Developmental Neurobiology - Cortical Development
Week 3

Monday May 18th

Lecture 3: Brain disease modelling for understanding neurodevelopmental disorders in humans.

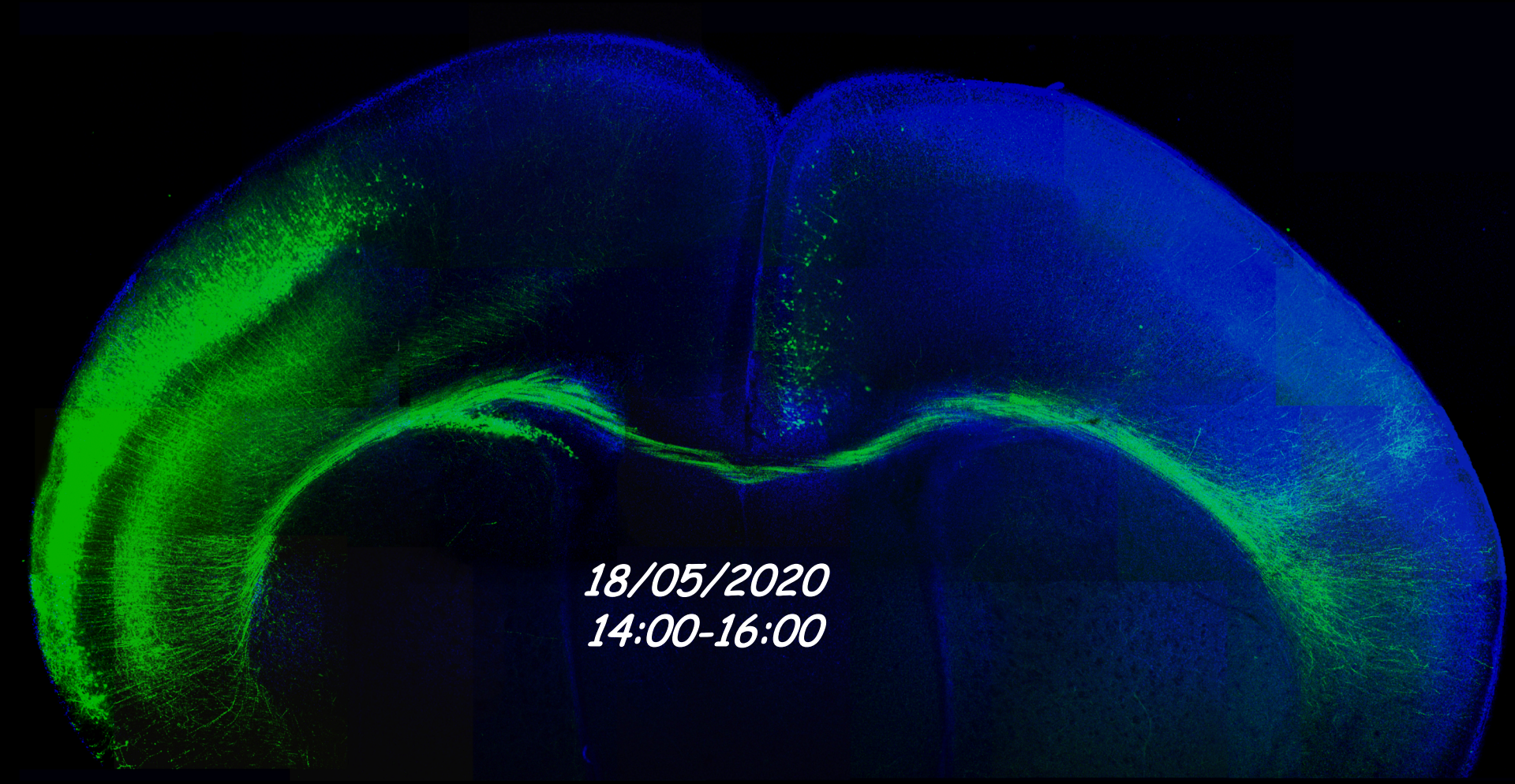
14:00-16:00 – ***Lecture and questions***

Tuesday May 19th

11:00-13:00 – **Student presentation on novel technologies**
(5 groups - 2-3 per group → 15-20' per group + questions)

Task for students:
Work on the fellowship proposal

Brain disease modelling for understanding neurodevelopmental disorders



18/05/2020
14:00-16:00

Michèle Studer

Neurodevelopmental disorders (or Intellectual Developmental Disorders -IDD) are impairments of the growth and development of the brain:

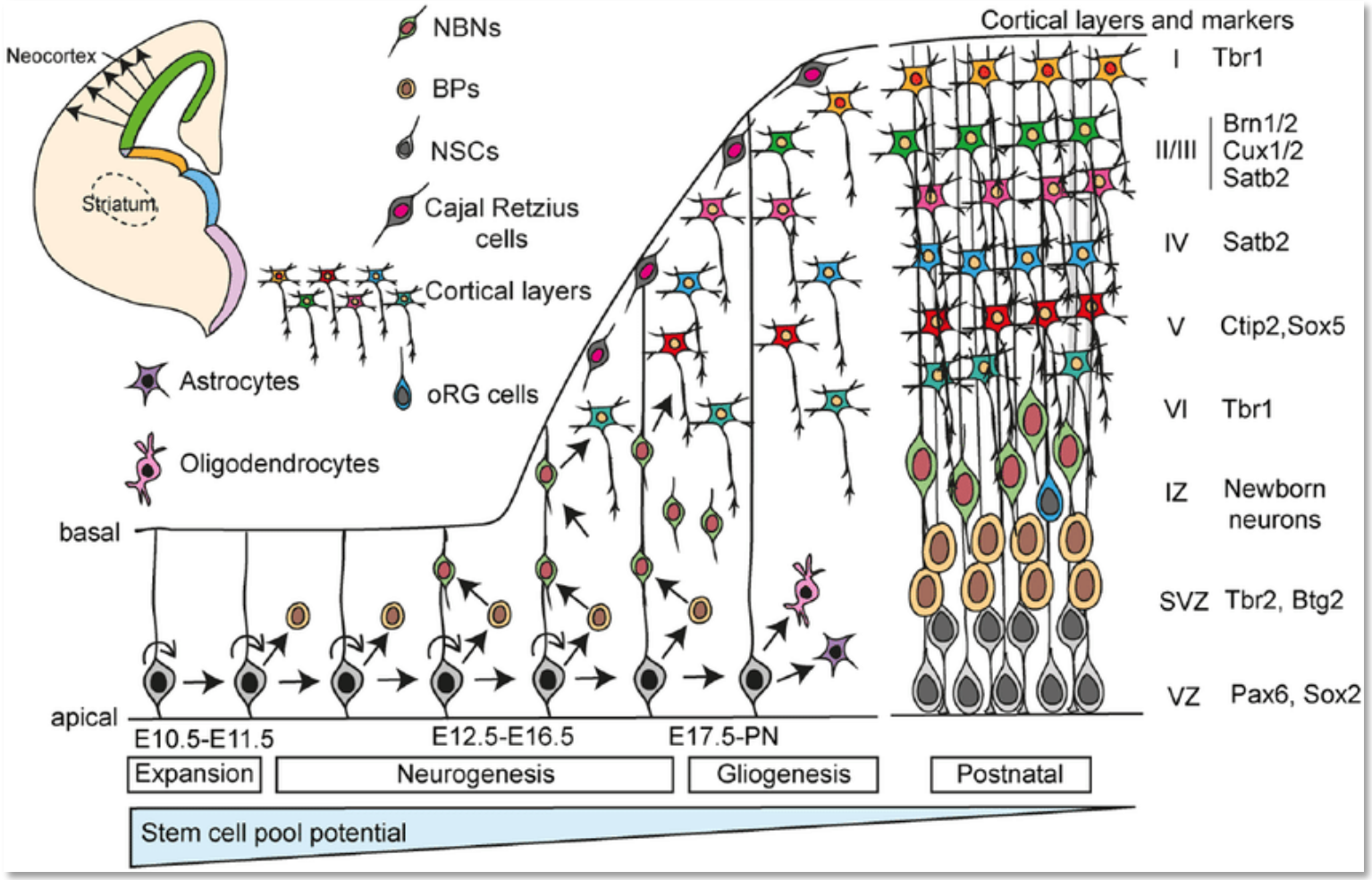
- *affects emotion, learning ability and memory;*
- *communication, speech and language;*
- *unfolds in infancy and childhood.*

Neurodevelopmental disorders are associated with mental, emotional, physical, and economic burden to individuals, families and society in general.

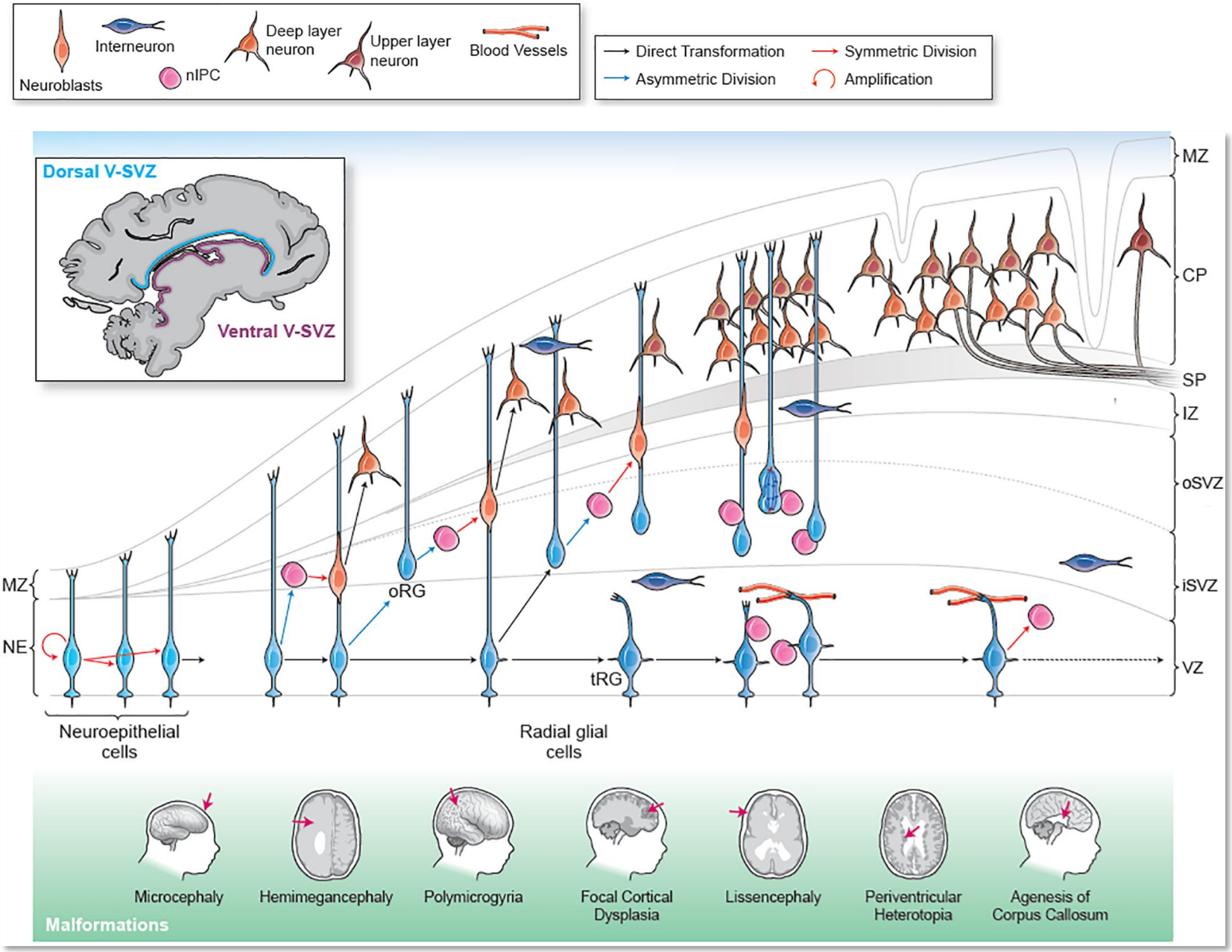
- *Chromosomal disorders: Down syndrome, etc.*
- *Genetic disorders: autism spectrum disorders (ASD), microcephaly, lissencephaly, etc*
- *Traumatic brain injury*
- *Fetal alcohol spectrum disorder*
- *Viral infections, etc*

Neurodevelopmental disorders result from the disruption of normal cortical development processes.

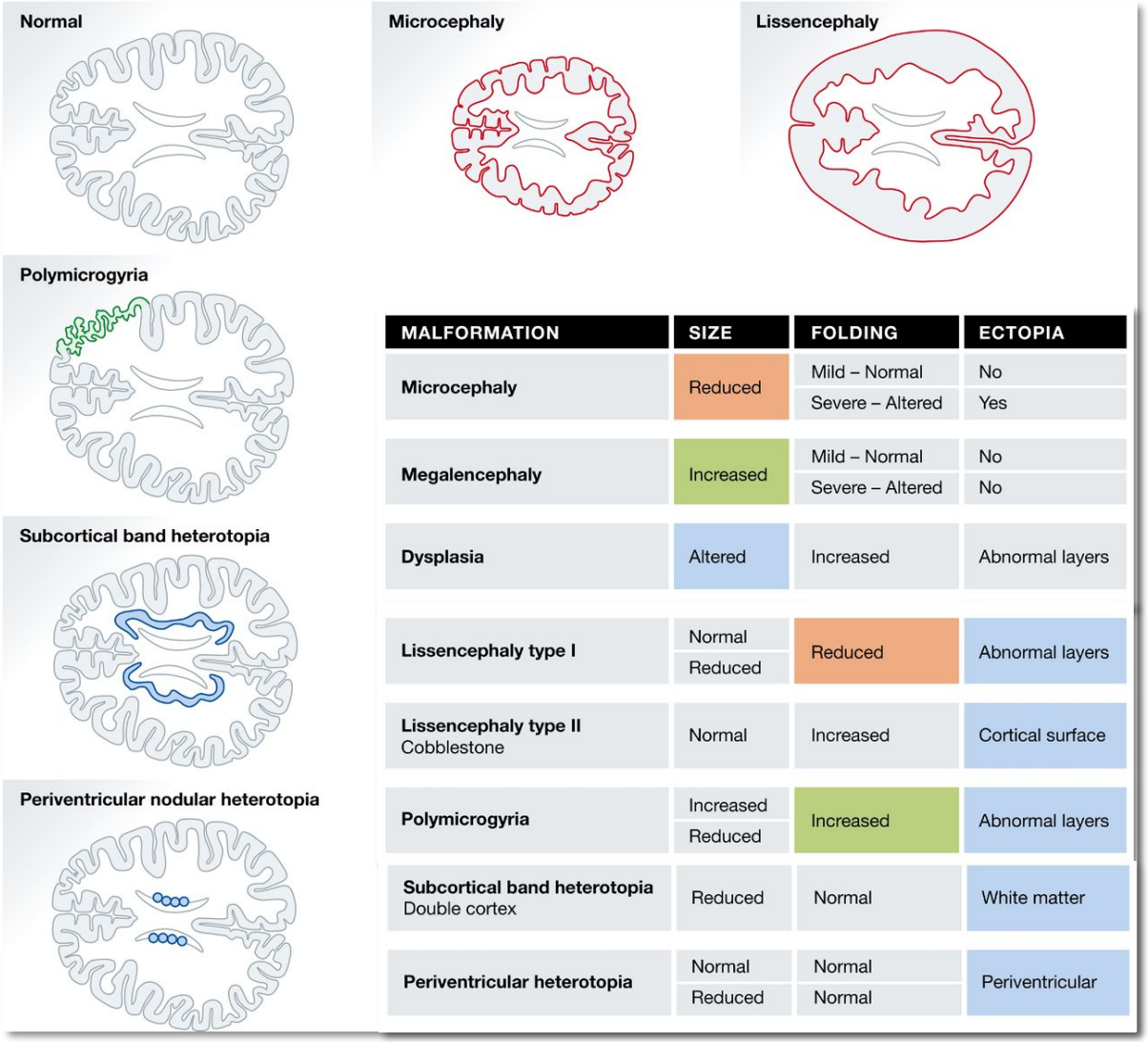
Different steps in mammalian corticogenesis (radial organization)



Human cortical development and stages of malformation



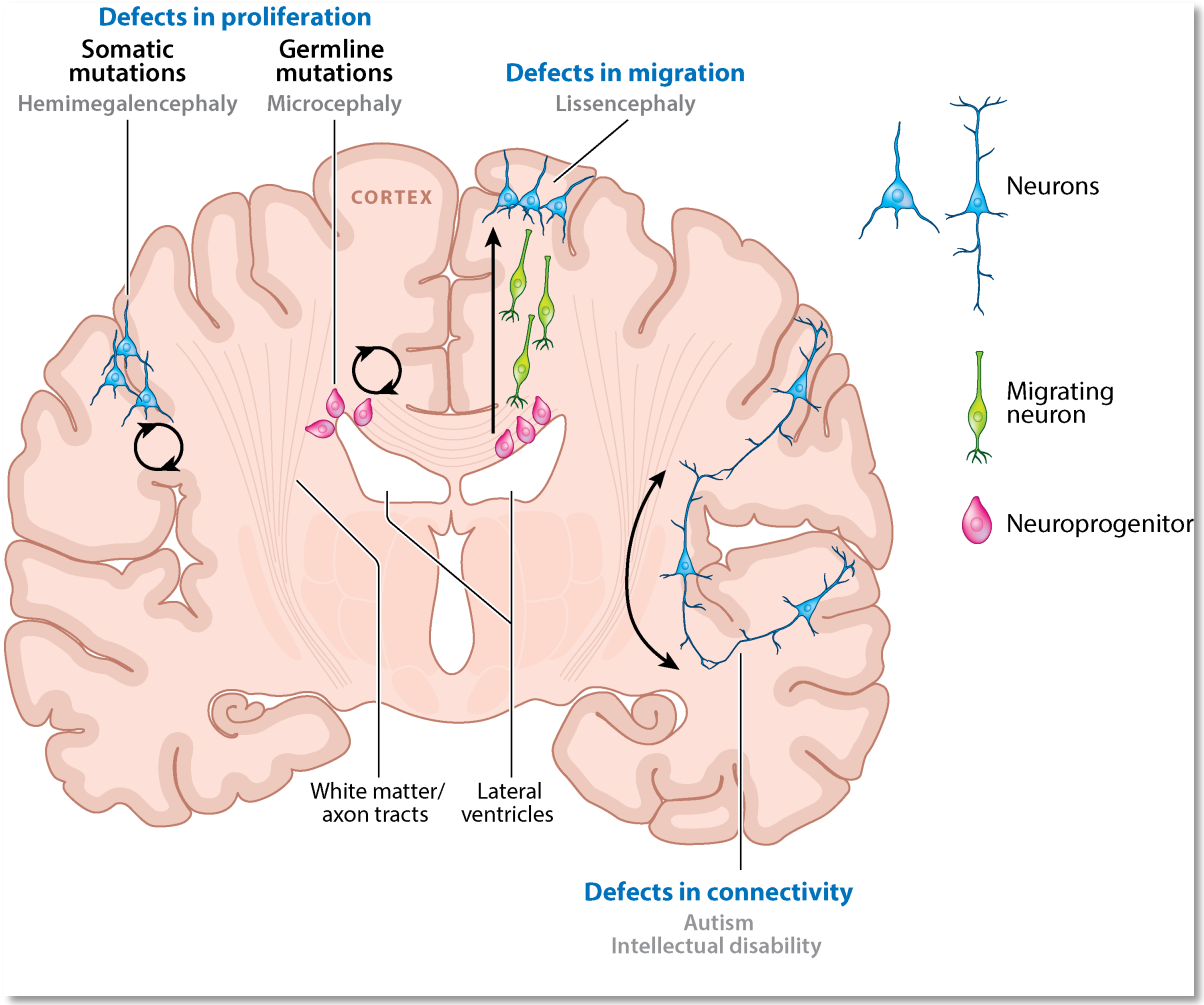
Human cortical malformations and their phenotypic manifestations



MALFORMATION	SIZE	FOLDING	ECTOPIA
Microcephaly	Reduced	Mild – Normal Severe – Altered	No Yes
Megalencephaly	Increased	Mild – Normal Severe – Altered	No No
Dysplasia	Altered	Increased	Abnormal layers
Lissencephaly type I	Normal Reduced	Reduced	Abnormal layers
Lissencephaly type II Cobblestone	Normal	Increased	Cortical surface
Polymicrogyria	Increased Reduced	Increased	Abnormal layers
Subcortical band heterotopia Double cortex	Reduced	Normal	White matter
Periventricular heterotopia	Normal Reduced	Normal Normal	Periventricular

