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Review

Subplate Zone of the Human Brain: Historical Perspective and New Concepts

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A B S T R A C T

Subplate zone (SP) is prominent, transient laminar compartment of the human fetal cerebral wall. The SP develops around 13 and gradually disappears after 32–34 postovulatory weeks. The SP neurons can be found as late as nine postnatal months, while remnants of the SP neurons can be traced until adult age in the form of interstitial neurons of the gyral white matter. SP is composed of postmigratory and migratory neurons, growth cones, loosely arranged axons, dendrites, glial cell and synapses. The remarkable feature of the SP is the presence of large amount of extracellular matrix. This feature can be used for delineation of SP in magnetic resonance images (MRI) of both, in vivo and post mortem brains. The importance of SP as the main synaptic zone of the human fetal cortex is based on the rich input of »waiting« afferents from thalamus and cortex, during the crucial phase of cortical target area selection. SP increases during mammalian evolution and culminates in human brain concomitantly with increase in number and diversity of cortico-cortical fibers. The recent neurobiological evidence shows that SP is important site of spontaneous endogeneous activity, building a framework for development of cortical columnar organization. The SP, which can be readily visualized on conventional and DTI (diffusion-tensor-imaging) MRI in vivo, today is in the focus of interest of pediatric neurology due to the following facts: (1) SP is the site of early neural activity, (2) SP is the major substrate for functional plasticity, and (3) selective vulnerability of SP may lead to cognitive impairment.

Key words: *fetal brain, early endogeneous activity, cortico-cortical fibers, magnetic resonance imaging, cognitive impairment, mammalian brain evolution*

The discovery and original concepts

Subplate zone (SP) was discovered and originally described at The Johns Hopkins University during 1973 and 1974, when dr. I. Kostović, at that time on leave of absence from School of Medicine University of Zagreb, joined the team of dr. M. Molliver. The initial report described all major features of the human SP[1]:

1. Laminar position between the cortical plate and the intermediate zone,
2. The presence of synapses,
3. The presence of postmigratory, well-differentiated neurons
4. Fibrillar, plexiform organization, and
5. Prominent size in the human brain, when compared with other mammals.

The emphasis of initial report was on a new interpretation of laminar development, demonstrating that the zone below the cortical plate initially named the subplate layer is not a part of the fetal white matter, but a prominent, hitherto neglected and transient synaptic layer, which represent an important part of the neocortical anlage (Figures 1, 2). At that time it was already known that there are well-differentiated neurons below the developing mammalian cortical plate (Figures 3, 4)[2–4]. The origin and significance of these neurons was not known but they were considered, by some investigators, to be neurons of future layer VIb (Figure 4, for review see Kostović and Rakic 1990)[5]. It is interesting that Marin-Padilla[3] obtained excellent impregnation of pyramidal neurons using rapid Golgi staining but this method failed to demonstrate many of deep neurons, which were seen with Stensas modification of Rio del Hortega method[6].

Upon initial discovery, very little attention was paid to this prominent embryonic zone by most of the experi-

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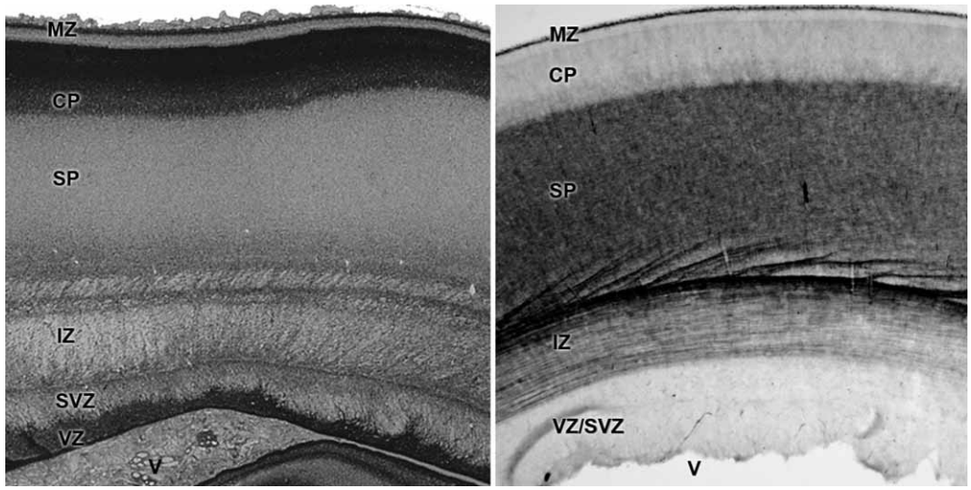

