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Pregled
Review

DEVELOPMENTAL REORGANIZATION OF THE HUMAN CEREBRAL CORTEX

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This paper reveals data on developmental reorganization of the human cortex. Three criteria were used to determine reorganization: (1) presence of transient cellular zones: ventricular (VZ), subventricular (SVZ), intermediate (IZ) zone, subplate (SP), cortical plate (CP) and marginal zone (MZ); (2) intensity of specific neurodevelopmental cellular events: proliferation, migration, differentiation, growth of axon and synaptogenesis; (3) pattern of functional organization: (a) endogenous, transient circuitry and (b) permanent, sensory driven circuitry. First half of gestation is characterized by proliferation and migration. During the second half of gestation major axonal pathways grow through the intermediate zone and "wait" in the subplate. Initial synaptogenesis begins during third month of gestation and is related to the endogenous, spontaneous circuitry. In early preterm thalamocortical fibers relocate from the subplate (after 24th postconceptional weeks) and first evoked potentials may be recorded. The fundamental pattern is coexistence of endogenous and permanent, sensory driven circuitry. In neonatal brain synaptogenesis is main neurogenetic event and there is gradual disappearance of transient endogenous circuitry and transient cellular zones. The review support ideas of developmental "windows", selective vulnerability of specific transient cellular zones (subplate) and increased vulnerability of the human fetal and neonatal brain.

Descriptors: PREMATURUS, KORTIKALNE VEZE, TALAMOKORTIKALNA VLAKNA, SINAPTOGENEZA, HISTOGENEZA

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Introduction

Fetal cortex differs from the neonatal in three different aspects of organization:

- presence of transient cell zones in which cellular events takes place;
- intensity of specific neurodevelopmental cellular events;
- presence of transient circuitry and transient functions (1).

In this review we will discuss reorganization of developing brain based on these three basic patterns of organization. Our focus will be on fetal, early preterm, late preterm and neonatal period. In order to describe each of this periods of development it is necessarily to define transient zones, neurogenetic events and types of transient functional patterns.

- Transient zones (Figure 1) in which neurodevelopmental events take places are ventricular zone (VZ), subventricular zone (SVZ), intermediate zone (IZ), subplate (SP), cortical plate (CP) and marginal zone (MZ).
- The neurodevelopmental cellular events which will be considered in this review are proliferation, migration and differentiation of neurons, axonal growth and synaptogenesis. Myelinization and cell death will be not discussed in this review.
- Functional patterns in developing brain might be (a) endogenous (spontaneous), transient circuitry, mostly characterized with oscillatory properties and (b) sensory driven, permanent circuitry (2, 3).

Transient patterns and their reorganization during prenatal and perinatal developmental "windows"

Fetal period

Fetal period is dominated by two neurodevelopment events, proliferation and migration (4, 5). It is also a period when synaptogenesis begins and axonal pathways (projections) establish. *Proliferation*: Neurons are generated in ventricular and subventricular zone from the neuronal stem cells by asymmetric and symmetric divisions. The period of proliferation of neurons is between 4th and 28th postconceptional week (Rakic 2006, Cerebral Cortex). According to recent evidence radial glia cells also serve as neural stem cell and might produce pyramidal neurons (Rakic 2006). The GABA-ergic (inhibitory interneurons) in

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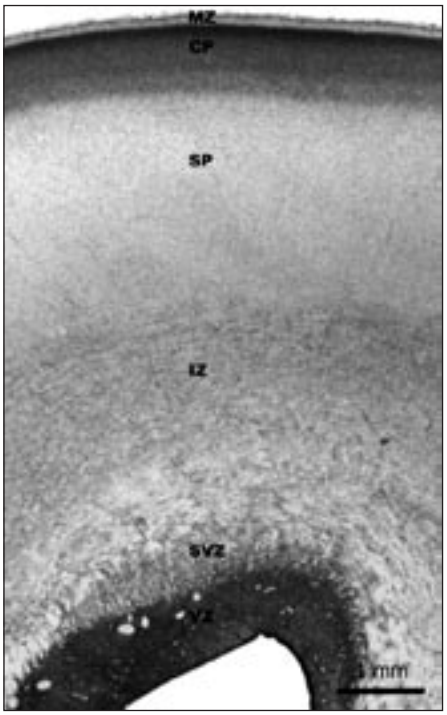

