"Understanding Brain Development as a Foundation for Understanding Brain Diseases"

John Rubenstein, UCSF

BBRF Webinar

May 13, 2014

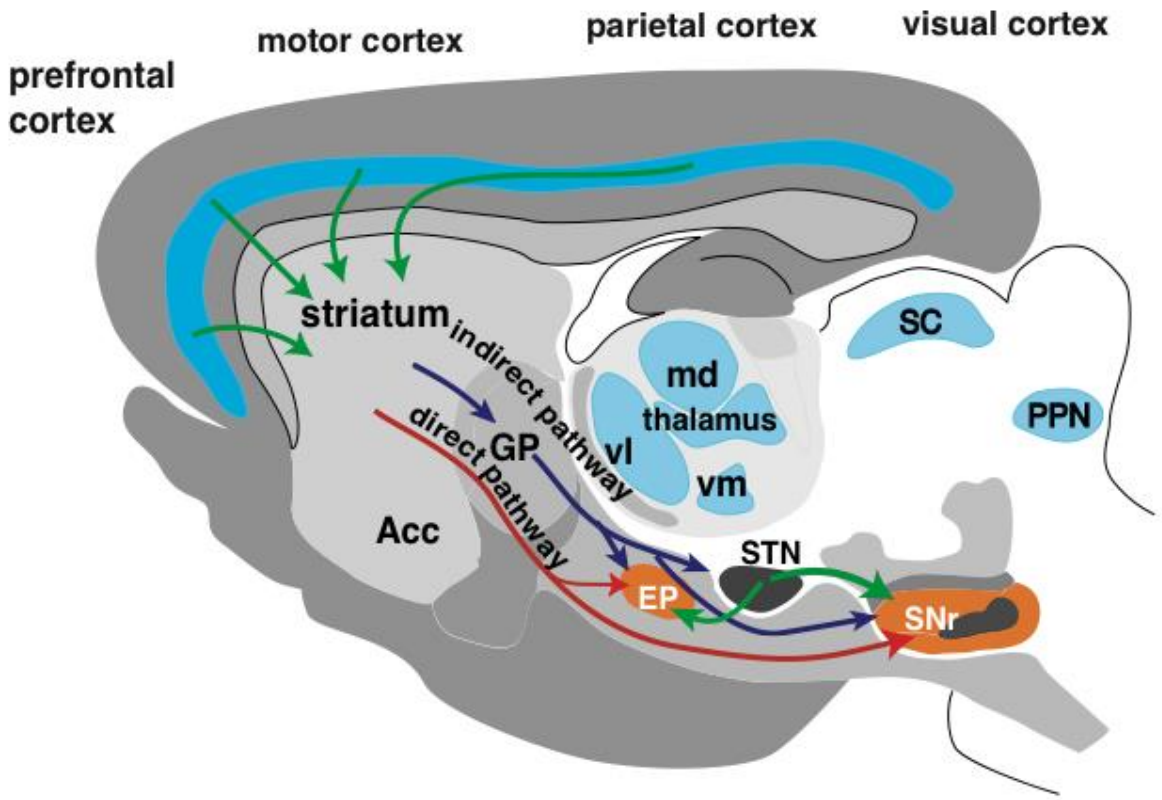
Hypothesis:

Many Psychiatric Disorders Are Caused by Dysfunction of Brain Circuits

Due to Abnormal Development and/or Function of Specific Circuits

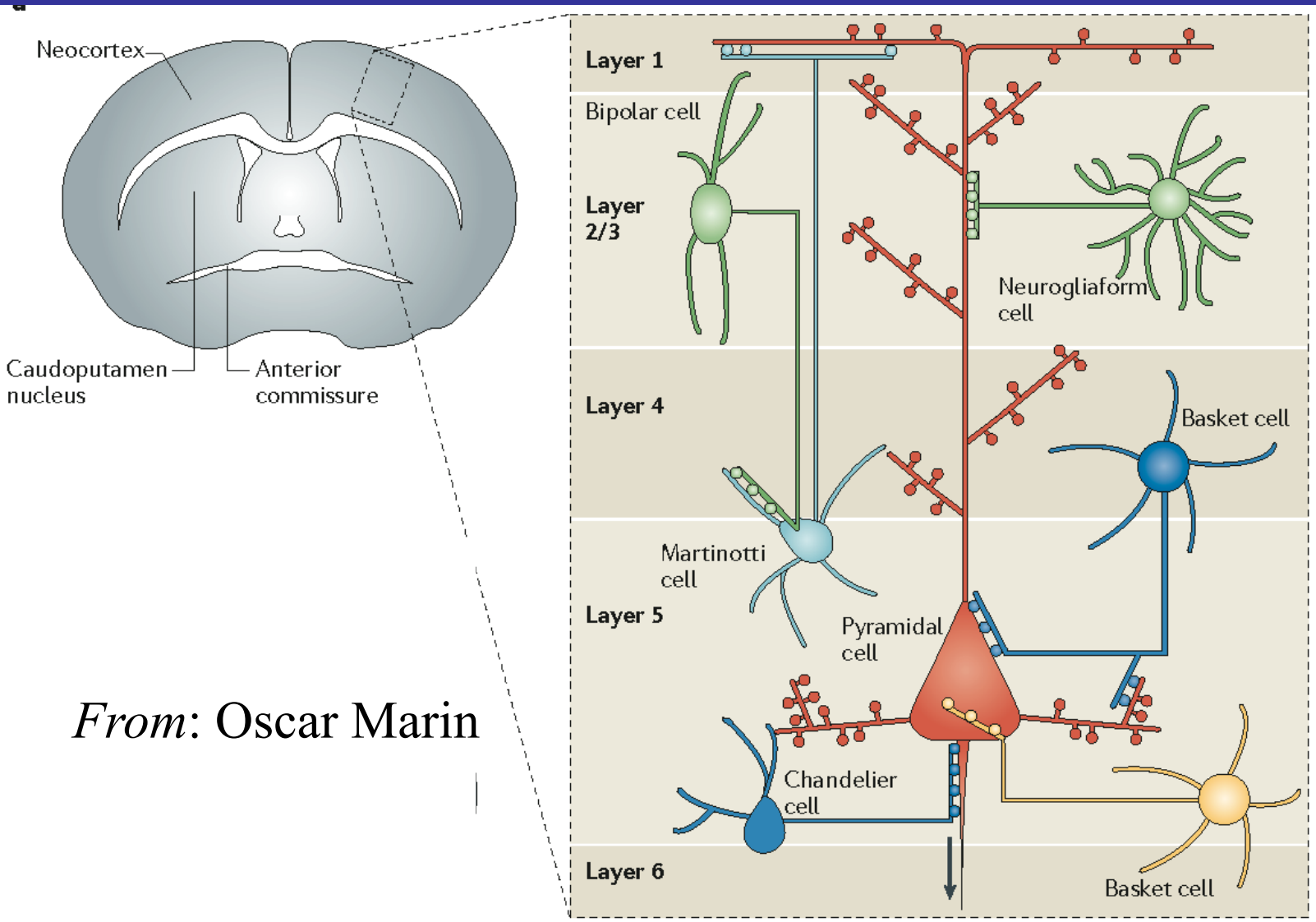
Two General Types of Circuits

Long Distance Circuits



From: Charles Gerfen

Local Circuits



From: Oscar Marin

Review of Major Steps in Brain Development

Steps In Neural Development

Induction

Neurulation

Regional Patterning (anteroposterior, dorsoventral)

Proliferation

Migration (mediolateral patterning of the neural tube)

Axon Pathfinding and Synapse Formation

Myelination

Steps In Neural Development

Induction*

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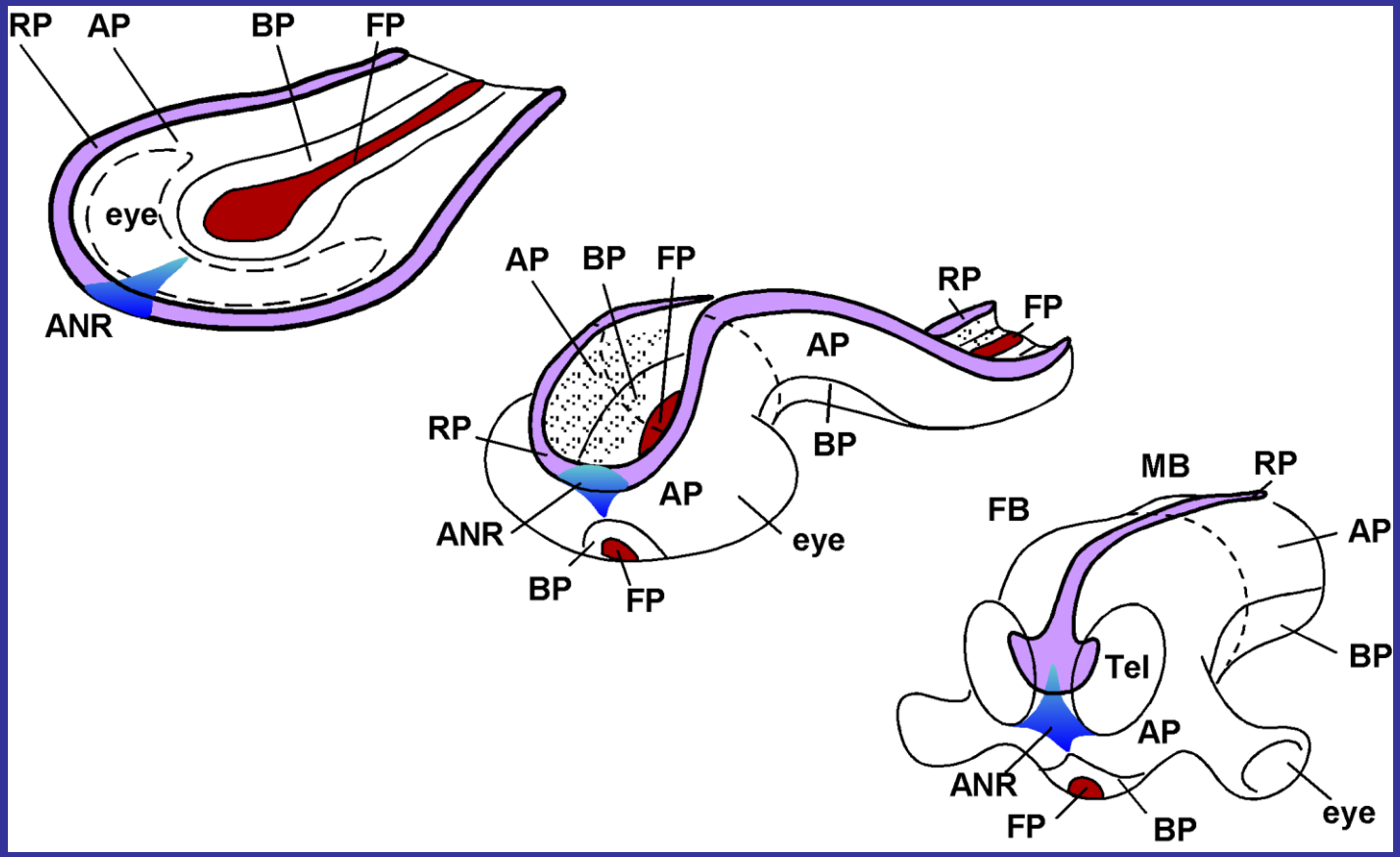
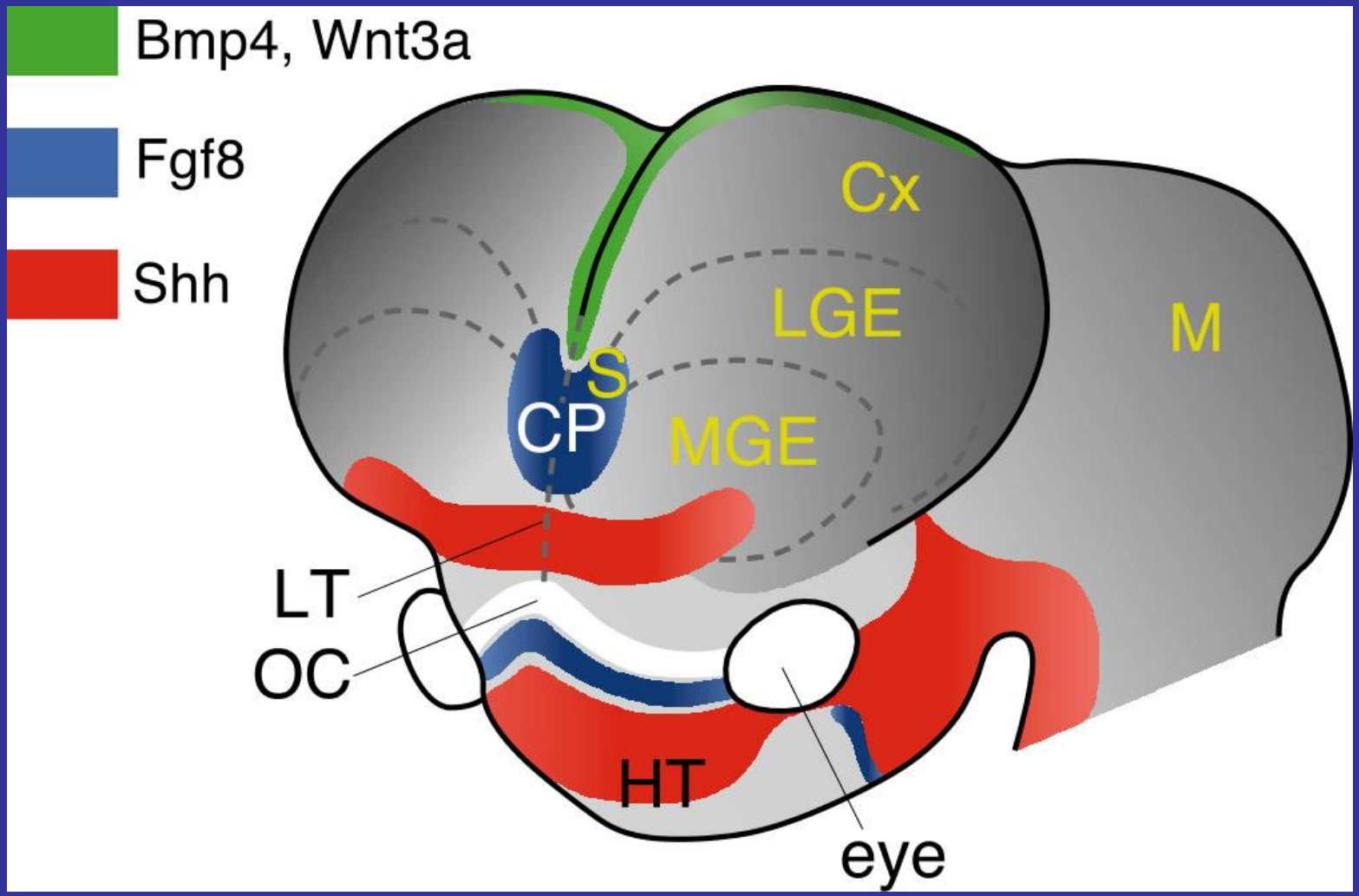
Neurulation and Early Patterning Centers



