapted with permission from: (a) Colonnese MT and Khazipov R (2010) "Slow activity transients" in infant rat visual cortex: A spreading synchronous oscillation patterned by retinal waves.* Journal of Neuroscience *30: 4325–4337; (b) Minlebaev M, Ben Ari Y, Khazipov R (2009) NMDA receptors pattern early activity in the developing barrel cortex* in vivo. Cerebral Cortex *19: 688–696.*

resting periods, and it remains unknown whether ENOs in the somatosensory cortex are associated with movements. Nevertheless, optical ENOs appear similar to the electrographically defined spindle-bursts, including duration of events and inter-event intervals. Although the dynamics of intracellular calcium increases during ENOs were rather smooth and no high-frequency component characteristic oscillation was evident, this may be due to slow dynamics of intracellular calcium and the limited temporal resolution of calcium imaging methods compared to electrophysiological recordings. Further experiments using simultaneous electrophysiological and imaging approaches are needed to determine whether or not spindle bursts and ENOs reflect the same fundamental physiological patterns. Before speculation about the functional role of the early spontaneous patterns, we discuss the available observations that provide insights into their physiological mechanisms.

8.4 MECHANISMS OF EARLY NETWORK PATTERNS

The synaptic basis of the generation of the early activity patterns was explored using whole-cell patch-clamp recordings from neonatal rat somatosensory (Khazipov et al., 2004b; Minlebaev et al., 2007, 2009) and visual (Colonnese and Khazipov, 2010; Colonnese et al., 2010; Hanganu et al., 2006) cortex. These studies have revealed a pivotal role for glutamatergic and GABAergic synapses in the generation of the early activity patterns.

The mechanisms of spindle-bursts were investigated in detail in the neonatal rat barrel cortex (Minlebaev et al., 2007, 2009) using a superfused cortex preparation *in vivo*, enabling the application of drugs directly to the cortex. Pharmacological analysis revealed that generation of spindle-bursts in the neonatal barrel cortex primarily involves glutamatergic mechanisms (Figure 8.4). Interestingly, the relative contribution of AMPA/kainate and NMDA-Rs to the generation of the delta and alpha–beta components is different. Rapid alpha–beta oscillations mainly require AMPA/kainate receptors, and blockade of NMDA-Rs has no significant effect on this rapid oscillatory component. On the other hand, delta waves are generated by both types of glutamate receptors acting in concert, though with a primary contribution of NMDA-Rs. The differential contribution of the AMPA/kainate and the NMDA-Rs to the two components of the spindle-burst probably reflects a difference in the kinetics of the synaptic currents mediated by these receptors. AMPA-R-mediated synaptic currents have fast rise and decay times in the millisecond range (see, e.g., Crair and Malenka, 1995; Kidd and Isaac, 1999; Khazipov et al., 2004b) and therefore are ideally suited for synchronization of the rapid activities, such as alpha–beta oscillations. NMDA-R-mediated synaptic currents have rise times in the range of tens of milliseconds and decay times of hundreds of milliseconds; they are particularly slow at the immature synapse (Carmignoto and Vicini, 1992; Chittajallu and Isaac, 2010; Hestrin, 1992; Khazipov et al., 1995; Monyer et al., 1994). The slow kinetics of NMDA-R-mediated synaptic currents enables their powerful summation during rhythmic activation of synaptic inputs during spindle-bursts. The high NMDA/AMPA ratio at the immature synapses is another important factor contributing to the

increased contribution of NMDA-Rs to the delta wave (Chittajallu and Isaac, 2010; Crair and Malenka, 1995; Durand et al., 1996; Gasparini et al., 2000; Isaac et al., 1997; Voronin et al., 2004).

NMDA-R-dependent patterns of activity in developing cortical networks have also been described in cortical tissue *in vitro*, including hippocampal giant depolarizing potentials (GDPs) (Ben-Ari et al., 1989) and associated calcium oscillations (Allene and Cossart, 2010; Allene et al., 2008; Crepel et al., 2007; Leinekugel et al., 1997) and neocortical bursting and oscillatory activity (Arumugam et al., 2005; Dupont et al., 2006; Garaschuk et al., 2000; Kandler and Thiels, 2005; LoTurco et al., 1991). Interestingly, in the case of hippocampal GDPs, depolarizing γ-aminobutyric acid (GABA) may facilitate activity of NMDA-Rs by attenuation of their voltage-dependent magnesium block (Khazipov et al., 1997; Leinekugel et al., 1997). Activation of NMDA-Rs during spindle-bursts may be directly linked to the plasticity mediated by these receptors in the developing cortex. Indeed, pharmacological or genetic manipulations associated with a loss of function in NMDA-Rs results in malformations of barrel cortex development and functional deficits (Dagnew et al., 2003; Fox, 2002; Fox et al., 1996; Iwasato et al., 2000; Lee et al., 2005a,b; Schlaggar et al., 1993). During the critical period, thalamocortical synapses display an enhanced NMDA-R contribution and increased NMDA-R-dependent synaptic plasticity, including the conversion of 'silent' pure NMDA-R-based synapses to fully functional mixed AMPA/NMDA-R synapses, as well as a switch to fast AMPA-receptor-mediated synaptic transmission from slow kainate-mediated transmission (Bannister et al., 2005; Barth and Malenka, 2001; Carmignoto and Vicini, 1992; Crair and Malenka, 1995; Daw et al., 2006; Feldman et al., 1998, Hestrin, 1999, 1992; Isaac et al., 1995, LoTurco et al., 1997, 1991; Monyer et al., 1994). Activation of NMDA-Rs achieved by massive summation of thalamocortical input during spindle bursts provides a long time window for coincident activation of cortical neurons by the thalamocortical cells. This physiological paradigm may underlie the NMDA-R-dependent plasticity in developing thalamocortical synapses, including both potentiation/maintenance of the activity during spindle-burst synapses and depression/elimination of those synapses that are less recruited by spindle-bursts. Plasticity in developing synapses is spike-time-dependent, and the synaptic strength can be bi-directionally modified by correlated pre-/postsynaptic spiking within a narrow time window on the order of 10 ms (Mu and Poo, 2006; Chapter 9). While recent findings indicated that the early oscillatory patterns may induce bi-directional plasticity at thalamocortical synapses (Minlebaev et al., 2011), whether STDP occurs during early oscillatory patterns is an important question for the further research.

