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IV. Kolokvij u organizaciji
Hrvatske akademije znanosti i umjetnosti i Hrvatske zaklade za znanost

ŠTO JE POSEBNO U RAZVITKU LJUDSKOG MOZGA?

3. svibnja 2017.

Plan:

- Prikaz problema
- Faze razvitka organizacije i funkcije subplate zone
- Moguća uloga u nastanku mentalnih i neuroloških poremećaja
- Zaključci

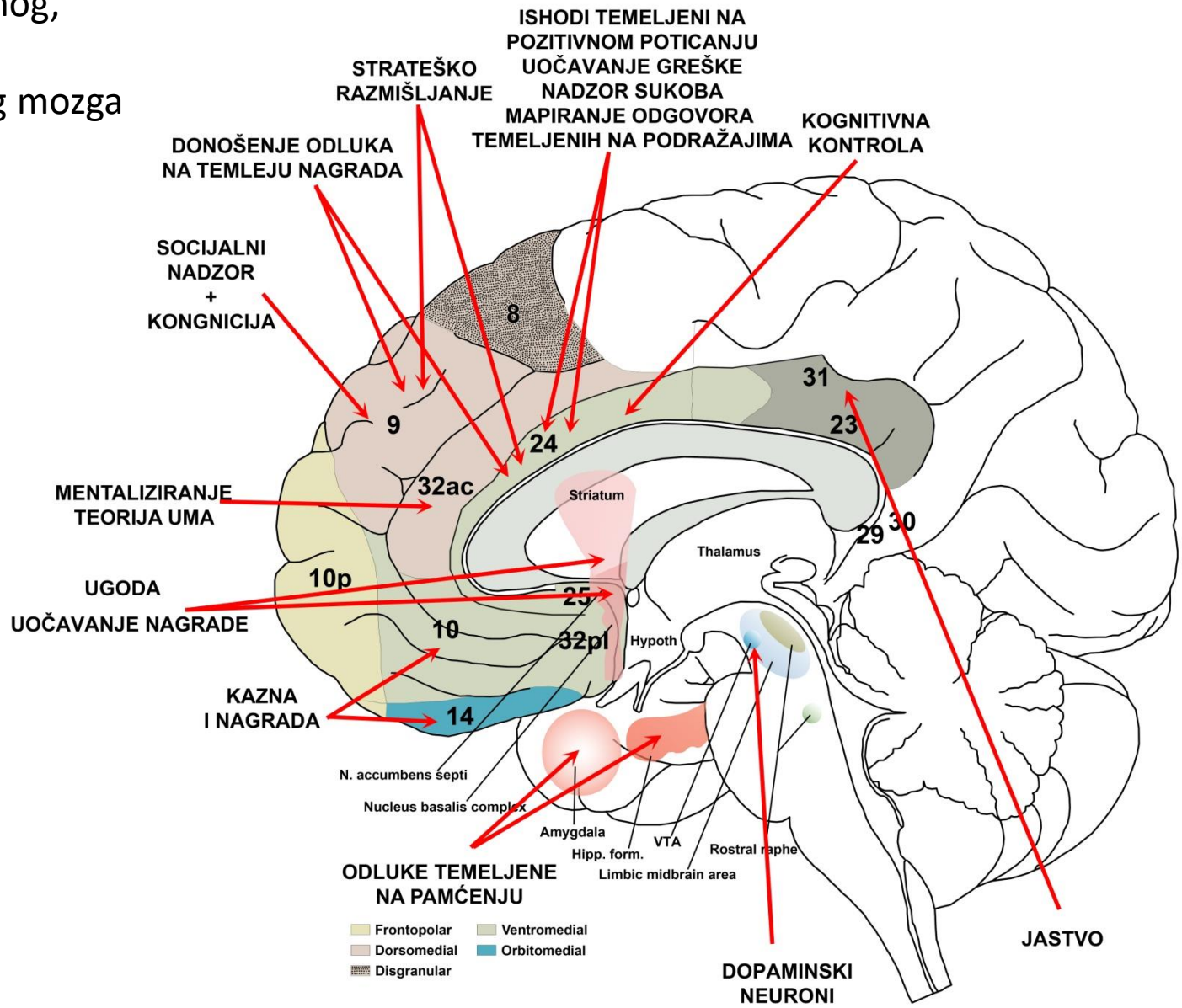
- Što nas čini ljudima?
- Što je jedinstveno za čovjeka?

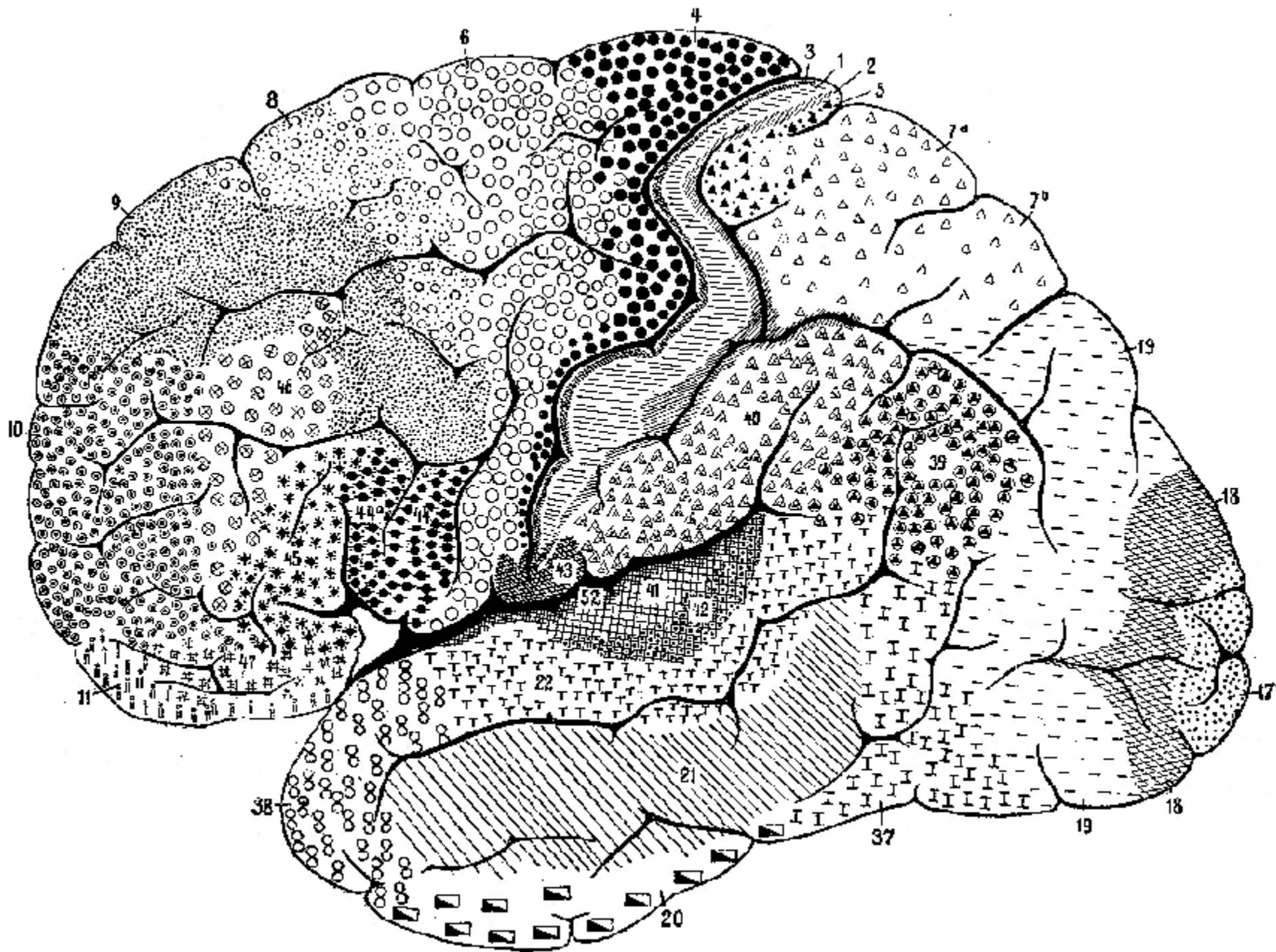
Susret socijalnog, kognitivnog i emocionalnog mozga

ZADACI U VREMENU I PROSTORU

AKCIJA

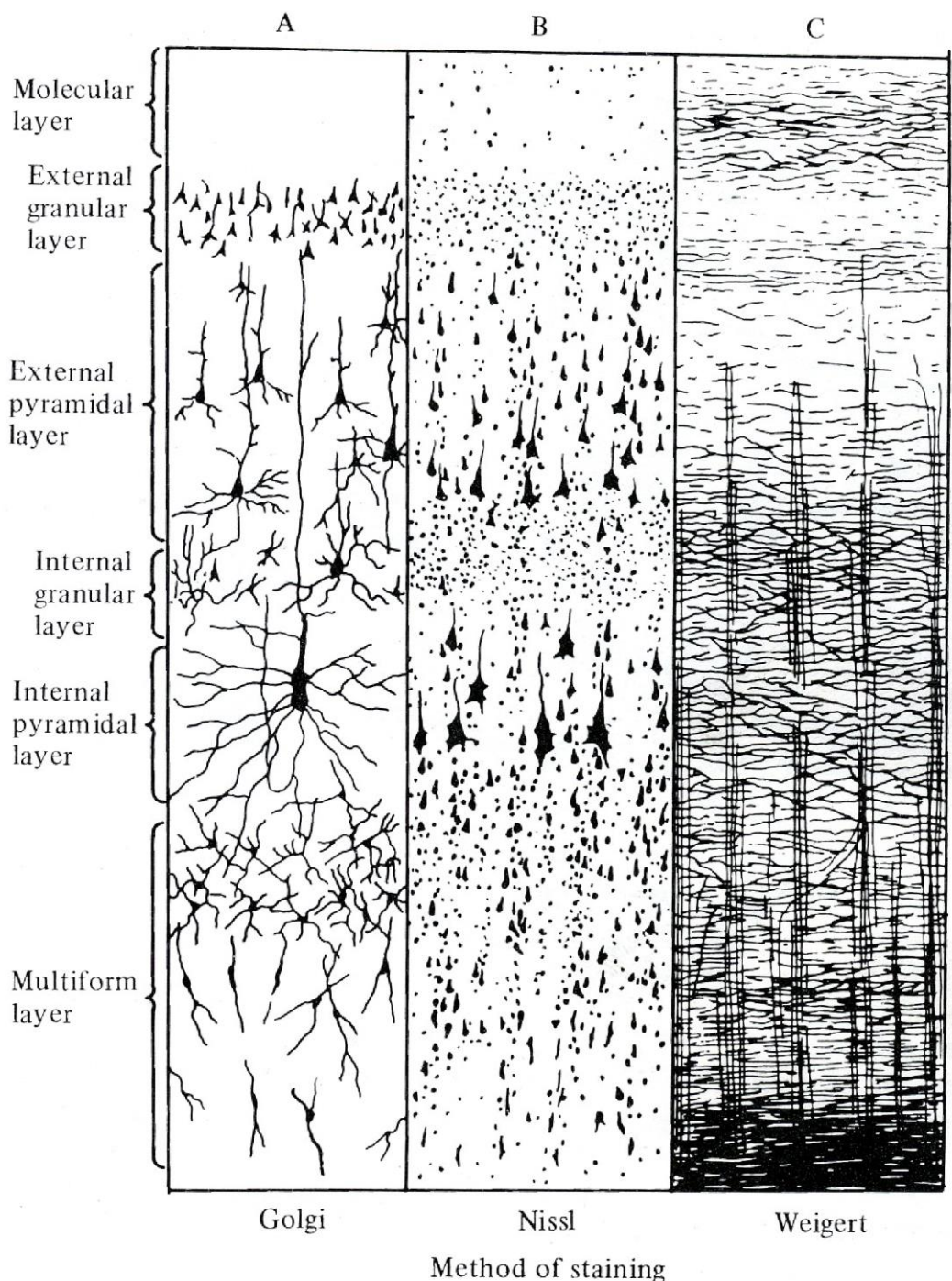
STANJE OKOLINE





Klasična kortikalna mapa po Brodmannu

Laminarna organizacija korteksa – prikaz iz udžbenika



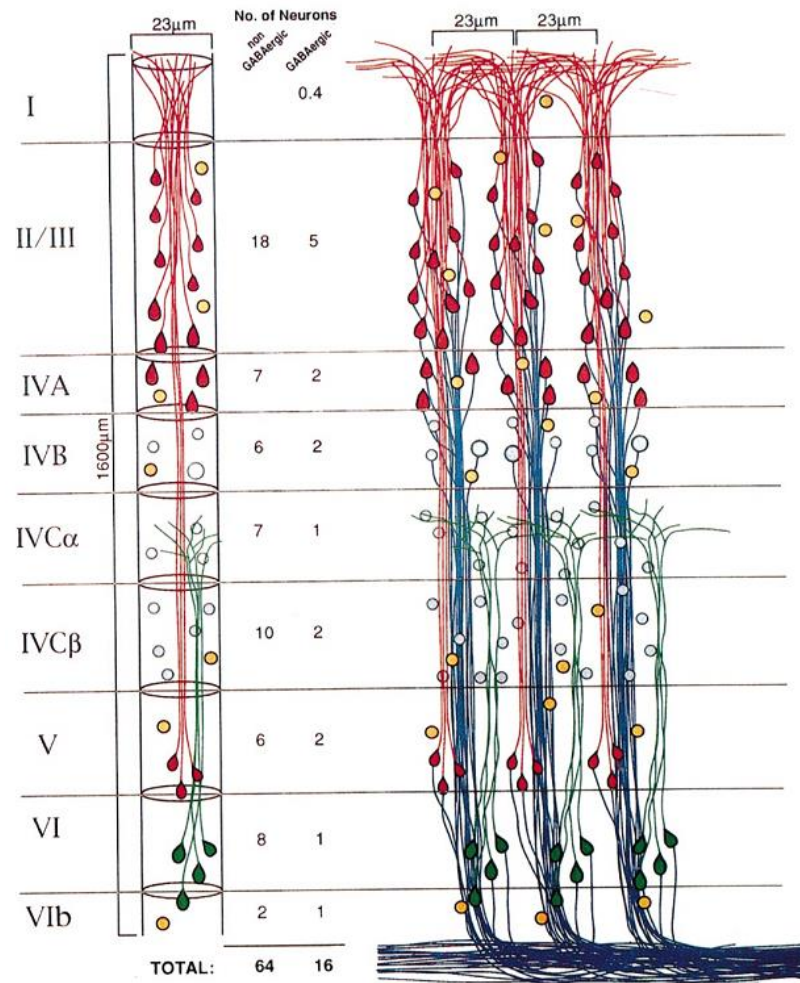
Golgi

Nissl

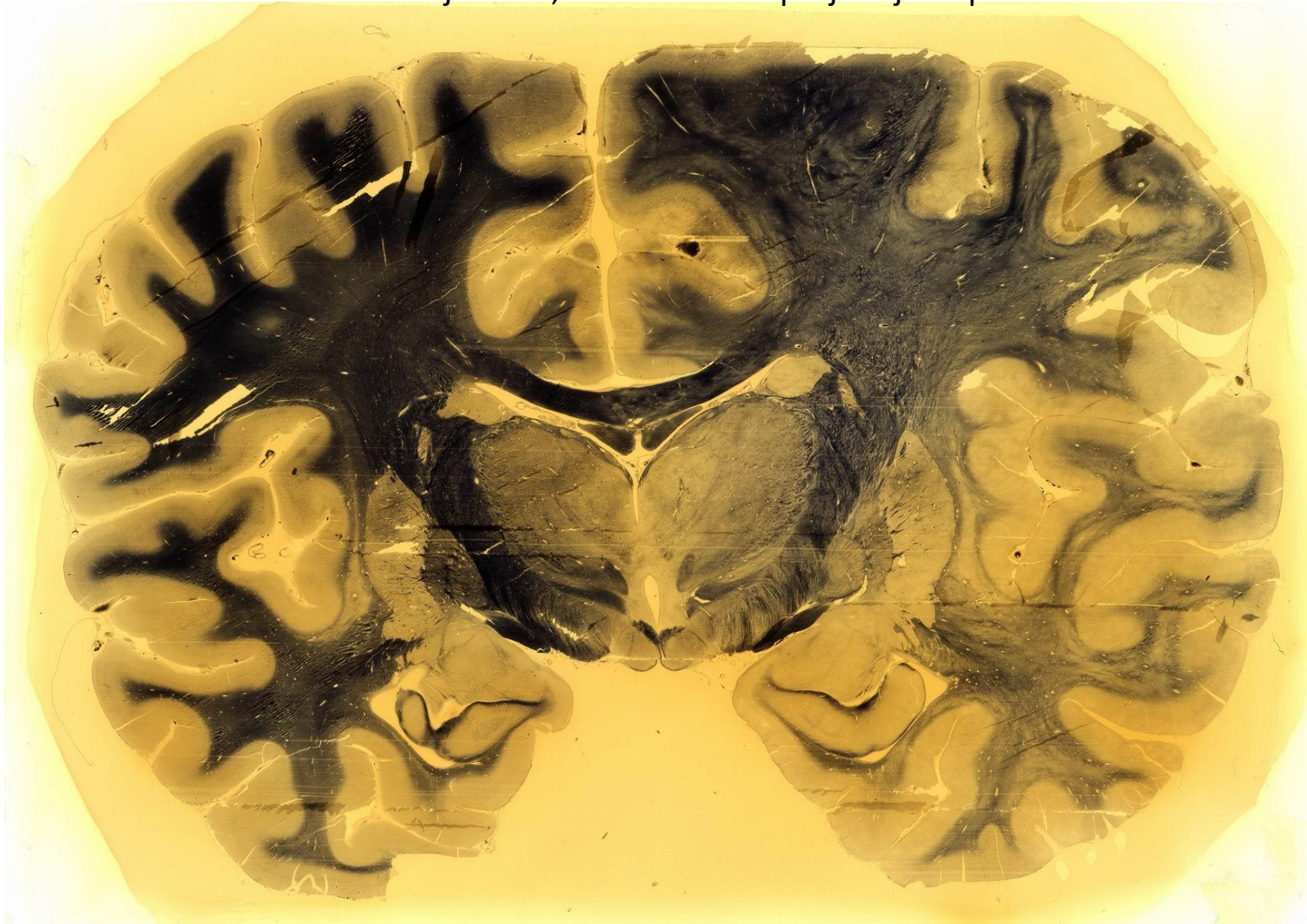
Weigert

Method of staining

KOLUMNARNO USTROJSTVO



Voluminoznost “bijeleg” tvari (tamno bojanje - Weigert) u čovjeka
Množina asocijativnih, komisuralnih i projekcijskih putova





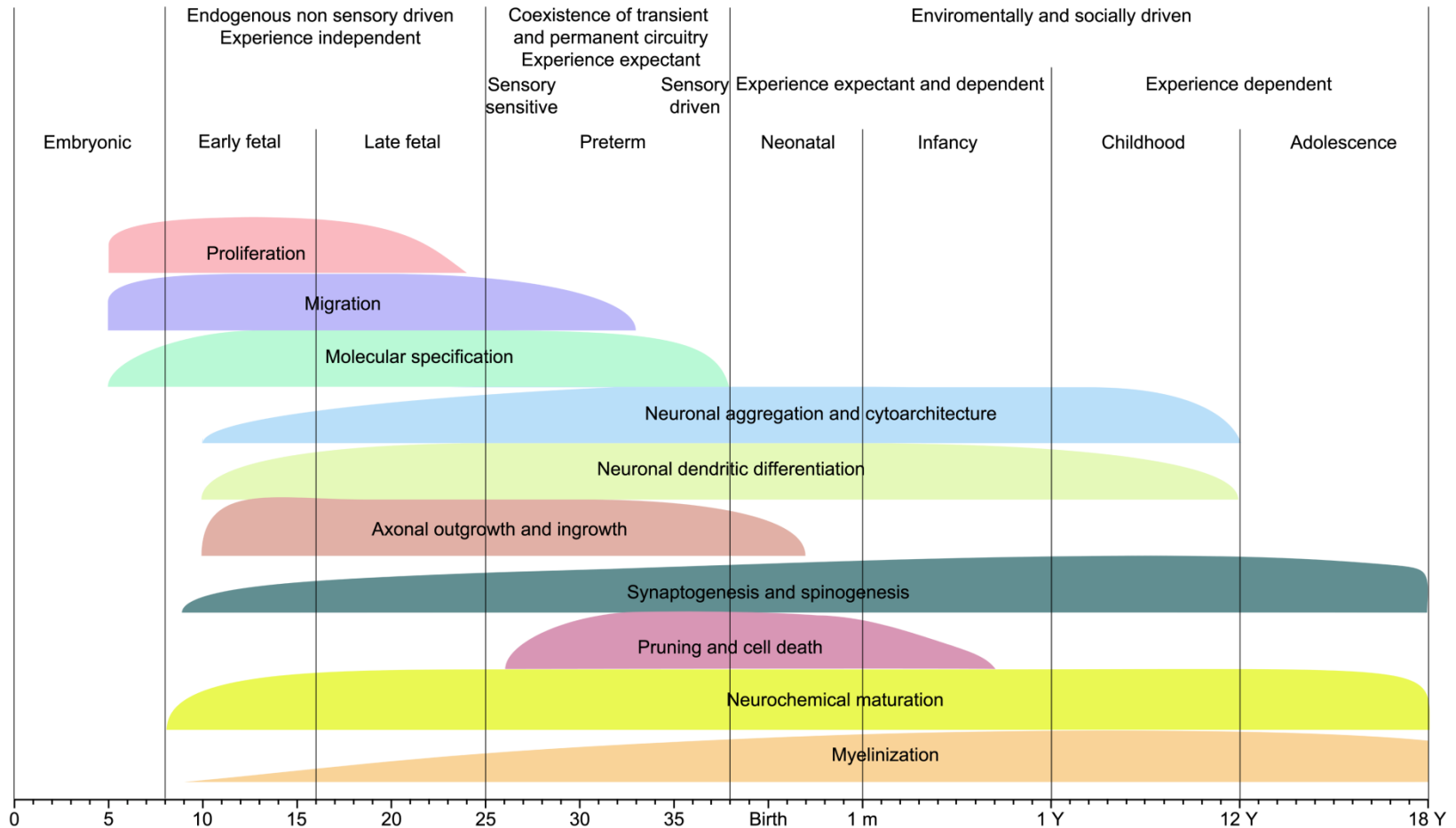
Subplate zona ljudskog mozga: neriješeni problemi
Subplate zone of the human brain: unsolved problems