Rubenstein, JLR and Puelles, L. (2008) Development of the Nervous System. Molecular Basis Of Inborn Errors of Development. Second Edition. Epstein CJ, Erikson RP and Wynshaw-Boris A, editors. Oxford University Press. Chapter 7.

Patterning Centers in the Forebrain



Steps In Neural Development

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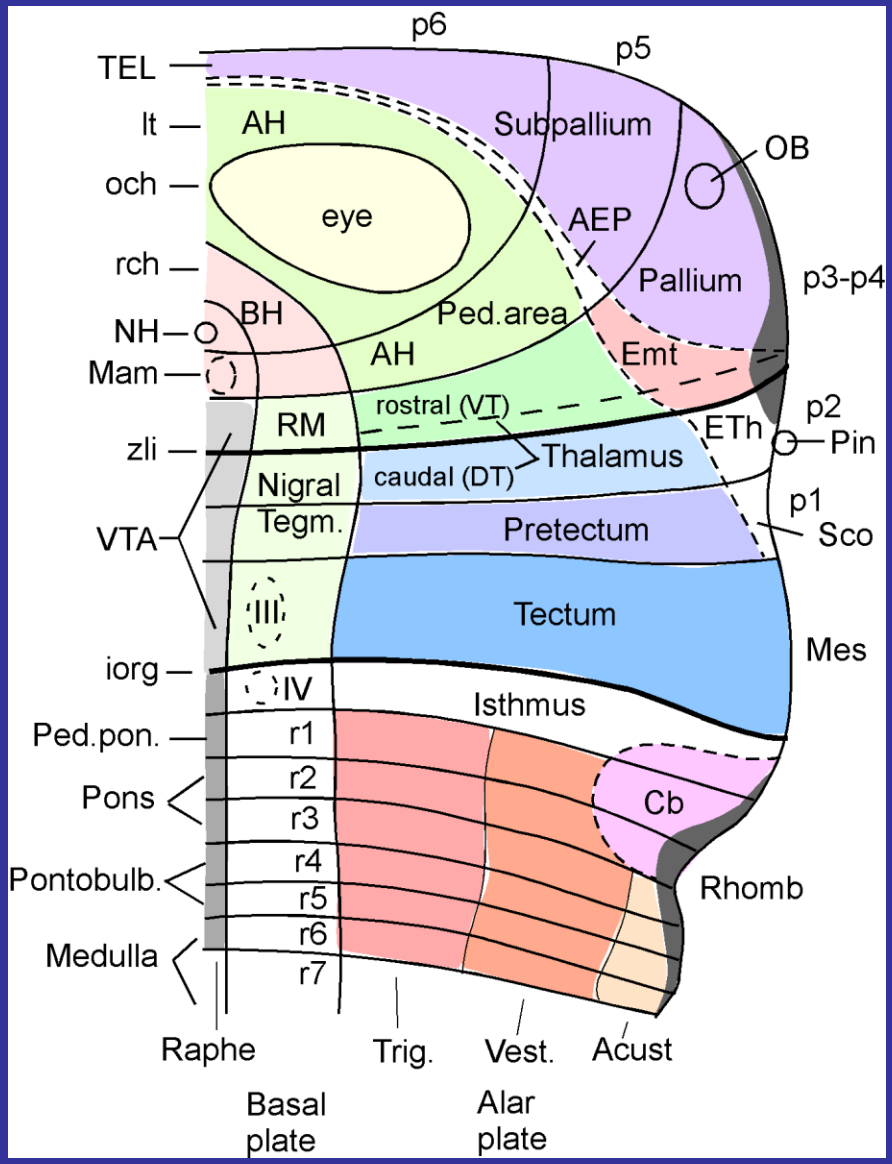
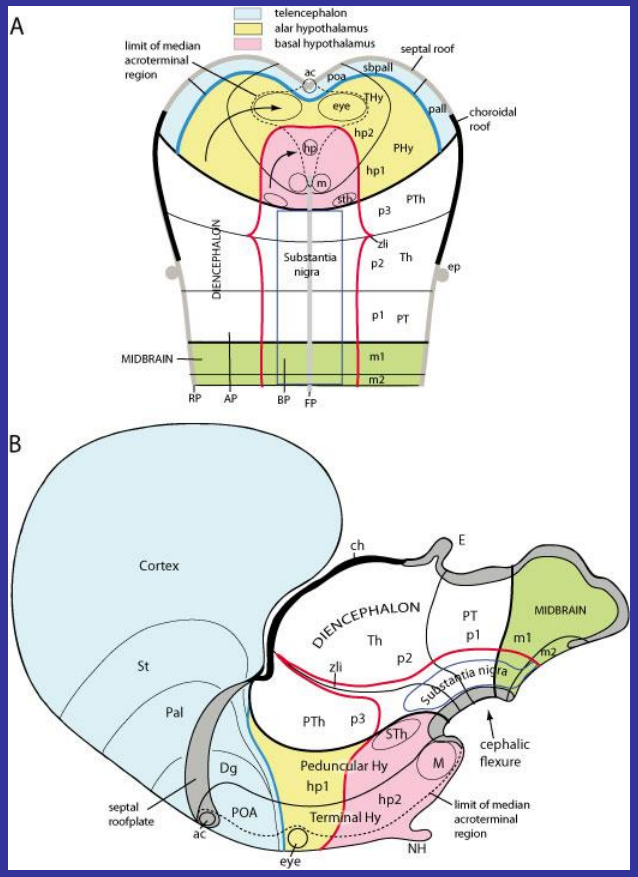
Blueprint of the Brain



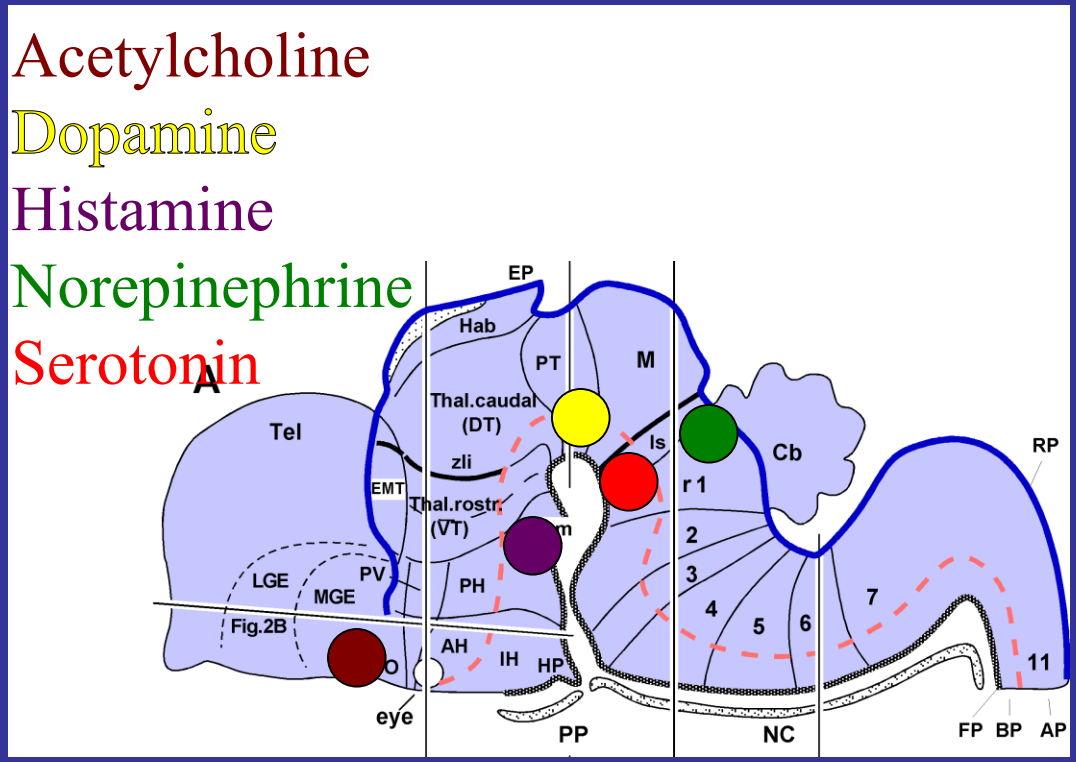
Transverse and Longitudinal Organization of the CNS



