Critical Periods in Brain Development

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DOHaD Summer Course
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DOHaD

Low Birth Weight

⇩

Cardiovascular/ Metabolic Disease

Developmental Insult

⇩

Adverse Long-Term Outcome

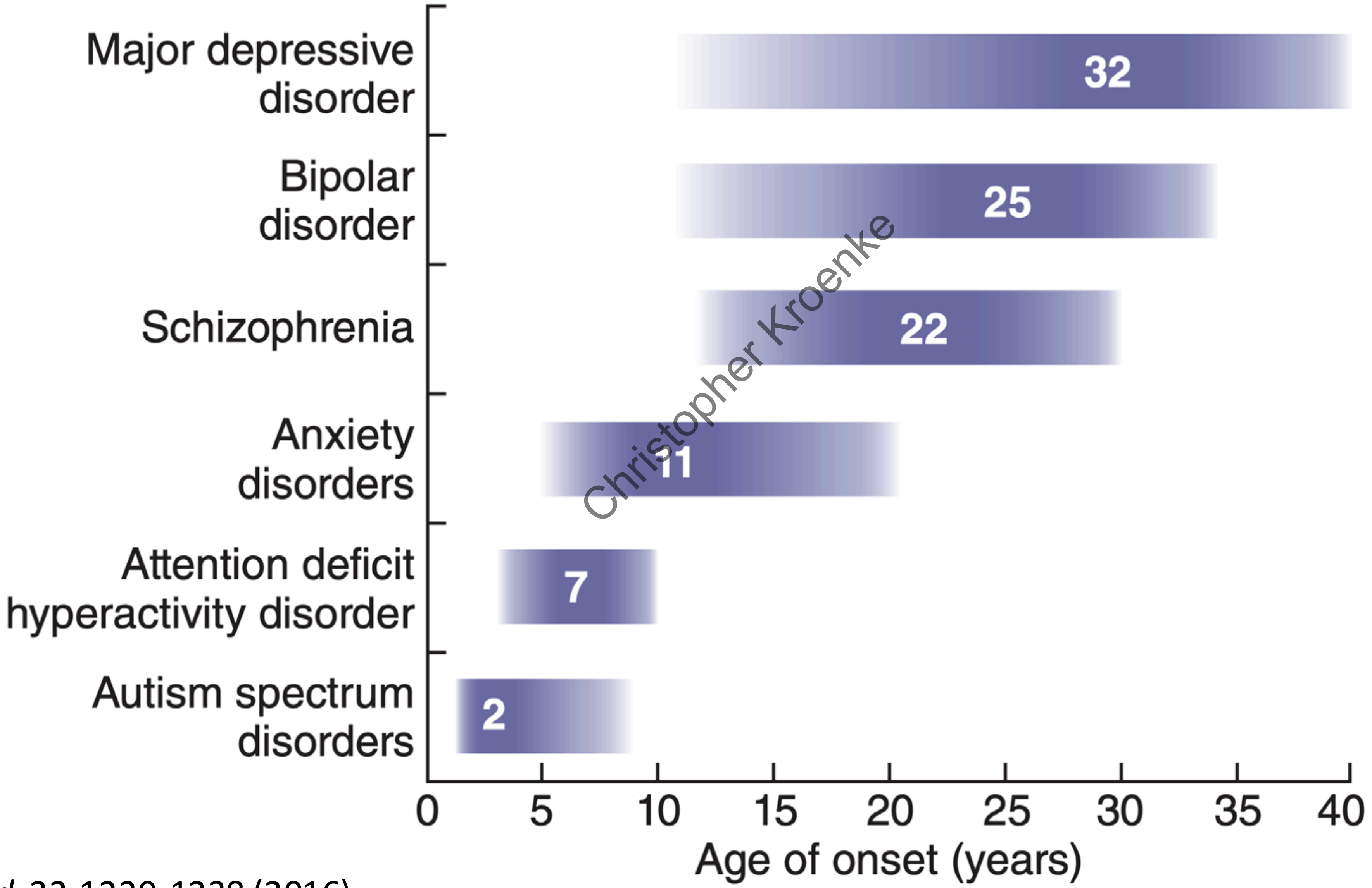
CNS Development

Perturbed Environmental Stimulus

⇩

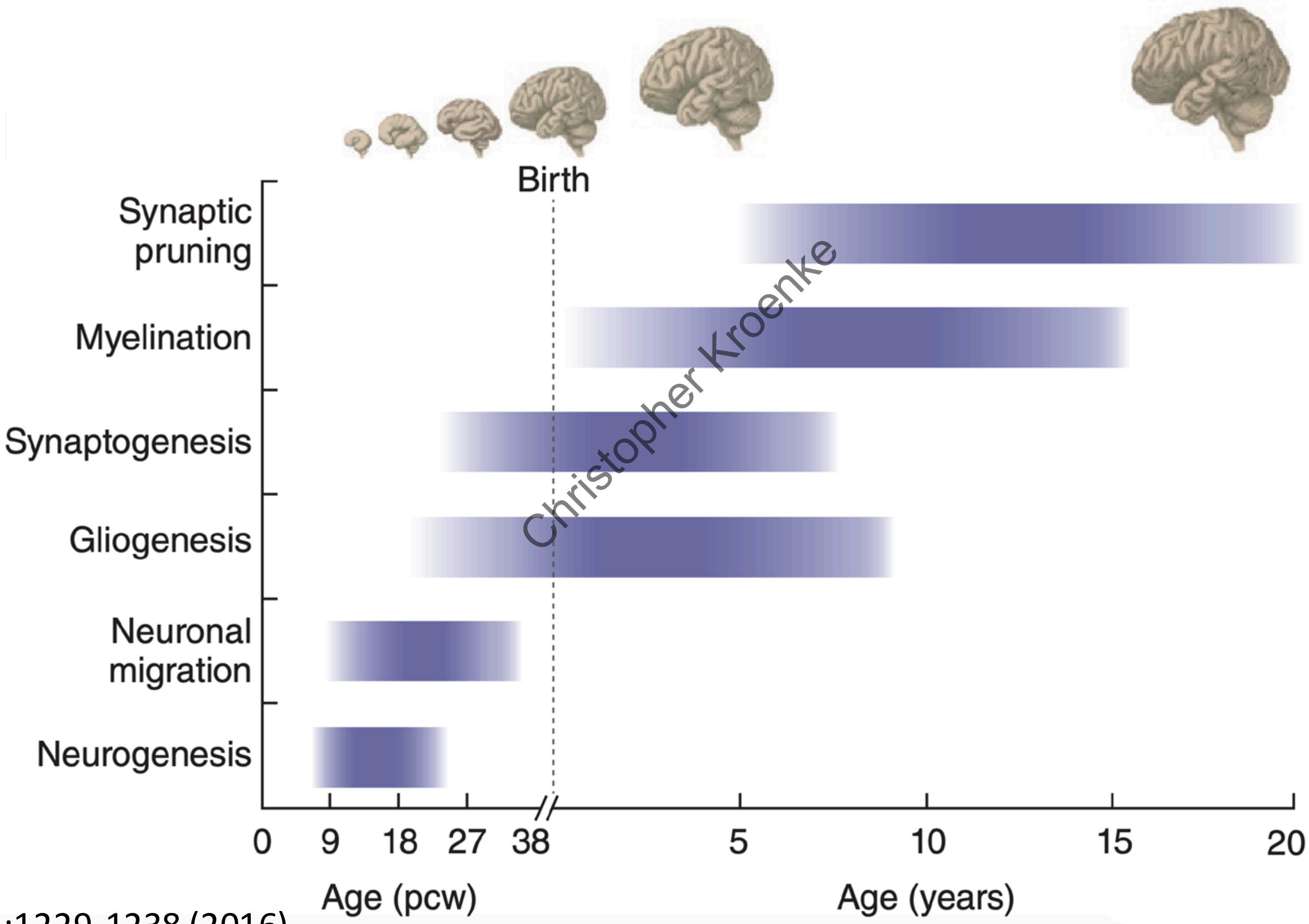
Altered Neural Function/Neuro developmental Disease

Neurodevelopmental and Neuropsychiatric Disorders



Marin, *Nat. Med.* 22:1229-1238 (2016)

Neurons and Glia Undergo Protracted Differentiation



Marin, *Nat. Med.* 22:1229-1238 (2016)