Fig. 1. Microphotographs of horizontal sections of telancephalic wall from human fetus 20 weeks post ovulation: left-prospective neocortical region, stained by Nissl method, and right-prospective occipital region processed with acetylcholinesterase histochemical staining, shows that subplate zone is several times thicker than any other developmental zone of the telencephalic wall. MZ-marginal zone, CP-cortical plate, SP-subplate zone, IZ-intermediate zone, VZ-ventricular zone, V-lateral ventricle. Source: Zagreb Neuroembryological collection.

mental researchers. One of the reasons was that this zone is poorly developed in experimental rodents and it is several times thinner than the cortical plate, while in the human brain the SP is 4 to 5 times thicker than cortical plate (Figures 1, 2). However, some experimental groups of neuroscientists immediately recognized the significance of the SP. First of all, Rakic[7] demonstrated that in the rhesus monkey thalamocortical fibers destined to visual cortex wait in the SP before they penetrate in cortical plate at later stages (Figure 1, right). The concept of »waiting« compartment was further elaborated and documented in joint papers by Kostović and Rakic[8], and Kostović and Goldman-Rakic[9]. The significance of SP for development of thalamocortical connections in the

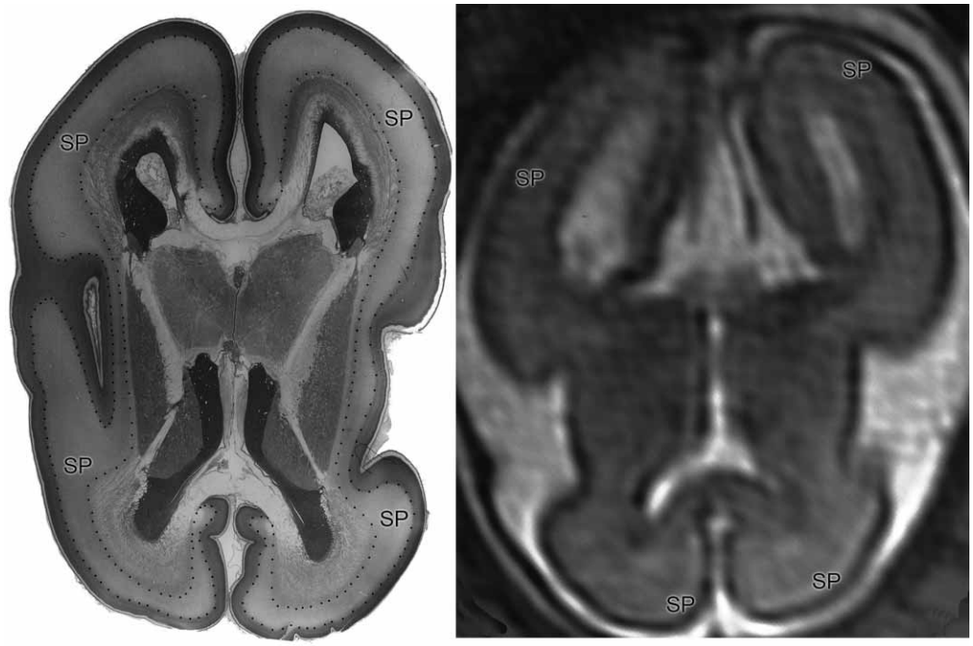

Fig. 2. Horizontal sections through human fetal telencephalon 24 weeks post ovulation: left-stained by Nissl method and right- acquired by in vivo magnetic resonance imaging (MRI, 1,5 Tesla). Figure shows remarkable size of subplate zone in developing human telencephalon (outlined by dots on the left section) and demonstrates a possibility that subplate zone may be recognized by in vivo MRI (right). SP-subplate zone. Source: Zagreb Neuroembryological collection.