(HUMANSUBPLATE, IP-2014-09-4517, project leader Ivica Kostović)

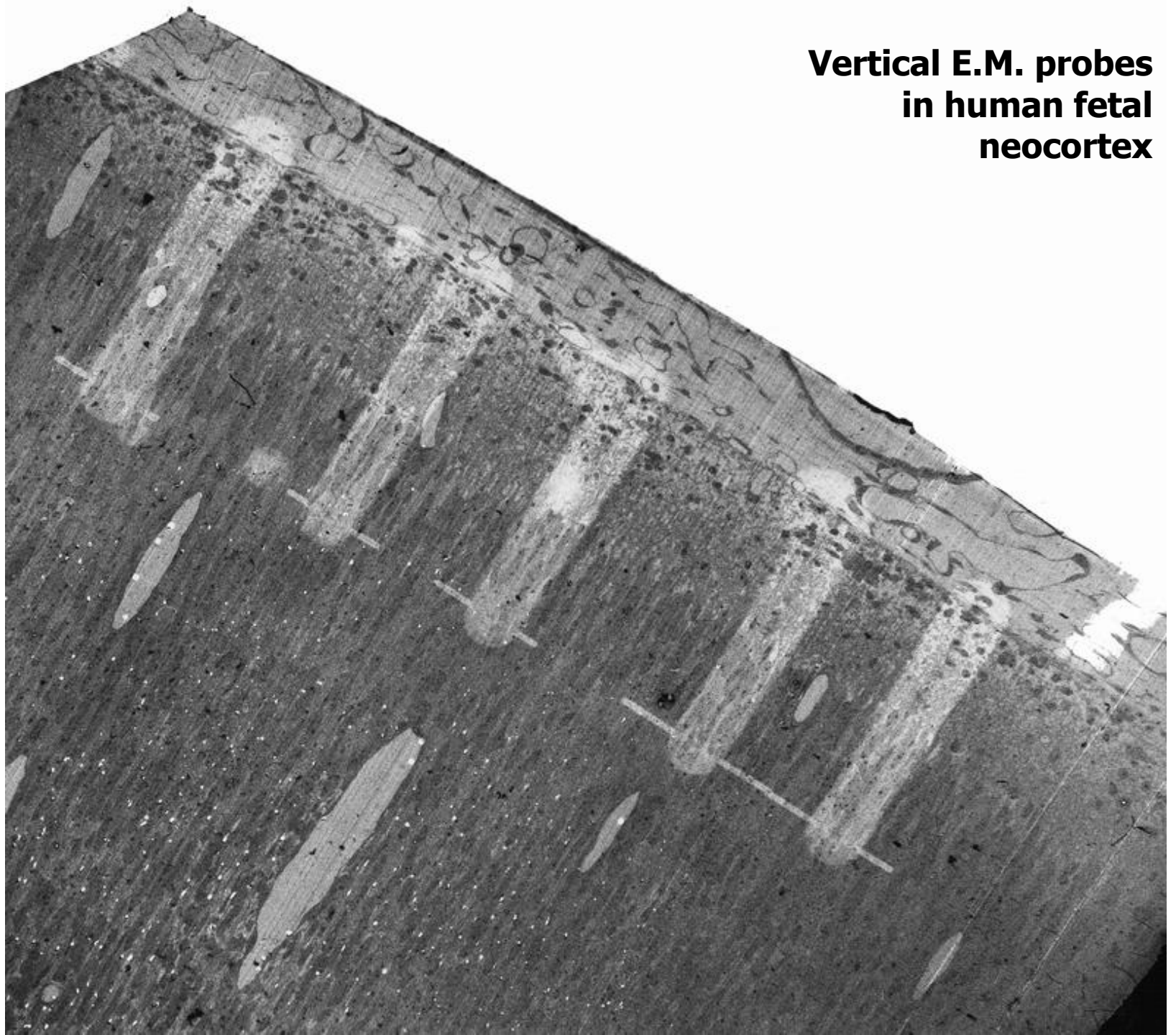
Neurorazvojni događaji u kortikalnoj histogenezi

Ključno pitanje: kada?

Kritična (vulnerabilna) razdoblja razvitka?

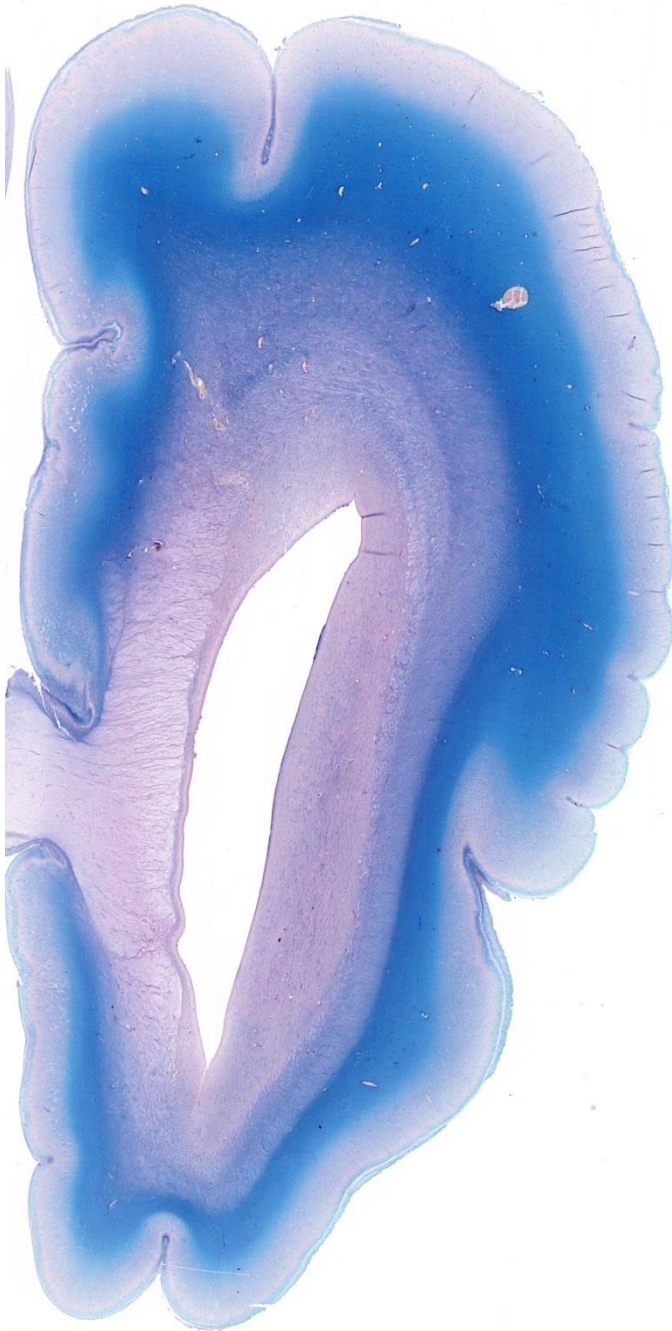


**Vertical E.M. probes
in human fetal
neocortex**

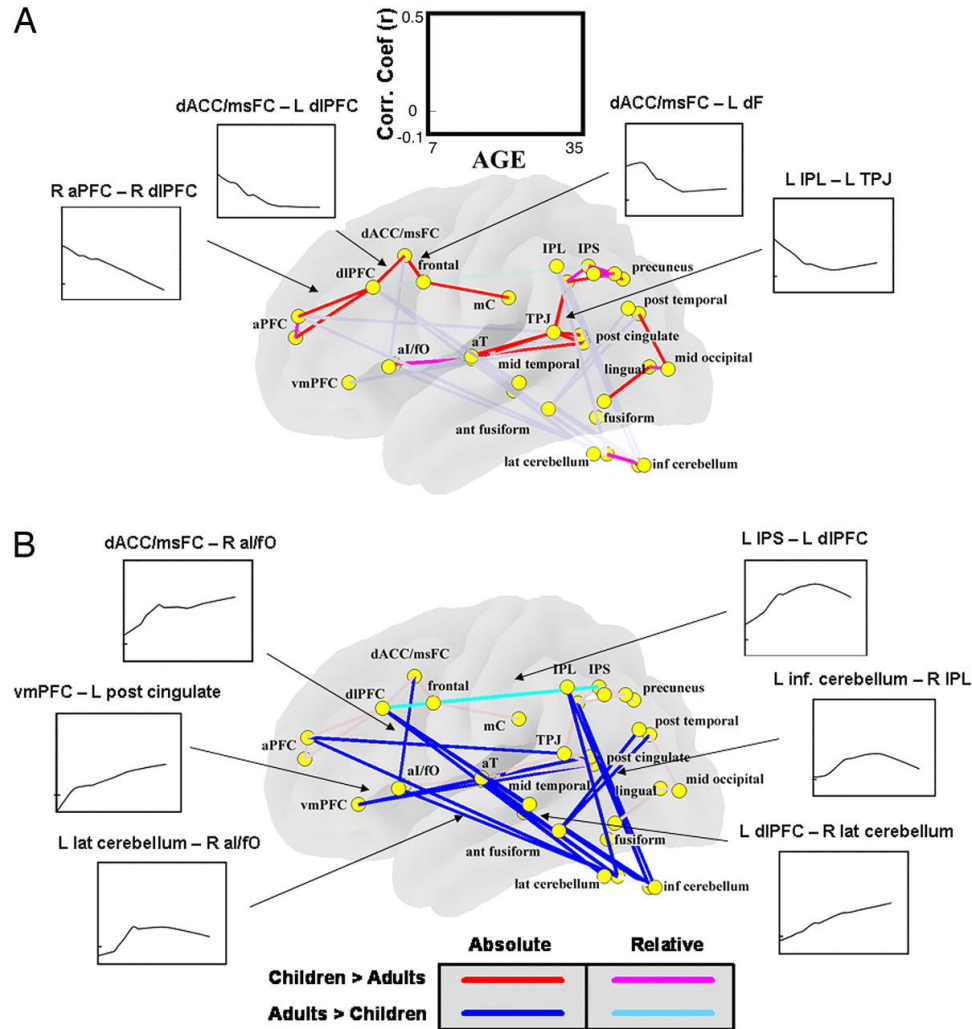


20 PCW

Kontinuitet
subplate
zone
prikazan
histokemijs
kom
metodom
za ECM i
AChE



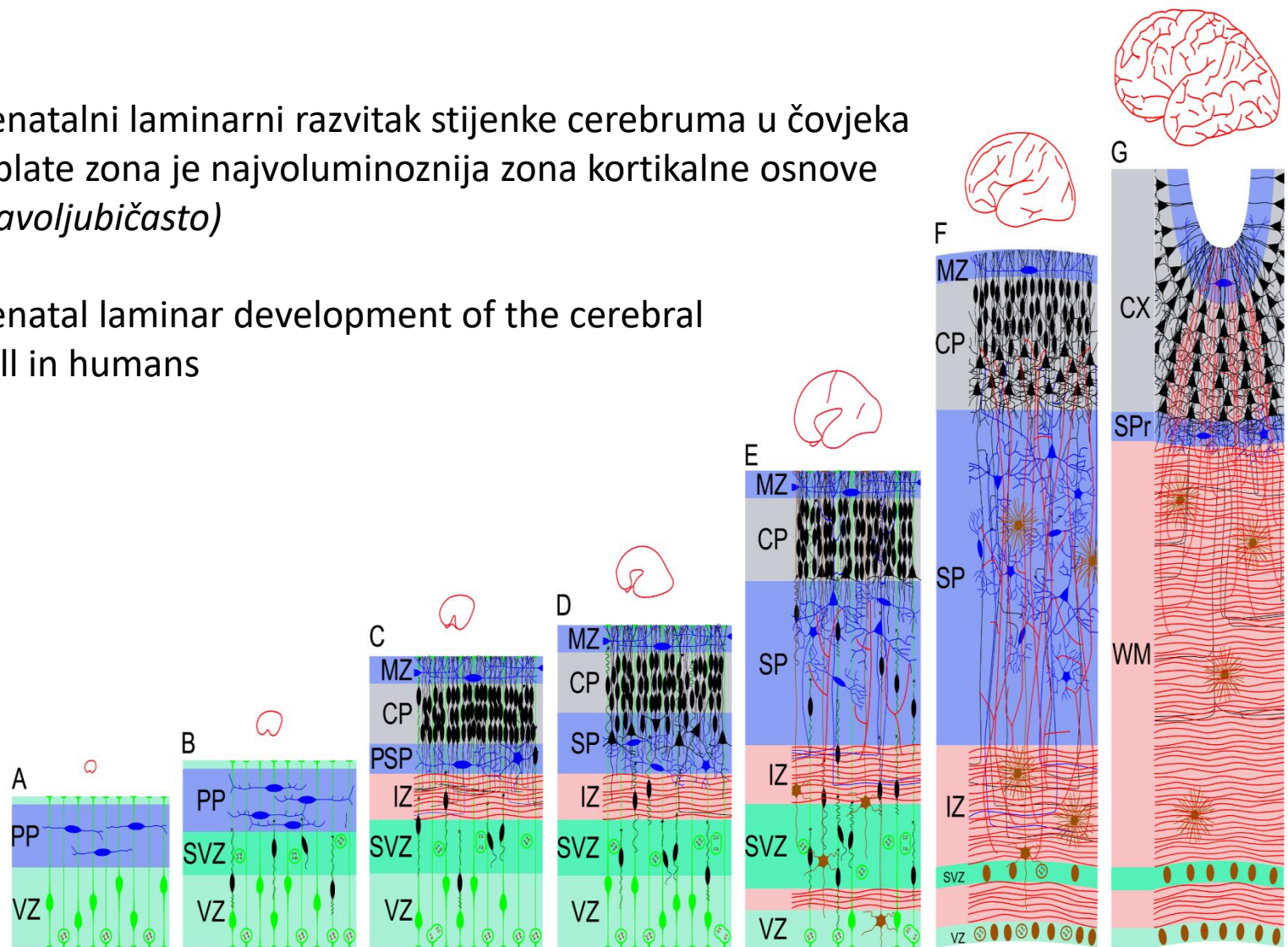
KLJUČNA ULOGA RAZVOJNOG PRISTUPA FUNKCIJAMA LJUDSKOG MOZGA: PORAST VEZA DUGOG DOMETA I SMANJIVANJE VEZA KRATKOG DOMETA (“mali svijet”) TIJEKOM RAZVITKA



Fair D A et al. PNAS 2007;104:13507-13512

Prenatalni laminarni razvoj stijenke cerebruma u čovjeka
Suplate zona je najvoluminoznija zona kortikalne osnove
(plavoljubičasto)

Prenatal laminar development of the cerebral
wall in humans

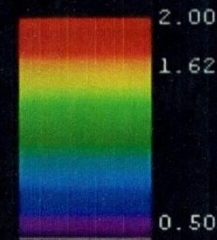
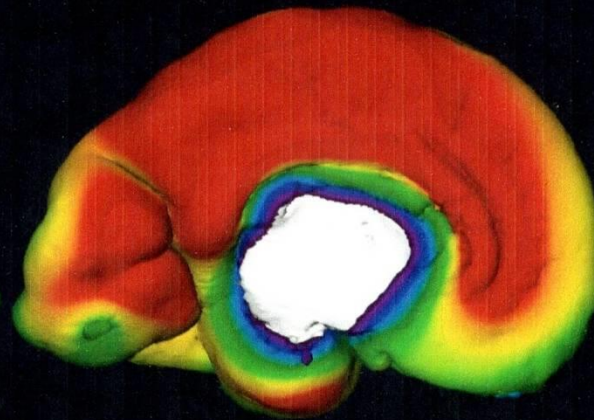


Kostovic & Judas, chapter in Brain Mapping: An Encyclopedic Reference, 2014

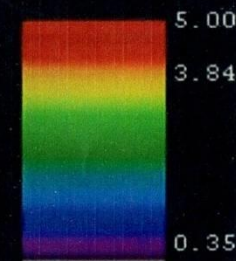
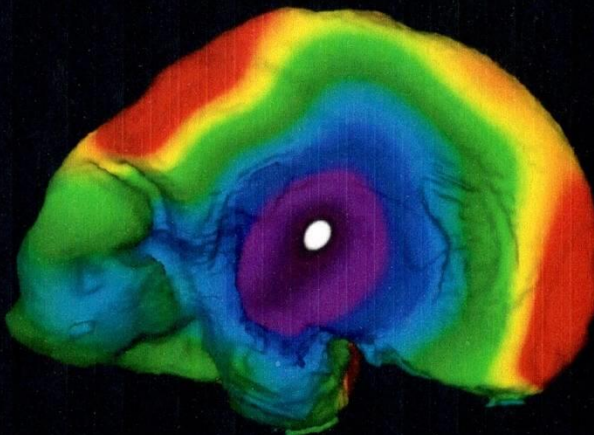
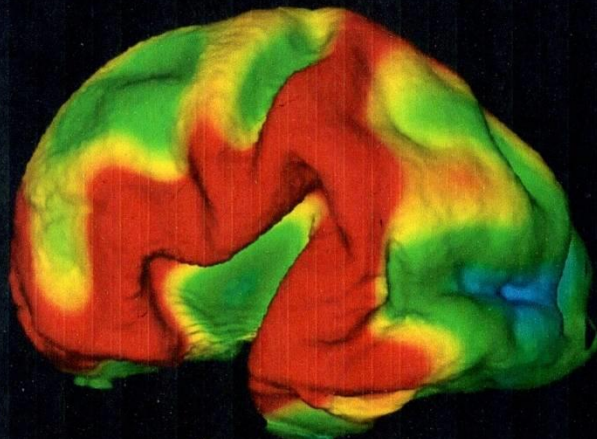
Cortical plate thickness (mm)

Age= 26 PCW

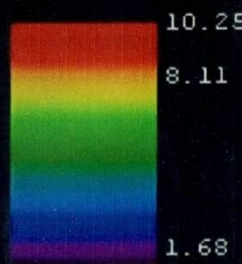
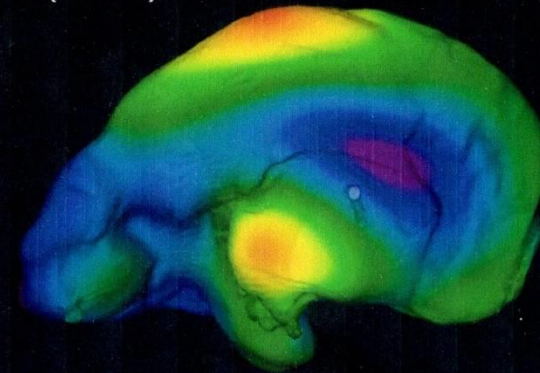
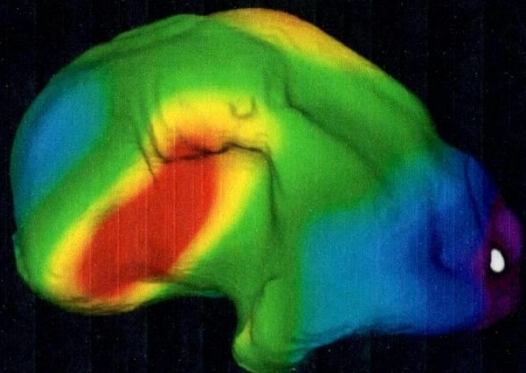
Regional differences in layer thickness



Subplate thickness (mm)