DOHaD

Low Birth Weight

Epigenetic Changes

Cardiovascular/ Metabolic Disease

Developmental Insult

Adverse Long-Term Outcome

CNS Development

Perturbed Environmental Stimulus

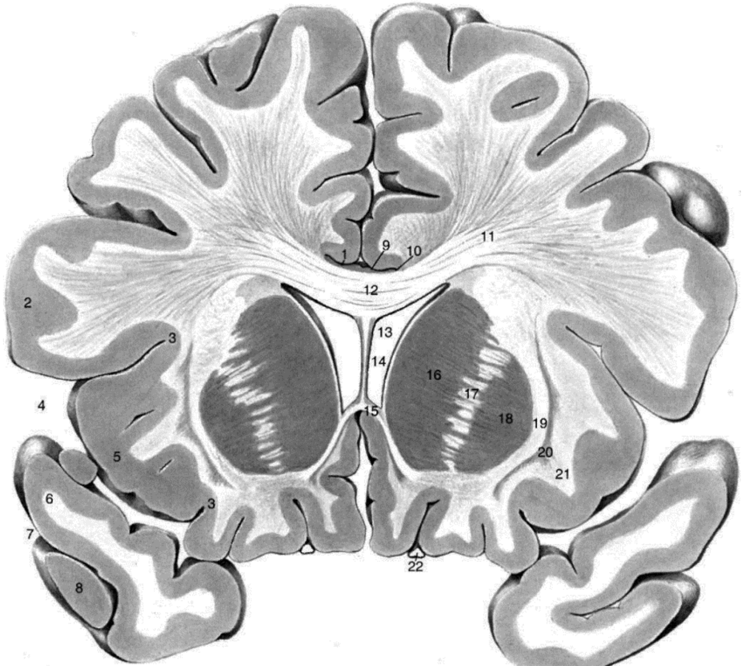
Altered Cellular Differentiation

Altered Neural Function/Neurodevelopmental Disease

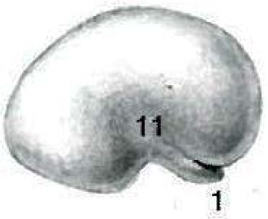
Cerebral Cortex

Table 15.1. Quantitative data on the human cerebral cortex

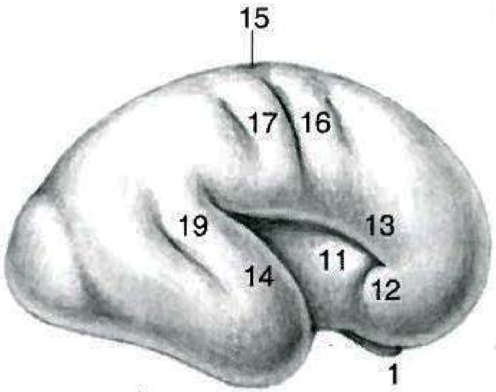
Volume (both hemispheres)	517 cm^3 (males) 440 cm^3 (females)	Pakkenberg and Gundersen [525]
Surface (both hemispheres)	1470–2275 cm^2	Blinkov and Glezer [56] Elias and Schwartz [173] Pakkenberg and Gundersen [525]
Depth of neocortex	1.5–5 mm	von Economo and Koskinas [796]
Total number of neurons (both hemispheres)	22.8×10^9	Pakkenberg and Gundersen [525]



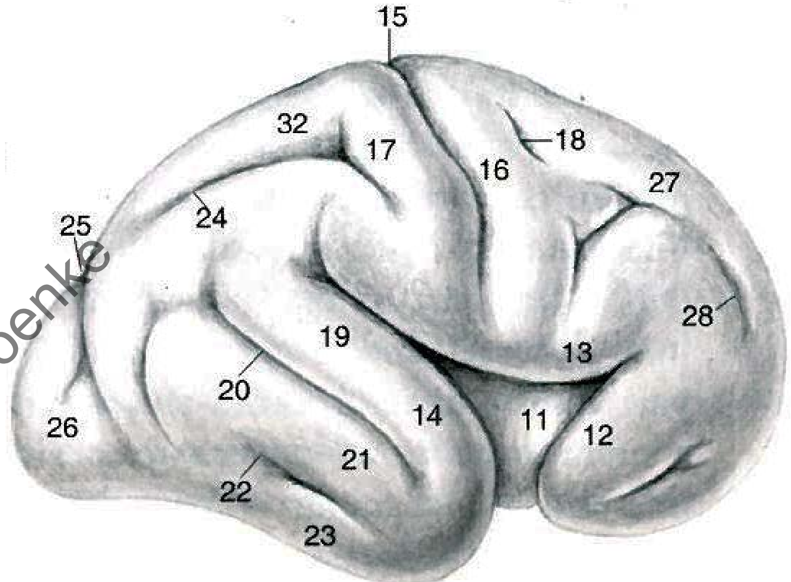
Human Brain, 14 Weeks to End of Gestation



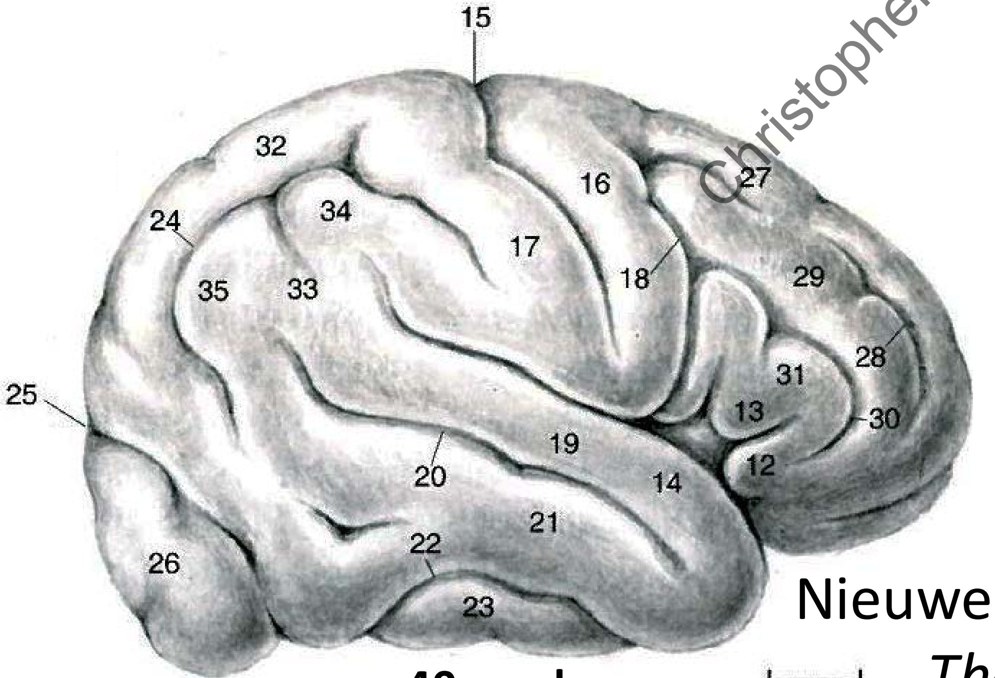
14 weeks



21 weeks



28 weeks

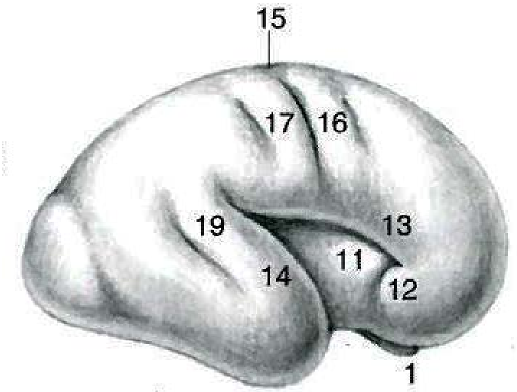


40 weeks

1 cm

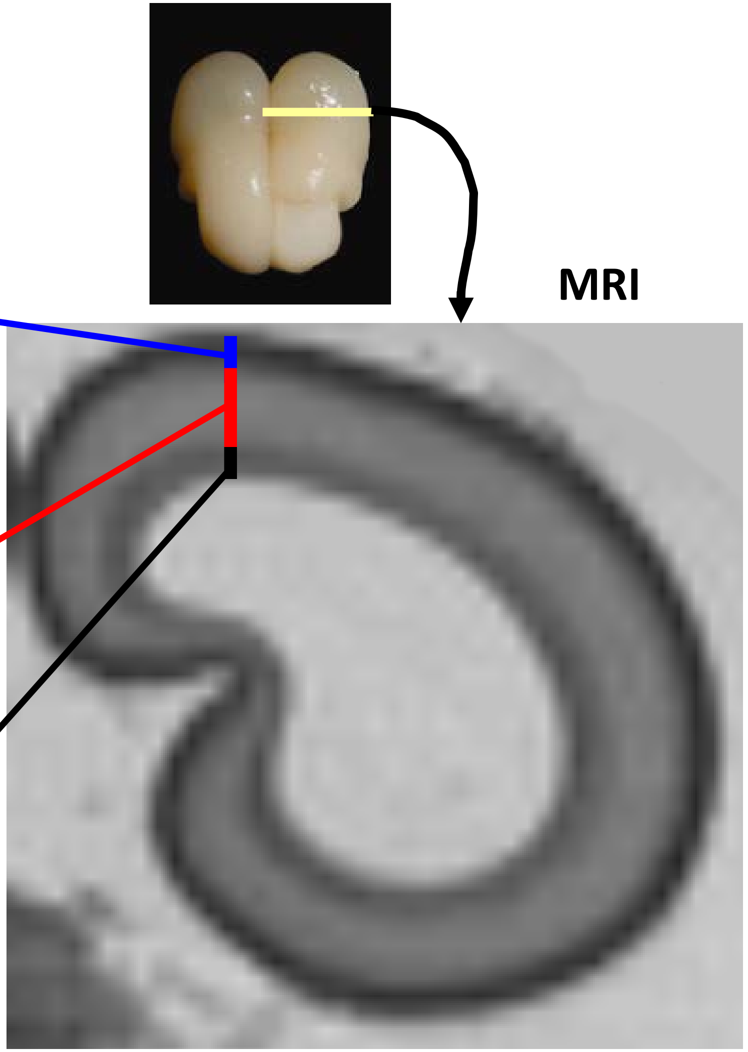
Nieuwenhuys, Voogd, vanHuijzen, (2008)
The Human Central Nervous System

