Neuronal Migration

Cerebral cortex

Cerebellar cortex

Rostral migratory stream

Subcortical tangential migration

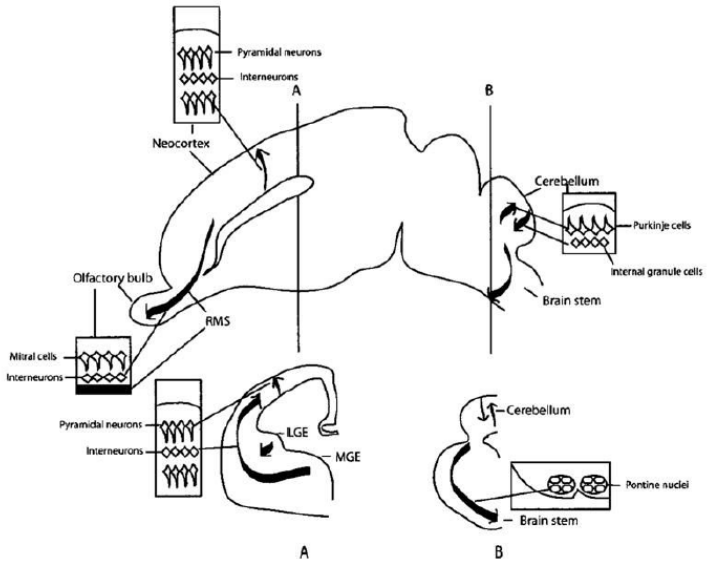
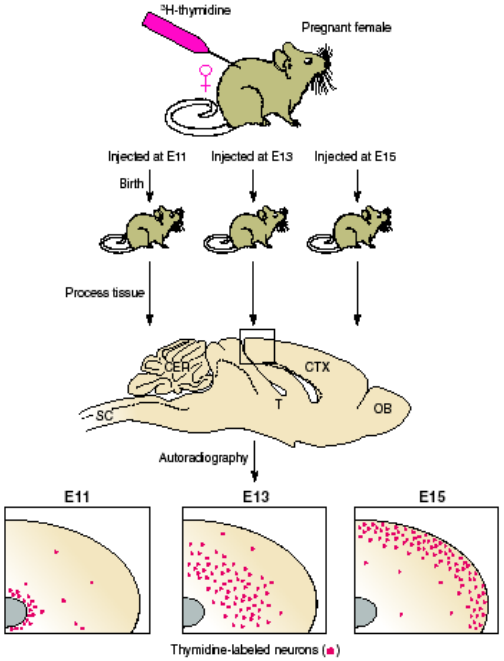
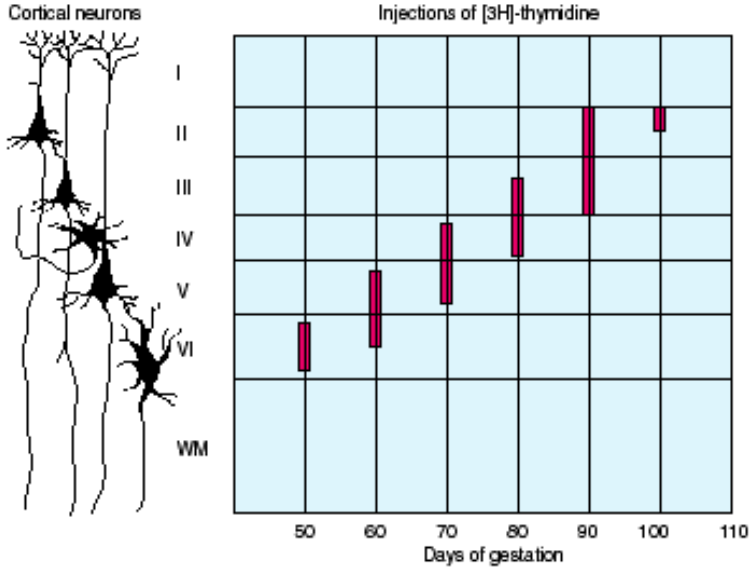
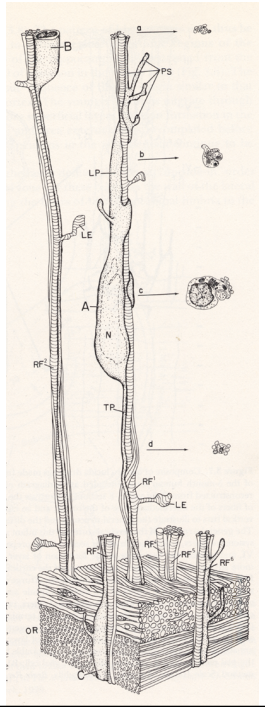