While a considerable amount of data has now accumulated about network mechanisms of spindle-bursts, the generation of gamma-bursts is less well understood. In the adult brain, neuronal synchronization by gamma oscillations is a fundamental process in cortical computation (Buzsaki, 2006; Fries, 2009). Synchronized by inhibition (Bartos et al., 2007), gamma oscillations subserve perceptual binding (Gray and Singer, 1989) and support synaptic plasticity (Wespatat et al., 2004). The ontogeny and role of gamma oscillations in developing networks, however, remain controversial. It was generally accepted that gamma oscillations emerge relatively late in development (Uhlhaas et al., 2010) as associative cortical layers and large-scale connections (Bureau et al., 2004; Luhmann et al., 1986), which are required for perceptual binding, and GABAergic inhibition (Daw et al., 2007; Doischer et al., 2008; Luhmann and Prince, 1991), which is pivotal for gamma rhythmogenesis, both develop on a delayed timescale. Yet, several studies have now indicated the existence of transient, local, gamma-burst oscillations in the neonatal rat somatosensory (Yang et al., 2009) and visual (Colonnese et al., 2010) cortices. Moreover, studies in the neonatal rat barrel cortex revealed that the early gamma oscillations (EGOs) are specifically evoked in a single cortical barrel by stimulation of the corresponding (principal) whisker (Minlebaev et al., 2011). Simultaneous recordings from the ventro-posterior-medial (VPM) barreloids and cortical barrels have shown that the EGOs are primarily driven by a thalamic oscillator and synchronize neurons in a single thalamic barreloid and the corresponding cortical barrel. Basing on these findings and the results of whole-cell recordings from L4 neurons, the following network EGOs model has been suggested: (1) Sensory input from a whisker activates the gamma oscillator in the thalamic barreloid, which provides topographic feedforward synchronization in the corresponding cortical barrel; (2) cortical interneurons become involved in EGOs in an age-dependent manner: until ~P5, EGOs are independent of cortical inhibition, but starting from P5, along with the development of feedforward inhibition, interneurons are recruited and support EGOs by controlling runaway recurrent cortical excitation. Thus, during the first postnatal week, EGOs undergo evolution from a primitive form of cortical activity passively following a thalamic oscillator to a more complex interactive model in which an active cortical oscillator, by virtue of emerging inhibition, starts to support gamma oscillations. Interestingly, artificial EGOs mimicked by pairing subthreshold gamma-rhythmic thalamic input with action potentials in L4 neurons in thalamocortical slices resulted in long-lasting potentiation of thalamocortical EPSPs. It has been suggested that in contrast to the inhibition-based "adult" gamma oscillations, which emerge at the end of the second postnatal week and

enable horizontal synchronization, EGOs are primarily driven by gamma-rhythmic excitatory thalamic inputs and provide vertical synchronization between topographically aligned thalamic and cortical neurons. Multiple replay of the sensory input in the thalamocortical synapses during EGOs ("repetitio est mater studiorum!") may allow thalamic and cortical neurons to be woven into vertical topographic functional units prior to the development of horizontal binding and other integrative cortical functions subserved by "adult" gamma oscillations in the mature brain.

Another intriguing question concerns the contributions of depolarizing and excitatory GABA actions to the early cortical-activity patterns. GABA is the main inhibitory neurotransmitter in the adult brain. Synchronous inhibition by hyperpolarization and a shunt provided by GABAergic interneurons are instrumental for the generation of various activity patterns in the adult brain (Bartos et al., 2007; Buzsaki, 2006; Freund and Buzsaki, 1996; Wang, 2010). However, slice preparations suggest that early in development – including the embryonic period and the first postnatal week in rodents – GABA, acting via chloride-permeable GABA (A) receptors, exerts a depolarizing and excitatory action on immature neurons as a result of their elevated intracellular chloride concentration (LoTurco et al., 1995; Luhmann and Prince, 1991; Owens et al., 1996; Tyzio et al., 2006; Yamada et al., 2004; Yuste and Katz, 1991; reviewed in Ben Ari et al., 2007; and is discussed extensively in Rubenstein and Rakic, 2013). Elevated intracellular chloride in the immature neurons is a result of high activity of the chloride-loading co-transporter NKCC1 and delayed expression of the chloride extruder KCC2 (Rivera et al., 1999; Yamada et al., 2004). Depolarizing GABA is involved in the generation of the primitive pattern of neuronal network activity in the immature hippocampus and cortex – so-called GDPs (Allene et al., 2008; Ben-Ari et al., 1989; Dzhala et al., 2005; Khazipov et al., 2004a; Rheims et al., 2008; Sipila et al., 2005). During GDPs, both pyramidal cells and interneurons fire randomly within a very large time window of few hundreds of milliseconds. Excitation of pyramidal cells and interneurons during GDPs is brought about by synergistic excitatory actions of GABA and glutamate (Bolea et al., 1999; De la Prida et al., 1998; Khazipov et al., 1997; Lamsa et al., 2000; Leinekugel et al., 1997; Menendez et al., 1996; Valeeva et al., 2010).

Does GABA play a similar excitatory action in the generation of the early oscillatory patterns of cortical activity *in vivo*? Unfortunately, at present there is surprisingly little experimental evidence that GABA exerts excitatory actions on immature cortical neurons *in vivo*, as it does *in vitro*. At present, the only information available about the roles of GABAergic interneurons *in vivo* is based on the effects of pharmacological manipulations of GABAergic synaptic transmission on network-driven activities. In the neonatal rat hippocampus, the dominant neuronal network patterns of activity (GDPs *in vitro* and sharp waves *in vivo*) are blocked by the NKCC1 antagonist, bumetanide, which shifts the reversal potential of the GABA(A)-receptor-mediated responses toward negative values (Dzhala et al., 2005; Sipila et al., 2006; Tyzio et al., 2006). Although a similar effect of bumetanide on the GABA(A) reversal potential was found in neocortical neonatal neurons (Tyzio et al., 2006; Yamada et al., 2004), bumetanide did not significantly affect spindle-bursts in the barrel cortex *in vivo* (Minlebaev et al., 2007). Therefore, it appears that early hippocampal patterns of sharp waves *in vivo* and GDPs *in vitro* are more dependent on the depolarizing actions of GABA than the neocortical pattern of spindle-bursts, consistent with observations *in vitro* (Garaschuk et al., 2000; Rheims et al., 2008).