Figure 1
Transient laminar organization of the telencephalic wall:
Cresyl violet (Nissl) staining of the telencephalic wall in the human fetus during midgestation; transient zones in which neurodevelopmental events take place are ventricular zone (VZ), subventricular zone (SVZ), intermediate zone (IZ), subplate (SP), cortical plate (CP) and marginal zone (MZ)

Slika 1.
Prolazna laminarna organizacija stjenke telencefalona:
Krezil violet (Nisslovo) bojanje stjenke telencefalona u fetusa čovjeka tijekom srednje trećine trudnoće: prolazni stanični slojevi koji su mjesto specifičnih neurorazvojnih događaja su: ventrikularni (VZ), subventrikularni (SVZ), intermedijarni (IZ) sloj (zona), sloj ispod ploče (subplate-SP), kortikalna ploča (CP) i marginalni sloj (zona) (MZ)

humans originate in the pallial (cortical) ventricular zone, while in rodent brain main source of GABA-ergic neurons is in another germinal structure called ganglionic eminence. Several distinct features distinguish human brain from other species, especially rodents (4). This is on the first place increased number of mitotic cycles (35 in human compared to 11 in the rodents). Second, there is local generation of the GABA-ergic interneurons (as stated above). Third, ganglionic eminence which is the basal enlargement of the basal telencephalic ventricular zone generates also neurons for thalamus (4).

Migration: Newly generated neurons migrate along radial glia cells through intermediate zone and form embryonic column (4). The disturbances of proliferation and migration might result in so called migratory disorders, which are frequently associated with epilepsy and mental retardation. *Transient laminar pattern*: After 13 postconceptional week a new lamina develops below cortical plate and became very soon thickest lamina of the telencephalon. This lamina is subplate zone which can be seen on both Nissl preparations and magnetic resonance images in vivo and in vitro (6, 7). Prominent subplate zone is the main characteristic of fetal pattern of laminar organization. It is easy to distinguish the following layers (from ventricle to pia): VZ, SVZ, IZ, SP, CP and MZ (Figure 1). The subplate zone is site of early synaptogenesis, endogenous neural activity and neuronal differentiation.

Growth of axonal pathways: The earliest pathways which arrive in fetal cortex are monoaminergic afferents from brain stem tegmentum and cholinergic afferents from the basal nucleus of Maynert (8-10). Next afferents in sequentional growth are massive pathways originating in thalamus. Thalamic fibers originate not only from sensory thalamic nuclei, but also from associative thalamic nuclei (2, 5, 11-13). This most massive input grows throughout subplate zone during prolonged period of axonal pathfinding (14). At the end of fetal period that is between 21-23 postconceptional weeks, thalamocortical afferents accumulate in the superficial part of the subplate zone (5, 13). These fibers are described as "waiting" fibers.

Synaptogenesis: Early synapses develop above and below cortical plate. Below cortical plate is plexiform presubplate layer and above cortical plate is marginal zone. This early fetal pattern of synaptic distribution might be described as period of two synaptic strata (15, 16). The early postsynaptic elements are preplate and marginal zone neurons, as well as branches of cortical plate neurons which are distributed in marginal zone and preplate (15).

Pattern of functional organization: In the fetal cortex there is no sensory driven activity. However, synapse seems to be very active (3). This type of oscillatory activity was described as spontaneous activity (2, 3, 5, 17). Early thalamic input to subplate might participate in this circuitry, as a transient input. Subplate neurons have also efferent projection to thalamus and subcortical centers and this presumably glutamatergic output might contribute to generation of fetal general movements (18). In conclusion, early fetal circuitry is transient and it is related to transient pattern of structural organization. This concept is accepted by most modern neurophysiologist and it is in contrast with some classical opinions about reflex type generation of fetal motility.

