Maturation of Cerebral Connections and Fetal Behavior

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Abstract: Modern imaging methods enabled systematic studies of fetal behaviour as well as a continuation of that behaviour in prematurely born infants (for a review, see 1-4). The following question represents a great challenge for human developmental neurobiologist: what is the neurobiological basis of various behavioural patterns observed in human fetuses and preterm infants?[2] First of all, it is essential to determine whether there is an early spontaneous (non-sensory-driven) activity and to what extent the cerebrum and the cerebral cortex may be involved. In addition, it is necessary to describe for each successive phase, the developmental status of neuronal circuitry and synaptic organization.

In this review, we present evidence on the development of cortical connections during different phases of fetal development and evaluate a possible functional significance of cerebral involvement.

ENDOGENOUS AND SENSORY-DRIVEN ACTIVITY

Early Fetal Period: Early Endogenous Network and Spontaneous Activity

Experimental evidence in several mammalian species has revealed that early neural network has endogeneous features and is characterized by spontaneous activity.[5-8] In humans, that endogeneous cortical network is already present at 8 weeks post conception (WPC), i.e. at the end of embryonic period and the beginning of the fetal life. It contains very few synapses[9] and it is very likely that some early born neurons[10] communicate through nonsynaptic intercellular junctions.[7,11] The early network displays a characteristic oscillatory activity.[12,8] It seems likely that this early spontaneous cortical activity has no correlates at the level of fetal motor behavior. However, endogeneous networks may elicit some motor activity in other parts of the brain and spinal cord.[13] In particular, coordinated endogenously active oscillations of non-synaptic and synaptic junctions in the spinal cord may be actively patterned.[13,7] The concept of early spontaneous activity is very important for the developmental neuroscience (for a review, see 7) and fetal neurology, for several reasons. First, it contradicts the old dogma which stated that the early activity was predominantly reflexogenic. Second, that spontaneous activity generates patterns needed for a refinement of developing neural connections. Indeed, this activity may shape the synaptogenesis.[7] Third, the spontaneous activity contains spatiotemporal information required for activity-dependent competition.[7] It should be emphasized that spontaneous activity may appear in a given brain «center» significantly before the onset of specific function of that part of the brain.

Midfetal Period: Transient Neural Circuitry and Transient Behavioral Patterns

Transient neural networks are determined by transient distribution of synapses, transient position of axons and the existence of transient postsynaptic neurons. These networks are interconected and form transient circuitry. Transient neural circuitry is spatially largely confined to transient fetal cellular zones. The largest and the most prominent of these transient fetal architectonic zones is the fibrillar and synapse-rich subplate zone, which also contains waiting axons and the majority of differentiated postmigratory neurons.[14] From the clinical viewpoint, it is important to emphasize that subplate zone can be visualized by MR imaging[15] *in vitro* and *in utero*/*in vivo*.[16-18] In the midfetal period, transient fetal zones contain specific parts of endogeneous neuronal networks and represent the site of spontaneous activity. For example, this activity may manifest itself as some kind of (presently unspecified) complex fetal movements,[1] which would eventually became modified by cerebral activity. The transient connectivity between transient cerebral zones and thalamus may serve this functional purpose as somatosensory trigger. One should bear in mind that, during the midfetal period, the neuronal migration is at its peak. A myriad of neurons generated in proliferative (ventricular and subventricular) zones migrate through the subplate zone toward the cortical plate. These migrating neurons may also be

electrically active and thus contribute to transient patterns of activity. Further studies are needed to ascertain whether transient patterns of cerebral organization represent a structural basis for transient patterns of motor behaviour during the midfetal period.