However, GABAergic interneurons do clearly participate in the generation of spindle-bursts and gamma-bursts in an age-dependent manner, as evidenced by the effects of the GABA(A)-receptor antagonists and positive allosteric GABA(A)-receptor modulators. Although blockade of GABA(A) receptors does not significantly affect the frequency of oscillations in the alpha–beta frequency domain, it does increase the power of these oscillations, as well as increase the amplitude of the delta component and the occurrence of spindle-bursts. Gamma oscillations are little affected by blockade of cortical inhibition until P5, but they are suppressed in older animals. The opposite manipulation, enhancement of GABA(A)-receptor-mediated currents by diazepam, reduces by twofold the occurrence of spindle-bursts. These results suggest that GABAergic interneurons play an inhibitory role in spindle-burst generation. In keeping with these findings, blockade of GABA(A) receptors strongly increases the size of cortical areas activated during spindle-bursts. Spindle-bursts are local events, and the diameter of the cortical zones activated during spindle-bursts usually does not exceed 0.5 mm. After blockade of GABA(A) receptors, spindle-bursts can be recorded at distances up to 1–2 mm. Thus, the spread of spindle-bursts is determined not only by the topographic thalamocortical excitatory input (Agmon et al., 1996; Bureau et al., 2004; Ferezou et al., 2006; Higashi et al., 2002; Khazipov et al., 2004b; Kidd and Isaac, 1999; Petersen and Sakmann, 2001), but also by surround GABAergic inhibition that prevents horizontal spread of the activity via long-range glutamatergic cortical connections, a pattern also observed in the adult neocortex (Chagnac-Amitai and Connors, 1989; Fox et al., 2003; Sun et al., 2006). The inhibitory action of GABA at the network level does not necessarily imply a hyperpolarizing action, as even depolarizing GABA may produce strong inhibition via shunting mechanisms amplified by activation of the voltage-gated potassium channels and inactivation of sodium channels (Borg-Graham

et al., 1998; Gao et al., 1998; Gulledge and Stuart, 2003; Lu and Trussell, 2001). These results, which suggest an inhibitory role of GABA during generation of spindle-bursts, are in general agreement with the finding that GABA(A) antagonists induce hypersynchronous seizure-like activity in the neocortex *in vivo* by P3 (Baram and Snead, 1990) and *in vitro* by P2 (Wells et al., 2000). These results are also in keeping with the plasticity changes induced in the developing barrel cortex by chronic treatment with the GABA(A)-receptor agonist, muscimol (Wallace et al., 2001).

8.5 DISCONTINUOUS TEMPORAL ORGANIZATION OF THE EARLY ACTIVITY

The uniqueness of immature cortical activity consists not only of developmentally restricted patterns of activity, but also stems from its *discontinuous temporal organization* (Figures 8.5 and 8.6). The first reports of the discontinuous nature of early cortical activity were made in human preterm neonates using scalp electrographic recordings by Dreyfus-Brisac, Monod, and their colleagues. Analyzing EEGs from preterm neonates during the second half of gestation (Dreyfus-Brisac, 1962; Dreyfus-Brisac and Larroche, 1971; Dreyfus-Brisac et al., 1956), they noted that the cortical EEG was organized in intermittent bursts separated by periods of isoelectric EEG that could last for tens of seconds. This temporal organization was named *tracé discontinu*. With maturation, flat periods between the bursts became shortened, and starting from about 30 weeks of postconceptional age, *tracé discontinu* evolves to *tracé alternant* with low-voltage activity between the bursts, though even at term, some discontinuity is still evident (Lamblin et al., 1999; Stockard-Pope et al., 1992).

Such extreme discontinuity of cortical activity is striking. Indeed, showing EEG recordings obtained from a healthy premature neonate to an "adult" neurophysiologist without revealing the age of the patient would result in a diagnosis such as severe posthypoxic encephalopathy or barbiturate coma. Yet, this discontinuity is a normal feature of the immature cortex, and this raises several questions: Does discontinuity simply reflect immaturity of the nervous system, which is incapable of maintaining continuous activity, or, in keeping with Mozart's claim that the most meaningful element of a musical masterpiece is a pause, has it physiological roles for development?

The first question about human discontinuity is whether it results from true network silence as observed during slow-wave sleep in adults, or is it the result of temporally uncoordinated activity of neurons? This question has been examined in neonatal rats. Extracellular recordings of multiple unit activity showed that neurons fire virtually no action potentials during isoelectric EEG epochs. In agreement with this result, patch-clamp recordings revealed that neurons stay relaxed at their resting membrane potential ~80 mV and receive very little synaptic input during isoelectric EEG periods. This means that isoelectric EEG epochs reflect synchronous neuronal silence. Such a state of collective silence, called the down-state, also exists in the adult EEG. Considerable evidence suggests that isoelectric epochs are by nature the same phenomenon as down-states of long duration. In adults, down-states with durations from tens of milliseconds to a few hundred milliseconds occur during deep sleep in alternation with up-states (Buzsaki, 2006; Steriade, 2001; Steriade et al., 1993). Oscillation