Early preterm period

During early preterm period several reorganizational events take place. This period is characterized by development of primary gyri and sulci (19-21). *Transient laminar organization*: For the first time there is initial lamination in cortical plate, which coexists with extremely prominent subplate zone. This is a special feature of preterm cortex and mixture of fetal and permanent patterns (2, 14). *Neurogenetic events*: Intensity of proliferation and migration during preterm period decreased significantly. Ventricular zone become thinner and neural stem cells gradually stop producing neurons and continue to produce glia cell lines (proolygodendrocites, astrocytes). Migration decreases in intensity and late born neurons only might be found to migrate through intermediate zone.

Axonal growth: The crucial event in axonal growth is relocation of thalamic afferents from subplate zone and their ingrowth into cortical plate. That event occurs almost simultaneously in primary and associative cortex (11-13). Parallel to the thalamo-cortical ingrowth there is rapid areal differentiation (14, 22). *Synaptogenesis*: In the early preterm infant synapses are formed, for the first time, within deep part of the cortical plate (15, 16). This intracortical synaptogenesis is related to development of thalamo-cortical circuitry (12-14).

Functional pattern of organization: Development of thalamocortical connectivity explains early evoked potential in preterm infant (23-27). The early development of evoked potential in preterm infant together with transient circuitry in subplate shows that there are interactions between endogenous circuitry of the subplate zone, and thalamic sensory driven circuitry (2, 3). Same thalamic terminals might activate cell in the cortical plate and form synapses in subplate. This coexistence with transient endogens and permanent driven circuitry might exist in the human preterm for a prolonged time (2). This combined circuitry seems to be essential feature of the preterm infant and underlie transient electrophysiological and behavioral phenomena (23, 28-30). Establishment of thalamo-cortical connection with somatosensory cortex attracted recently a great attention among anesthesiologists, due to the fact that this pathway may represent anatomical substrate for pain input to cortex in early preterm infants (7, 14, 16, 31, 32). The final prove that pain stimuli can reach human cortex in early preterm infants comes from study of M. Fitcgerald showing changes in cortical blood flow detected by infrared monitoring after pain peripheral stimuli (33).

Late preterm

Transient laminar pattern: In the late preterm transient laminar pattern gradually disappear and six layer Brodmann grundtypus appeared (1, 14). *Developmental events*: There is no production of neurons, except in hippocampal cellular formation and olfactory region. All neurons are in final position and migratory processes stopped. Radial glial cells which were main guides for radial migratory neurons undergone transformation in atrocities (4). *Axonal growth*: Callosal fibers show overgrowth phenomena (exuberance) and the number of axons in corpus callosum is higher then in adult brain. The overgrowth of corpus callosum was proven by counting axons on the midsagital sections (34). Within the hemisphere there are three major patterns of callosal distribution. Some axons are distributed within the white matter around ventricles, other axons are still waiting in subplate, and majority of "permanent" axons are already in the cortical plate.

Synaptogenesis and neuronal differentiation: Synaptogenesis is proceeding very fast in superficial part of cortical plate paralleled with accelerated development of dendrites pyramidal neurons (35, 36). *Functional pattern*: Due to the fast synaptogenesis in superficial cortex, cortical electrical dipole changes and surface negative response dominates in electrical recordings. There is gradual disappearance of giant potentials and synchronization of EEG (23, 37).

Neonatal period

During neonatal period fetal and preterm patterns are reorganized dramatically. This reorganization from transitional patterns to final organization is crucial for understanding physiological and behavioral phenomena in neonatal period. *Laminar organization*: Neocortex develops into typical six layered pattern. However, layer IV (granular layer) is still present in motor cortex (in adult motor cortex is agranular) (14). Second, subplate zone is not different cytoarchitectonic layer due to the full development of white matter in cortical gyri. However, subplate neurons remain as the interface between layer VI and white matter. In the associative cortex neurons of the subplate might exist as a distinct population as long as 6 months (38). Some of the cells die by naturally occurring cell death (4, 15).