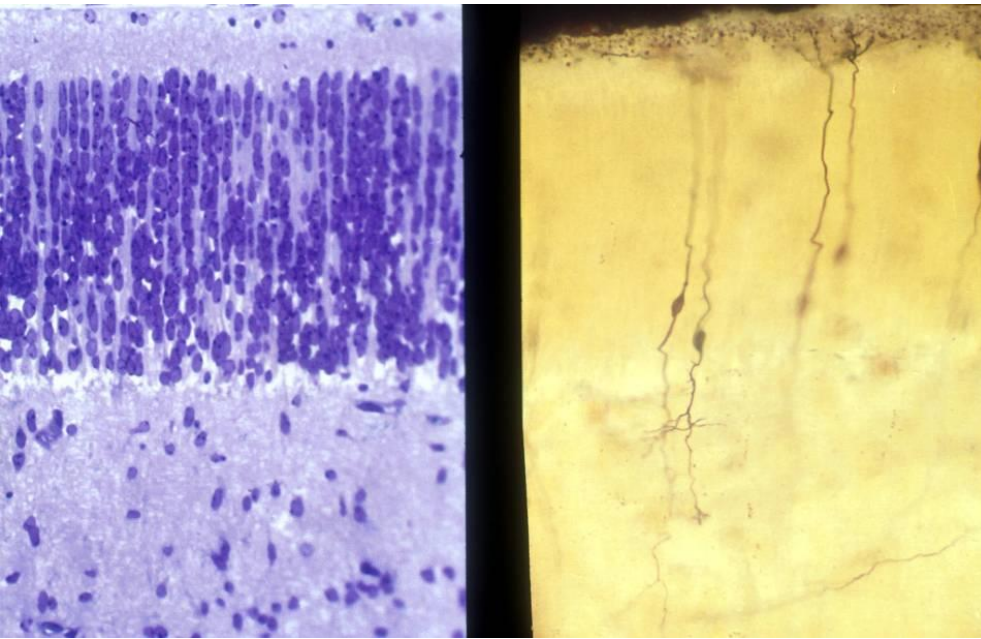


Intermedial zone thickness (mm)



L.Vasung
Doctoral Thesis
Zagreb University

Bilaminar distribution of dendrites – 10,5w

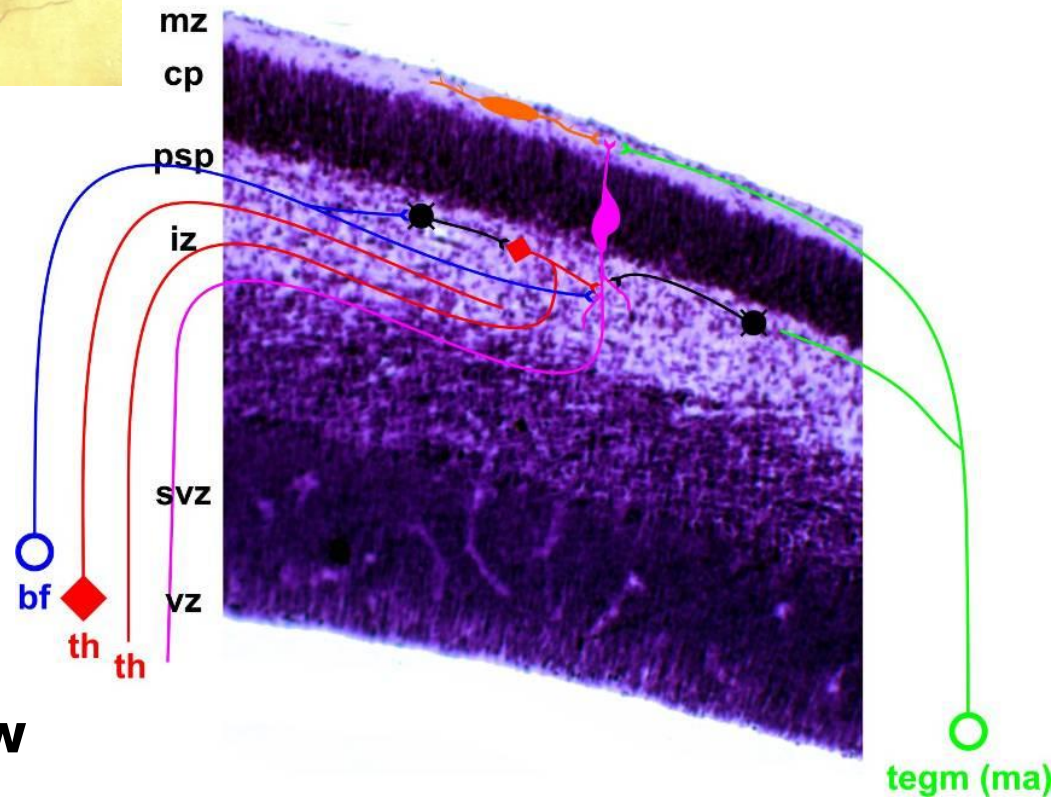


Nissl

Golgi

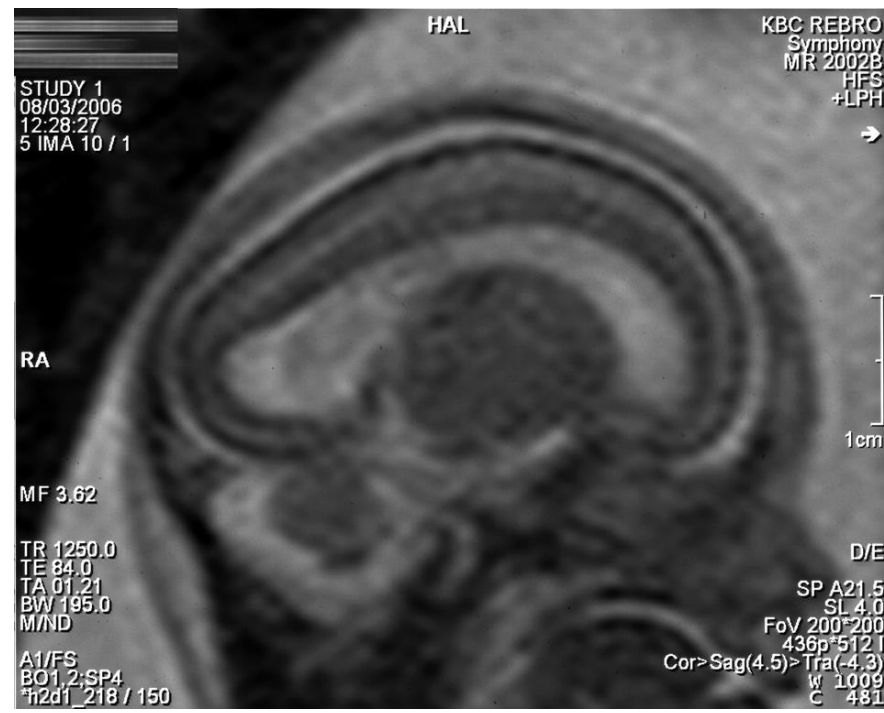
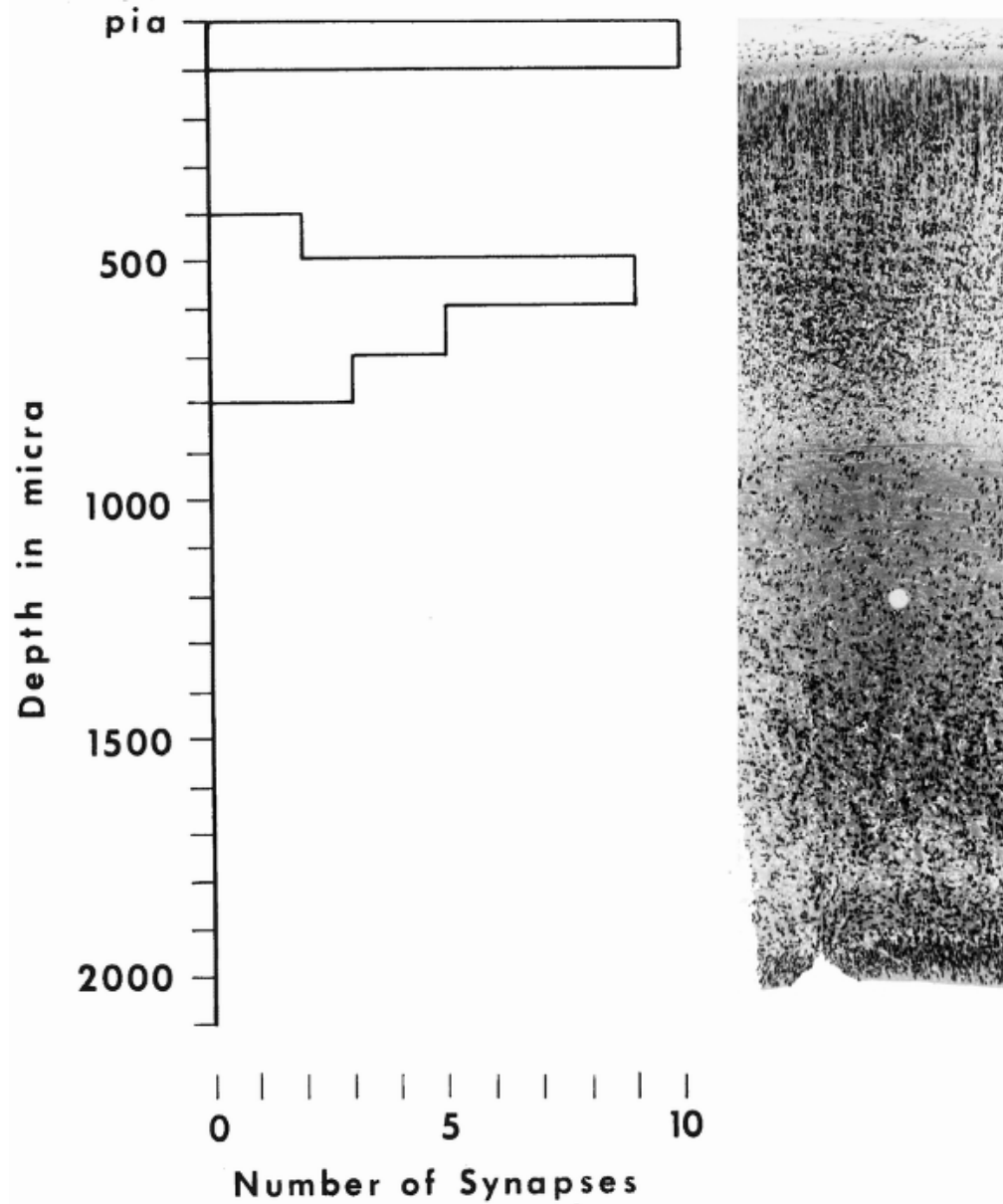
Rani bilaminarni razmještaj aksona, dendrita i sinapsi: presubplate faza
Unutarnja (endogena) spontana aktivnost

Early bilaminar circuitry - 8,5w



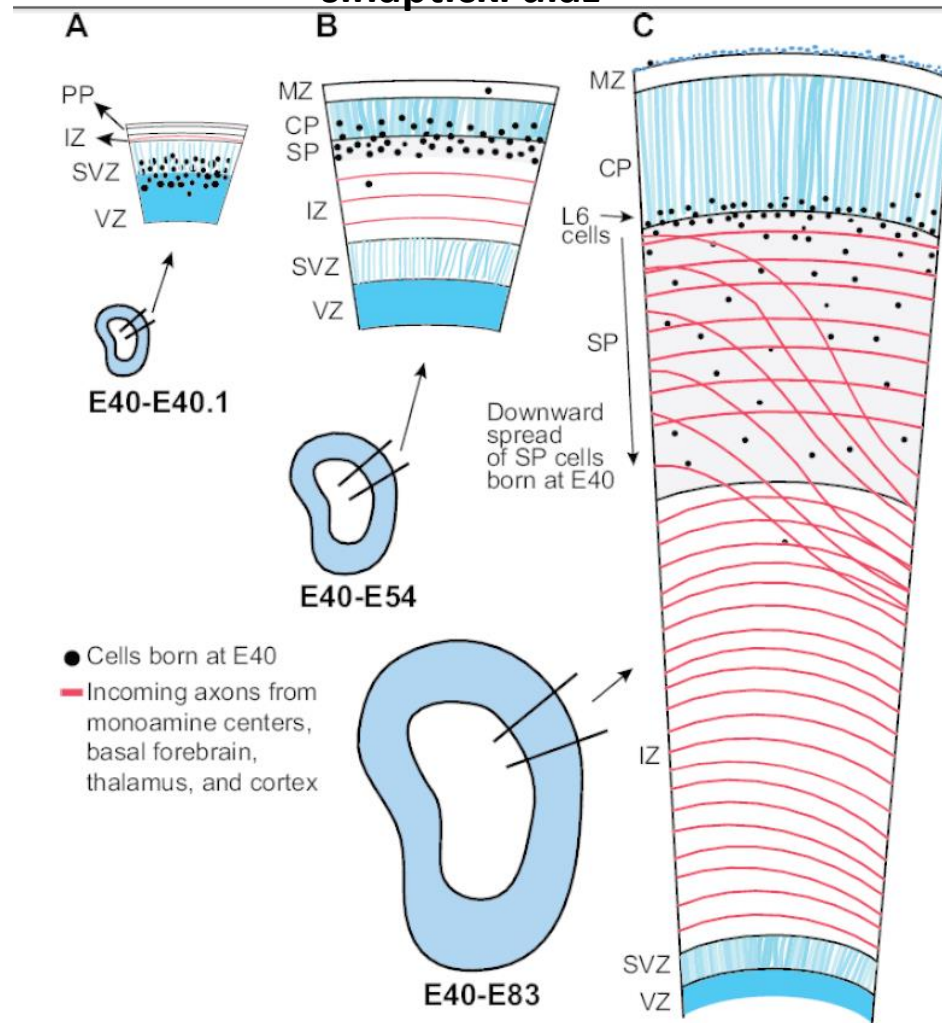
Subplate formation stage (synapses in the second CP, E.M.-Nissl)

13w



Summary model of the secondary expansion of the transient SP zone

Ulaz talamokortikalnih vlakana bazalnog telencefalona označava pripremu za “vanjski” sinaptički ulaz

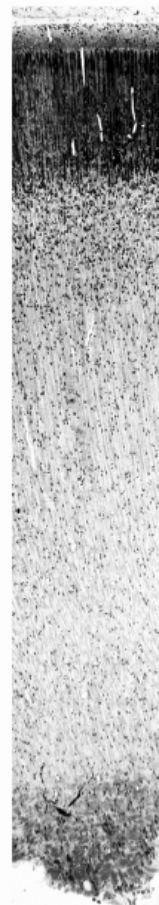
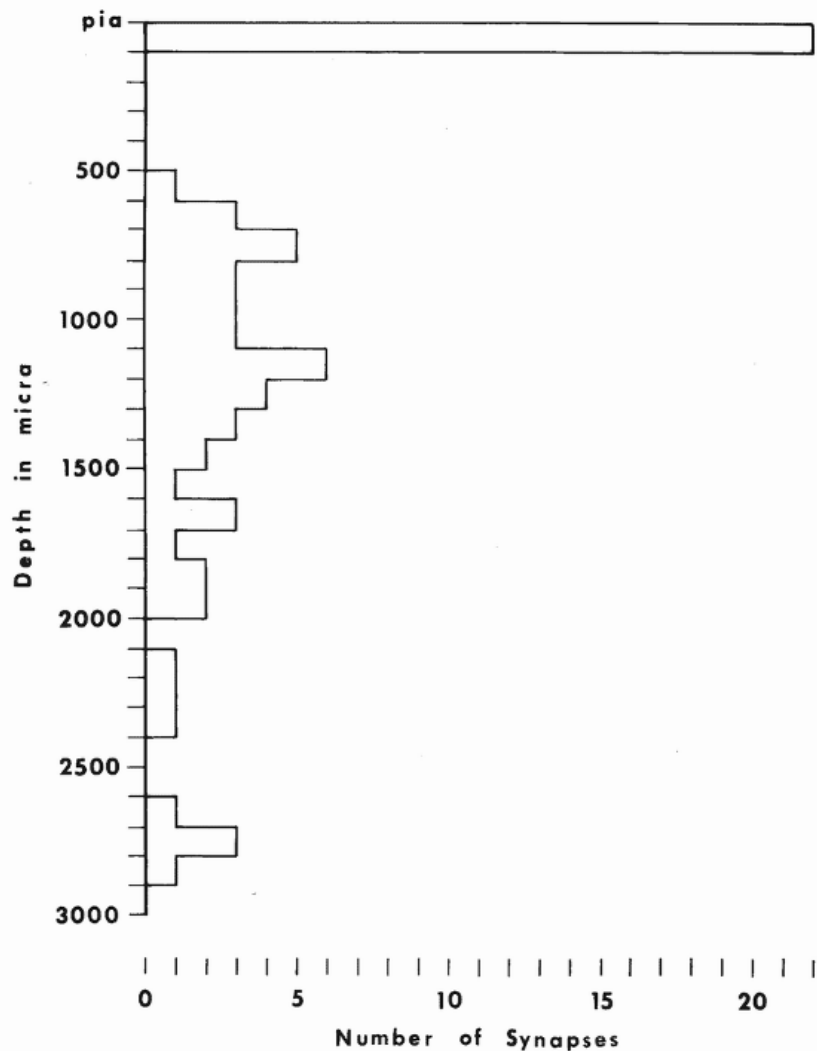


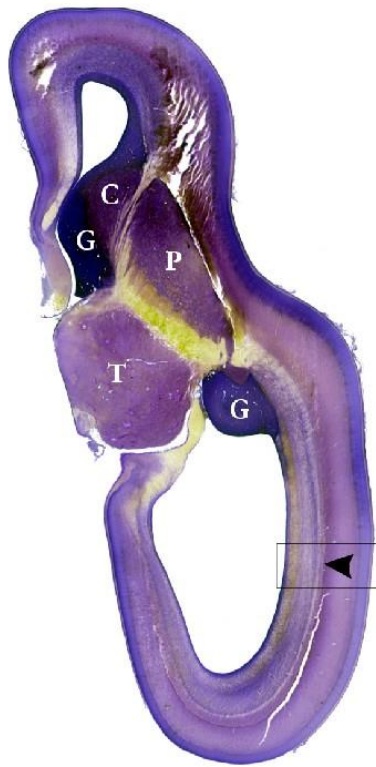
Pathway Selection and Waiting Compartment - 18w

Aferentni putovi, zona čekanja u subplateu i razmještaj sinapsa sredinom trudnoće – vidljiv kontinuitet (žuto)

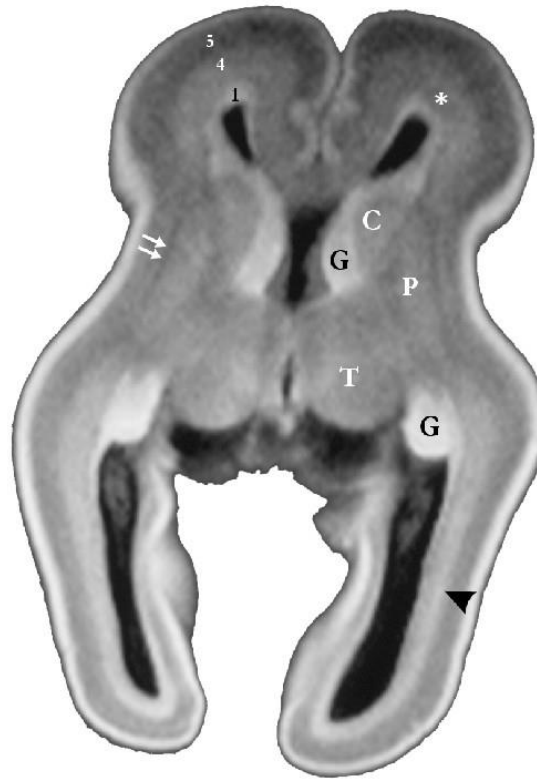


Bilaminar Distribution of Synapses - 15w





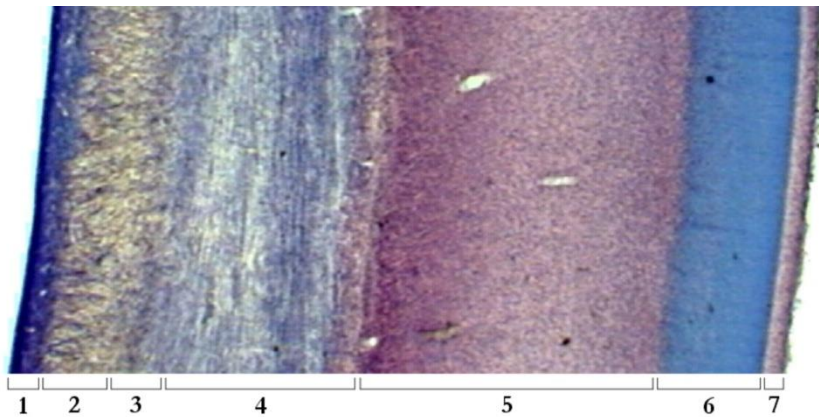
A



B



C

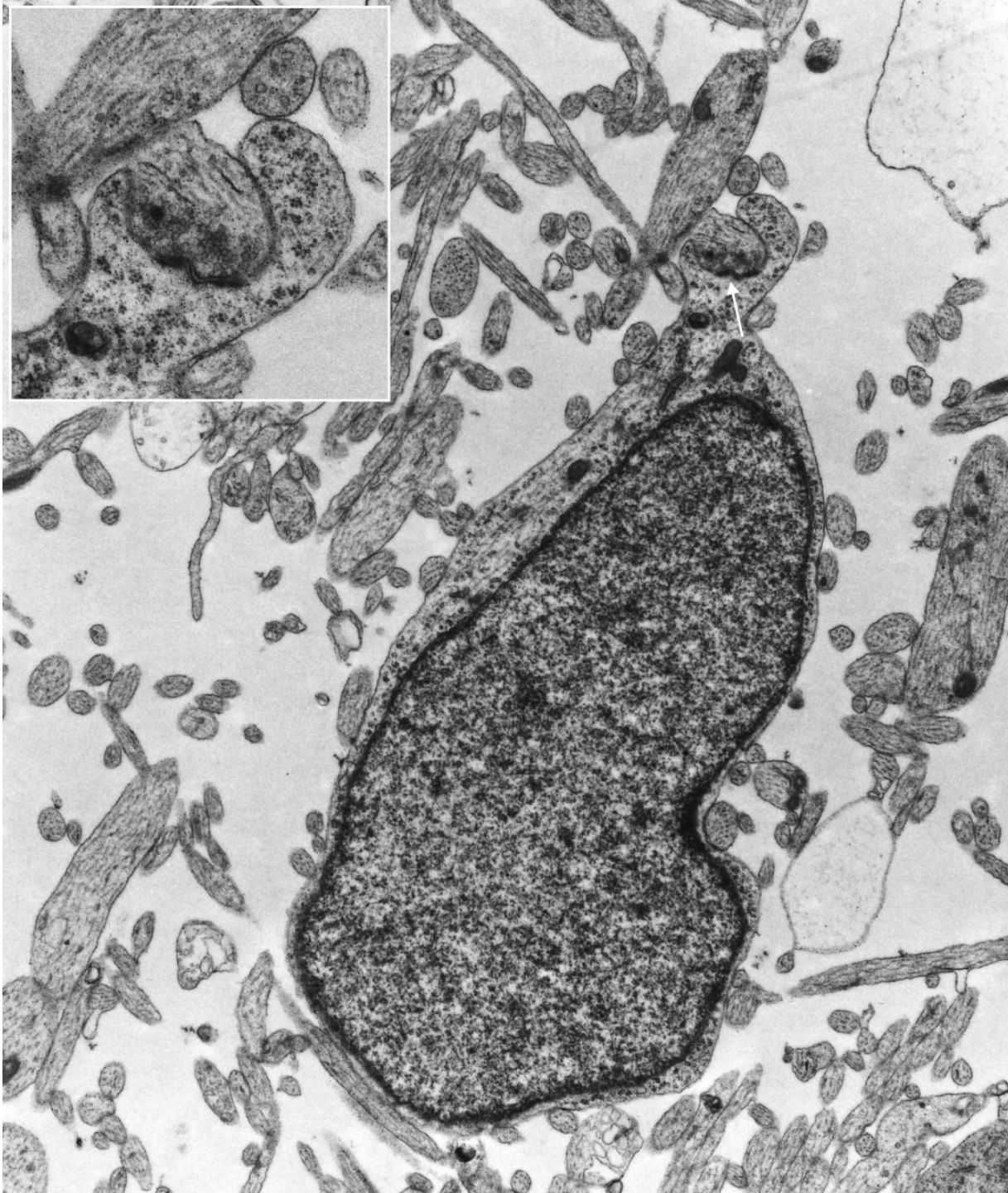


D

- 1 = Ventricular zone (germinal matrix)
- 2 = Periventricular fibre rich zone
- 3 = Subventricular cellular zone
- 4 = Intermediate zone (fetal "white" matter)
- 5 = Subplate zone
- 6 = Cortical plate
- 7 = Marginal zone