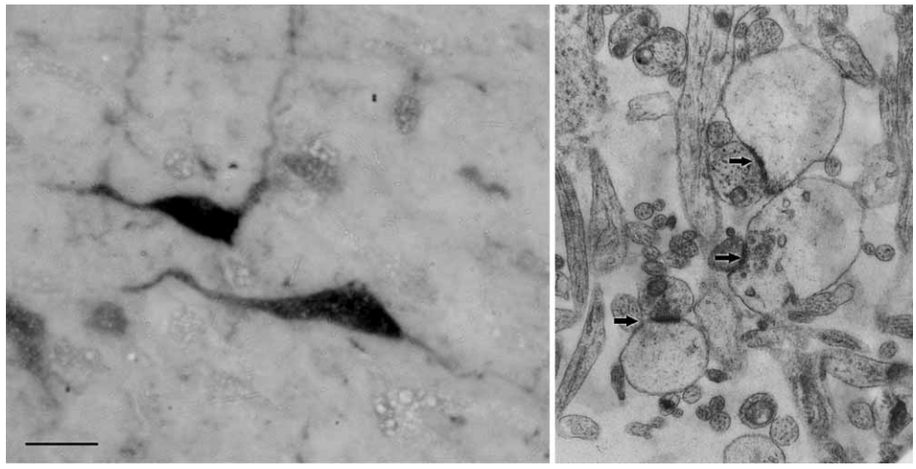

Fig. 3. Microphotographs of subplate zone: left- in the region of so-called callosal plate, in fetus aged 26 weeks post ovulation, labeled immunocytochemically with anti-micro-tubules-associated protein-2 (source: Doctoral Thesis of Jovanov-Milošević[68], bar indicates 20 μm), and right-electron micrograph (x 28,000) which shows three axo-dendritic synapses in subplate zone (indicated with arrows) 24 weeks post ovulation. Source: unpublished data of I. Kostović.

human brain was also documented in auditory cortex[10], somatosensory cortex[8] and recently reviewed in several articles[11–13].

Carla Shatz led other group of scientists working on origin, developmental history, significance and fate of the SP. This group confirmed early origin of subplate neurons in the cat[14], which is in a good agreement with the finding of early origin of subplate neurons in the primate brain[15]. Neurotransmitters of the subplate neurons were described in detail by the same experimental group[16–20] and recently reviewed in the paper of McQuillen and Ferreiro[21]. The complexity of neurotransmitter organization of the SP was also documented in the human brain[22–24] as well as in experimental primates[25,26]. In summary, this early complexity of neurotransmitters in the SP corresponds to obvious structural complexity of subplate neurons (Figures 3, 4)[6]. Most authors agree that some neurotransmitters and growth modulators show either transient expression or transient over-expression in the SP. The transient nature of this zone below the cortical plate stimulated early investigations of the developmental fate of SP and subplate neurons. The attractive concept of SP regression and cell death, and experimental labeling of subplate neurons, led to the conclusion that many subplate neurons die during subsequent stages of development. Since the SP is the most prominent architectonic zone in the developing human telencephalic wall (Figure 2), reorganization and decline or loss of SP is obviously quantitatively the most significant regressive event in the developing telencephalon. In that respect, the fate of subplate neurons is similar to the fate of Cajal Retzius cells. Kostović and Rakic[15] convincingly demonstrated that the majority of subplate neurons become morphologically transformed and incorporated in gyral white matter as »interstitial« neurons (Figure 4). The final proof of neuronal nature of interstitial neurons was based on the presence of synapses on cell bodies and