Neurogenetic events: Two neurogenetic events dominate early postnatal development. First this is explosive development of synapses and second is the extensive production of postsynaptic spines (39, 40). *Axons*: The major reorganization during neonatal period is related to exuberant callosal axons. The newborn monkey shows three times grater number of axons than adult monkey (34). The same phenomena have been described in the human brain (41). However, the exact time of axon reduction in man is not known, but is expected to occur during early postnatal time (41). During neonatal period there is continuation of short corticocortical fiber growth as it was show by Burkhalter et al. (42). *Functional pattern*: The main characteristic of neonatal period is establishment of sensory driven activity. This is particularly important for development of columnar organization in sensory cortices (3). Also, there is synchronization in EEG and sleep pattern, transient general movements still persist in the neonatal period indicating immaturity of cortical and subcortical circuitry (18).

Discussion

In this review we have presented evidence that fetal and preterm cortex shows transient pattern of organization and permanent developmental reorganization. These phenomena were also observed using different structural approaches and physiological recordings (1, 4). Neurodevelopmental cellular event occur with different intensity throughout development. The periods of increased cellular activity might also be described as developmental "windows". Throughout each developmental window transient zones display characteristic structural and chemical properties. In our review we have emphasized out that transient zones are essential spatial parameters for cellular events (4, 6). Using imaging techniques it is possible to visualize all transient cellular zones (7). Exception is marginal zone which is visible in the hippocampal cortex only, while in neocortical areas is beyond resolution of 1.5 T imaging.

The demonstration of transient cellular zones is important for in-vivo assessment of structural and functional development and reorganization of the human fetal and preterm brain (5). In addition, magnetic resonance imaging of transient patterns of organization is important for contemporary diagnostic procedures (20, 21, 43-45). We believe that abnormalities of transient cellular zones might be objectively analyzed in different genetic and epigenetic pathologies. The knowledge about reorganization of developing cortex is of great significance of our understanding of structural plasticity and vulnerability of the human brain. For example, thalamocortical afferents are in "waiting" position in the

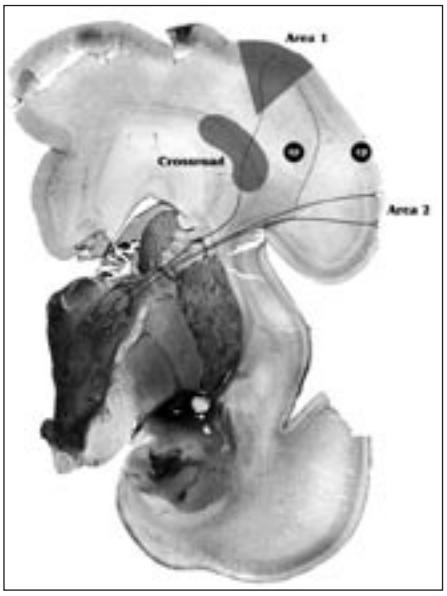

Figure 2
Fiber "rerouting" after lesion: Pattern of structural plasticity of thalamocortical fiber pathways in the human fetus; fiber "rerouting", where growing fibers can be redirected to other final destination in the case of original target area lesion

Slika 2.
Preusmjeravanje rastućih aksona nakon lezije: Mehanizam strukturalne plastičnosti talamokortikalnih aksonskih putova u fetusa čovjeka; rastući aksoni mogu biti preusmjereni prema drugom cilju u slučaju oštećenja primarne ciljne areje ("rerouting")

subplate zone during waiting period. During this period thalamocortical afferents can be "detoured" around the periventricular lesions and arrive in the cortex of their original destination, or rerouted in adjacent cortical area (see also our figure 2) (46).

The structural plasticity of the major pathways is limited to prenatal period due the fact that pathways are later in the final position (5, 14). An important factor in determination of plasticity limitations is expression of guidance molecules. The guidance molecules are essential for growth of axonal pathways and their activity decreases towards the end of gestation (6, 47). Imaging of the transient zones offers unique opportunity to study selective vulnerability of the cortical layers. For a long time it was considered that fetal white matter is the major target in ischemia-hypoxia sequel (48). However, recently it was found that subplate neurons show selective vulnerability in hypoxia-ischemia (44, 49). It was proposed that subplate neural elements might be partially involved in diffuse periventricular "lesion", so called DEHSI (5, 44, 48, 50). It was found using diffusion tensor imaging that DEHSI is the most frequent finding in preterm infants (51-53). Searching for structural correlates and pathogenesis of this important MR finding remains the most challenging task in the contemporary perinatal medicine.

