First symposium
„Toward translational research in brain and heart studies: Achievements and challenges in knowledge and technology transfer“

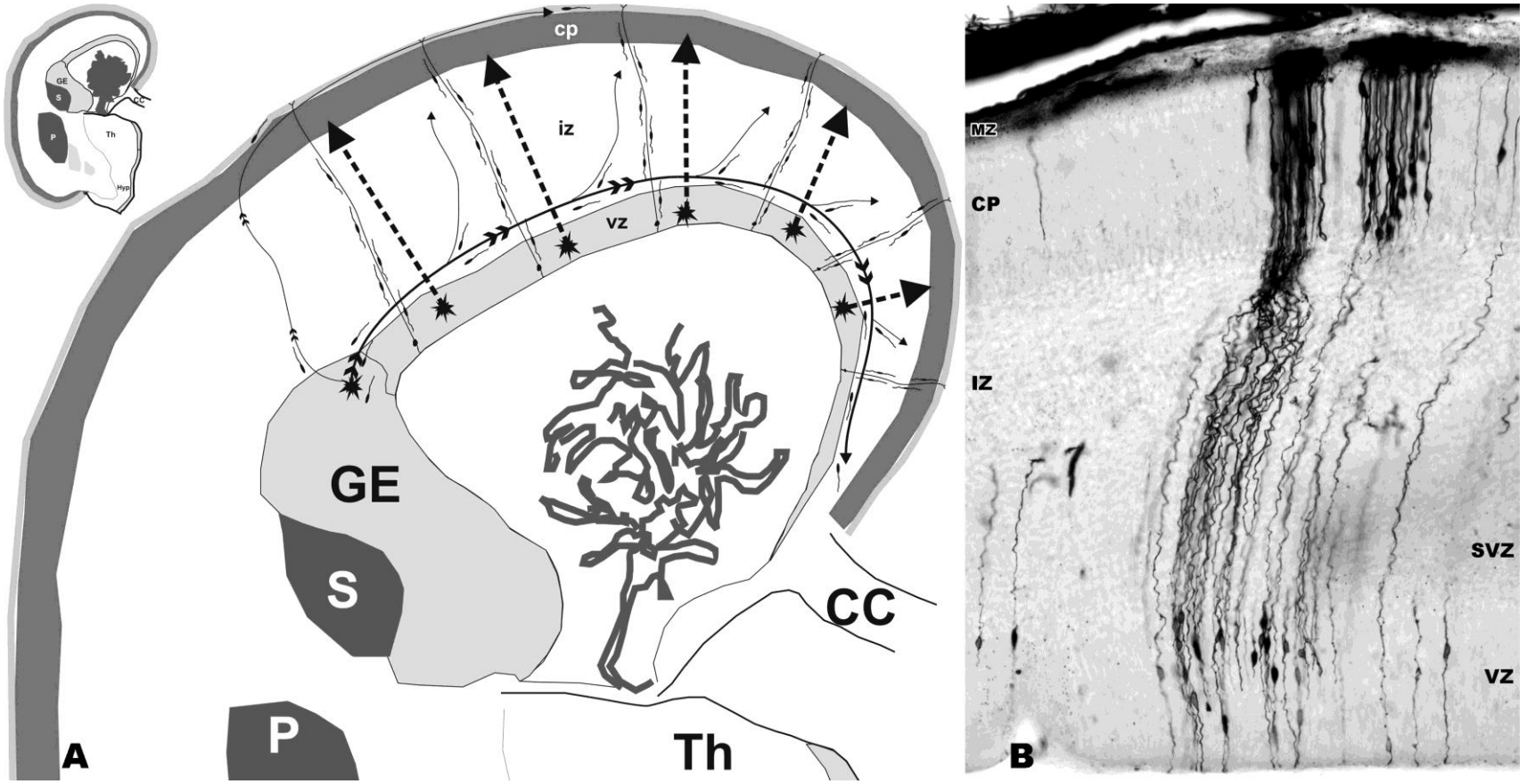
February 18, 2008, Zagreb, Croatia

Prof.dr.sc. Ivica Kostović
Croatian Institute for Brain Research
School of Medicine, University of Zagreb