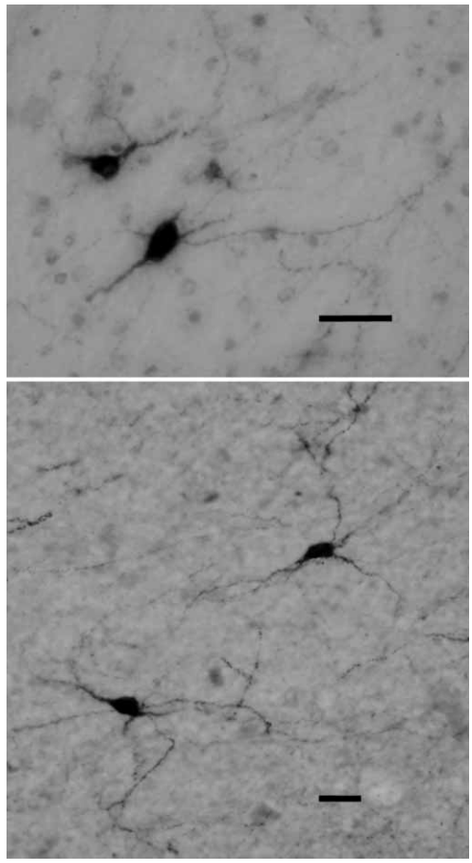

Fig. 4. Microphotographs of neurons: above- two subplate neurons in the neocortical region from the brain of newborn child, and below- two interstitial neuron of gyral white matter of the same region from the brain of 6 year old infant, labeled immunocytochemically with anti-neuropeptide Y (bar indicates 20 μm). Source: Zagreb Neuroembryological collection.

proximal dendrites of deeply situated interstitial neurons[15]. Similar concept of white matter neurons was presented by group of Shatz[27,28]. However, some authors quoted paper of Kostović and Rakic[15] as evidence for massive cell death, which is unfortunate misinterpretation, because that paper demonstrated that some subplate neurons may die, the majority survives as a population of interstitial neurons[15].

The subplate zone of the limbic cortex was noticed soon after its discovery in other cortical regions[30], and described as a narrow zone in the medial cingulate cortex, diminishing in thickness towards the limbus and archicortical rudiment of the induseum griseum[31] and even more narrow zone in the human hippocampus. In both of these papers, the subplate zone was defined on the basis of cytological features and the presence of synapses. However, in the cortical limbic areas, the marginal zone is much thicker than in the neocortex and synapses in the limbic marginal zone are more numerous than in the SP. This observation extended the original concept and pointed to the existence of clear regional differences in the appearance of the subplate zone along the curvature of the cerebral wall. The prominence of limbic marginal zone in comparison to less developed limbic SP led Super and Uylings[32] to conclude that the relative prominence of the subplate vs. marginal zone reflects different evolutionary significance of basic cortical types (neocortex vs. archicortex). Further evidence on regional differences of the SP is related to thalamocortical input. The most striking example is early developed pulvinar input to extrastriate cortex[8] while geniculate input appears later in the less developed SP of the primary visual cortex (for thalamocortical input – see below).

Recent concepts: Functional significance of the subplate zone and subplate neurons

In 1967, Molliver observed that deep synaptic activity, evoked by peripheral stimulation, may cause changes in cortical electrical responses[33]. However, group of Carla Shatz obtained the conclusive evidence of thalamocortical connectivity of subplate neurons[34–37] and properly described spontaneous endogeneous activity of subplate neurons[37]. The early endogeneous network driven by transient synaptic and signaling mechanisms was recently described by patch-clamp techniques in rodent[38]. The significance of the prolonged existence of endogeneous activity was discussed in a recent review[39]. The early subplate network has a major role in the establishment of the adult cortical circuitry[34–36]. The most attractive example is development of columnar organization, which is an essential feature of cortical modular organization. The group of Carla Shatz demonstrated that without SP, functional cortical columns failed to form[40,41].