Neural Plate

Neural Tube

Monoamine Neurons: Specific Locations



Steps In Neural Development

Induction

Neurulation

Regional Patterning (anteroposterior, dorsoventral)

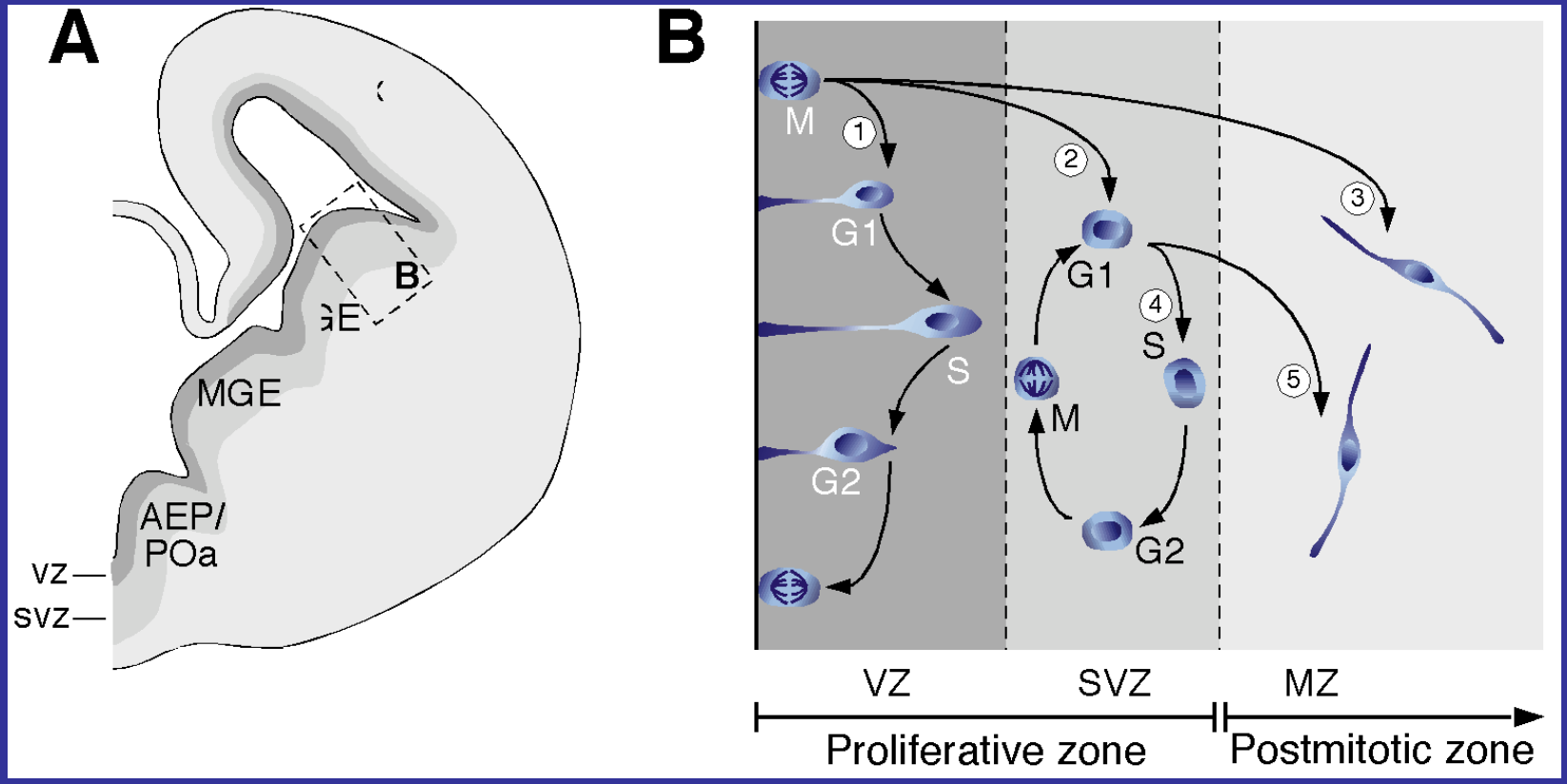
Proliferation*

Migration (mediolateral patterning of the neural tube)

Axon Pathfinding and Synapse Formation

Myelination

Progenitor Zones



Steps In Neural Development

Induction

Neurulation

Proliferation

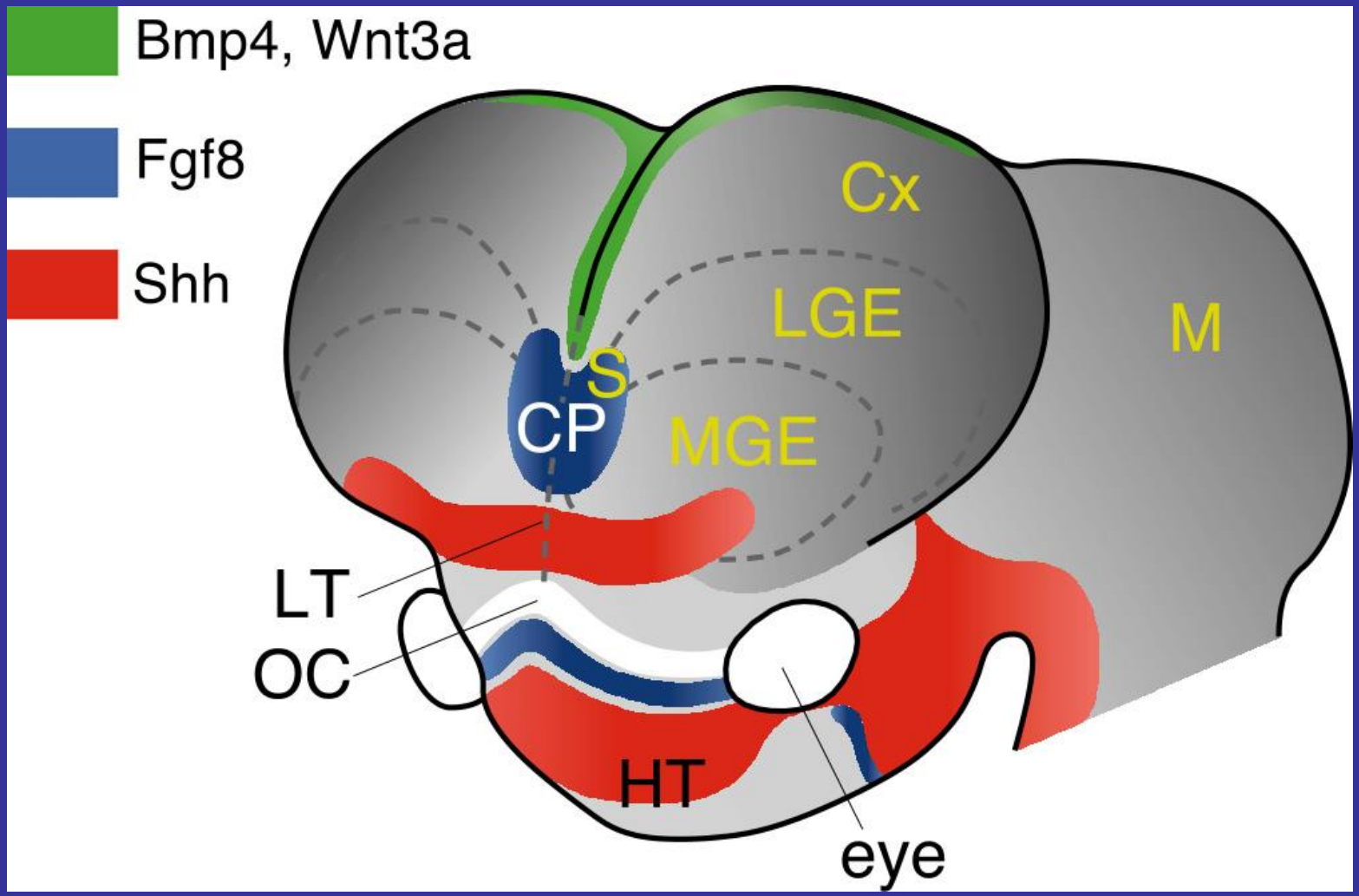
Regional Patterning (dorsoventral)*

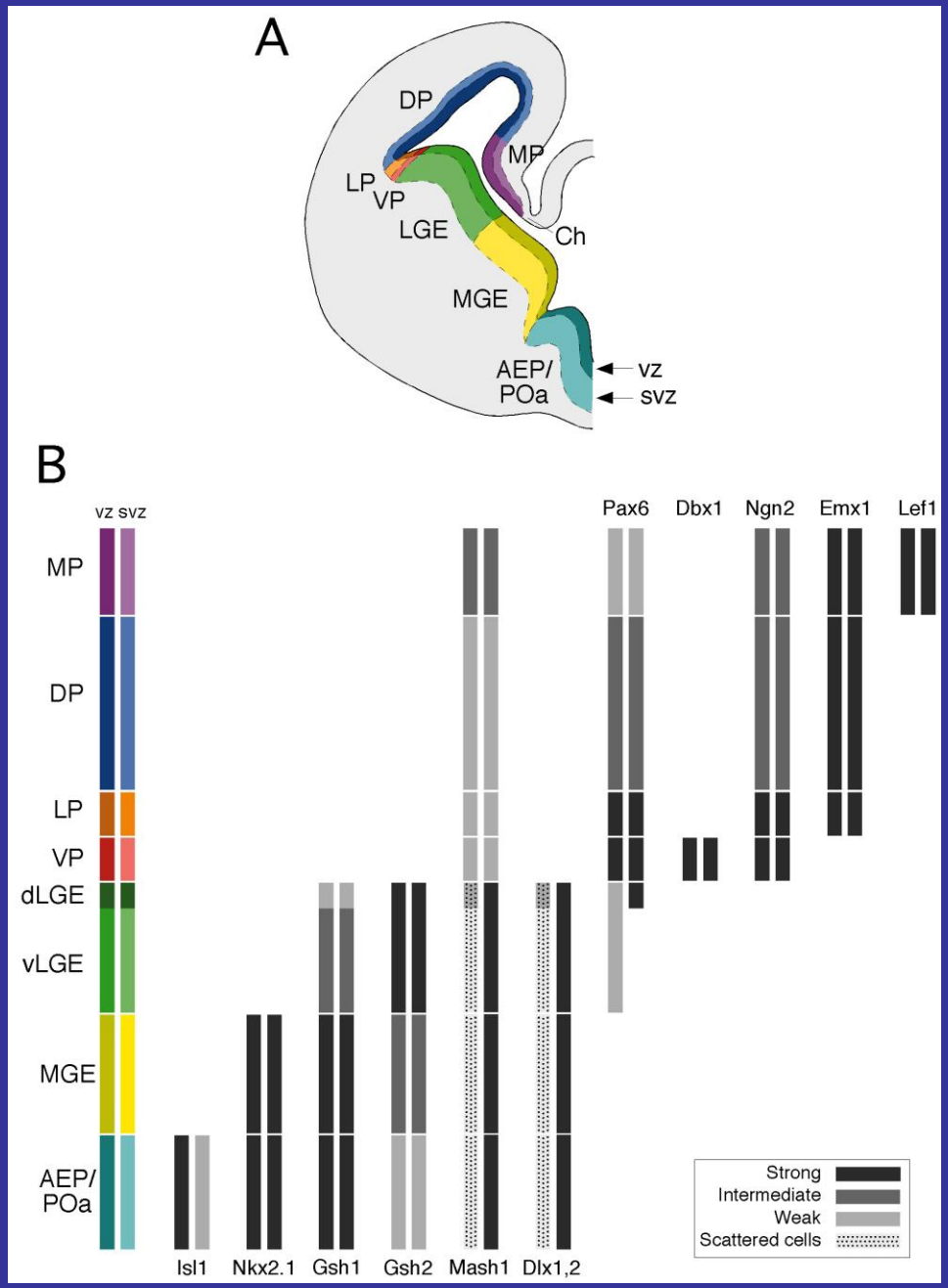
Migration (mediolateral patterning of the neural tube)