„Neuroimaging in developmental cortical disorders“


Hrvatski institut za istraživanje mozga

Migracija kortikalnih neurona



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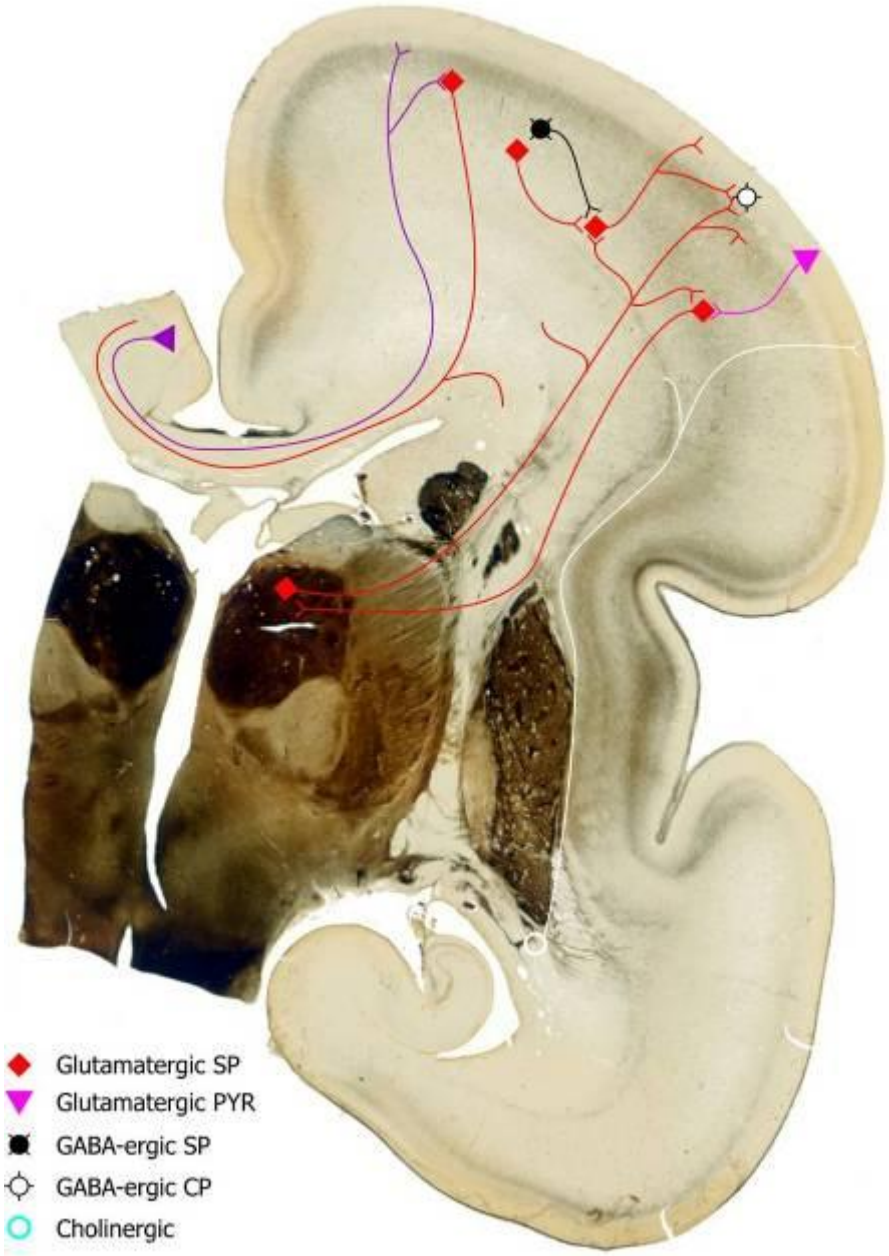
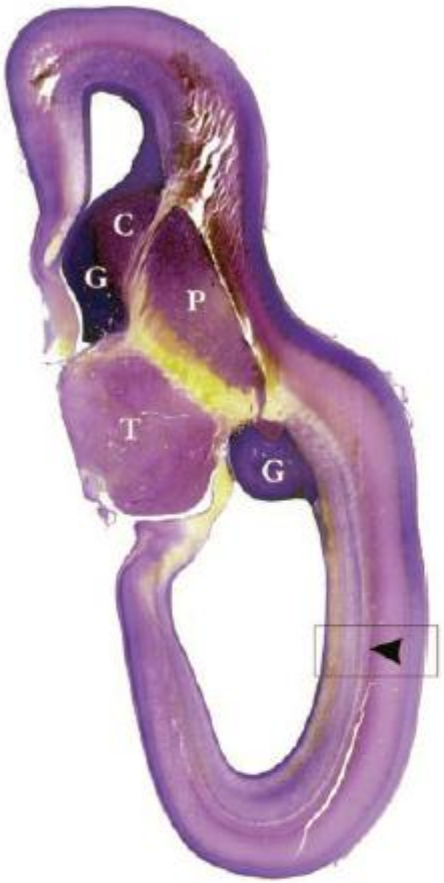
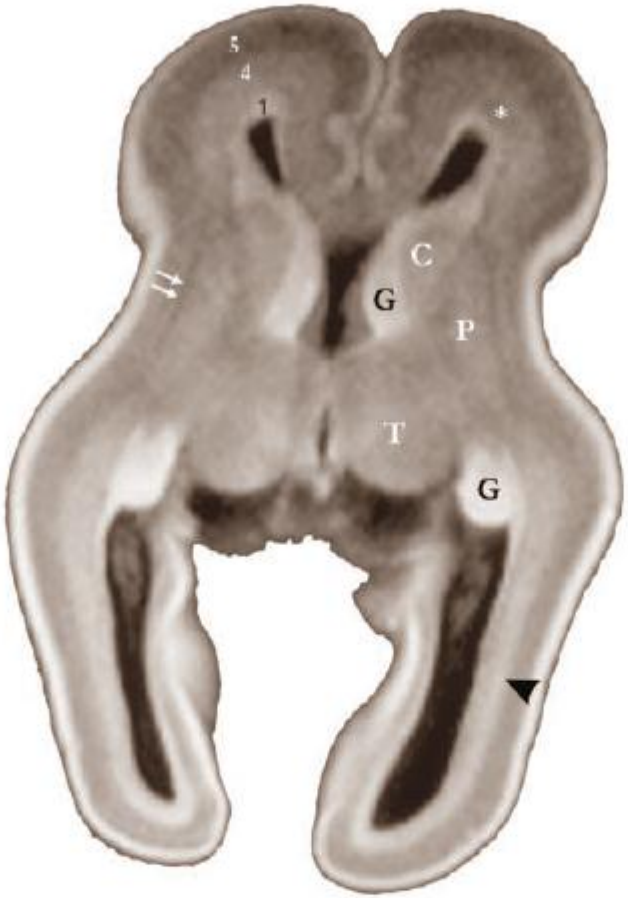
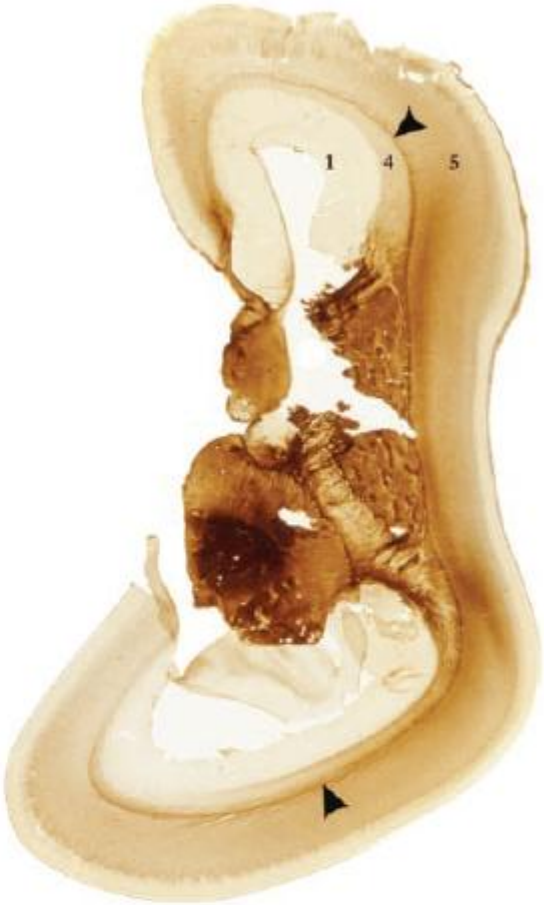
Transient Circuitry of the Human Fetal Cortex