Late Fetal and Early Preterm Period: The Coexistence of Transient and Permanent Circuitry

After 22-24 WPC, due to the development of afferent input from thalamus to cortical sensory areas,[19-21] a new period of cortical functional organization begins. On the basis of experimental evidence[22,7] and our data on the simultaneous presence of thalamocortical axons in the subplate zone and in the cortical plate, we proposed that during the late fetal and early preterm period the coexistence of transient and permanent circuitry (Fig. 1) represents a salient feature of the developing human cerebrum.[23] This period has a central role in development and shaping of afferent thalamocortical pathways because at that developmental ages thalamocortical afferents maintain a strong input to neurons of the subplate zone but concurrently begin to relocate to their final target destination, i.e. the cortical plate.[6] That type of structural organization very likely contributes to the appearance of characteristic and developmentally specific cortical waves.[24-26] We believe that massive and heterogeneous afferent input to transient deep tiers of the developing cortex together with rapid laminar shifts in the distribution of afferent fibres represents the structural basis of the discontinuous nature of the early cortical activity in preterm infants.[24] In this period both axons and neurons of the subplate zone may display a selective vulnerability, and that vulnerability in turn may exert a strong effect be on cognitive neurodevelopmental outcome after perinatal lesions.[27,28] The most frequent «abnormal» finding in preterm infants, observed in more than 50% of cases, is so-called DEHSI.[29] With respect to its spatial distribution within the fetal cerebral wall, that type of MRI signal abnormality almost certainly involves a portion of the subplate zone.[29,28] Thus, it is reasonable to assume that lesions of this transitional zone may exert similar efects as lesions of the entire subplate zone.[28]

Late Preterm and Newborn Period: Sensory-driven Activity

At present, very little is known about sensory-driven activity and possible effects of precocious stimulation of the cerebral cortex in late preterm infants and full-term newborns. It was demonstrated experimentally that precocious visual stimulation in prematurely born rhesus monkeys did not change the rate of accretion of synapses in the visual cortex.[30] However, the same authors observed changes in the length of synaptic profiles. These findings strongly suggest that neurogenetic events which normally enfold before birth in preterm primates are predominantly enfolding according to intrinsic (genetic) programs, but upon sensory stimulation display a certain level of structural plasticity. That plasticity becomes more prominent with increasing age and in the neonatal period sensory-driven activity may assume a decisive role. For example, that was experimentally demonstrated for the formation of ocular dominance columns, suggesting that initial functional architecture of the cerebral cortex was established very early but undergoes plastic changes during subsequent critical period, which relay on distinct developmental mechanisms.[31-33]

THE INVOLVEMENT OF CORTICAL CONNECTIONS IN FETAL AND PRETERM BEHAVIOR

As already stated, in the human cerebral cortex the first synapses develop around[8] WPC.[9] These synapses display structural features of functionally active synapses. However, they are present in very small number. During that early period, neither neurons involved in motor behavior or cortical cells which receive major somatosensory input from thalamus are not yet generated.[34] Thus, at that early fetal period motor and somatosensory axes are not yet established. Cortical connections consist of monoaminergic afferents from the brain stem,[35,36] cholinergic afferents from the basal forebrain[37] and postsynaptic neurons of the so-called presubplate layer.[14] Postsynaptic candidate cells in the cortical plate are immature[38,39] and synapses are formed only on their apical dendrites.[9] All that evidence clearly suggests that cerebral cortex and associated subcortical structures, such as striatum and thalamus, are quite immature and not yet involved in the earliest patterns of fetal behavior.

However, a new connectivity framework for possible functional involvement of the cerebral cortex develops during the midfetal period (15-20 WPC) due to concurrent increase in number of synapses[9,14] and thalamocortical afferents[14,40-42] in the subplate zone[19,21,23] as well as the parallel development of efferent cortical pathways.[43]

During the midfetal period, thalamocortical afferents which convey somatosensory information are still waiting within the subplate zone and did not reach their synaptic targets in the cortical plate.[14] As this massive contingent of thalamocortical afferents still displays a crude and diffuse topographical distribution, it may be responsible for some noncoordinated movement patterns. The motor axis develops at a similar pace and cortical efferent projections are still on their way toward targets in striatum[44] and the spinal cord.[43] Such immaturity of thalamocortical and corticomotoneuronal connections suggests that cerebral cortex has no prominent role in generation of behavioral patterns during the midfetal period. It is only after 22-24. WPC that neural circuitry begins to connect cerebral cortex with somatic periphery.[19,23] Two sets of data present the evidence for the first real functional involvement of the cerebral