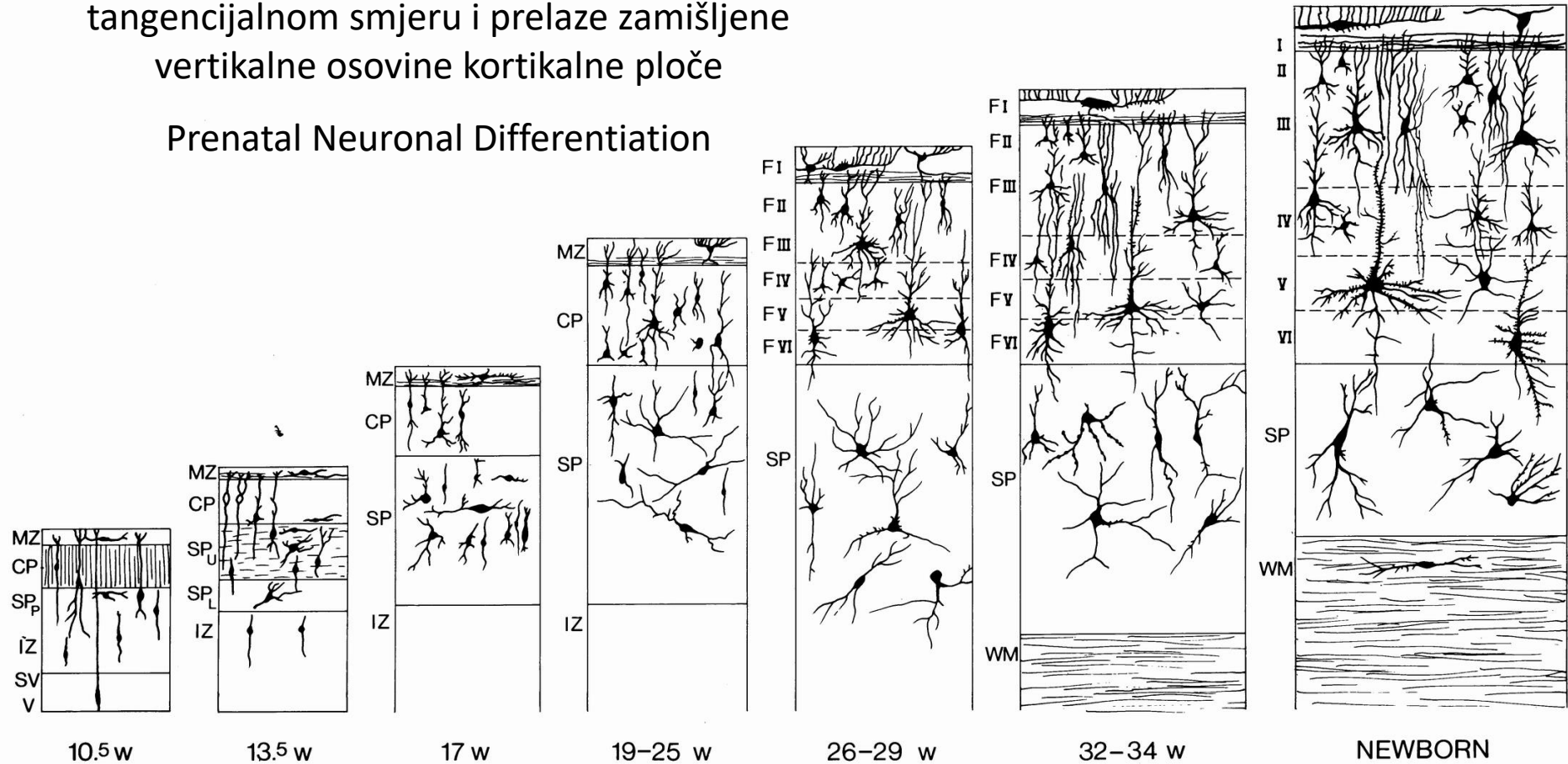
*Kostović et al (2002):
MRI-histological correlation of fetal lamination*

Sinapse na subplate neuronima u svim područjima korteksa
Zapaziti ogromni ekstracelularni prostor

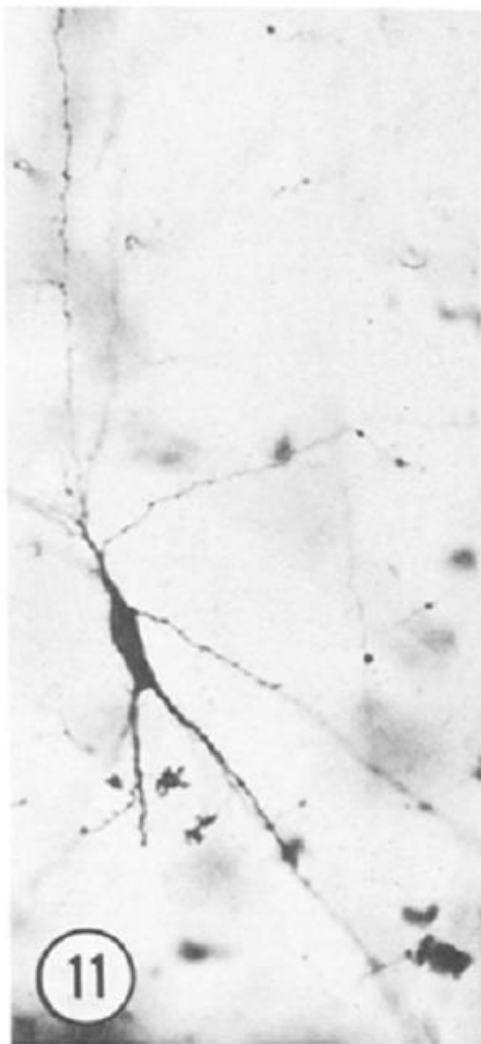


Prenatalna diferencijacija postsinaptičkih neurona i rani razvoj u tranzitornoj subplate zoni : zapaziti velike dendrite koji se protežu u tangencijalnom smjeru i prelaze zamišljene vertikalne osovine kortikalne ploče

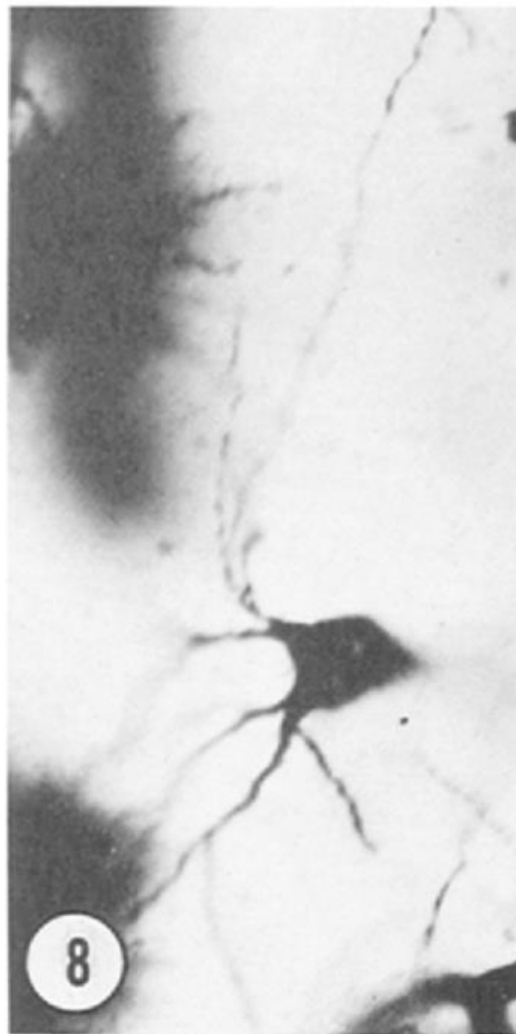
Prenatal Neuronal Differentiation



Dugi dendriti subplatea doprinose kontinuitetu nexusa suplate zone

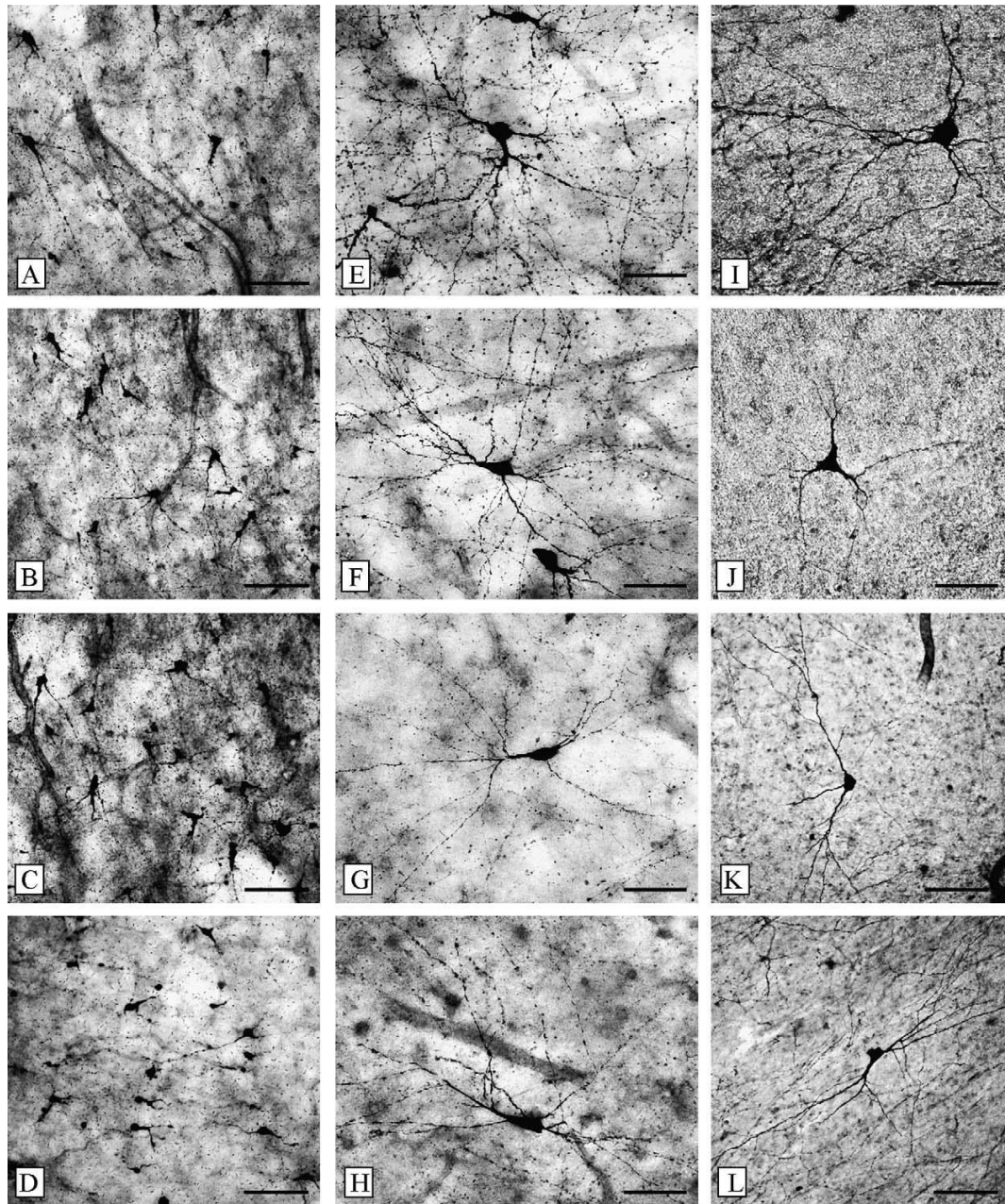


SP neuron



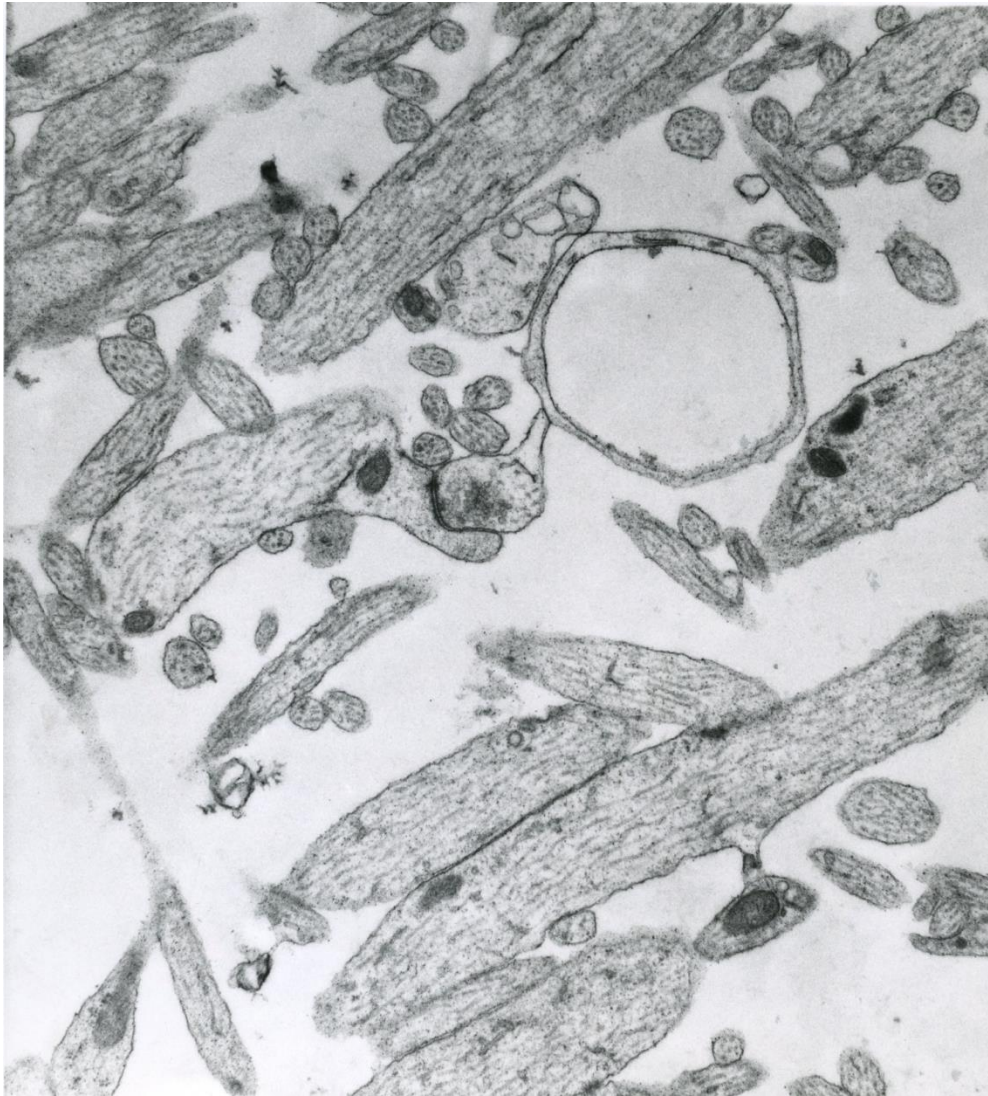
Interstitial neuron

Raznolikost
neurona
subplate zone
i neurona
odrasle bijele
tvari
Radijacija
dendrita
izražena u
fetusa



Extracellular matrix

Kontinuitet matriksa omogućuje tangencijalno urastanje putova i ekstrasinaptičku transmisiju



ECM rich neuropil
in SP

PROLAZNE VEZE SUBPLATEA ČINE TEMELJ POVEZANOSTI (NEXUS) U CIJELOJ
HEMISFERI

Projekcija iz bazalnog telencefalona i pulvinara u asocijativni korteks prethodi
inervaciji primarnog korteksa

CF 180 4 (71) AchE

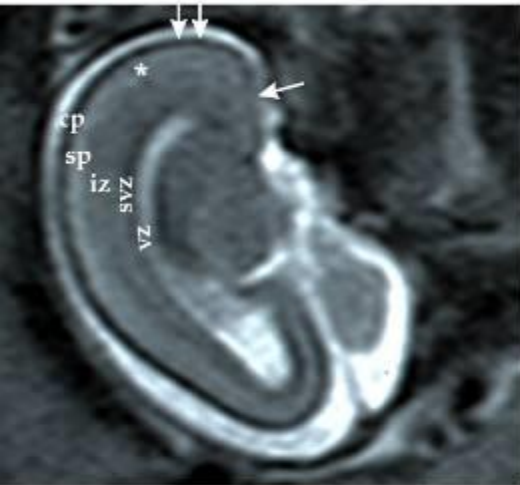


CF 198 SAG2 (11) AchE



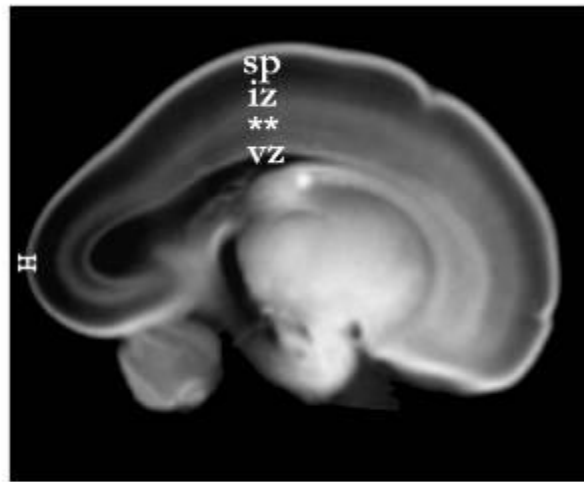
Midfetal laminar organization
Vidljiv kontinuitet i potpuni opseg subplate zone

in vivo MR



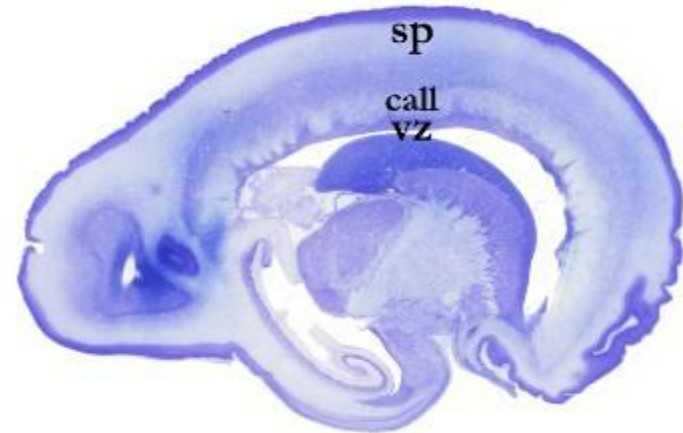
20w

in vitro MR



20w

Nissl



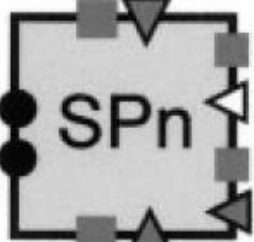
20w

CP

V/VI

SP

Thal.