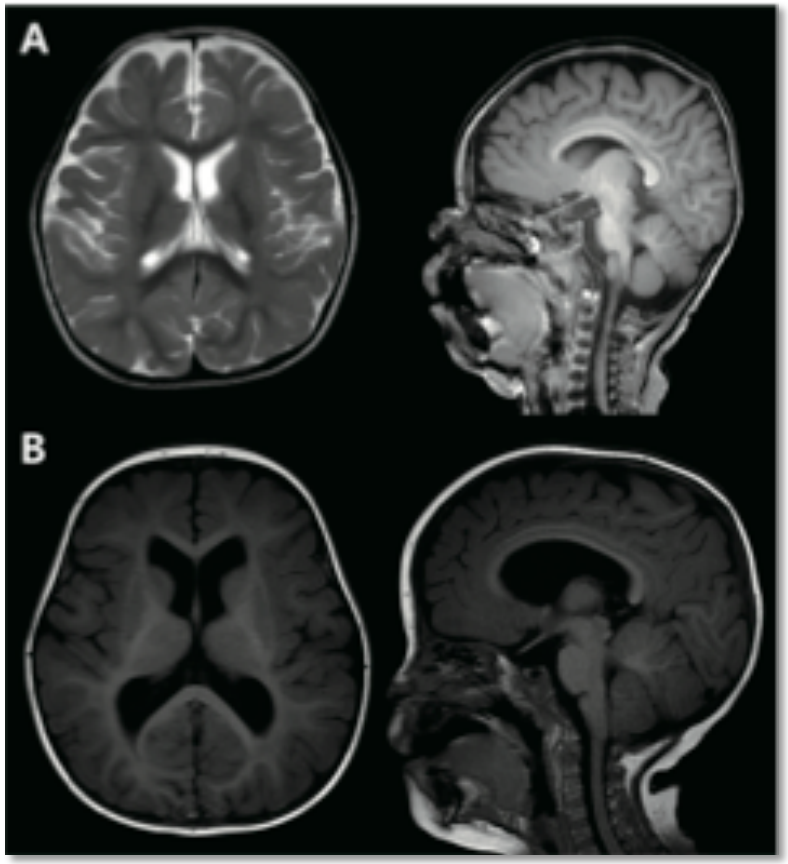
Fernández et al. EMBO J. 2016

Defects affecting different steps of neurodevelopment



Modified from Hu WF et al., 2014

Malformations of cortical development: clinical features

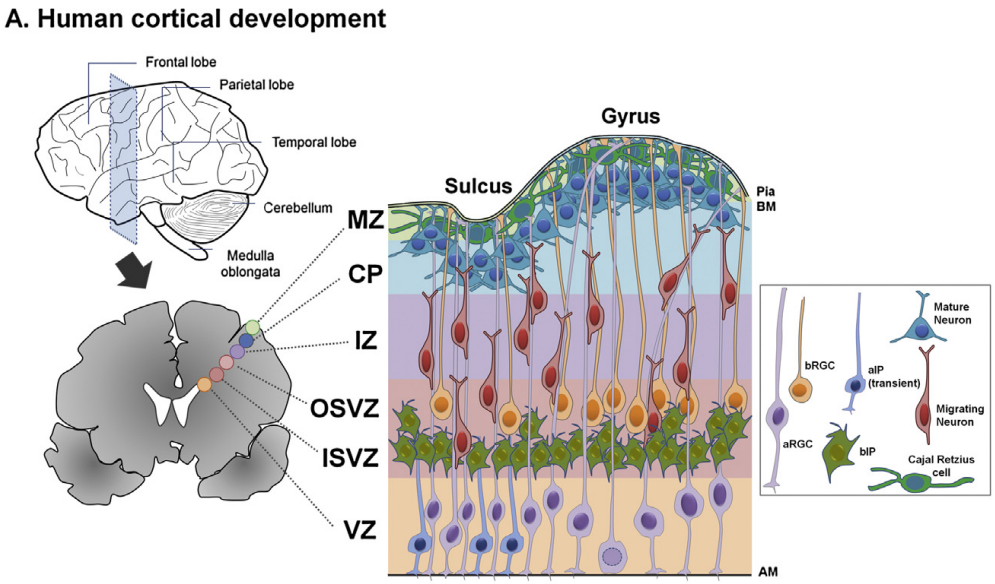


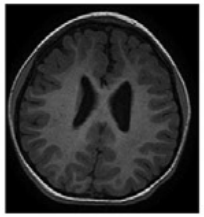
Microcephaly
(small brain)

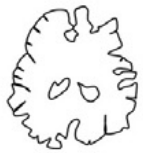
Megalencephaly
(large brain)

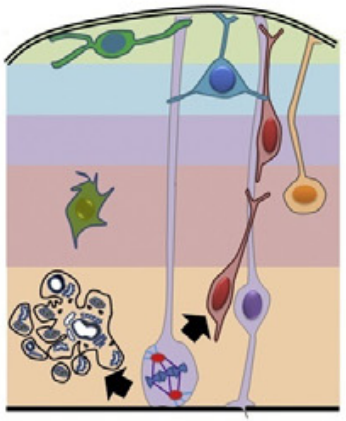
Lee, 2017

Congenital Microcephaly



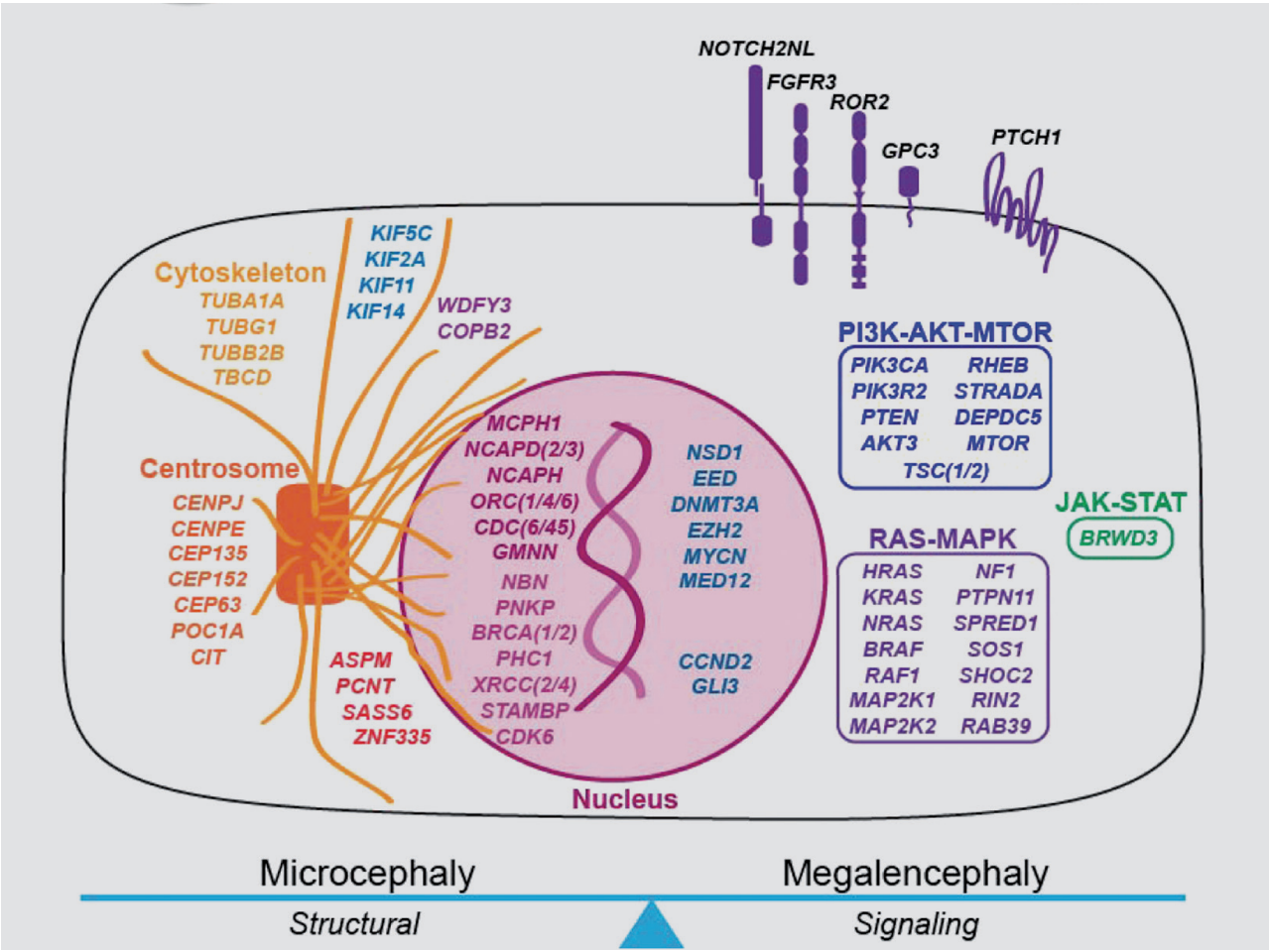






ASPM, CK5RAP2, MCPH1, CENPJ, WDR62, STIL, KNL1, CEP135, CDK6, CEP152, CEP63, KIF2A, TUBB, TUBB3, DYNC1H1, RTTN , EOMES, PAX6, RAB3GAP1, RAB3GAP2, RAB18

Cell cycle, proliferation and/or survival



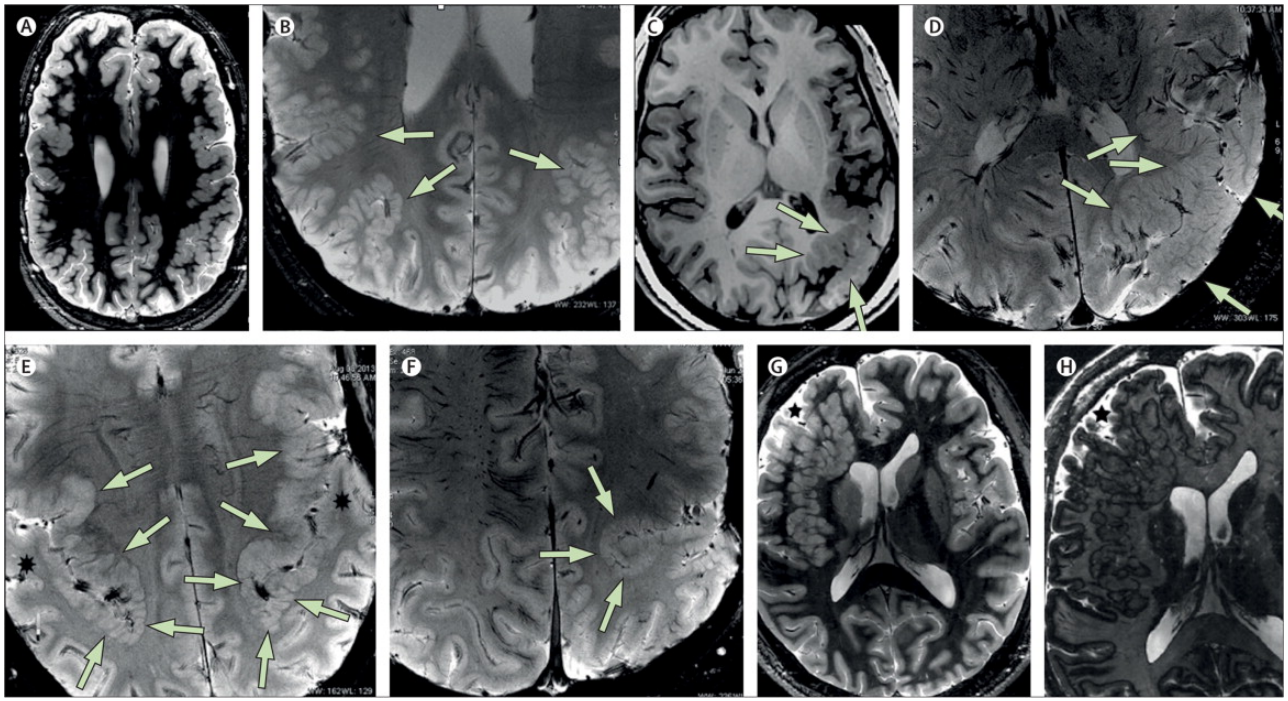
→ organization, maturation and distribution of the centrosome and spindle fibers

→ plane of division, aRG vs bRG

→ cell growth, cell cycle progression, proliferation, decreased apoptosis in oRG

Pirozzi et al., 2018

Different morphological aspects of polymicrogyria

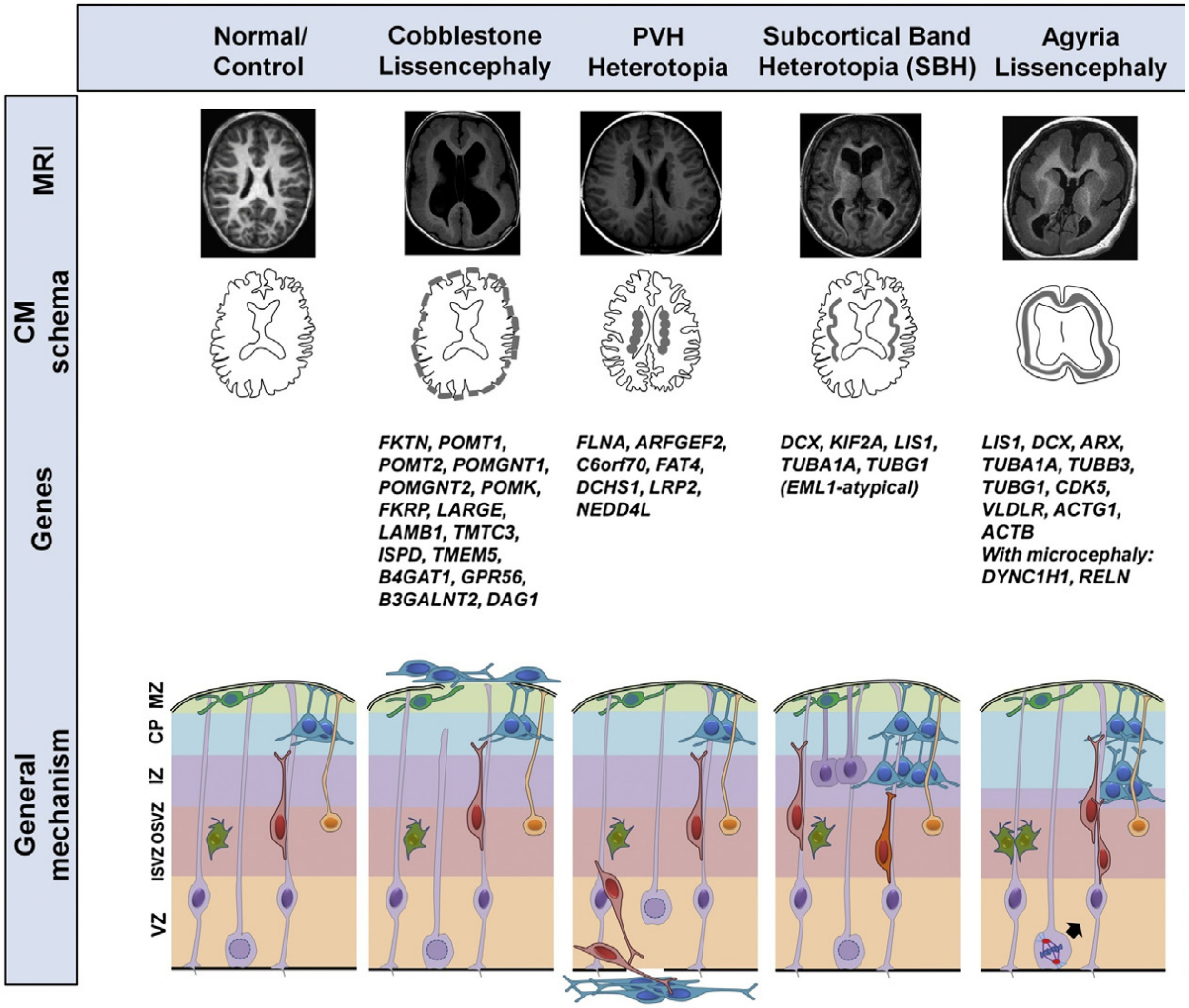


Thick and overfolded brain (small gyri and sulci)

- GPR56 (adhesion G-protein-coupled receptor) regulates pial basement membrane integrity and cortical lamination
- Growth factor signaling pathways (PTEN-AKT cascade)

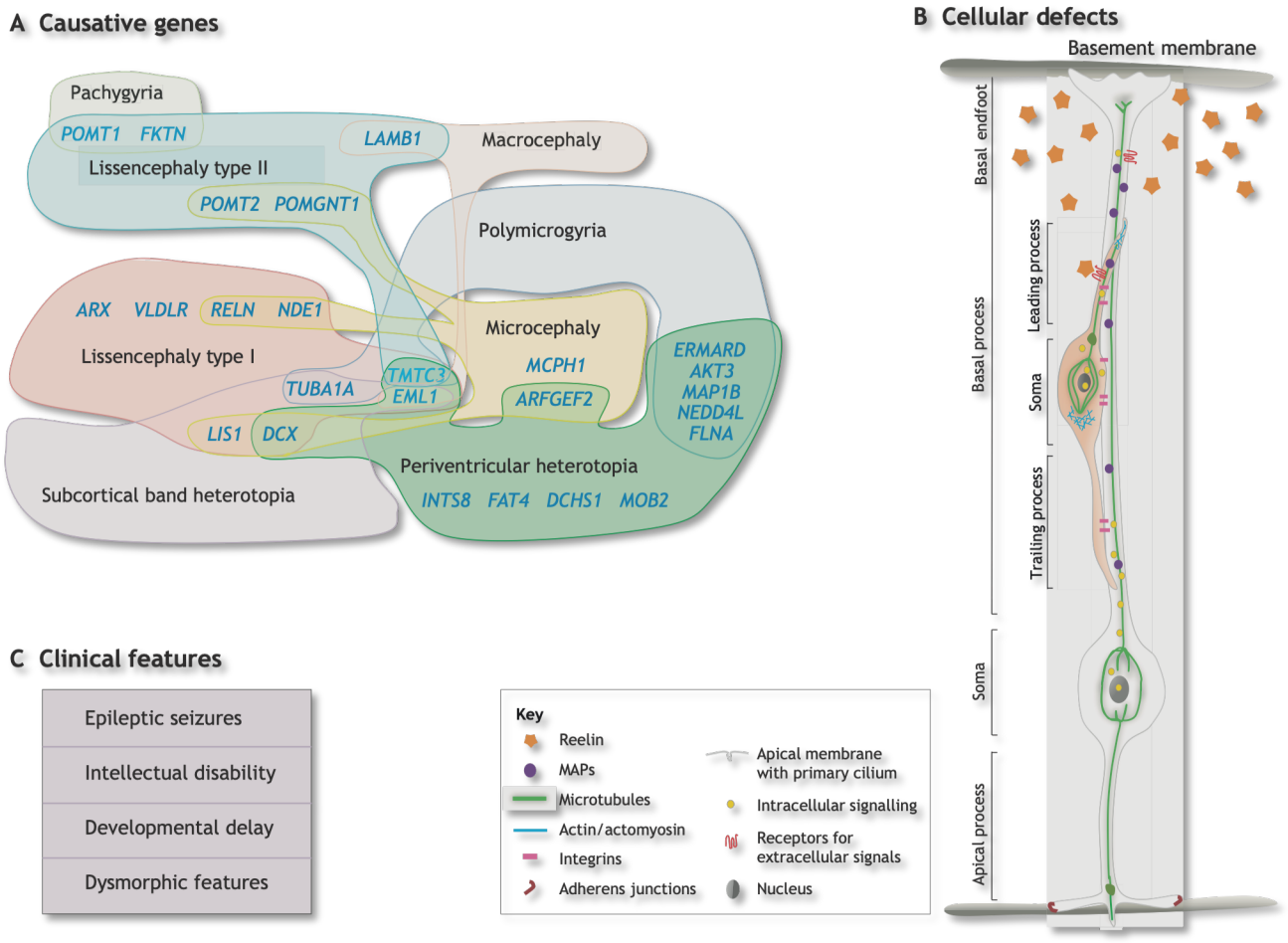
Guerrini & Dobyns, Lancet Neurol, 2014

Neuronal migration malformations



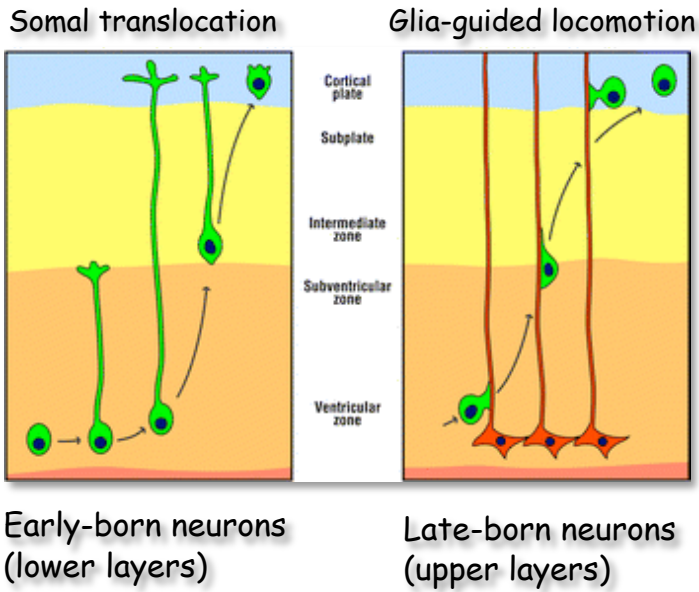
Romero et al., 2018

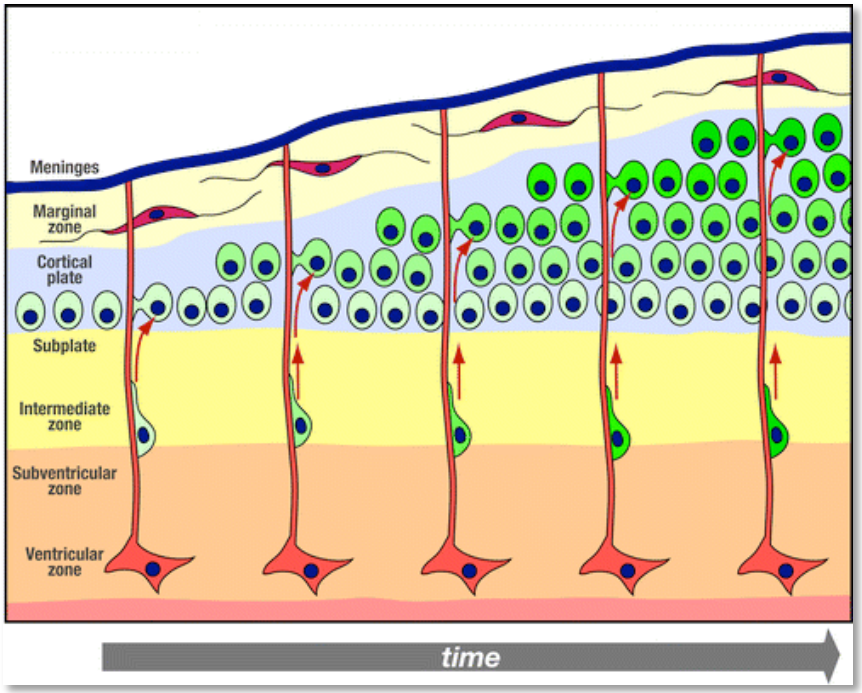
Heterogeneity of neuronal migration disorders at the genetic, cellular and clinical levels



