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Review

Between molecules and experience: Role of early patterns of coordinated activity for the development of cortical maps and sensory abilities

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ABSTRACT

Sensory systems processing information from the environment rely on precisely formed and refined neuronal networks that build maps of sensory receptor epithelia at different subcortical and cortical levels. These sensory maps share similar principles of function and emerge according to developmental processes common in visual, somatosensory and auditory systems. Whereas molecular cues set the coarse organization of cortico-subcortical topography, its refinement is known to succeed under the influence of experience-dependent electrical activity during critical periods. However, coordinated patterns of activity synchronize the cortico-subcortical networks long before the meaningful impact of environmental inputs on sensory maps. Recent studies elucidated the cellular and network mechanisms underlying the generation of these early patterns of activity and highlighted their similarities across species. Moreover, the experience-independent activity appears to act as a functional template for the maturation of sensory networks and cortico-subcortical maps. A major goal for future research will be to analyze how this early activity interacts with the molecular cues and to determine whether it is permissive or rather supporting for the establishment of sensory topography.

Contents

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Abbreviations: A1, Primary auditory cortex; BFn, Basal forebrain; $[Ca^{2+}]_i$, Intracellular Ca2+ concentration; EEG, Electroencephalography; ENOs, Early network oscillations; IBI, Interburst interval; LGN, Lateral geniculate nucleus; mAChR, Muscarinic acetylcholine receptors; mGluR, metabotropic glutamate receptors nAChR, Nicotinic acetylcholine receptors; ODC, Ocular dominance columns; PFC, Prefrontal cortex; RGCs, Retinal ganglion cell; S1, Primary somatosensory cortex; SB, Spindle bursts; SPn, Subplate neurons; V1, Primary visual cortex; VPM, Ventroposterior medial nucleus

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1. Introduction

A mandatory competence for individual survival is the behavioral adaptation to the external environment. The first step to adapt to a wide range of external conditions is to percept and translate them into internal representations based on a neural code that allows precise discrimination of stimulus features. To maximize the efficiency of encoding, external stimuli acting on peripheral receptors are topographically represented as sensory maps at cortical level, where either two-dimensional physical space (visual or somatosensory system) or one-dimensional stimulus feature (auditory system) are encoded. Such systematic organization of sensory information is essential for perception and stimulus-directed behavior. As long ago as in the 17th century, René Descartes empirically introduced the idea of internal topographic representation of the external world. Later on, Vernon Mountcastle proposed a columnar functional organization of the cerebral cortex (Mountcastle, 1957). Based on this theory David Hubel and Torsten Wiesel revealed the presence of functional maps in the primary visual cortex (V1) (for review see Hubel and Wiesel, 2005) and numerous studies demonstrated subsequently the conservation of topographic order along the pathway retina–thalamus–V1 (Mooney et al., 1996; Katz and Crowley, 2002; Huberman et al., 2006). Somatotopic organization of information as "homunculus" has been reported for the primary somatosensory cortex (S1) (Whitsel et al., 1978; Schott, 1993; Morecraft et al., 2002), whereas tone processing is reliably achieved within tonotopic maps of primary auditory cortex (A1) (Merzenich et al., 1975; Kandler et al., 2009). Finally, odor perception relies on discrete olfactory maps (Xu et al., 2000; Zou et al., 2005), even if their relationship with the stimulus seems to be rather coarse (Soucy et al., 2009) and they do not involve the thalamic relay function.

Accomplishment of complex sensory tasks with maximal efficiency requests information processing within ordered functional maps rather than within randomly distributed structures. These maps represent the optimal state of connectivity within and between neural networks (Chklovskii and Koulakov, 2004). In spite of area-, task- and experience-dependent differences in the architecture of sensory maps (Schreiner and Winer, 2007), the high functional precision of underlying neural networks is their constant. A key question in neuroscience, which was addressed by an impressive number of studies, is how neuronal networks responsible for sensory perception reach such high degree of precision during ontogeny. Meanwhile it is generally accepted that the development of neural networks equally requires molecular cues and electrical activity (Katz and Shatz, 1996; Khazipov and Luhmann, 2006). As proposed initially by Sperry (1963) in the chemoaffinity hypothesis, the early establishment of connectivity critically depends on a large variety of genetic factors, including axon guidance cues, adhesion and recognition molecules. Their ability to set the coarse architecture of neural connectivity as well as their relevance for brain maturation has been highlighted in detail elsewhere (Goodman and Shatz, 1993; Tropea et al., 2009). With ongoing maturation, the genetically encoded information appears unable to govern alone the further development of neural networks that should adapt to a large variety of environmental conditions. Therefore, the electrical activity is essential to refine the existing coarse connectivity. However, molecular cues and electrical activity do not act independently from each other but tightly interact to control the brain maturation (Hanson and Landmesser, 2003; Sahay et al., 2005). The neuronal activity that shapes developmental processes can be further subdivided into experience-dependent and experience-independent (Khazipov and Luhmann, 2006). Many behavioral abilities are shaped by experience-dependent activity during developmental time windows termed as "critical periods." The duration and onset of critical periods vary significantly among brain regions, sensory systems and species (Rice and Van der Loos, 1977a; Fagiolini et al., 1994) and their definition and restriction to the developmental stage are still at issue (Morishita and Hensch, 2008). Yet, the relevance of critical periods for the refinement of neuronal networks in accordance to the surrounding environment is widely accepted. Deprivation of normal neural activity during these developmental time windows produces permanent behavioral impairment, whereas deprivation after the critical period has a small, if any, effect on sensory performance. Here, one classical example is the maturation of visual system and the subsequent establishment of visual perception. Both human clinical studies and animal models have shown that monocular deprivation (e.g. occlusion of one eye) only during a defined developmental stage yields a persistent unilateral loss of visual abilities (Hubel and Wiesel, 1965). An infant cataract untreated for 1–2 weeks induces permanent amblyopia in humans, whereas removal of a cataract in adults, even untreated for years, restores normal vision (Daw, 1994). Similarly, the development of hearing abilities critically depend on normally patterned sound inputs (Chang and Merzenich, 2003; Villers-Sidani et al., 2007). Exposure of rat pups during the second week of postnatal development to pure tones or white noise led to altered sound representation

in the primary auditory cortex (de Villers-Sidani et al., 2007). Stimulus deprivation or abnormal sensory input strongly interferes with the refinement of cortical connectivity during the critical period by shifting/modifying the neuronal spiking response (Wiesel, 1982; Kral et al., 2005; Leake et al., 2006; Ghoshal et al., 2009; Lee et al., 2009). Several mechanisms seem to control the critical periods in different sensory systems. Among them, the regulatory function of GABAergic circuits involving parvalbumin-positive neurons that switch from depolarization to inhibition has been reported for the visual system (Hensch, 2005).

Although during the past five decades an impressive number of studies documented the essential role of experience-dependent activity in the establishment of cortical circuitry responsible for sensory perception, comparably poor attention has been paid to experience-independent activity and its role for brain maturation. Spontaneously generated activity that occurs before the onset of any external sensory input has been described in several sensory systems at peripheral, subcortical and cortical level (Feller, 1999; Jones et al., 2001). In spite of its variable patterns, the recently identified spatiotemporal organization of such spontaneous neuronal activity makes it suitable to control the refinement of cortico-subcortical connectivity already before the critical periods.