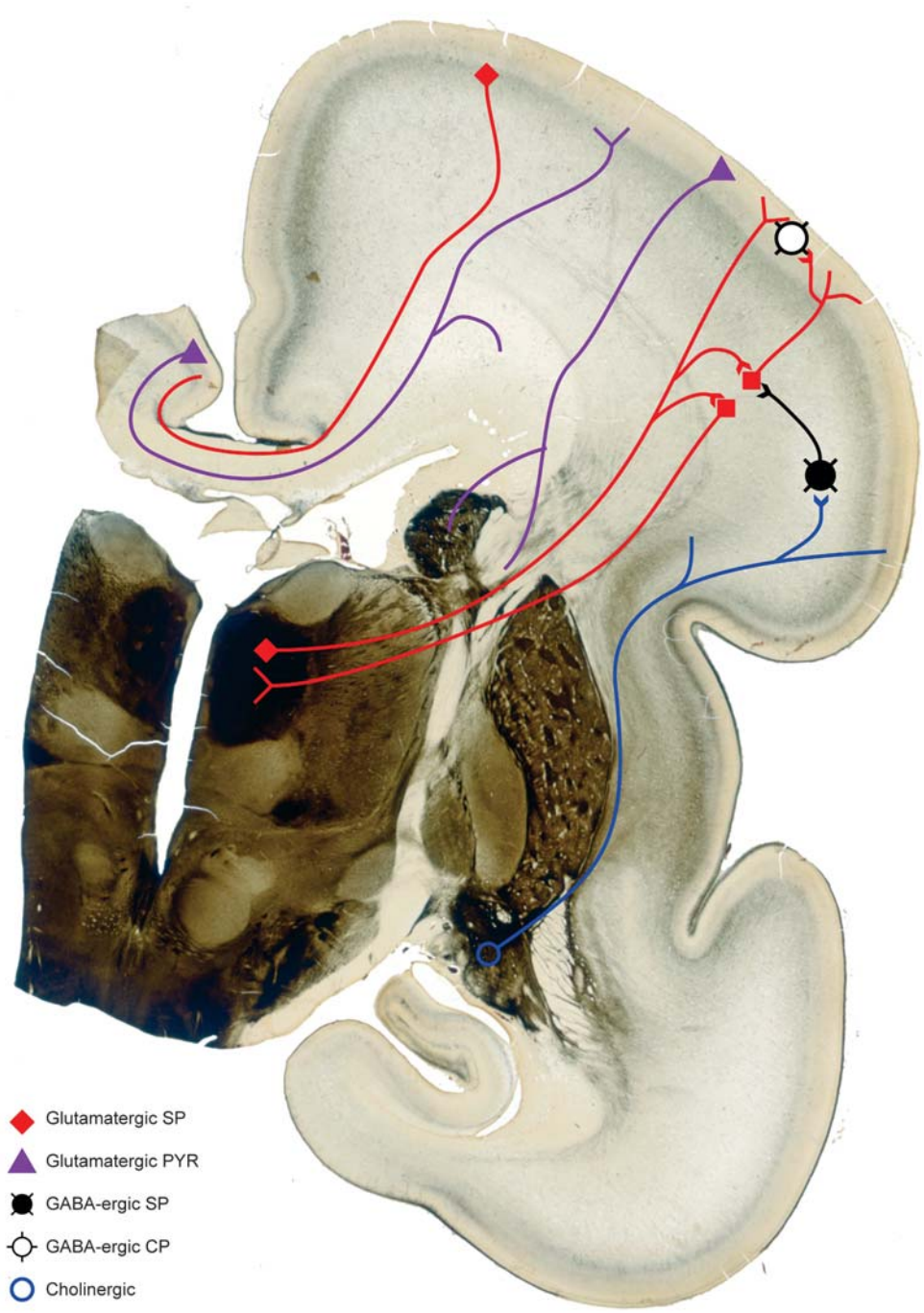

Fig. 1: The organization of neural connections in the cerebrum of early preterm infant. The circuitry shema is superimposed on the coronal histological section through the right cerebral hemisphere stained with acetylcholinesterase (AChE) technique.
Glutamatergic neurons (red diamonds) in the thalamus project simultaneously to subplate neurons and interneurons of the cortical plate, and receive reciprocal projections from glutamatergic neurons of the subplate zone. The subplate zone contains both glutamatergic (red diamonds) and GABAergic (red circle) neurons. Glutamatergic subplate neurons project to the cortical plate and establish the first synapses with cortical GABAergic interneurons (white circle). Transient neuronal circuits of the subplate zone receive cholinergic axons from the basal forebrain which establish synapses with GABAergic subplate neurons. Glutamatergic pyramidal neurons of the cortical plate (violet triangles) project and terminate in the striatum; however, callosal projection axons of another subset of glutamatergic pyramidal neurons did not enter the contralateral cortical plate and are situated in the deep periventricular position.

cortex. First, after 24-26. WPC one can elicit evoked potentials in preterm infants.[45-47] Second, it was recently demonstrated that cortical responses can be elicited by peripheral pain stimulus in early preterm infants.[20] The existence of functional thalamocortical connections after 24 WPC was also predicted on the basis of neuroanatomical evidence[40,14,19] and clinical studies.[48,49,26] In addition, after 24. WPC synapses rapidly accumulate in the cortical plate in parallel with the ingrowth of thalamocortical axons[9,21] which suggests the development of direct thalamocortical synapses. There is a concurrent development of descending cortical motor pathways to the spinal cord and the brain stem, and corticospinal axons finally enter their target areas in the spinal cord.[43]