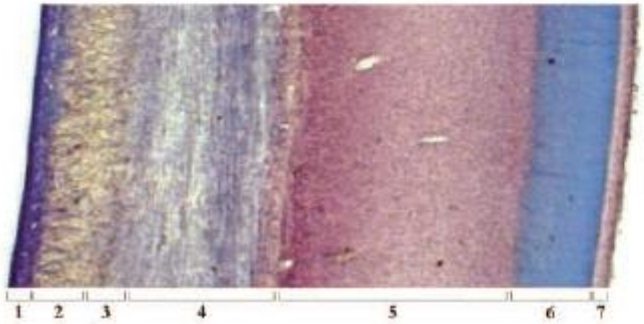








A B C



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

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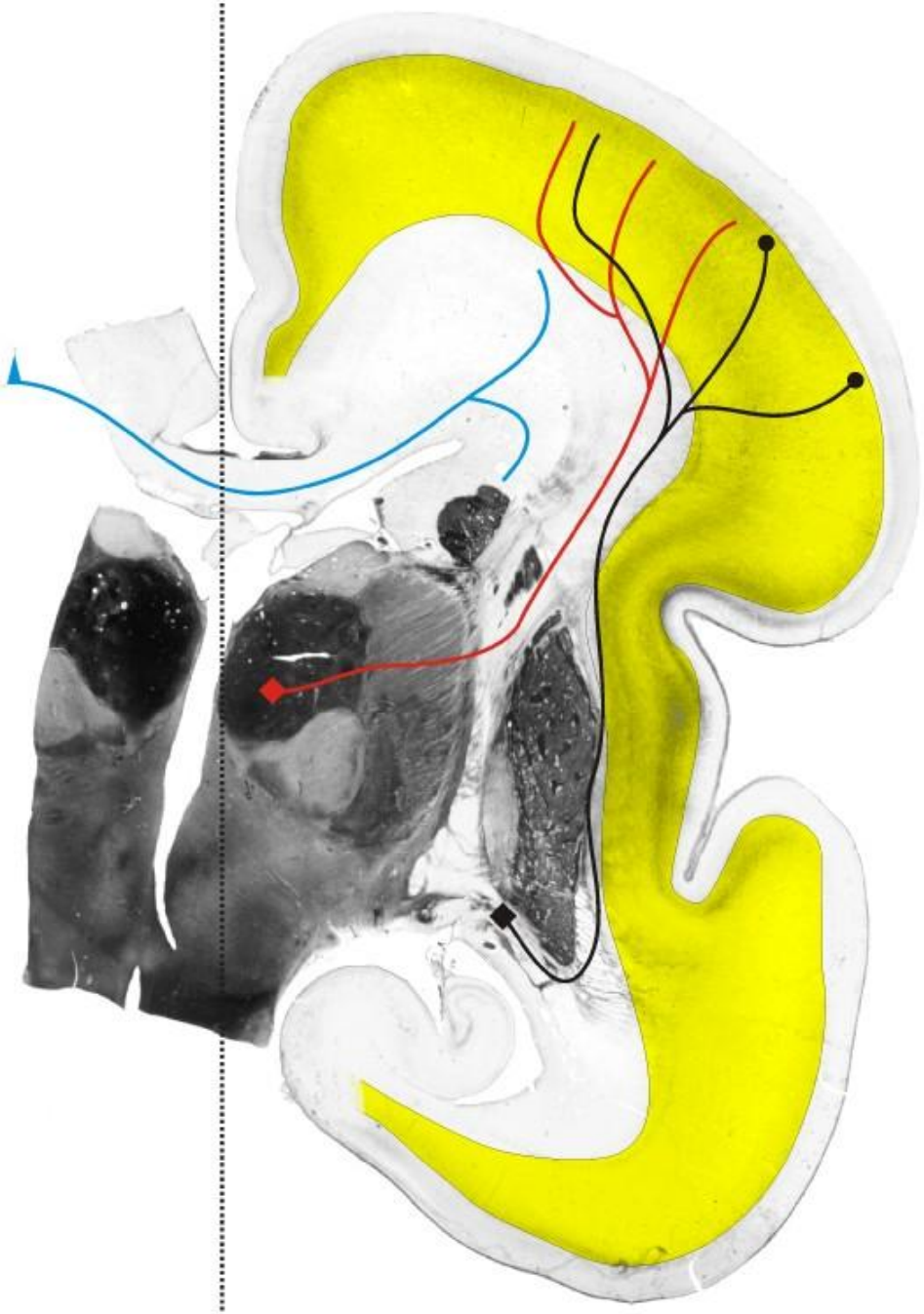
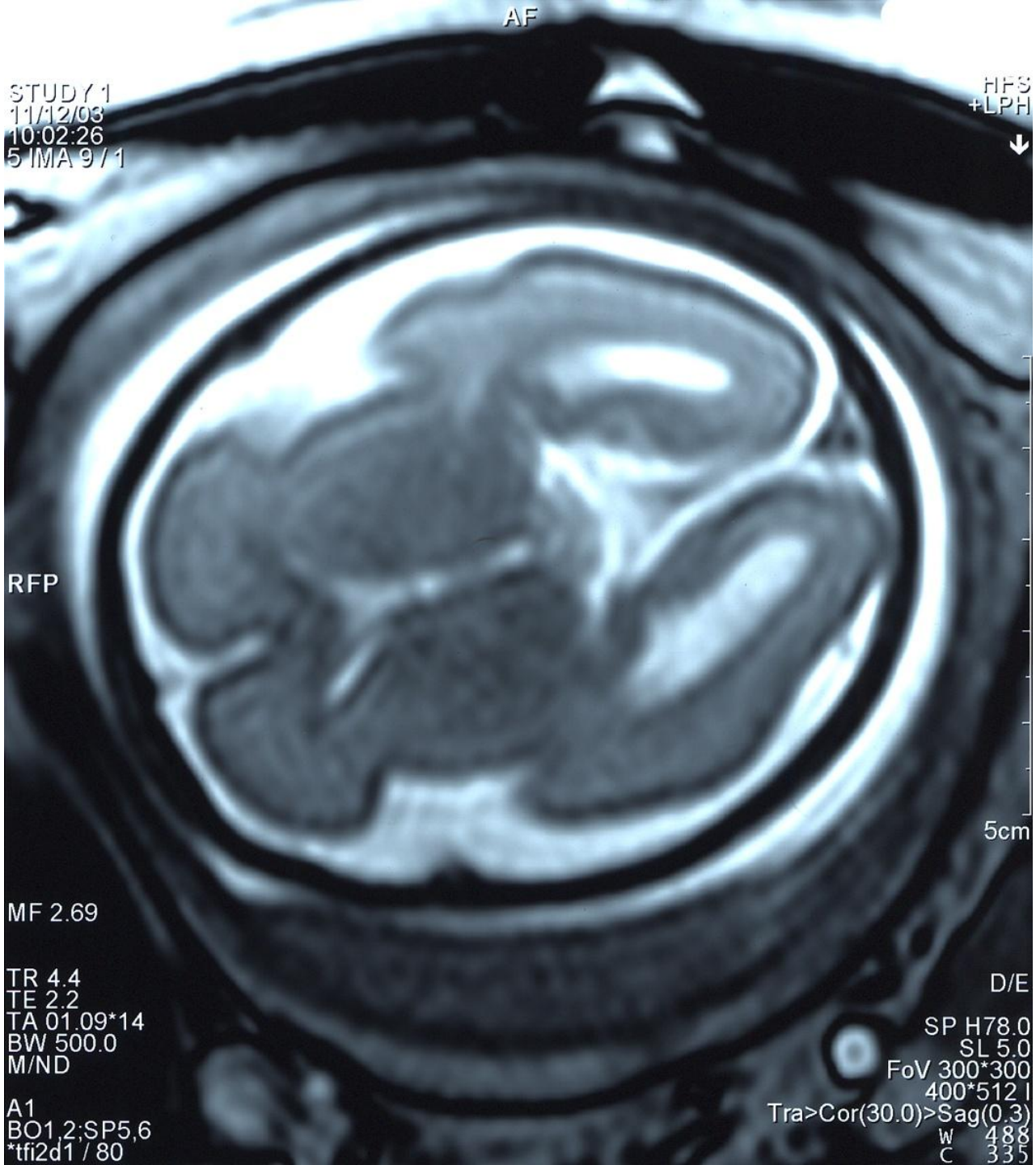
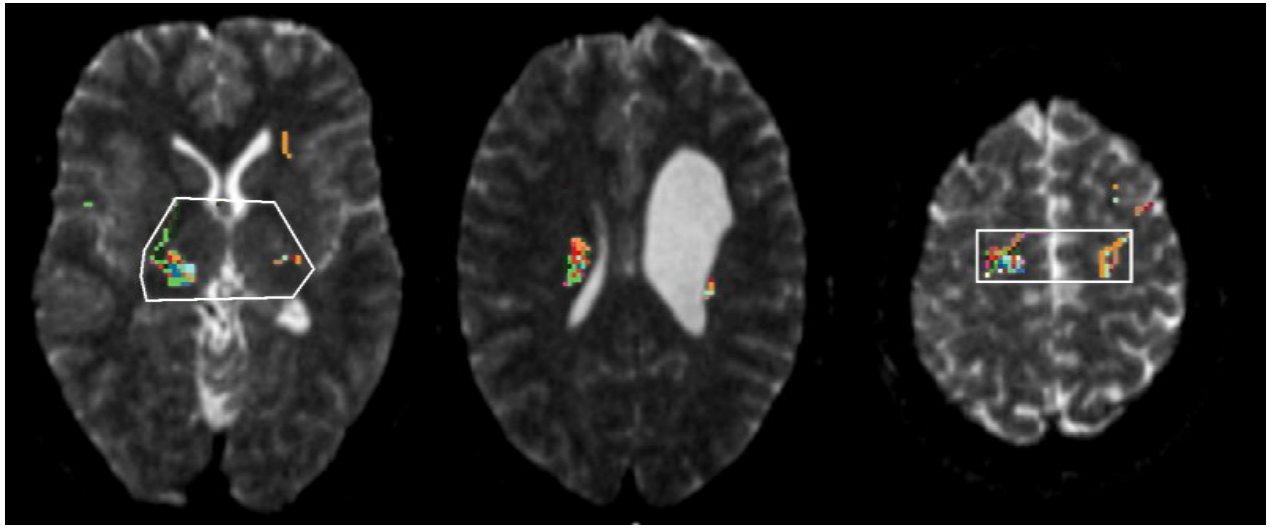
Accumulation below the CP