The aim of this review is to evaluate the role of early, experience-independent activity for the establishment of neuronal connectivity and future functional maps in sensory systems in the light of recent findings from visual, somatosensory and auditory systems. The following aspects will be addressed: in the first instance, the properties, the formation, and the role of cortical maps and underlying neural networks in different sensory systems will be shortly recapitulated. For a more detailed discussion of these topics, the reader is referred to several excellent reviews that were recently published (Inan and Crair, 2007; Schreiner and Winer, 2007; White and Fitzpatrick, 2007; Huberman et al., 2008). Secondly, the properties of early experience-independent activity patterns will be analyzed and compared in rodents and humans. In the last part of the review, the mechanisms underlying the early experience-independent activity patterns, their synchronization, spatiotemporal organization as well as functional relevance for refinement of connectivity will be addressed. In contrast to the similar high degree of organization of the three sensory systems mentioned above, there is a much coarse chemotopic map in the olfactory system, as recently shown (Soucy et al., 2009). This different organization and the scarcity of data on the activity-dependent development of the olfactory cortex preclude its discussion in the present review.

2. Cortical maps of sensory perception and their establishment

Functional maps are the neuronal substrate to encode information about specific properties of different stimuli. This encoding process takes place at various anatomical levels and correspondingly, stimulus-related maps are organized at both subcortical and cortical levels.

2.1. *Functional maps in the visual cortex*

Reliable visual perception requires recognition and processing of various features of the stimulus in the visual field and involves subcortical and cortical areas (Fig. 1). The position, the direction of movement and the orientation of stimulus are encoded by individual neurons differently tuned. In accordance with the evolutionary improvement of visual perception and acuity, the cortical maps were intensively investigated in carnivores and primates. Here, microelectrodes and imaging studies allowed the classification of functional maps in the primary visual cortex into two categories: (1) topographic maps that mirror the thalamic organization in the V1 and (2) processing maps that mirror stimulus properties as result of intracortical encoding with no correspondent at thalamic level. The ocular dominance columns (ODC) as non-overlapping, alternating V1 stripes receiving the projections of thalamic neurons located in one or the other eye-specific layer (Wong, 1999) are certainly one of the best-investigated example of topographic cortical maps (Hensch, 2004; Huberman et al., 2008). The ODC were firstly identified by Hubel and Wiesel (1962) in the V1 of the cat and were visualized by specific staining or by functional magnetic resonance imaging in carnivores, primates and humans (Wiesel et al., 1974; LeVay et al., 1978; Horton et al., 1990; Cheng et al., 2001). Shortly after their identification, it became clear that the eye-specific V1 columns were modulated by alteration of the visual experience. Monocular eye deprivation led to size reduction of columns corresponding to the sutured eye, whereas columns corresponding to the non-deprived eye expanded (LeVay et al., 1980; Hubel et al., 1977). Since deprivation led to such major anatomical and functional changes of ODC only during a defined developmental time window (critical period), the major question to address was how this columnar architecture initially forms and develops in V1. Even if the ODC received much of attention as a typical example of how experience shapes anatomical structures during the critical period, it was shown shortly after their identification that the ODC exist already before this developmental phase (Rakic, 1976). If ODC formation is experience-independent, two other mechanisms may drive their initial establishment: molecular cues and/or experience-independent spontaneous electrical activity. In a pioneering experiment, Crowley and Katz (1999) showed that eye removal before development of visual perception did not prevent segregation of geniculocortical axons into alternating stripes corresponding to ODC. Therefore, they ruled out the role of electrical activity for the establishment of ODC. This conclusion was also supported by the initial precision of ODC segregation and the absence of an elaborated subsequent refinement of the ordered architecture in V1 (Crowley and Katz, 2000). Unfortunately, none of the molecules that should trigger the formation of ODC has been identified so far. Although it is conceivable that members of the ephrin family may contribute to the formation of ODC like they control barrel formation in the S1, only the capability of ephrin-A to establish the retinogeniculate mapping has been demonstrated (Pfeiffenberger et al., 2005). In contrast, more and more experimental data point out the contribution of spontaneous experience-independent electrical activity to the formation of V1 topography (Penn and Shatz, 1999: Huberman et al., 2006).

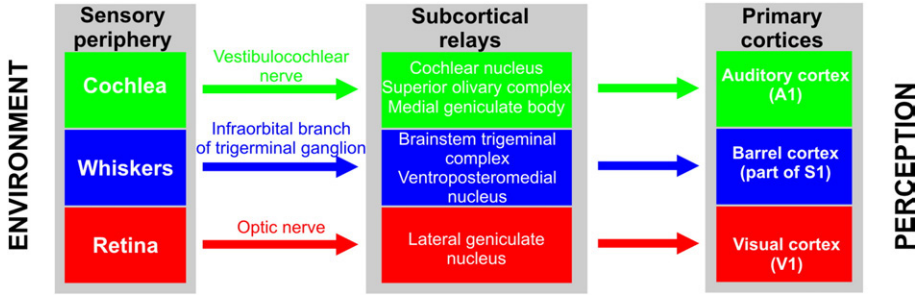

Fig. 1 – Sensory pathways relaying environmental stimuli to visual, somatosensory and auditory cortices in rodent. Sensory information from the periphery (retina, whiskers, inner hair cells/cochlea) is forwarded to distinct brainstem and thalamic nuclei where an initial processing/mapping takes place. Subsequently thalamic axons project to topographically defined cortical areas (A, S1, V1) and allow sensory inputs to reach their final target on cortical layer IV.

Remarkably, such experience-independent activity appears to be mandatory also for the establishment of the second type of functional maps, the processing intracortical maps. V1 neurons are tuned both by the orientation and the direction of movement of visual stimulus (Hubel and Wiesel, 1962; Weliky et al., 1996). As for ODC, the presence of orientation and direction maps has been mostly studied in cats, primates and ferrets (Crair et al., 1998; Krug et al., 2001; White et al., 2001) due to their exceptional visual acuity. In contrast to the role that molecular cues seem to have for the initial formation of ODC, no experimental data currently support the involvement of molecules for the establishment of intracortical maps. Dark-reared ferrets develop a coarse orientation selectivity to which experience-independent neuronal activity seems to contribute (White et al., 2001). However, high-levels of orientation selectivity can be achieved only in the presence of visual stimulation (Chapman and Stryker, 1993). A different picture was obtained when investigating the establishment of direction maps. Neither molecular cues nor spontaneous activity, but visual experience seems to be requested for tuning V1 neurons to stimulus direction (Li et al., 2006).