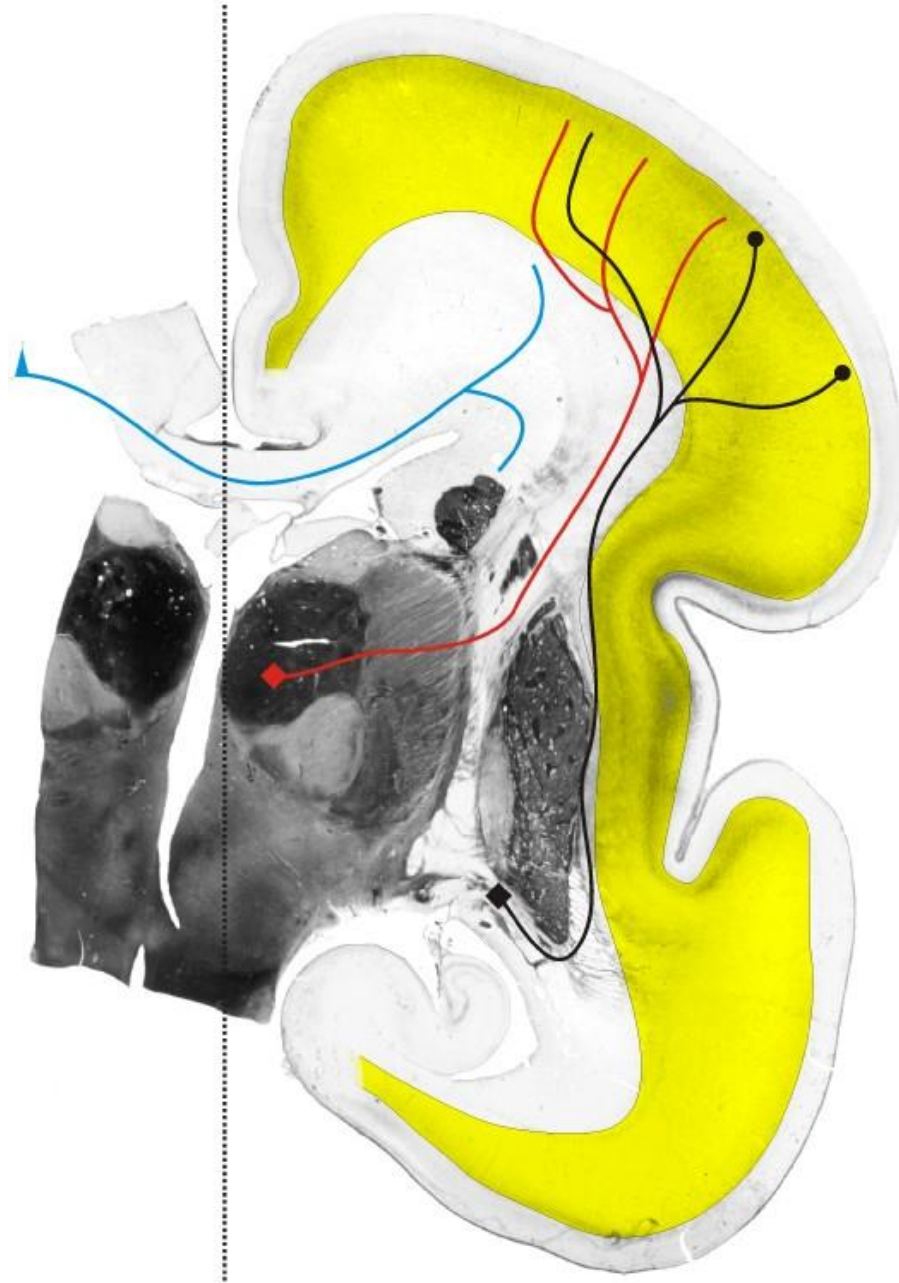


**Early circuitry:
Transmitters
Oscilatorni
krugovi subplatea:
eksperimentalni model ukazuje na
koegzistenciju
unutarnje i vanjske (talamičke)
funkcije**



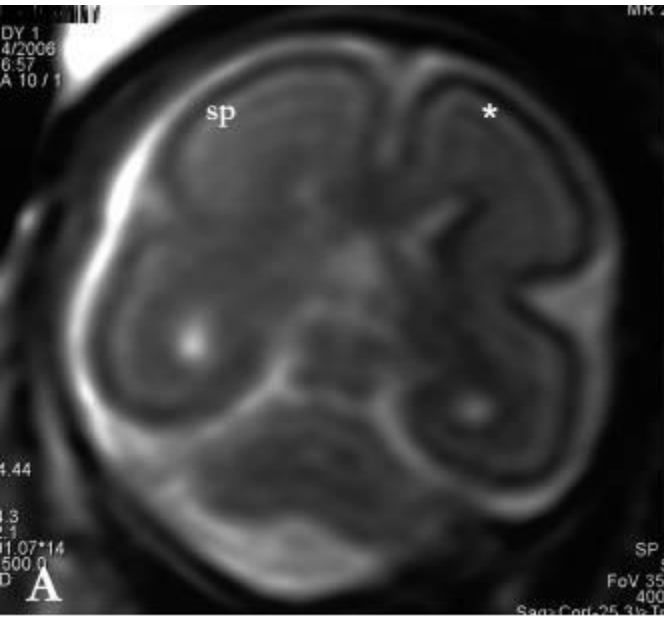
- AMPA receptor
- ◁ "classical" NMDA receptor
- ◁ NMDA receptor active at -70 mV
- GABA_A receptor (depolarizing)

Target selection



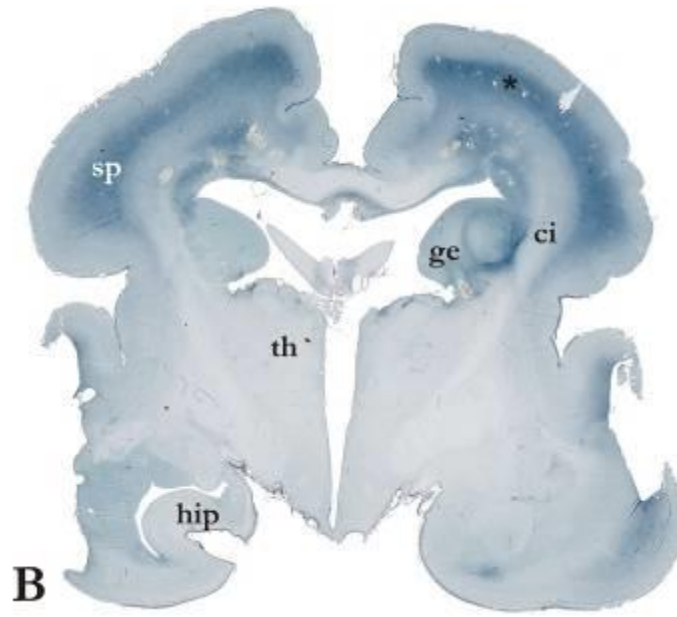
Accumulation of thalamocorticals
U fazi akumulacije talamokortiklanih aksona
vidljive regionalne razlike subplate zone, ali je
elementarni kontinuitet sačuvan

22w



in vivo MR

22w



Fibronectin

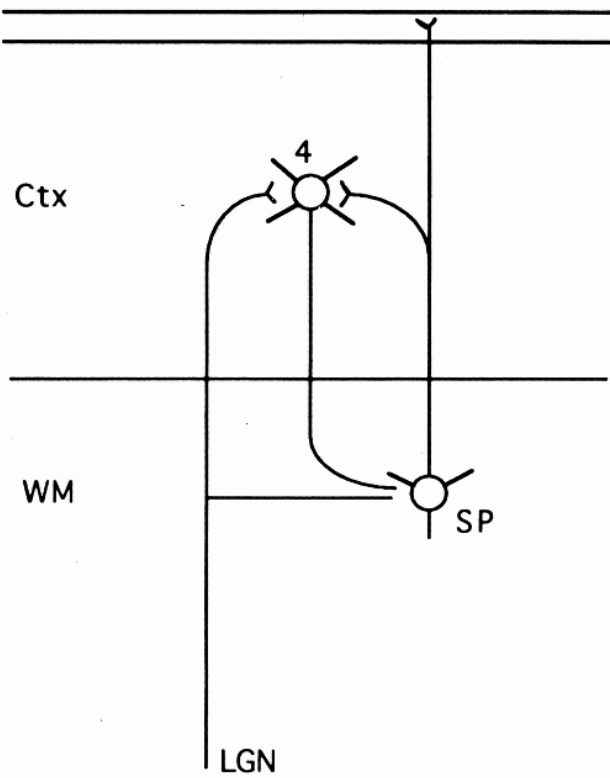
23w



AchE

Early circuitry: subplate

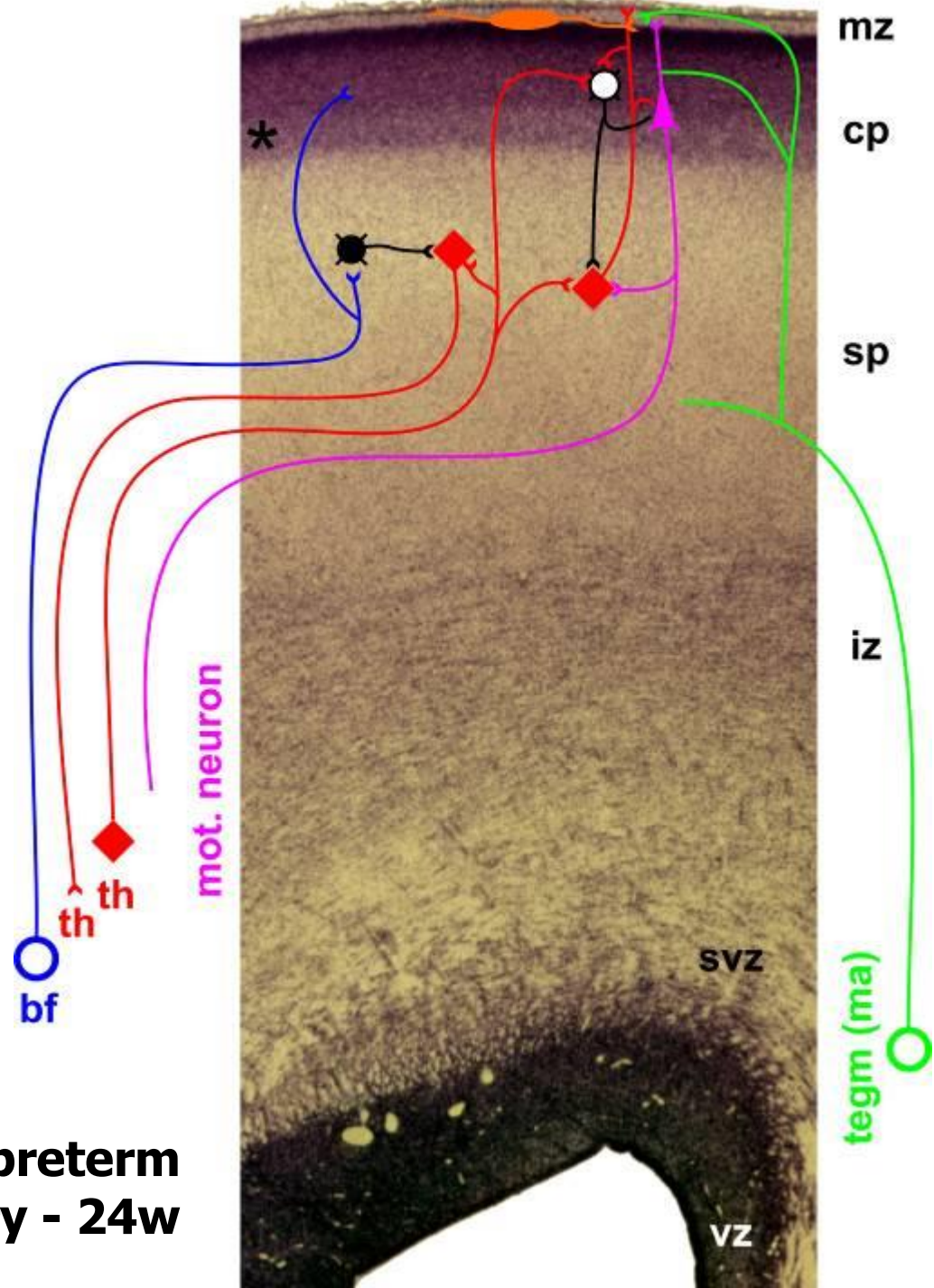
The Journal of Neuroscience, June 1994, 14(6) 3877



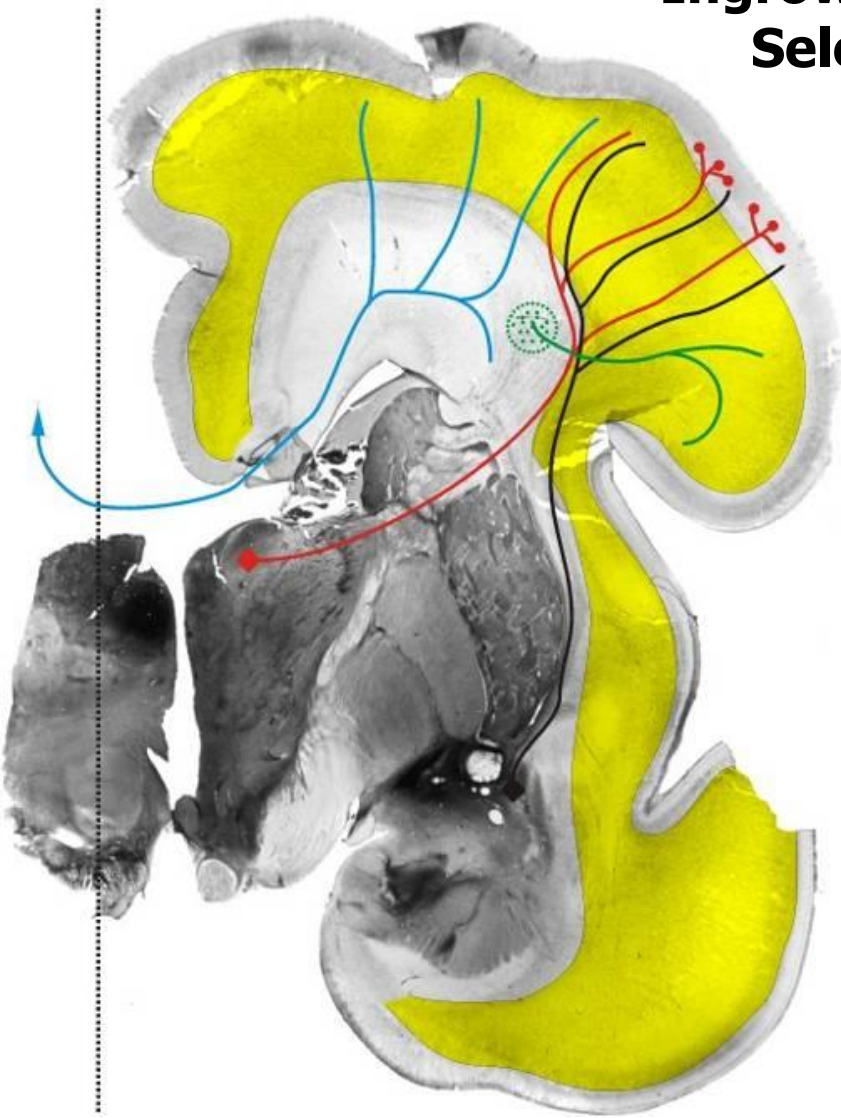
*Allendoerfer & Shatz (1994):
Transient circuitry in the subplate zone*

Rani prematurus: neuronski krugovi subplatea i talamokortikalnog sustava
Koegzistencija tranzitornih i trajnih funkcionalnih krugova

Early preterm Circuitry - 24w

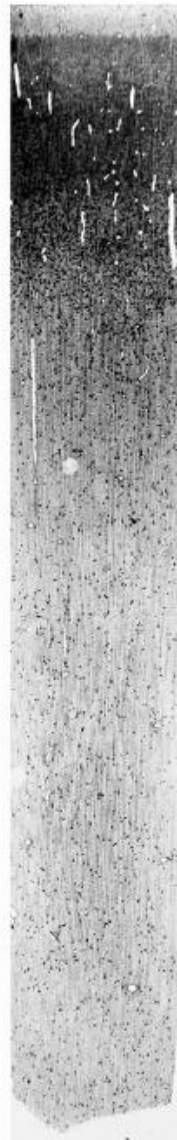
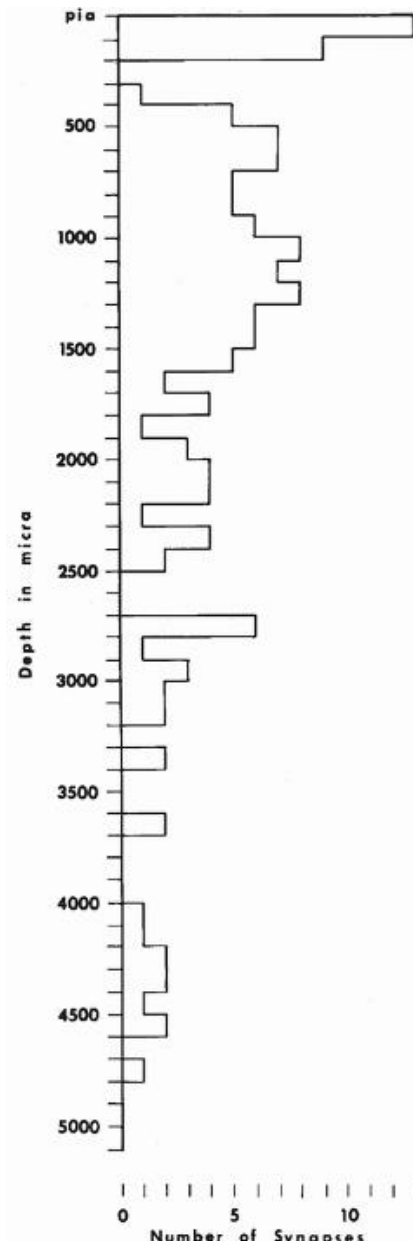


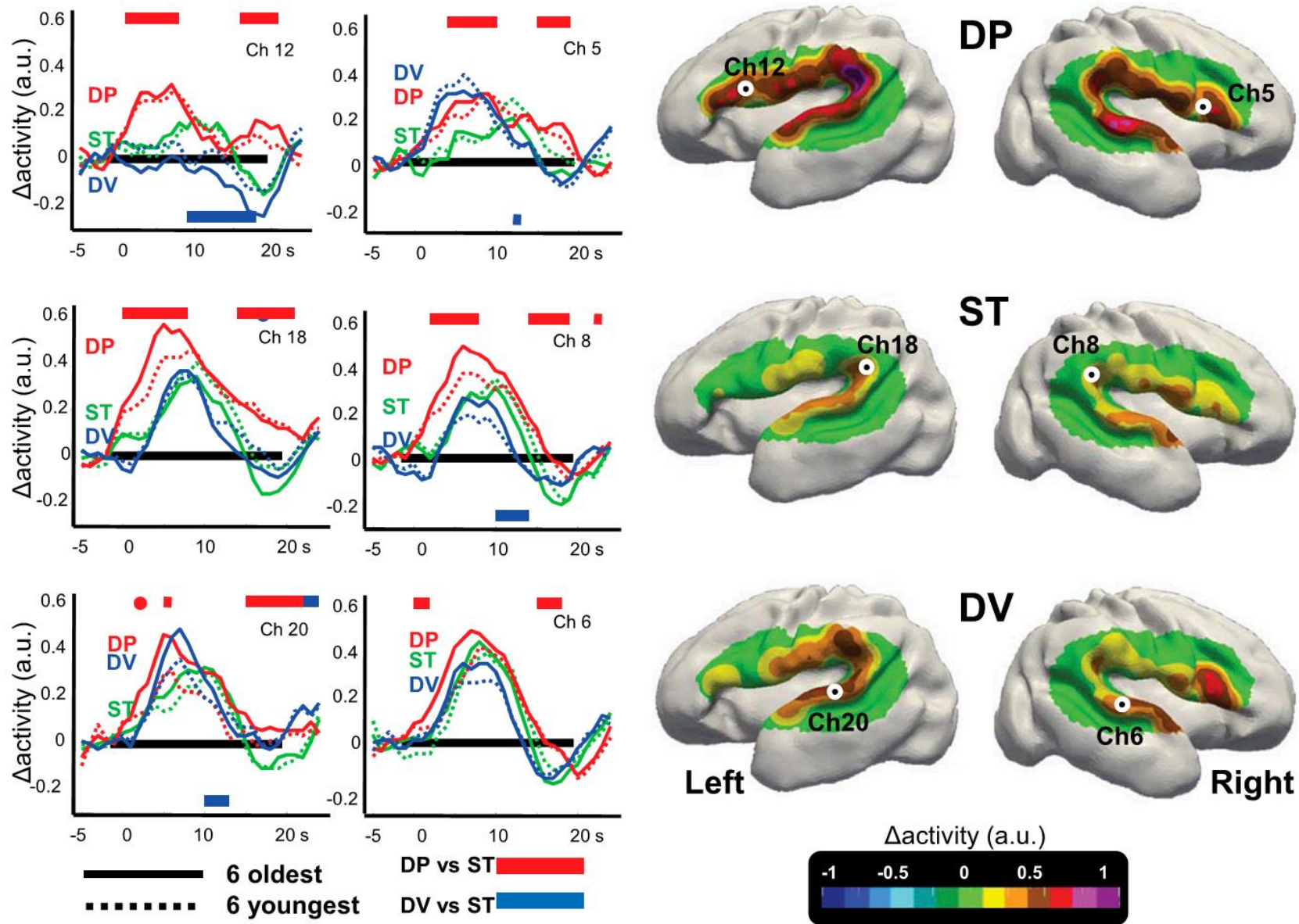
Ingrowth and Address Selection - 24-32w



Ključna faza: prve sinapse u kortikalnoj ploči, postojanje sinaptičkih veza duž subplatea i rast asocijativnih putova (zeleno)