Besides this functional neurogenetic role, subplate neurons may have other morphogenetic and inductive functions. The most attractive possibility is that they regulate the ingrowths of specific thalamocortical axons.

Subplate zone and cortical afferent systems

It was clear from the beginning that SP is important for growth of thalamocortical afferents serving as a »waiting« compartment[5,11,12]. Within the SP, afferent thalamocortical axons select the proper cortical target area and prepare for selection of postsynaptic targets. There are many candidate molecules for the substrate of this »morphogenetic recognition«[12]. We have emphasized that SP contains large amount of extracellular matrix, containing typical ECM-molecules, different growth factors and guidance cues[42,43,44].

After thalamocortical fibers penetrate into the cortical plate, there is dramatic decrease in the ECM content of the SP[12,42]. In the human brain, we have demonstrated that other afferents, i.e. from basal forebrain, approach the SP somewhat earlier than thalamocortical axons[45]. In addition, the arrival of monoaminergic afferents from the brain stem occurs even earlier[46–48]! In that respect, very little is known about growth and arrival of callosal fibers. Callosal fibers grow and steer around the ventricles, as a thickest bundle after 24 weeks post ovulation, when thalamocortical fibers already penetrated the cortical plate. We proposed that existence of subplate neurons during postnatal period is related to the growth of associative pathways[49]. Group of Carla Shatz described »supportive« growth of axons from subplate neurons into thalamus during development of cortico-thalamic pathways[50]. Other authors accepted the attractive possibility that subplate neurons guide the growth of cortico-thalamic axons and may be meeting thalamocortical fibers in the internal capsule which is known as »hand shake« hypothesis[51]. We also propose that guidance molecules from subplate neurons and subplate ECM play role in other neurogenetic processes, including neuronal migration, synaptic recognition and transport of signaling molecules.

The significance of subplate zone in clinical neuroscience and pediatric neurology

Since the SP is the most prominent zone of the developing human cortex it is a crucial question how it can be visualized in the human living brain. As the SP exists during the period from 13 postovulatory week and 6–9 postnatal months, a key question is: what is the role of the subplate zone in the human brain development and what are the consequences of SP lesions? Several related questions are: (a) Is there a functional role of SP in the preterm infant? (b) What is the pathology of SP in hypoxic lesions? (c) What is the role of SP in cortical plasticity? (d) How it can be visualized by routine diagnostic imaging of the living human brain? (e) How can we recognize abnormalities caused by genetic factors?

1. Subplate neurons and afferent synaptic connections are the most significant functional network during the preterm age when cortical synaptic arrangements are very immature or absent. Therefore, developmen-

tal neurologists agree that subplate neurons and afferents are important factors in early cortical function[11,12,13,52,53]. The functional activity of SP may also be crucial for early response to painful stimulation[54–56]. On the other hand, functional elements of SP may be the basis of functional plasticity after brain lesion and its potential may be used in rehabilitation process[52,57].