Whereas most of the data concerning the development of functional topography in the primary visual cortex was obtained from species known to exhibit excellent visual acuity, more and more studies focused recently on the visual system of rodents (Fig. 2). In spite of their relatively modest visual performance, rodents represent a suitable model for development of the visual system by offering the option of genetic manipulations. Since rats and mice do not express ODC, the first question to answer was whether they do exhibit certain topography in the V1 at all. Although the organization degree in the rodent V1 is far below the precise topography of carnivores and primates (Ohki et al., 2005, 2006), the response properties of rat V1 neurons are surprisingly well tuned (Parnavelas et al., 1981; Girman et al., 1999). Using the

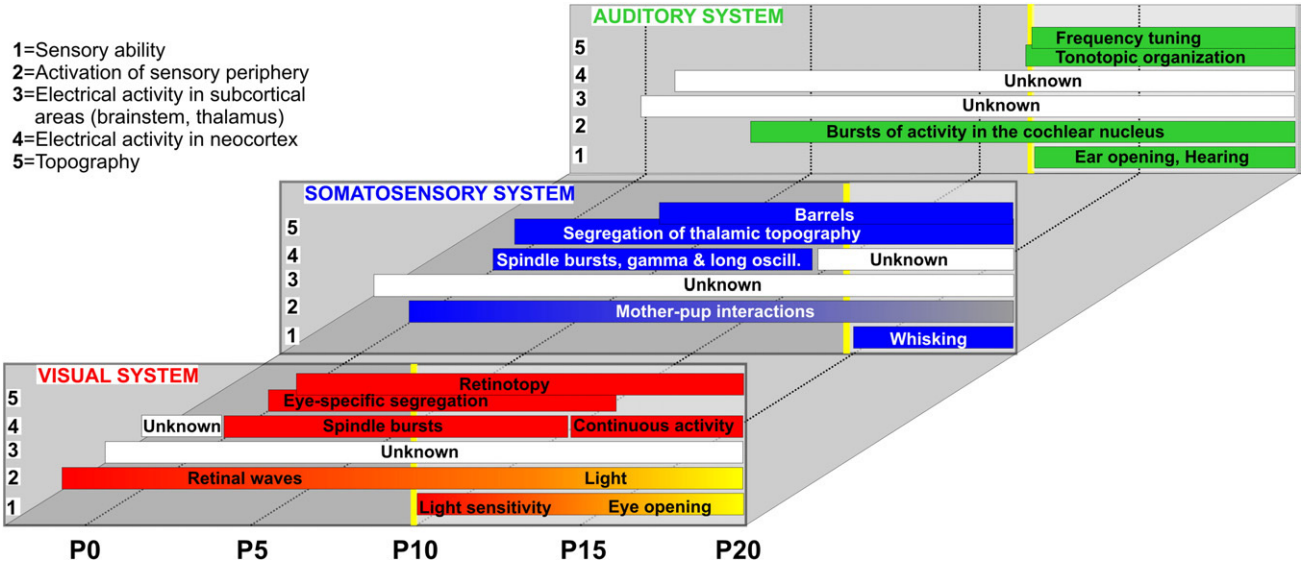

Fig. 2 – Activity-dependent and -independent development of sensory systems in rodents. Whereas the interaction with the environmental stimuli (e.g. light, sound) develops during the second postnatal week, topographic organization of cortical areas (e.g. eye-specific segregation, barrels, tonotopy) starts to emerge before the critical periods and requires both molecular cues and experience-independent activity. Vertical yellow bars mark the onset of experience-dependent phase of development.

recently developed imaging methods that monitor large neuronal populations in vivo it remains to decide how the micro-architecture of rodent V1 develops and achieves its function.

2.2. *Functional maps in the somatosensory cortex: focus on the barrel field*

A comprehensive knowledge on the topography and development of the somatosensory cortex and consequently on the maturation of the tactile performance accumulated during the last decades. The primary somatosensory cortex represents a topographic map of the body surface (Penfield and Rasmussen, 1950), the relative representation of which correlates with the functional abilities and species-dependent relevance of each body part (Elbert et al., 1995; Buonomano and Merzenich, 1998). In accordance with the preponderant perception of their environment (object location) with the whiskers (Welker, 1964), rodents express highly ordered maps within a well-defined S1 area that stands for the whisker representation at cortical level. This area, histochemically highlighted firstly by Woolsey and Van der Loos (1970) as rows of barrel-like cell aggregates, was consequently defined as barrel cortex. Barrels form soon after birth and can be firstly identified morphologically between postnatal day (P) 0 and P5 (Jhaveri et al., 1991; Schlaggar and O'Leary, 1994). Each barrel encodes the tactile information from a single whisker on the contralateral muzzle pad by processing the identity of activated afferents, the timing and the intensity of activation (Knutsen and Ahissar, 2009). The peripheral information is preliminary organized as "barrellets" in the brainstem and "barreloids" in the thalamic ventroposterior medial nucleus (VPM) (O'Leary et al., 1994; Fox et al., 1996) (Fig. 1). Hence the rodent barrels illustrate another example of topographic maps mirroring subcortical and peripheral organization (Hensch, 2004). As for the V1 ODC, the barrels can be shaped by manipulation of the periphery, such as cutting the infraorbital nerve or lesioning the whisker follicles (Killackey et al., 1994) during a short time window confined to early development (Rice and Van der Loos, 1977; Schlaggar et al., 1993; Stern et al., 2001). The presence of a critical period for the development of S1 topography raises the question on the contribution of molecular cues and neuronal activity to barrel formation. The shrinkage of deprived barrels corresponding to cauterized or pulled whiskers (Van der Loos and Woolsey, 1973; Glazewski and Fox, 1996) accompanied by the increased responsiveness of spared whiskers (Fox, 1992; Polley et al., 1999) as well as the disorganization of receptive fields, reduction of spine motility of cortical neurons and deterioration of tactile acuity following trimming of whiskers (Stern et al., 2001) are convincing experimental proofs that normal experience is required for the refinement of S1 maps (Fig. 2). However, the whisker-dependent exploratory behavior of rodents develops during the second postnatal week (Welker, 1964) and therefore other mechanisms than experience-dependent plasticity must contribute to the establishment of previously emerged topography. The ability of different classes of molecules to guide thalamocortical connections has been extensively demonstrated (Lopez-Bendito and Molnar, 2003) by using the advantages of genetically-modified mice. In mice lacking transcription factors, like Gbx2, Mash1, Pax6, thalamic axons fail to innervate the appropriate S1 region (Tuttle et al., 1999; Hevner et al., 2002). Moreover, members of Ephrin family directly control the cortical mapping (Vanderhaeghen et al., 2000). A remarkable property of barrels' maturation is its dependence on several neurotransmitters (Erzurumlu and Kind, 2001). Alteration of serotonergic transmission by genetic or pharmacological manipulation of the monoamine degradation enzyme, monoamine oxidase A, disrupted the segregation of the thalamocortical afferents and led to disappearance of barrels (Vitalis et al., 1998; Cases et al., 1998; Rebsam et al., 2002). An equally strong impact on barrel formation has the glutamatergic transmission that interferes with the establishment of S1 topography via NMDA and metabotropic glutamate receptors (mGluR). Blockade of NMDA receptors during early development significantly impairs the integrity of barrels (Fox et al., 1996). Mice lacking NR1 or NR2 subunit show no ordered organization at subcortical level and no segregation of thalamocortical afferents. The early lethality before P2 of these mice that precluded further investigation of developing cortical barrels (Li et al., 1994; Kutsuwada et al., 1996) was circumvented by ectopic expression of a transgene of NR1 splice variants (Iwasato et al., 1997). High levels of NR1 transgene along the somatosensory pathway restored the whisker-specific patterns in the S1. The absence of NMDA-mediated transmission exclusively restricted to cortical area in region specific NR1 KO mice (Iwasato et al., 2000) correlates with the absence of barrel pattern in the S1, in spite of normal brainstem and thalamic topography. The contribution of mGluR to the establishment of barrels has been demonstrated by the abnormal segregation of thalamocortical axons and absence of barrels after deletion of mGluR1/ mGluR5 genes or impairment of the downstream signaling pathway (Hannan et al., 2001).