Buchsbaum & Cappello, 2019

Radial-directed cortical neuronal migration

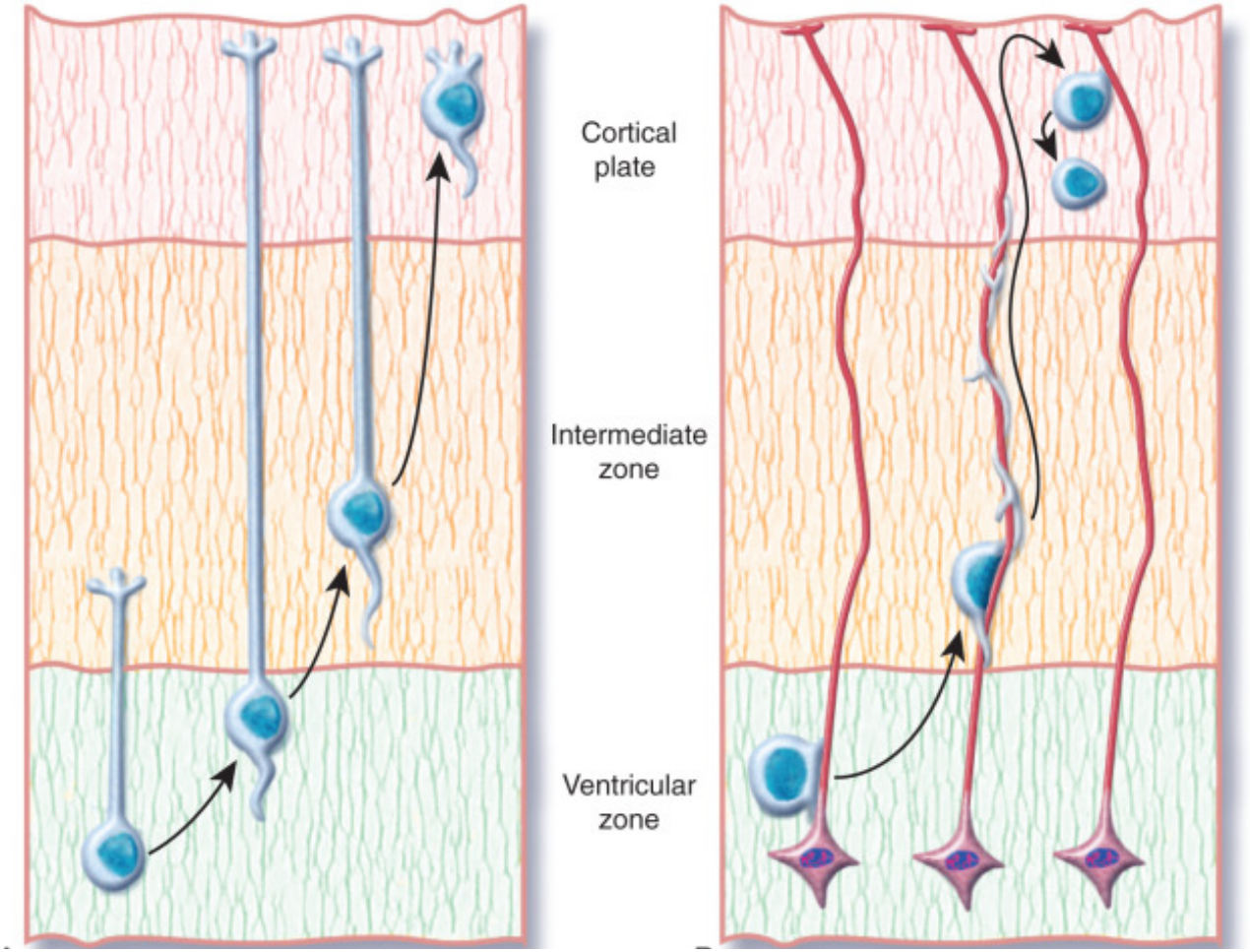


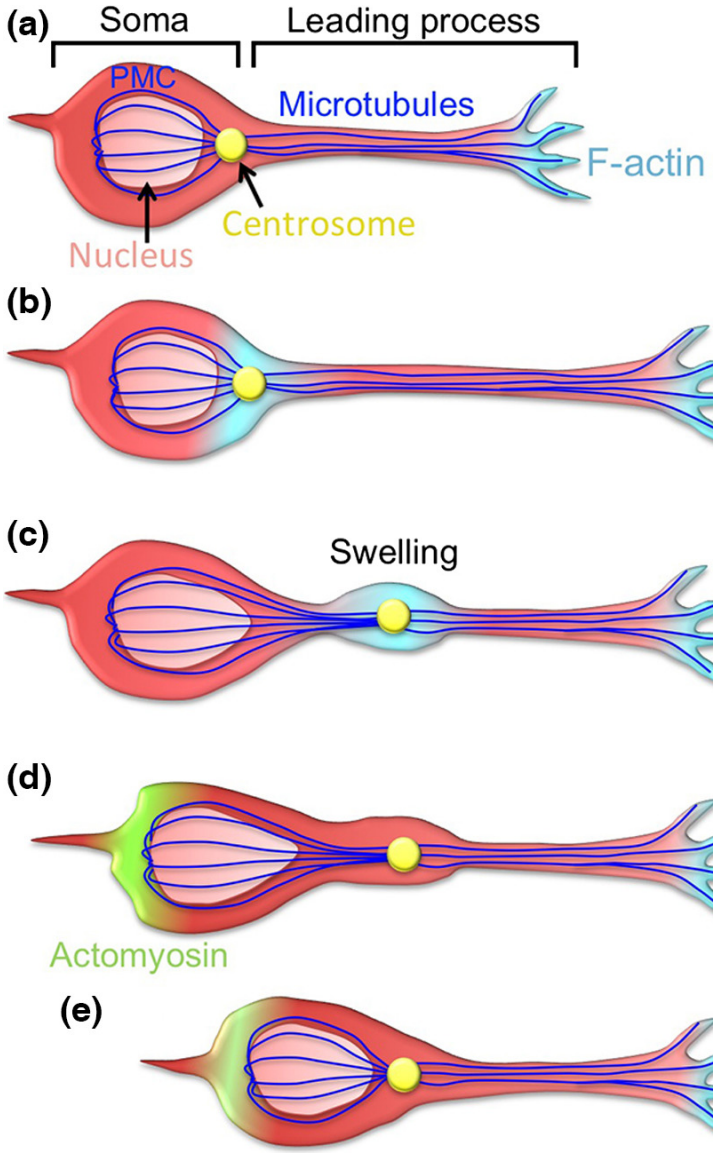


From J. Gleeson, 2004

Somal translocation

Glia-guided cell migration





Leading process extension

Actin regulation: Rac1, Vav3, WAVE1, Drebrin, Fascin

Microtubule organization: Cdk5, Dcx

Swelling formation and centrosome migration

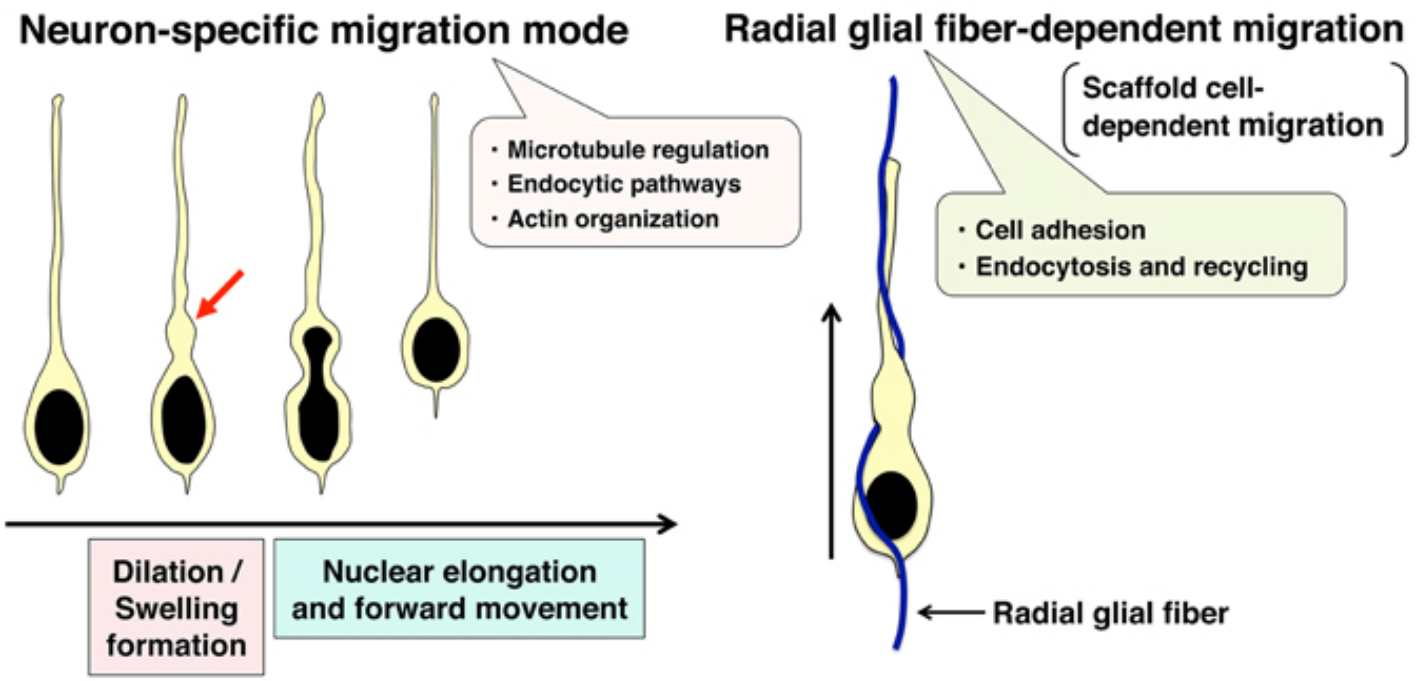
Swelling formation: RhoA, Gmip

Centrosomal migration: RhoA, mDia

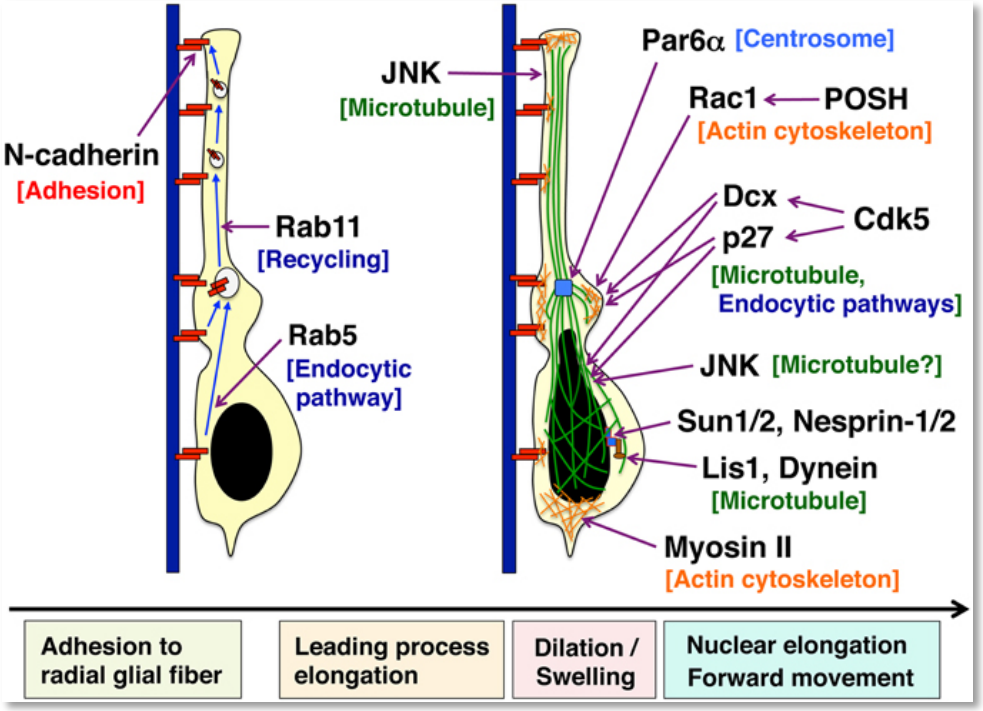
Somal translocation

Actomyosin contraction: RhoA

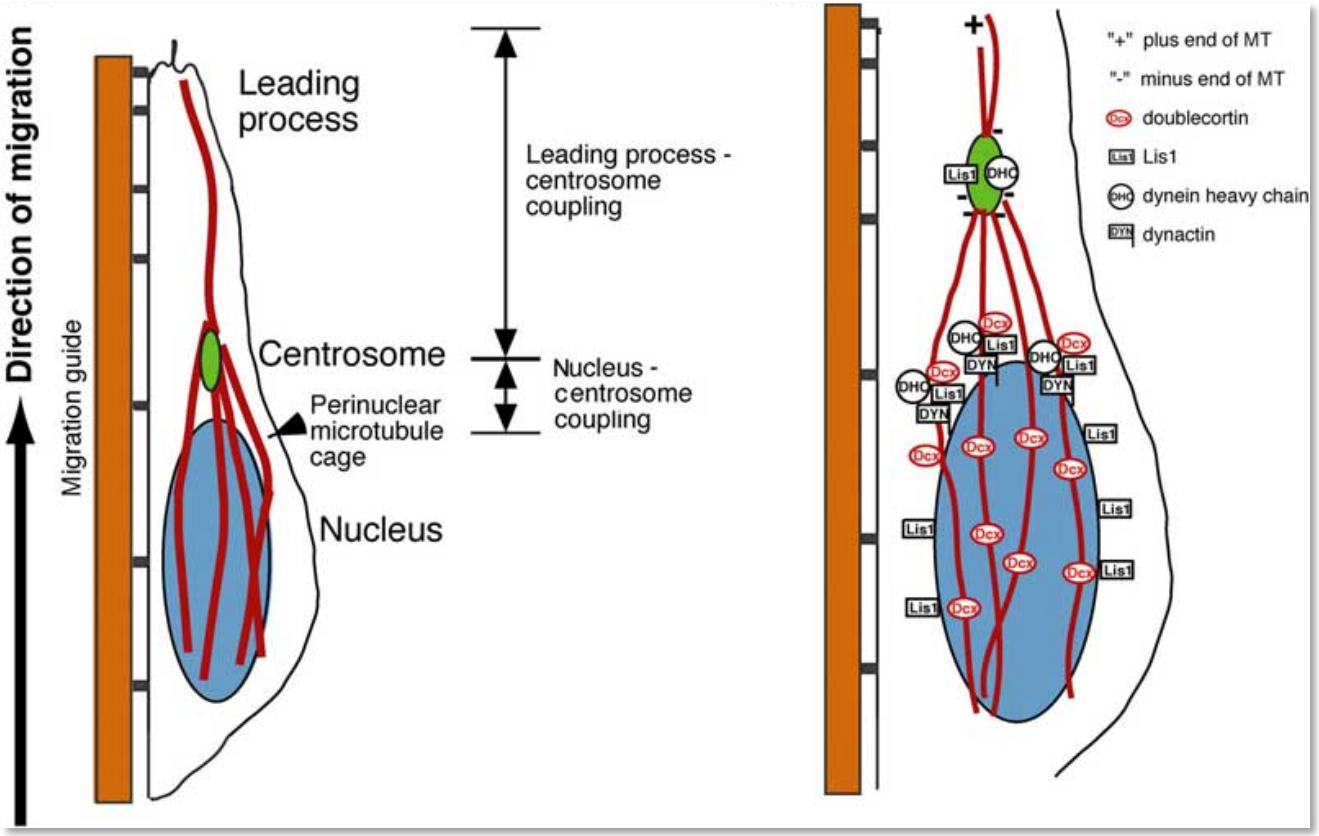
Microtubule regulation: Dcx


Neuron-specific migration mode
・Microtubule regulation
・Endocytic pathways
・Actin organization
Dilation / Swelling formation
Nuclear elongation and forward movement
Radial glial fiber-dependent migration
Scaffold cell-dependent migration
・Cell adhesion
・Endocytosis and recycling
Radial glial fiber

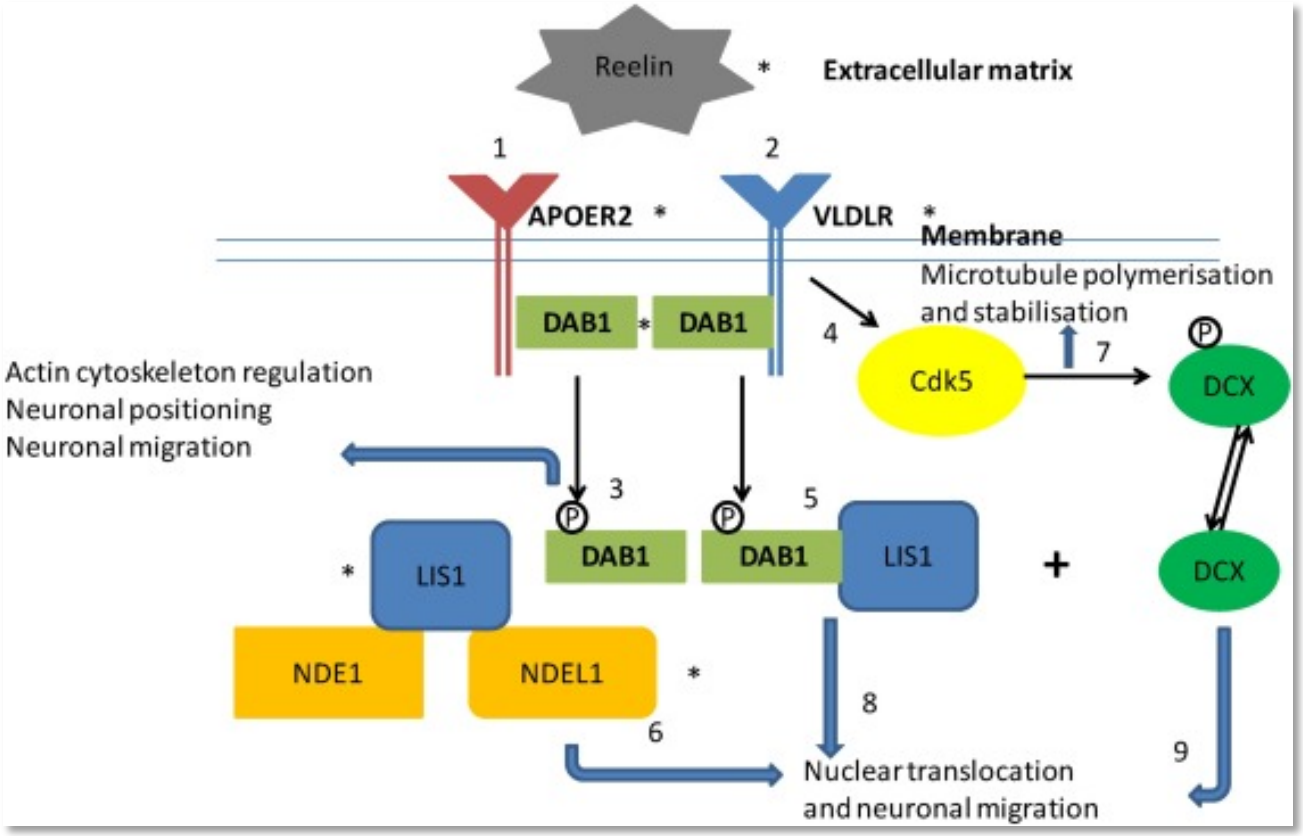
Molecular control of radial-glial fiber-dependent migration



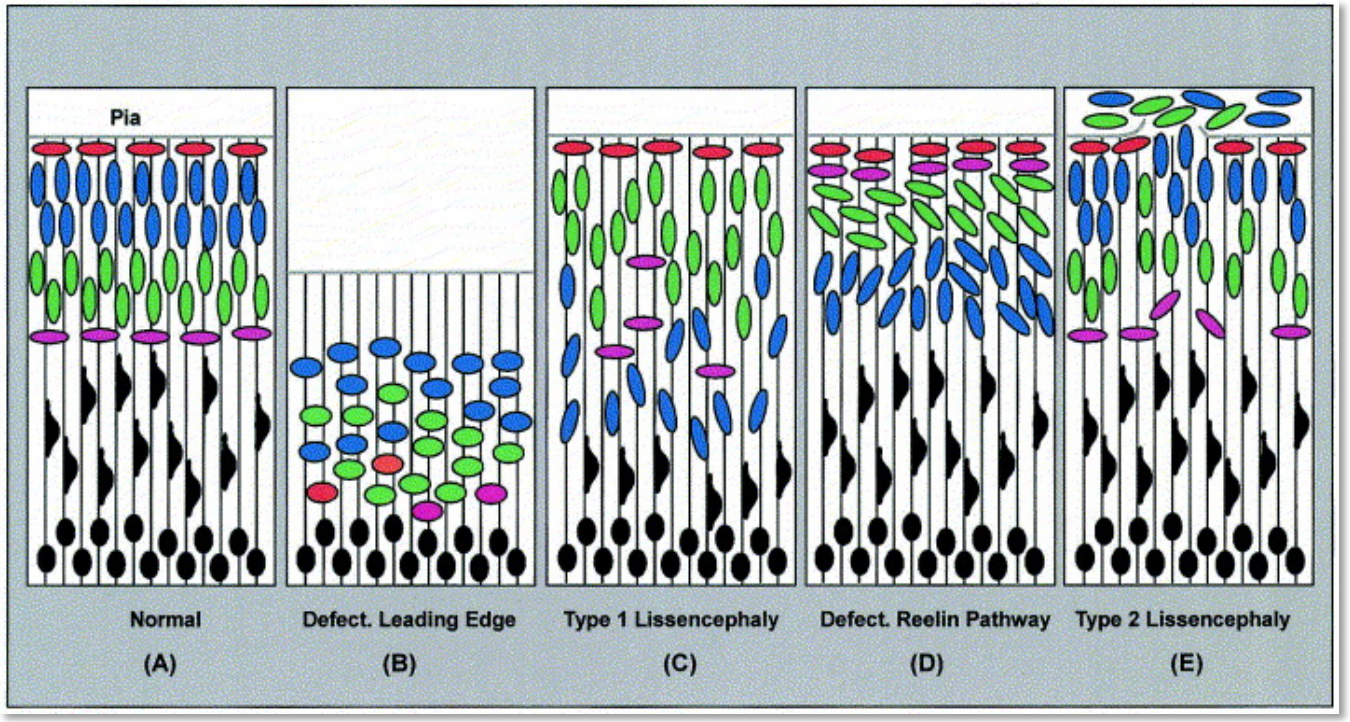
Molecular control of radial-glial fiber-dependent migration



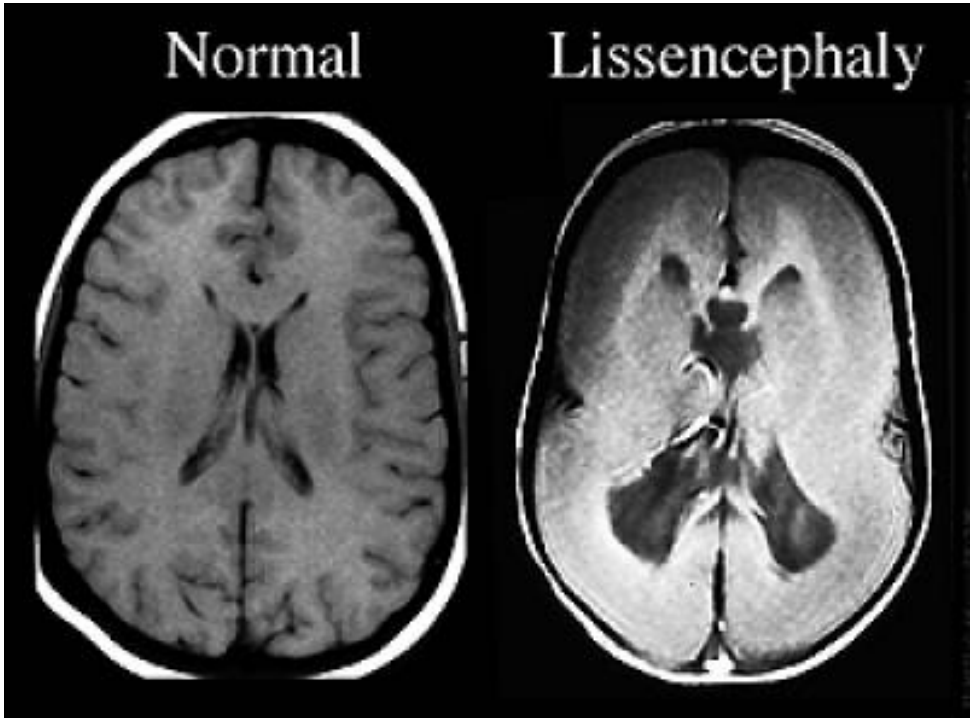
Reelin signalling pathway in neuronal migration



Defects in neuronal migration lead to altered lamination



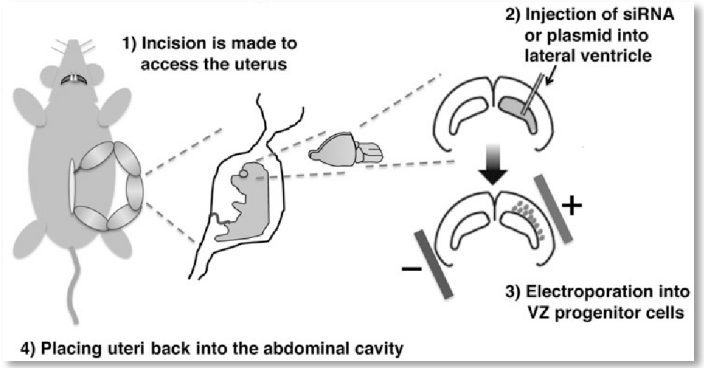
Goffinet, 2001

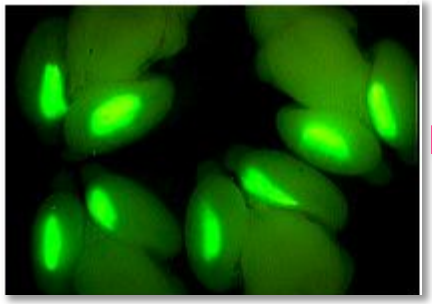

Normal
Lissencephaly

How do we study cell migration in experimental models?