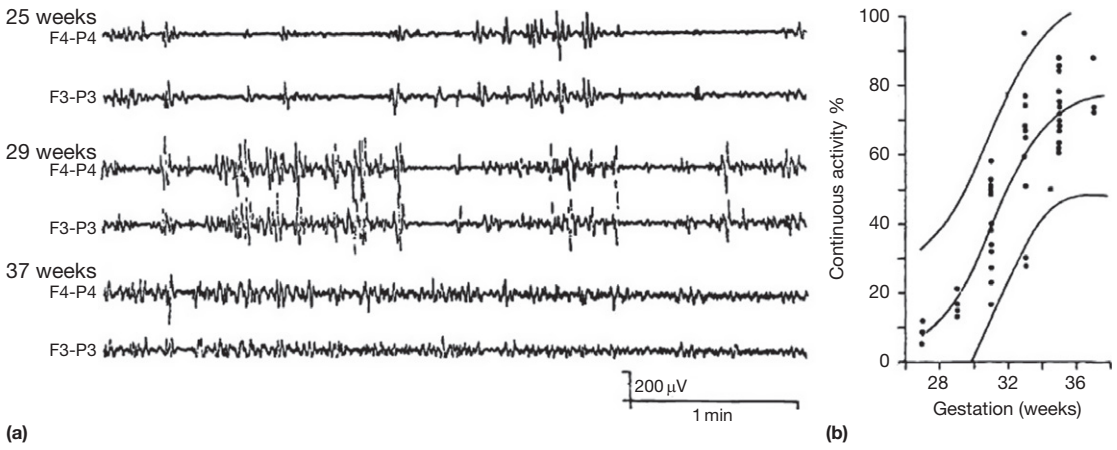

FIGURE 8.5 Developmental changes in continuity of human cortical activity. (a) EEG of preterm infants at 25, 29, and 37 gestational weeks. The duration of silent periods decreases, while the length of periods of continuous activity increases with age. (b) Quantification of the proportion of EEG containing continuous activity (continuity defined as >80% continuous activity in 5-min epochs with attenuated activity 10–20 µV lasting no longer than 5 s). *Adapted with permission from Connell JA, Oozeer R, Dubowitz V (1987) Continuous 4-channel EEG monitoring: A guide to interpretation, with normal values, in preterm infants.* Neuropediatrics *18: 138–145.*

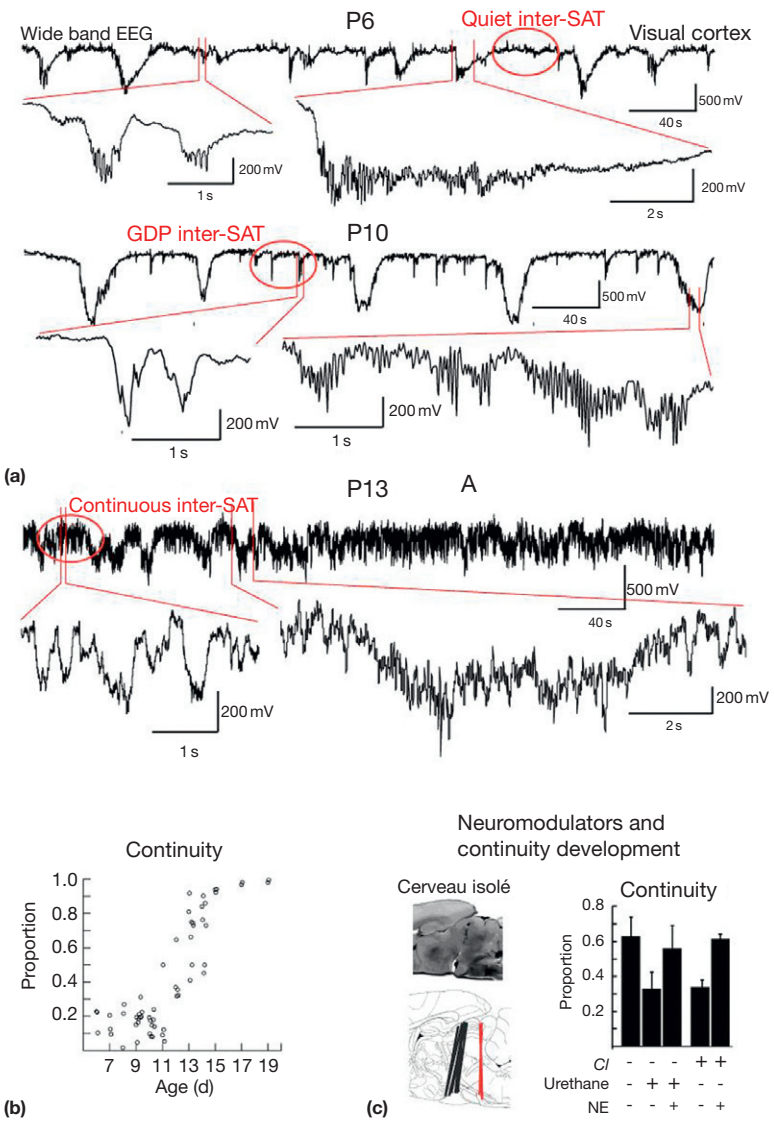

FIGURE 8.6 Developmental changes in diversity and continuity of rodent cortical activity. (a) Wide-band extracellular recording of spontaneous activity in layer 4 of the visual cortex in awake rats at P6, 10, and 13. At P6, all events consist of retinal-wave driven (see Figure 8.3), slow negative-activity transients (SATs) of varying length that contain faster rhythmic oscillations (left and right example). Inter-SAT activity is rare. During the second postnatal weeks, SATs become elongated (left example), while inter-SAT activity consists of occasional 200-ms–1-s bursts of action potentials (giant-depolarizing potentials (GDPs), right example). At the end of the second week, SATs become reduced and irregular (left example), while inter-SAT activity becomes continuous and diverse (right example). See Figure 8.3(c) for quantification. (b) Continuity of activity by post-natal age. Continuity of activity as a function of post-natal age was measured as the proportion of 500-ms epochs that contain at least one action potential in multi-unit recordings. (c) Role of ascending neuromodulators in the development of continuous activity. Surgical isolation at the rostral midbrain border (right image, CI) or urethane anesthesia reduces the continuity of spontaneous activity in P13–15 rats. Application of norephinephrine (NE) to the cortical surface increases continuity in lesioned and anesthetized animals. Error bars SEM. *Adapted with permission from Colonnese MT and Khazipov R (2010) "Slow activity transients" in infant rat visual cortex: a spreading synchronous oscillation patterned by retinal waves.* Journal of Neuroscience *30: 4325–4337 (a) and Colonnese MT, Kaminska A, Minlebaev M, Milh M, Bloem B, Lescure S, Moriette G, Chiron C, Ben-Ari Y, Khazipov R (2010) A conserved switch in sensory processing prepares developing neocortex for vision.* Neuron *67: 480–498 (b, c).*

between up- and down-states generates slow waves in the EEG, and therefore these deep stages of sleep are also called slow-wave sleep oscillations. Intracellular studies indicate that when the level of mutual excitation in the cortical network falls below the critical level maintaining the up-state, which is partly due to the activity-dependent depression in glutamatergic synapses, neurons return to their resting membrane potential during down-states (Contreras et al., 1996; Sanchez-Vives and McCormick, 2000; Shu et al., 2003).