Even if during the first postnatal week the whiskers of neonatal rodents are not used for exploratory behavior, they do receive stimuli from the environment. At early postnatal age, before the maturation of barrels, the neonatal whisker system is behaviorally relevant, although not yet precise for sensory discrimination (Rice, 1985). This "passive" activation of pup's whiskers results in a generalized behavioral activation that facilitates the interactions with the mother and the littermates (mouthing, head movements, etc.) by focusing the behavior on encountered targets (Landers and Sullivan, 1999; Sullivan et al., 2003). Consequently, it has been hypothesized that trigeminal and thalamic nuclei process the early whisker activation (Landers and Sullivan, 1999). Its contribution to the subcortical/cortical processing of information that triggers refinement of barrels remains to be elucidated.

2.3. *Functional maps in the auditory cortex*

Whereas visual and somatosensory systems map physical space, the auditory system provides precise representation of a different stimulus attribute: the optimal frequency of the neuronal response to acoustic stimulation. Therefore, in contrast to the two-dimensional visual and somatosensory receptor surface, the cochlea–as auditory receptor surface–provides only one-dimensional rendition of the impinging acoustic energy distribution along the organ of Corti (Rubel and Fritzsch, 2002). The cochleotopic maps in the primary auditory cortex reproduce with high fidelity the preferred frequencies range. Similar to the other perception systems, the auditory system processes the information in an ordered

way from the periphery, the inner hair cells along the auditory nerve, to the second order nuclei (in mammals, nucleus cochlearis) and third order nuclei (superior olivary complex and inferior colliculus) (Jhaveri and Morest, 1982; Friauf et al., 1997) (Fig. 1). The ordered information from the inferior colliculus reaches the thalamic medial geniculate body that provides projections to the auditory cortex. Here multiple functional topographies co-exist and their complex organization and function have been described in detail elsewhere (Schreiner and Winer, 2007; Nelken, 2008). As for the visual and somatosensory maps, the establishment of auditory topography involves both molecular cues and electrical activity. When considering the onset of hearing and the growth of projections from the periphery to the brainstem and, via thalamus, to the cortex in different species, it becomes evident that at least the basic auditory circuitry establishes in the absence of acoustically evoked activity (Fig. 2). For example, the connections between cochlea and brainstem develop during early fetal maturation (Kandler and Friauf, 1993; Carr and Boudreau, 1996). In rodents, the connection to the auditory cortex is present as early as embryonic day 14.5 (Gurung and Fritzsch, 2004), whereas the ability to respond to acoustic stimuli maturates firstly at P12 (Ehret, 1976; Uziel et al., 1981; Kelly, 1992). Remarkably, the topography of connections between cochlea and brainstem is extremely precise and aberrant connections usually do not occur (Angulo et al., 1990; Snyder and Leake, 1997; Fritzsch et al., 1997). Therefore, the pathfinding and the rough target selection by axons appear to be independent of acoustic experience and only the fine-scale refinement of auditory networks, although questioned by some groups (Rubel and Fritzsch, 2002), is controlled by experience-dependent activity (Friauf and Lohmann, 1999). Because experience is not, at least at very early ages, the main factor contributing to the maturation of tonotopic maps, molecular cues and/or spontaneous activity might control the establishment and maintenance of appropriate connections in the auditory system. Currently, few classes of molecules have been identified to organize the tonotopic organization. Among them, neurotrophins like BDNF and NT-3 (Ernfors et al., 1992; Hossain et al., 2008), ephrins (Huffman and Cramer, 2007; Miko et al., 2008) and semaphorins (Gu et al., 2003; Webber and Raz, 2006) have been reported to guide auditory innervation. A special attention was paid to the members of the ephrin family. Their abundant expression in the cochlea and the auditory brainstem (Bianchi and Gray, 2002; Cramer, 2005) as well as their function for establishment of auditory topography (Huffman and Cramer, 2007) and circuitry (Miko et al., 2008) have been demonstrated. However, the development of auditory circuitry is not exclusively controlled by molecules but, as recently shown, patterns of spontaneous electrical activity may additionally contribute to the establishment of tonotopic maps before the onset of hearing. Spontaneous release of ATP in the cochlea causes depolarization of nearby inner hair cells and generation of rhythmic burst discharge in the A1 neurons (Jones et al., 2001, 2007; Tritsch et al., 2007). This spontaneous ATP-dependent signaling could further refine and maintain the tonotopic architecture set by molecular cues, but subsides after the onset of hearing to prevent interference with the experience-dependent activity and with the reliable processing of acoustic information.

3. Coordinated activity in the developing cortex: from humans to rodents

The previously summarized data from visual, somatosensory and auditory cortex highlight the essential contribution of electrical activity to the development of topographic organization of the primary sensory cortices. Patterns of electrical activity are present in these cortical areas already before the maturation of sensory perception and therefore, do not represent responses to environmental stimuli, but intrinsic neuronal activation. Remarkably, such spontaneous patterns of activity have been described in sensory areas of the developing nervous system in a wide range of species.

An impressive body of knowledge on the features of early patterns of electrical activity in humans has accumulated over the last 40 years (Dreyfus-Brisac, 1962). These patterns develop already in utero. Due to the similar behavior and brain function between fetus and age-matched premature neonates (Rose and Eswaran, 2004; Abrahám et al., 2007), electroencephalographic (EEG) recordings in premature infants mirror the fetal brain activity. However, its characterization during this very early developmental stage was hampered not only by the fact that very premature infants are highly prone of abnormal outcome and therefore, the number of normal subjects was relatively low, but also by the variability of interpretation/analysis and the absence of agreement in the literature (Anderson, 1985; Connell et al., 1987; Stockard-Pope et al., 1992; Vecchierini et al., 2003; Vecchierini et al., 2007). In spite of these difficulties, EEG recordings from premature infants demonstrated that in contrast to the adult brain, the neonatal EEG is characterized by a highly discontinuous and fragmented temporal organization (Lamblin et al., 1999). Bursts of cerebral activity alternate with interburst intervals (IBI) lacking any activity. The duration of these bursts increased continuously from the 24th to 30th postconceptional week and the IBI become shorter with age (Hahn et al., 1989; Vecchierini et al., 2003; Victor et al., 2005). Abnormally long IBI toward the end of this phase correlate with a poor neurological prognosis in premature infants (Maruyama et al., 2002; Selton et al., 2003). Not only the discontinuous aspect of the EEG trace in premature infants differs from the adult activity, but also its fine scale properties are different. Some of the rhythmic patterns of activity in premature infants are specific to particular gestational ages (Table 1). From the 24th to the 27th postconceptional week the dominant pattern of early activity is the slow delta wave with frequency ranging from 0.3 to 2 Hz and similar properties over temporal and occipital areas (Selton et al., 2000; Vecchierini et al., 2003). Over frontal areas delta waves with a different morphology, including occasionally a superimposed high-frequency component, have been described (Lamblin et al., 1999; Vecchierini et al., 2003). From 28th postconceptional week to near term similar waves with a higher theta or alpha-beta frequency component accompanied the slow delta waves in all cortical areas and have been defined as delta-brushes (Dreyfus-Brisac and Larroche, 1971; Selton et al., 2000; Selton et al., 2008). Their shape varies in EEG recordings carried out using conventional recording bandwidth (AC-coupled EEG) when compared with DC-coupled EEG recordings (Vanhatalo et al., 2005). The delta-brushes are accompanied by several other patterns of synchronized activity (Anderson et al., 1985; Scher, 2006;

Table 1 – Patterns of oscillatory activity during matched-stages of early development in humans and rodents.