Layers of Developing Brain



21 weeks

Nonhuman Primate Brain,
Mid-Gestation



Neural Proliferation

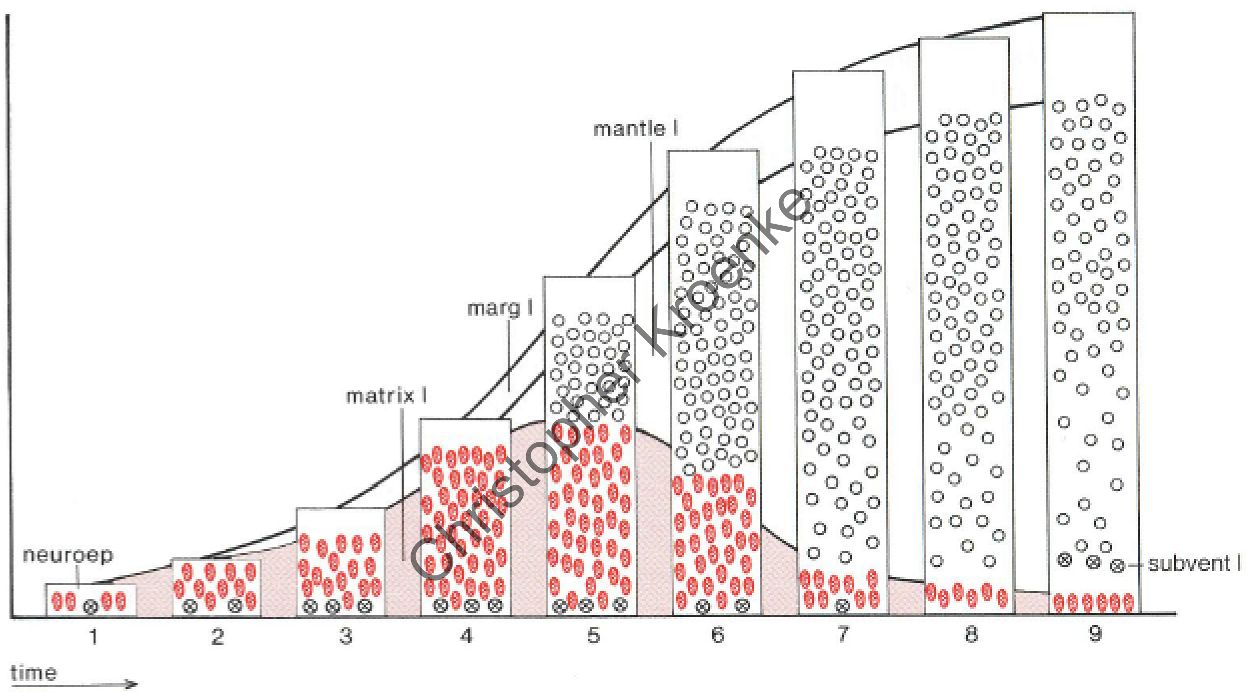
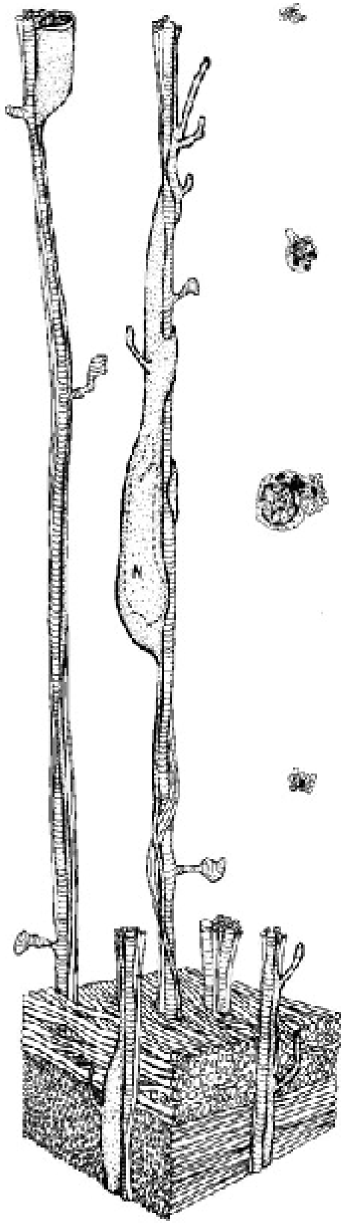
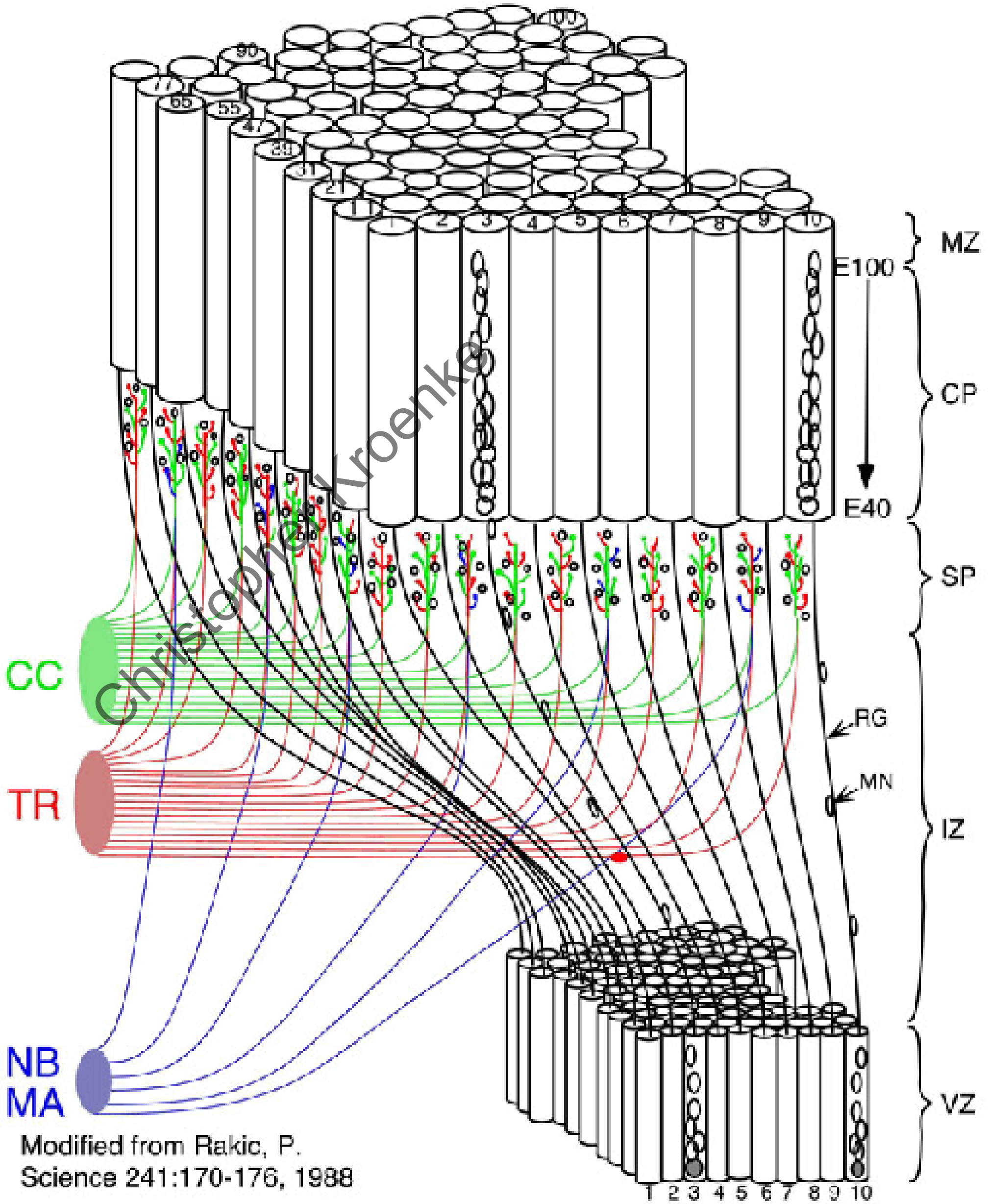


Fig. 2.7. Ontogeny of the CNS. The histogenesis of the wall of the neural tube is subdivided into nine phases. The following developmental events are indicated: Transformation of monolayered neuroepithelium into a pseudostratified epithelium (*1* → *4*); increase (*2* → *4*), culmination (*5*), decrease (*5* → *7*) and depletion (*8*) of matrix layer; appearance (*3*) and development (*3* → *9*) of marginal layer; appearance (*5*) and expansion (*5* → *9*) of mantle layer; appearance of subventricular layer (*9*). *mantle l*, mantle layer; *marg l*, marginal layer; *matrix l*, matrix layer; *neuroep*, monolayered neuroepithelium; *subvent l*, subventricular layer (modified from [89] Fig. 33 a)

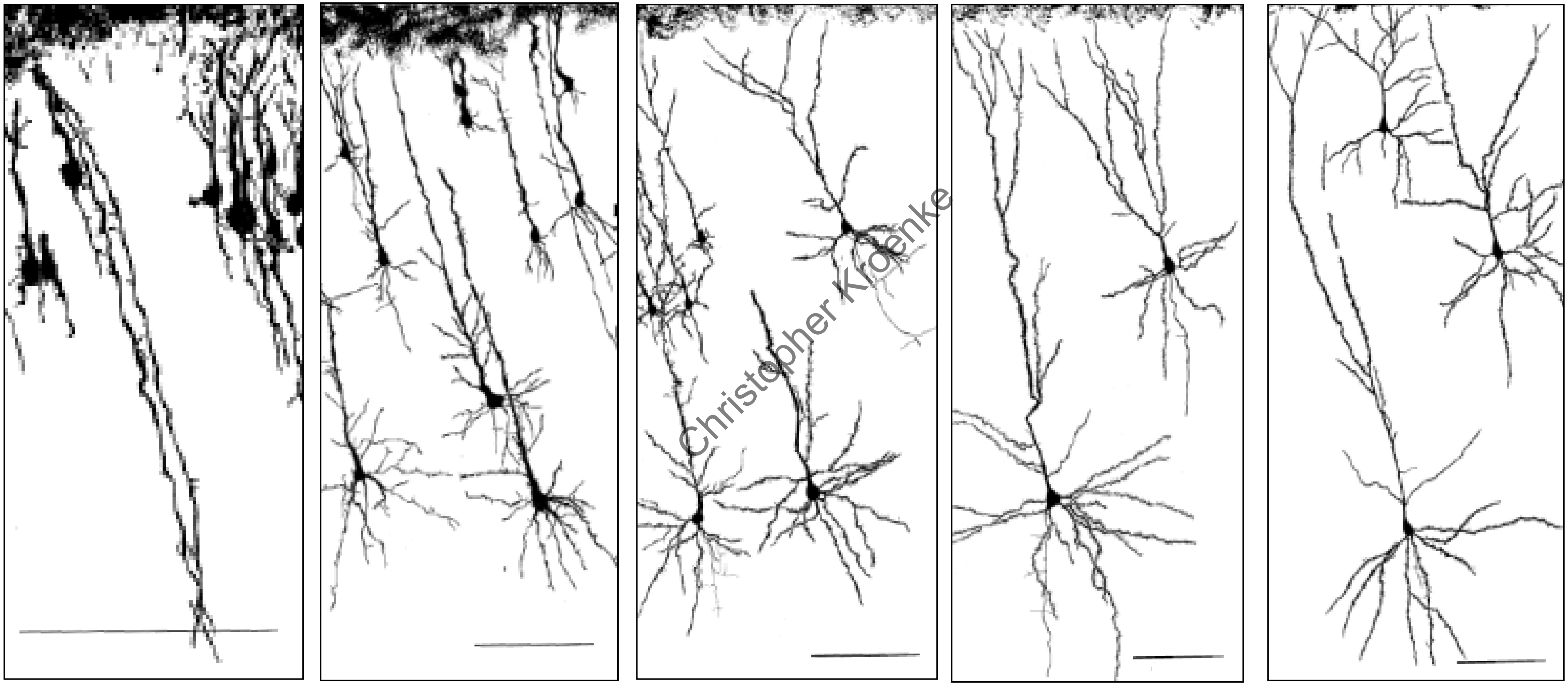
Neural Migration from Ventricular Zones to Cortex





