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Review

Early patterns of activity in the developing cortex: Focus on the sensorimotor system

Roustem Khazipov[a,b,*], Mathieu Milh[c]

[a] INMED, Aix-Marseille University, INSERM, Marseille, 13273, France
[b] Laboratory of Neurobiology, Kazan Federal University, Kazan, 420008, Russia
[c] Hôpital de la Timone, Marseille, 13009, France

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ABSTRACT

Early development of somatotopic cortical maps occurs during the fetal period in humans and during the postnatal period in rodents. During this period, the sensorimotor cortex expresses transient patterns of correlated neuronal activity including delta waves, gamma- and spindle-burst oscillations. These early activity patterns are largely driven by the thalamus and triggered, in a topographic manner, by sensory feedback resulting from spontaneous movements. Early cortical activities are instrumental for competitive interactions between sensory inputs for the cortical territories, they prevent cortical neurons from apoptosis and their alteration may lead to disturbances in cortical network development in a number of neurodevelopmental diseases.

Contents

* Corresponding author at: INMED/INSERM U901, 163 avenue de Luminy BP13, 13273 Marseille, France.
E-mail address: roustem.khazipov@inserm.fr (R. Khazipov).

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1. Introduction

During the early stages of development, cortical neuronal networks display unique activity patterns. The first organized activity patterns, notably delta waves and delta-brushes in human preterm neonates, and homologues delta waves and spindle/gamma-bursts in rodents are expressed during the period of the most intense period of neuronal growth and synaptogenesis, the so-called “brain spurt” occurring during the second half of gestation in humans and during the postnatal period (from the postnatal days P0 to P10) in rodents. There are several reviews describing the features of the early cortical activity patterns and their developmental roles in the activity-dependent wiring of cortical neuronal networks including circuit development [1,2], network mechanisms and synaptic plasticity [3–15], methodological aspects of recording early brain activity [16–19], development in the state-dependence of the brain activity [20,21] and emergence of consciousness [22]. This review focuses on the most recent advance in the mechanisms underlying the early activity patterns obtained in the developing sensorimotor system of rodents and on the relevance of these findings to human fetal development.

2. Early activity in the fetal human cortex: an overview

Most of our knowledge of the cortical activity during the fetal stages of development in humans is based on scalp EEG recordings from preterm neonates. These studies revealed two remarkable features of early cortical activity during the fetal developmental period: (i) discontinuous temporal organization, characterized by intermittent bursts of activity separated by periods of suppression of activity that tend to become shorter with maturation and (ii) age-specific electrographic characteristics of the early intermittent activity patterns, that are often organized in oscillations. The earliest recordings of activity performed at a gestational age of 24–25 postmenstrual weeks revealed intermittent “smooth” delta waves that barely contain any rapid (theta/alpha) rhythmic component and occur at the background of electrical silence (so-called *trace discontinu*) [23]. With development, there is an evolution of this primordial delta wave activity towards “delta-brushes”, a predominant electrographic pattern during the period from the seventh month of gestation to near term, consisting of intermittent bursts of activity lasting for 0.5–3 s organized in rapid alpha-beta (and eventually gamma) oscillations that are nested in an envelope of the delta wave. The last trimester is also characterized by an increase in the background activity between the delta-brushes and a transformation of the *trace discontinu* to *trace alternant*. Delta-brushes may be organized in groups; summation of the slow potentials during such complex events produces large slow activity transients (SATs) of up to millivolts in amplitude which are most prominent in the occipital cortex [24,25]. Delta-brushes are abundant in the central, temporal and occipital areas and they disappear first in central cortical areas and lastly in the occipital cortex just before term.

While delta-brushes have long been considered as a spontaneous activity pattern, several observations indicate that in the sensory areas, they are driven by signals from the sensory periphery. In the somatosensory cortex, delta-brushes can be efficiently evoked in a topographic manner by the somatosensory stimulation of different parts of the body [26–29]. Delta-brushes are also reliably evoked by light flashes in the occipital cortex and by auditory stimuli in temporal cortical regions [28,30,31]. Interestingly, the fetus possesses mechanisms for self-activation of the sensory inputs to trigger cortical delta-brushes in a topographic manner. For example, spontaneous movements in the form of twitches (*aka* physiological myoclonies) characteristic of immaturity, reliably trigger delta-brushes in the somatosensory cortex, with the topographic activation of delta brushes in the hand-representing area of the somatosensory cortex following twitches in the contralateral hand and in the foot-representing areas following the twitches [27]. Consistent with these findings, positive blood oxygen level-dependent functional responses in the contralateral (left) primary somatosensory and motor cortices were observed following both induced and spontaneous right wrist movements [32] Whether similar mechanisms operate in other sensory systems remains unknown. However, the results obtained in animal models suggest that spontaneous activity at the sensory periphery may play similar roles in the visual cortex, where delta-brushes and SATs are driven by the retinal waves [33–38](for review, [39,40]). Similar drive by the sensory periphery can also be provided in the auditory system, where delta-brushes may be driven by spontaneous activity in the cochlea, although this remains to be experimentally demonstrated [41,42] (for review, [43]). Because the sensory stimuli from the external world hardly reach the fetus in utero, such mechanisms of endogenous stimulation could be important for coordinated activity at the sensory periphery and cortex of the fetus to support construction of the topographically aligned circuits including formation of the somatotopic, retinotopic and tonotopic cortical sensory maps. On the other hand, a preterm newborn is exposed to the external world prematurely and the environmental sensory stimuli may interfere with the developmental program based on endogenously generated activity patterns. This interference may lead to malformations in the developing networks and contribute to the neurobehavioral deficits frequently observed in preterm born patients. This has been elegantly demonstrated in the mouse visual system, where optogenetic manipulation of retinal activity before onset of vision disrupted the development and maintenance of visual maps [37]. Therefore, understanding the mechanisms underlying the generative mechanisms of the early activity patterns and their roles in developmental plasticity is critical not only for the understanding of the physiological mechanisms underlying early brain development, but also for an improvement of care and prevention of the neurodevelopmental deficits in the vulnerable group of the preterm born patients.

3. Early cortical activity patterns in animal models

Studies in animal models have provided insights into the mechanisms underlying the generation of early activity patterns in the developing cortex during the corresponding fetal stages in humans. In the most frequently used animal models, such as rats and mice, the neonatal period from birth (postnatal day P0) to P10 approximately corresponds to the second half of gestation in humans. Initial EEG studies only revealed delta-oscillations during quiet sleep as the first organized activity pattern which could be observed starting from P8 onwards [44]. However, intracortical recordings from head-restrained animals revealed organized activity already at birth (that roughly corresponds to mid-gestation in humans). The electrographic features of this activity and their developmental evolution during the postnatal period showed a developmental profile very similar to that in humans during the second half of gestation including developmental transformations in temporal organization of activity and the sequence of the activity patterns. A combination of various recording techniques including multisite silicone probe recordings of the local field potentials and multiple units across different layers in the cortex and subcortical structures, patch-clamp recordings from neurons in different cortical layers, voltage-sensitive dye and intrinsic optical signal imaging, dynamic biphoton imaging of intracellular calcium transients, and pharmacological manipulations and optogenetics enabled the detailed

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