The cerebral cortex develops from the most anterior part of the neural plate, a specialized part of the embryonic ectoderm. The neural plate folds and closes to form the neural tube. From the cavity inside the neural tube develops the ventricular system, and, from the epithelial cells of its walls, the neurons and glia of the nervous system. The most anterior (frontal) part of the neural tube, the telencephalon, gives rise to the cerebral hemispheres and cortex.
Cortical neurons are generated within the ventricular zone, next to the ventricles. At first, this zone contains "progenitor" cells, which divide to produce glial and neuronal cells. The glial fibers produced in the first divisions of the progenitor cells are radially oriented, spanning the thickness of the cortex from the ventricular zone to the outer, pial surface, and provide scaffolding for the migration of neurons outwards from the ventricular zone. The first divisions of the progenitor cells are symmetric, which duplicates the total number of progenitor cells at each mitotic cycle. Then, some progenitor cells begin to divide asymmetrically, producing one postmitotic cell that migrates along the radial glial fibers, leaving the ventricular zone, and one progenitor cell, which continues to divide until the end of development, when it differentiates into a glial cell or an ependymal cell. The migrating daughter cells become the pyramidal neurons of the cerebral cortex.

Cell types of the cerebral Cortex:
1. Pyramidal Cell
2. Stellate (Granule) & Basket Cells
3. Fusiform Cell
4. Horizontal Cell of Cajal
5. Ascending Axon Cell of Martinotti or so called “Inverted Pyramidal Cell”
Cytoarchitectonic Structure of the Cerebral Neocortex: (Cell layers of the Neocortex)
1. Molecular of Plexiform layer
2. External Granular layer
3. External Pyramidal layer
4. Internal Granular layer
5. Internal Pyramidal layer
6. Fusiform or Multiform layer

Myeloarchitectonic Structure of the Cerebral Neocortex: (Organization of Fiber Systems of the Neocortex)
I. Tangential Fiber Plexus layer
II. Dysfibrous layer
III. Suprastriate layer
IV. External Band of Baillarger layer
V. Internal Band of Baillarger layer
VI. Infastriate layer

Fiber Connections of Neocortex:
1. Thalamo-cortical fibers:
   - Specific projections from Specific Thalamic Nuclei
   - Non-Specific projections from Reticular Formation
2. Association fibers:
   - Arcuate fasciculus
3. Commissural fibers:
   - Corpus Callosum
   - Anterior Commissure
   - Posterior Commissure
   - Hippocampal Commissure
4. Intracortical fibers and Collaterals:
   - White Matter: ← Internal Capsule
Histogenesis and Morphogenesis of the Cerebral Cortex:

Steps in the early development of the nervous system:

1. Specification
2. Migration
3. Formation of axonal connections

Migration is a fundamental process in the development of the central nervous system:

Cell migration is particularly complex in the developing forebrain:

The cerebral cortex contains two major classes of neurons:

- **Projection neurons**
  - Excitatory (Glutamate)
  - Connections with other cortices or subcortical regions
  - 80%

- **Interneurons**
  - Inhibitory (GABA)
  - Local connections
  - 20%
What mechanisms control radial migration in the cerebral cortex?

Radial migration is the main mechanism of cellular translocation in the cerebral cortex.

Radial migration allows the transfer of positional information from the ventricular zone to the mantle.
Reelin is a protein that helps regulate processes of neuronal migration and positioning in the developing brain. Besides its important role in early development, reelin continues to work in the adult brain. It modulates the synaptic plasticity by enhancing the induction and maintenance of long-term potentiation. It also stimulates dendritic and synaptic growth development and regulates the continuing migration of neurons and synapses generated in adult neurogenic sites like subventricular and subgranular zones. It is found not only in the brain, but also in the spinal cord, blood, and other body organs and tissues.

Reelin has been suggested to be implicated in the pathogenesis of several brain diseases. The expression of the protein has been found to be significantly lower in schizophrenia and psychotic bipolar disorder, but the cause of this remains uncertain as studies show that psychotropic medication itself affects RELN expression and the epigenetic hypothesis aimed at explaining the changed levels has received some contradictory evidence. Total lack of reelin causes a form of lissencephaly. Reelin may also play a role in Alzheimer’s disease, temporal lobe epilepsy and autism.