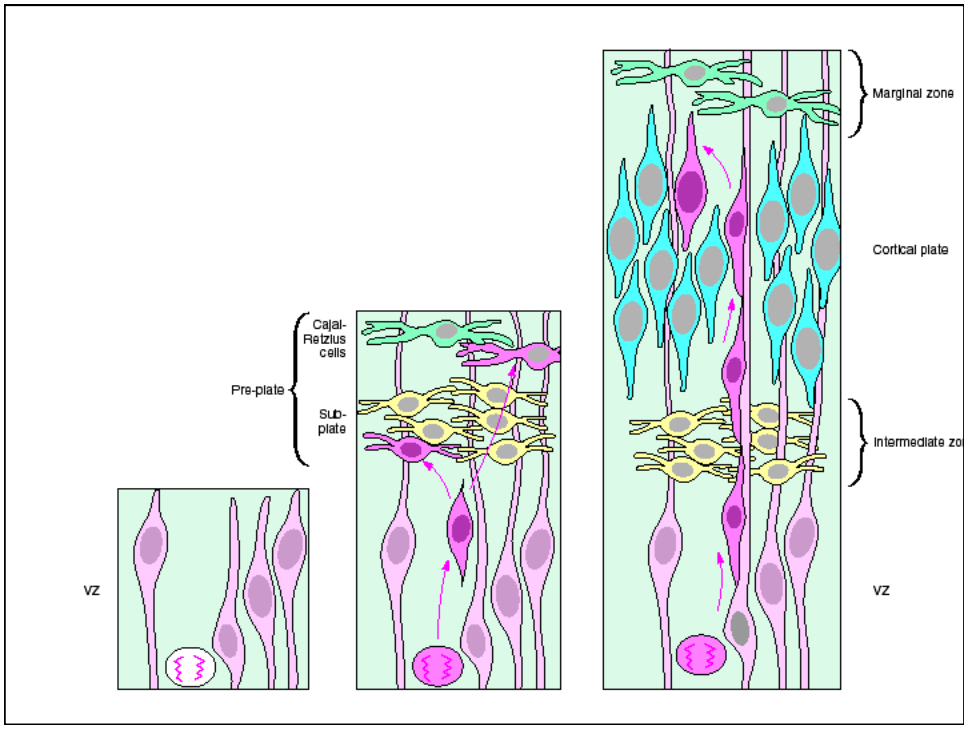
Table 1. Genes Responsible for Human Congenital Disorders Featuring Neuronal Migration Defects

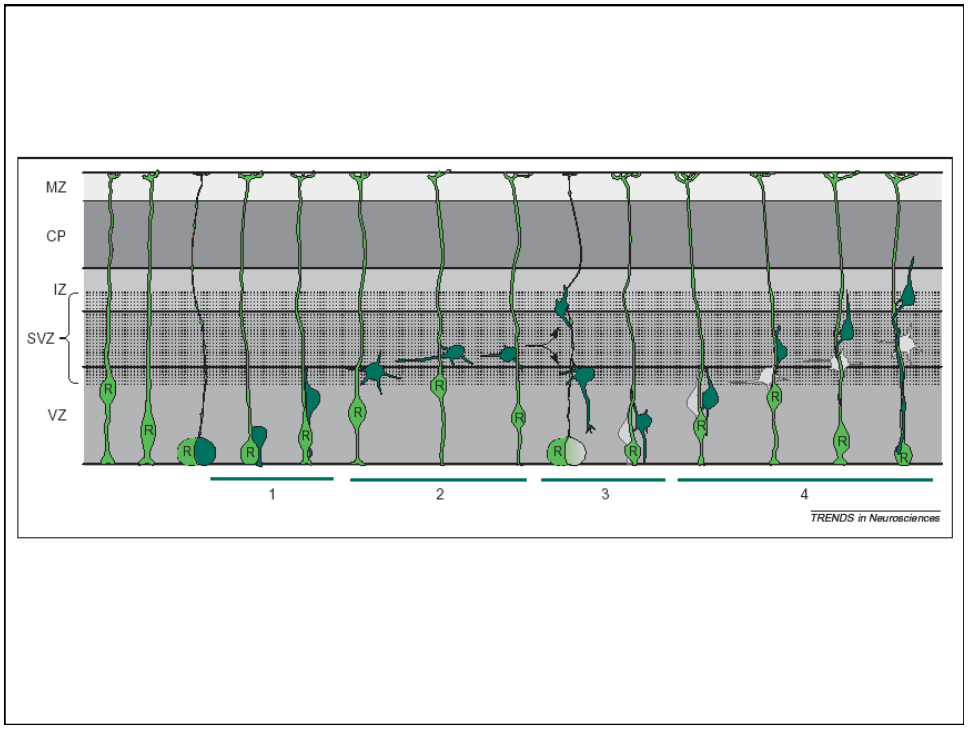
Genes	Human Disorders	Gene Loci	Syndromes	Reference
Reelin	Lissencephaly with cerebellar hypoplasia	7q22	Mental retardation, hypotonia, epilepsy, and myopia	Hong et al., 2000
Lis1	Isolated lissecencephaly sequence and its severe form Miller-Dieker Syndrome	17p13.3	Mental retardation, epilepsy, and premature death; Miller-Dieker Syndrome also has craniofacial abnormalities	Ozmen et al., 2000; Reiner et al., 1993
14-3-3 ε	Miller-Dieker Syndrome	17p13.3	Craniofacial abnormalities	Toyo-oka et al., 2003
DCX	Isolated lissecencephaly sequence in males and Subcortical band heterotopia in females	Xq22.3-23	Mental retardation, and epilepsy; less severe in female due to X mosaic inactivation	Lambert de Rouvroit and Goffinet, 2001
Filamin A	Periventricular heterotopia	Xq28	Epilepsy and vascular signs	Fox et al., 1998
Fukutin	Fukuyama-type congenital muscular dystrophy	9q31	Mental retardation, epilepsy and muscular dystrophy	Gressens, 2005
POMGnT1 (protein O-mannose β-1,2-N-acetylglucosaminyltransferase)	Muscle-eye-brain disease	1p32-34	Mental retardation, severe myopia, glaucoma and muscular dystrophy	Yoshida et al., 2001
Disc-1	Schizophrenia	1q42.1	Schizophrenia	Kamiya et al., 2005; Millar et al., 2000