Immature neurons do just the same, but for much longer periods of time; however, one important difference between immature cortical activity and adult sleep is that the immature cortex maintains these long-duration down-states even when the animal is awake. In adults, the awake state is characterized by a continuous (a.k.a. activated or desynchronized) mode of cortical function. Intracellular recordings show little difference between continuous cortical activity during awake, REM sleep, and up-states during slow-wave sleep. The activated cortical state is not present in neonatal rats or young premature neonates and starts to emerge in the rat during the second postnatal week and a month before term in humans, coinciding with the emergence of clearly differentiable sleep states in both species (Jouvet-Mounier et al., 1970; Lamblin et al., 1999). Interestingly, the active state does not emerge simultaneously in the entire cortex. Increase in the amount and continuity of spontaneous activity occurs first in the somatosensory and then in the visual cortex, both in the rat and humans, which also coincides with elimination of delta-brushes and spindle-bursts in these areas (Colonnese et al., 2010; Curzi-Dascalova et al., 1993; Dreyfus-Brisac and Larroche, 1971; Lamblin et al., 1999).

At least two developmental factors are likely involved in the emergence of the activated cortical state: development of arousal systems and intracortical connections. In the rat, maturation of sleep/wake transitions depends on noradrenergic development (Gall et al., 2009) and maturation of cholinergic (Mechawar and Descarries, 2001) and noradrenergic afferents and receptor distributions (Latsari et al., 2002; Venkatesan et al., 1996) around this time. Isolating the forebrain from ascending neuromodulatory arousal inputs in P13–15 rats reverses the developmental increase in spontaneous cortical activity, reinstating an immature mode of discontinuity (Figure 8.6). Continuity can then be reinstated by cortical application of norepinephrine (Colonnese et al., 2010), a key initiator of the activated cortical state (Berridge and Waterhouse, 2003; Foote and Morrison, 1987a,b). However, this is not to say that arousal systems are not functional before this time. Actually, many aspects of brainstem and forebrain arousal systems operate well before the emergence of the active cortical state; for example, infant rats and humans give evidence of behavioral sleep–wake cycles, state-dependent firing of hindbrain sleep control neurons (Karlsson et al., 2005), and modulation of cortical EEG patterns by the sleep state (Seelke and Blumberg, 2010). Furthermore, functional monaminergic and cholinergic connections are in place quite early (Hanganu et al., 2007; Johnston and Coyle, 1981). Yet, arousal systems appear incapable of inducing a continuous active state in the immature cortex. Thus, the acquisition of brainstem control of cortical states likely requires more than a simple engagement of neuromodulatory systems, and also thalamocortical changes. A prominent candidate is the strengthening of long- and short-range intracortical connectivity, required for maintenance of the activated cortical state (Sanchez-Vives and McCormick, 2000; Shu et al., 2003).

A number of observations are consistent with an increase in functional cortical connectivity over this time period. First, while k-complexes and sleep-spindles, stimulated by light in adults, are synchronized throughout the cortex (Amzica et al., 1998) via horizontal cortical and corticothalamic connections (Contreras et al., 1996, 1997), delta-brushes are local events (Khazipov et al., 2004b; Yang et al., 2009). Second, as noted earlier, in adults, episodes of network silence (down-states) during sleep do not exceed 500 ms (Steriade, 2001), whereas the silent periods in the young rat pups or preterm infants can run to tens of seconds. Such long silent periods are observed in cortical slabs and slices, that is, under conditions of markedly reduced cortical connectivity (Sanchez-Vives et al., 2000; Steriade et al., 2005; Timofeev et al., 2000). Finally, the network of horizontal connections between pyramidal neurons emerges shortly before eye opening in cats (Callaway and Katz, 1990; Galuske and Singer, 1996) and ferrets (Durack and Katz, 1996; Ruthazer and Stryker, 1996), independently of visual input. In humans, dense horizontal connections are also first observed at GW37 (Burkhalter et al., 1993). Therefore, emergence of the continuous mode of cortical activity likely results from a coincidence of two developmentally regulated factors: (1) maturation of the brainstem arousal input to the cortex, which provides tonic neuronal depolarization, and (2) formation of excitatory synaptic connections between cortical neurons, which are needed for maintenance of the activated cortical state.

In conclusion, it is tempting to propose a hypothesis whereby discontinuity and long silent periods are important for circuit development. Growing evidence indicates that developing synapses display very high levels of plasticity, as governed by the Hebbian principle "neurons that fire together wire together" (Hebb, 1949), which in a more elaborated way is formulated as STDP (Dan and Poo, 2006; Mu and Poo, 2006). STDP implies that the strength of synaptic connections can be bi-directionally modified – either potentiated or depressed – depending on spike timing in pre- and postsynaptic neurons. If the spike in a presynaptic neuron precedes the spike in the postsynaptic neuron (as in the case the postsynaptic neuron was driven by the presynaptic neuron), the synapse will be potentiated; if the opposite occurs, the synapse is depressed. The most efficient changes in both directions occur when correlated spiking occurs within a time window of ten of milliseconds. These functional changes in the strength of synaptic connections were proposed as precursors of further anatomic changes – synapse stabilization and elimination in the cases of potentiation and depression, respectively.

Let us put STDP into the context of temporal organization, that is continuity/discontinuity, and examine how this is expected to impact plasticity in a thalamocortical synapse. We know that a sensory input triggers topographic delta-brushes, providing pre-before-post firing in the appropriate thalamocortical synapse and thus conditions for potentiation/stabilization. From the plasticity standpoint, the ideal case for potentiation would be if two conditions are met: (1) each pre-spike is followed by a post-spike, and (2) each post-spike is preceded by a pre-spike. These conditions will be achieved if topographic thalamocortical synapses provide a necessary and sufficient excitatory drive to cortical cells. Excitation of cortical neurons by intracortical synapses during intracortically generated spontaneous activity would introduce noise to the system, as random – in relation to thalamic input – firing of cortical neurons will create variable conditions for STDP in the thalamocortical synapse. In the developing cortex, this noise is eliminated by delayed introduction of horizontal connections, which strongly increases the plasticity impact of sensory-driven thalamocortical bursts. This hypothesis is supported by

studies in the developing *Xenopus* retinotectal system, in which it was shown that activity-induced synaptic modifications are quickly reversed either by subsequent spontaneous activity in the tectum or by exposure to random visual inputs (Zhou and Poo, 2004b; Zhou et al., 2003). This reversal depended on the burst spiking and activation of the *N*-methyl-D-aspartate subtype of glutamate receptors. Stabilization of synaptic modifications could be achieved by an appropriately spaced pattern of induction stimuli. These findings underscore the vulnerable nature of activity-induced synaptic modifications *in vivo* and suggest a temporal constraint on the pattern of visual inputs for effective induction of stable synaptic modifications. These findings are also linked to the developmental changes in the sensory-evoked activity patterns that will be discussed in the next section.