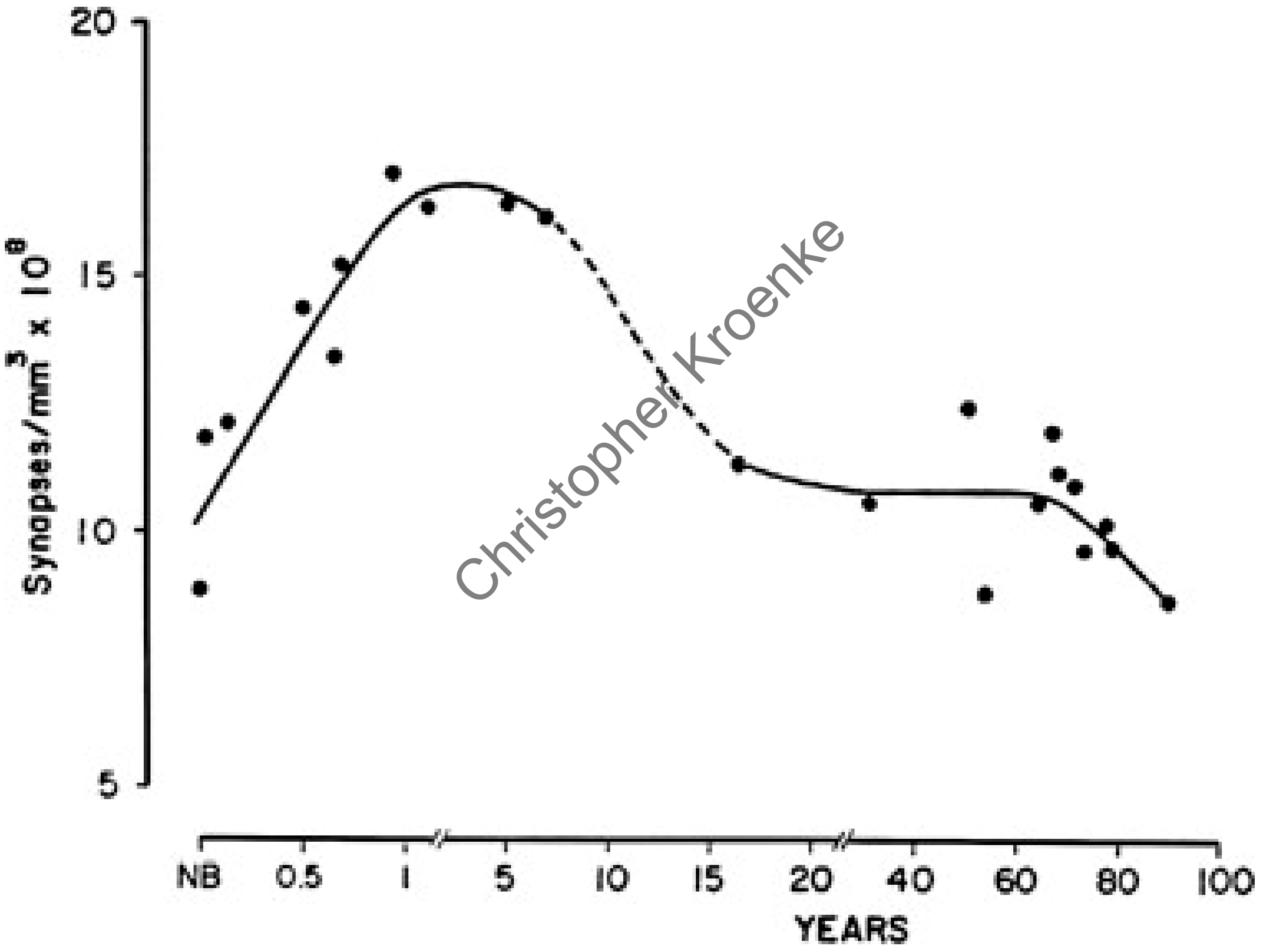
Modified from Rakic, P.
Science 241:170-176, 1988

Temporal Pattern for Cerebral Cortical FA: Relationship with Morphological Differentiaion



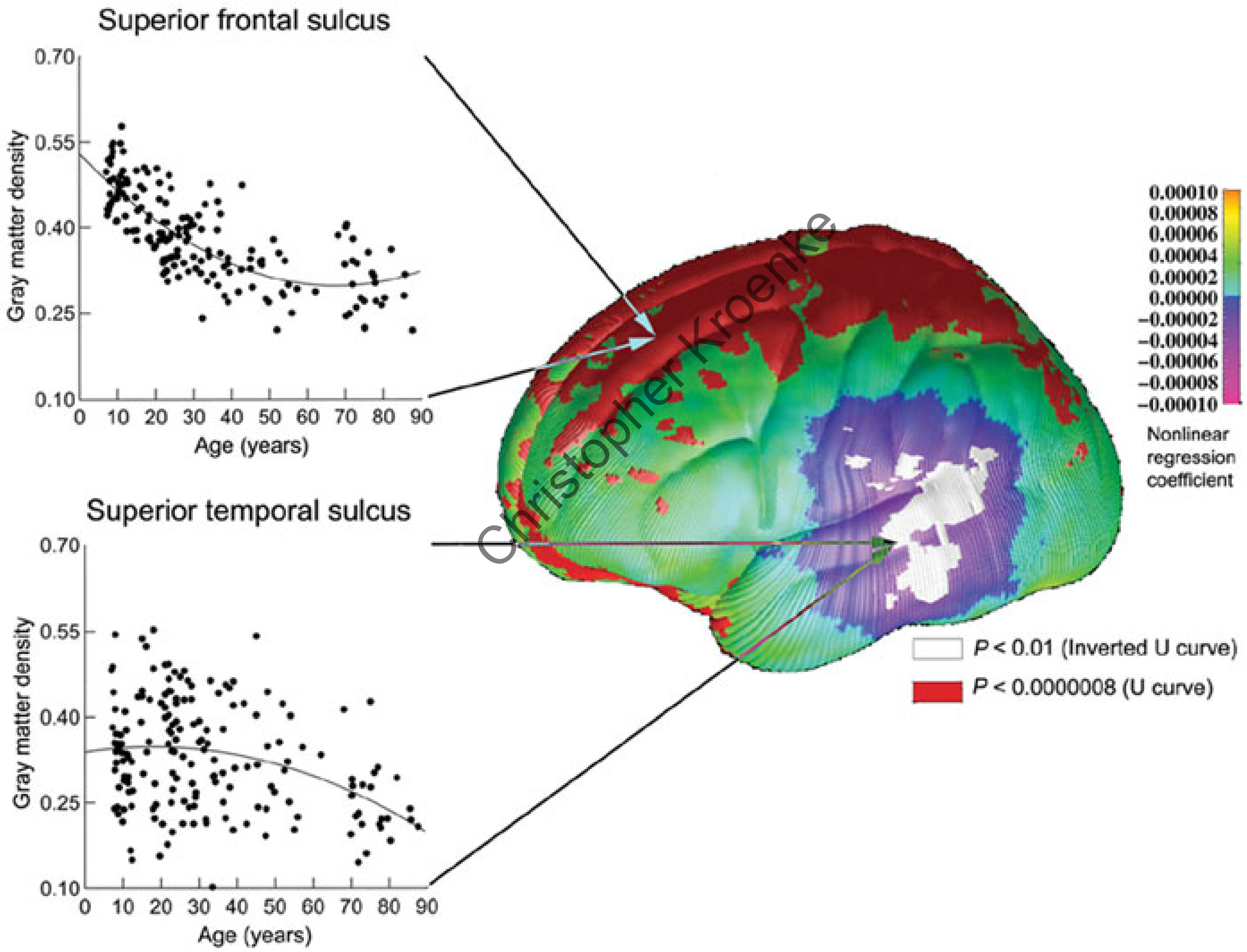
Zervas and Walkley, (1999) *J. Comp. Neurol.* 330:48-64