Cortical neurons
Injections of [3H]-thymidine
I
II
III
IV
V
VI
WM
50
60
70
80
90
100
110
Days of gestation

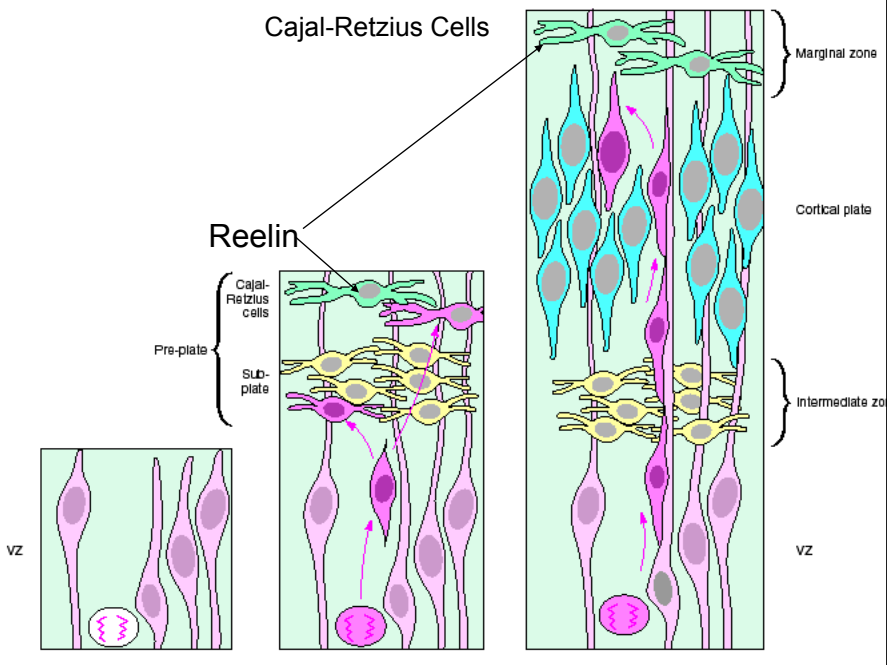

B
a
PS
b
LP
LE
c
A
N
RF
TP
d
RF'
LE
RF
RF'
RF'
RF'
OR
C

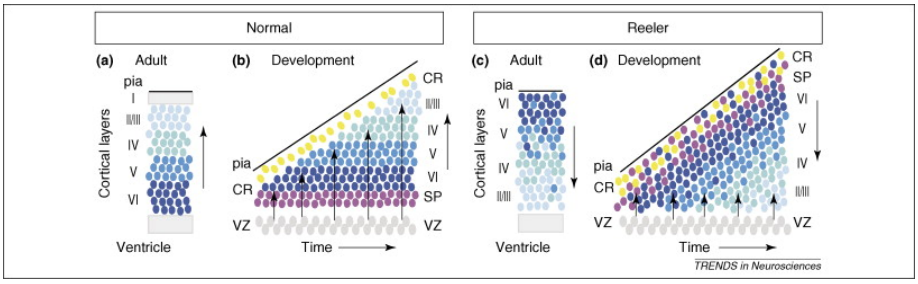

Marginal zone
Cortical plate
Intermediate zo
VZ
Cajal-Retzius cells
Pre-plate
Sub-plate
VZ


MZ
CP
IZ
SVZ
VZ
R
1
2
3
4
TRENDS in Neurosciences

Mouse mutants disrupt cortical development: Reeler

- Mouse mutant with disrupted cerebral cortical and cerebellar lamination
- Mutation in reelin protein
- Large extracellular matrix protein
- Expressed by Cajal Retzius cells
- Migrating neurons extend processes at oblique angles and do not bypass subplate.