Specie	Patterns	Area			Time window (weeks of gestation/post-natal days)	Amplitude (μV)	Frequency (Hz)	Other specifics	References
		Occipital/V1	Central/S1	Temporal/A1					
Human	*Slow delta wave*	X	–	X	24–27	> 300	0.3–2		Dreyfus-Brisac and Larroche, 1971; Lamblin et al., 1999; Selton et al., 2000
	Delta brushes (= Slow waves superimposed with fast rhythms)	X More prominent	X More prominent	X	28–newborn	30–300 superimposed with 10–60 μV	0.5–2.1 superimposed with > 8 Hz	Max. peak of occurrence between 28 and 34 weeks	Vecchierini et al., 2007
	Bursts of theta rhythm	X	–	X More prominent	24–34	20–260	4–6	Max. peak of occurrence between 29 and 31 weeks	
Rodent	*Spindle bursts*	X	X	?	P0–?	50–600	5–25	Dominant pattern of oscillatory activity	Khazipov et al., 2004; Hanganu et al., 2006; Hanganu et al., 2007; Yang et al., 2009
	Gamma oscillations	–	X	?	P0–?	20–300	30–50	Short duration (0.05–0.5 s)	
	Long oscillations	–	X	?	P0–?	250–750	6–20	Long duration (> 40 s)	

Vanhatalo and Kaila, 2006). Among them, bursts of sharp theta rhythms are present predominantly in temporal areas. They are initially diffuse, but predominate with ongoing maturation and differentiation of sleep cycles (Monod and Tharp, 1977; Hughes et al., 1987; Scher et al., 1994; Curzi-Dascalova, 1995).

EEG and field potential recordings from fetal monkeys, newborn cats and ferrets at ages mirroring the human brain development during the second and third trimester of gestation (Clancy et al., 2001) revealed similar discontinuous organization of the early activity patterns (Huttenlocher, 1967; Isler et al., 2005; Chiu and Weliky, 2001). Identification and characterization of the early activity patterns in neonatal rodents have been initially hampered by technical difficulties (e.g. size of the pups, mechanical stability of the skull). Rodents represent extremely valuable tools for assessment of principles governing the neuronal development, since they are born at very immature stage of brain development, corresponding to the end of the second gestational trimester in humans, and their brains maturate mostly postnatally (Romijn et al., 1991; Clancy et al., 2001). Overcoming the technical problems of in vivo extracellular and patch-clamp recordings in neonatal rats and mice (Khazipov et al., 2004; Hanganu et al., 2006; Hanganu-Opatz & Isbrandt, unpublished observations) opened remarkable opportunities for characterization of early rodent activity and of its underlying mechanisms. In vivo recordings from primary visual, somatosensory (including the barrel field), and prefrontal cortex (PFC) of neonatal rat and mouse showed that the temporal organization and the properties of cortical activity resemble between rodents and premature infants (Khazipov et al., 2004; Hanganu et al., 2006; Hanganu et al., 2007; Yang et al., 2009). In the rodent neocortex transient periods of rhythmic discharge alternate with periods of silence. The dominant activity pattern in rodents is an intermittent network burst associated with spindle-shape field oscillations (Table 1). This activity has been defined as spindle burst (SB) (Khazipov et al., 2004; Hanganu et al., 2006) and resembles in many aspects the delta-brushes recorded in preterm human neonates (Vanhatalo and Kaila, 2006; Milh et al., 2007; Vecchierini et al., 2007). The SB synchronize the neonatal cortex for 1–2 s in frequencies ranging from theta to beta band (5–25 Hz) (Khazipov et al., 2004; Yang et al., 2009). As in premature neonates these fast frequency oscillations are superimposed on a slow delta wave (Minlebaev et al., 2009). Depending on cortical region, SB can be accompanied by other patterns of oscillatory activity. Whereas SB appear to be the unique pattern of activity in V1 during the first postnatal week (Hanganu et al., 2006), they are accompanied by short oscillations in gamma frequency band as well as by long (~60 s) oscillations with frequencies restricted to the beta band in the neonatal S1 (Yang et al., 2009). On the other hand, complex activity patterns, e.g. intermittent slow theta oscillations with superimposed gamma epochs, have been recently characterized in the neonatal prefrontal cortex of the rat (Brockmann and Hanganu-Opatz, unpublished observations). In all cortical areas, the occurrence, the amplitude, and the duration of oscillatory patterns augmented with ongoing maturation (Hanganu et al., 2006; Yang et al., 2009). Except the long oscillations none of the activity patterns travels over cortical areas (Yang et al., 2009).

Development of an optical fiber-based approach enabled monitoring the synchronous rise of intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) over large cortical areas in newborn mice

(Adelsberger et al., 2005; Rogers et al., 2007). These as early network oscillations (ENOs) defined $[Ca^{2+}]_i$ fluctuations have similar occurrence and duration as the SB. However, most of the ENOs properties (propagation, trigger, spatial distribution) differ significantly from those of SB. The limitations of optical methods precluded the identification of high-frequency component of SB. Whether the ENOs are the optical correspondent of SB remains to be demonstrated unequivocally by performing simultaneously calcium imaging and field potential recordings from neonatal rodents.

4. Early oscillatory patterns of activity: possible template for cortical maps

The presence of prominent activity over occipital, central and temporal areas corresponding to visual, somatosensory and auditory cortices of premature humans and neonatal rodents leads to the question whether this activity correlates with environmental stimulation and how it facilitates the establishment of cortical topography. Few studies focused on the EEG reactivity of premature infants to external stimuli. Almost 40 years ago Hrbek et al. (1973) demonstrated the presence of evoked responses in the visual and somatosensory cortex of premature infants. Later, Milh et al. (2007) showed that sporadic hand and foot movements as well as tactile stimulation of extremities in human neonates at 29–31 postconceptional weeks correlate with delta-brushes in the corresponding contralateral central cortex. At similar age in utero, the fetus embeds in the uterus and through sporadic movements receives similar tactile signals as the investigated premature infants. Therefore, under these conditions of limited sensory input from the environment, the sensory feed-back resulting from the spontaneous fetal movements has been proposed to stimulate early patterns of cortical activity and to contribute to the formation of cortical body maps. Remarkably, decreased motility with less startles and twitches correlates with poor neurological and behavioral outcome (Prechtl, 1997).

For obvious reasons, the mechanisms by which early patterns of activity shape the brain development and may act as template for later-emerging functional maps cannot be addressed experimentally in premature humans. However, due to the similarities between the EEG activity of humans during second trimester of gestation and the activity patterns of neonatal rodents, the rat and mouse pups turned out to be a valuable model for addressing these questions. According to the current experimental evidence, the early oscillatory activity is generated and modulated within a complex neural network including the peripheral sensory organs, subcortical nuclei and corpus callosum as well as cortical areas (Fig. 3). The relevance of each of these regions for the generation of coordinated patterns of activity in primary sensory cortices will be discussed in detail.

4.1. *Sensory periphery triggers early activity patterns*

Around birth, when the barrels become visible in S1 (Rice and van der Loos, 1977) but the pups do not use the whiskers for active whisking (Welker, 1964), the S1 expresses three distinct patterns of oscillatory activity: SB, gamma and long oscillations (Fig. 2, 3i). Remarkably, these oscillations differ not only in their intrinsic properties (occurrence, dominant frequency, amplitude, duration), but also in their spatial distribution and their dynamics of synchronization (Yang et al., 2009). Both SB and long oscillations occur over the entire S1, whereas gamma oscillations were confined to a defined S1 region (Yang et al., 2009). A limb-related somatotopic organization has been described for SB in the S1 (Khazipov et al., 2004) and involves feedback coupling with spinal sensorimotor circuits (Schouenborg, 2007). Multi-site recordings in the barrel cortex followed by coherence and cross-correlation analysis of signals demonstrated that SB synchronize the activity of neurons in columns of similar size as the later emerging barrels (200–400 μm). Gamma oscillations locally synchronize the future barrel field. The presence of barrel-related topography already by birth supports the role of columnary synchronized activity patterns as a template for the establishment/refinement of cortical maps. In contrast, the long oscillations that synchronize large neuronal networks and propagate over S1 may entrain the local and non-propagating SB and gamma oscillations, thereby promoting the formation of functional neuronal ensembles (Yang et al., 2009).