2. One of the most attractive concepts is that there is a selective vulnerability of subplate neurons after hypoxic/ischemic lesions in preterm infants[21,58]. The idea is that subplate neurons, which have early maturing glutamatergic signaling and numerous synaptic connections, would be more vulnerable than cortical plate neurons after neuroexcitotoxicity cascade. However, there is no definitive histopathological evidence for massive apoptotic death of subplate neurons. In our laboratory in Zagreb, we were unable to demonstrate extensive cell death in SP as was described by the groups of Volpe and Kinney from Harvard Medical School[59]. The most important task in this respect is to define how much of the SP is involved during diffuse periventricular leukomalacia[21] and furthermore, we should search for neuropathological substrate of so-called diffuse and excessive high-signal intensity –DEHSI (present in more than 15% of low birth weight infants) that can describe the most significant lesion of SP.
3. The attractive hypothesis of apoptotic cell death and selective vulnerability of the subplate neurons should not detract our attention from transient presence of numerous afferents in the SP, including cholinergic afferents from basal forebrain, thalamocortical pathways, callosal fibers and long associative fibers. All of these fiber systems may be re-routed and detoured after particular cortical lesion, provided that they did not yet grow into the cortical plate. We have predicted this role of SP[31,60]. However, definitive evidence came from attractive neuroimaging work of Staudt[61]. They have shown that thalamocortical fiber designated to somatosensory cortex can be detoured around the lesion from the SP waiting position.
4. An essential requirement for clinical studies of the importance of SP is that the SP can be visualized *in vivo* and not only post mortem. In co-operation with neuroradiologists from University Hospital Center Zagreb, we have found that SP is the most prominent landmark in postmortem brain analyzed by MR neuroimaging. The co-operation with neuroradiologists Radoš and Štern-Padovan and obstetrician Škrablin-Kučić gave us the opportunity to visualize the SP *in vivo in utero* (Figure 2, right)[39,62]. Leading experts using DTI methods have already demonstrated SP in the living brain[63–65]. Finally, the SP entered the level of textbook and everyday diagnostic work[66].
5. A number of genes were described to be expressed in the subplate neurons. It is logical to assume that disturbance in their expression would led to the failure of the developmental role of SP and consequently to cortical abnormality. Thus far, there is no evidence for specific genetic pathology in the SP. We believe that the persistence of the SP is as important as the failure of its development. Increased numbers of interstitial neurons and their chemical abnormalities was described in schizophrenia and some others psychiatric disorders[67].

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SUBPLATE ZONA LJUDSKOG MOZGA: POVIJESNA PERSPEKTIVA I NOVI KONCEPTI

S A Ž E T A K

Zona pod kortikalnom pločom (subplate zona, SP) je istaknuti, prolazni, pločasti odjeljak fetalnog ljudskog mozga. SP se razvija oko 13. tjedna i postepeno nestaje nakon 32–34. tjedna poslije ovulacije. Neuroni SP mogu se naći i 9 mjeseci postnatalno, a kasnije sve do odrasle dobi su prisutni kao intersticijski neuroni bijele tvari moždanih vijuga. SP se sastoji od: migrirajućih i post-migrirajućih neurona, rastućih čunjića aksona, rijetko položenih aksona, dendrita i različitih glija stanica te sinapsi. Istaknuto obilježje SP je prisutnost velike količine međustanične tvari (ekstracelularnog matriksa). Ovo obilježje omogućava vizualizaciju SP na slikovnim prikazima mozga magnetskom rezonancijom (MRI) *in vivo* i postmortalno. Važnost SP kao sinaptičke zone ljudskog fetalnog mozga, temelji se na obilju »čekajućih« vlakana iz talamusa i moždane kore, tijekom faze odabira cilja u arejama moždane kore. Tijekom evolucije SP se povećava, a njena veličina doseže najveće vrijednosti u ljudskom mozgu što se podudara s povećanjem broja i složenosti kortiko-kortikalnih veza. Najnoviji neurobiološki dokazi ističu SP kao važno mjesto spontane neuralne endogene aktivnosti, te je time neophodna za razvitak kolumnarne organizacije moždane kore. Subplate zona, koja se može lako prikazati primjenom konvencionalnog MRI ili DTI (diffusion-tensor-imaging) *in vivo*, danas je u žiži interesa pedijatrijske neurologije zahvaljujući njenim sljedećim obilježjima: (1) SP je temelj rane neuralne aktivnosti, (2) SP je u podlozi funkcionalne plastičnosti, (3) SP je selektivno ranjiva, što može voditi do oštećenja kognitivnih funkcija.