Schematic illustration of the various modes of neuronal migration in the developing cerebral cortex. During early development the prevalent mode of radial migration is somal translocation (a). As development proceeds and the cortex thickens, the predominant mode of migration is glia-guided locomotion (b). Cortical interneurons that arise in the ganglionic eminence follow tangential migratory paths to reach the cortex (c) and seek the ventricular zone (ventricle-directed migration) (d). A subset of neurons that switch from radial to tangential modes of movement show active branching (branching cells) (e).

Mechanisms controlling radial migration in the cortex

Detachment and laminar acquisition

Reelin

Corticogenesis in a normal (left) and reeler (right) mice

What mechanisms control tangential migration in the cerebral cortex?

Origin and routes of interneuron tangential migration
Origin and routes of interneuron tangential migration

A combination of repulsive and attractive cues guides tangential interneuron migration to the cortex

1. The preoptic area (POa) contains a repulsive activity
2. The striatum contains a repulsive activity
3. The cerebral cortex contains an attractive activity

Nestin (radial glia)
GAD65-GFP (interneurons)

Attractive and repulsive cues guide interneuron migration to the cortex

Interneurons migrating towards the cortex avoid the developing striatum

References:
- Marks et al. (2001) Science 293: 872-875

Wichterle et al. (2000) Proc Natl Acad Sci USA 97: 13727-1382
Neuregulins are a family of four structurally-related proteins that are part of the EGF family of proteins. These proteins have been shown to have diverse functions in the development of the nervous system and play multiple essential roles in vertebrate embryogenesis including: cardiac development, Schwann cell and oligodendrocyte differentiation, some aspects of neuronal development, as well as the formation of neuromuscular synapses. Included in the family are neuregulin: neuro differentiation factor, acetylcholine receptor synthesis stimulator, glial growth factor, and sensory and motor-neuron derived factor. Multiple family members are generated by alternate splicing or by use of several cell type-specific transcription initiation sites. In general, they bind to and activate the erbB family of receptor tyrosine kinases (ErbB2 (HER2), erbB3, and erbB4), functioning both as heterodimers and homodimers.

Neuregulins

Neuregulin-1

Neuregulin-2

Neuregulin-3

Neuregulin-4

Neuregulin family

The neuregulin family includes:

Neuregulin-1 (NRG1), with numerous alternative names: NRG-1, neuregulin-1, NRG-1β, Heregulin, NDF, or acetylcholine receptor inducing activity (ARIA).

Neuregulin-2 (NRG2)

Neuregulin-3 (NRG3)

Neuregulin-4 (NRG4)

It has been shown that, in the mouse, the neuregulin family members are products of 4 genes NRG1, NRG2, NRG3, and NRG4, respectively.

The transmembrane form of neuregulin 1 (NRG1) is present within synaptic vesicles including those containing glutamate. When NRG1 binds to the postsynaptic EGF receptor (e.g., ErbB2), this activates the EGF receptor, leading to an increase in the expression of certain glutamate receptor subunits NRG1, NRG2, and NRG3. This has been shown to increase the expression of certain glutamate receptor subunits expression, localization, and/or phosphorylation facilitating subsequent glutamate transmission. The NRG1 gene has been identified as a potential gene determining susceptibility to schizophrenia by a combination of genetic linkage and association approaches.

Neurexins

Neurexin-1 (α-NRXN1), an adhesion molecule (adhesion molecule) important for the formation and maintenance of connections between neurons, is a presynaptic protein that helps to glue together neurons at the synapse. Neurexins are type I membrane proteins that can be classified into two types, α-NRXNs and β-NRXNs. The α-NRXNs are larger and have different amino-terminal extracellular sequences. Neurexins mediate signaling across the synapse, and affect the properties of neural networks by specifying synaptic functions. In humans, alterations in genes encoding neurexins are implicated in autism and other cognitive diseases. Neurexins were discovered as receptors for α-conotoxin, a toxin in black widow spider venom. Their functional roles in insects are likely similar to those in vertebrates.

β-Neurexins (located presynaptically) act as receptors for neurexin (located postsynaptically). Neurexin and neurexin "shake hands," resulting in the connection between the two neurons and the production of a synapse. Additionally, β-Neurexin has also been found to play a role in angiogenesis.