Axon Pathfinding and Synapse Formation

Myelination

Patterning Centers in the Forebrain

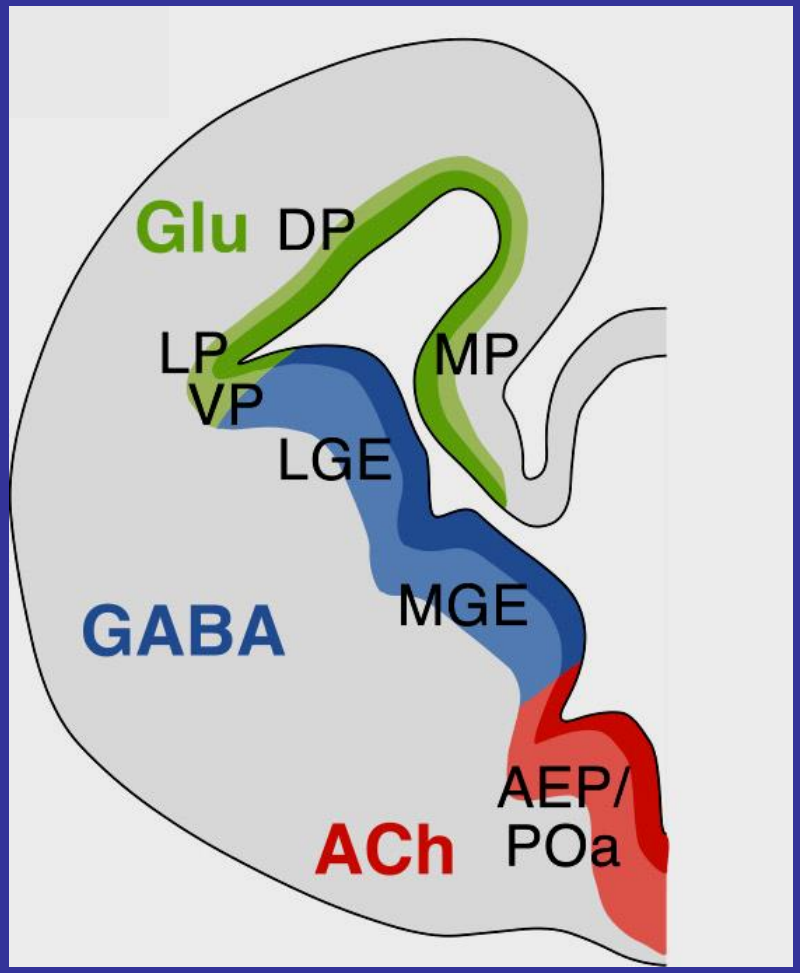




"Dorsoventral" Subdivisions Of the Telencephalon

Transcription Factors Which Regulate Regional Patterning And Differentiation of the Telencephalon

Patterning of Regions and Neural Identity



Marín O, Rubenstein JL. Nat Rev Neurosci. 2001 Nov;2(11):780-90

Steps In Neural Development

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Proliferation

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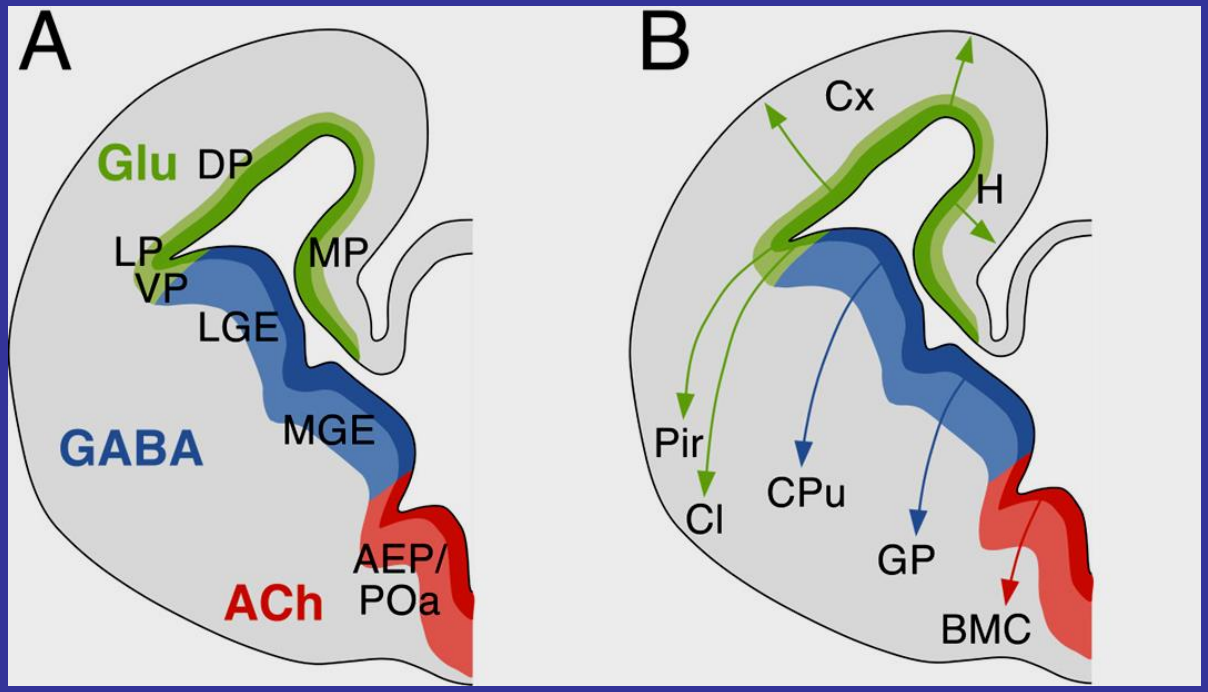
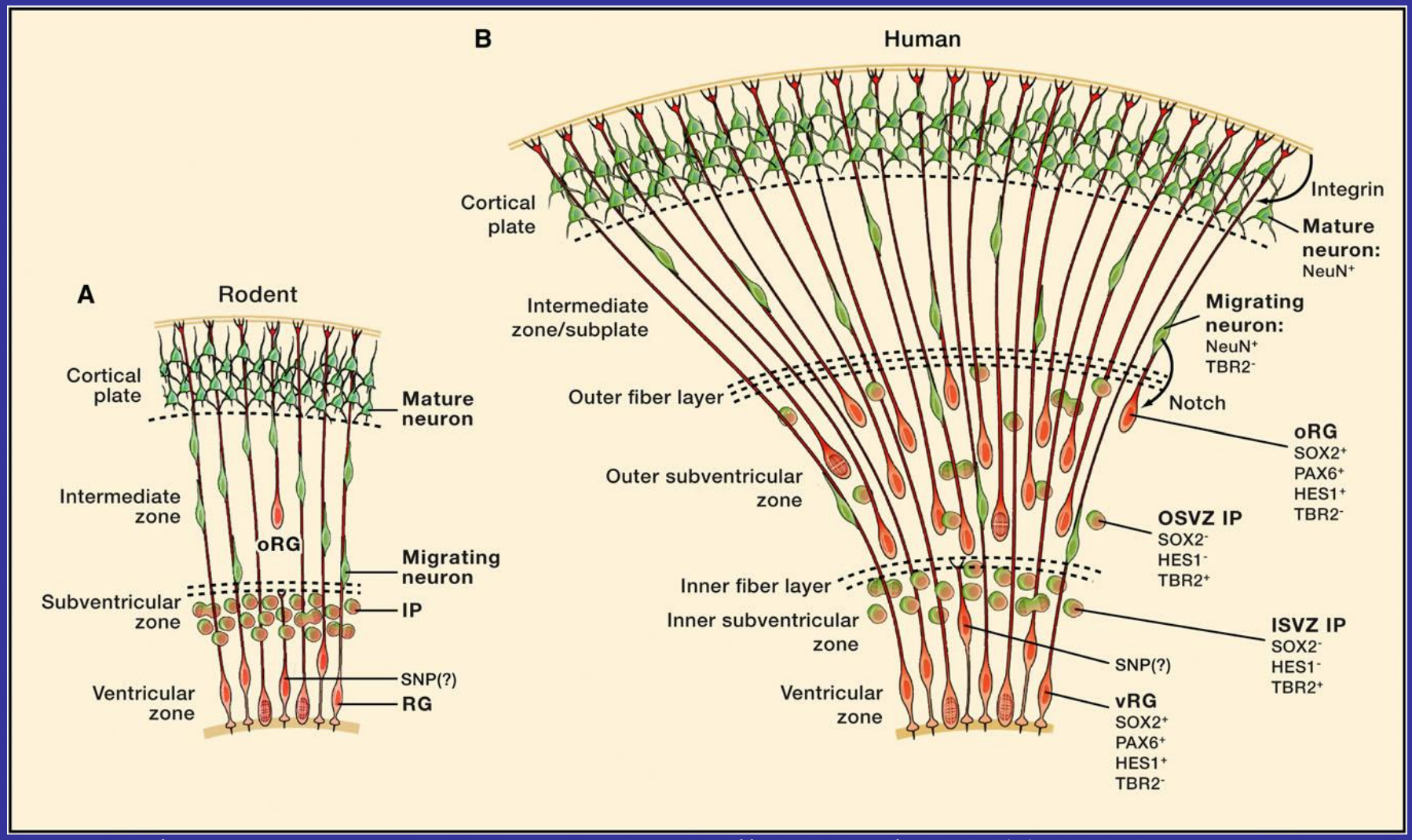
Myelination