These observations raise the question whether the early patterns of oscillatory activity are triggered by information from the sensory periphery before the onset of whisking and synchronize the neural networks as a template of future barrels. Recent experimental evidence revealed that single tactile or electrical stimulation of whiskers/whisker pad elicits SB and gamma oscillations, whereas generation of long oscillations requires repetitive stimulation of the periphery (Yang et al., 2009). If the pups do not whisker actively until P14, what are the physiological stimuli that may trigger early oscillations in the barrel cortex via brainstem and thalamus? Besides olfaction-directed behavior (Miller and Spear, 2009), the initially blind and deaf rat pups modulate and focus their behavior according to whisker-triggered information (Sullivan et al., 2003). Thus, it appears very likely that the interactions with the mother (nipple search, huddling, mouthing) or the siblings are source of whisker activation that triggers topographically synchronized oscillations in the barrel cortex (Fig. 3i).

The whisker–barrel system is not unique in its ability to process periphery-related information before the onset of corresponding perception. In the case of the developing visual system, the retinal ganglion cells (RGCs) fire spontaneously even before the development of photoreceptors and light-sensitivity of the retina. The time window and the spatiotemporal characteristics of this spontaneous activation as revealed firstly by ex utero microelectrode recordings from the fetal rat retina (Maffei and Galli-Resta, 1990) argue for the relevance of retinal firing for the refinement of visual pathways. The RGCs bursts of action potentials separated by quiescence periods have been extensively characterized in vitro, where monitoring of $[Ca^{2+}]_i$ in a large group of RGCs revealed their particular firing pattern resembling a “wave” traveling over the retina (Meister et al., 1991; Wong et al., 1993; Feller et al., 1996; Blankenship et al., 2009). Synaptic transmission (glutamatergic, GABAergic, cholinergic) as well as gap junctional coupling contributes to the generation of such retinal waves (Torborg and Feller, 2005; Guido, 2008). Recently,

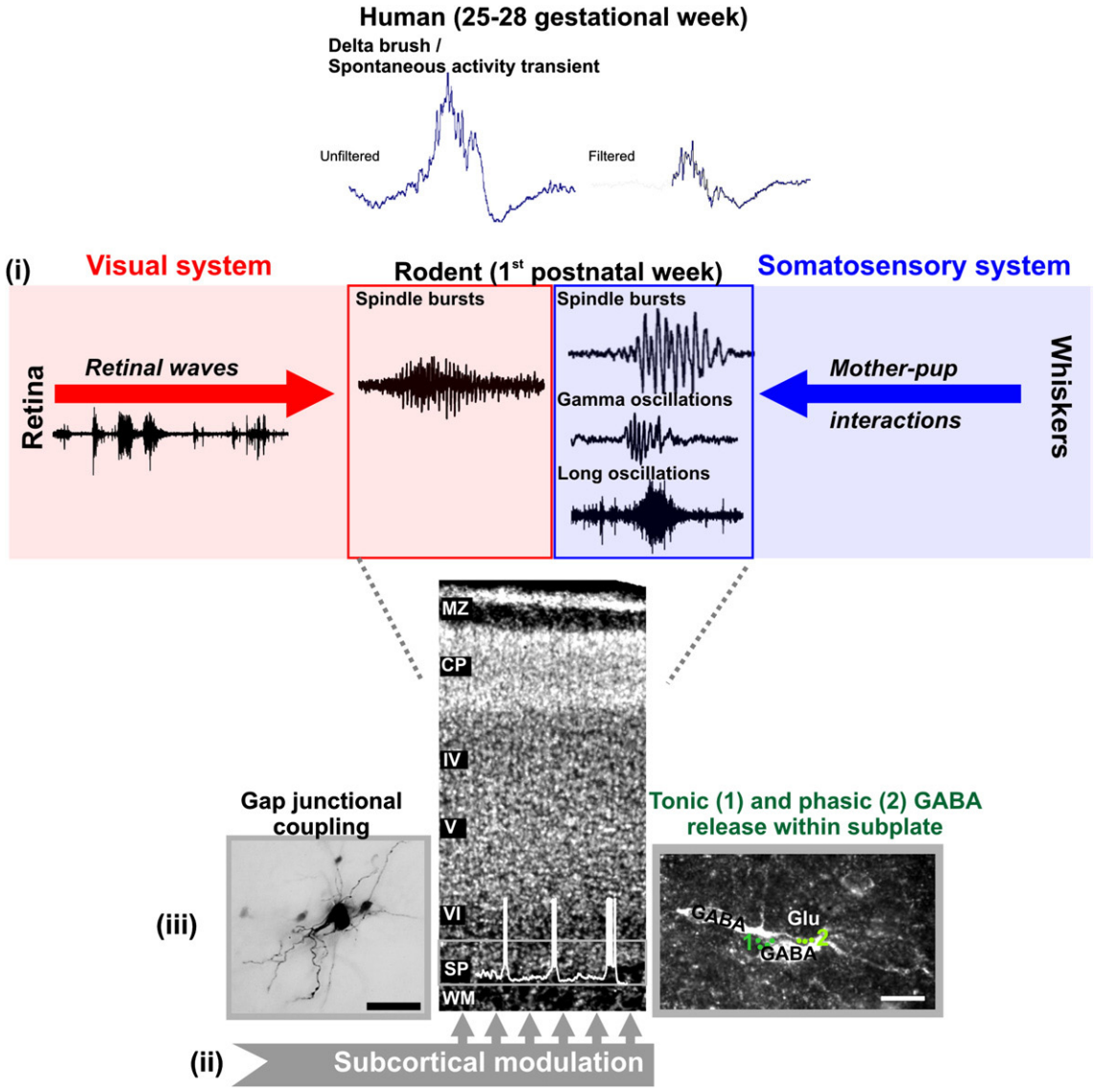

Fig. 3 – Mechanisms underlying the generation of early oscillatory activity in visual and somatosensory (barrel) cortex. During similar stages of brain development, the sensory cortices of humans and rodents show similar patterns of early coordinated activity. At least three mechanisms appear to be responsible for these activity patterns: (i) inputs from the sensory periphery lacking the adult function (light perception, whisking); (ii) modulatory subcortical/callosal inputs; (iii) intracortical circuitry organized by subplate neurons. Subcortical (e.g. cholinergic) and cortical inputs are processed and amplified by the SPn that switch their firing pattern to a bursting one (white trace). Tonic and phasic release of depolarizing GABA by subplate neurons (right inset) increases the level of excitation and boosts the network activity. Gap junctional coupling between subplate neurons (left inset) as well as within newly formed cortical layers contributes to generation and transmission of network oscillations over the entire cortex. The trace of spontaneous activity transient (DC-coupled EEG) was kindly provided by Dr. S. Vanhatalo (Vanhatalo and Kaila, 2006). For more details, see Hanganu et al., 2009.