Acute (somatic) manipulation of cell identity and cell behavior

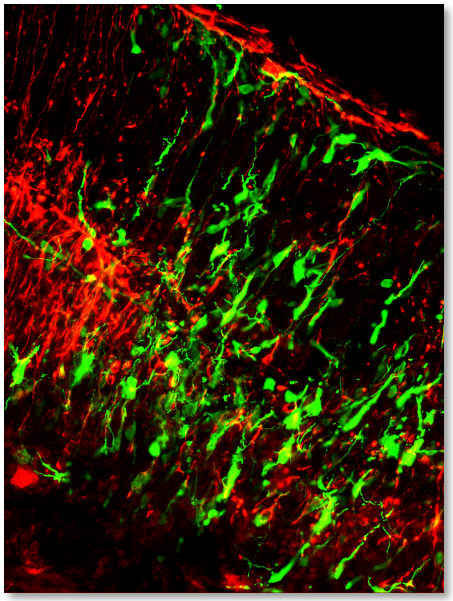
In utero electroporation





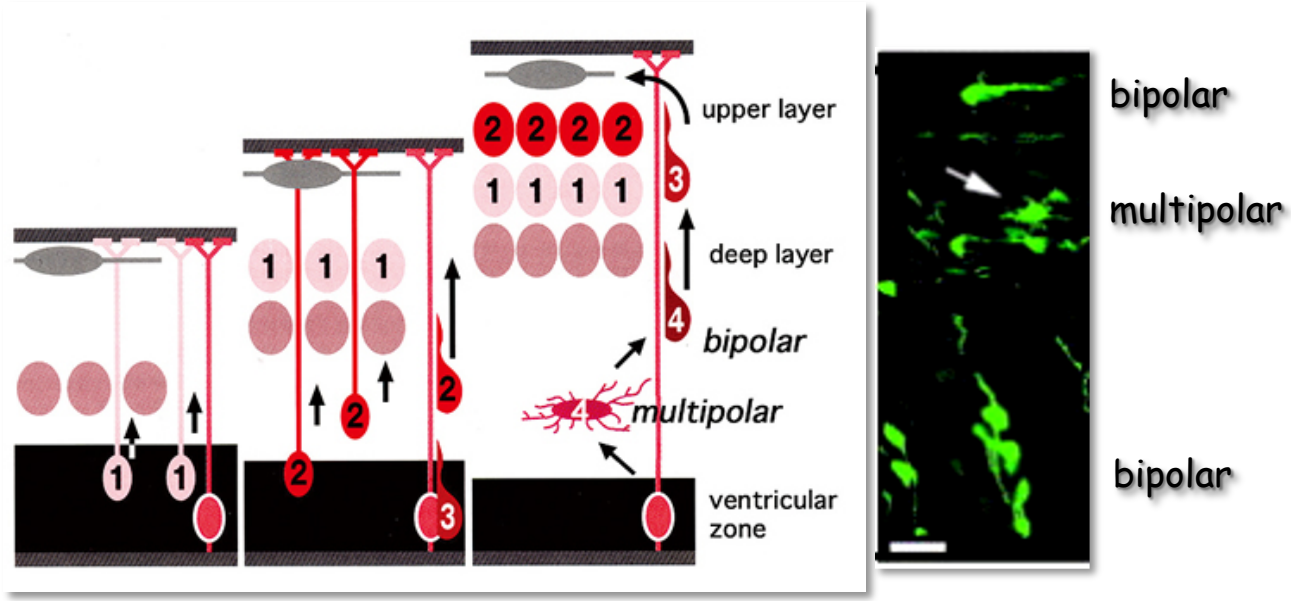
normal pregnancy and birth

organotypic culture of brain slices (up to 4 days)

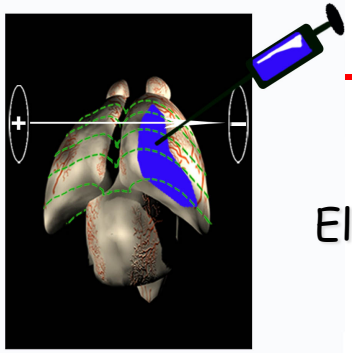


Cell migration
Cell morphology
Cell specification
Genetic interactions
Single cell recording
Connectivity

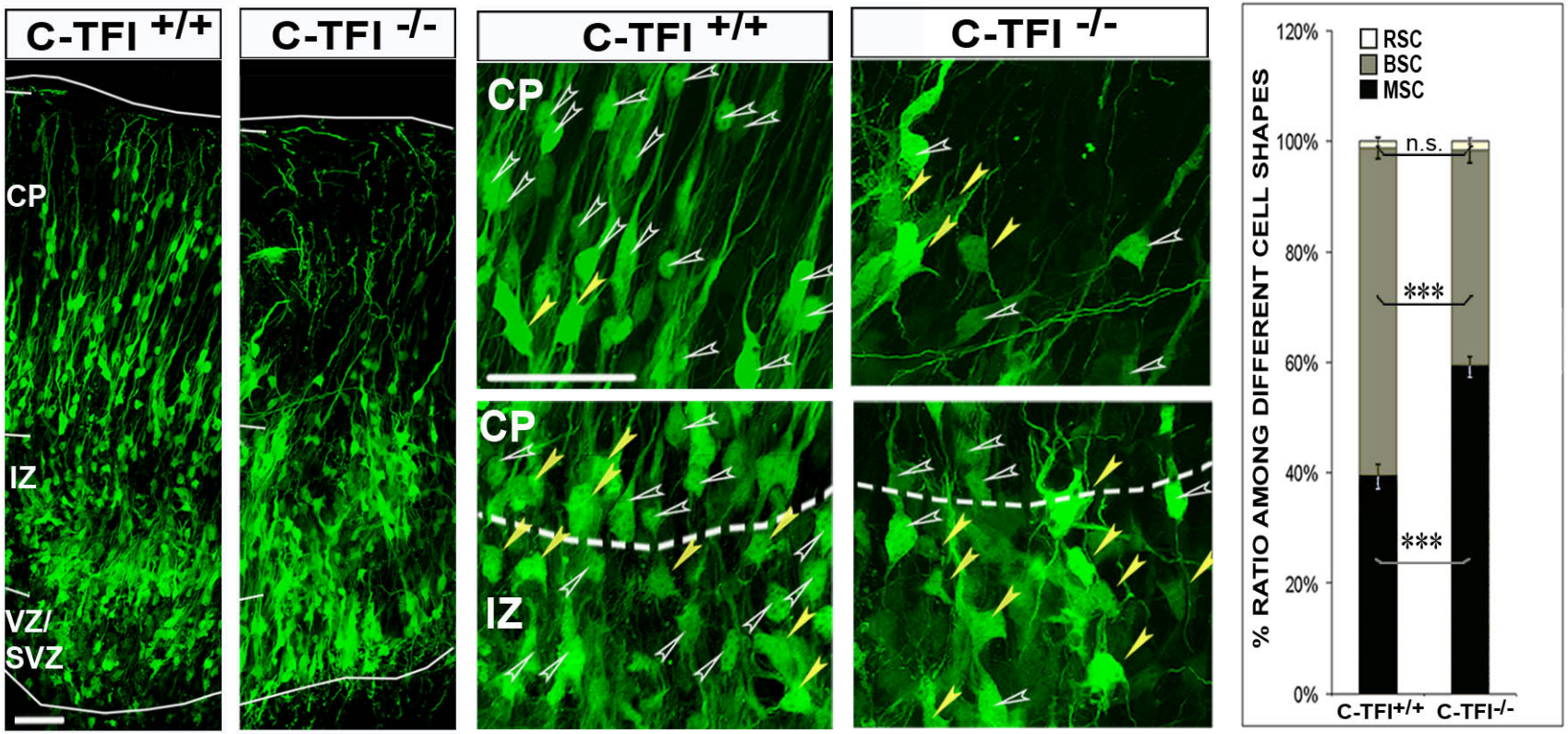
Radial migration and morphological transition



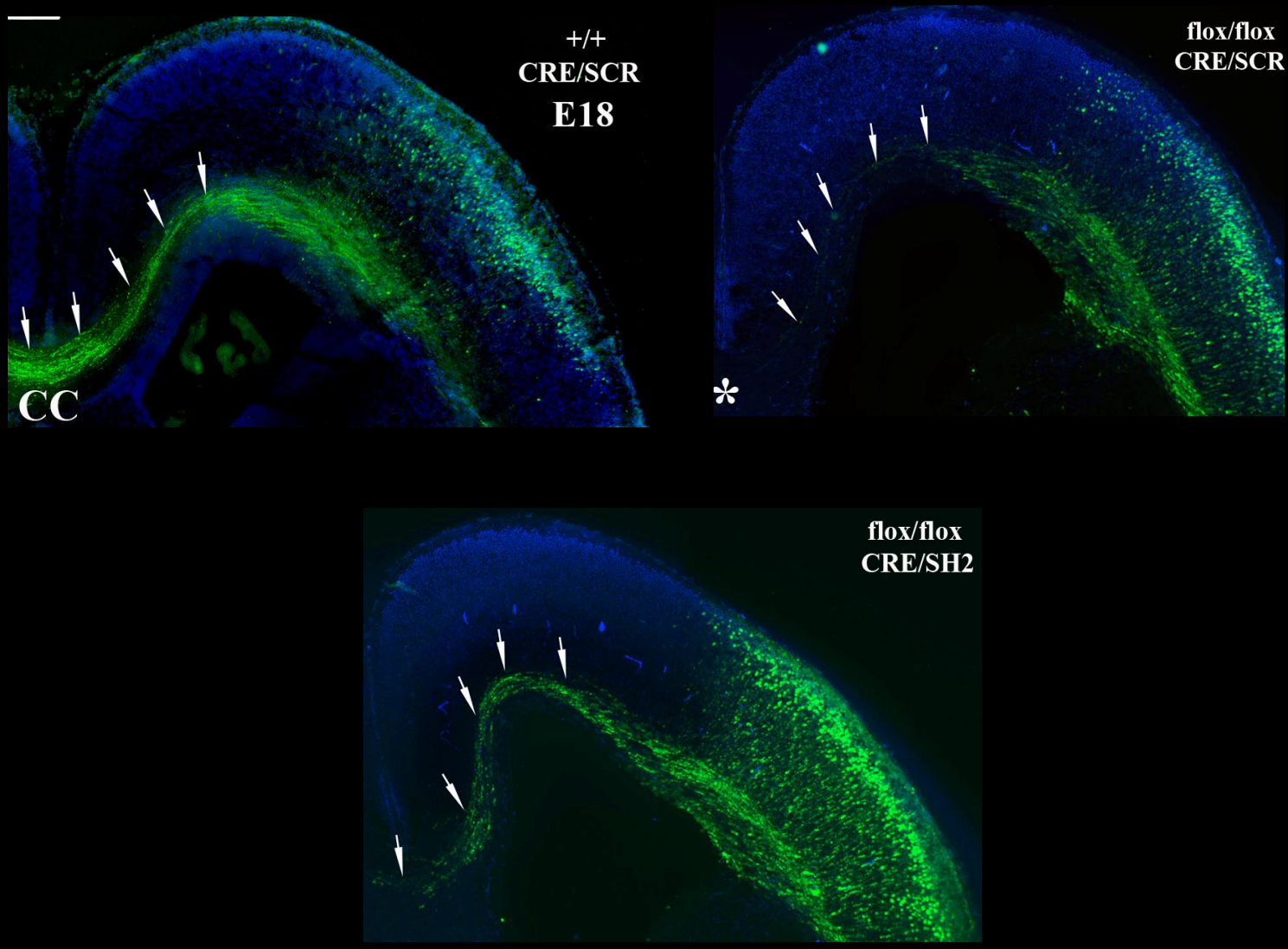
Accumulation of multipolar-shaped cells in the IZ



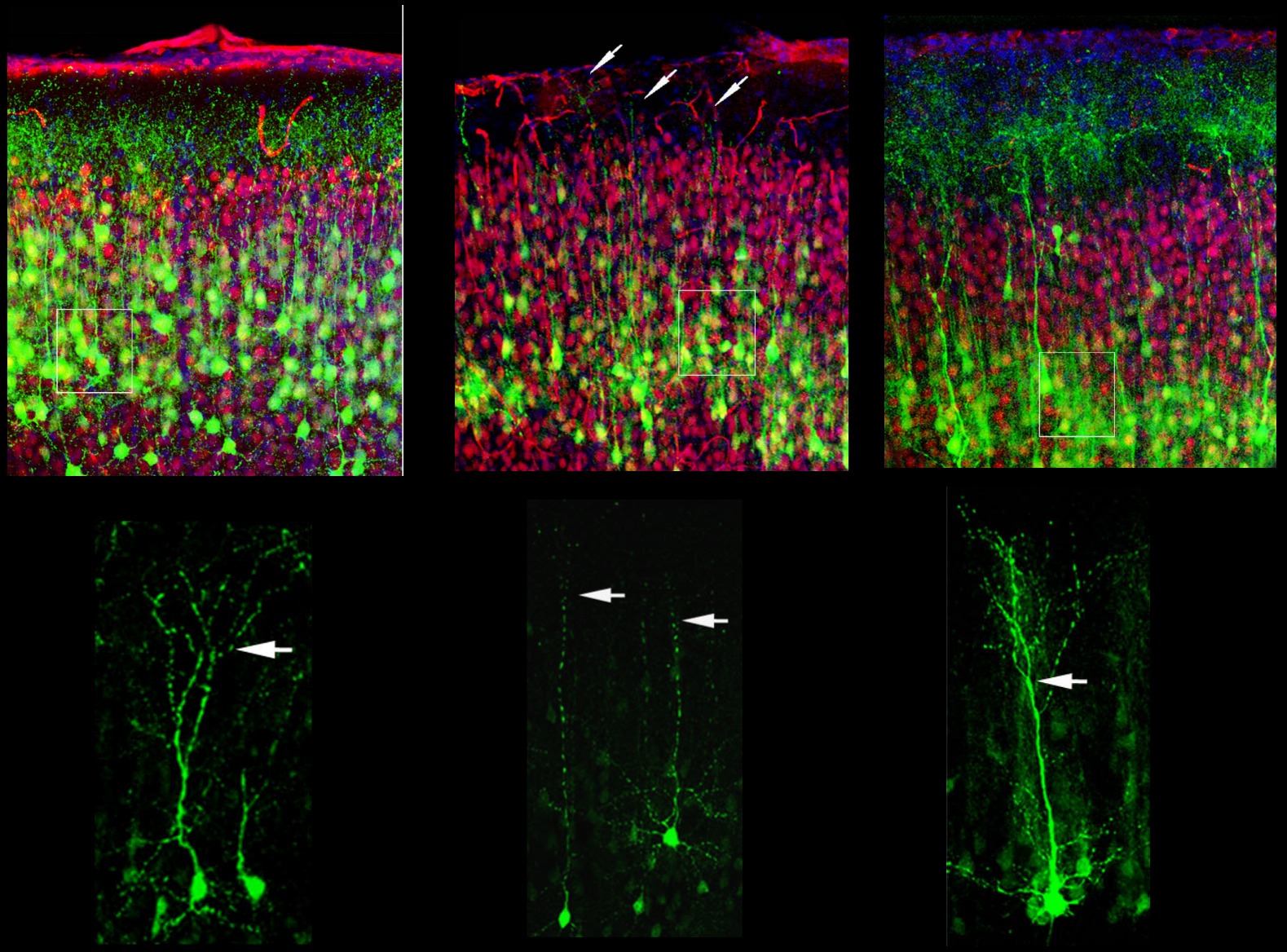
Electroporation of a GFP-expressing vector at E14.5 + 4 DIV in culture



Restored cell migration rescues axonal elongation

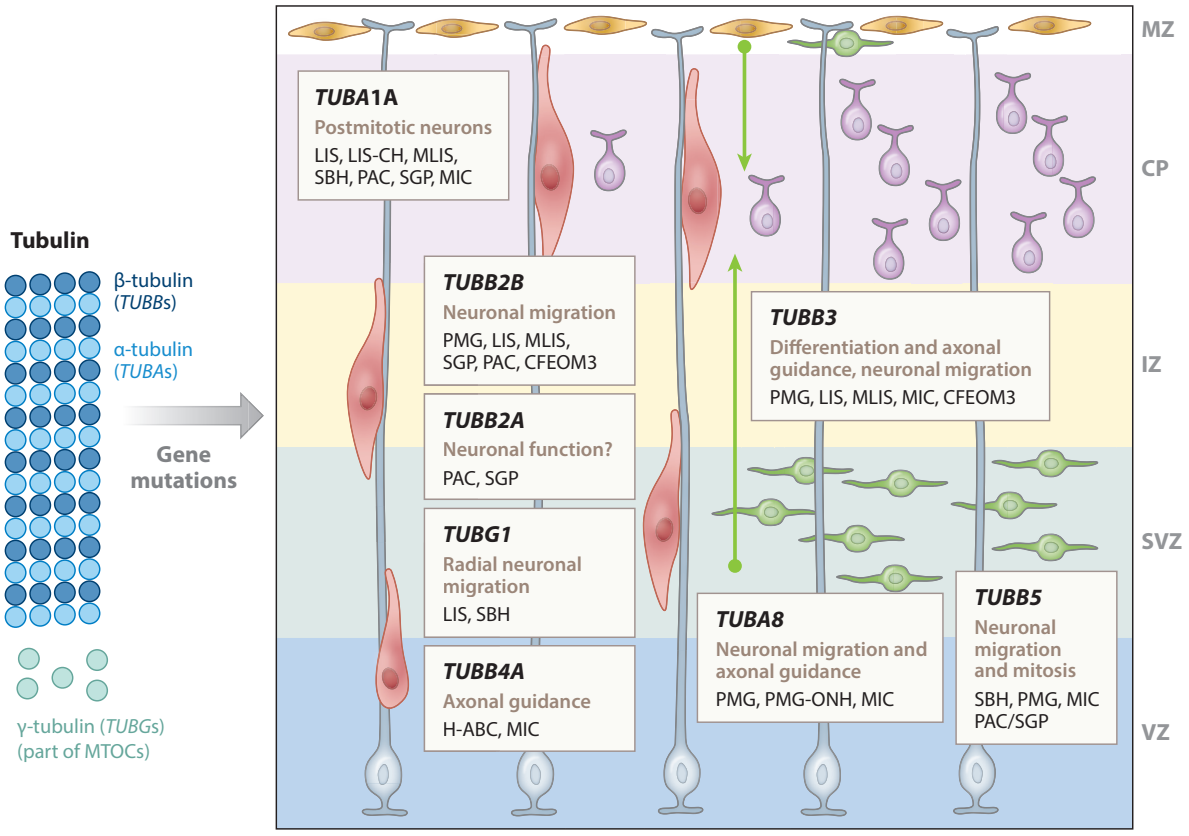


Restored cell migration rescues neuronal maturation



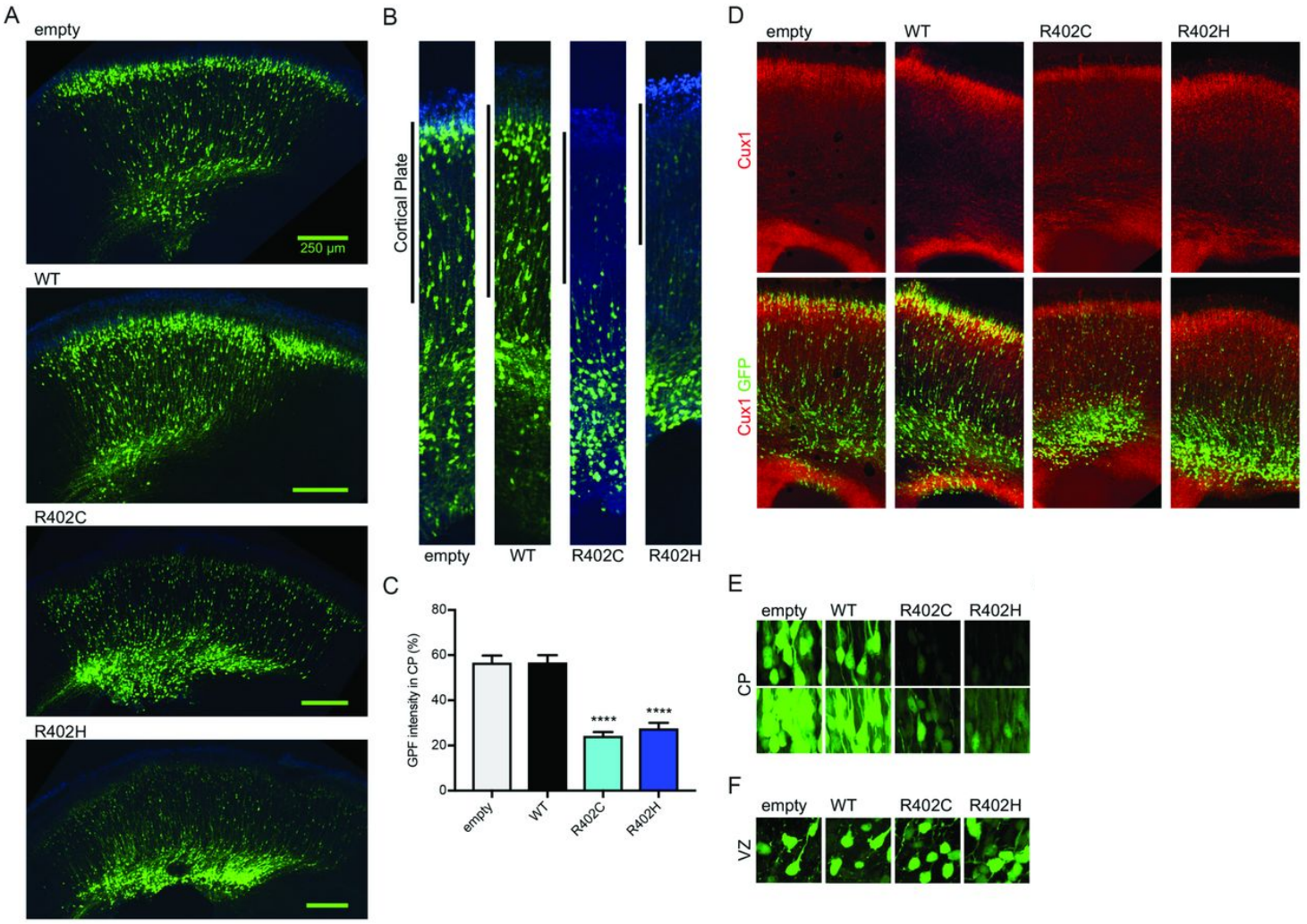
The appearance of glia-guided migration, unique to mammals, is linked to axonal growth and maturation of late-born pyramidal neocortical neurons.