8.6 EARLY ACTIVITY PATTERNS AND THE DEVELOPMENT OF PERCEPTION

In this chapter, we have identified two characteristics of neocortical activity during the time of cortical layer formation and thalamic in-growth and map formation: the presence of "slow-activity transients" containing rapid oscillations (including spindle-bursts and delta-brushes) and a discontinuous pattern of activity, that is, the presence of long periods of neuronal silence. We argue that these features are the result of a unique network state specific to early development that is optimized to drive synaptic plasticity in thalamocortical networks in response to spontaneous activity generated in the sense organs. Because early spontaneous activity at the sensory periphery is infrequent, the early cortex must remain mostly quiet. Secondly, because cortical circuits are concerned primarily with the presence and absence of activity within topographic space, they produce bursts of highly correlated firing containing little additional information.

The final question that concerns us is the transition to mature patterns of cortical activity: when do they occur and what are their behavioral correlates and mechanisms? This issue has been studied most extensively in the visual system. Here the activity patterns in the sense organ are best understood, and relative roles of neuronal activity and the environment in maturation can be examined. Cortical visual development can be roughly divided up into four periods: (1) the completely pre-visual period, when phase 2 retinal waves are transmitted to the cortex; (2) an obscured visual phase, when phase 3 (glutamatergic) retinal waves are prominent but coexist with initial photo-receptor-driven light responses (Huberman et al., 2008) that allow cortical visual responses to be driven through the closed eye-lids (Akerman et al., 2004; Chapman and Stryker, 1993; Ohshiro and Weliky, 2006); (3) a pre-critical period (Feller and Scanziani, 2005) that follows eye-opening, during which new visual experience drives development of binocularity, orientation, and direction selectivity (Smith and Trachtenberg, 2007; White et al., 2001); and (4) the classical critical period for monocular deprivation plasticity (Hubel and Wiesel, 1970).

As reviewed above, the early period of spontaneous cortical activity, consisting of delta-brushes, SATs, and discontinuity occurs throughout the first and second visual development periods, rapidly maturing around the time of eye-opening and the transition to the third period. Colonnese et al. (2010) examined the role of this transition of thalamocortical networks in determining visual-response properties in rats and human preterm infants. In the somatosensory system, both spontaneous muscular twitches and direct touch are effective in eliciting cortical delta-brushes. Perhaps this is not surprising, given that the ultimate effect on the sense organ was similar. However, the activation of retinal ganglion cells by light is weaker and patterned differently than during retinal waves (Blankenship et al., 2009; Kerschensteiner and Wong, 2008; Tian and Copenhagen, 2003). This casts doubt on a possible interaction between these transmission systems for spontaneous and evoked visual activity. Furthermore, primate retinas have weaker and less-organized spontaneous activity during the later gestational period (Warland et al., 2006), further questioning a potential interaction between spontaneous and evoked activity patterns in humans.

Despite these facts, whole-field light flashes directed to the closed eyelids of rats evoked a complex of oscillatory patterns in the cortex typical of the spontaneous activity patterns observed at this age (Figure 8.7(a)). Despite weak or absent retinal visual responses *in vitro*, robust light responses could be evoked as early as P8. Cortical light responses consisted of a complex of described activity patterns, including an initial response that included a gamma-burst and a GDP, followed by an evoked delta-brush. Electrical stimulation of the retina showed that these patterns did not result from simply the triggering of retinal waves by light, but emerged in the thalamocortical circuit following even brief inputs. Similar visual stimuli evoked a similar complex of activity patterns, including delta-brushes, in the occipital EEGs of sleeping preterm infants from as early as they could be recorded (27 gestational weeks). Thus, the network properties dedicated to transmitting retinal waves are also recruited during visual stimulation, even though the importance of such stimuli to thalamocortical activity at these ages is questionable. Together, these data show that the early activity bursts are a fundamental response to thalamic input, regardless of source, that shapes sensory processing.