the retinal activity patterns have been recorded in vivo and analyzed in their dynamic patterns during early postnatal development (Hanganu et al., 2006; Kerschensteiner and Wong, 2008). The crucial question is whether and how this coordinated activity of the retina influences refinement of visual connectivity and cortical oscillations. In a pioneering study, Mooney et al. (1996) showed that spontaneous retinal activity is transmitted via optic nerve to the lateral geniculate nucleus (LGN), where it drives bursts of activity. Moreover, retinal waves appear to have an instructive role in the development/refinement of retinogeniculate/retinocullicular connectivity (Shatz and Stryker, 1988; Torborg et al., 2005). Increasing or lowering/blocking of the retinal activity led to augmentation or reduction of the LGN/superior colliculus territory innervated by the axonal projections from the retina (Stellwagen and Shatz, 2002; Muir-Robinson et al., 2002; Chandrasekaran et al., 2005; Mrsic-Flogel et al., 2005; Butts et al., 2007). Additionally, abnormal patterns of retinal activity before the onset of vision have been reported to disturb the establishment of geniculocortical connectivity and this effect

seems to be independent from the defective formation of retinogeniculate projections (Cang et al., 2005). However, the direct impact of abnormal retinal firing on the cortical activity patterns and the V1 topography was long time unknown. In vivo recordings of the retina simultaneously with the V1 demonstrated that retinal bursts trigger SB in the newborn rat (Hanganu et al., 2006) (Fig. 3i). Interestingly, the spatial distribution of SB mirrors the absence of columnar topography in the V1 of rodents (Ohki et al., 2005). SB recorded at different stereotaxic locations over V1 showed similar properties and frequency distribution (Hanganu et al., 2006; Hanganu et al., 2007). This feature distinguishes the early activity patterns in the rodent V1 from those of S1. However, in both cortical areas the sensory periphery, which at that time lacks the dedicated function and inputs, triggers the early coordinated activity. Huberman et al. (2006) showed that retinal waves shape also the segregation of ODC in species with column-like organization of V1, such as ferrets. In light of these findings it is tempting to speculate on the role of such precisely synchronized and periphery-related activity patterns in developing cortical areas during the pre-critical period. Do they represent a by-product of progressive maturation of cortical connectivity or do they facilitate as a sort of template the development of sensory perception? The experimental data, which are still currently sparse, rather support the second hypothesis. Blockade of the peripheral input either mechanically (removal of the retina, shaving of the whiskers) or pharmacologically (lidocaine-induced blockade of trigeminal nerve, TTX-infusion into the eye) led to diminishment of cortical activity both in S1 and V1 (Hanganu et al., 2006; Yang et al., 2009). Unfortunately, these manipulations were irreversible and acute. A more convincing proof for the mandatory role of early activation of the sensory periphery during pre-critical period for the acquirement of corresponding perception would represent its reversible blockade confined to the pre-critical period. Whether this manipulation, followed by a normal critical period, is sufficient to impair the sensory performance and the associated cortical topography remains to be elucidated. On the other hand, no data are available on the function of early peripheral activation and early cortical synchronization during the pre-critical period in auditory or olfactory systems. Whether they share similar developmental mechanisms as the visual and somatosensory systems is currently unknown.

4.2. *Subcortical areas control the early cortical activity*

Several lines of evidence indicate that the cortical activity is not uniquely triggered and modulated from the sensory periphery. In the first instance, disconnection of the sensory inputs from the hindlimb by severing the spinal cord led to a diminishment, but not abolishment of cortical activity in the S1 (Khazipov et al., 2004). Secondly, both SB and gamma oscillations in the barrel cortex of the neonatal rat persisted at a lower occurrence after blockade of action potential transmission from the whisker pad (Yang et al., 2009). Thirdly, in the absence of retinal waves, the cortical activity in the V1 persisted, although at lower occurrence and amplitude (Hanganu et al., 2006). The presence of coordinated activity in sensory cortices after deafferentiation indicates that other endogenous (cortical or subcortical) triggers may contribute to its generation/modulation. One source of oscillatory activity in sensory cortices may be represented by the thalamus. Cang et al. (2005) showed that, during the first postnatal week, the geniculocortical connections are independently defective from the retinogeniculate connections in mice showing genetically-disrupted retinal waves. This may suggest the involvement of thalamic activity in the generation of cortical patterns. As relay station, the thalamus conveys the activity from the periphery to the cortex and it has been shown that the oscillatory activity in VPM is tightly correlated with the S1 SB (Khazipov et al., 2004). However, except for its relay function, the thalamus seems to play a rather limited role in the generation of cortical oscillations, as suggested by several lines of evidence: (1) pharmacological blockade or cut of the optic nerve suppresses LGN bursts in the intact retina/LGN preparation in vitro (Mooney et al., 1996); (2) optic nerve cut transiently suppresses LGN but not cortical bursts in vivo (Weliky and Katz, 1999; Chiu and Weliky, 2004); (3) in mouse thalamocortical slices, oscillations cannot be evoked by internal capsule stimulation before P12 (Warren et al., 1994; Warren and Jones, 1997).

Besides the thalamus, several other subcortical nuclei densely innervate the primary sensory cortices already during early development and thus, may contribute to the generation of cortical oscillations (Fig. 3ii). Abundant cholinergic projections that originate from the basal forebrain nuclei (BFn), including the nucleus basalis magnocellularis, the medial septal nucleus, and the horizontal limb nuclei of the diagonal band of Broca innervate the primary sensory areas (Mesulam et al., 1984; Woolf, 1991). The cholinergic innervation is known to interfere with the cortical development at different levels, by modulating neuronal proliferation, differentiation and apoptosis (Lipton and Kater, 1989; Role and Berg, 1996; Pugh and Margiotta, 2000). In addition to this trophic role, the cholinergic input contributes to maturation of functional synaptic contacts and wiring of synaptic circuits (Maggi et al., 2003; Kuczewski et al., 2005; Myers et al., 2005; Origlia et al., 2006). Although the role of ACh for cortical activity and plasticity during the critical period is well understood (Bear and Singer, 1986; Gu and Singer, 1993; Siciliano et al., 1997), little is known about its ability to influence the cortical networks before this developmental phase. The ingrowing cholinergic axons reach the primary sensory areas by birth (Rye et al., 1984; Mechawar and Descarries, 2001; Hohmann and Berger-Sweeney, 1998) and by the end of the first postnatal week control the generation of cortical oscillatory patterns. Acute blockade of mAChR or of acetylcholinesterase in vivo modified the early SB in the V1, whereas electrical stimulation of the BFn in vivo potentiated the cortical oscillations (Hanganu et al., 2007). Even stronger effects on the cortical activity patterns were obtained after chronic manipulation of the cholinergic drive. Selective lesion of the cholinergic neurons in the BFn by the toxin 192 IgG-saporin directly after birth led to dramatic decrease of V1 oscillatory activity towards the end of the first postnatal week (Hanganu et al., 2007). These experimental findings argue for the contribution of cholinergic drive to the organization of coordinated activity patterns in the primary sensory cortices.