Synaptogenesis in the CP - 28w



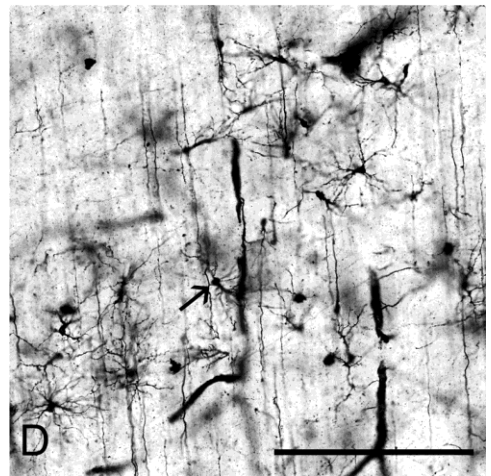
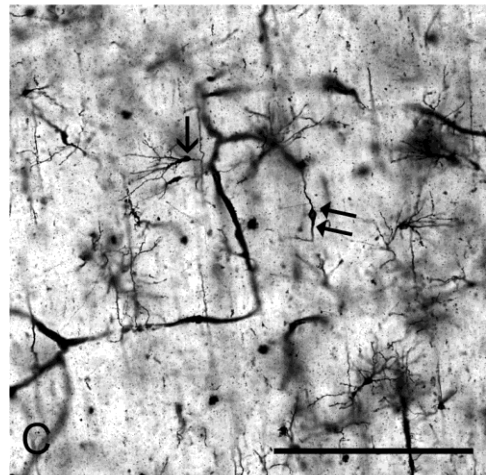
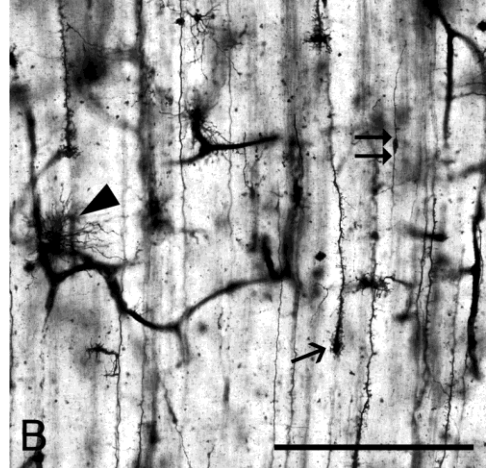
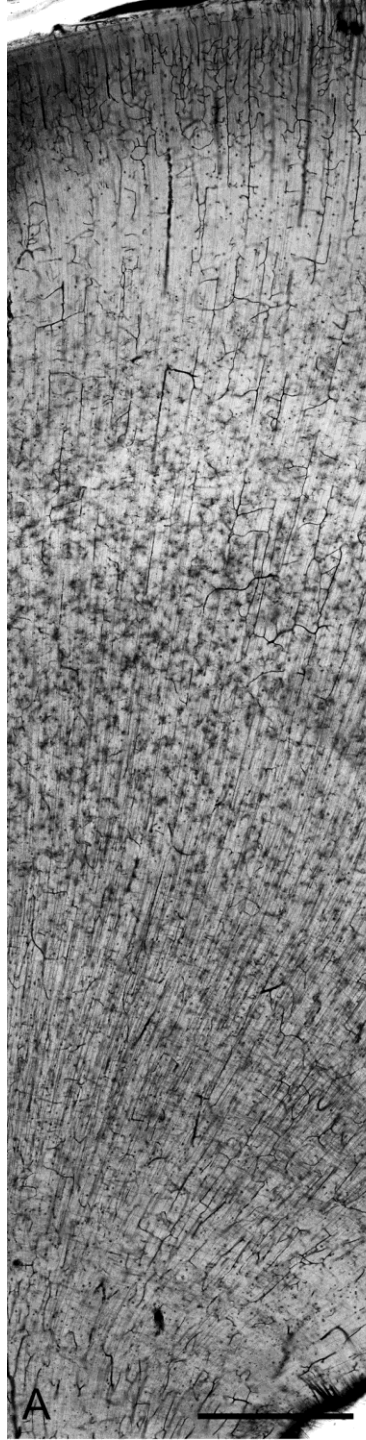


Razlikovanje odgovora na auditornu stimulaciju (fonemi konsonanti) u prematurusa 28 tjedana trudnoće
 Rašireni odgovor upućuje na asocijativnu povezanost; po našoj hipotezi subplate doprinosi toj povezanosti

Mahmoudzadeh et al. 2013, PNAS

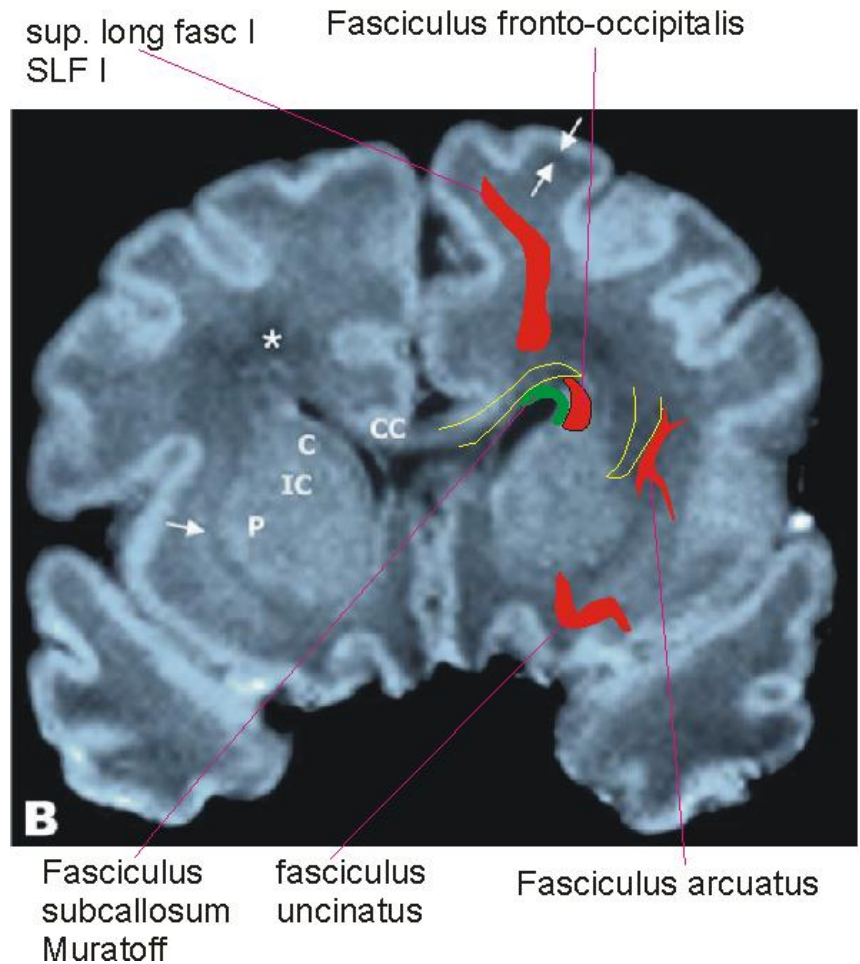
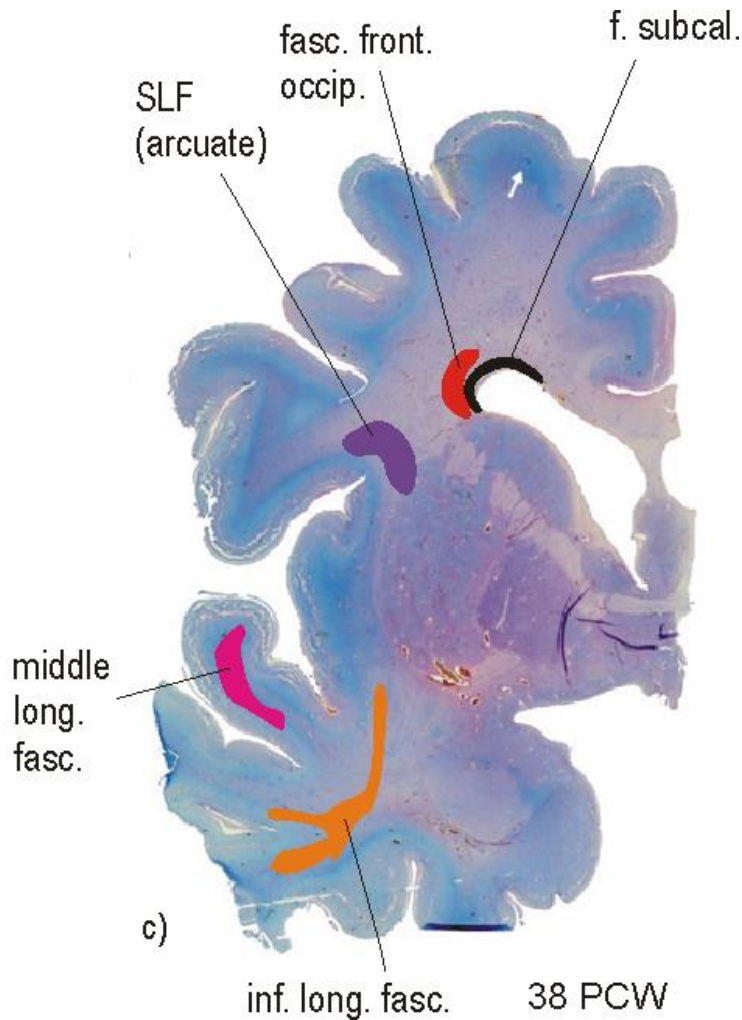
Veliki subplate neuroni
rasprostranjeni u svim područjima
subplatea

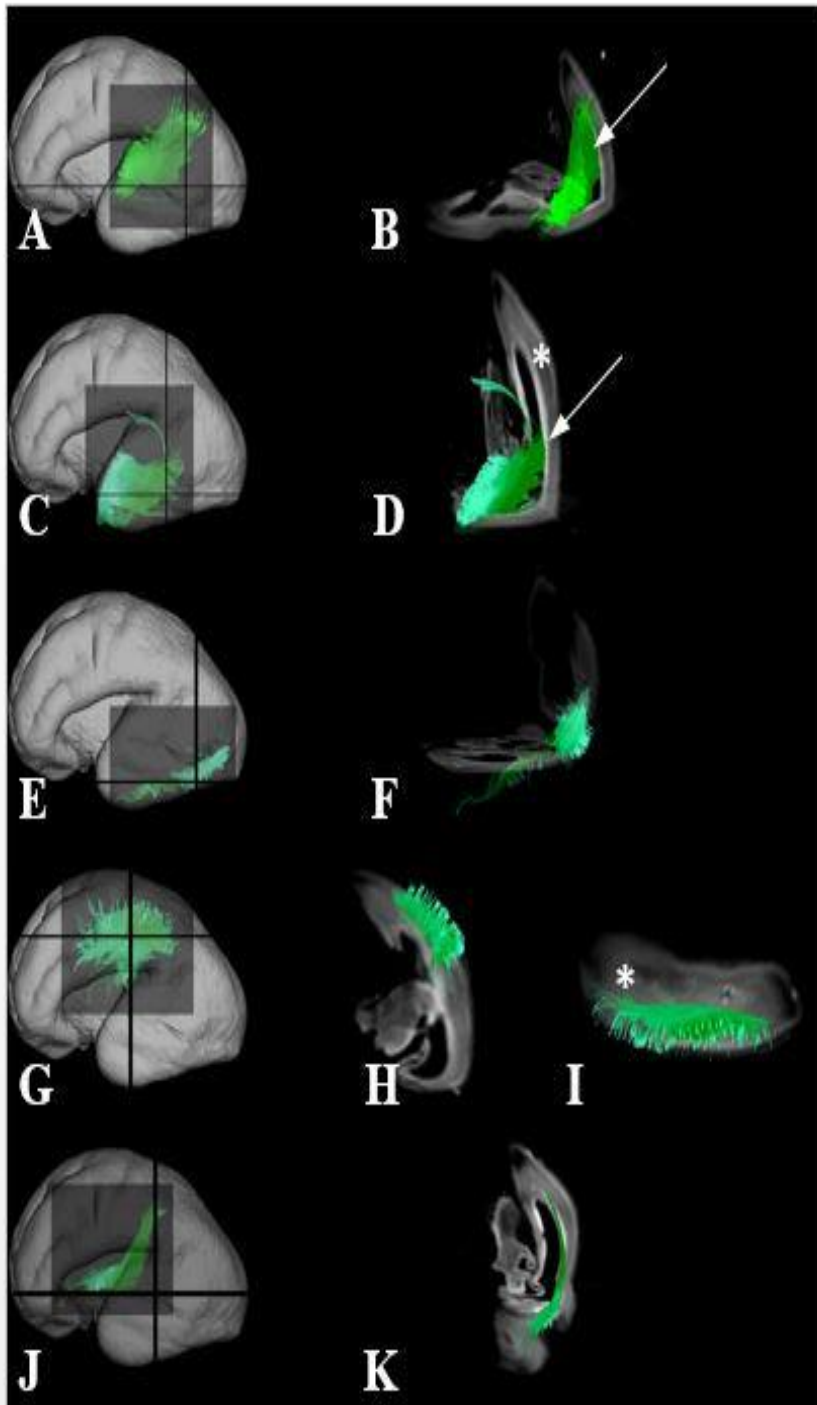
Stensaas'
modification of Del Rio Hortega method
in 23
PCW-old preterm infant



Asocijativni putevi u prematurusa

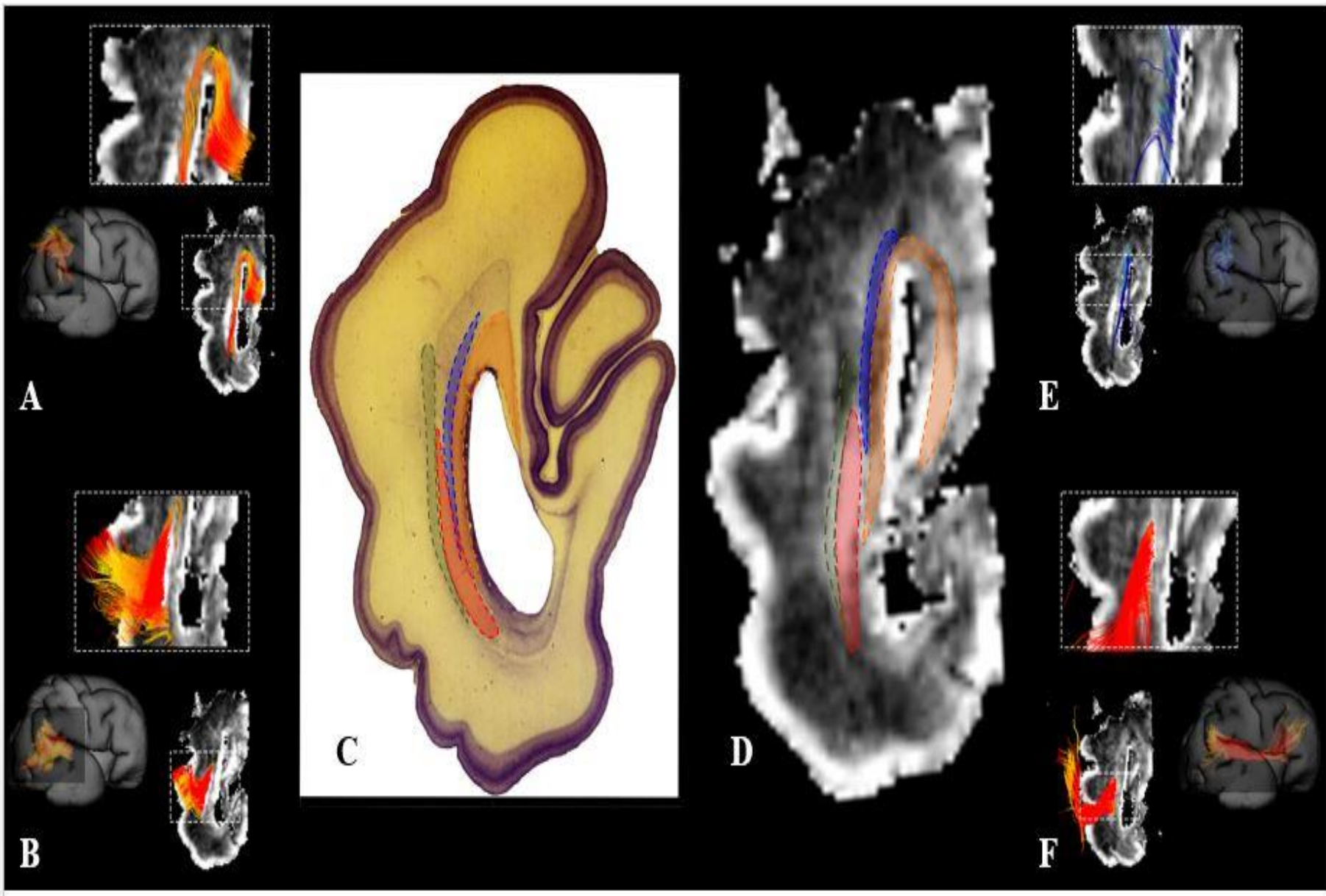
Associative and PVP pathways in preterm





Asocijativni putovi rastu uz duboku zonu subplatea, ali ne prodiru u korteks

Vasung et al. Atlasing Fiber Pathways of the Brain During Human Fetal Development using High-Angular Resolution Diffusion MR Imaging and Histology. 2017 in preparation



Sagitalni slojevi projekcijskih, komisuralnih i asocijativnih putova prikazani HARDI tehnikom. Subplate je zona susjedna asocijativnim putovima (zeleno).