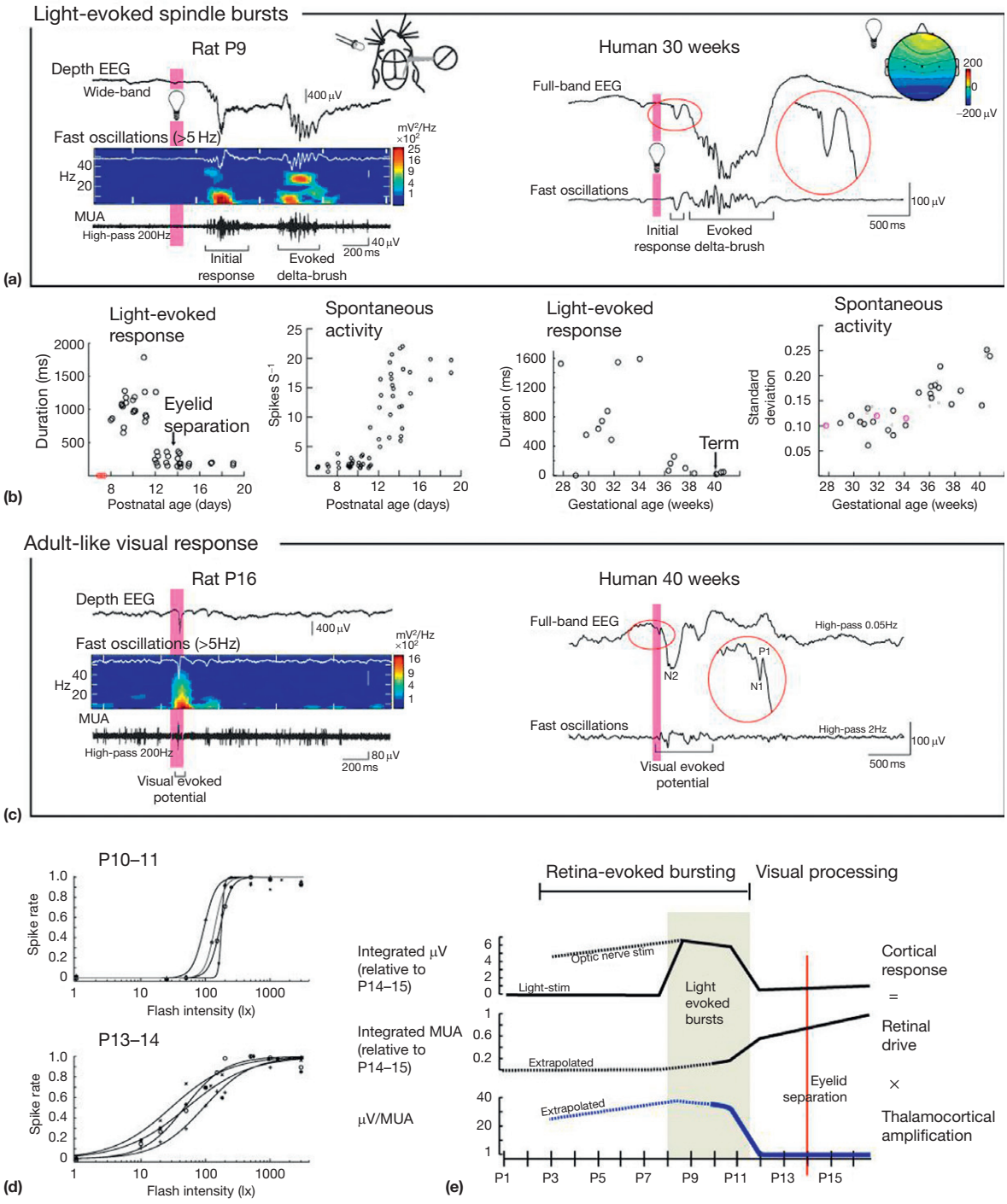

FIGURE 8.7 Role of thalamocortical-network changes in the development of visual processing. (a) Cortical visual responses during early development in rats (left) and preterm infants (right). During the period of discontinuous cortical activity, full-field light flashes trigger bursts of endogenous delta-brush oscillations resulting in a large amplitude potential and long-lasting response. Example wide-band traces from depth EEG (rat) or surface EEG (human) are shown along with a time-series spectrogram and MUA for the rat and a high-pass filtered trace to show rapid oscillations for the human. Electrode map in the top-right corner shows localization of the negative slow wave to occipital electrodes. (b) Linked development of the mature pattern of visual processing and continuous activity. In both species, short visual responses and continuous cortical activity rapidly emerged just before active visual exploratory behavior at eye-opening (rats) or birth (humans). (c) Example traces of visual-evoked responses after eye-opening (rats) or birth (humans). (d) Bursting behavior of early cortical circuits prevents graded visual responses. Spike rates in layer 4 of the rat visual cortex during the initial response show all-or-nothing bursting to graded light intensities during the period of discontinuity. Graded visual responses are observed rapidly following the switch in cortical activities. (e) Early cortical oscillations amplify thalamic input during the early period. This amplification is downregulated to allow for graded visual processing just before pattern vision. Thalamocortical amplification was estimated by dividing the evoked cortical potential by the *in vitro* retinal spiking response in age-matched rats. *Adapted with permission from Colonnese MT, Kaminska A, Minlebaev M, Milh M, Bloem B, Lescure S, Moriette G, Chiron C, Ben-Ari Y, Khazipov R (2010) A conserved switch in sensory processing prepares developing neocortex for vision.* Neuron *67: 480–498.*

Using this controlled stimulation to assay the development of the thalamocortical response properties revealed that the developmental transition to mature patterns of visual response occurs as a rapid switch 1–2 days before eye-opening in rats (Figure 8.7(b) and 8.7(c)). In addition to this switch in visual-response patterns, the amount and continuity of spontaneous activity began to increase (and would continue to do so over the next weeks) on the same day. A similar switch in evoked and spontaneous activity occurred in the occipital cortex of human infants between 34 and 36 gestational weeks, that is, just before natural term (human fetuses open their eyes at the end of the second trimester). In both species, this switch consisted of a loss of the early cortical burst oscillations and their replacement by the visual evoked potential (VEP). As such, it results in a surprising decrease in the size and duration of visual responses.

Functionally, why would visual responses need to become reduced in size just before the onset of visual processing? One clue comes from examining the response curves to varying light intensities before and after the switch (Figure 8.7(d)). Before the switch, visual responses were 'all-or-none' bursts, effectively registering the presence of a minimal stimulation, but not its intensity. Only after the reduction of visual response with the switch could graded responses be attained. Measurement of the spiking responses of retinal ganglion cells in acutely excised retina allowed further quantification of the input–output relationships before and after the switch (Figure 8.7(e)). These revealed an inverse relationship between retinal and cortical light responses, with the reliability of retinal spiking to light flashes rapidly increasing just as the amplitude of the cortical response decreased. This had the effect of massively decreasing the amplification in thalamocortical circuits. Thus, we suggest that the primary role of early activity patterns, in addition to precisely synchronizing activity, is to amplify weak, young inputs. Such an amplification is incompatible with visual processing and thus is downregulated before vision is initiated at eye-opening or birth.

This switch in cortical-activity patterns, from a discontinuous mode with early bursting oscillations to continuous baseline activity with more restricted, graded response, appears to be universal for all sensory systems studied so far (Figure 8.8). Intriguingly, while the developmental template remains the same, the timing of the switch appears to differ between sensation and species, with the common feature being that it occurs shortly before the onset of active sensation for that system. This is best illustrated in the somatosensory whisker system, where passive activation (i.e., external touch of the whisker) is distinguished from active touch, or whisking. Rats begin active whisking 2–3 days before eye-opening (Landers and Philip, 2006). Similarly, they experience the same switch in cortical activity before the visual cortex (Figure 8.8, top). The issue has not been examined in depth in human infants, but the available data suggest less heterogeneity in the timing of the switch between