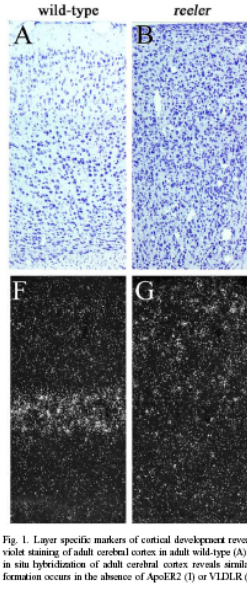


Fig. 1. Layer specific markers of cortical development reve
violet staining of adult cerebral cortex in adult wild-type (A)
in situ hybridization of adult cerebral cortex reveals simil
formation occurs in the absence of ApoER2 (I) or VLDLR (

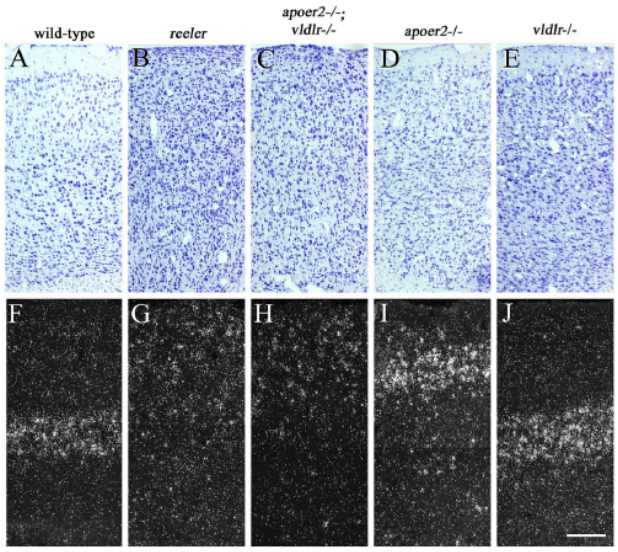
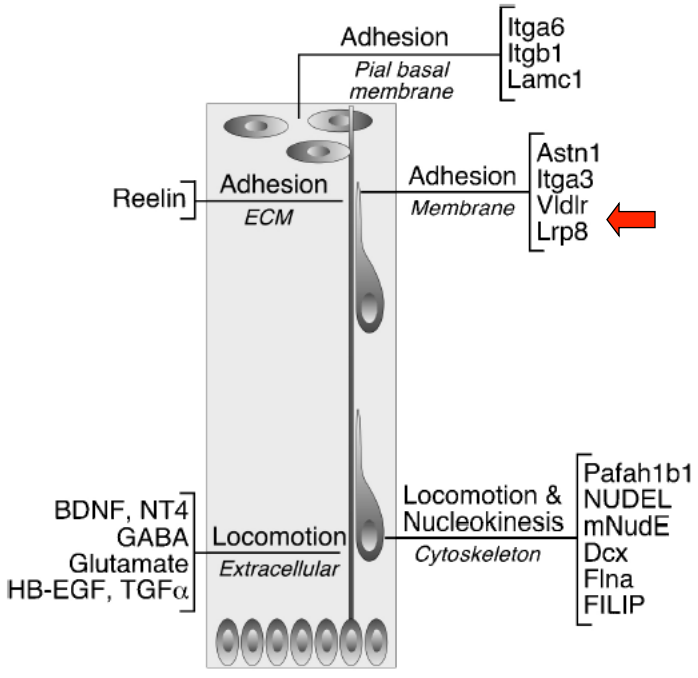
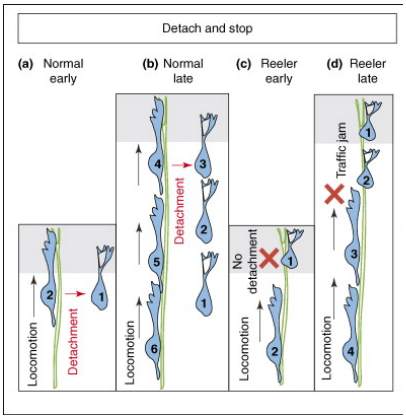