Radial Migration in the Telencephalon

Radial Migration of Projection Neurons

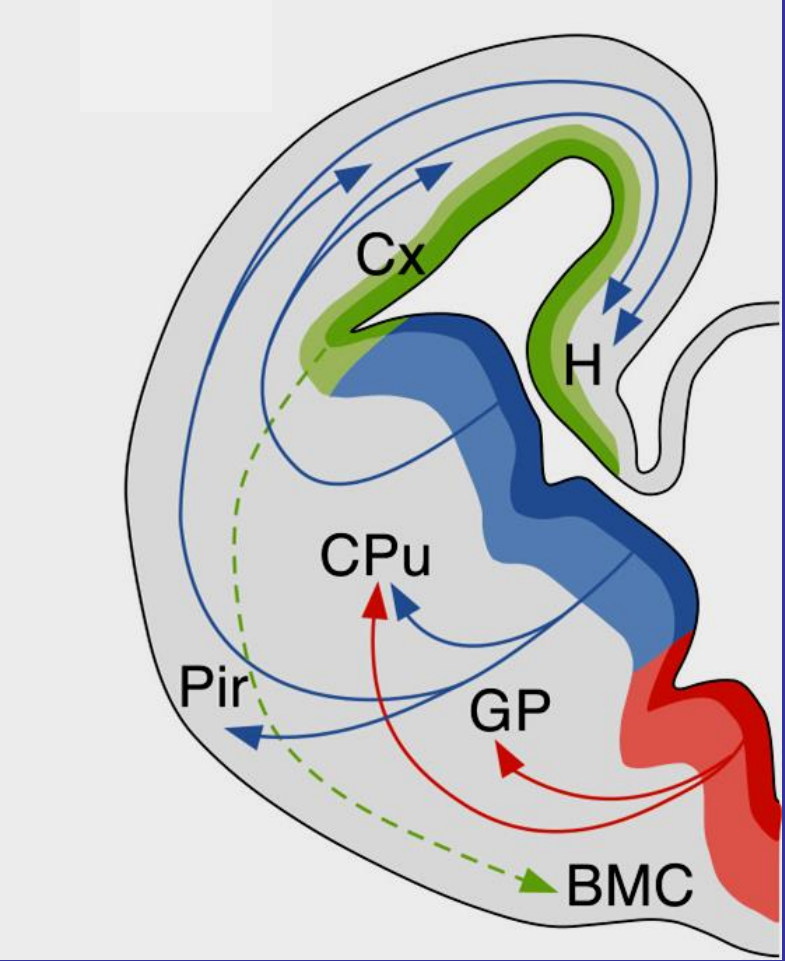


Radial Migration to Build the Cortex



From: Lui JH, **Hansen** DV, **Kriegstein** AR. Cell. 2011 Jul 8;146(1):18-36

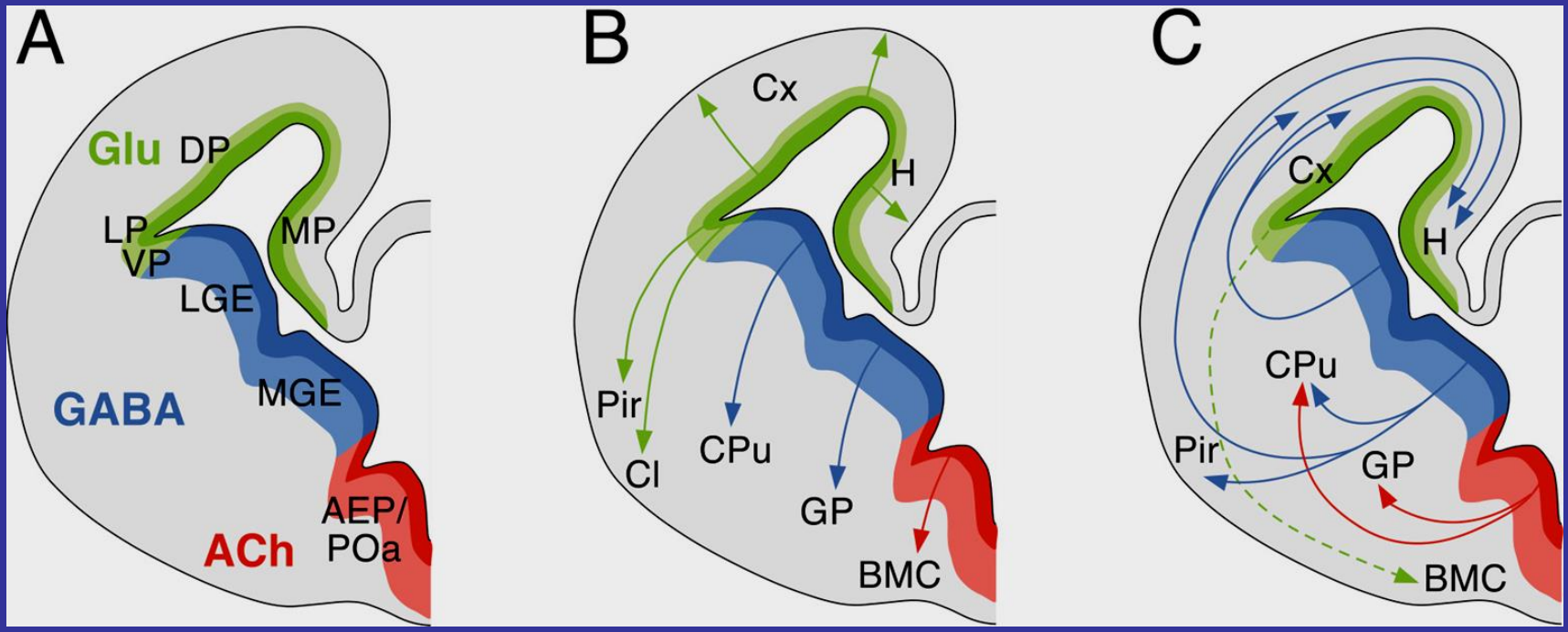
Tangential Migration of Interneurons



Marín O, Rubenstein JL.
Nat Rev Neurosci. 2001
Nov;2(11):780-90

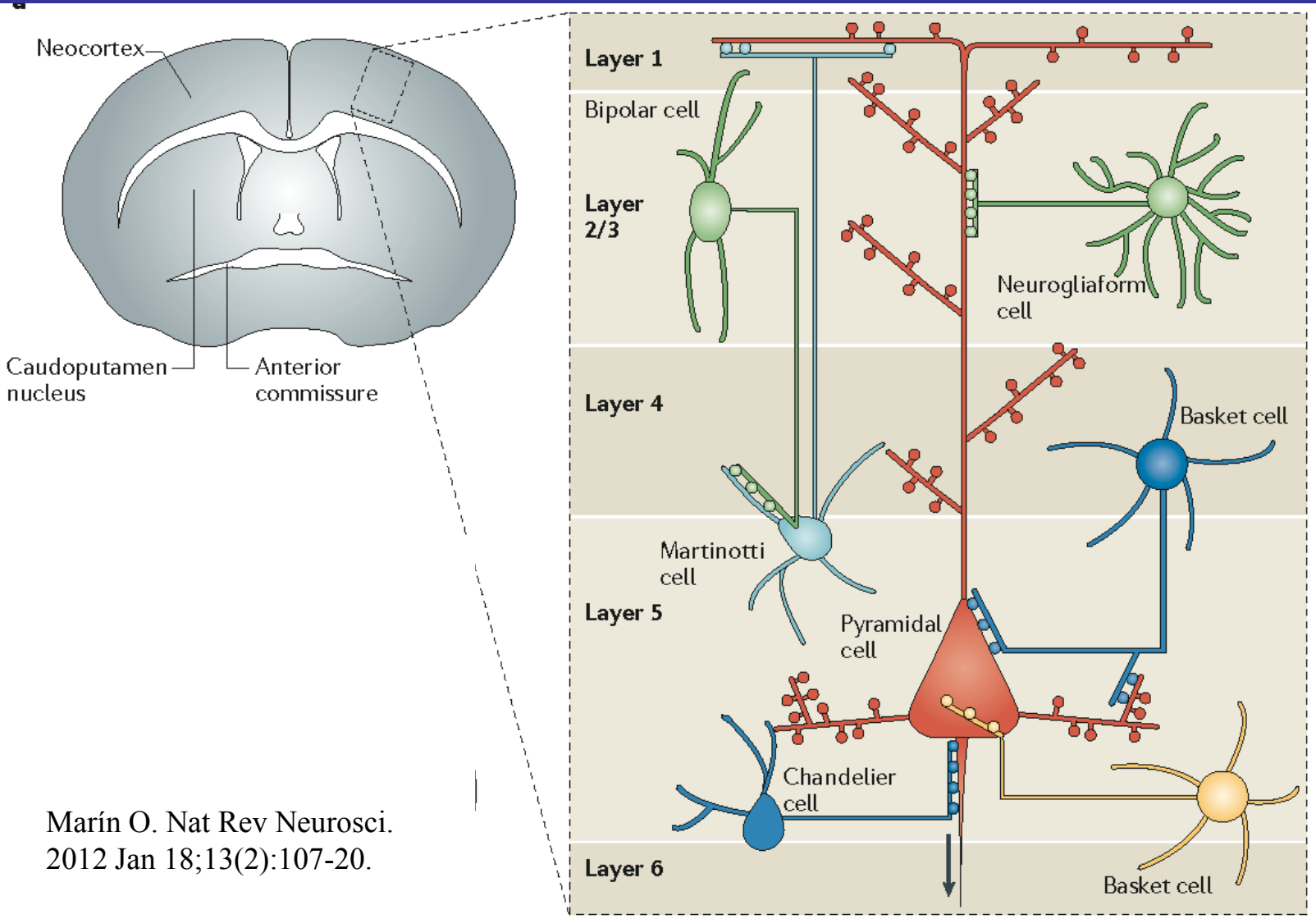
Radial and Tangential Migration in the Telencephalon

Radial Migration of Projection Neurons	Tangential Migration of Local Circuit Neurons



Assembly of Circuits

Cortical Circuits: Projection Neurons and Interneurons



Marín O. Nat Rev Neurosci. 2012 Jan 18;13(2):107-20.

Steps In Neural Development

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Migration (mediolateral patterning of the neural tube)