In rhesus monkeys of a comparative developmental age, the use of tract-tracing methods enabled a direct demonstration of cortico-striatal connections,[44] which are also very important for motor behavior. The existence of such cortico-striatal connections in human fetuses was demonstrated indirectly, by cytoarchitectonic changes which reflect an ingrowth and modular arrangement of corticostriatal terminals in the putamen.[50]

Whereas there is no evidence for the establishment of long corticocortical connections between motor cortical regions, the interhemispheric communication may already be mediated by existing callosal fibres. However, studies of event-related potentials suggest that preterm infants already display a certain level of cortico-cortical processing of information (for review, see 2).

After 28. WPC, there is an intensive synaptogenesis in developing sublayers of the cortical plate, concurrent with the development of long cortico-cortical pathways and interhemispheric connections. Furthermore, the elaboration of corticomotoneuronal pathway becomes a structural basis for efferent (motor) functions.[43,51]

This transient but distributed cortical network provides a required biological basis for all transient behavioural[1] and physiological phenomena[24] observed in preterm infants.

The cortical network in the brain of full-term newborns is still clearly immature. For example, although callosal axons are at the peak of their overproduction phase, they nevertheless did not enter the cortical plate.[52,53] In addition, there are numerous other signs of immaturity: the circuitry of the deep and transient subplate zone is still prominent; developing cortical layers II-VI of the cortical plate are still immature; the future cortical layer I still contains a number of well-developed fetal Cajal-Retzius cells; layer III pyramidal neurons have very few dendritic spines; granular layer IV[54] is still present in all parts of the cortex;[19] and short corticocortical fibers did not reach their final position and continue with active growth.[55,56]

The disappearance of transient fetal elements and growth of short cortico-cortical pathways[55] seems to coincide with maturation of general movements.[57] Between 6. and 9. postnatal month, transient pathways disappear and there is a rapid development of goal-directed movements (for a review, see in 2, 58).