Synaptic Pruning in Frontal Human Cerebral Cortex



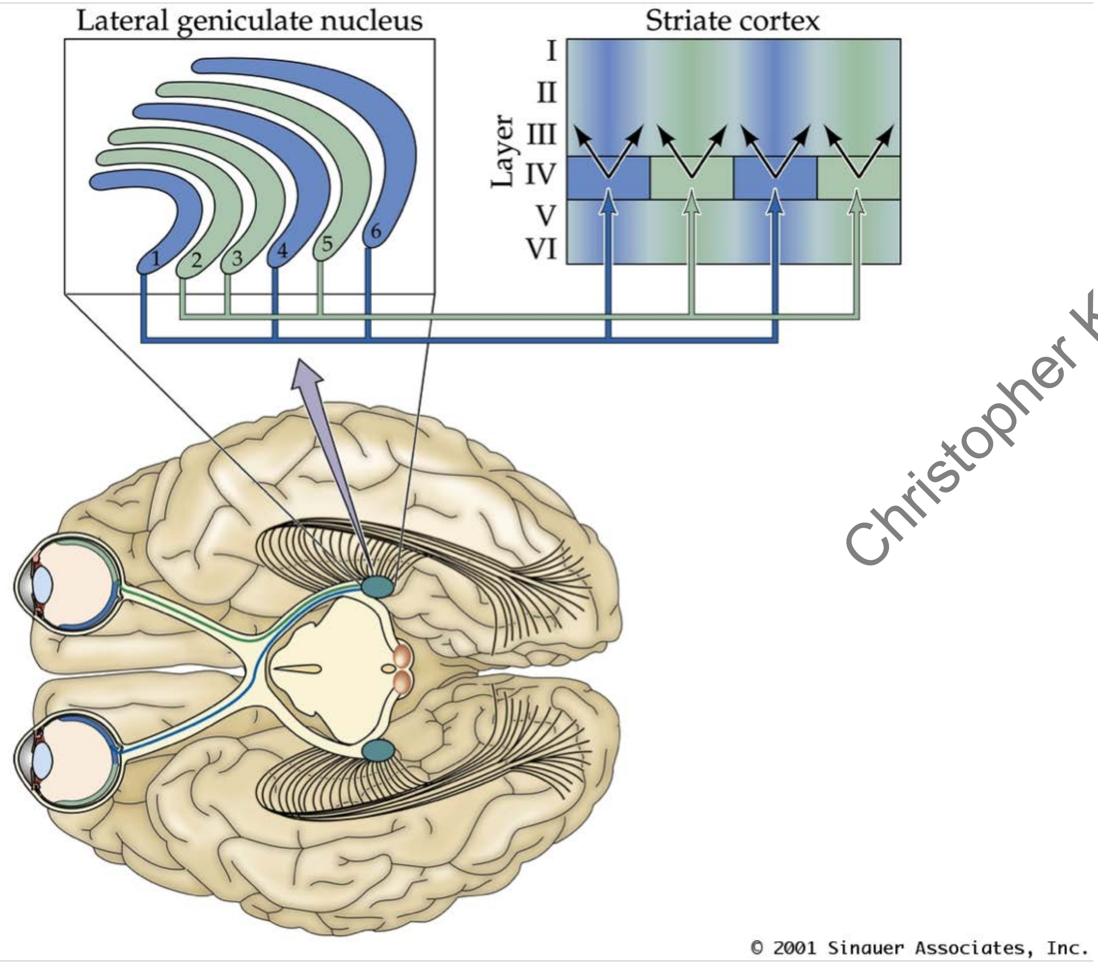
Huttenlocher et al.

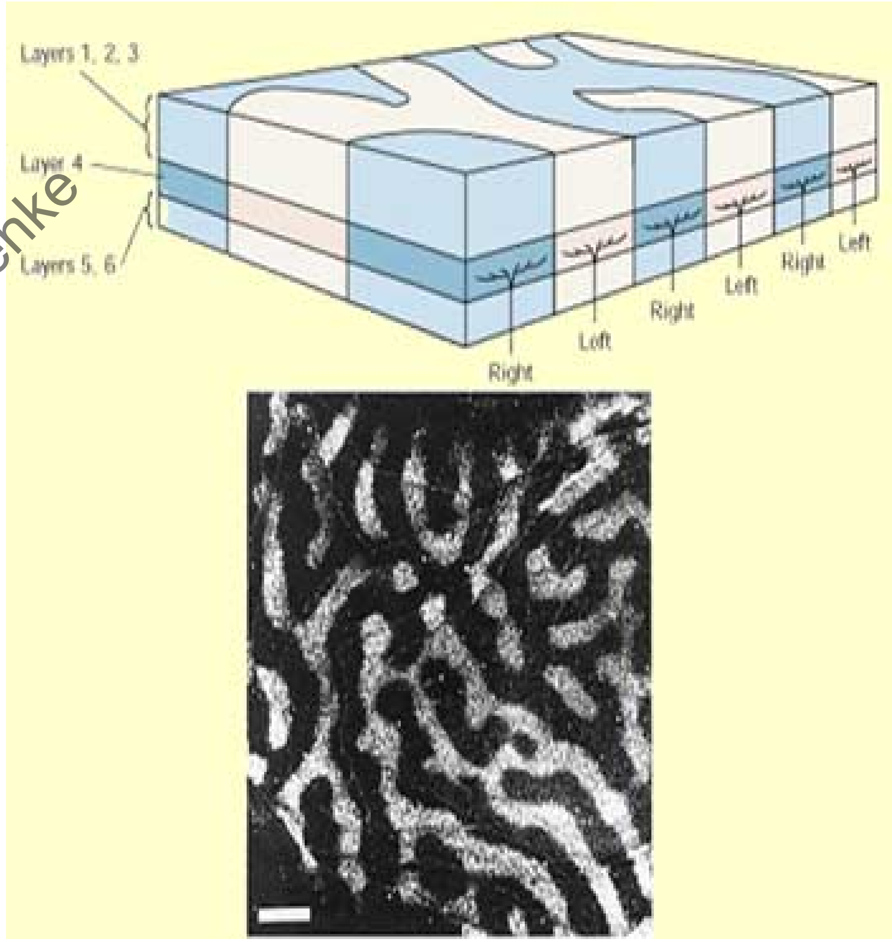
Cerebral Cortical Thickness Changes Throughout Human Lifespan



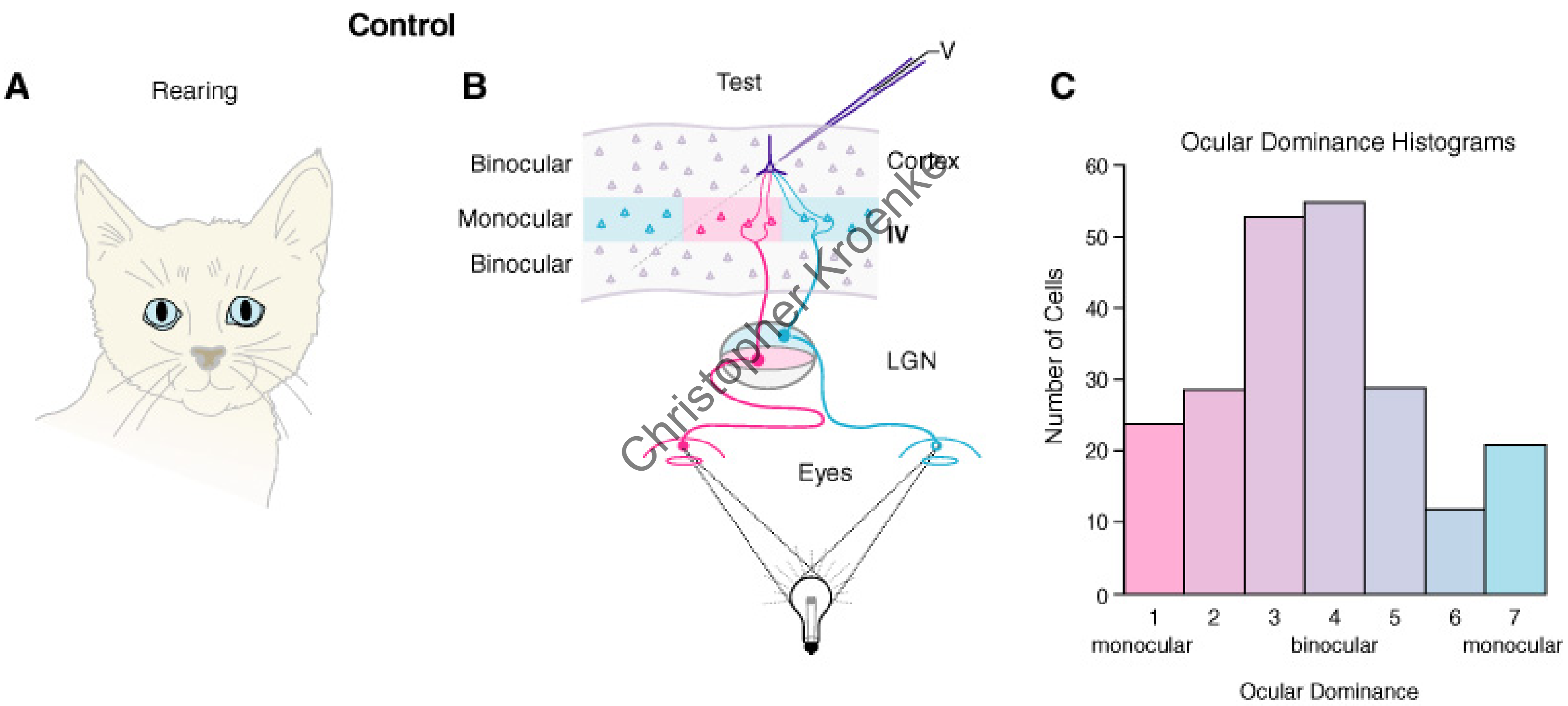
Sowell, Thompson, Toga, et al.