Fig. 1. Layer specific markers of cortical development reveal disruptions similar to *reeler* in animals lacking both ApoER2 and VLDLR. (A–E) Cresyl violet staining of adult cerebral cortex in adult wild-type (A), *reeler* (B), ApoER2$^{-/-}$:VLDLR$^{-/-}$ (C), ApoER2$^{-/-}$ (D), and VLDLR$^{-/-}$ (E). (F–J) *er81* in situ hybridization of adult cerebral cortex reveals similar disruptions of layer V neurons in *reeler* (G) and ApoER2$^{-/-}$:VLDLR$^{-/-}$ (H). Layer V formation occurs in the absence of ApoER2 (I) or VLDLR (J), however it is displaced superficially in the absence of ApoER2. Scale bar in J=200 μm.





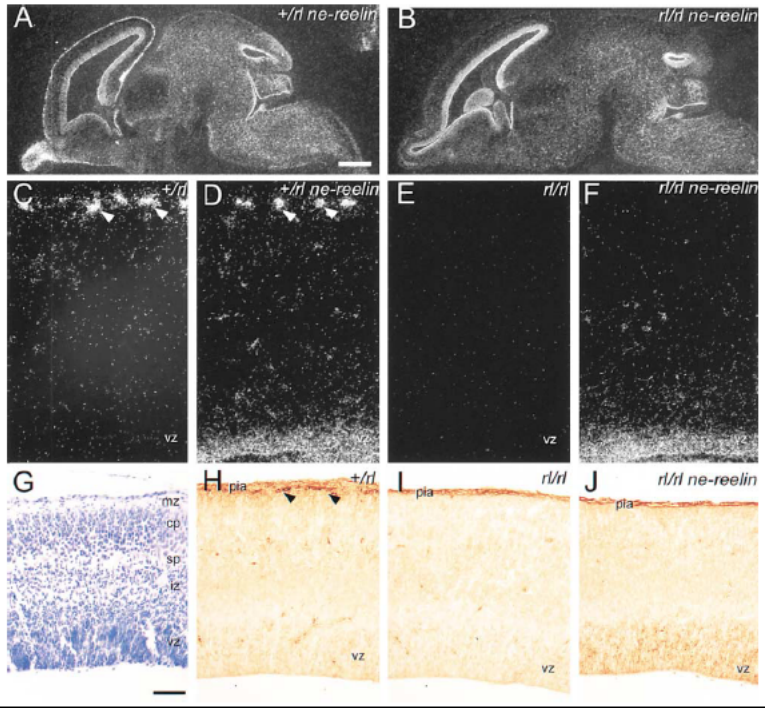
Hypothesis:
Reelin causes cells to detach from the radial glia and stop

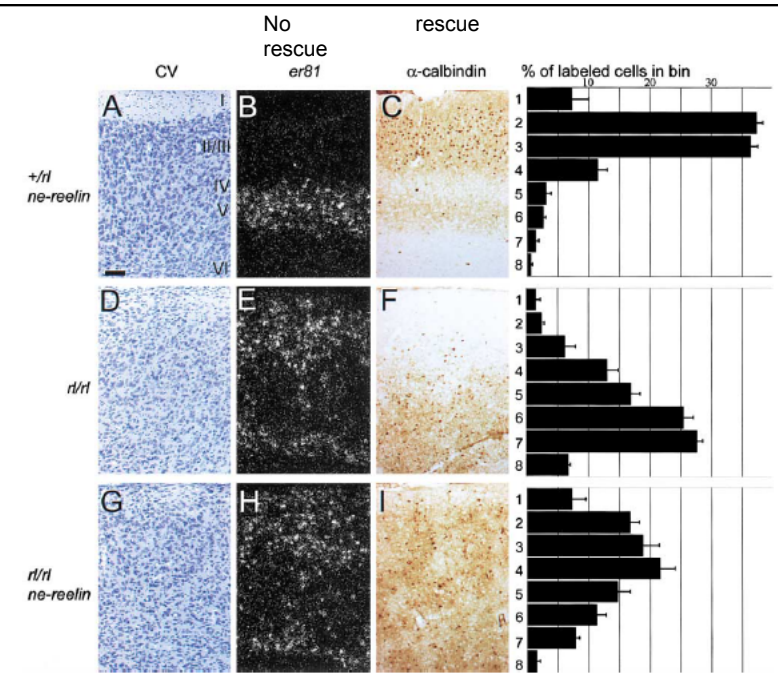
Neuron, Vol. 33, 573–586, February 14, 2002, Copyright ©2002 by Cell Press

Rescue of Ataxia and Preplate Splitting by Ectopic Expression of Reelin in *reeler* Mice

