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## Snapshot: Cortical Development

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This SnapShot summarizes current knowledge of mammalian cortical development, with a particular focus on the molecular controls that orchestrate the stepwise decisions leading from multiple types of undifferentiated forebrain progenitors to fully mature projection neurons with correctly-targeted axons and carefully-elaborated dendritic trees, as well as appropriate electrophysiology and gene expression, reflective of precise subtype and area identity.

### Neocortical Progenitors

Early in development, the telencephalic wall is composed of undifferentiated neuroepithelial (NE) cells, which give rise to diverse progenitor populations. Radial glial cells (RG) divide asymmetrically to self-renew and generate intermediate progenitor (IP) cells or neurons. IP cells divide symmetrically to produce two neurons. In the mouse, small numbers of neurons are produced by radial glia-like (oRG) cells, but oRG cells are abundant in the outer SVZ of human fetal cortex where they generate transit amplifying cells that in turn produce most cortical neurons.

### Projection Neuron Diversity

Specific subtypes of neocortical projection neurons are generated by neural progenitors during distinct temporal windows, beginning in mice at approximately E11.5, and continuing through late embryonic development. These young postmitotic neurons migrate away from the ventricular zone to populate progressively more superficial positions in the cortical plate. Projection neurons can be classified on the basis of their mature axonal projections: corticothalamic projection neurons (CThPN) are located in layer VI and send axons to thalamus; subcerebral projection neurons (SCPN) are located in layer V and send axons to optic tectum, brainstem, or spinal cord; and callosal projection neurons (CPN) are located in layers II/III, V, and VI and send axons to contralateral cortex. Importantly, neurons of each subtype are further specialized based on their positions in specific cortical areas. For example, CThPN establish area-specific connections with thalamic nuclei (motor cortex CThPN with VL; sensory cortex CThPN with VP; visual cortex CThPN with dLG).

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## Molecular Controls over Subtype and Area Identity

Both subtype and area identity are specified in a stepwise fashion, with early overlapping expression of critical controls resolving over the course of development to specific subtypes and areas. Area identity begins to be imparted embryonically by smooth gradients of transcription factors in progenitors and postmitotic neurons, but during the first postnatal week, expression of critical controls, such as *Lmo4* and *Bhlhb5*, becomes restricted to domains that sharply delineate cortical areas. Similarly, subtype identity is progressively specified, as molecular controls that are initially co-expressed by newly-generated postmitotic neurons later refine to a single subtype, or to high levels in some subtypes and low levels in others. Several central identified controls over subtype development, including *Fezf2*, *Ctip2*, *Satb2*, and *Tbr1*, interact combinatorially (although not linearly) as part of a broader molecular network and nested molecular logic that directs subtype identity acquisition.

### Abbreviations

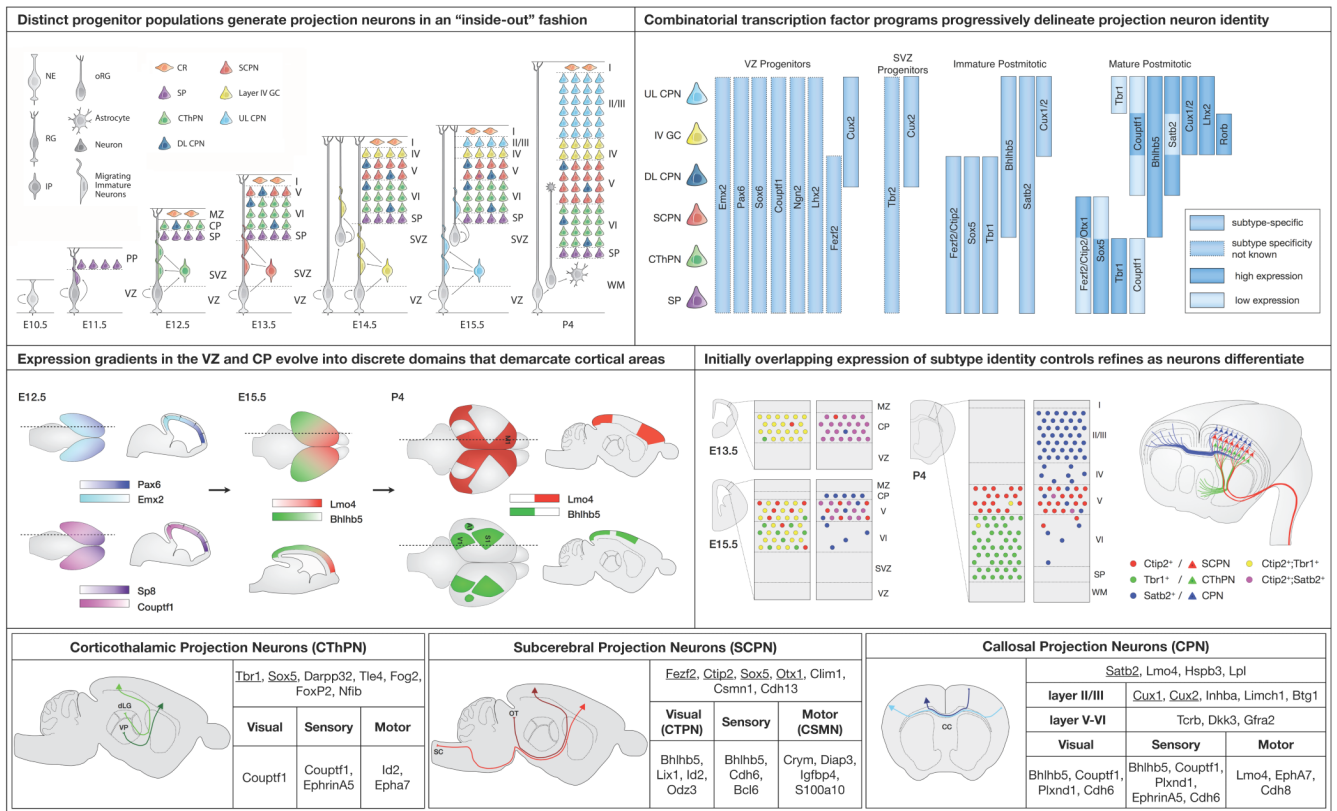
<b>A1</b>	primary auditory cortex
<b>Bhlhb5</b>	basic helix-loop-helix domain-containing, class B5
<b>Btg1</b>	B cell translocation gene 1, anti-proliferative
<b>Cdh6</b>	cadherin 6
<b>Cdh8</b>	cadherin 8
<b>Cdh13</b>	cadherin 13
<b>Clim1</b>	carboxyl-terminal LIM domain-binding protein 1
<b>Couptf1</b>	chicken ovalbumin upstream transcription factor I
<b>CC</b>	corpus callosum
<b>CP</b>	cortical plate
<b>CPN</b>	callosal projection neuron(s)
<b>CR</b>	Cajal-Retzius cell(s)
<b>Crym</b>	mu crystallin
<b>CSMN</b>	corticospinal motor neuron(s)
<b>Csmn1</b>	zinc finger protein 703
<b>CThPN</b>	corticothalamic projection neuron(s)
<b>CTPN</b>	corticotectal projection neuron(s)
<b>Ctip2</b>	Couptf-interacting protein 2
<b>Cux1</b>	cut-like homeobox 1
<b>Cux2</b>	cut-like homeobox 2
<b>Darpp32</b>	dopamine- and cAMP-regulated neuronal phosphoprotein
<b>Diap3</b>	diaphanous homolog 3
<b>Dkk3</b>	dickkopf homolog 3
<b>DL</b>	deep-layer (layers V and VI)
<b>dLG</b>	dorsal lateral geniculate nucleus of thalamus