Visual system: Retina -> Thalamus -> Cortex



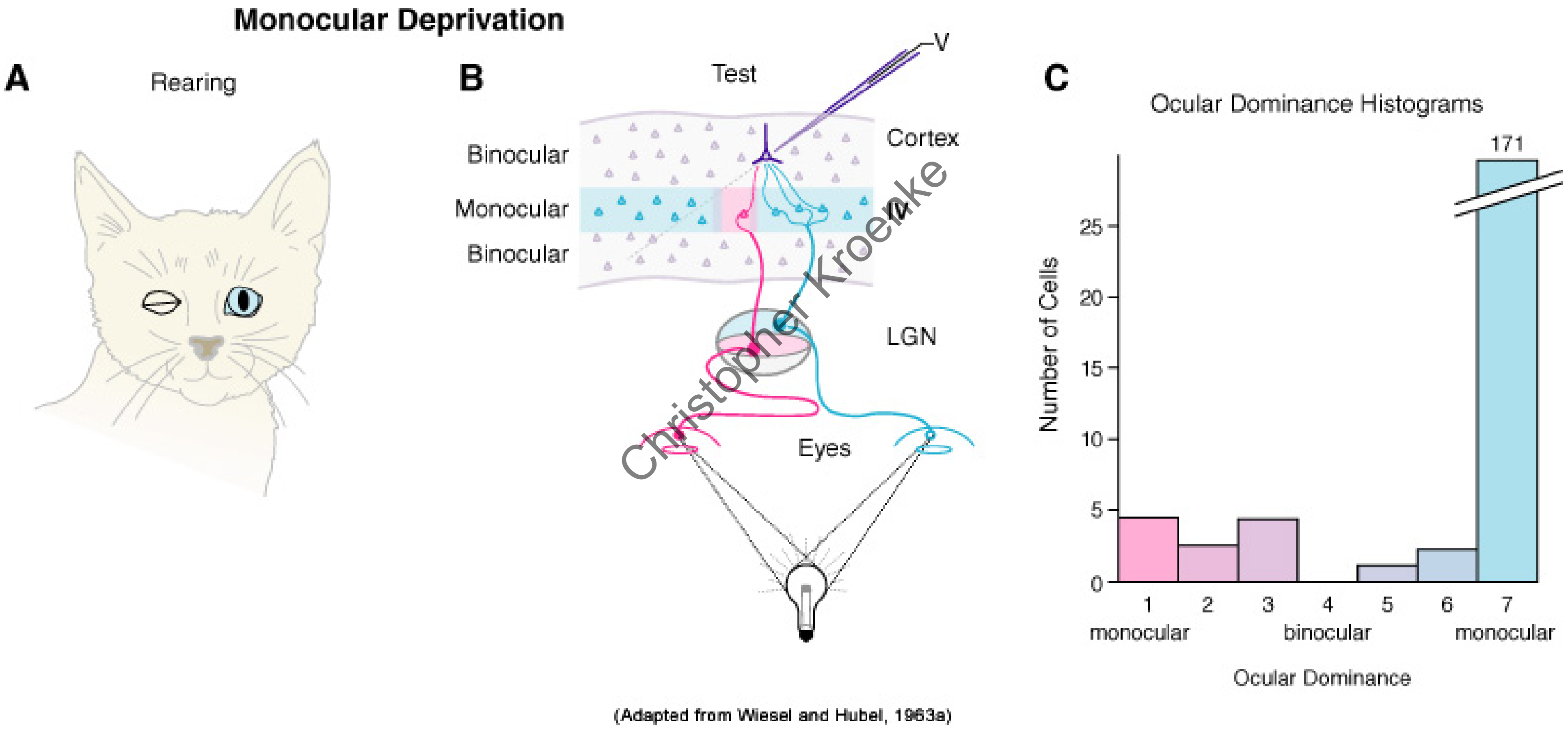


Ocular Dominance Revealed by Electrophysiology

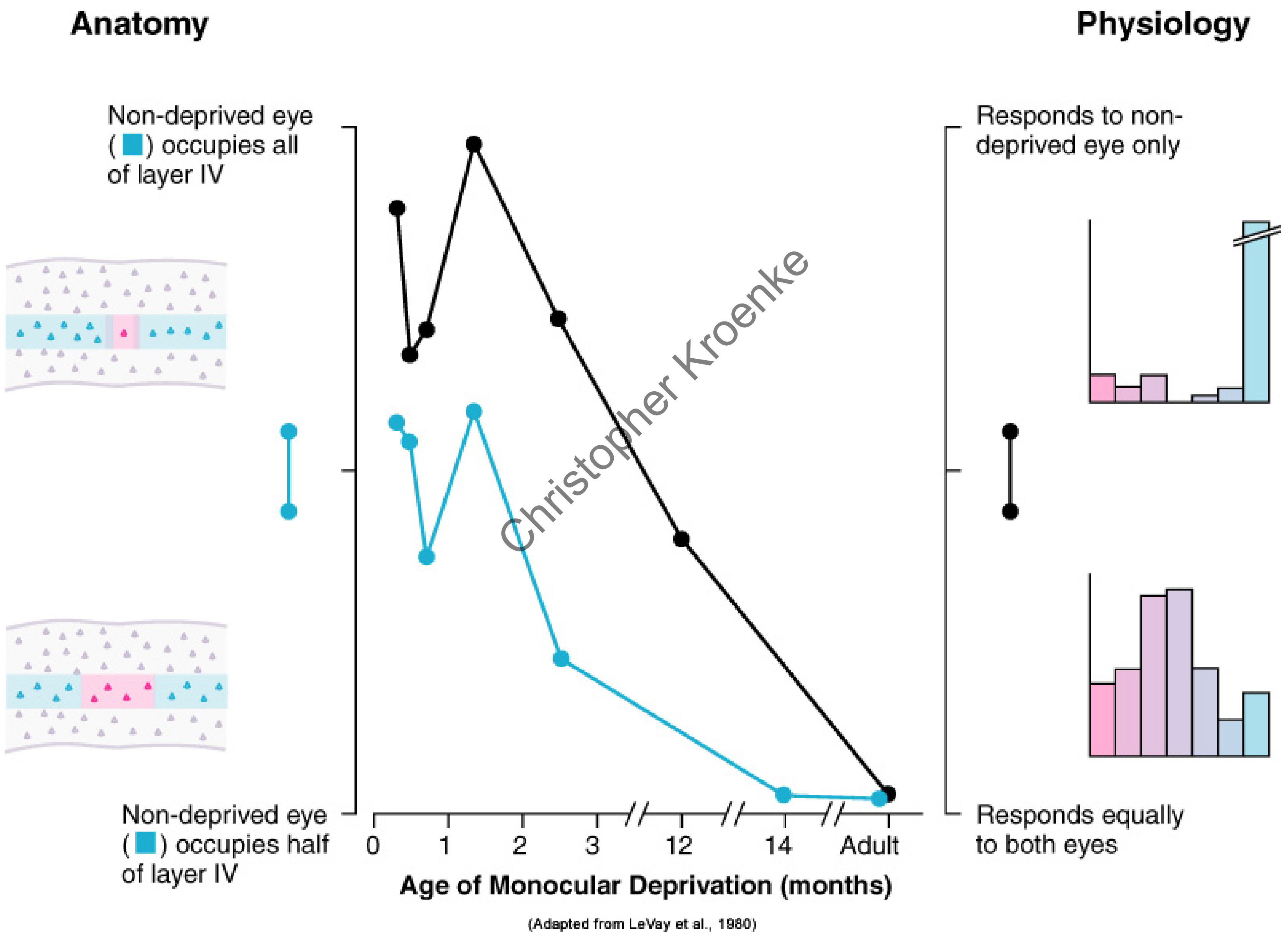


(Adapted from Hubel and Wiesel, 1962)

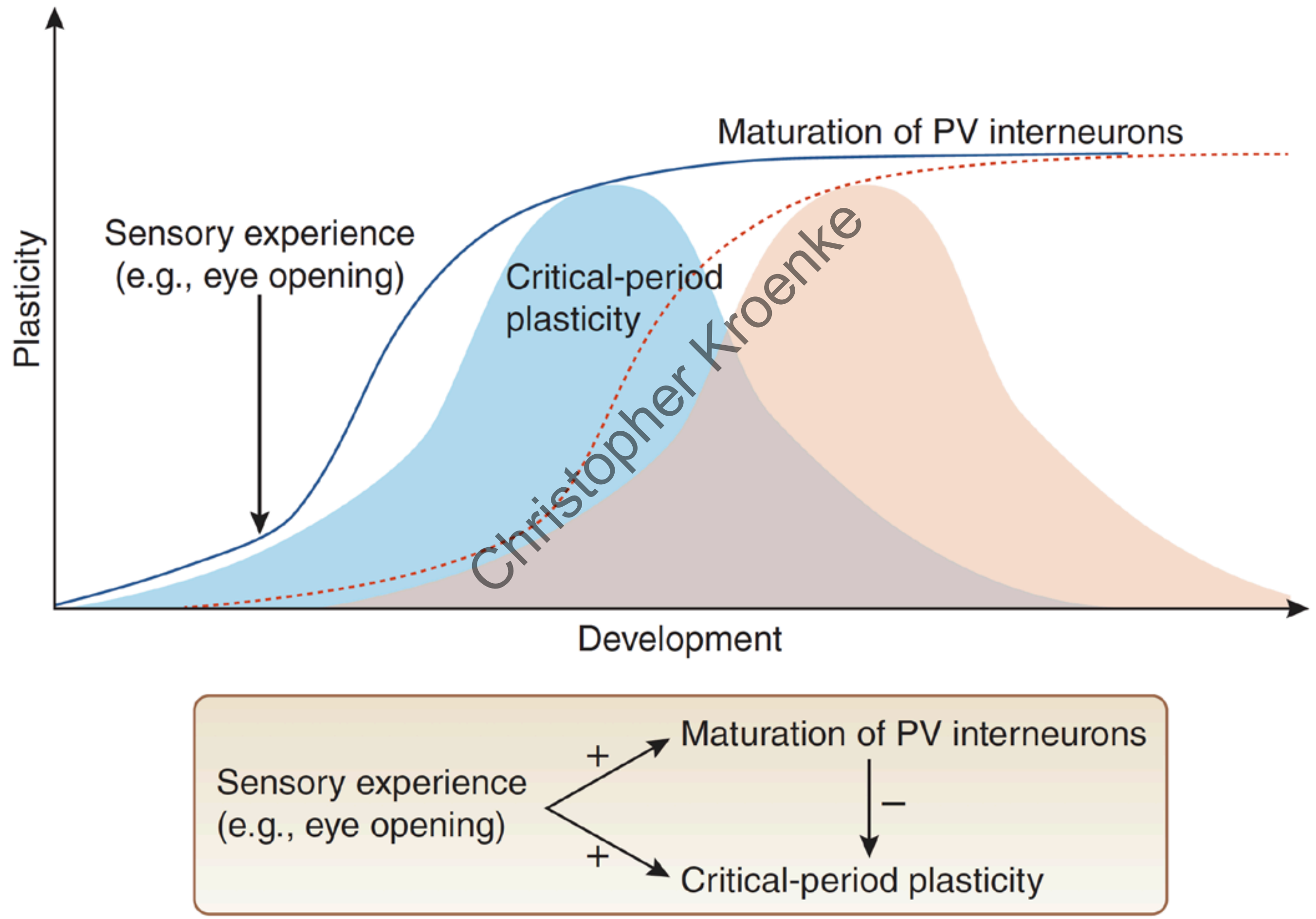
Monocular Deprivation: Cortex Responds to Non-Deprived Eye