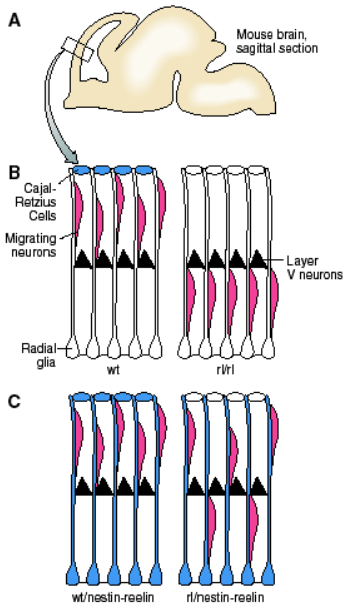
Susan Magdaleno, Lakhu Keshvara, and Tom Curran[1]
Department of Developmental Neurobiology
St. Jude Children's Research Hospital
332 North Lauderdale
Memphis, Tennessee 38105

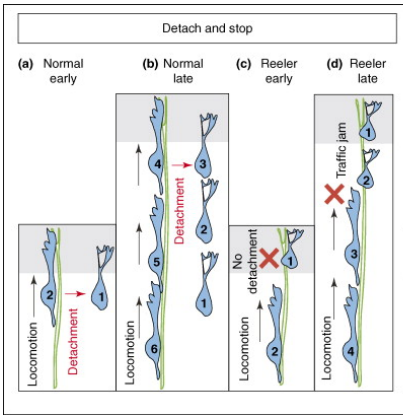
germinal layer (EGL) to support proliferatior
cell precursors. This results in a dramatic r
the size of the cerebellum and a lack of folia
shiba et al., 1983). Remarkably, these anat
tures are present in other strains of mutan
alterations in the disabled-1 (*dab-1*) gene (H
1997b; Sheldon et al., 1997) or disruption
very low density lipoprotein receptor (*vldlr*) a


A
+/rl ne-reelin
B
rl/rl ne-reelin
C
+/rl
D
+/rl ne-reelin
E
rl/rl
F
rl/rl ne-reelin
vz
G
mz
cp
sp
iz
vz
H
pia
+/rl
I
pia
rl/rl
J
rl/rl ne-reelin
pia


CV
No rescue
er81
rescue
α-calbindin
% of labeled cells in bin
10
20
30
+/rl ne-reelin
rl/rl
rl/rl ne-reelin
I
II/III
IV
V
VI
1
2
3
4
5
6
7
8

Reelin doesn't seem to be simply a stop signal

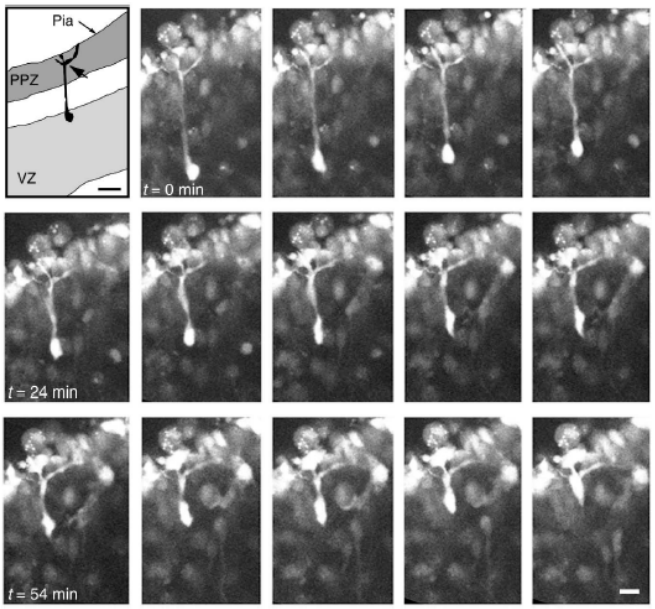




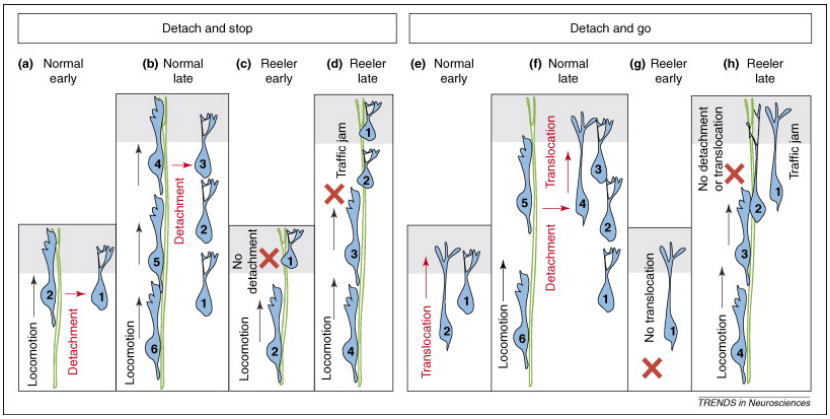
Hypothesis:
Reelin causes cells to detach from the radial glia and stop

Not likely, since cells still moved out of the ventricular zone, even when reelin was expressed there.