Conclusion

Developmental reorganization of the human cortex may be demonstrated by sequentional analysis of transient cellular zones, magnitude of and intensity of neurogenetic events and changes in functional pattern. All cellular zones in the fetal cerebral wall are transient and they have no adult counterparts. The thickness, cellular composition and chemical properties of transient zones reflect intensity of cellular events throughout ontogeny. Proliferation and migration are dominant events during the first half of gestation, and occur in subventricular and ventricular zone. Major axonal pathways grow and find their pathway in the intermediate zone and enter subplate "waiting" zone while approaching their cortical target. Synaptogenesis begins early in fetal life as a part of transient circuitry of the subplate zone and marginal zone. However, synaptogenesis is predominantly postnatal event and it is modified during interaction with environment.

Functional pattern shows three phases: first, endogenous, spontaneous circuitry in fetus; second, coexistence of endogenous and sensory driven circuitry in preterm; and third, sensory driven circuitry in neonatal period. In this review we demonstrated developmental reorganization of the neocortex based on transient cellular zones, changing intensity of cell events and functional pattern. The developmental "windows" with increase intensity of events are vulnerable periods (temporal factors). Transient cellular zones show selective vulnerability (spatial factors). Search for the basis of selective vulnerability of periventricular crossroad of pathways, vulnerability of growing axons and subplate zone, possibilities of neuroprotection and their visualization with modern magnetic resonance imaging techniques, is the most challenging task in modern developmental neurology. The role of transient neuronal circuitry and plasticity opens new visitas for the treatment of the children with perinatal brain injury.

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Sažetak

RAZVOJNA REORGANIZACIJA KORE MOZGA ČOVJEKA

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U ovom preglednom članku osvrnuli smo se na razvojnu reorganizaciju ljudskog mozga. Tri kriterija korištena su u svrhu određivanja reorganizacije: (1) prisutnost prolaznih staničnih slojeva: ventrikularni (VZ), subventrikularni (SVZ), intermedijarni (IZ) sloj (zona), sloj ispod ploče (subplate-SP), kortikalna ploča (CP) i marginalni sloj (zona) (MZ); (2) intenzitet specifičnih neurorazvojnih staničnih događaja: proliferacija, migracija, diferencijacija, izrastanje aksona i sinaptogeneza; (3) obrazac unutarnje funkcionalne organizacije: (a) prolazni, endogeni neuralni krugovi, te (b) trajni, osjetno stimulirani neuralni krugovi. Prva polovica trudnoće obilježena je proliferacijom i migracijom. Tijekom druge polovice trudnoće glavni aksonski putovi urastaju kroz intermedijarni sloj i "čekaju" u sloju pod pločom. Prve sinapse vidljive su tijekom trećeg mjeseca trudnoće i povezane su s unutarnjim, spontanim neuralnim krugovima. U ranog prematurusa (nakon 24. postkoncepcijskog tjedna) talamokortikalna vlakna premještaju se iz sloja pod pločom i urastaju u kortikalnu ploču, te se mogu po prvi puta zapaziti evocirani potencijali. Osnovno obilježje je istodobna prisutnost unutarnjih i trajnih, osjetno stimuliranih neuralnih krugova. U mozgu novorođenčeta sinaptogeneza je glavno neurorazvojno događanje, a također dolazi i do postupnog nestanka prolaznih unutarnjih neuralnih krugova i prolaznih staničnih slojeva. Ovaj pregledni rad podupire hipotezu o razvojnim "prozorima", selektivnoj vulnerabilnosti i specifičnim, prolaznim fetalnim slojevima (subplate), te povećanoj vulnerabilnosti mozga fetusa i novorođenčeta čovjeka.

Deskriptori: PRETERM INFANT, CEREBRAL PATHWAYS, THALAMOCORTICAL AFFERENTS, SYNAPTOGENESIS, HISTOGENESIS