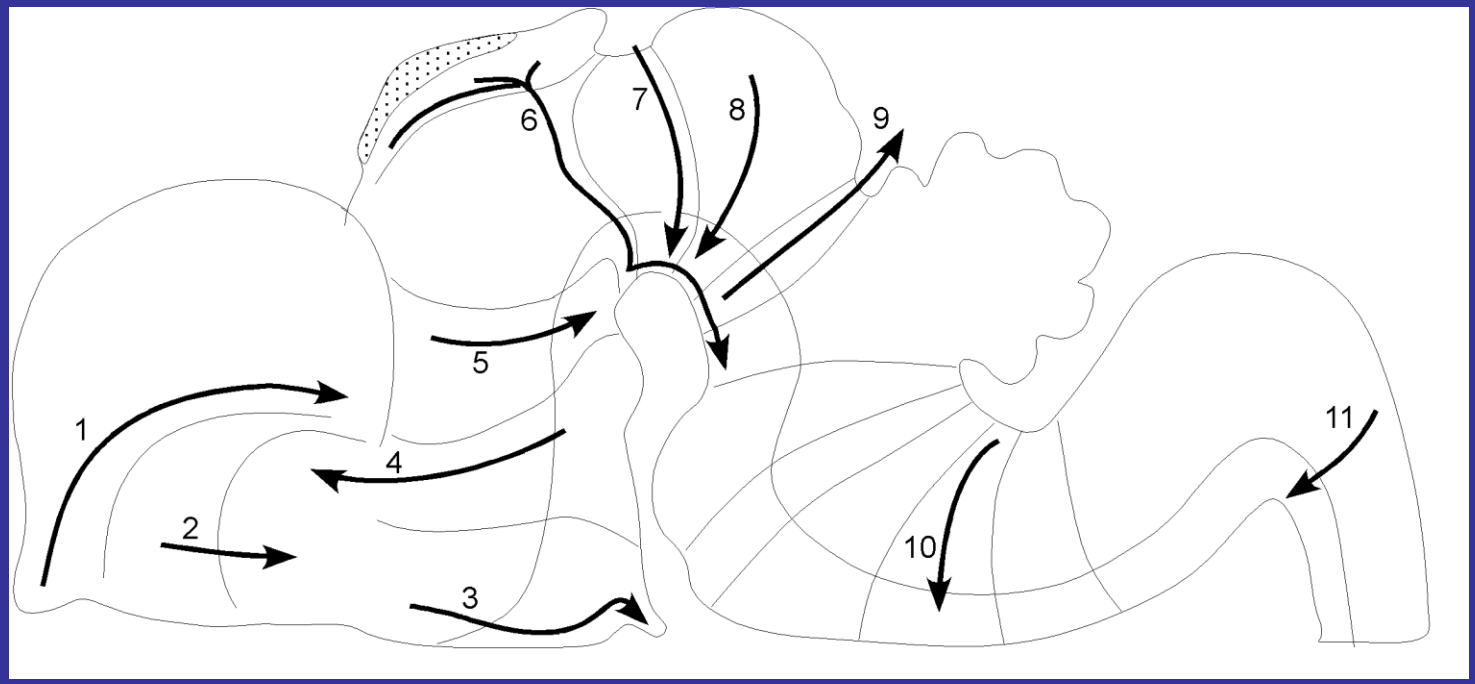
Axon Pathfinding and Synapse Formation*

Myelination

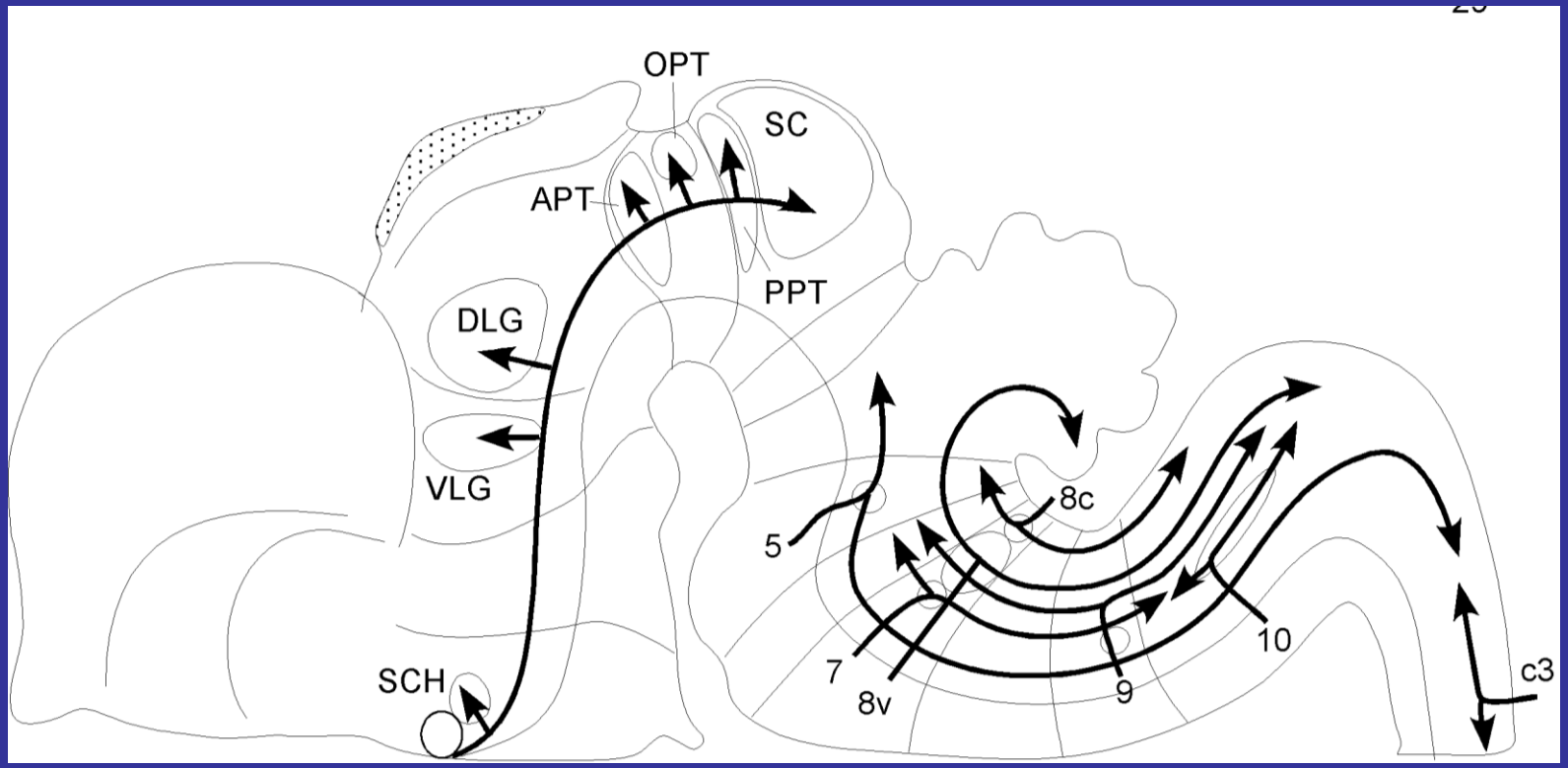
Axons Grow Transversely or Longitudinally

Follow Specific Molecular Landmarks

Transverse Pathways



Longitudinal Pathways: Branch at Functionally Related Nuclei



Corpus Callosum

Autism Traits in Individuals with Agenesis of the Corpus Callosum

Lau YC, Hinkley LB, Bukshpun P, Strominger ZA, Wakahiro ML, Baron-Cohen S, Allison C, Auyeung B, Jeremy RJ, Nagarajan SS, Sherr EH, Marco EJ.

J Autism Dev Disord. 2012 Oct 5.

Steps In Neural Development

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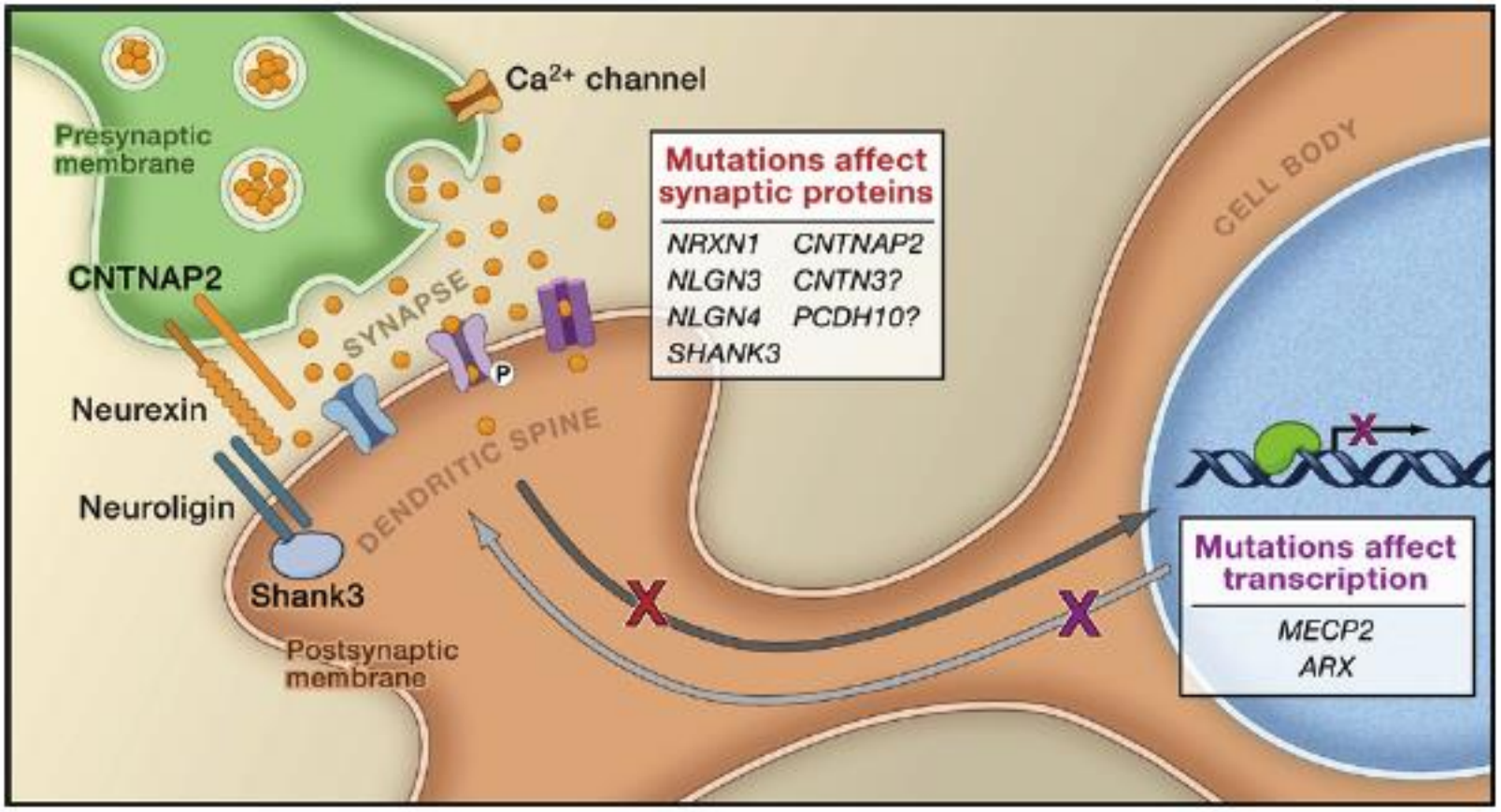
Synapse Formation and Function*

Myelination

Molecular Defects at the Synapse in Autism



Walsh, Morrow and Rubenstein, 2008

Steps In Neural Development

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Synapse Formation and Function

Myelination, and Functions of Non-neural cells*

Models For Mechanisms of Neurodevelopmental Disorders

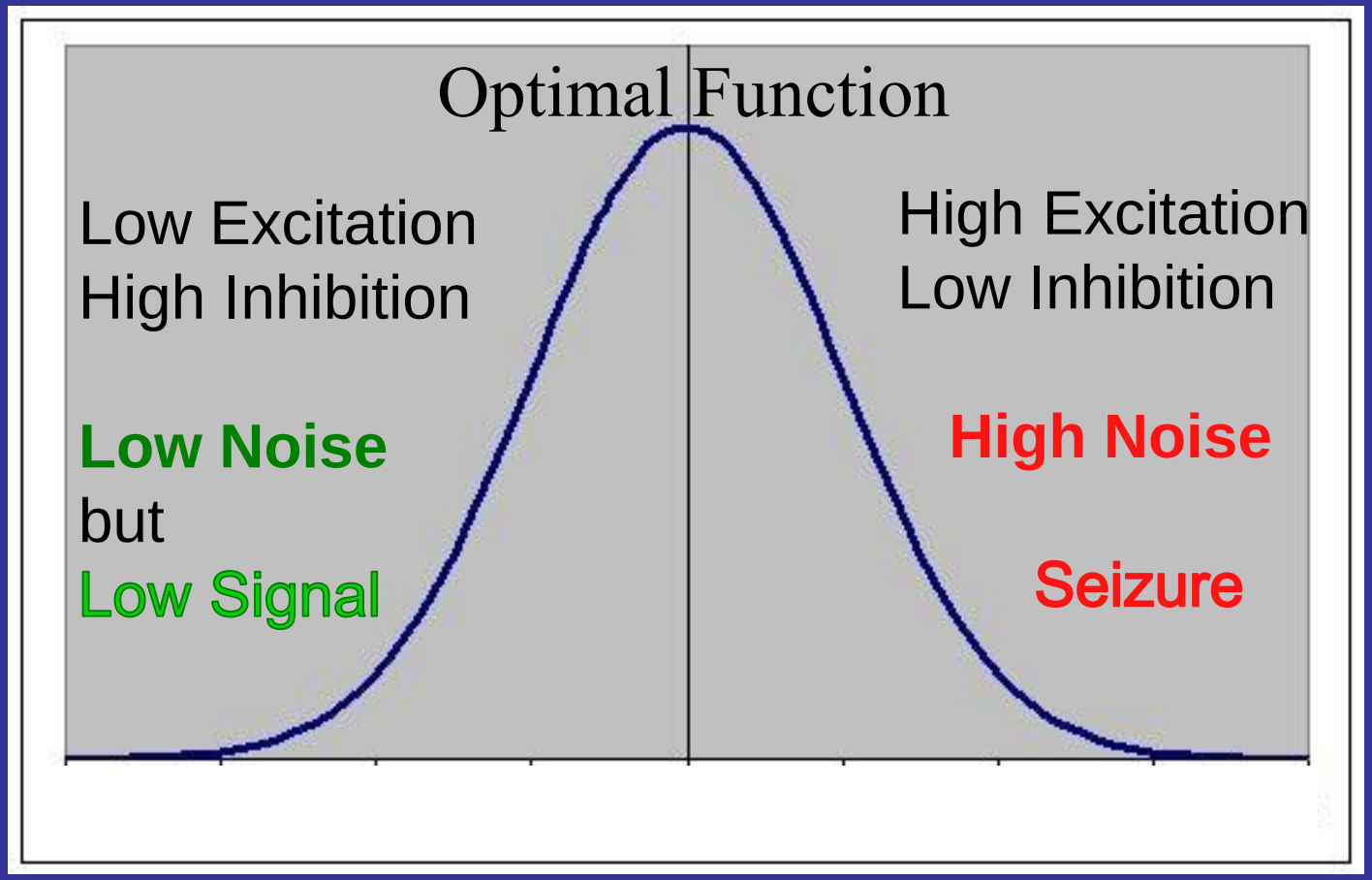
Rubenstein JL, (2010).
J Child Psychol Psychiatry. 2010.
52(4):339-55.