<b>E</b>	embryonic day
<b>Emx2</b>	empty spiracles homeobox 2
<b>Epha7</b>	Eph receptor A7
<b>Fezf2</b>	Fez family zinc finger 2
<b>Fog2</b>	friend of GATA 2
<b>FoxP2</b>	forkhead box P2
<b>GC</b>	granule cell(s)
<b>Gfra2</b>	glial cell line derived neurotrophic factor family receptor alpha 2
<b>Hspb3</b>	heat shock protein 3
<b>Id2</b>	inhibitor of DNA binding 2
<b>Igfbp4</b>	insulin-like growth factor binding protein 4
<b>Inhba</b>	inhibin beta-A
<b>IP</b>	intermediate progenitor
<b>Lhx2</b>	LIM homeobox protein 2
<b>Limch1</b>	LIM and calponin homology domains 1
<b>Lix1</b>	limb expression homolog 1
<b>Lmo4</b>	LIM domain only 4
<b>Lpl</b>	lipoprotein lipase
<b>M1</b>	primary motor cortex
<b>MZ</b>	marginal zone
<b>NE</b>	neuroepithelial cell
<b>Nfib</b>	nuclear factor IB
<b>Ngn2</b>	neurogenin 2
<b>Odz3</b>	odd Oz/ten-m homolog 3
<b>oRG</b>	outer radial glia
<b>OT</b>	optic tectum (superior colliculus)
<b>Otx1</b>	orthodenticle homolog 1
<b>P</b>	postnatal day
<b>Pax6</b>	paired box gene 6
<b>Plxnd1</b>	plexin D1
<b>PP</b>	preplate
<b>RG</b>	radial glia
<b>Rorb</b>	RAR-related orphan receptor beta
<b>S1</b>	primary sensory cortex
<b>S100a10</b>	S100 calcium binding protein A10
<b>Satb2</b>	special AT-rich sequence binding protein 2

<b>SC</b>	spinal cord
<b>SCP</b>	subcerebral projection neuron(s)
<b>Sox5</b>	SRY box-containing gene 5
<b>Sox6</b>	SRY box-containing gene 6
<b>SP</b>	subplate neuron(s)
<b>Sp8</b>	trans-acting transcription factor 8
<b>SVZ</b>	subventricular zone
<b>Tbr1</b>	T-box brain gene 1
<b>Tbr2</b>	T-box brain gene 2
<b>Tcrb</b>	T cell receptor beta chain
<b>Tle4</b>	transducin-like enhancer of split 4
<b>UL</b>	upper-layer (layers II/III and IV)
<b>V1</b>	primary visual cortex
<b>VL</b>	ventral lateral nucleus of thalamus
<b>VP</b>	ventral posterior nucleus of thalamus
<b>VZ</b>	ventricular zone
<b>WM</b>	white matter

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## 1. . SnapShot: Cortical Development