The neurexin genes are α-NRXN1, α-NRXN2, and α-NRXN3.
A secreted isoform of Neuregulin-1 is expressed in the cortex during interneuron migration

Interneurons migrating to the cortex express ErbB4, a Neuregulin-1 receptor

NRG1-Ig attracts cells migrating from the MGE in vitro

Ectopic expression of NRG1-Ig in slice cultures reorients the migration of cortical interneurons

Perturbed interneuron tangential migration in Nrg1 mutant embryos

Guidance mechanisms controlling the tangential migration of cortical interneurons

1. The basal telencephalon contains an unidentified repulsive activity
2. Semaphorins prevent cortical interneuron migration to the striatum
3. The cortex contains an attractive activity that is, at least in part, mediated by NRG1
What cellular mechanisms underlie directed neuronal migration?

Migration requires cell polarization

Are radial and tangential migration mechanisms segregated in different populations of neurons?

Cellular dynamics in tangentially migrating interneurons

PI3K inhibition precludes neuronal polarization during tangential migration

Are radial and tangential migration mechanisms segregated in different populations of neurons?

Interneurons migrate radially to adopt their final laminar position in the cerebral cortex
Assembly of Complex Neuronal Systems:

Figure 2.2: The fate maps for amphibian, avian, and mammalian neural plates. The basic forebrain regions are common to all vertebrates; however, the basic pattern has been elaborated upon to generate the wide diversity of brains that are found in vertebrates. The floor plate is shown in red; the basal plate, from which neural projections are derived, is shown in light red; and the alar plate, from which sensory neurons and most of the forebrain are derived, is pink. The segmental regulation (rhombomers and prosomers) of the mouse brain can already be recognized at this early stage by the pattern of expression of certain genes.

Figure 2.14: Proximodistal model of forebrain development: longitudinal and transverse patterns of gene expression that subdivide the neural tube into a grid of regional identities. The expression of some of these genes is shown for the mouse embryo at two different stages of development. Two genes of the set are expressed in the telencephalon, one in the anterior half of the central heterochromatin (90-18), and the other in the posterior half of the telencephalon (90-26). Analysis of the expression patterns of additional genes has led to the conclusion that the prosencephalon can be subdivided into six prosomers. These are marked from caudal to rostral, and so the prosomere 1 is adjacent to the mesencephalon (M), and prosomere 2 and 3 subdivide what is traditionally known as the diencephalon, and prosomere 4 and 5 divide the telencephalon.

Figure 2.16A: Correlations between gradients of time of gene expression. The subsecond differences in time of expression are shown as a function of distance from the organizer. These differences are due to the variations in the formation of the secondary prosencephalon. The expression of the various genes is shown in the neural plate (E 3.5) and the neural tube (E 10.5 and E 12.5) of the embryonic mouse brain. D: diencephalon; E: eyes; H: rhombencephalon—hindbrain; I: isthmus; M: mesencephalon—midbrain; os: optic stalk; sc: spinal cord; SE: secondary prosencephalon (From Rubenstein).
Development of the cerebral cortex. From the earliest stage of rapidly multiplying cells in the ventricular zone (A) to the definitive cortex (E). Layers 2-5 develop according to an 'inside-out' sequence, as they derive from the cortical plate (blue in D), which begins to form inside the primordial plexiform layer. (From Heimer, 1995)

Diagram of the radial unit hypothesis. Radial glial cells (RG) in the ventricular zone (VZ) project their processes in an orderly map through the various cortical layers, thus maintaining the organizational structure specified in the ventricular layer. After their last division, cohort of migrating neurons (MN) first traverse the intermediate zone (IZ) and then the subplate zone (SP) where they have an opportunity to interact with 'waiting' afferents that arrive sequentially from the nucleus basalis (NB), monoaminergic axons (MA), from the thalamic radiation (TR) and the contralateral cortex (CC). After newly generated neurons bypass the earlier generated ones that are situated in the deep cortical layers, they settle at the interface between the developing cortical plate (CP) and the marginal zone (MZ), and eventually, form a radial stack of cells that share a common site of origin but are generated at different times.