Models For Mechanisms of Neurodevelopmental Disorders

1. Detection of salient synaptic information – signal/ noise processing (excitation/inhibition balance)

Epilepsy and Cognitive Dysfunction in Autism

"Tuning" Curve for Optimal Neural Circuit Function



Changes in the Numbers and Functions of GABA Interneurons Can Alter the Tuning Curve

Autistic-like behavior in $Scn1a^{+/-}$ mice.

Han et al. (Bill Catterall Lab)

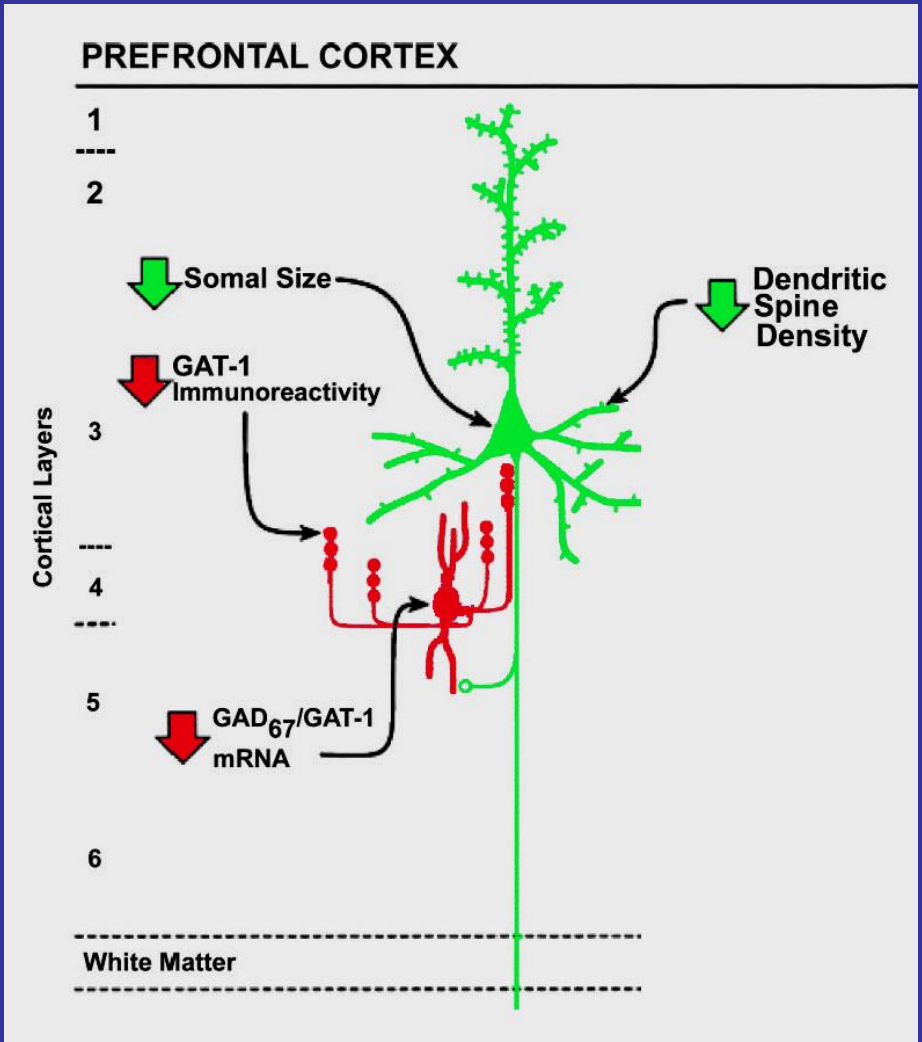
Nature. 2012 Sep 20;489(7416):385-90

Scn1a: Sodium Channel.

Model of Dravet Syndrome (Epilepsy, Cognitive Dysfunction with Autistic Behaviors).

Autistic-like behavior in $Scn1a^{+/-}$ mice was rescue by enhanced GABA-mediated neurotransmission (clonazepam treatment).

Projection and Local Circuit Neuron Defects in the Prefrontal Cortex in Schizophrenia

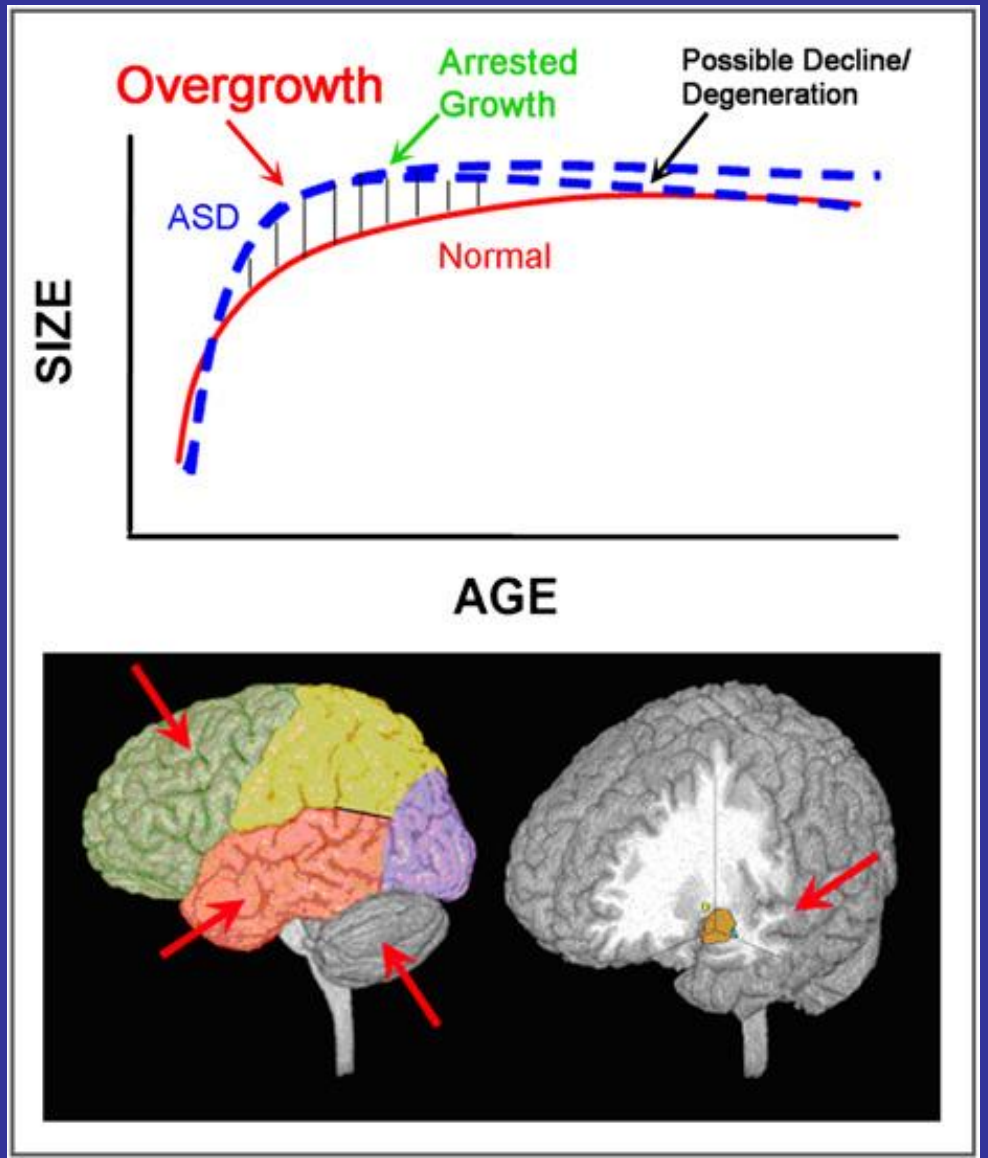


From the work of the Lewis, Jones, Benes labs. Reviewed in Frankle et al., 2003

Models For Mechanisms of Neurodevelopmental Disorders

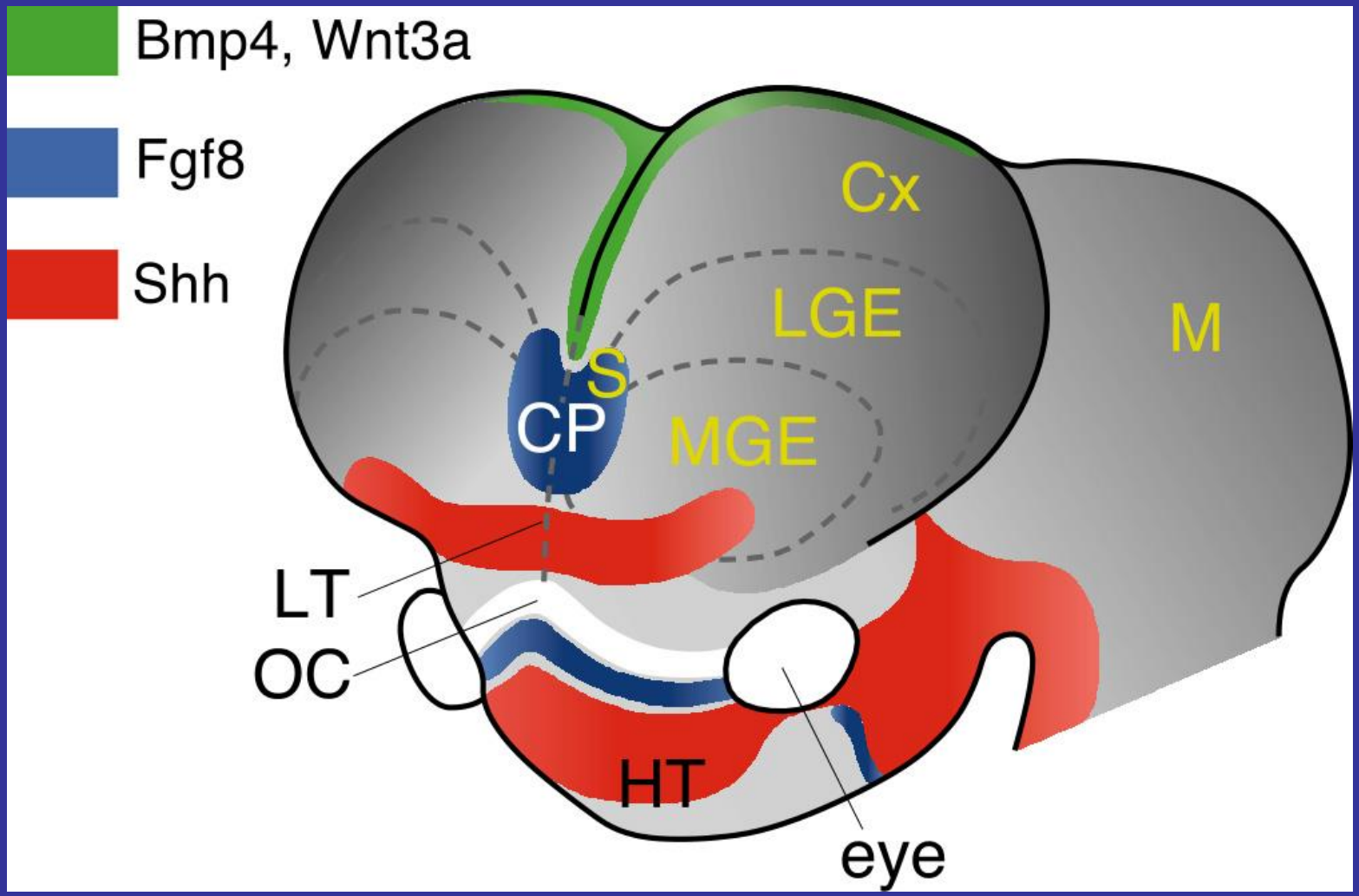
2. Cerebral hyperplasia secondary to increased growth factor signaling.