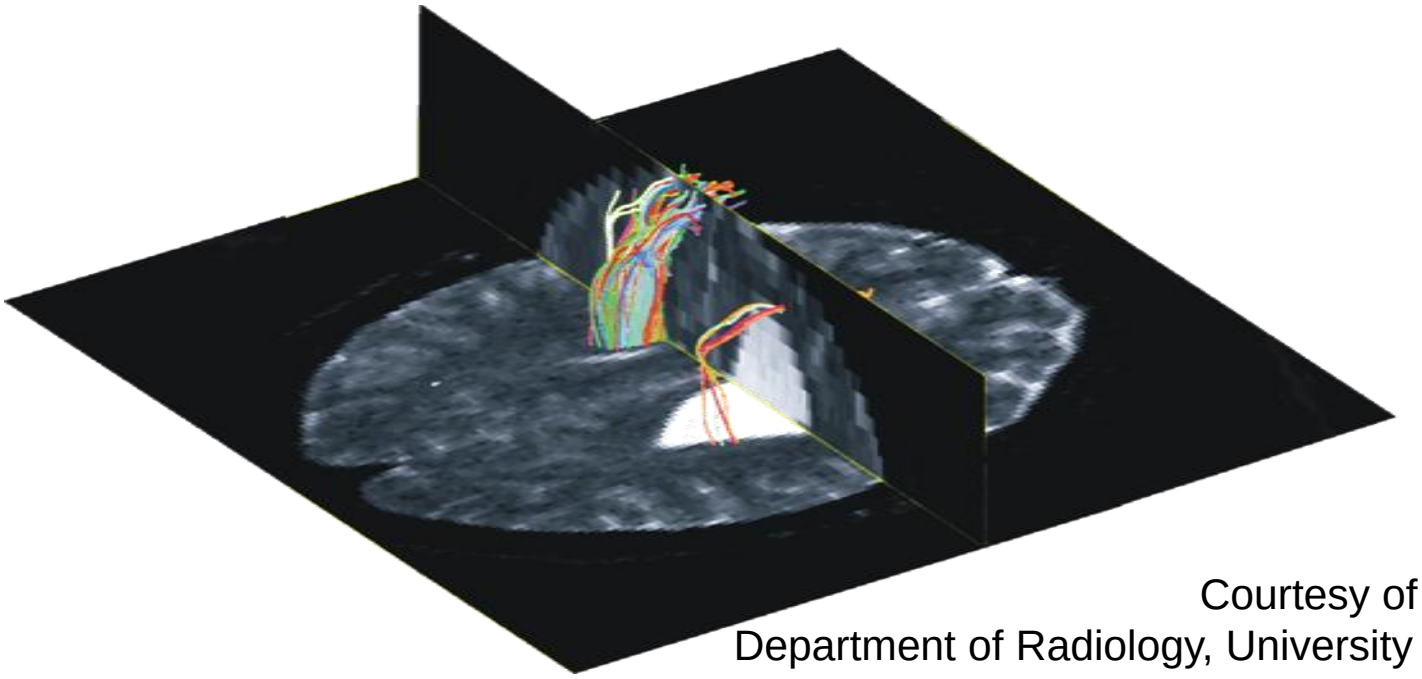




In vivo
MR – transient lamination

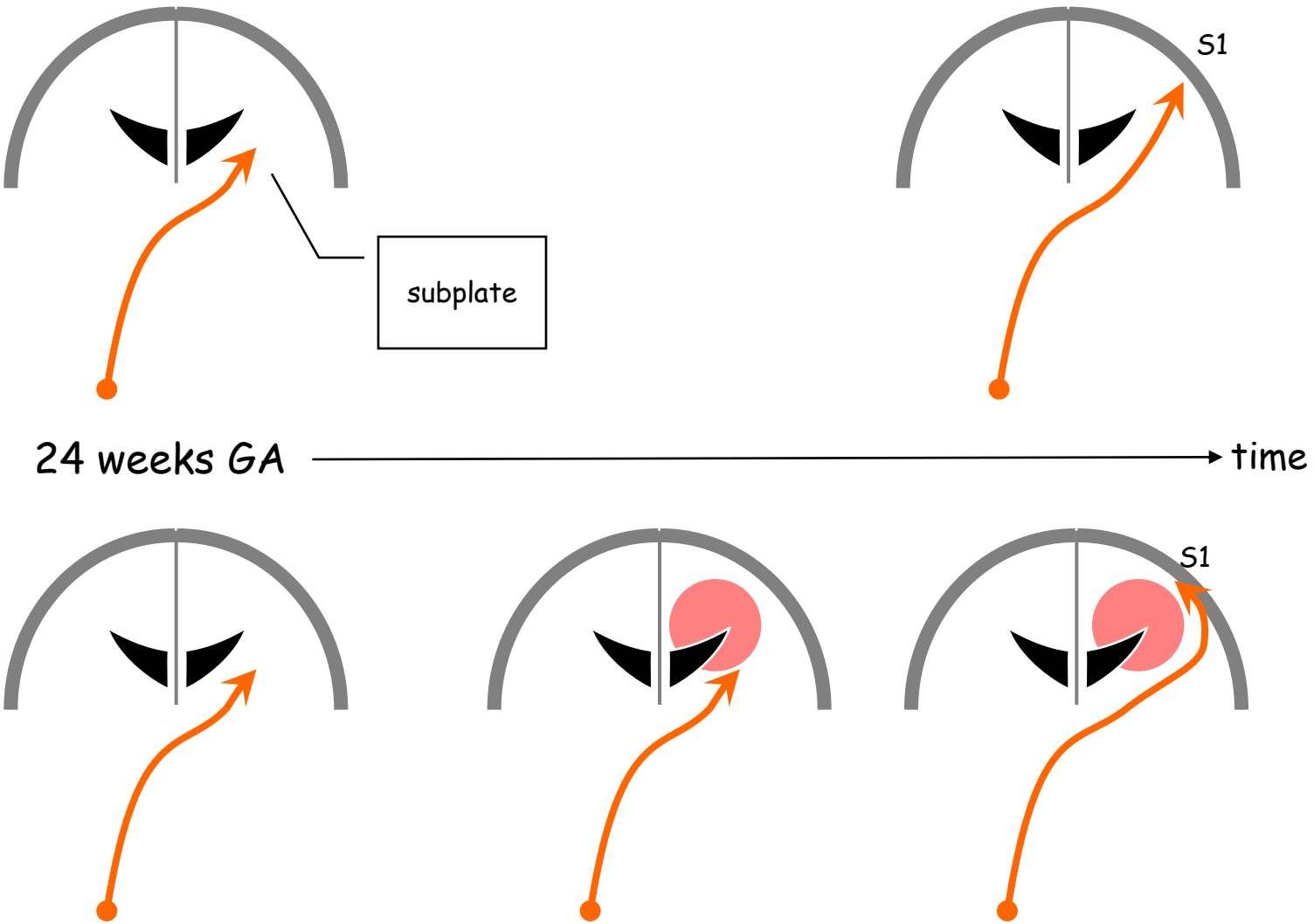
Diffusion Tensor Imaging / Fiber Tracking