Critical Period for Normal Ocular Dominance



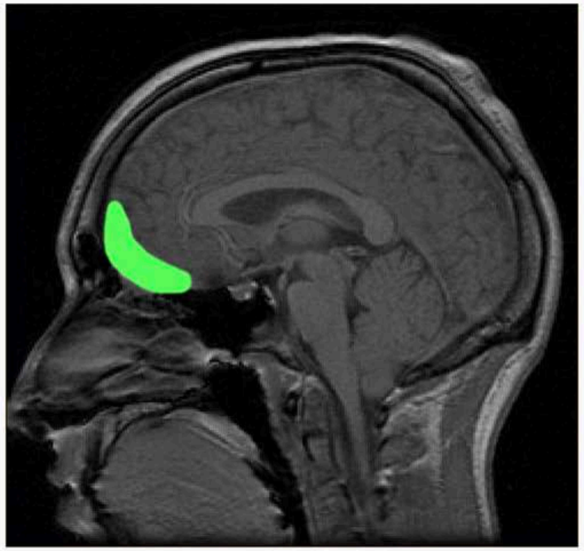
Critical Period – An Interval of Development in which Function at Maturity Depends on External Stimuli



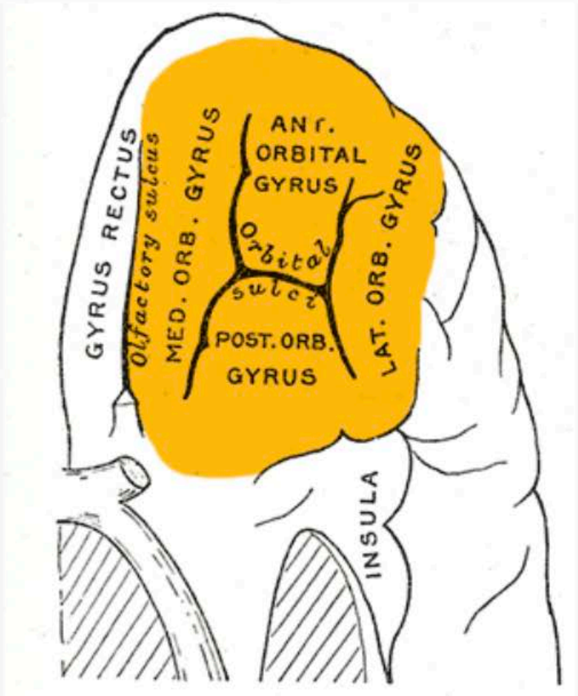
Marin, *Nat. Med.* 22:1229-1238 (2016)

Interference with Earlier Developmental Processes

Orbitofrontal cortex

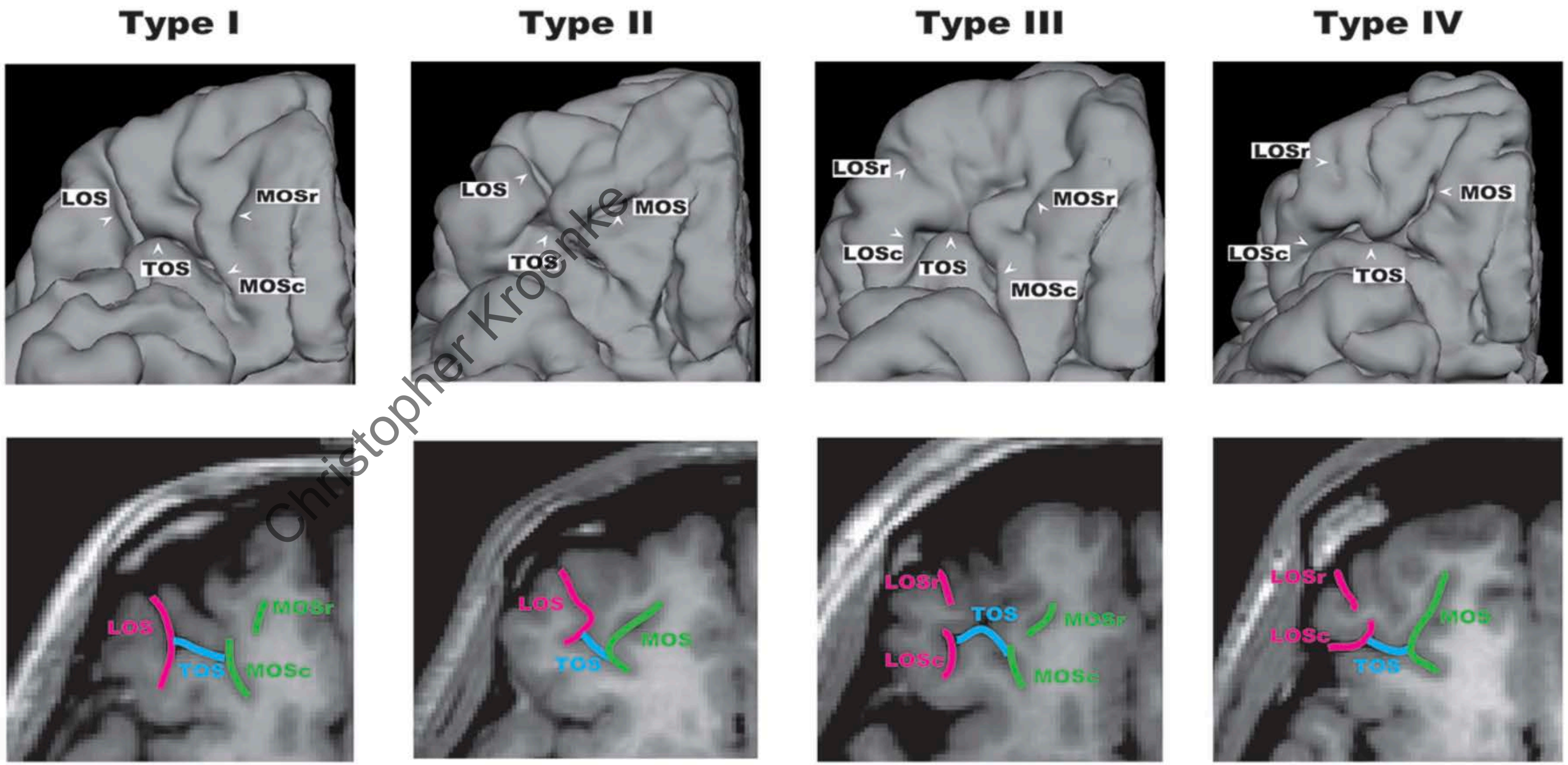


Approximate location of the OFC shown on a sagittal MRI



Orbital surface of left frontal lobe.

Four Folding Variants in the Human OFC



Nakamura et al., *Clin. EEG and Neurosci.* 51:275-284 (2020)

Findings from 26 Studies Comparing Sz, ASD to Controls

Type I pattern represented with greater frequency in controls

Type III pattern represented with greater frequency in Sz and ASD

Table 2. Summary Table of Major Findings of Previous Studies.