Tubulinopathies affect multiple processes in cortical development and cause heterogeneous MCDs



Jurik-Sekhar & Hevner et al., 2019

TUBA1A-R402C/H mutants dominantly disrupt neuronal migration in the mouse cortex



Aiken et al., 2019

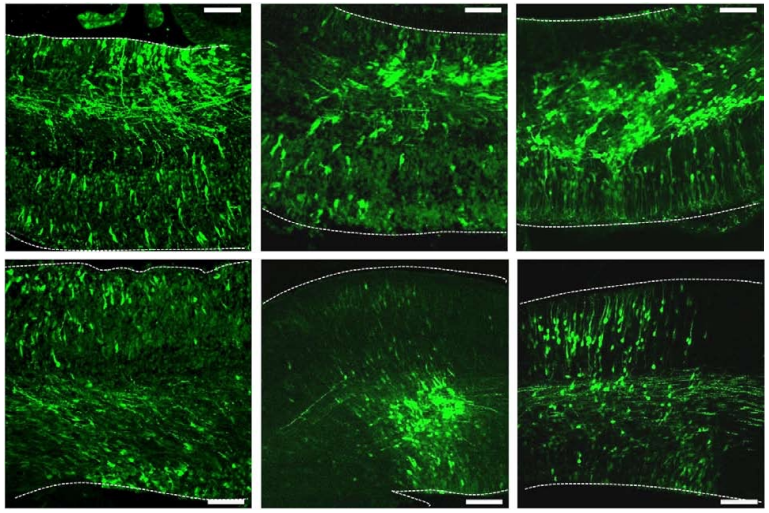
Abnormal cell migration and neuronal heterotopia in mice and humans

DCHS1 &FAT4: protocadherins act as planar cell polarity genes

Mouse IUE

Dchs1 mutant forms

IUE E13-E16



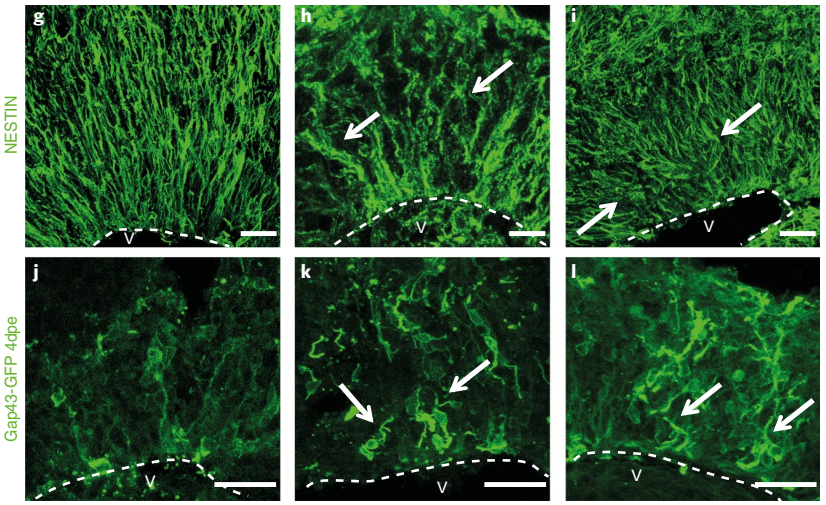
Fat4 mutant forms

Cappello et al., 2013

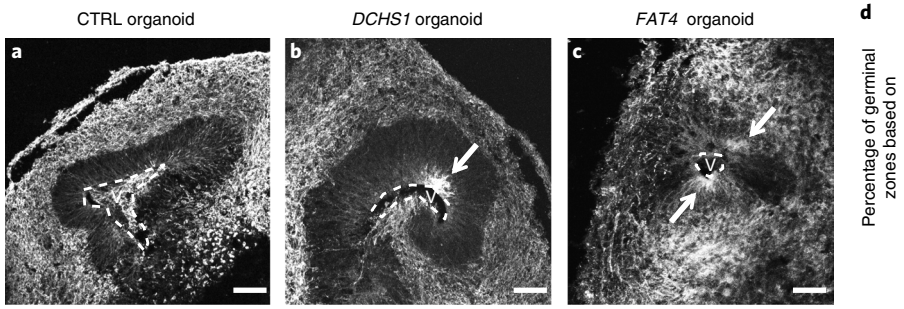
Human organoids

DCHS1

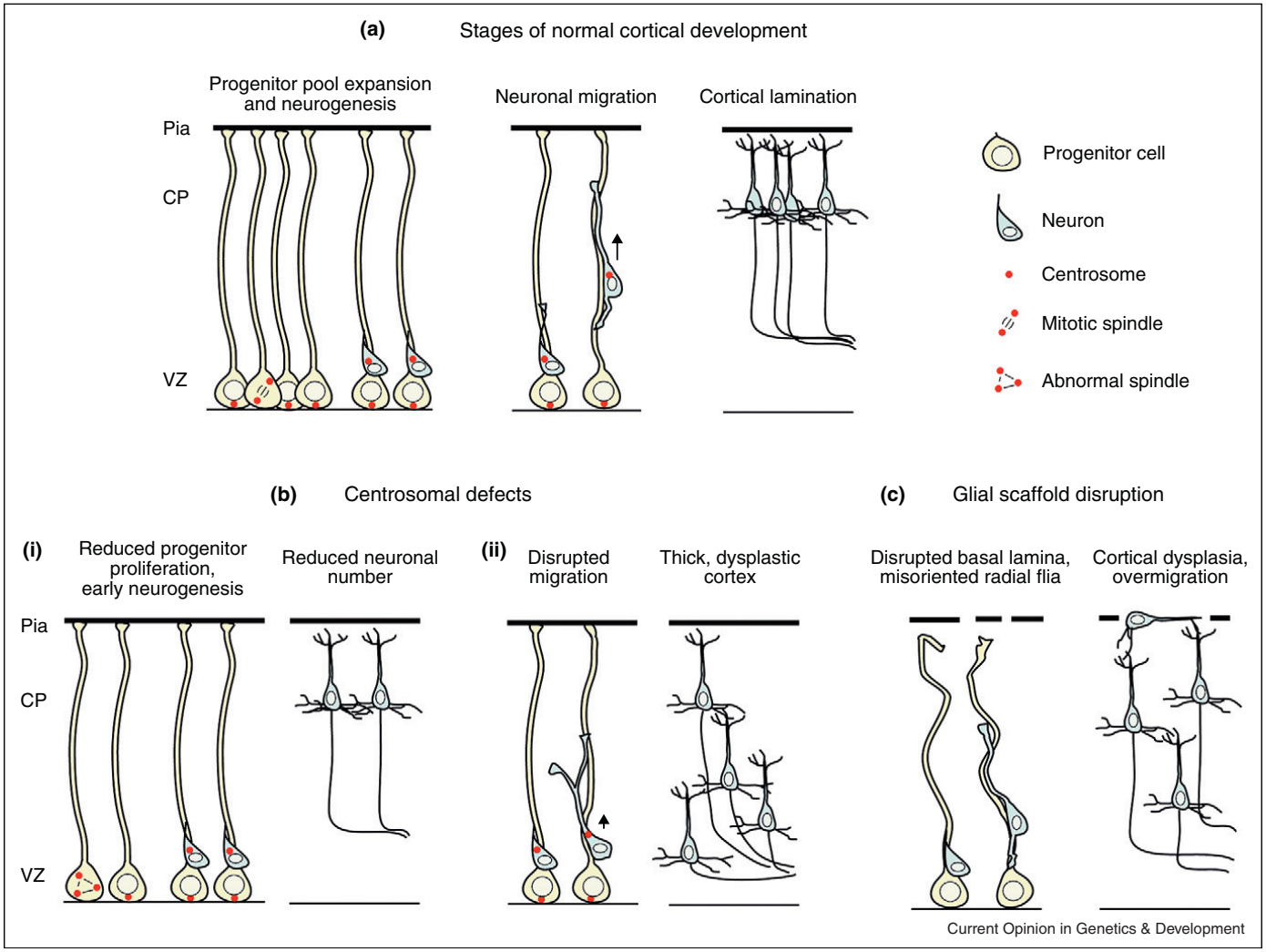
FAT4



Klaus et al., 2019



Cellular mechanisms of abnormal cortical development leading to malformations



Manzini & Walsh, 2011

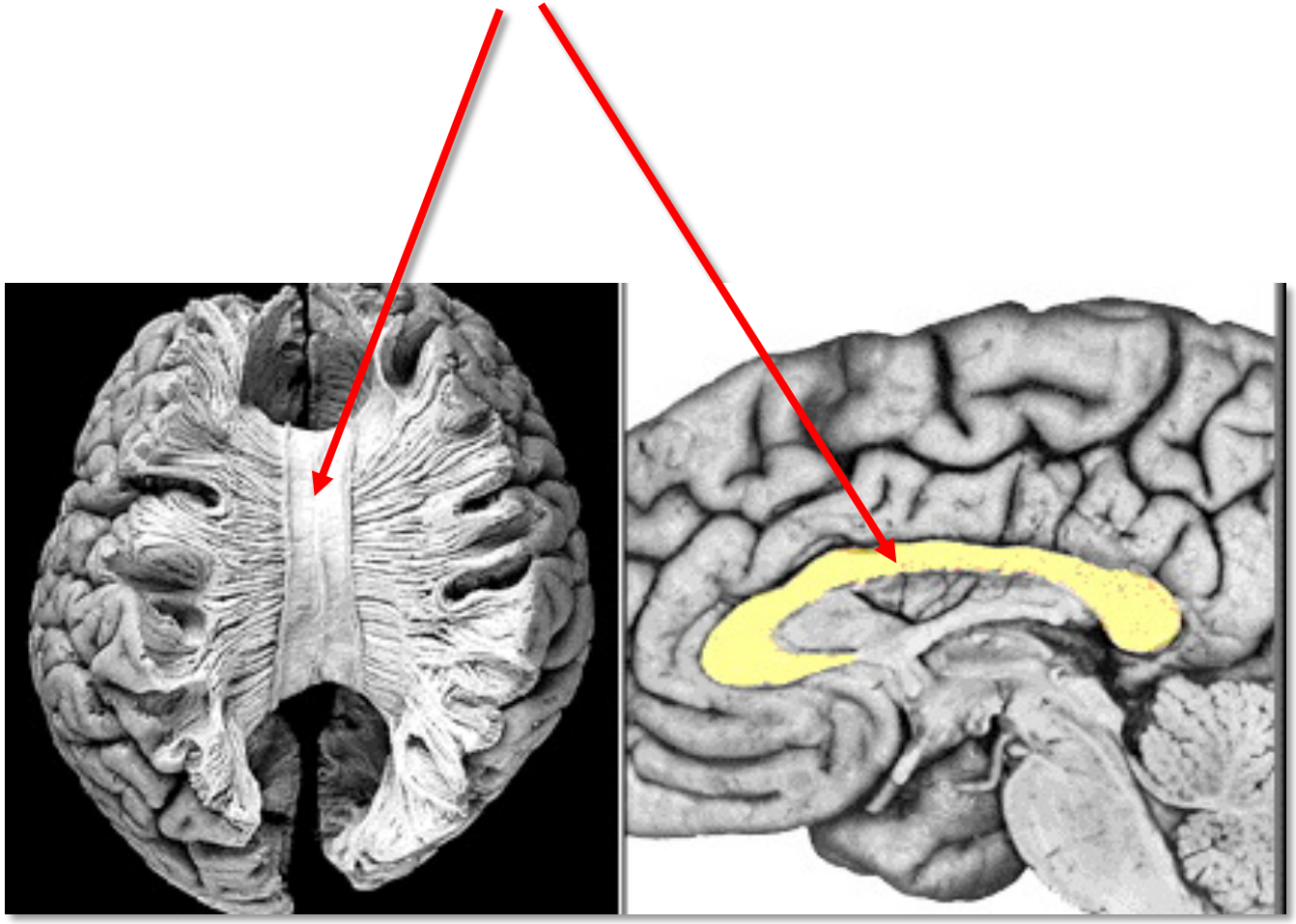
Different categories of Malformations of Cortical Develeopment (MCD)

MCD group	MCD type	Morphologies	Related pathways
Disorders of proliferation, apoptosis, and/or differentiation	Microcephalies	Microcephaly, microlissencephaly Alobar, lobar, and variant holoprosencephaly	Tubulinopathies, microtubule-associated proteins Decreased RTK → PI3K → AKT → mTOR signaling Sonic hedgehog pathway Midline differentiation
	Cortical overgrowth disorders (focal and diffuse)	Megalencephaly, hemimegalencephaly, polymicrogyria, FCD-II	Overactive RTK → PI3K → AKT → mTOR signaling
Disorders of neuronal migration	Classic lissencephaly spectrum	Smooth lissencephaly, microlissencephaly, subcortical band heterotopia	Tubulinopathies, microtubule-associated proteins Variant lissencephalies (noncytoskeletal)
	Cobblestone malformations	Rough lissencephaly, polymicrogyria, leptomeningeal glioneuronal heterotopia	Dystroglycanopathies Other basement membrane–glia limitans interaction disorders
	Periventricular heterotopia	Nodular or linear periventricular heterotopia	Microtubule-associated proteins
	Dyslamination without cytologic dysplasia or growth abnormality	FCD-I	Overactive RTK → PI3K → AKT → mTOR signaling Other rare forms (e.g., variant Rett syndrome)
Disorders of axon pathway formation	Isolated callosal defects	Agenesis, hypogenesis, dysgenesis of corpus callosum	Axon growth and guidance Midline differentiation
	Other isolated axon defects (putative)	Unknown	Axon growth and guidance

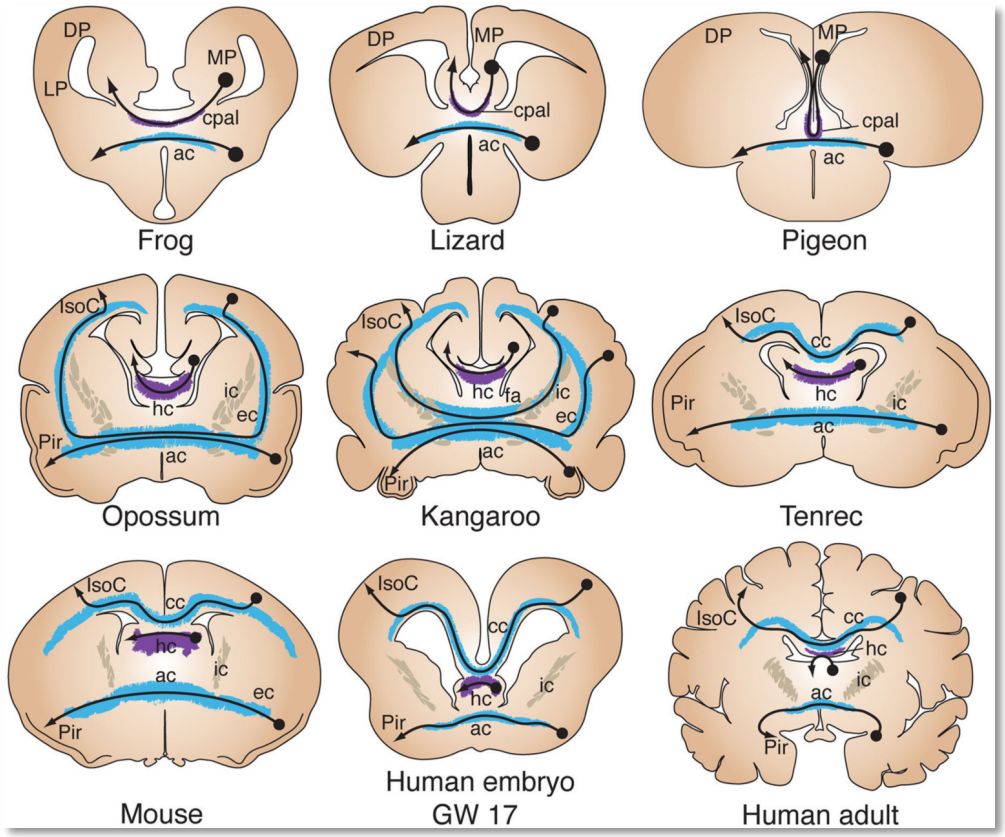
Abbreviations: FCD-I, focal cortical dysplasia type I; FCD-II, focal cortical dysplasia type II; MCD, malformation of cortical development.

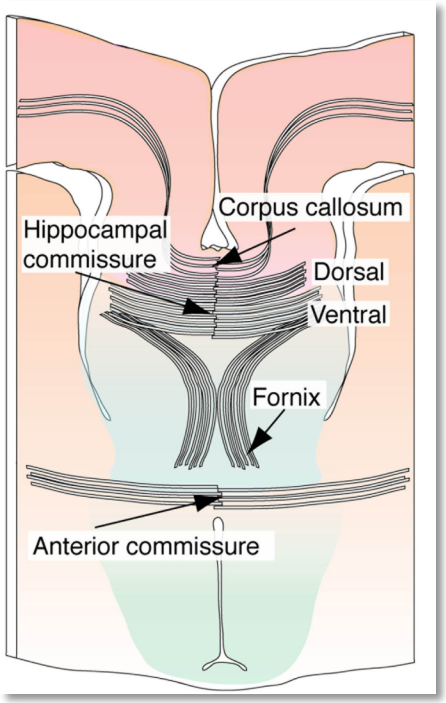
Hevner et al., 2019

Corpus Callosum



Cortical commissures - axonal connections between the two hemispheres

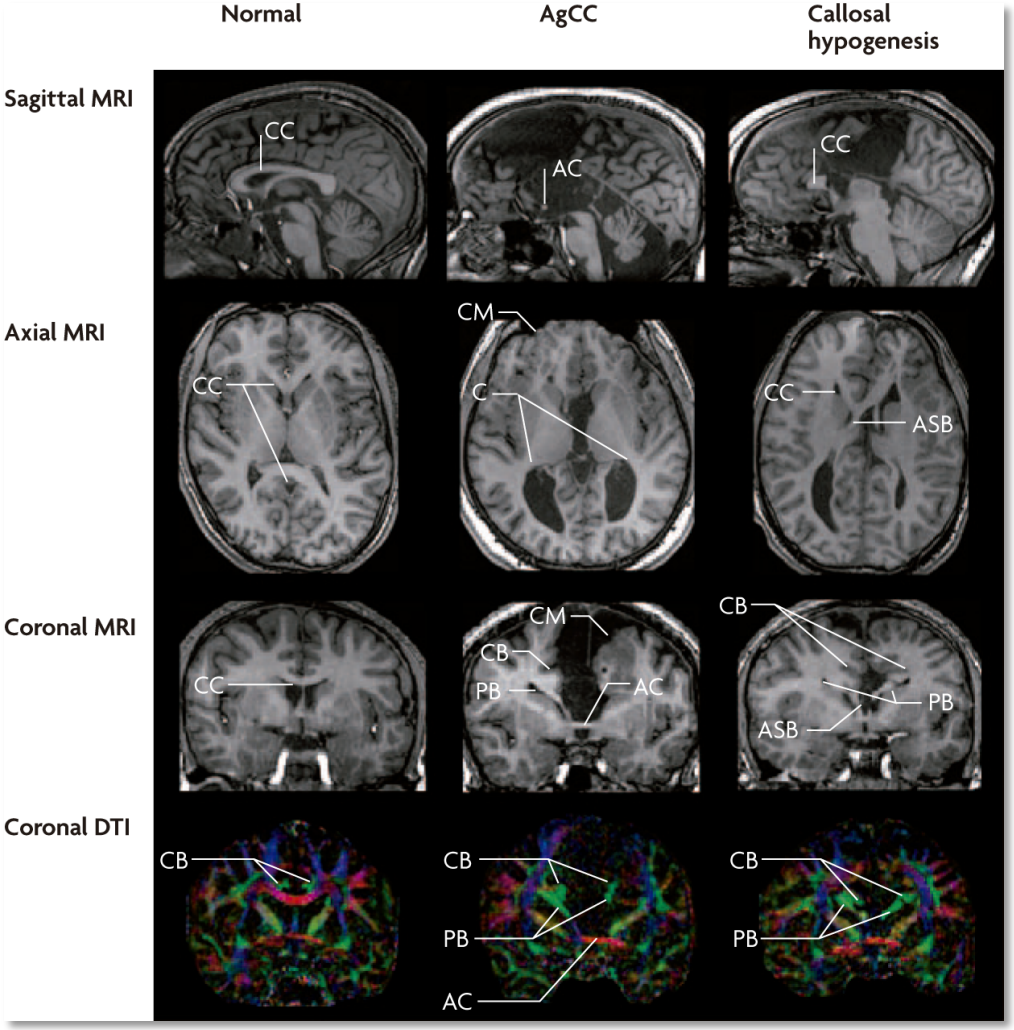




- ✓ Vertebrate evolution resulted in increased brain complexity;
- ✓ additional commissures to provide interhemispheric connections between pallial territories;
- ✓ increase in cortical volume is positively correlated with increase in CC area and number of callosal fibers