Courtesy of dr.M.Staudt
Department of Radiology, University of Tubingen

Somatosensory afferent projections

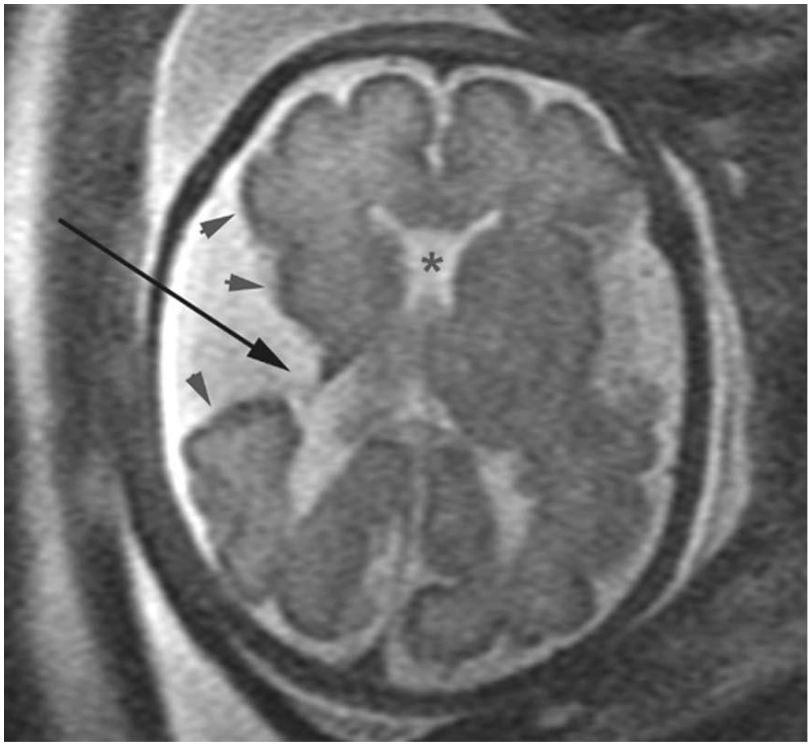


Courtesy of dr.M.Staudt
Department of Radiology, University of Tubingen

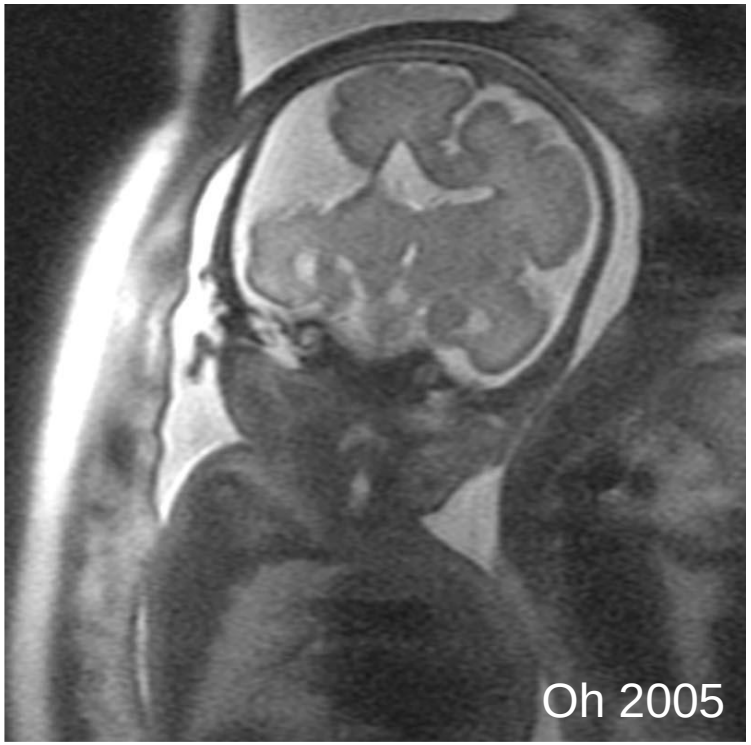
Major neuronal migratory defects

Phase	Morphological manifestation	Candidate gene	Clinical manifestation
Proliferation of neuronal and radial glia cells, (cell fate determination defect)	Schizencephaly	-Homeobox genes, *EMX2*	-prominent cognitive disturbances -frontal motor disturbances -seizures
Onset of migration	Bilateral periventricular (subependymal) nodular heterotopia	-Xq28, *FILAMIN1*, (*FLN1*), actin-binding phosphoprotein	-average intelligence -seizures as dominant clinical feature
Ongoing migration (incomplete neuronal migration from ventricular neuroepitelium)	Classical lissencephaly (type I)	-17p13.3, gene *LIS1*, subunit of PAFAH1B1 and Xq22.3-23, gene *DCX (XLIS)*, protein dublecortin -associated with MAPs	-severe mental retardation, subtle facial deformation, epilepsy, other neurological abnormalities
	Subcortical "band" neuronal hetrotopia	-autosomal dominant deletion in 17p13.3 and a ring chromosome	-Miller-Dieker syndrome (MDS) -severe lissencephaly with profound mental and physical disabilities, characteristic faces
	Pachygyria	-autosomal recessive inheritance	-similar to lissencephaly but less severe
Neuron migration stop signal	Lissencephaly type II Cobblestone complex	-9q34.1, *FKRP* gene	-Walker-Warburg syndrome, macrocephaly, retinal malformations, CMD
		-1p32-34, *POMT1* gene	-Muscle-eye-brain disease
		-9q31, *FCMD* gene encodes ECM-fukutin)	-Fukuyama congenital muscular dystrophy (FCMD)
Any phase of migration and cortical organization	Focal cortical dysplasia -FCD1B -altered laminations and giant neurons -FCD2A -dysmorphic neurons -FCD2B - Taylor type-balloon cells	-both genetic and non genetic etiology -reduction in GABA-ergic interneuron density (altered $GABA_A$-receptor mediated inhibition) -reduction in GABA-transporter expression	-common cause of medically refractory epilepsy in children (intractable focal epilepsy, drug-resistant epilepsy) -described also as neurological entity after lobectomy - neurological symptoms usually begin in first few years -may be associated with febrile seizures and status epilepticus
Post-migration defect	Polymicrogyria	-autosomal recessive mutation -encephalo-clastic process -maldevelopmental varieties -intoxication -infections -invasions, etc.	-generalized weakness, severe hypotonia, severe recurrent seizure -Zellweger cerebro-hepato-renal syndrome

Shizencephaly



a.



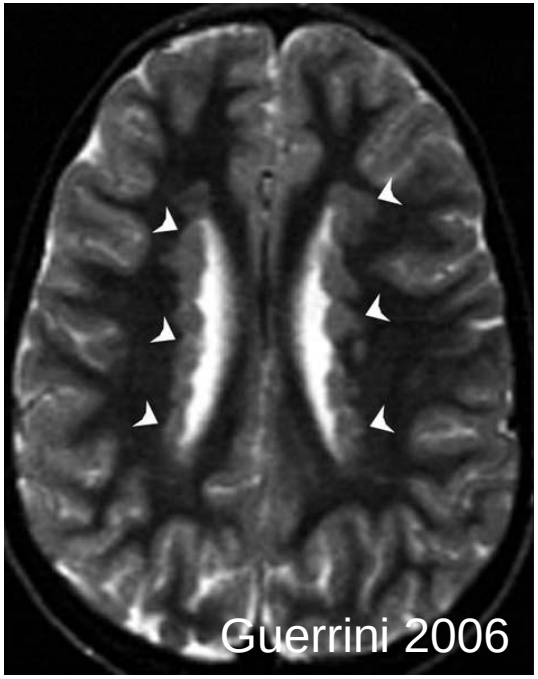
b.

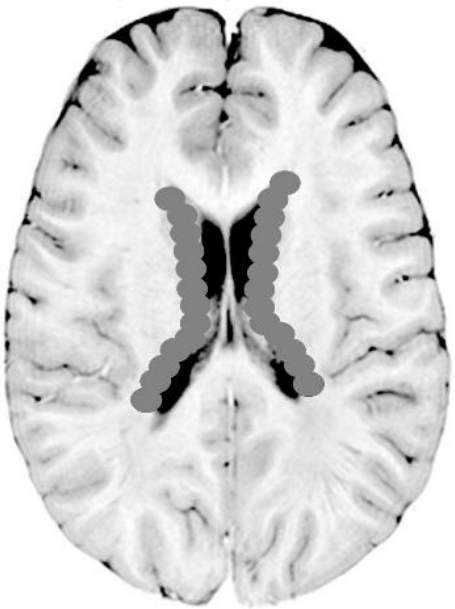
Phase: Proliferation of neuronal and radial glial cells

Transcriptional factors:
EMX1, EMX2, PAX6, OTX1, LHX2, COUP-TF1, LHX6, LHX7, -8, DLX1, -2, -5, -6, NOTCH1, -3, MASH1

Gene: EMX2

Periventricular nodular heterotopia





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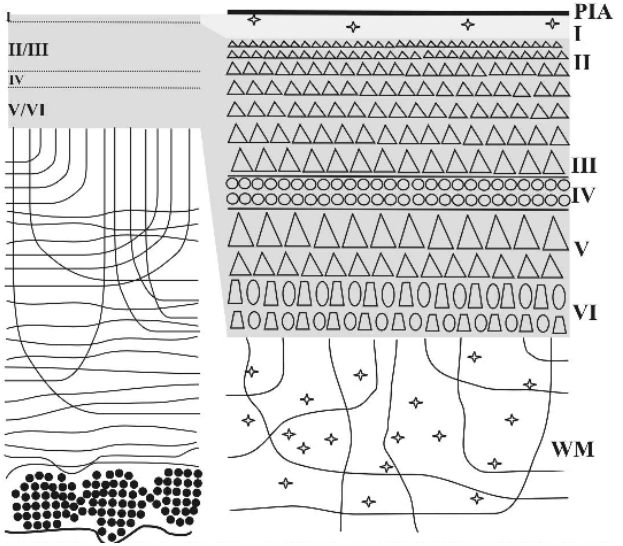