Due to the involvement of all cortical areas, i.e. unimodal, heteromodal and transmodal regions of primary, secondary and associative cortex, 9-month-old infants are able to perform delayed-response task[59] which requires the online presence of executive functions of the frontal lobe together with crucial delayed goal-directed movement in visual absence of the presented object target. It is interesting to note that this frontal cortex function develops simultaneously with the disappearance of transient fetal components, after the reduction in number of exuberant callosal axons[53] and during the intense overproduction of synapses[2,60-62] as well as with region-specific metabolic imaging pattern.[63]

THE ROLE OF NEUROIMAGING

Modern neuroimaging techniques are very important for elucidation of structure-function relationships in normal and abnormal development of the human brain. Although experimental models are important for explanation of basic electrophysiological phenomena,[64,5,12,65] the proper timing of developmental events can be studied in humans only. Four-D ultrasonography[3] offers an objective perspective on continuity of behavior from prenatal to postnatal life. Magnetic resonance imaging *in vivo* and *in utero*[16,17,18,66-71] reveals in great detail a transient laminar organization of the cerebral cortex which underlies transient functional organization. If these fine structural data are correlated with postmortem identification of neural pathways, synaptic distribution and maturation of neurons[15] one can arrive at the new interpretation of structural-functional development in human fetus and preterm infant. For studying neuronal connections, one of the most interesting findings was the visualization of the subplate zone1[5,16,28,71] which is the thickest and synapse-rich transient compartment of the developing cerebral cortex.[14] The disappearance of the subplate zone is an excellent indicator of maturity of cortical connections.[15] On the other hand, lesions of the subplate zone which are frequently seen in preterm infants[27-29,72] play an essential role in studying cognitive outcome after perinatal hypoxic-ischemic lesions. Modern tractography[17,70,71,73] offers a unique opportunity to study significance of individual cortical connections and their structural reorganization.[74]

CONCLUSIONS

Current evidence on developing neuronal circuitry in the human cerebrum reveals that development of functional connections between neurons begins early in fetal life and proceeds as a sequence of (partly overlapping) reorganizational events and

transformations of transient patterns of laminar and cellular organization. The early fetal circuitry is endogeneous and characterized by spontaneous, predominantly oscillatory activity which occurs among early maturing neuronal elements situated outside the cortical plate. The midfetal period is characterized by the following processes: the pathfinding of afferent axons; their accumulation in the transient subplate zone; the predominance of the deep synaptogenesis with GABAergic, peptidergic, glutamatergic, cholinergic and monoaminergic transmission. This circuitry, together with efferent projections to striatum and subcortical centers, may form the framework for some fragmented behavioural phenomena.

After 24 weeks post conception, thalamocortical fibers relocate to the cortical plate and form synapses conveying peripheral sensory information to cerebral cortex. For a fetal physiology, the initial establishment of thalamocortical connection represents a turning point because from 24 WPC onwards sensory signals (including pain signals) can reach cortical level with prospective sensory-driven activity. During this period, the transient subplate zone is still the most prominent compartment of the developing cerebral cortex. The prolonged coexistence of transient and permanent circuitry is a salient feature of cerebral cortex in preterm infants. This transient pattern of cortical organization, characterized by a progressive deep-to-superficial synaptogenesis in the developing cortex, represents a biological substrate for transient electro-physiological phenomena such as discontinuous oscillations, atypical surface-negative cortical response, and first event-related potentials. The neuronal activity in the subplate zone is vital for proper establishment of functional cortical architecture. In the neonatal period, sensory-driven activity is shaping development of cortical columns and plasticity occurs at synaptic level on dendritic spines.[31]

Due to the slow maturation of short corticocortical pathways and interhemispheric synchronization, there is a relatively late postnatal onset (around 8-9 months) of executive and cognitive functions of the frontal lobe. The functional circuitry subserving executive functions of the frontal lobe may be tested by delayed-response task.[59]

Future research of cortical connections which underlie fetal behavior should be directed towards correlated studies using magnetic resonance DTI and tractography studies, 4D-ultrasonography, direct electroencephalographic (EEG) recording, metabolic studies and postmortem studies with immunocytochemical identification of individual neuronal pathways.

ACKNOWLEDGEMENTS

This work was supported by Croatian Ministry of Science, Education and Sport grants no. 0108118 (to IK) and 0108115 (to MJ).

This paper was published in the book J.M. Carrera, A. Kurjak: Conducta Fetal: studio ecografico de la neurologia fetal, Barcelona: Masson 2008. The publisher kindly gave permission to print the paper in Donald School Journal of Ultrasound in Obstetrics and Gynecology.

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