Suarez et al., 2014

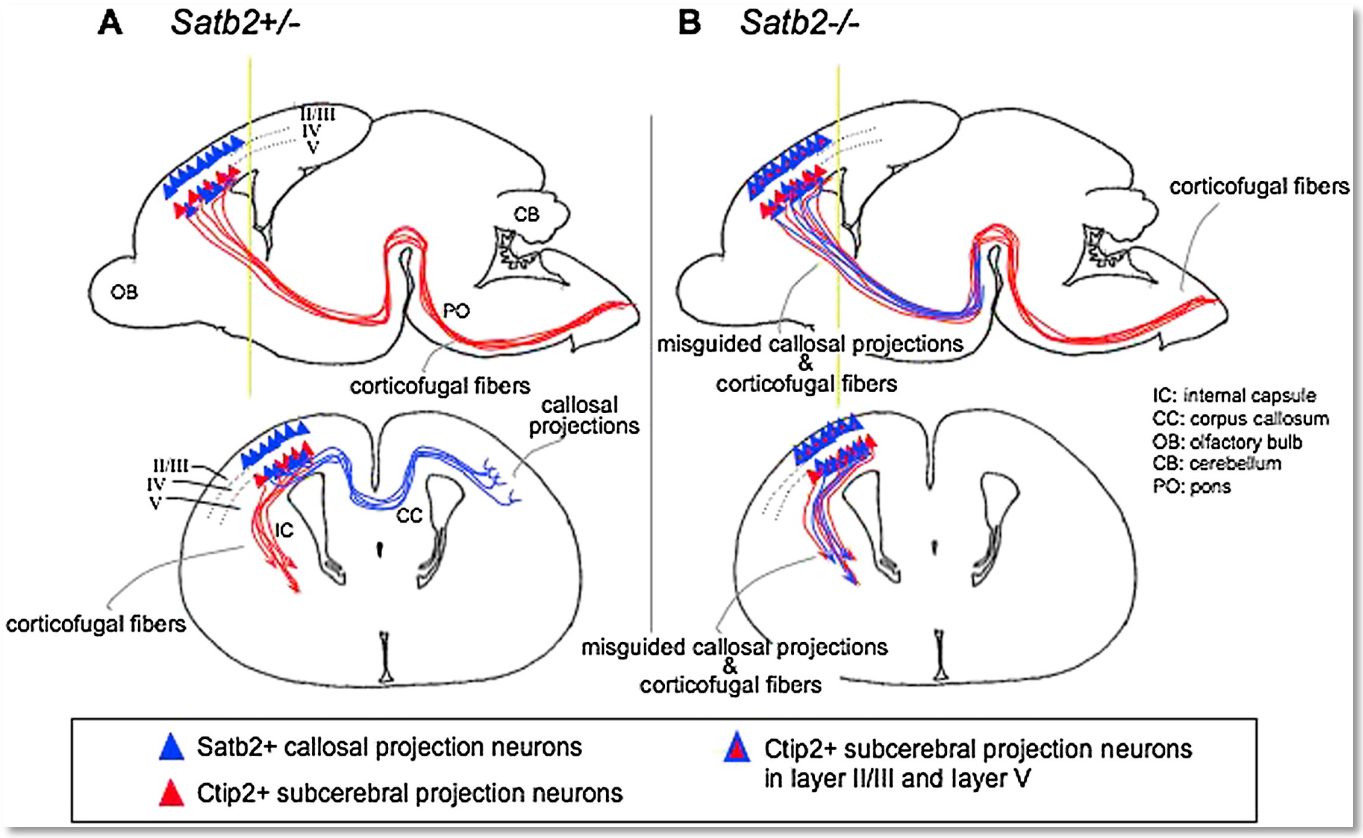
Agenesis of the corpus callosum in humans



- Behavioural and cognitive impairments:
  - ✓ deficiency in bimanually coordinated motor activity;
  - ✓ deficits in cognitive processing time, arithmetic, abstract reasoning and short-term memory;
  - ✓ Social and language deficits.

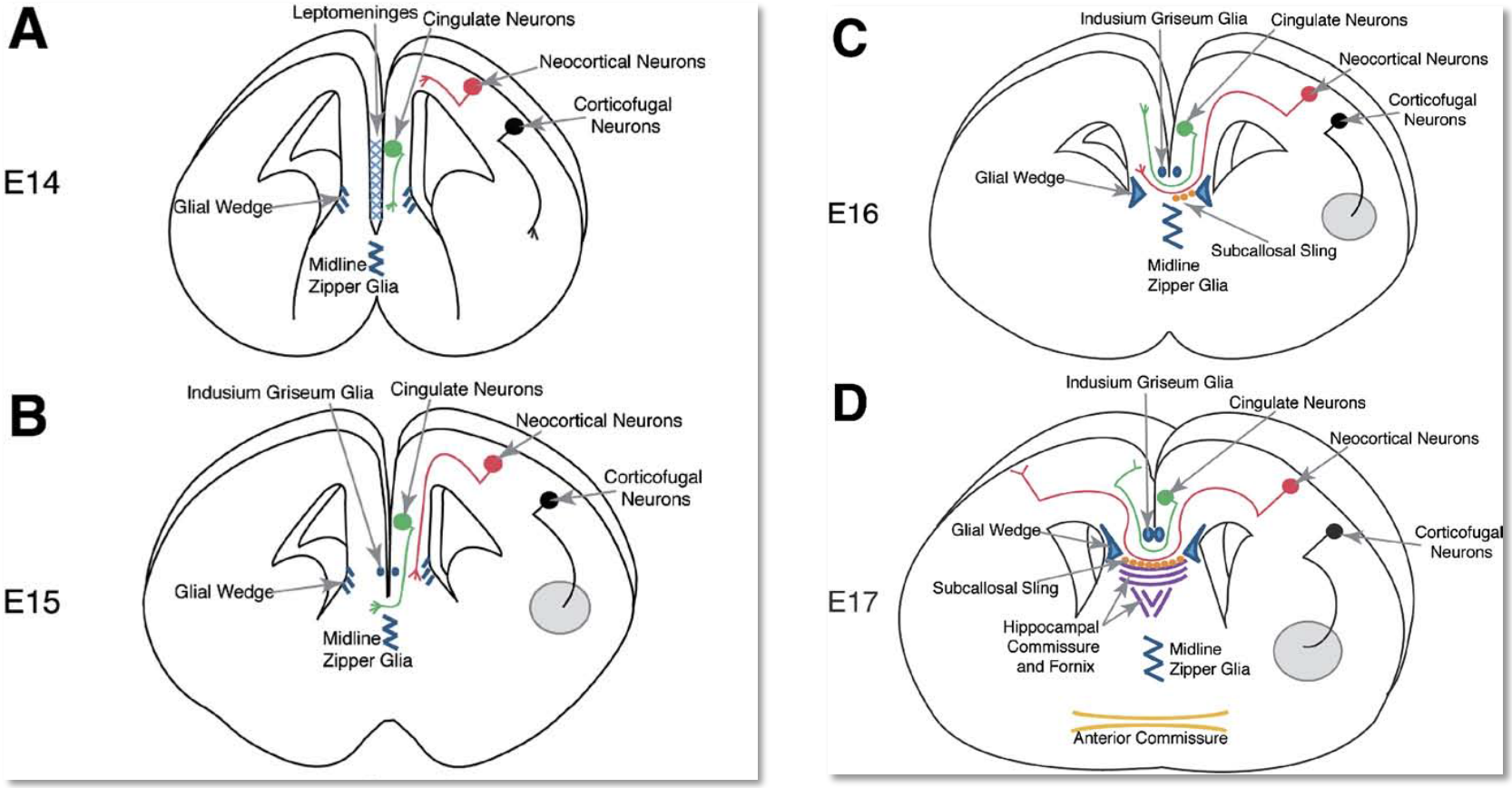
- Single gene MENDELIAN mutation, sporadic mutations and complex genetics.
- Environmental factors: fetal alcohol syndrome (FAS).
- 75% of the cases with complete AgCC have recognizable genetic syndromes

Postmitotic specification of callosal projection neurons



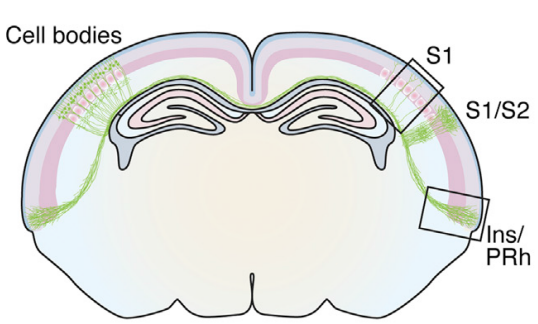
Fishell & Hanashima, 2008
Britanova et al., 2008
Alcamo et al., 2008

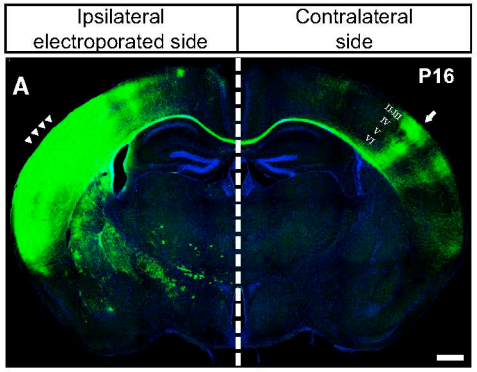
Corpus callosum development in the mouse

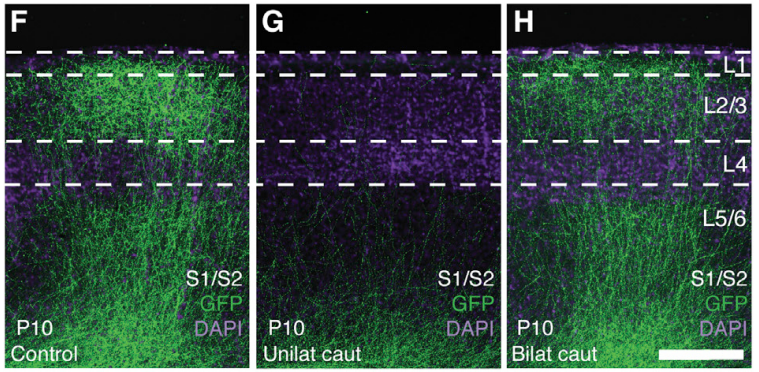


Postnatal neuron activity is essential for connecting the two halves of the brain

Balanced activity between the 2 hemispheres establish contralateral connectivity

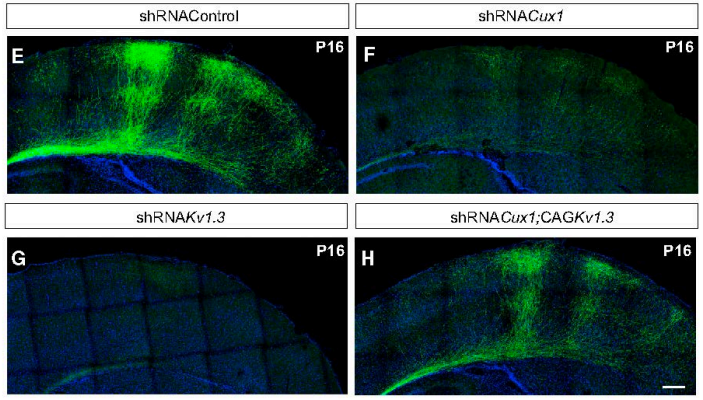


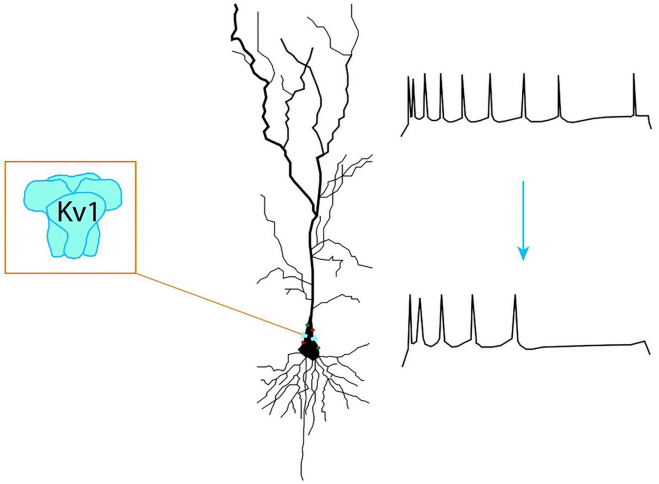




Suarez et al., 2014

Cux1 controls contralateral innervation by regulating callosal intrinsic excitability





Rodriguez-Tournos et al., 2016

Function

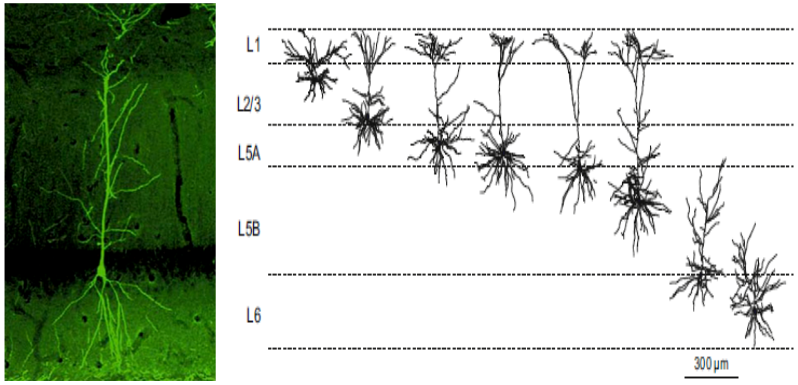
✓CC present in placental mammals;
✓largest fiber tract in the brain, connecting the two cerebral hemispheres;
✓facilitates the integration of motor and sensory information from the two sides of the body;
✓ influences higher cognition associated with executive function, social interaction and language.

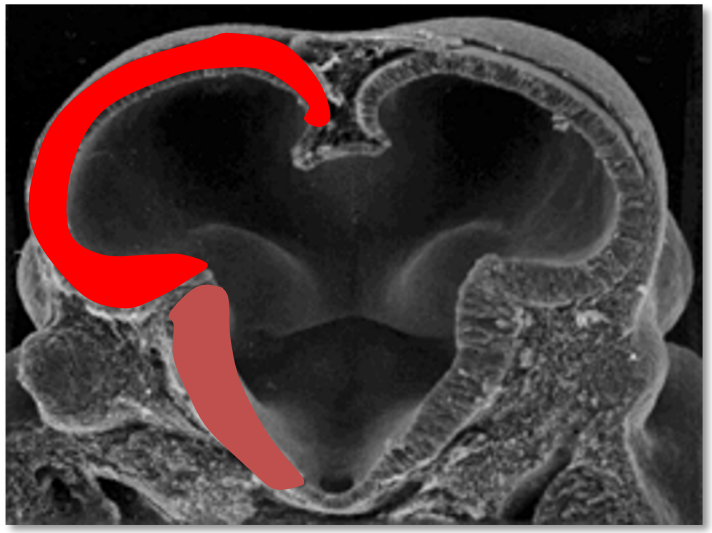
Development

✓Pioneers of the CC originate reach the midline around E15;
✓neocortical callosal axons grow along the pathway defined by the pioneers by E17;
✓midline cellular populations and extracellular cues assist in the turning and channeling of callosal axons across the midline;
✓proper contralateral innervation is a postnatal activity-dependent process.

Cortical Projection neurons (PNs) and Interneurons (INs) are born from different D/V regions of the telencephalon

Glutamatergic projection neurons

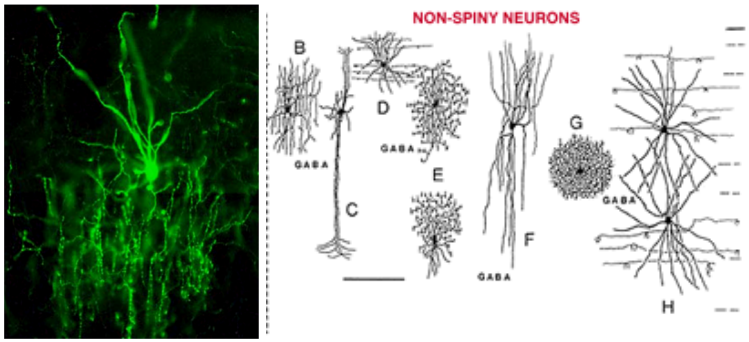




Dorsal (pallium)

Ventral (subpallium)

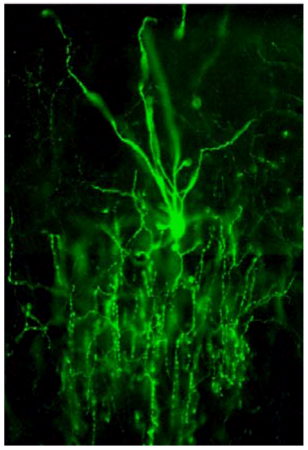
GABAergic cortical interneurons



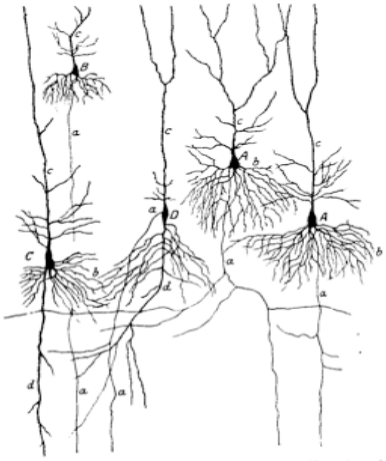
The cerebral cortex is controlled by a delicate balance of:

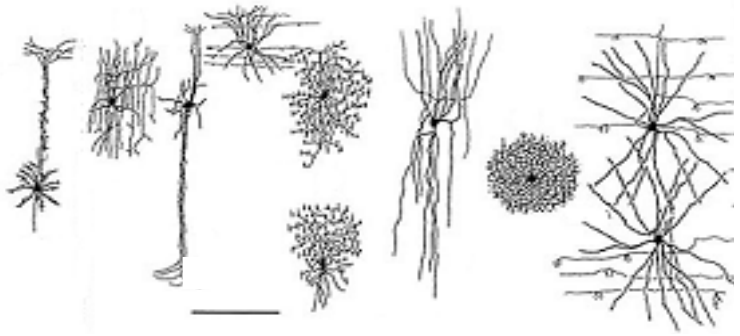
Pyramidal projection neurons
80% Glutamate

Inhibitory interneurons
20% GABA



Excitation and **Inhibition**

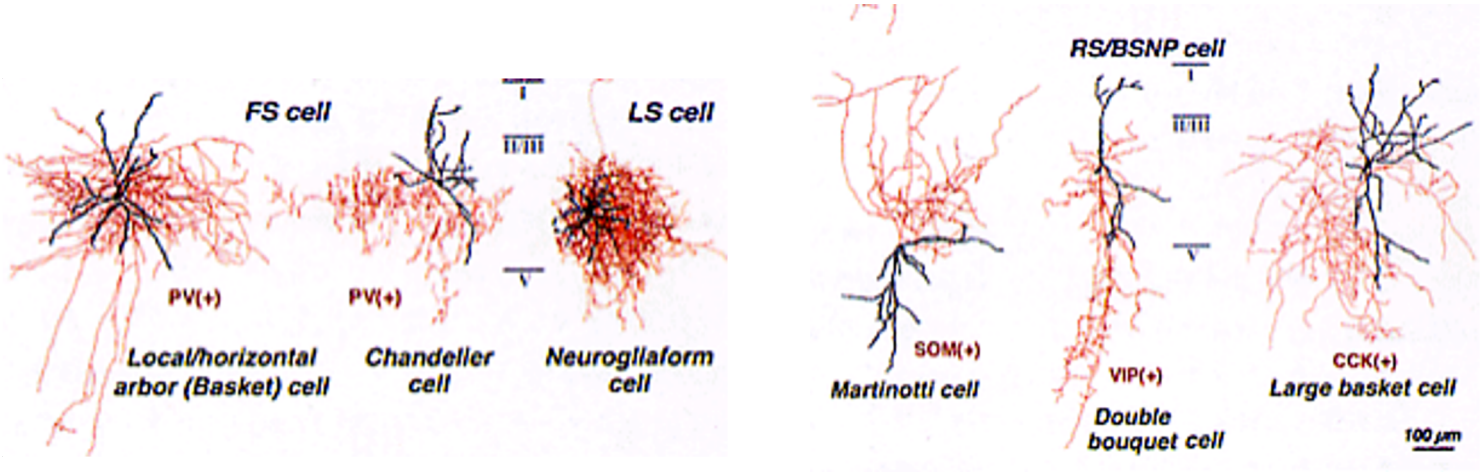




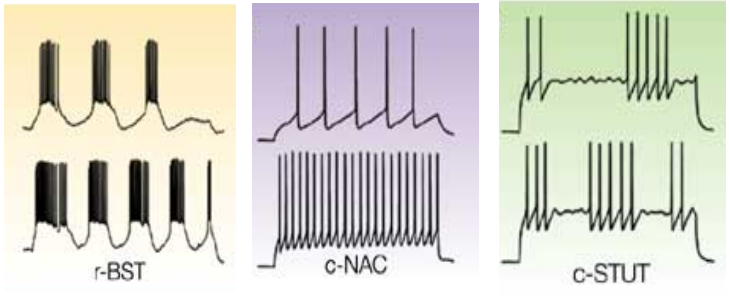
altered balance between excitation and inhibition
leads to epilepsy, autism or schizophrenia

Petilla Interneuron Nomenclature (2008)

Morphological features (axon, soma, dendrite properties):



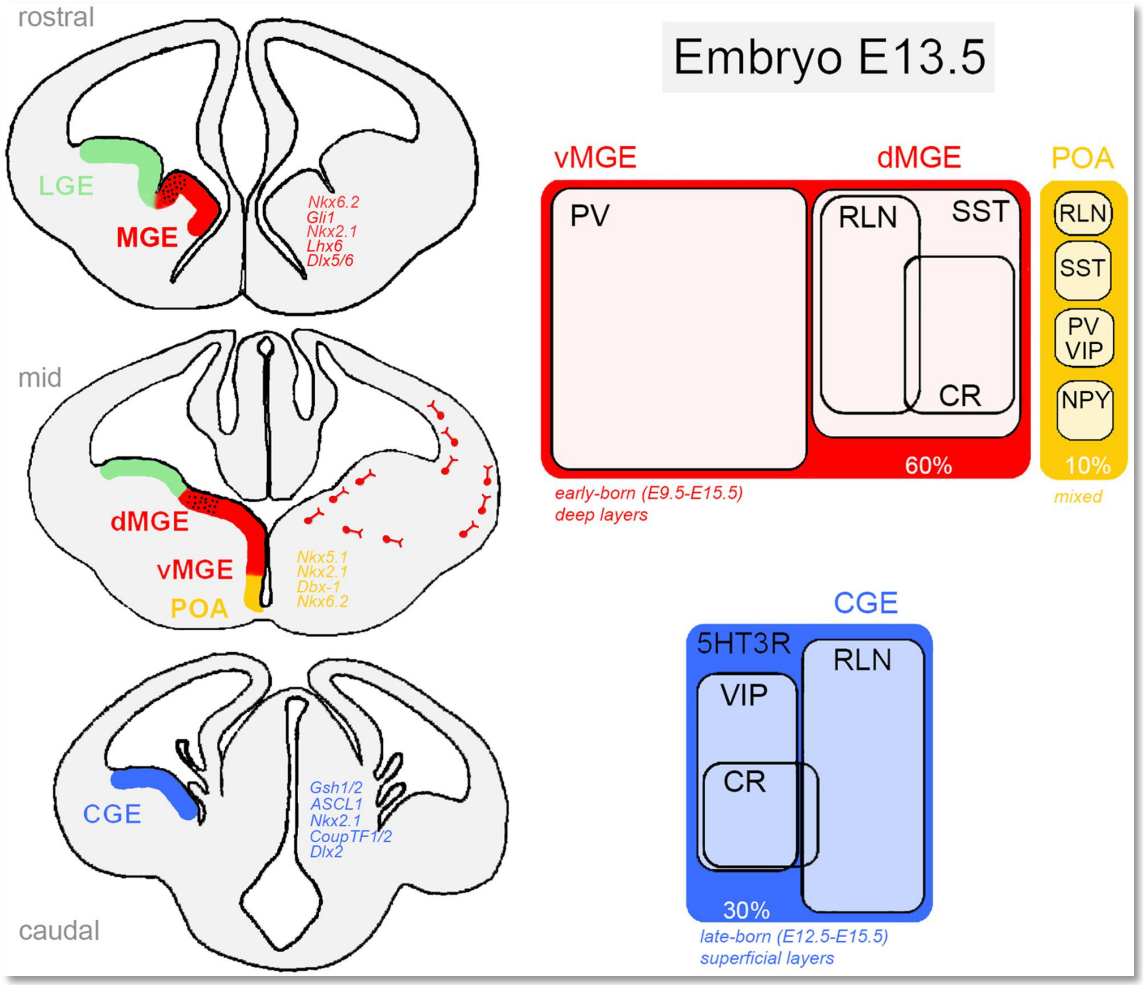
Physiological features
(action potential, firing pattern, postsynaptic responses).