Vasung et al. Atlasing Fiber Pathways of the Brain During Human Fetal Development using High-Angular Resolution Diffusion MR Imaging and Histology. 2017 in preparation

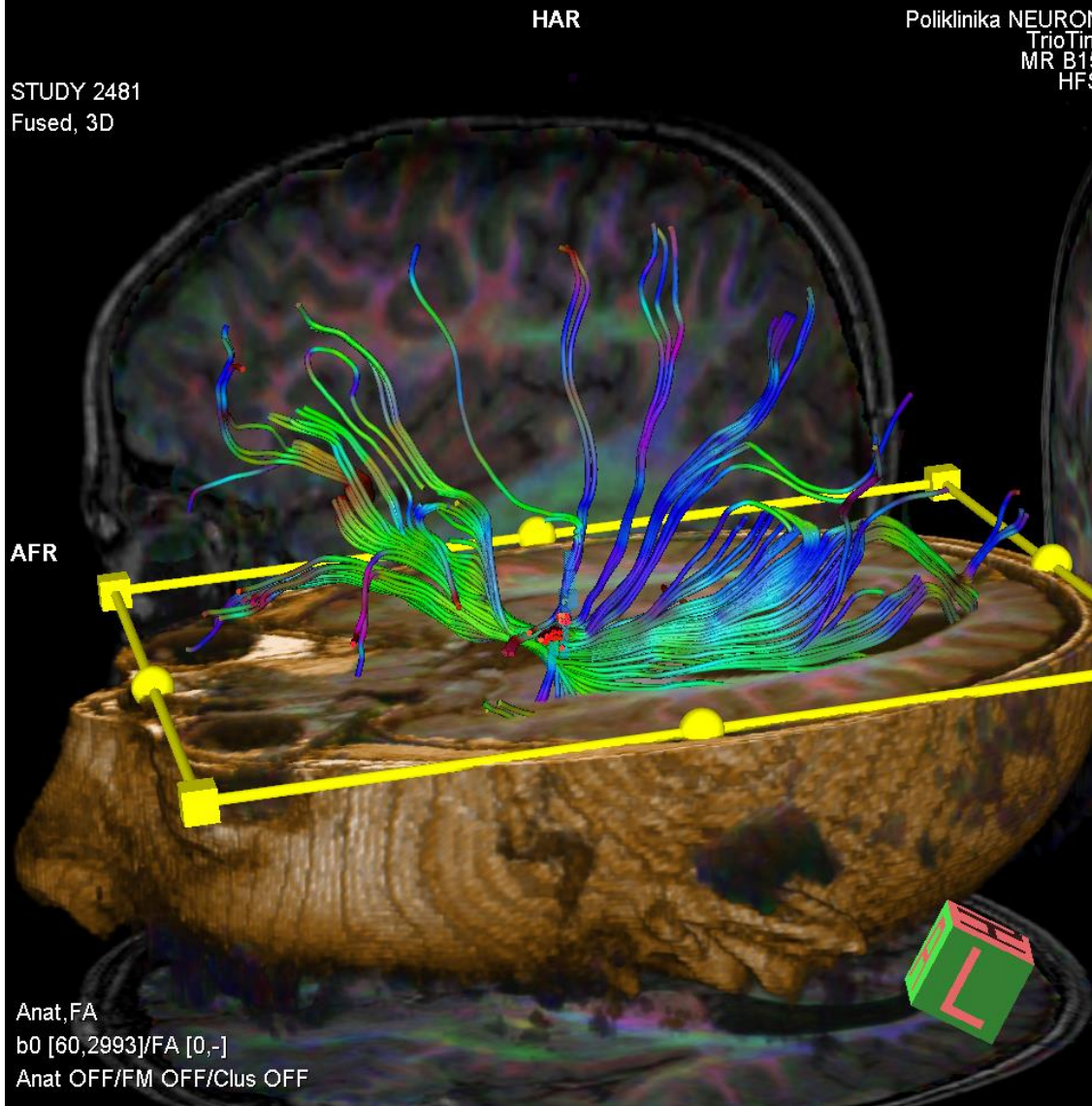
STUDY 2481
Fused, 3D

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Poliklinika NEURON
TrioTim
MR B15
HFS

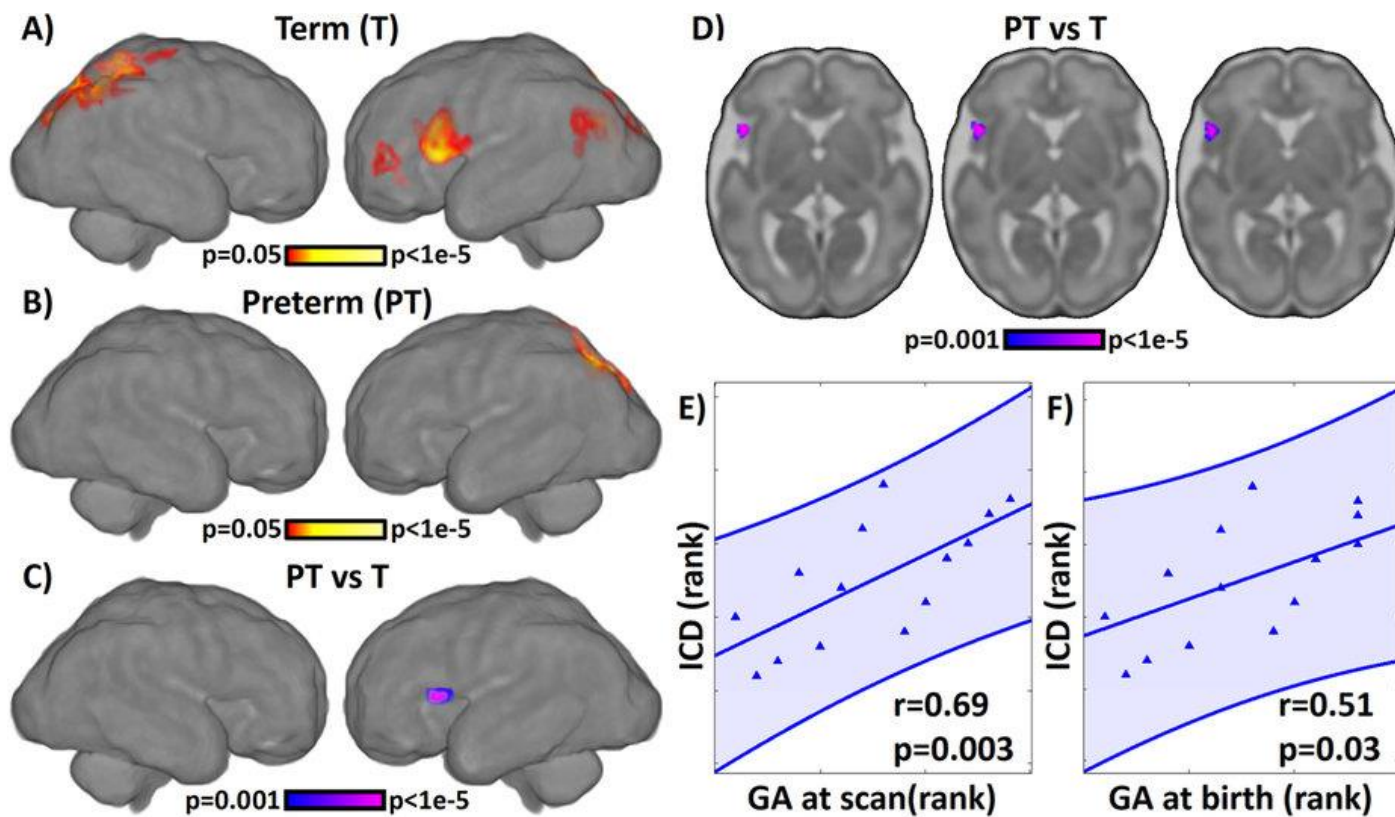
AFR

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Anat OFF/FM OFF/Clus OFF

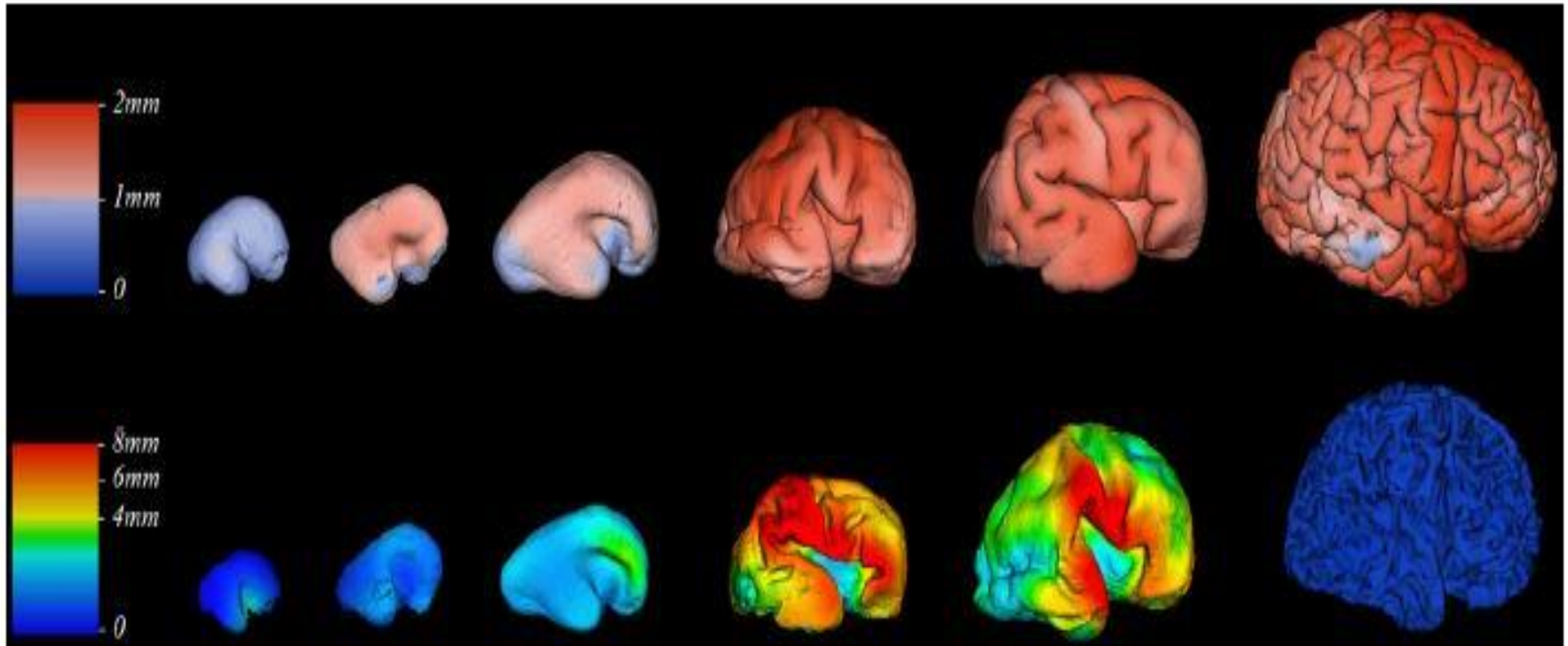


External capsula radiation and fasc. long inf., tractography, newborn
Dugi asocijativni putovi urastaju u korteks do rođenja. Subplate zona je ključna za povezanost girusa i area kao supstrat kratkih kortikokortikalnih putova (U-fibres)

Intrauterina aktivnost mozga obuhvaća rano i asocijativna područja
Po našoj hipotezi subplate nexus je ključan u povezanosti asocijativnih područja u
prematurosa (asocijativni putovi još nisu sinaptički povezani u korteksu)



Kontinuitet volumena subplate zone u asocijativnim područjima mozga



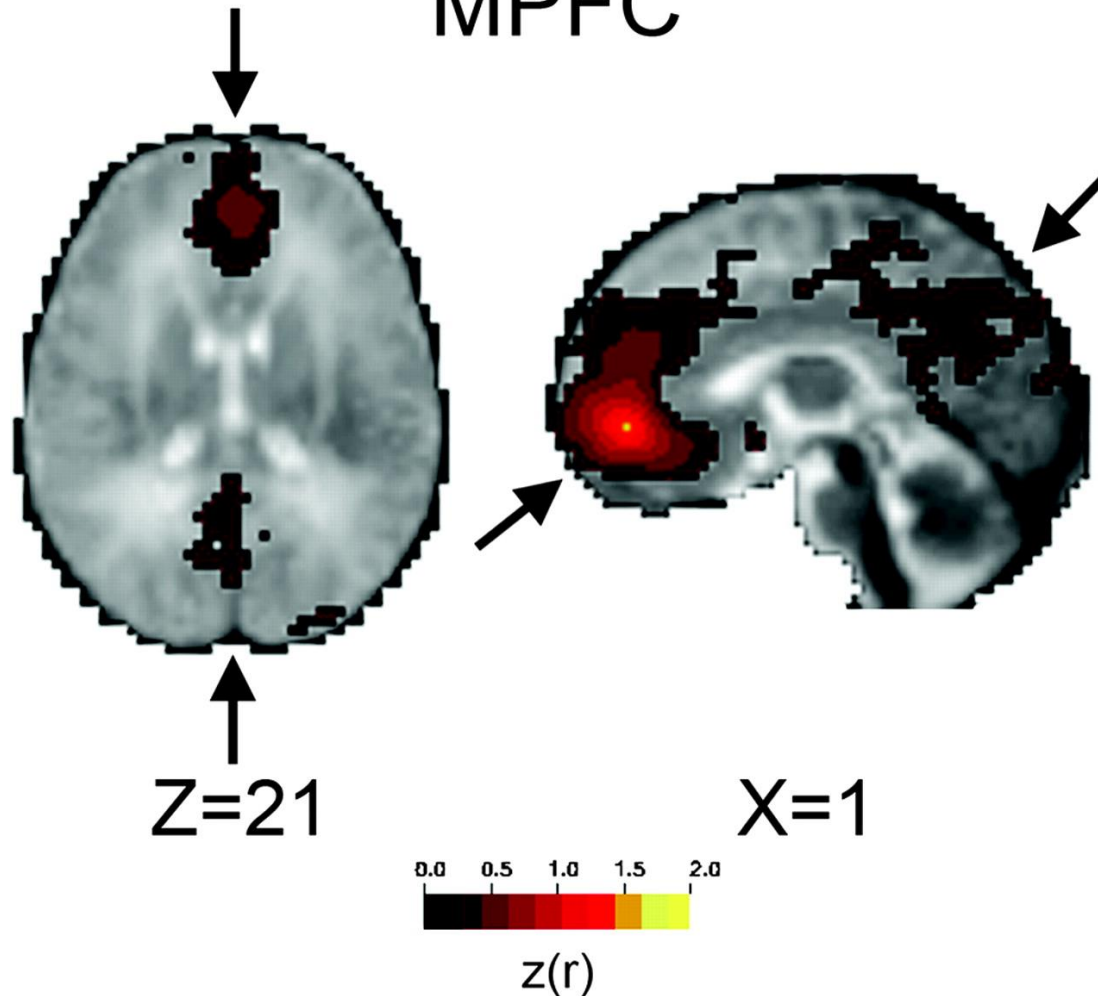
Vasung et al. Quantitative and Qualitative Analysis of Transient Fetal Compartments during Prenatal Human Brain Development.

Aktivnost mozga u mirovanju prisutna je i u prematurusa

Default mode network precursors identified in term infants

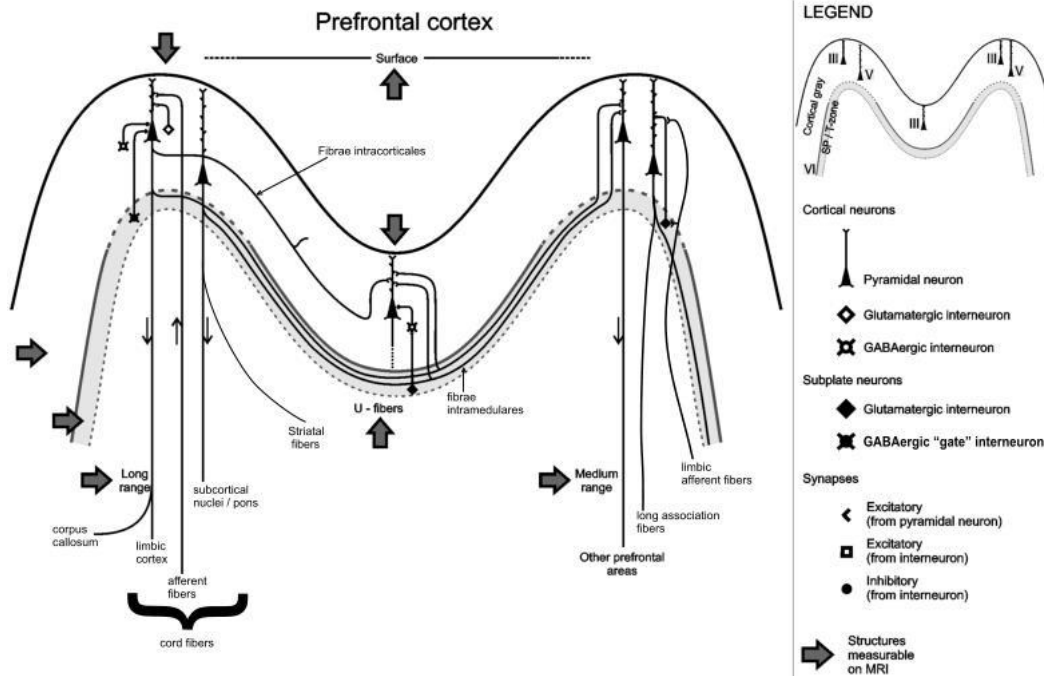
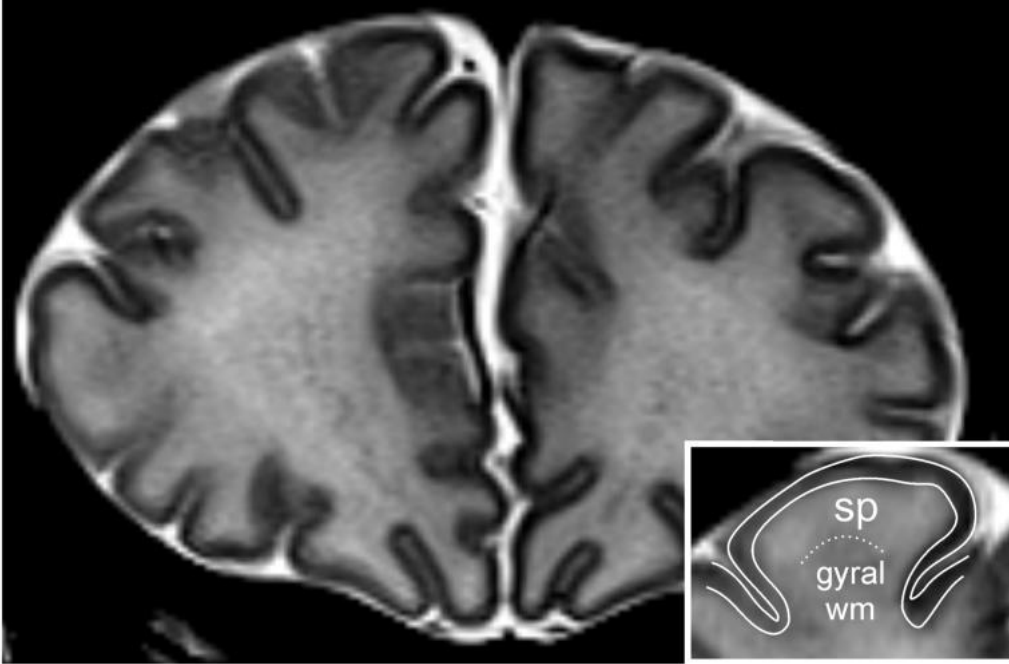
Pitanje: kakva je uloga subplatea, obzirom da se neuronski krugovi subplatea preko intersticijalnih neurona nastavljaju u postnatalno razdoblje

MPFC



Smyser C D et al. *Cereb. Cortex* 2010;20:2852-2862

The subplate and the gyral white matter in the human newborn brain



Perinatálna reorganizácia subplatea i rast kratkih kortikokortikalnih putova

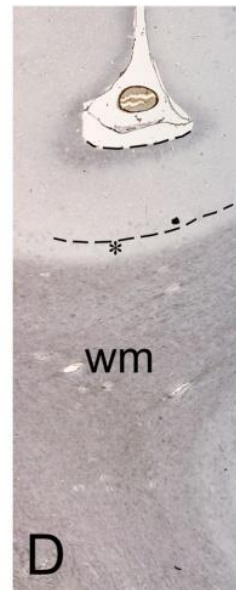
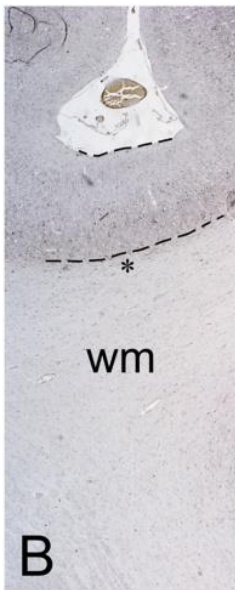
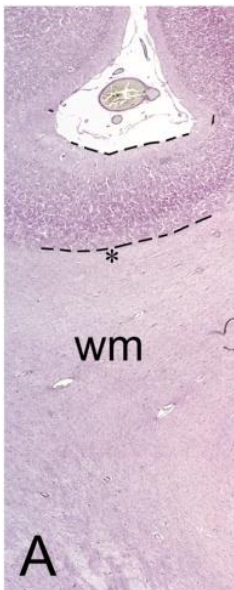
Remnants of SP shown with ECM and fibrillar markers-newborn

Nissl

MAP2

Alcian

CS-56



A

B

C

D

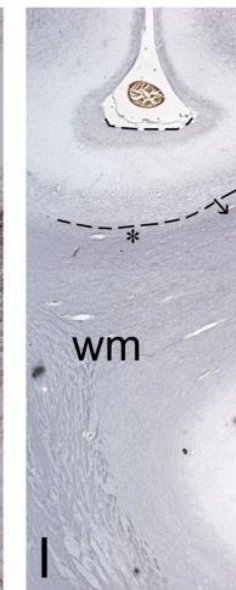
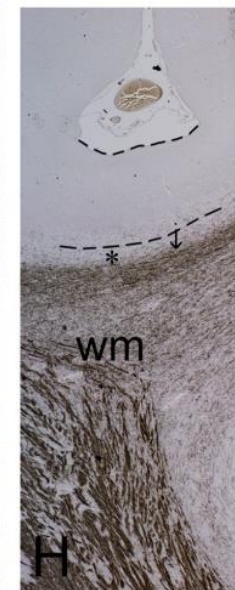
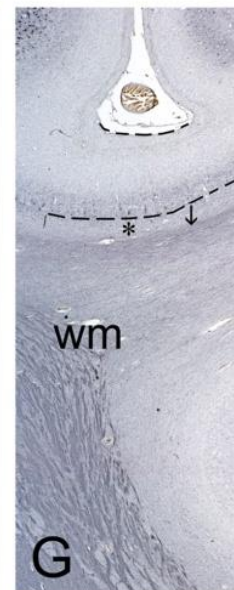
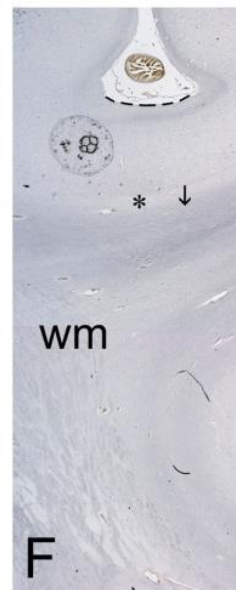
Gallyas

MAP1b

NF200

SMI99

SMI312



E

F

G

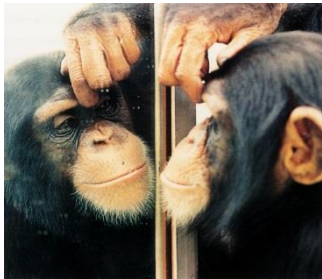
H

I

Consciousness of self



- ❖ Child recognizes its own mirror image (red dot test) around 18 months
- ❖ The phenomenon of self-recognition is present in apes.
- ❖ Other mammals can't recognize themselves in the mirror.