Somal translocation: another type of migration



Another hypothesis of reelin function:



Neuronal Migration

Cerebral cortex
Cerebellar cortex
Rostral migratory stream
Subcortical tangential migration

Cerebellar granule cell migration

- Mutant mice
  - Reeler
  - Weaver
  - staggerer
- In vitro assays
  - Bergmann glia/granule cell co-culture
  - Slice culture

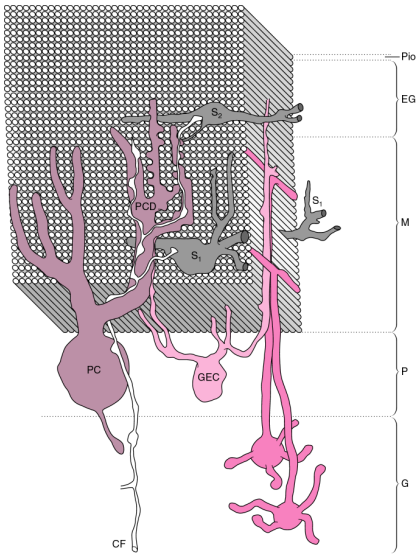


Figure 3.16—*Sanes: Development of the Nervous Sysytem*
Academic Press—Lineworks, Inc.—8/20/99—*tw*

External granule cell layer of the cerebellum

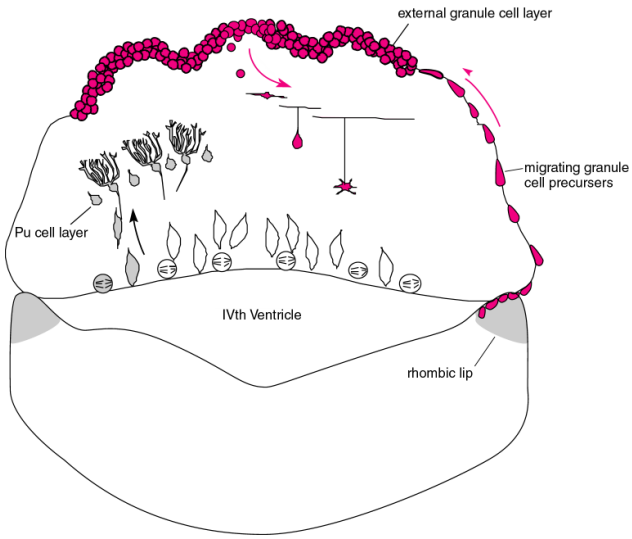
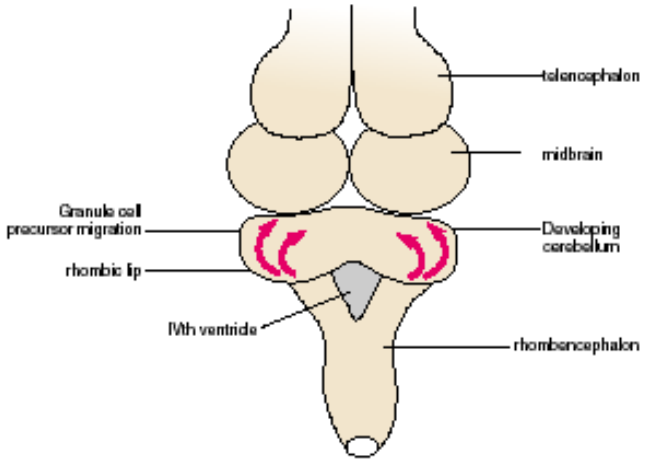
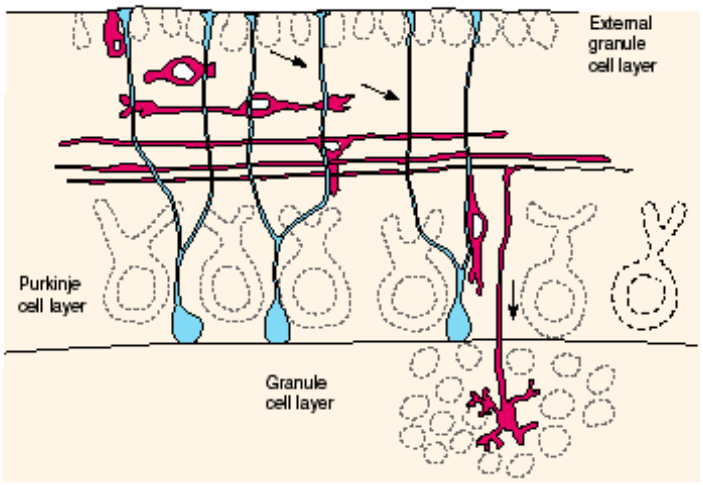