Transient Cortex Overgrowth in Some Autistic Individuals



Work of several labs, including:
E. Courchense
J. Piven

Growth Factor Expression in the Forebrain

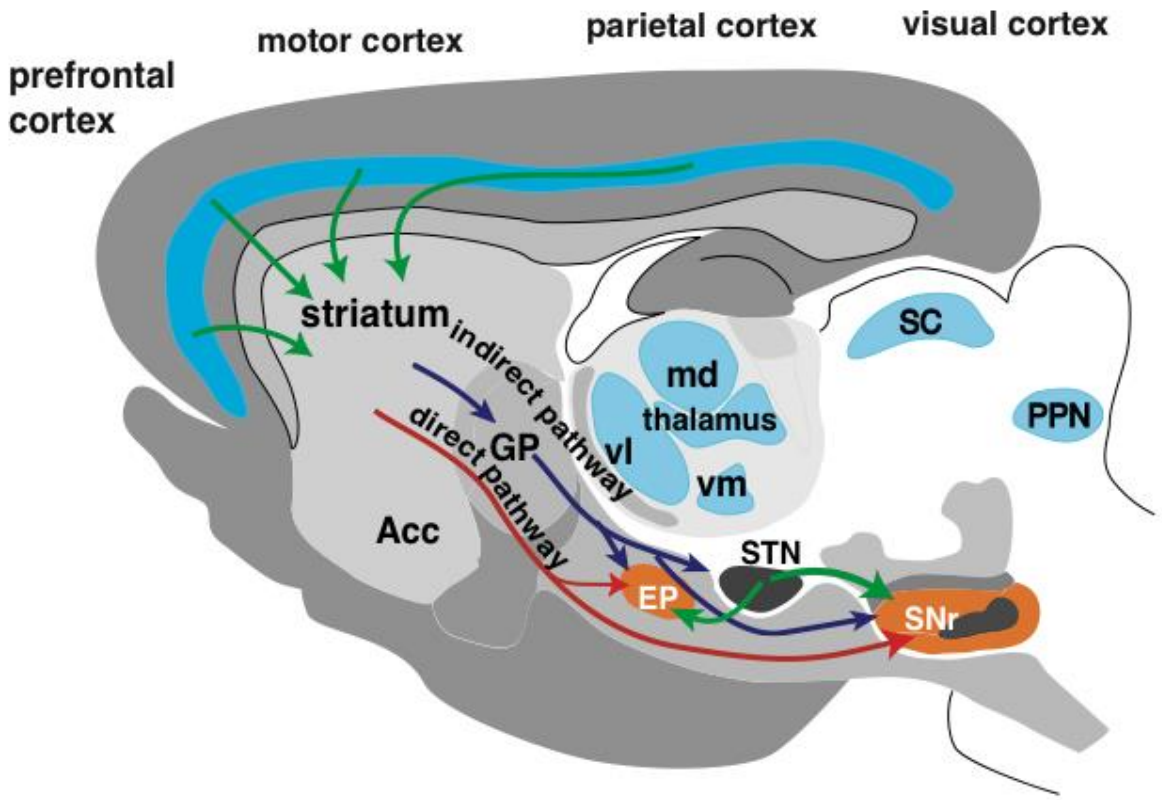


Models For Mechanisms of Neurodevelopmental Disorders

3. Dysfunction of cortical-basal ganglia circuits

Cortex-Basal Ganglia-Thalamus Circuit

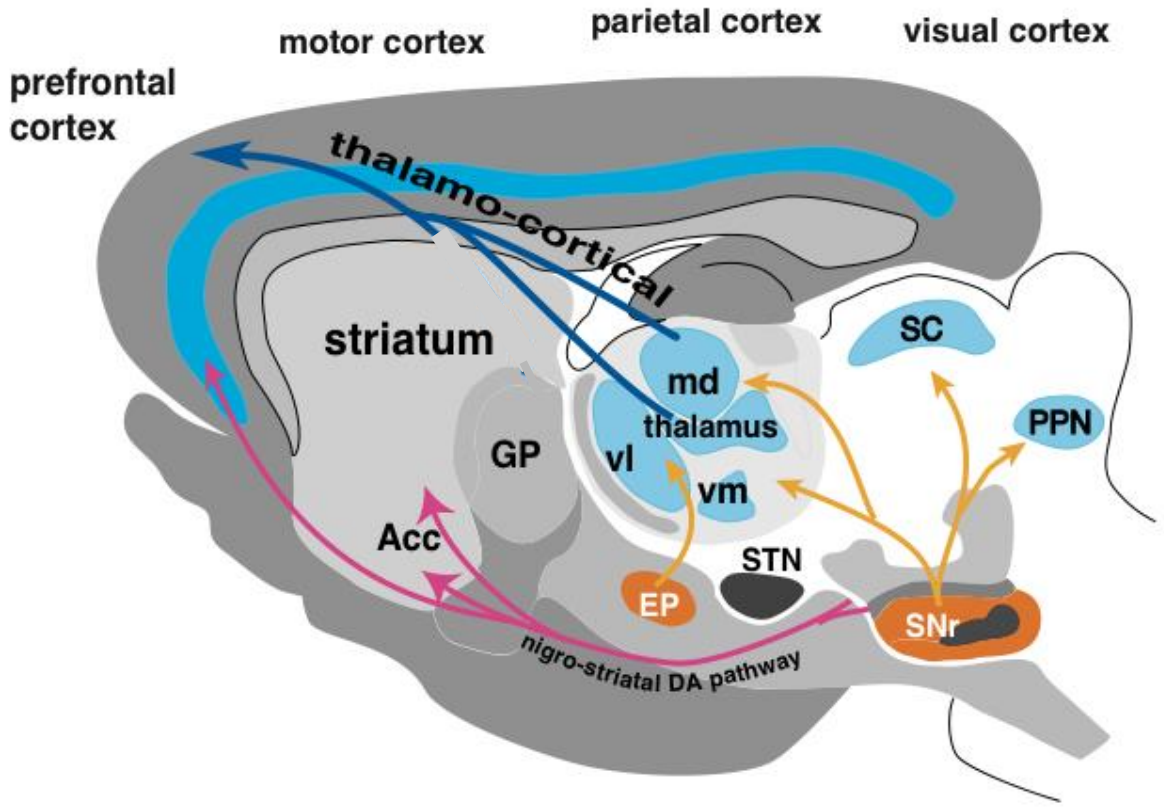
Descending Pathways



From: Charles Gerfen

Prefrontal Cortex-Basal Ganglia-Thalamus Circuit

Ascending Pathways



Adapted from Charles Gerfen

Shank3 mutant mice display autistic-like behaviors and striatal dysfunction

Peça J, Feliciano C, Ting JT, Wang W, Wells MF, Venkatraman TN, Lascola CD, Fu Z, Feng G.
Nature. 2011 Apr 28;472(7344):437-42.

Shank3 mRNA is highly expressed in the striatum.

Shank3 Regulates Assembly of Glutamate Receptor Complexes

Glutamate receptor protein subunits
GluR2, NR2A and NR2B
are reduced in striatal synapses
of Shank3$^{-/-}$ mice.

Schizophrenia

Defects in the Prefrontal Cortex-Basal Ganglia-Thalamus Circuit

Prefrontal Cortex

- Prefrontal Hypofunction and Hypoplasia

- Interneuron Defects:

Reduced GAD expression

- Projection Neuron Defects:

Reduced GABA-Receptor Expression

Basal Ganglia

- Striatal (Caudate) Hypoplasia

Thalamic Defects

- Mediodorsal Nucleus Hypoplasia

Models For Mechanisms of Neurodevelopmental Disorders

4. The male brain/genotype

Y Chromosome
Sex steroids

Perhaps the female brain is protected from the genetic and environmental influences that lead to the 4:1 male:female ratio in autism and other childhood disorders.

In evaluating etiologies and therapies consider the steps and mechanisms in neurodevelopment

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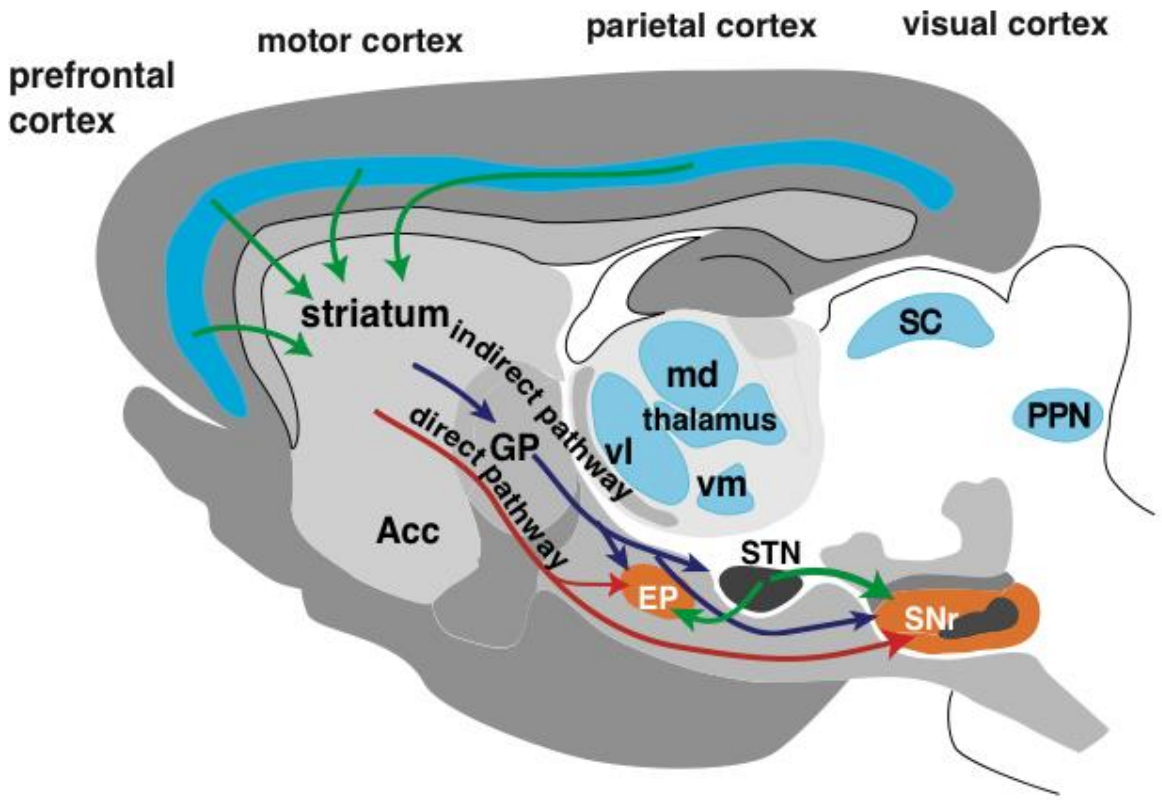
Synapse Formation and Function

Myelination, and Functions of Non-neural cells

And always consider the effects of those defects on the development and function of circuits



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