Understanding the cellular mechanisms how the cholinergic drive shapes the cortical activity requires the use of a less complex preparation than the entire brain. For this, in vitro

preparations like thick cortical slices (up to 1 mm) or the whole-cortex preparation are ideal candidates, since they preserve enough neuronal connectivity to support network oscillations, but permit at the same time the identification of pre- and postsynaptic targets of cholinergic innervation. Initially, the cholinergic innervation from the BFn is confined to a transiently-expressed layer of neurons, the subplate (Candy et al., 1985; Kostovic, 1986; Mechawar and Descarries, 2001). The location of subplate neurons (SPn) at the border between cortex and white matter, their early generation during embryonic development, their ubiquitary presence in rodents, monkeys and humans as well as their mature morphology by birth put them in an ideal position to pattern the corticopetal and corticofugal projections (Allendoerfer and Shatz, 1994; Luhmann et al., 2009). The ingrowing cholinergic projections act on the SPn (Fig. 3ii) that express already by birth functional nicotinic (nAChR) and mAChR (Hanganu and Luhmann, 2004; Hanganu et al., 2009). Whereas the excitatory cholinergic input mediated by nAChR causes a suprathreshold activation of SPn and most likely a stabilization of immature synapses and circuits, activation of mAChR of SPn has a more complex action on the neonatal cortex. Cholinergic input acting on predominantly m1/m5-assembled mAChR switches the firing pattern of SPn from individual spiking to bursts of action potentials (up states) (Hanganu et al., 2009). These bursts synchronize large neuronal populations and can be monitored as calcium transients (Garaschuk et al., 2000; Peinado, 2000; Calderon et al., 2005; Adelsberger et al., 2005; Hanganu et al., 2009). Several aspects regarding the analogy between *in vitro* ENOs/bursts and *in vivo* SB remain to be elucidated. However, the ability of mAChR to mediate coordinated activity patterns in the developing cortex makes them the target of neuromodulatory input from cholinergic basal forebrain.

Several other neuromodulatory systems (serotonergic, dopaminergic, etc.) may similarly modulate the coordinated activity in the developing neocortex by acting on metabotropic receptors. A switch of firing pattern as seen in the presence of cholinergic drive has been reported to occur in vitro when various G protein-coupled receptors are activated (Calderon et al., 2005; Wagner and Luhmann, 2006). Similarly, blockade of serotonergic receptors in vivo modified the oscillatory patterns of activity in the neonatal cortex (Hanganu-Opatz, unpublished observations).

In contrast to the facilitating action of the cholinergic drive, it has been recently shown that corpus callosum modulates inhibitory interactions between homotopic regions in left and right S1 (Marcano-Reik and Blumberg, 2008). This functional inhibition may contribute to the refinement of early S1 circuitry.

4.3. *GABAergic subplate neurons organize early cortical networks*

Since their initial identification and description in the early 1970s by Kostovic and Molliver (1974) in humans and by Rakic in monkeys (1977), an impressive amount of data accumulated and documents the functions of the early generated SPn during cortical development. The unique structural and functional properties of SPn have been highlighted in more detail elsewhere (Allendoerfer and Shatz, 1994; Luhmann et al., 2000; Friedlander and Torres-Reveron, 2009; Luhmann et al., 2009; Kanold and Luhmann, 2010). Here the contribution of SPn to the generation of early oscillatory patterns in the sensory cortices will be discussed (Fig. 3iii). According to their strongly ramificated dendritic and axonal architecture, SPn express mature electrical properties. They fire large action potentials at high frequency (~40 Hz) and show calcium and sodium currents with adult-like biophysical properties (Luhmann et al., 2000; Moore et al., 2008). SPn are part of a complex network, being coupled with other cortical neurons by both gap junctions and synapses (Dupont et al., 2006). They receive, process and integrate synaptic inputs mediated by glutamatergic and GABAergic receptors from thalamus/subcortical areas, cortical layers and other SPn (Friauf et al., 1990; Hanganu et al., 2001; Hanganu et al., 2002). The generation of cortical oscillatory activity in vitro critically depends on the presence of the subplate, its removal leading to abolishment of network SB (Dupont et al., 2006). These data are in accordance with recent results from neocortical slice cultures suggesting that the subplate may act as a pacemaker region to generate network activity (Lischalk et al., 2009). Several experimental findings support the contribution of SPn to the generation of network oscillations in vivo. Current source density analysis of S1 spindle bursts revealed the generator of early oscillations within subplate (Yang et al., 2009). Moreover, immunotoxic lesion of SPn led to disruption of SB in S1 (Tolner et al., 2009). Remarkably, not all SPn are equally involved in the generation of early oscillations. Even if they represent only ~30% of the total cell number in the subplate, GABAergic SPn seem to be the main target of subcortical inputs (e.g. cholinergic). Their depolarization propagates and amplifies the incoming inputs within the neonatal cortex by synaptic and non-synaptic release of depolarizing GABA as well as by gap junctional-coupling (Hanganu et al., 2009) (Fig. 3iii). The column-like electrical coupling over neocortical layers (Dupont et al., 2006) contributes to the columnar synchronization of electrical activity patterns in developing sensory cortices (Yang et al., 2009).

Thus, it is conceivable that the subplate-driven organization of cortical circuits before the critical period may contribute to the establishment of cortical architecture. Shatz and coworkers showed that in the absence of SPn, ODC failed to form in kitten V1 as the result of an increase in the uncorrelated activity between ingrowing thalamic axons and target cortical neurons in layer IV (Kanold et al., 2003). Moreover, SPn control the maturation of inhibition that is necessary in developing cortical networks for segregation of axons (Kanold and Shatz, 2006). Very few data document the cellular and molecular mechanisms by which SPn and their organized electrical activity interfere with the refinement of cortical architecture. Guidance factors, such as p75 and members of the ephrin family (McQuillen et al., 2002; Yun et al., 2003) are strongly expressed in the subplate and might direct thalamic axons to the corresponding columns. On the other hand it is likely that the patterns of experience-independent activity are able to induce persistent structural modifications of the cortical maps through translation into molecular signals. Activation of G-protein-coupled receptors (mAChR, mGluR) during early oscillatory patterns initiates activity-regulated signaling pathways. Consequently, second messenger molecules such as protein kinase A, calcium/calmodulin-dependent protein kinase II or cyclic AMP responsive element binding protein may yield to

refinement of connectivity within cortical maps (Inan and Crair, 2007). The mechanisms of interference between molecules and early activity aiming to establish templates of future cortical maps remain to be further explored.

5. Concluding remarks

In the past decades, a large number of studies have documented the relevance of experience-dependent activity for the formation of cortical maps and sensory networks. The experimental findings of the last years summarized in this review demonstrate in the first instance the early presence of experience-independent activity and highlight its contribution to the refinement of neuronal networks. Remarkably, the patterns of experience-independent activity appear to be conserved throughout all investigated species. The conservation of these patterns through evolution argues for their functional impact on brain development. As for the experience-dependent activity, it remains a question of debate whether the spontaneous patterns of activity are permissive or instructive for brain development and how they interact with molecular cues. Although the principles governing the impact of such early activity patterns on cortical development seem to be general for all sensory systems, the fine-scale organization of coordinated activity is distinct among them, probably reflecting the different requirements and/or relative developmental status of these areas. Further studies are necessary to clarify the cause of system-specific differences and the involvement of functional or evolutionary constraints. Although some basic principles regarding the mechanisms and the role of experience-independent activity have been unraveled, much remains to be learned about the relationship between early neuronal activity and the development of cortical maps and sensory abilities. Taking into account the wealth of studies proving that abnormal maturation of neuronal networks leads to behaviorally relevant deficits at adulthood, a better understanding of the role of experience-independent activity for brain development and its later function may improve the knowledge of several developmental disorders.

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