Neurochemical features
(Ca-binding proteins, neuropeptides):

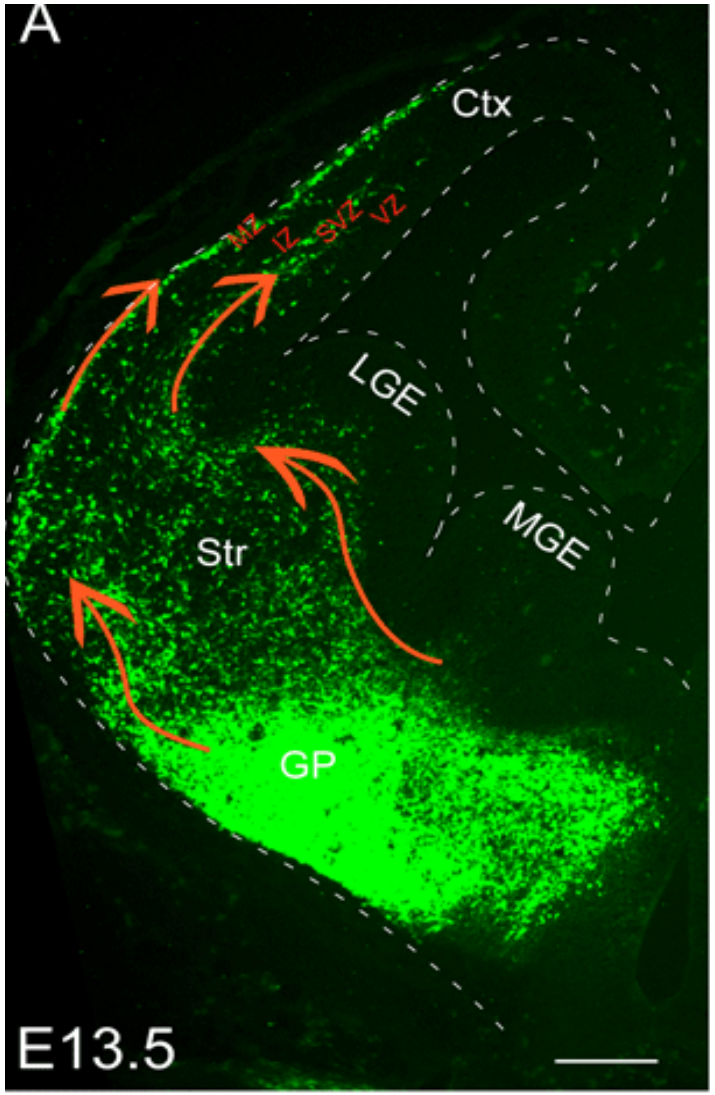
Parvalbumin (PV)
Calretinin (CR)
Somatostatin (SST)
Neuropeptide Y (NPY)
Vasointestinal Peptide (VIP)
Cholecystokinin (CCK)

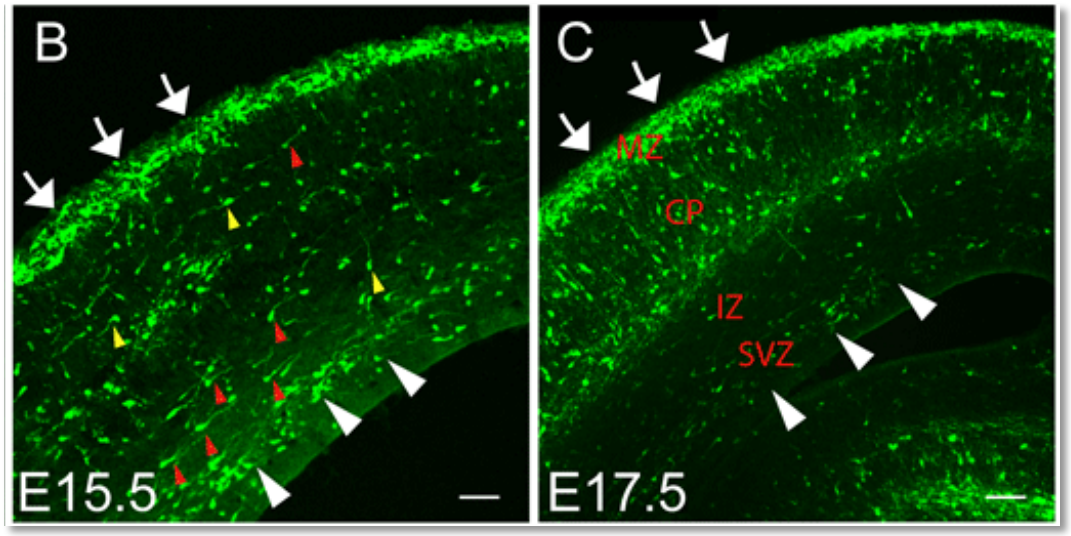
Subpallial origin of different subtypes of cortical interneurons

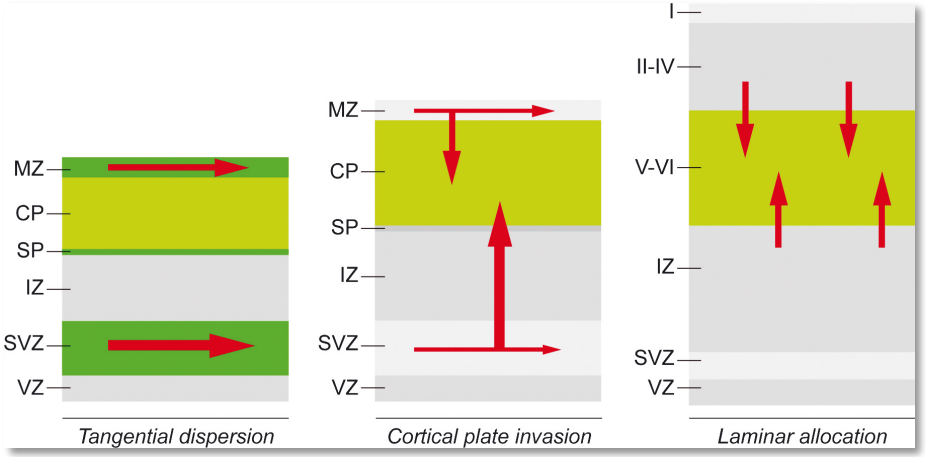


From Brandau et al., 2015

Tangential and radial migration of GE-derived interneurons

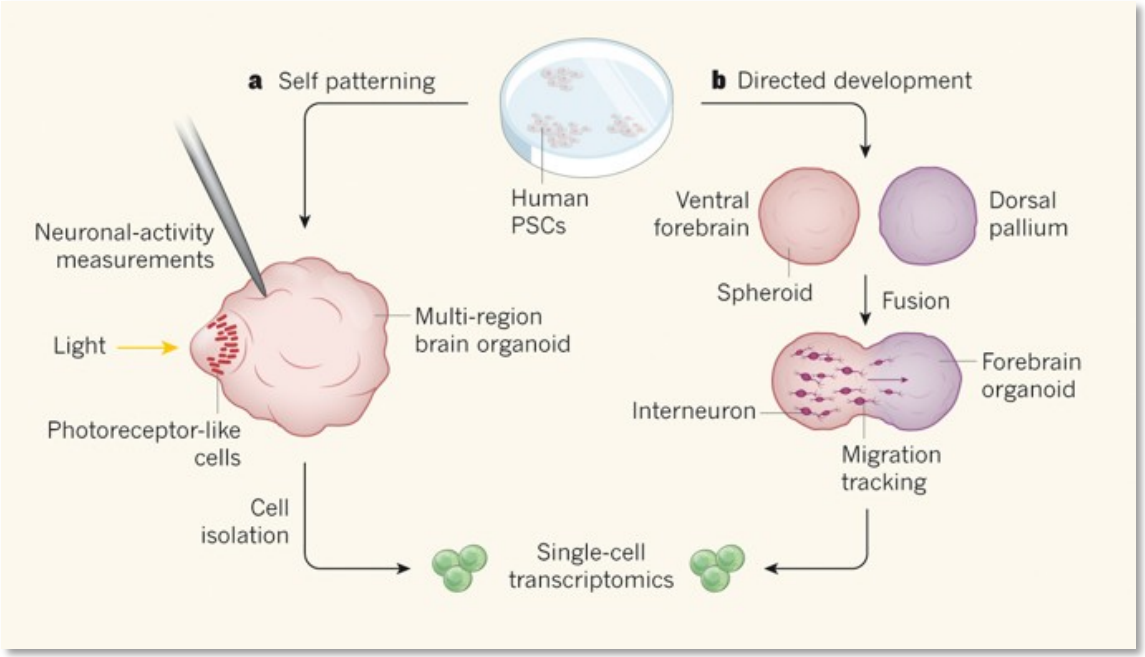


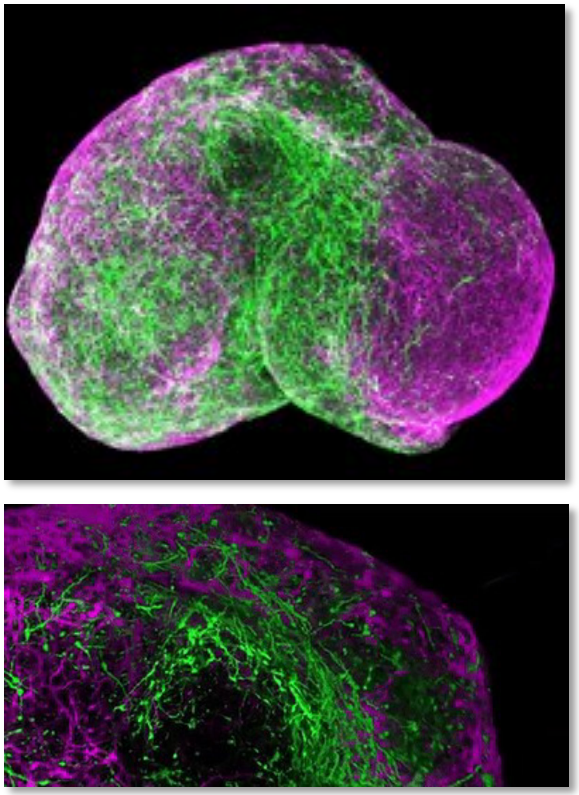




Marin et al., 2013

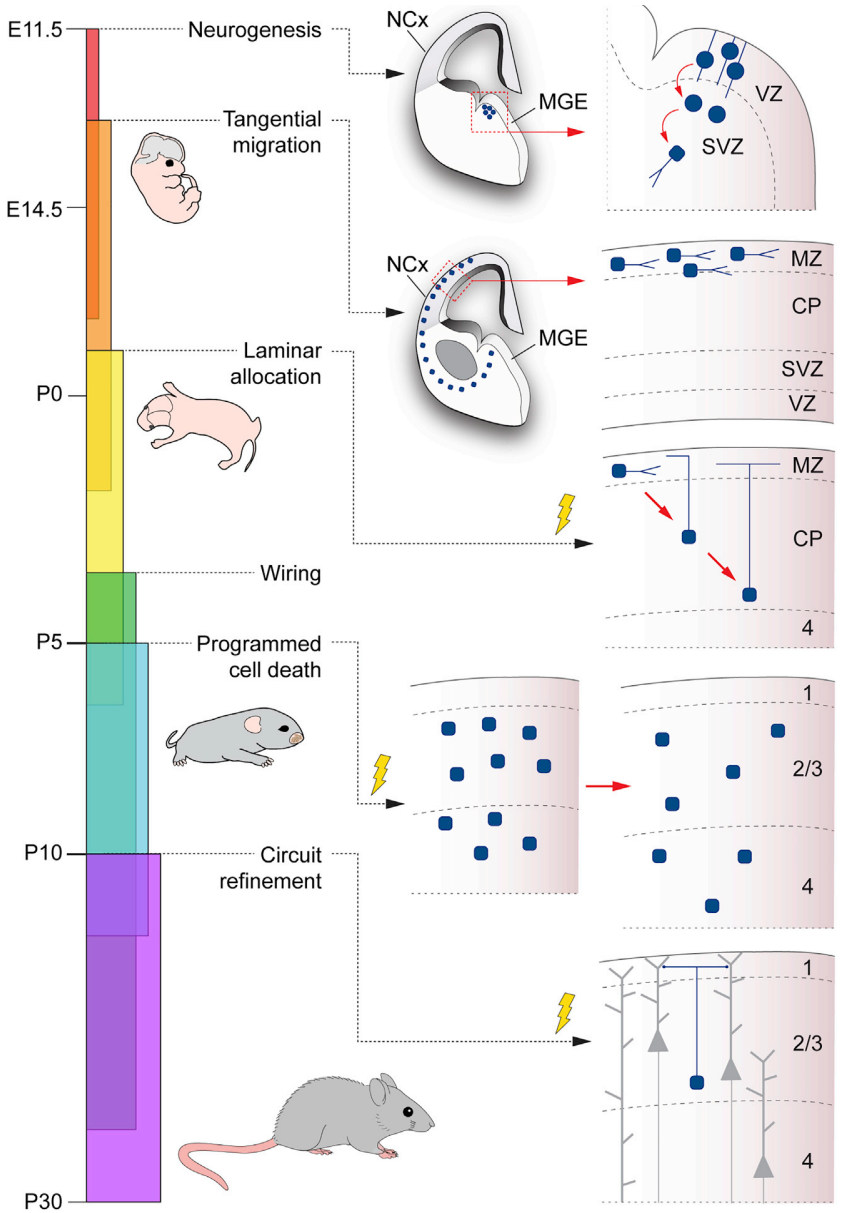
Self-organized organoids versus directed spheroids





Birey et al., Nature, 2017

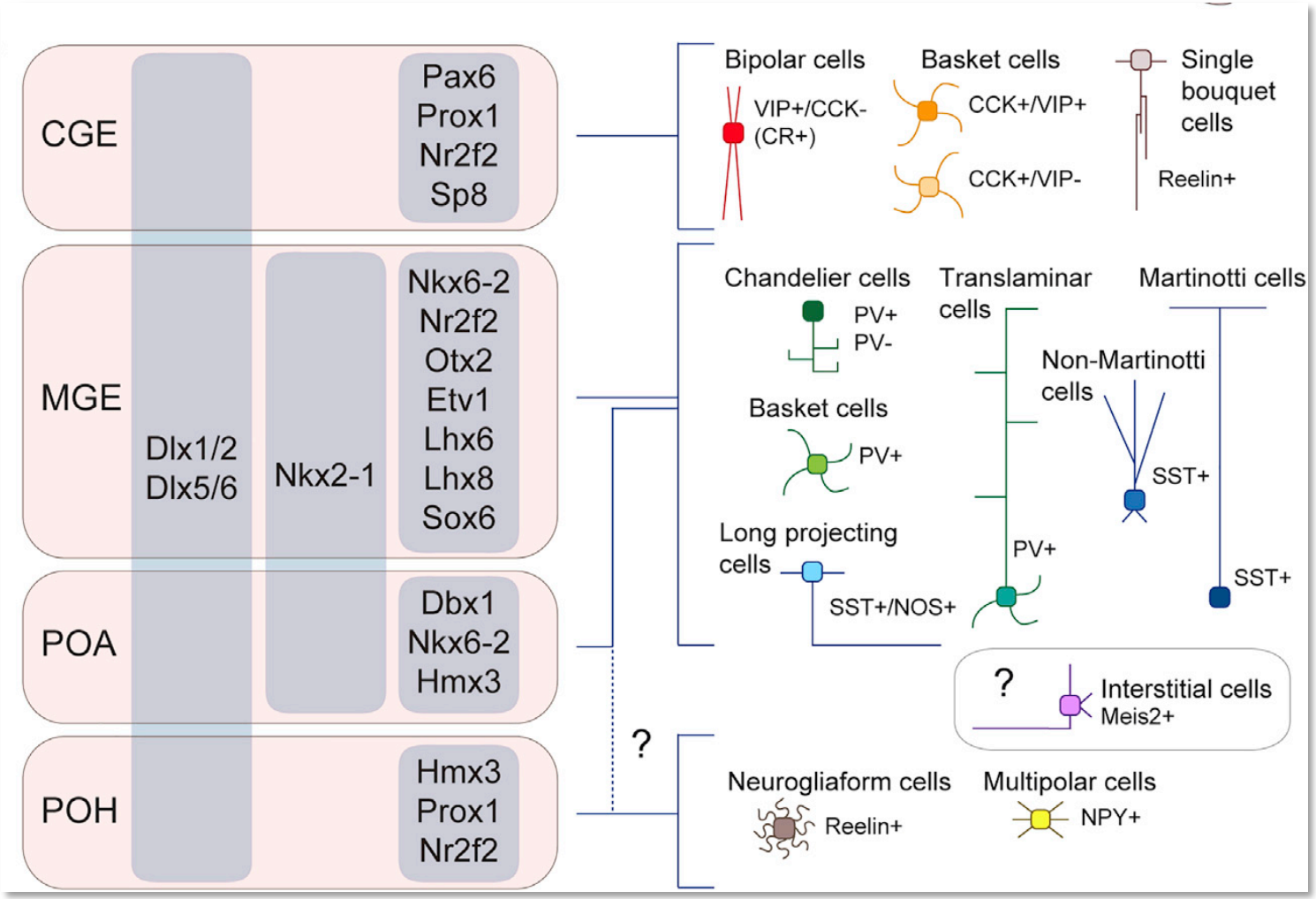
Milestones in the Development of Cortical Interneurons