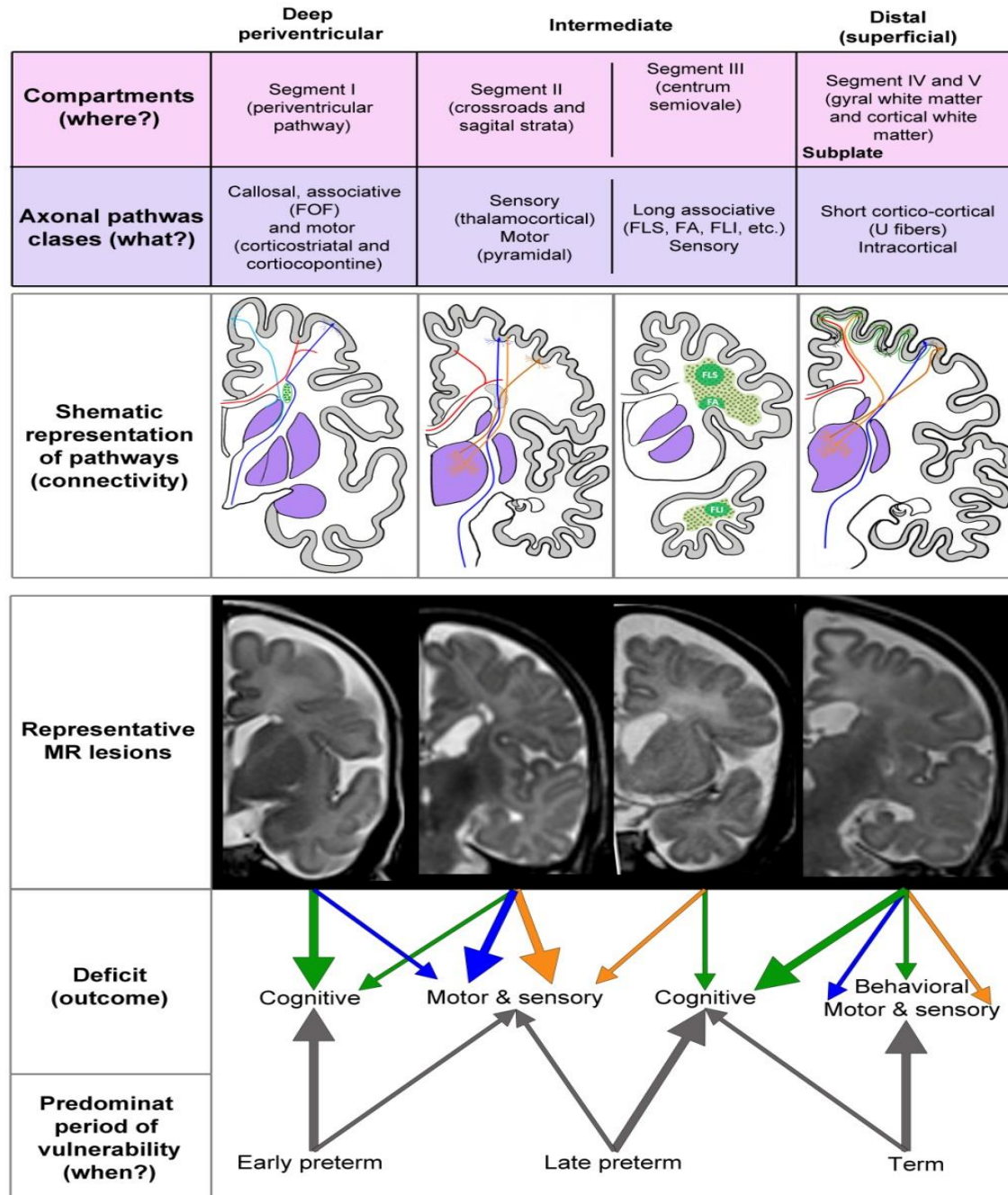


Tipično ljudske kognitivne funkcije pojavljuju se nakon iščeznuća subplate zone



Selective (?) radial vulnerability of cerebral compartments

Kostović et al. Front Neurol
2014

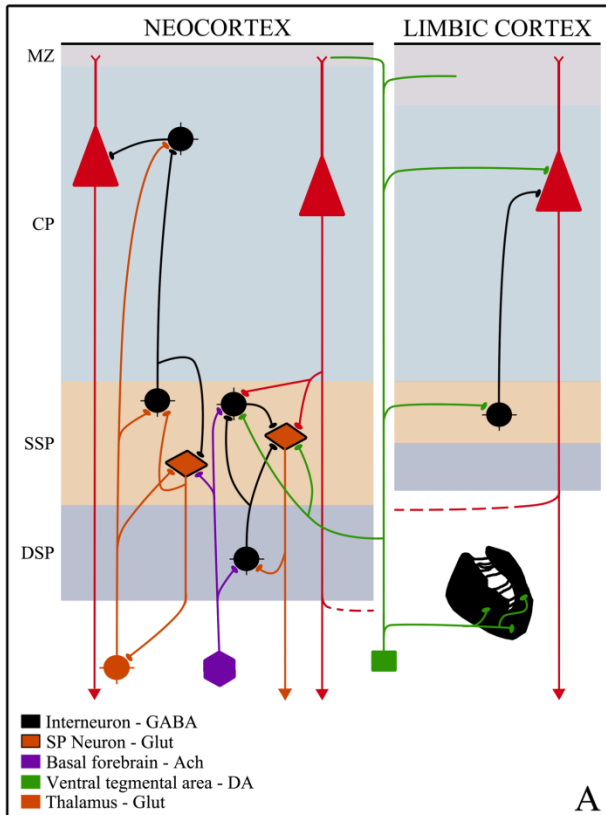


Razdoblja
vulnerabilnosti
pojedinih klasa
moždanih putova
(selektivna radijalna
vulnerabilnost?)
Zapaziti ulogu
oštećenja
asocijativnih putova
i subplate zone u
kasnog prematurusa

Possible involvement of SP neurons in pathogenesis of schizophrenia

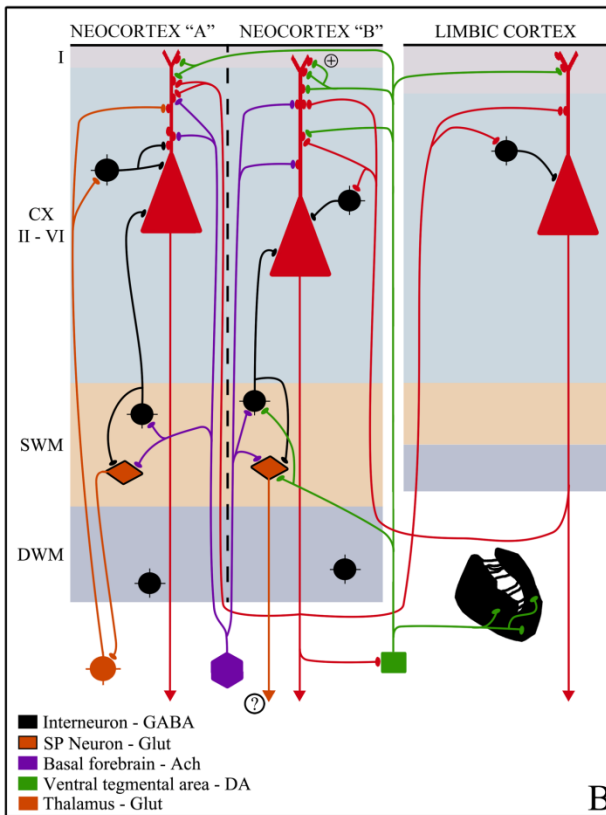
Oštećenja subplatea (razvojnog supstrata kortikalnih veza) kao mogući razvojni uzrok shizofrenije

FETAL



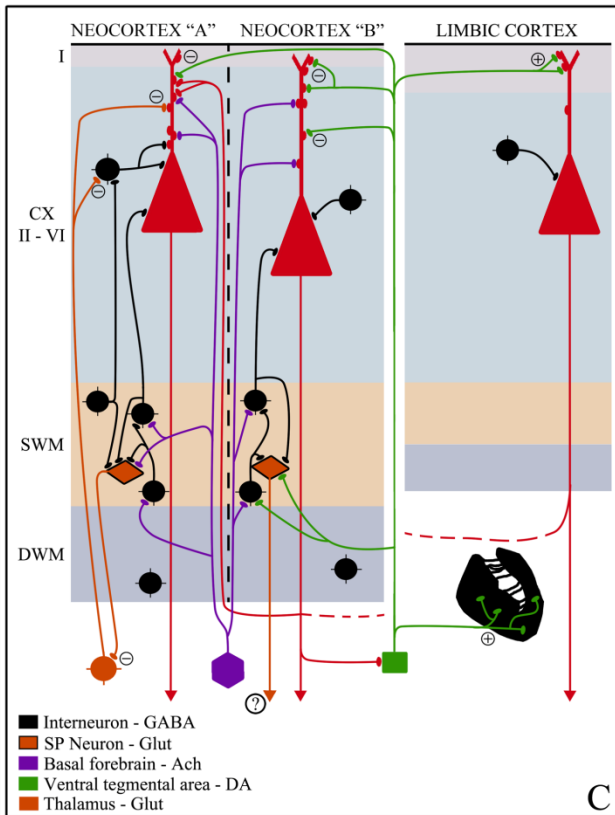
A

YOUNG ADULT

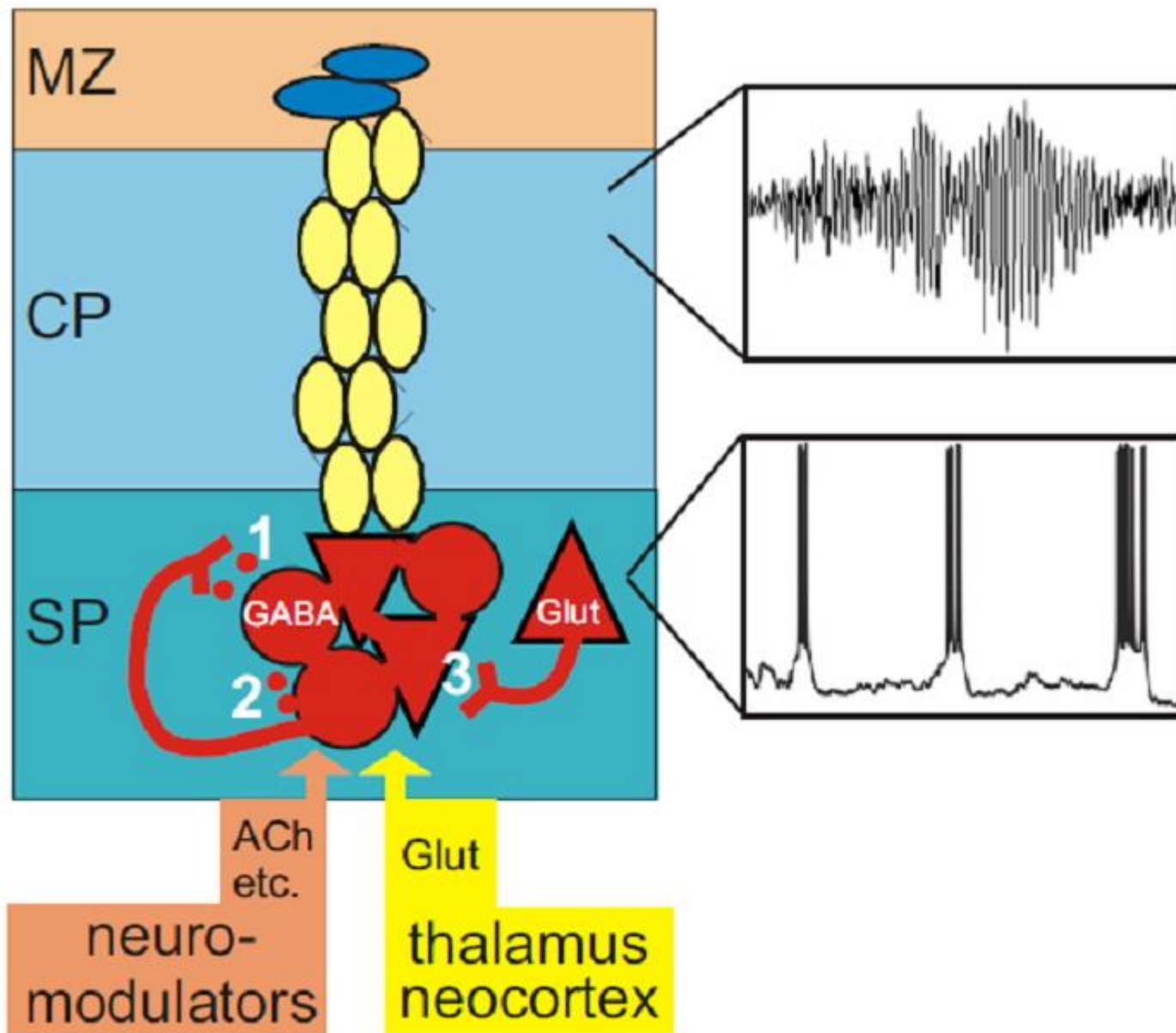


B

SCHIZOPHRENIA

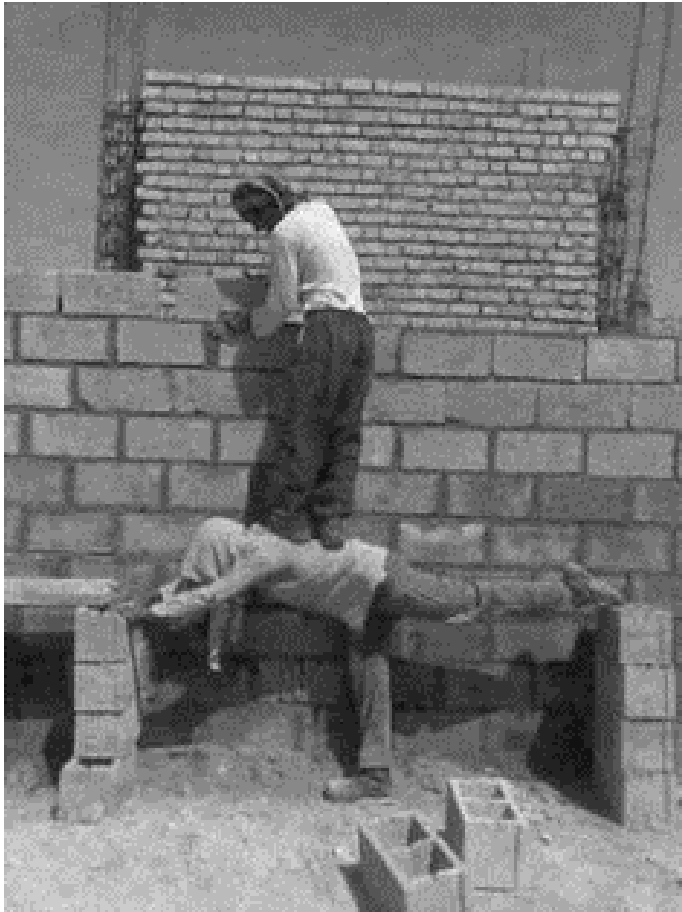


C



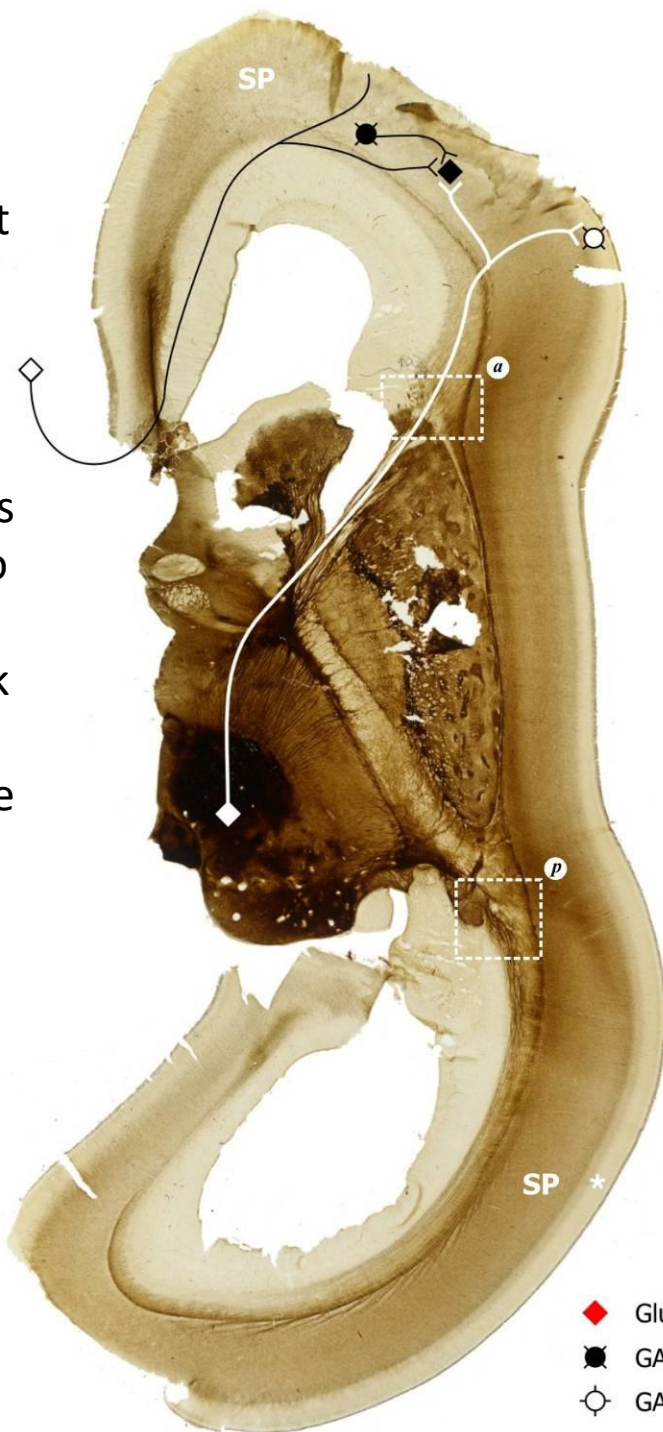
Prvi zaključak: subplate čini okvir za razvitak intrakortikalnih veza i omogućuje oscilatorne tangencijalno raspoređenu spontanu aktivnost (crveno) prije kolumnarnih kortikalnih funkcija (žuto)

Privremene strukture u arhitekturi (po Radošu: bauštele, construction site)



Drugi zaključak: morfogenetska uloga subplate zone: nije samo “site” nego i privremeni telefon, privremeni lift, skela i privremena ventilacija.

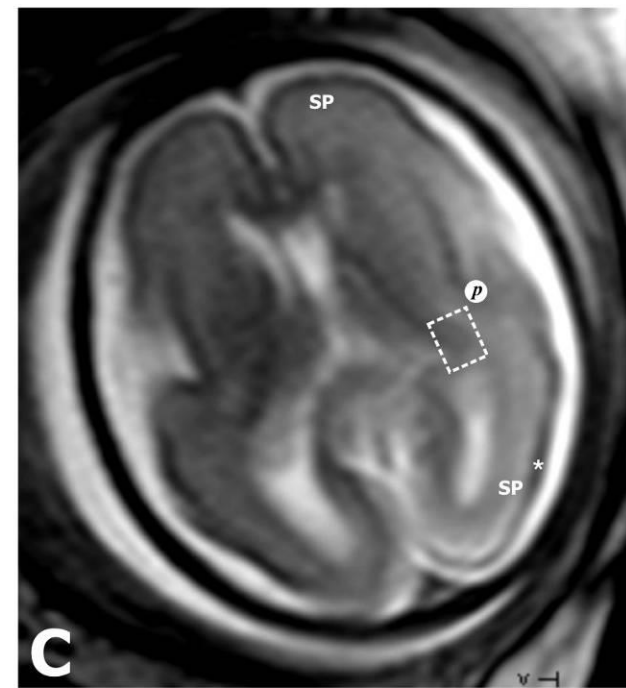
Treći zaključak:
subplate zona
(pretinac/compart
ment) je dosad
nedovoljno
prepoznati
kontinuirani
asocijativni neksus
kortexa. Posebno
je značajan za
produženi razvitak
tipično ljudskih
područja moždane
kore.



A



B



C

- ◆ Glutamatergic SP
- GABA-ergic SP
- GABA-ergic CP



Huang



Harvard University

*Rakic
Vasung*



*Radoš Marko, Benjak,
Ozretić, Barišić, Bunoza,
Grđan, Grizelj*



Rakic, Goldman-Rakic, Sestan



Nederlands Instituut voor Hersenonderzoek
Netherlands Institute for Brain Research



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Kostović Srzentić

Uylings



SPECIJALNA BOLNICA ZA KRONIČNE BOLESTI DJEČJE DOBI - GORNJA BISTRA



Gojmerac

Katušić



UNIVERSITÉ
DE GENÈVE

Huppi, Vasung



Evans



*Judaš, Petanjek, Radoš Marko, Radoš
Milan, Sedmak, Krsnik,
Jovanov Milošević, Raguž, Žunić*