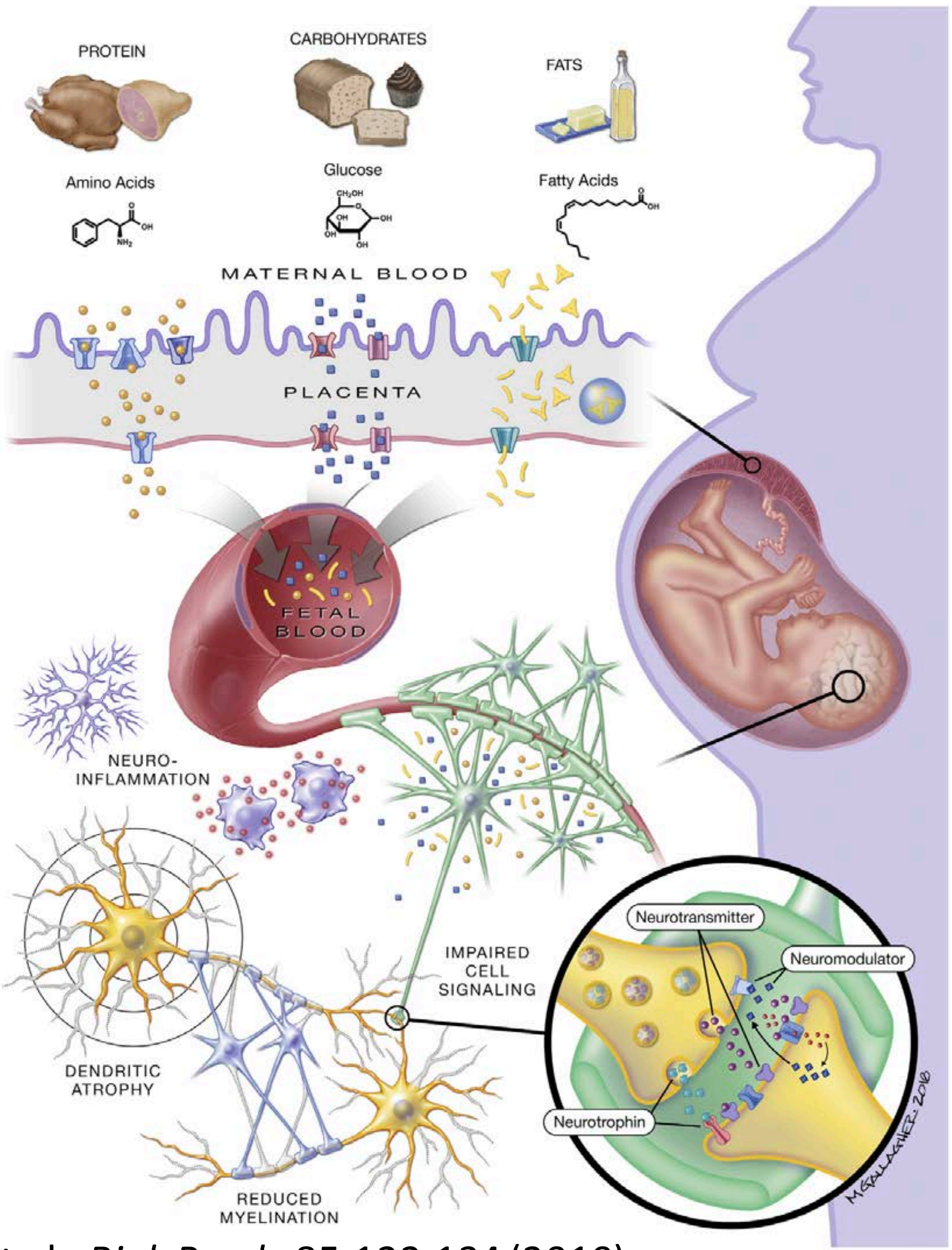
Study	Diagnosis	Results (Group Difference)
Chiavaras and Petrides (2000)	N/A	Type I was most common and type III was least common variant (HC).
Nakamura et al (2007)	Chronic Sz	Sz showed increased type III and decreased type I in right OFC dominant.
Nakamura et al (2008)	Chronic Sz	
Chakirova et al (2010)	High genetic risk of Sz	Difference between high-risk transitioned and nontransitioned (decreased type I and increased type III).
	First episode Sz	Difference between FESz and HC (decreased type I and increased type III).
Roppongi et al (2010)	Panic disorder	No difference
Uehara-Aoyama et al (2011)	Chronic Sz	Male Sz showed increased type III but not in female Sz.
Whittle et al (2014)	N/A	N/A
Watanabe et al (2014)	ASD	ASD showed increased type III in bilateral OFC. Fewer POS in ASD.
Bartholomeusz et al (2013)	First episode Sz	In right OFC, Sz showed decreased type I and increased type II. Fewer IOS in left OFC of Sz.
Takahashi et al (2014)	Sz	
Lavoie et al (2014)	UHR transitioned	UHR transitioned showed reduced type I in right OFC. UHR transitioned showed fewer IOS and POS.
	UHR nontransitioned	
Takahashi et al (2015)	Sz	
Ganella et al (2015)	EP/ELBW	In left OFC, EP/ELBW showed increased type II and fewer IOS and increased POS.
Nishikawa et al (2016)	Sz	Sz showed increased type III and decreased type I. SPD did not differ from HC. Sz and SPD showed shallower olfactory sulcus.
	Schizotypal (SPD)	
Cropley et al (2015)	Chronic Sz	Sz showed increased type II.
Yoshimi et al (2016)	Sz	Sz showed increased type III.
Takahashi et al (2016)	Sz	Sz and SPD showed fewer number of IOS and POS.
	Schizotypal (SPD)	
Zhang et al (2016)	N/A	N/A
Takahashi et al (2017)	Deficit Sz	Deficit Sz showed decreased type I, increased type III in right OFC, and fewer POS as compared with HC.
	Nondeficit Sz	
Isomura et al (2017)	Sz	Female Sz showed decreased type I and increased type II.
Chye et al (2017)	CB user	No difference
Patti et al (2017)	Sz	Sz and BP showed increased type III/IV and reduced type I in left OFC.
	Bipolar disorder	
	ADHD	ADHD group showed a trend-level difference from HC.
Nakamura et al (2018)	ARMS	ARMS as a whole had fewer number of IOS and POS. No difference in H-shaped sulci.
Delahoy et al (2019)	OCD	No difference
Takahashi et al (2019)	ARMS	Both ARMS and Sz showed increased type III in right OFC and fewer IOS and POS.
	Sz	
Li et al (2019)	PG	PG showed increased type II in bilateral OFC.

Nakamura et al., *Clin. EEG and Neurosci.* 51:275-284 (2020)

- Diet
- Stress

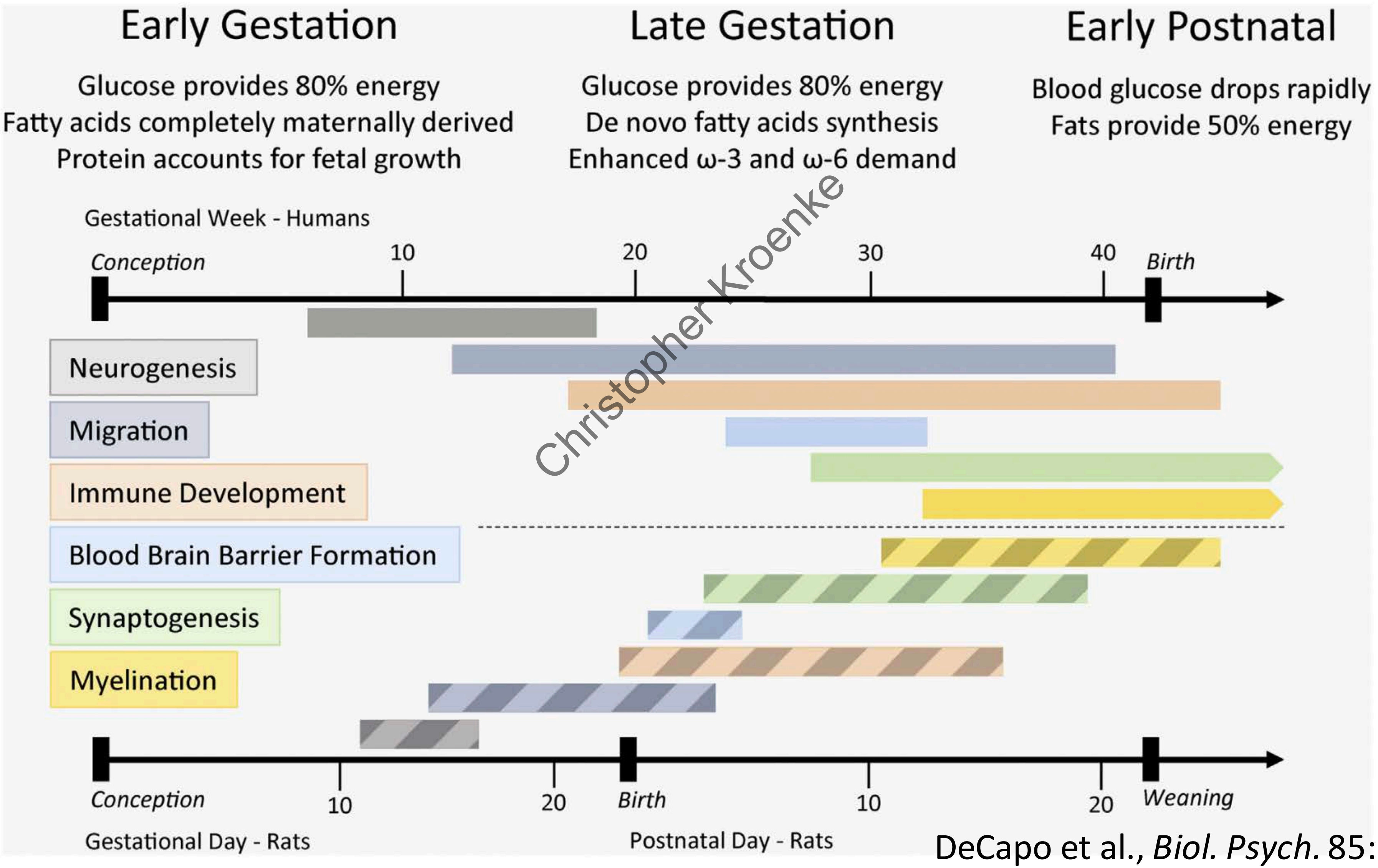
Placental Dysfunction

Neurodevelopmental Disorder Risk



DeCapo et al., *Biol. Psych.* 85:122-134 (2019)

Animal Model Studies are Critical for Understanding Biological Mechanisms



DeCapo et al., *Biol. Psych.* 85:122-134 (2019)

Maternal Obesity Linked to Brain Developmental and Functional Impairments

- Fetal Brain Inflammation/Activated Microglia
- Synaptic Development (eg. reduced spine density)
- Specific Effects on Neuromodulatory Circuits
- Accumulating Evidence Implicates Role of Placenta

Shook et al., *Prenatal Diagnosis* 40:1126-1137 (2020)

Conclusions

- Protracted development of the CNS renders the brain vulnerable to developmental perturbations
- Critical periods for CNS developmental plasticity may provide insights for understanding plasticity of other organs in DOHaD contexts
- Increasing evidence supports a role of the intrauterine environment in neurodevelopmental/neuropsychiatric disorders
- Current understanding primarily guided by observations of correlations, but indicate the importance of placental function