Activity-dependent events

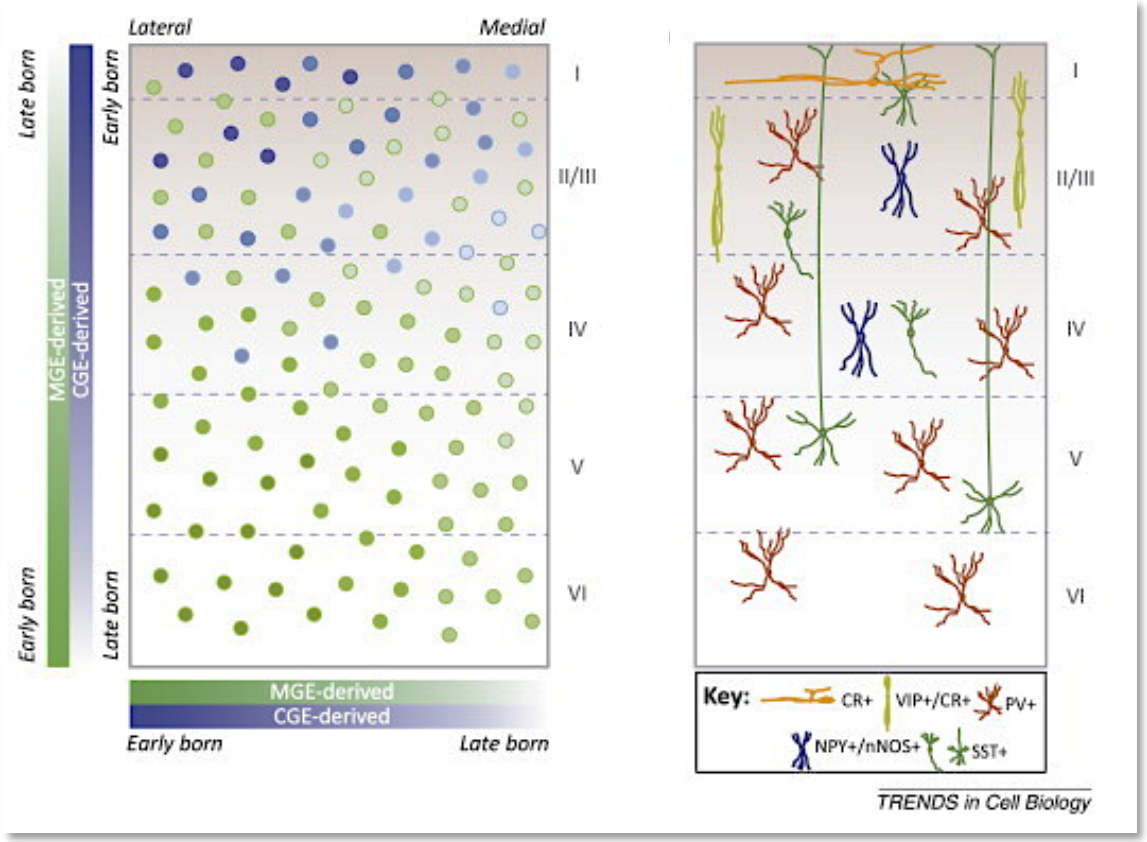
Lim et al., Neuron, 2018

GE-specific molecular codes to specify distinct interneuron subtypes

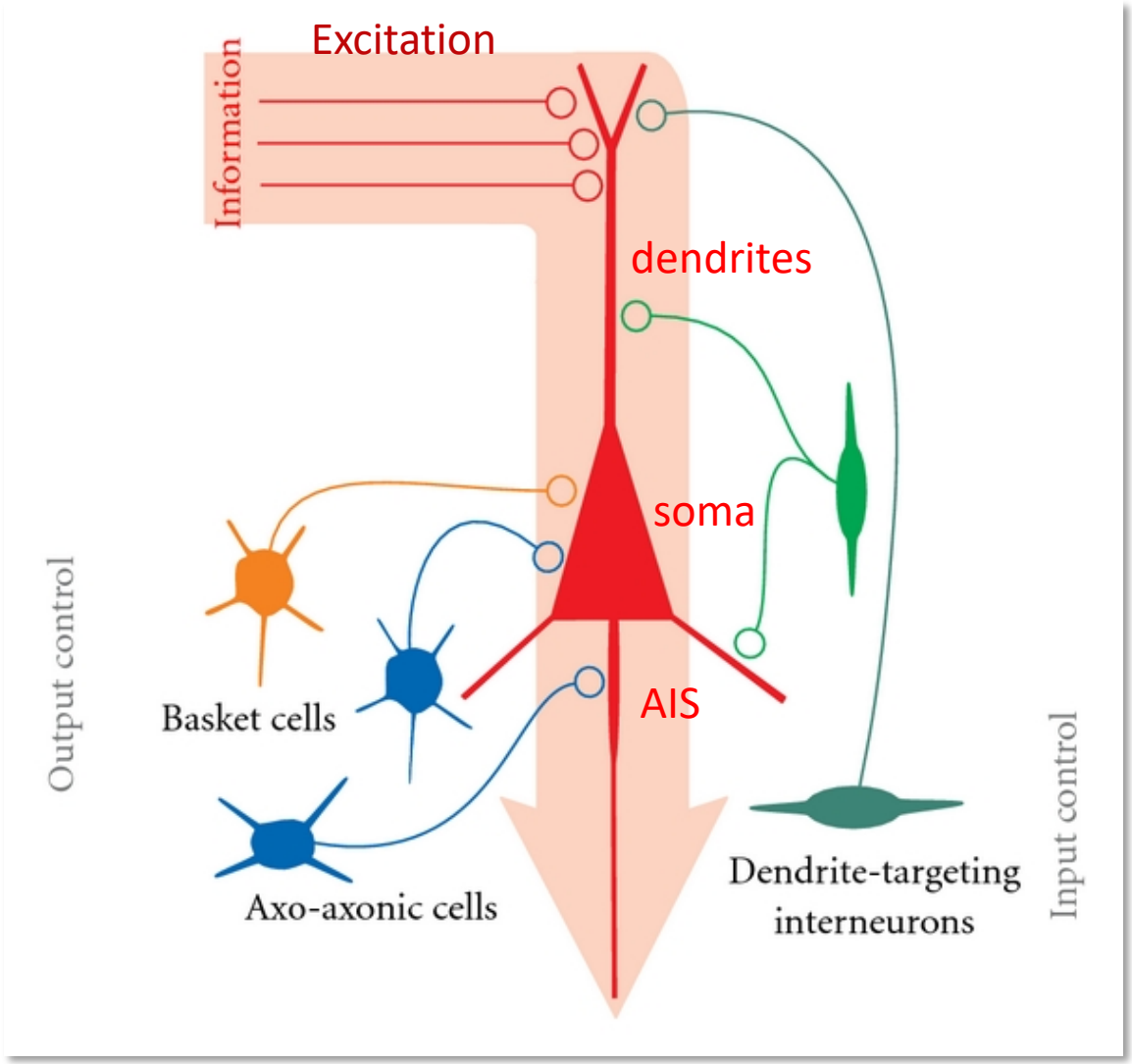


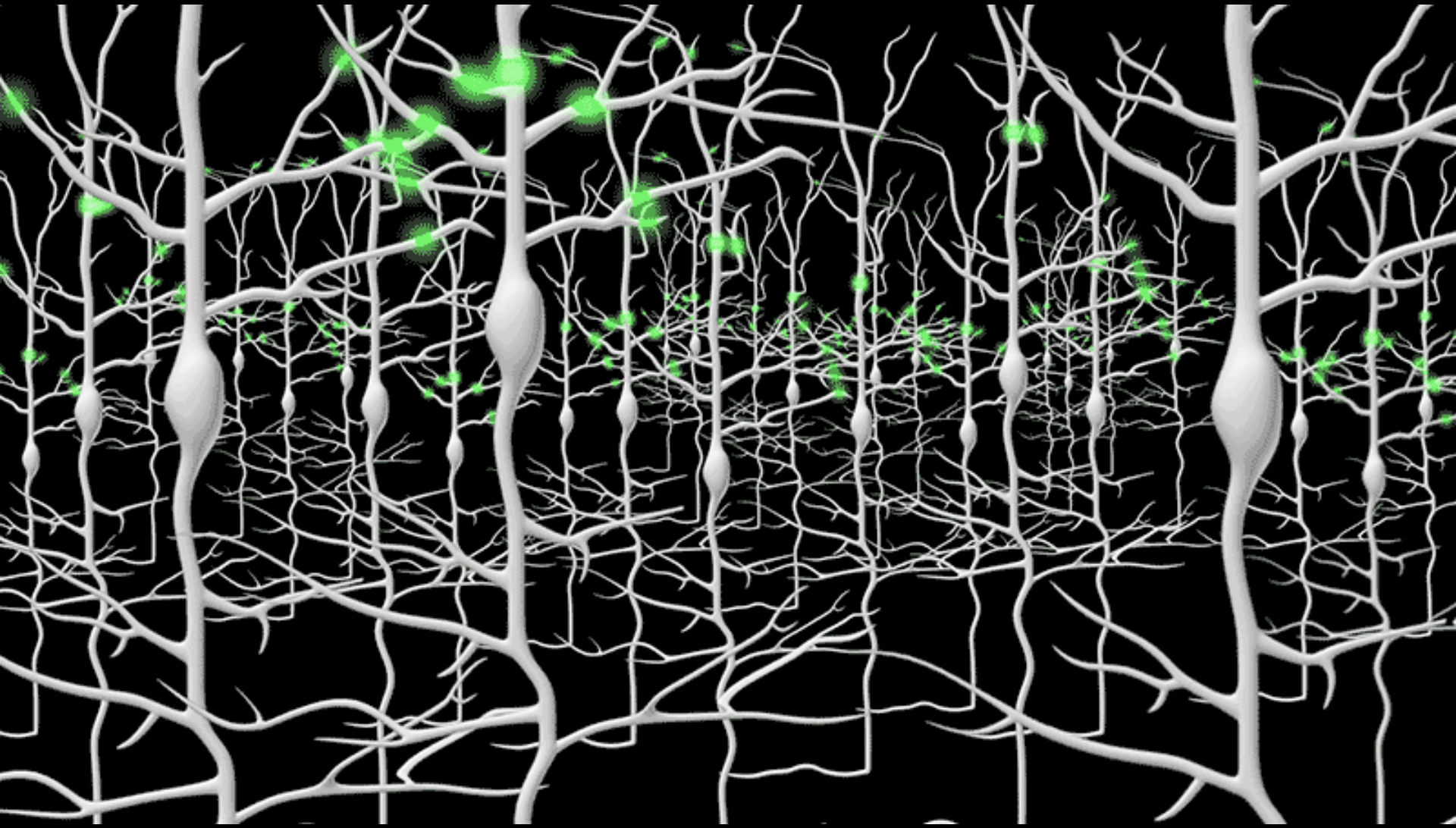
From Cauli et al., 2014
Lim et al., Neuron, 2018

Early and Late Development of Cortical Interneurons

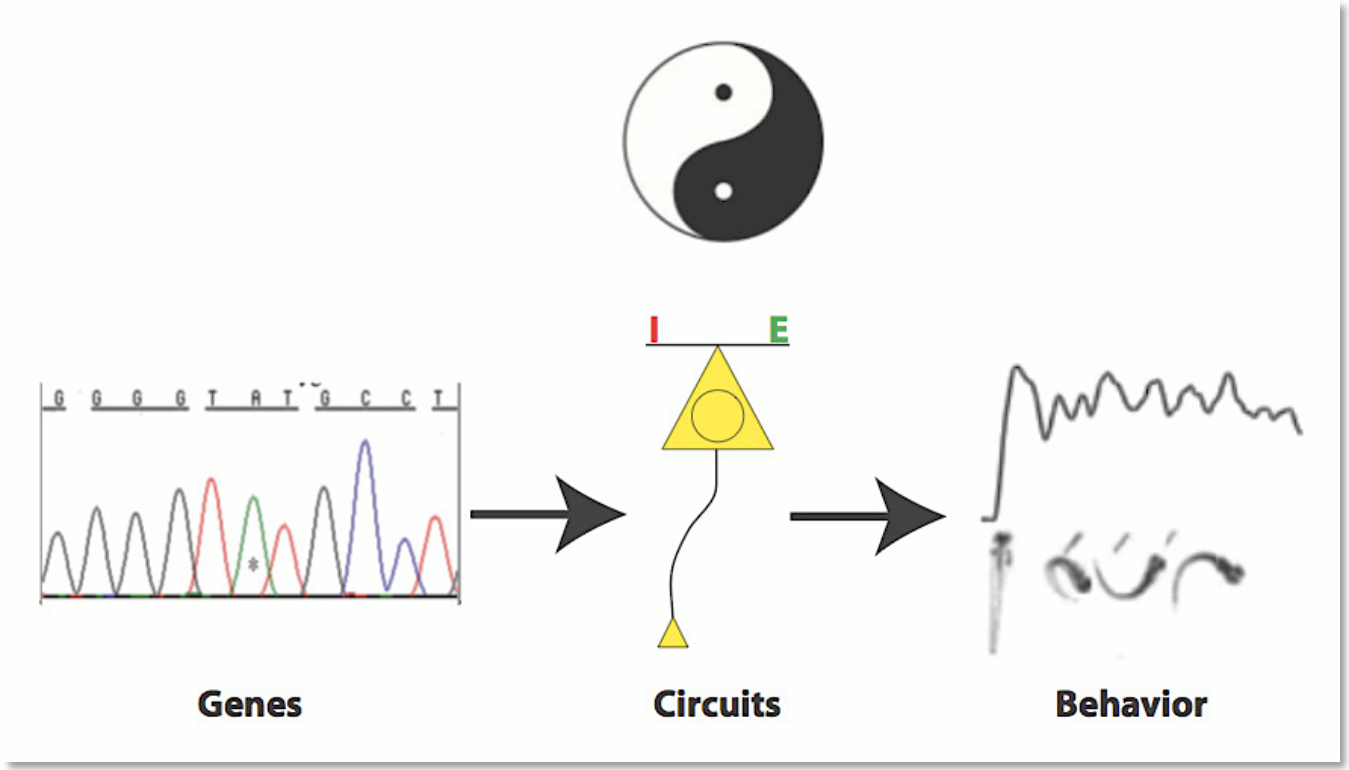


Inhibitory control of cortical pyramidal neurons by GABAergic interneurons

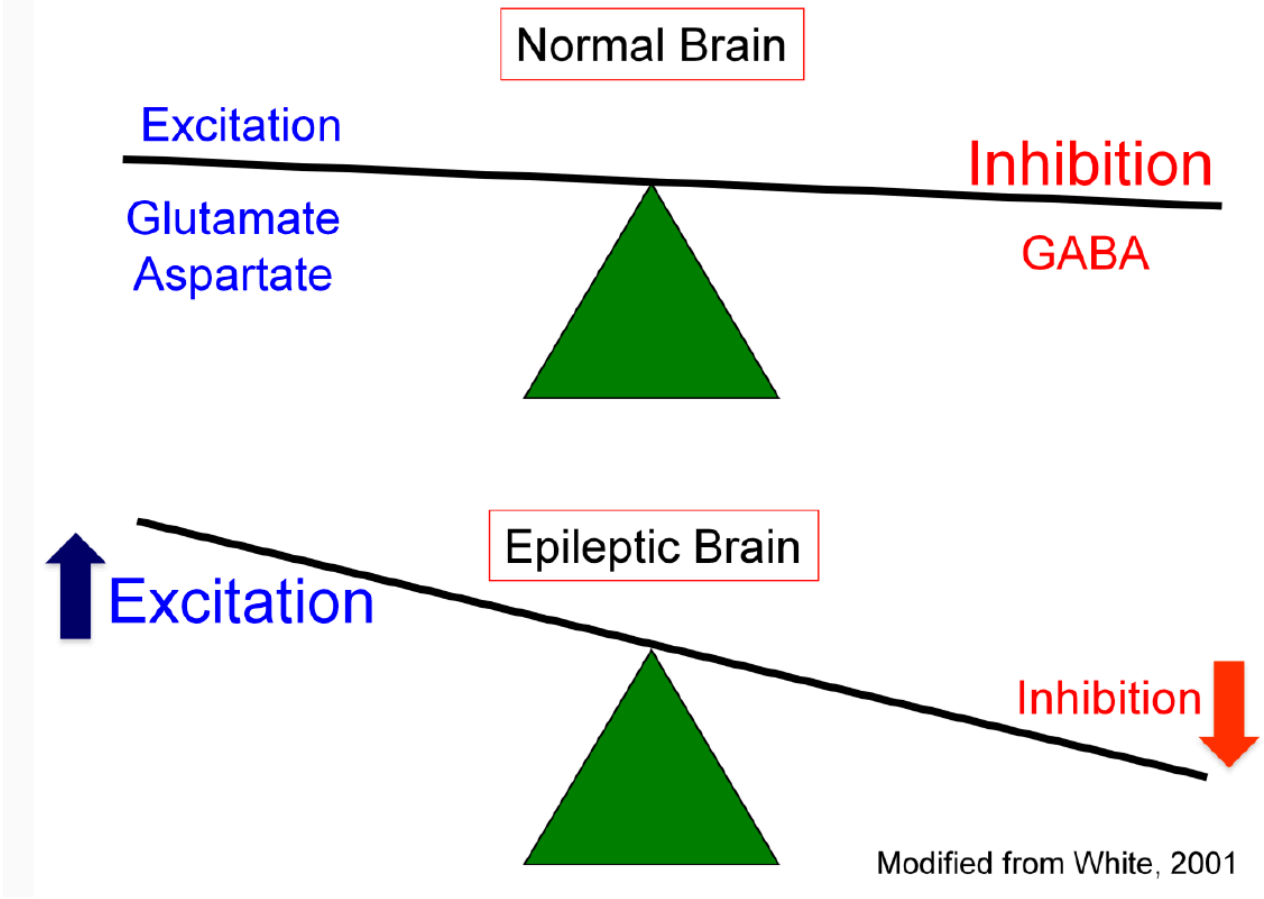




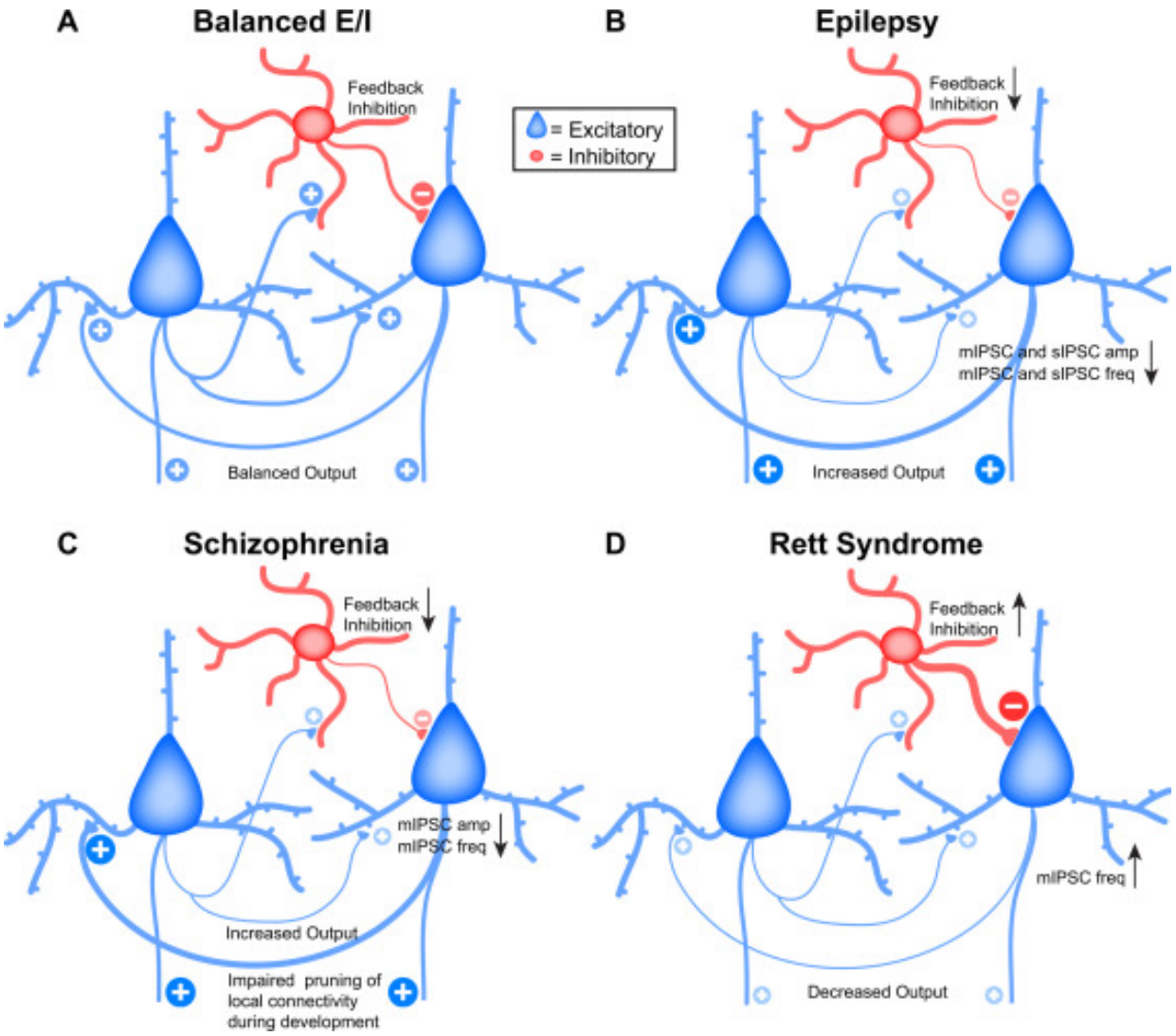
Balancing Neuronal Excitation and Inhibition for Functional Behavior



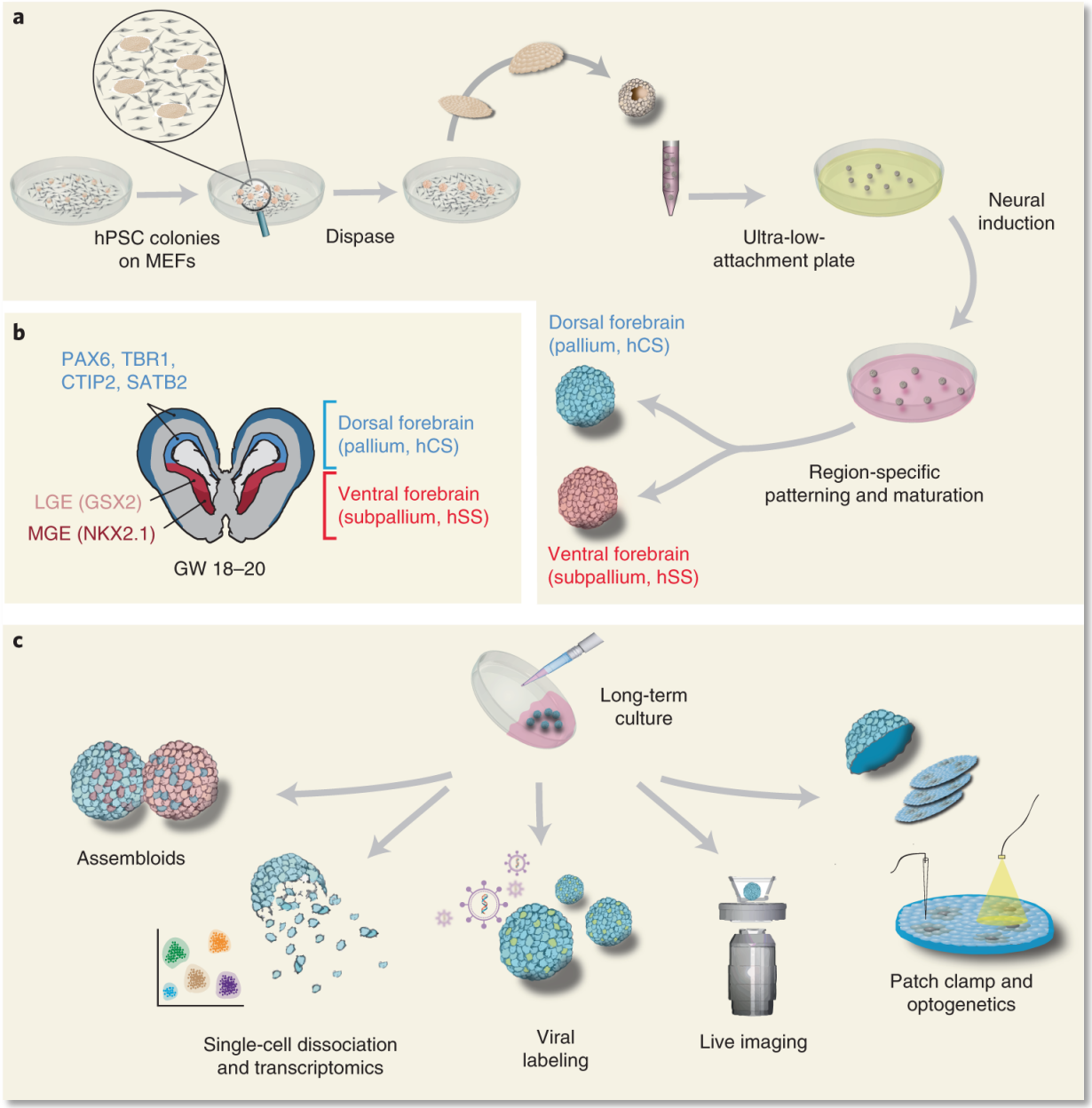
Balance of Neuronal Excitation and Inhibition for Proper Behavior



Changes in circuit excitability due to shifts in excitation/inhibition (E/I) balance



Can we reproduce E/I imbalance in cerebral organoids?




THANK YOU