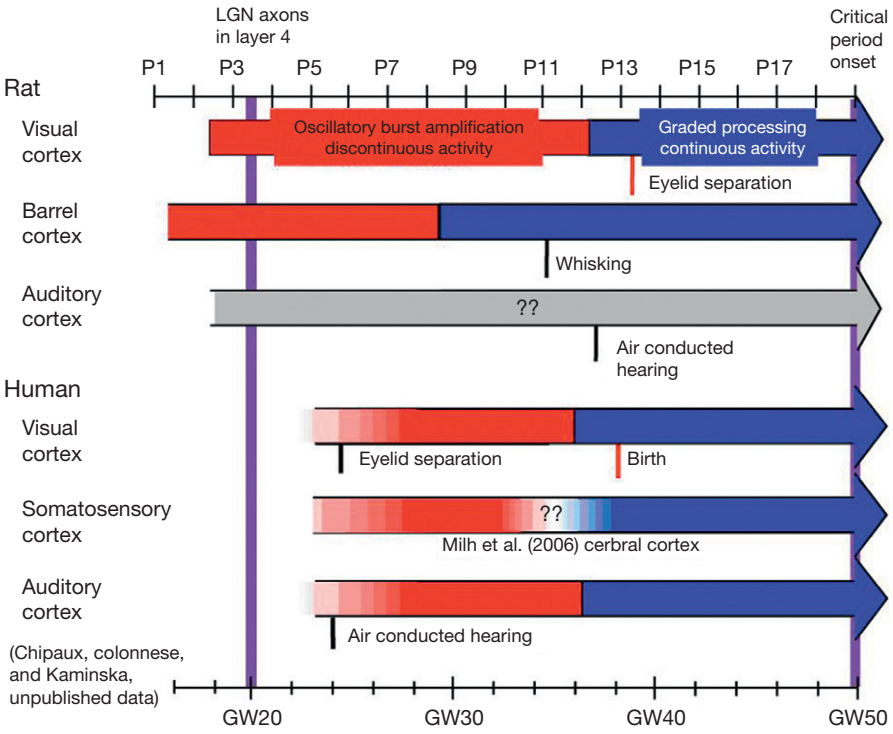

FIGURE 8.8 Two-state model of cortical-activity development. Known transition times from early bursting responses (evoked delta-brushes) to mature responses for multiple sensory systems in the human and the rat. Developmental timelines are aligned to the independent time points shown by purple lines. The timing of the switch in cortical circuits is correlated to the onset of exploratory sensation (e.g., whisking or eye-opening), which occurs at different times for the rat, but simultaneously at birth for humans, and this heterochrony is matched in the cortical-activity pattern development. ?? signifies unexplored time points. *Adapted with permission from Colonnese MT, Kaminska A, Minlebaev M, Milh M, Bloem B, Lescure S, Moriette G, Chiron C, Ben-Ari Y, Khazipov R (2010) A conserved switch in sensory processing prepares developing neocortex for vision.* Neuron *67: 480–498.*

sensory systems. This is consistent with our notion that timing is tied to active exploration, which in humans occurs for all systems around the same time, namely birth.

The mechanisms responsible for the timing of this switch are poorly understood. The close correlation with the acquisition of continuous activity implicates the regulation of spontaneous activity in the switch. This is confirmed by observations that surgical isolation of mid/hindbrain ascending neuromodulatory systems from the neocortex reinstates early bursting as well as increases the discontinuity of activity (Figure 8.6). Such a regulation of sensory processing by the level of synaptic background activity is consistent with observations in adult animals (Destexhe et al., 2003). Neocortical neurons, during waking or 'up-states' observed during slow-wave sleep, receive constant synaptic activity, which is maintained through local network dynamics (Haider and McCormick, 2009) that can modulate gain (Chance et al., 2002) and adjust the sensitivity to inputs (Arieli et al., 1996; Borg-Graham et al., 1998). The timing of this switch is closely linked to the surge in synaptic density observed in the cerebral cortex that begins just before birth in monkeys and humans (Bourgeois and Rakic, 1996; Huttenlocher and Dabholkar, 1997) and before nest-exit/eye-opening in rats (Blue and Parnavelas, 1983). Interestingly, this is one of the sole features of neocortical development that violates the conserved timing of neurogenic events across mammalian species (Clancy et al., 2001), suggesting it is independently regulated to support the active exploration of the sensory world that will follow. Despite this violation of neurogenic timing and heterogeneity between sensory systems, the timing of the switch does not appear to be experience-dependent, as neither dark rearing nor early eye-opening could modify its timing in rats (Colonnese et al., 2010).

The evidence reviewed so far in this chapter is consistent with the hypothesis that early circuit development is characterized by a unique state of cortical-network dynamics in which spontaneous activity is maintained in a discontinuous mode and inputs are amplified by cortical-burst oscillations. This period appears tightly regulated to coincide with the sensory isolation experienced in the womb (or maintained by eye- or ear-canal closure in rodents), and to end when sensory processing is initiated. From this point on, many of the gross characteristics of adult cortical activity can be discerned, including clear regulation of cortical EEG by sleep state (Jouvet-Mounier et al., 1970), increased frequency of delta-waves in slow-wave sleep (Seelke and Blumberg, 2008, 2010), and the reduction and eventual elimination of SATs in counterpoint to continuous activity (Vanhatalo and Kaila, 2006). However, the development of cortical activity is by no means complete by this point. Again, this has been examined most deeply in the visual system. Immediately following the change from immature patterns in the visual cortex, the pre-critical period is initiated and appears to exist in a transitional time, after the elimination of early activity patterns but before the acquisition of completely adult patterns. For example, cortical activity in ferrets freely viewing natural scenes just after eye-opening was dominated by highly correlated spontaneous activity bursts, an effect that was reduced by the time of the critical period (Fiser et al., 2004). These continuing changes are likely driven by many of the same developmental processes underlying the early switch in cortical activities such as increasing synaptic density and changes in neuromodulatory systems. However, several unique processes are also occurring over this time to mature cortical dynamics, including but not limited to the increasing sparcification of cortical circuits (Rochefort et al., 2009) driven by changes in intrinsic excitability (Golshani et al., 2009), increased reliability of the synaptic drive of layer 2/3 cells (Stern et al., 2001), the development of perisomatic inhibition (Hensch et al., 1998; Huang et al., 1999), and the final acquisition of strong sleep-associated rhythms (Miyamoto et al., 2003) that are necessary for the opening of the critical period for ocular-dominance plasticity.

Thus, throughout the development of the sensory systems, the changing network dynamics of the thalamocortical circuits are closely tied to the changing processes of synaptic plasticity and circuit formation that depend on them.

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