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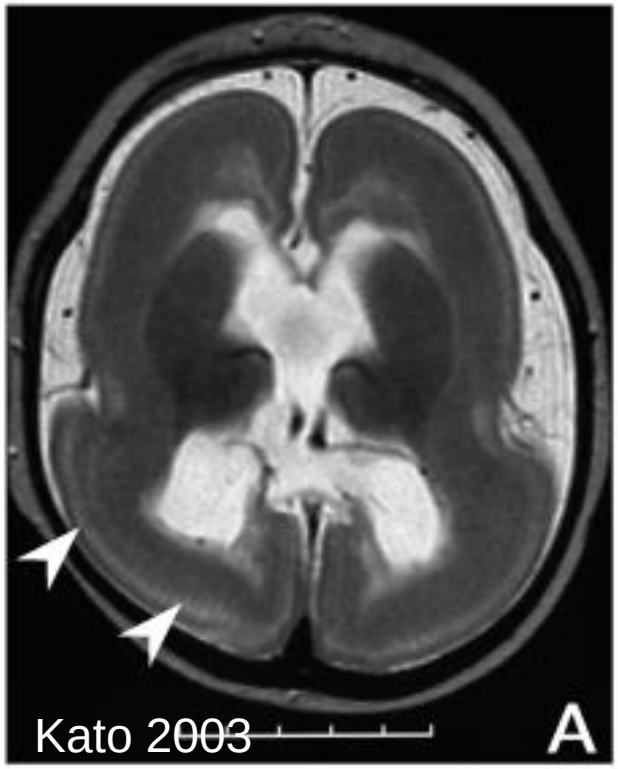
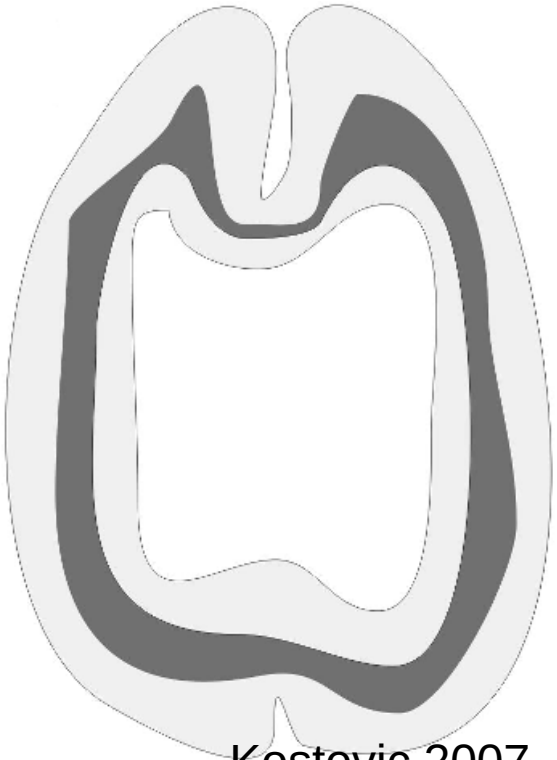
Phase: Onset of migration

Transcriptional factors:
DLX1, -2, NKX2.1, LHX6, ER81, SP8, GSH1, -2

Gene: FLN1

Lissencephaly type I





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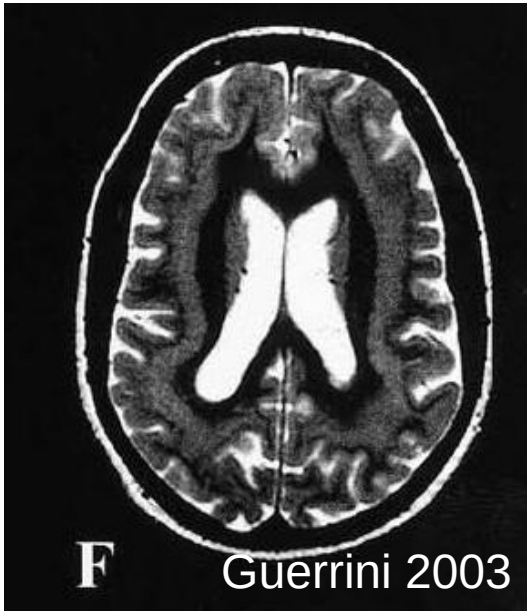
Phase: Ongoing migration

Transcriptional factors:
DLX1, -2, NKX2.1, LHX6, ER81, SP8, GSH1, -2

Gene: LIS1, DCX

Subcortical band heterotopia



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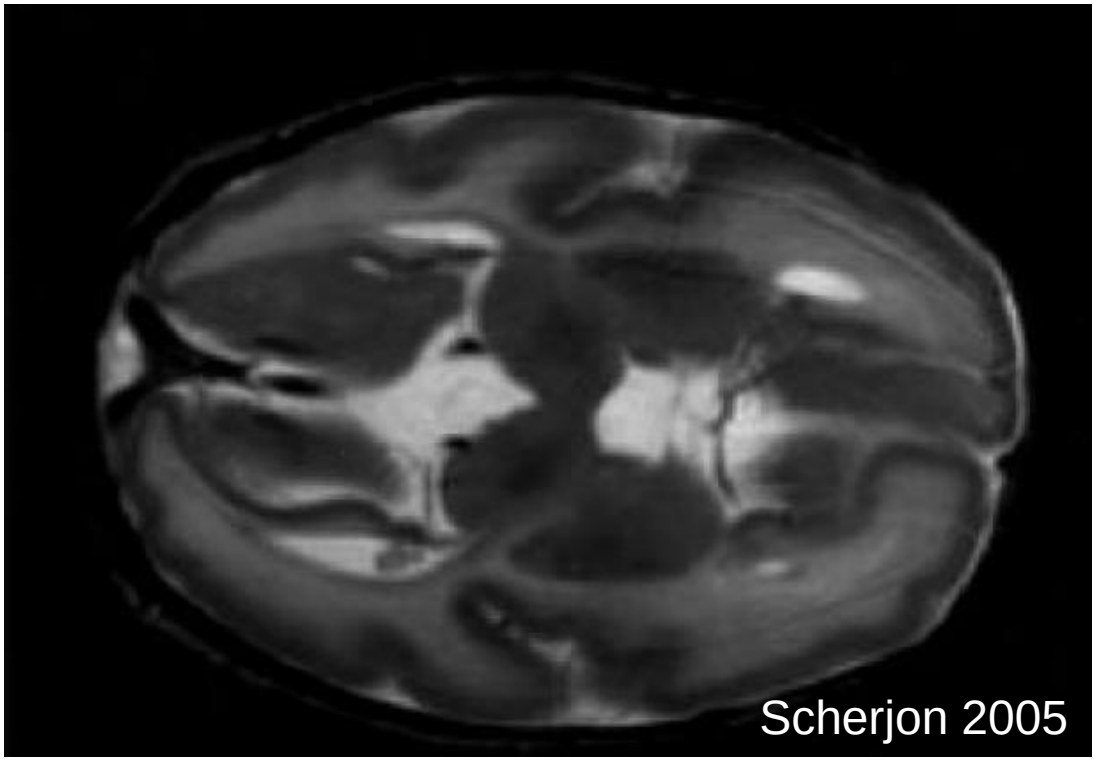
Phase: Ongoing migration