Regional differentiation in the cortex. A: barrels in the somatosensory cortex are somatotopic representations of the whiskers on the animal's face. Similar barrel representations of the whisker field are present in the brainstem and the thalamic nuclei that relay somatosensory inputs from the face to the cortex. B: A barrel field organization is induced when a region of the developing visual cortex is grafted into the site normally occupied by somatosensory cortex. The grafted region of visual cortex now acquires a barrel-like organization.

Formation of Cortical Plates:

Cell proliferation in the neuroepithelium of the recently closed neural tube. The wall of the neural tube is composed entirely of proliferating neuroepithelial cells at this stage and appears a a pseudostratified epithelium in histologic sections. This effect is created by interkinetic nuclear migrations occurring during G1 to S (DNA synthesis), and G2 phases of the cell cycle. During mitosis (M), the cells retract their distal processes, become rounded, and divide next to the lumen of the ventricle. (From Cohen)
The layered structure of the mature cerebral cortex is formed during development. The first pyramidal neurons generated migrate out of the ventricular zone and subventricular zone, together with Cajal-Retzius cells from the preplate. Next, a cohort of neurons migrating into the middle of the preplate divides this transient layer into the superficial marginal zone, which will become layer one of the mature neocortex, and the subplate, forming a middle layer called the cortical plate. These cells will form the deep layers of the mature cortex, layers five and six. Later born neurons migrate radially into the cortical plate past the deep layer neurons, and become the upper layers (two to four). Thus, the layers of the cortex are created in an inside-out order. The only exception to this inside-out sequence of neurogenesis occurs in the layer I of primates, in which, contrary to rodents, neurogenesis continues throughout the entire period of corticogenesis.
The Cajal-Retzius cells and Layer I:

Histogenesis of the Cortical Plates:
Table 3.1. Cell Cycle of Neocortical Germinal Cells

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Species</th>
<th>Age</th>
<th>Cycle Time (h)</th>
<th>G1</th>
<th>G2</th>
<th>M</th>
<th>G0</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Neocortex</td>
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<td>10</td>
<td>14</td>
<td>4</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>Fujita (1981)</td>
</tr>
<tr>
<td></td>
<td>Mouse</td>
<td>10</td>
<td>14</td>
<td>4</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>Fujita (1981)</td>
</tr>
<tr>
<td></td>
<td>Human</td>
<td>10</td>
<td>14</td>
<td>4</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>Fujita (1981)</td>
</tr>
</tbody>
</table>

Figure 3.3. Inside-out sequence of time of origin of neurons in the cerebral cortex of the monkey. Four different pregnant mice each received a single injection of 3Hthymidine on either the 13th, 14th, 15th, or 16th day of gestation. All the pups were killed 10 days after birth, after the neurons of the cerebral cortex have reached their final positions. Data show the positions of marked neurons in autoradiographs of sections of the occipital cortex of the cerebral cortex outlined in the rectangle. From J. B. Angerstein and H. H. Sohr, J. Anat. 122750-760 (1966).


Migration of Neurons into the Cortical Plate:
Development of the Cerebral Subventricular Germinal Zone:

Figure 17. The subventricular zone in the teleosts of the adult mouse. Dorsal view on the left, right lateral view on the right. The extent of the subventricular zone is shown by staining, and border staining shows where it is in black. CB = cerebral hemispheres, PM = fornix of Monro, N = lateral ventricle, OC = olfactory lobe. From J. J. Comp. Neurosci. 108:367–387 (1980).

Figure 17. Migration of neural precursor cells from two major substrates of the developing cerebral cortex: ventricular zone (VZ) and subventricular zone (SVZ). (A) Diagram showing the different layers of the cortex. (B) Diagram showing the different regions of the subventricular zone. (C) Diagram showing the different layers of the cerebral cortex. (D) Diagram showing the different regions of the cerebral cortex. (E) Diagram showing the different layers of the cerebral cortex. (F) Diagram showing the different regions of the cerebral cortex. (G) Diagram showing the different layers of the cerebral cortex. (H) Diagram showing the different regions of the cerebral cortex. (I) Diagram showing the different layers of the cerebral cortex. (J) Diagram showing the different regions of the cerebral cortex. (K) Diagram showing the different layers of the cerebral cortex. (L) Diagram showing the different regions of the cerebral cortex. (M) Diagram showing the different layers of the cerebral cortex. (N) Diagram showing the different regions of the cerebral cortex. (O) Diagram showing the different layers of the cerebral cortex. (P) Diagram showing the different regions of the cerebral cortex. (Q) Diagram showing the different layers of the cerebral cortex. (R) Diagram showing the different regions of the cerebral cortex. (S) Diagram showing the different layers of the cerebral cortex. (T) Diagram showing the different regions of the cerebral cortex. (U) Diagram showing the different layers of the cerebral cortex. (V) Diagram showing the different regions of the cerebral cortex. (W) Diagram showing the different layers of the cerebral cortex. (X) Diagram showing the different regions of the cerebral cortex. (Y) Diagram showing the different layers of the cerebral cortex. (Z) Diagram showing the different regions of the cerebral cortex.
Development of Cortical Nerve Fibers:

Figure 3.1. Schematic representation of the maturation of cortical connections in the visual cortex of the rat. By the day of birth, afferent cortical fibers penetrate the cortical gray matter to the very most superficial layer near a subarea restricted to the area of the visual field. Axons from layer IV of the lateral geniculate body project to the cortex by the second postnatal week. A critical role in the development of the visual cortex is played by the thalamus, which provides an important source of input to the developing visual cortex.
Synaptic formation on the pyramidal cell in the cerebral cortex.

Figure 6.5. Schematic illustration of the probable pathways and the neuroanatomical connections between the cells of the cerebral cortex. A = small pyramidal cell, B = large pyramidal cell, C = stellate cell, D = granule cell.

Figure 6.6. Synaptic junctions in the molecular layer of the cerebral cortex of the rat (3 days after birth). The high concentration of synapses in the molecular layer is evident, and the dark areas represent cell bodies and cell processes.

Figure 6.8. Rapid increase in the number of synapses in the cerebral cortex of the rat from birth to adulthood. The number of synapses increases significantly during the first few weeks of life and then stabilizes.
In many developing countries, early childhood malnutrition has resulted not only in stunt physical growth but also severely impaired cognitive and emotional development, and higher brain functions, such as intelligence, language, social and moral reasoning. In many instances, the problems does not occur merely because of the lack of or insufficient supply of food in the community due to poverty, but the lack of fundamental knowledge and proper management...
Marasmus

Kwashiorkor

WAY BEHIND SCHEDULE

Marasmus and Kwashiorkor are two forms of severe malnutrition that can occur in children. Marasmus results from chronic undernutrition and is characterized by a lack of body fat and muscle wasting. Kwashiorkor is a form of protein-energy malnutrition that occurs in children. It is characterized by edema, weight loss, and a loss of body fat. Kwashiorkor is also associated with a higher risk of infection and mortality.

Figure 3.1. Severe childhood malnutrition can result in a reduced DNA content of the liver. The DNA content of the liver of normal children (black line) and severely malnourished children (hashed line) is shown. From M. Strock, P. Lass, and J. Warden, Exp. N Engl. J. Med. 280:484-489 (1973), copyright Academic Press, Inc.

Figure 3.2. Alterations in peripheral Purkinje cell dendrites of undernourished rats. Rats were undernourished from birth by limiting their access to the mother's milk, killed at 10, 15, or 20 days after birth, and the total length and segment frequency of Purkinje cells were measured. From J. D. Cox, J. Comp. Neurol. 200:495-578 (1981).

Table 1. This shows the variation in the compositions of the protein diet.

<table>
<thead>
<tr>
<th>Compositions</th>
<th>Normal diet 100%</th>
<th>low protein diets</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>adequacy</td>
<td>75%</td>
</tr>
<tr>
<td>1. Casein</td>
<td>24</td>
<td>18</td>
</tr>
<tr>
<td>2. Topsoa flour</td>
<td>14</td>
<td>20</td>
</tr>
<tr>
<td>3. Skim milk</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>4. Salt mixture No.4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>5. Corn oil</td>
<td>8</td>
<td>8</td>
</tr>
</tbody>
</table>
Chart 2. This shows the first and final body weights of rats fed with different protein diets and times.

Chart 4. This shows the average brain weights of rats fed with different protein diets and times.

Chart 5. This shows the thickness of parietal association cortex in cross sections of rats fed with different protein diets and times.

Chart 6. This shows the number of pyramidal cells in 10,000 sq. microns, in cross sections of the fifth layer of the parietal association cortex of rats fed with different protein diets and times.