Transcriptional factors:
DLX1,

Gene: autosomal dominant deletion in 17 p 13.3

Pachygyria

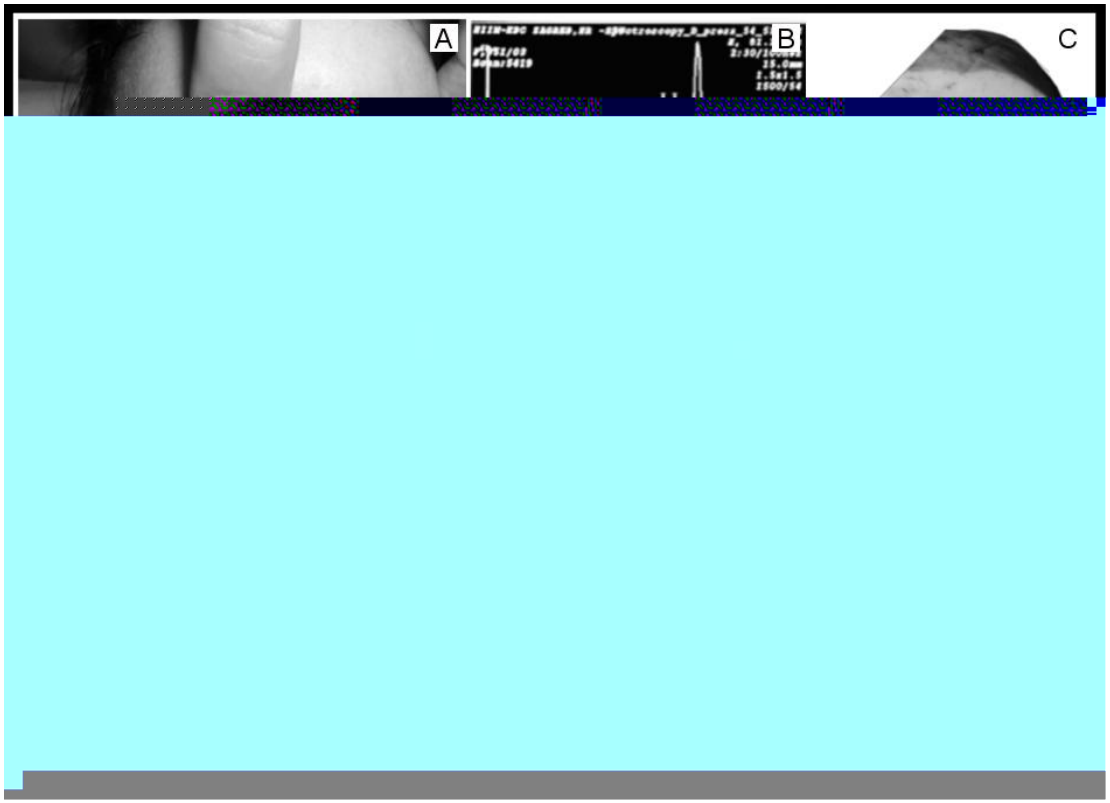


Phase: Ongoing migration

Transcriptional factors:
DLX1, -2, NKX2.1, LHX6, ER81, SP8, GSH1, -2

Gene: autosomal recessive inheritance

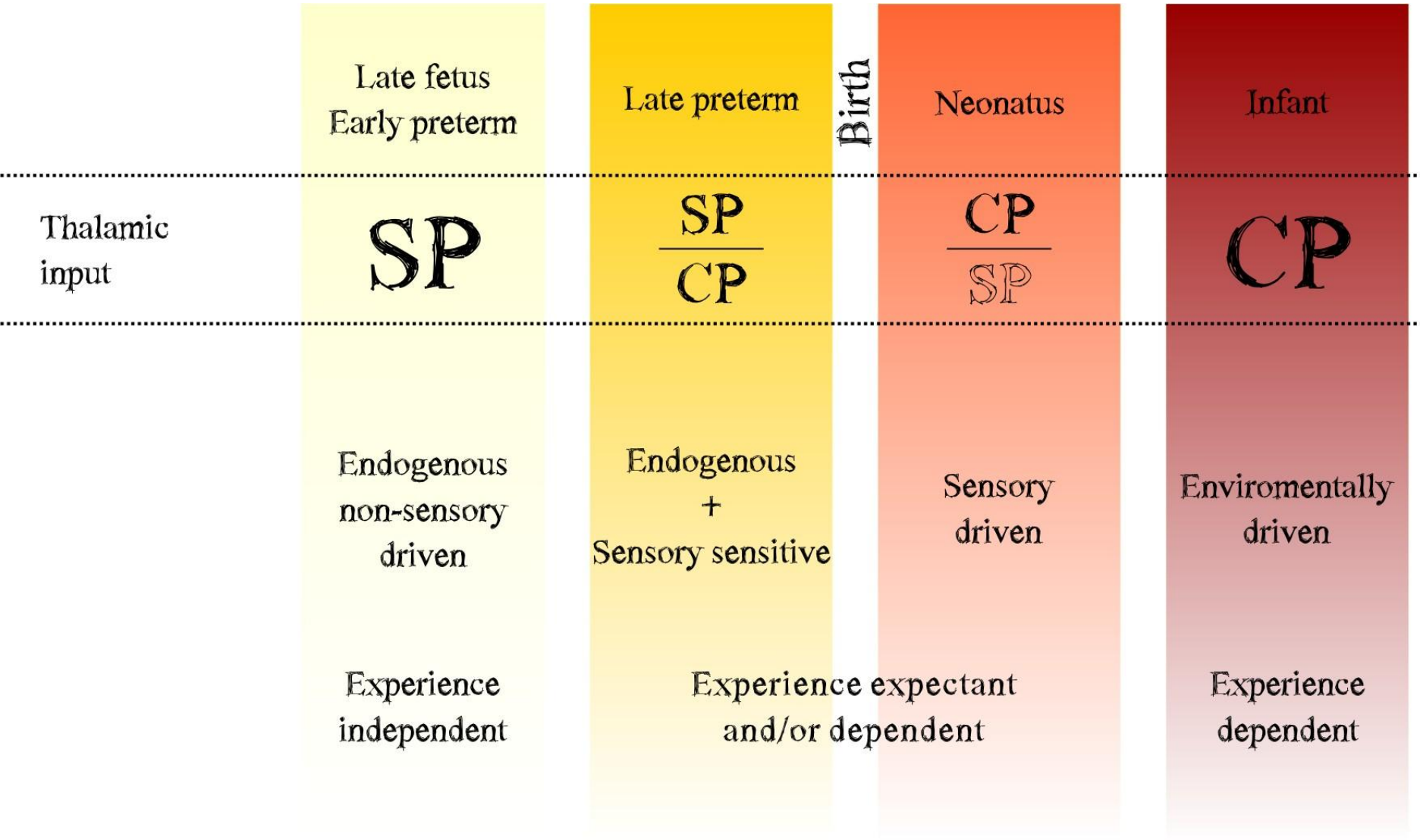
Lissencephaly type II



Phase: Neuronal migration stop signal

Transcriptional factors:
DLX1, -2, NKX2.1, LHX6, ER81, SP8, GSH1, -2

Gene: POMT1


Late fetus
Early preterm
Late preterm
Birth
Neonatus
Infant
Thalamic input
SP
SP
CP
CP
SP
CP
Endogenous non-sensory driven
Endogenous + Sensory sensitive
Sensory driven
Enviromentally driven
Experience independent
Experience expectant and/or dependent
Experience dependent