Figure 3.17—*Sanes: Development of the Nervous Sysytem*
Academic Press—Lineworks, Inc.—8/11/99—*tw*

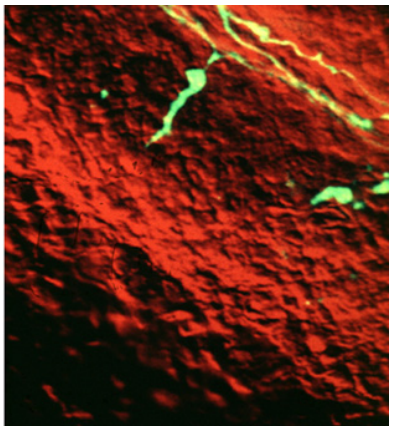
External granule cell layer forms from the rhombic lip

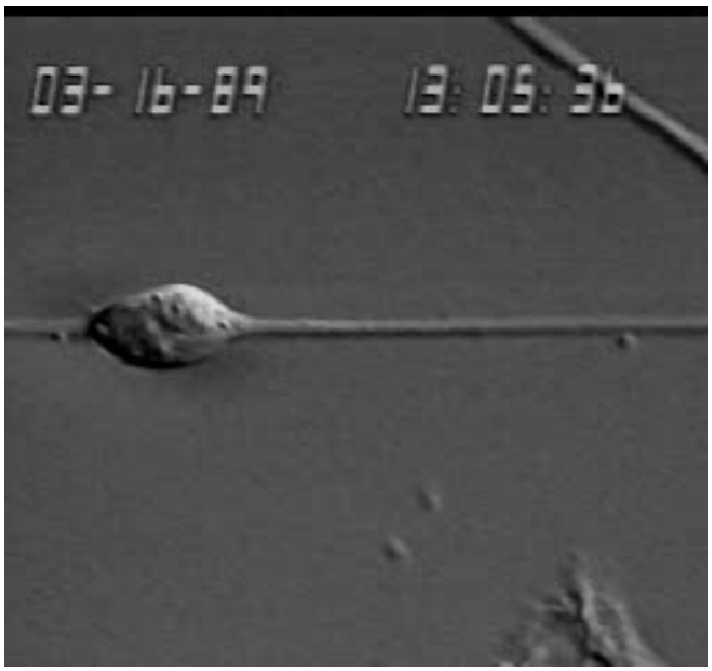




In vitro assay

Cell transplant assay

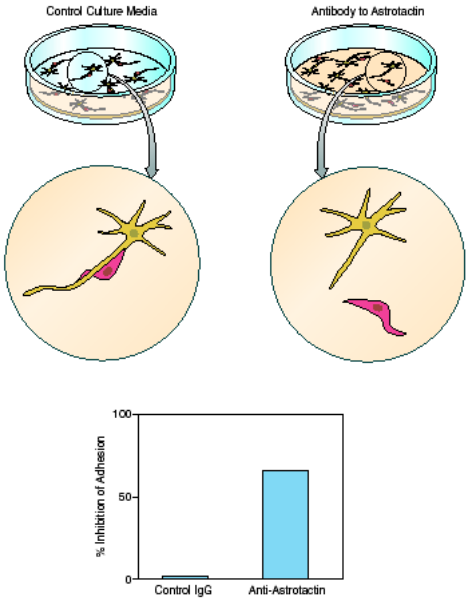




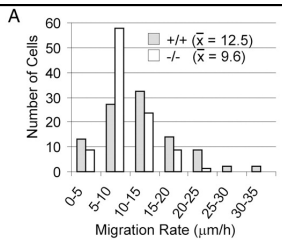
Some factors involved in cerebellar granule cell migration :

- Astrotactin
- Neuregulin
- reelin

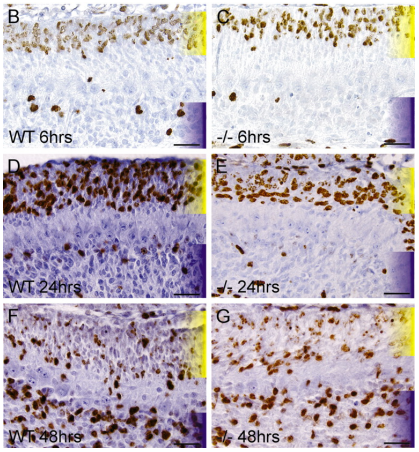
Astrotactin allows attachment of neurons to Bergmann glia

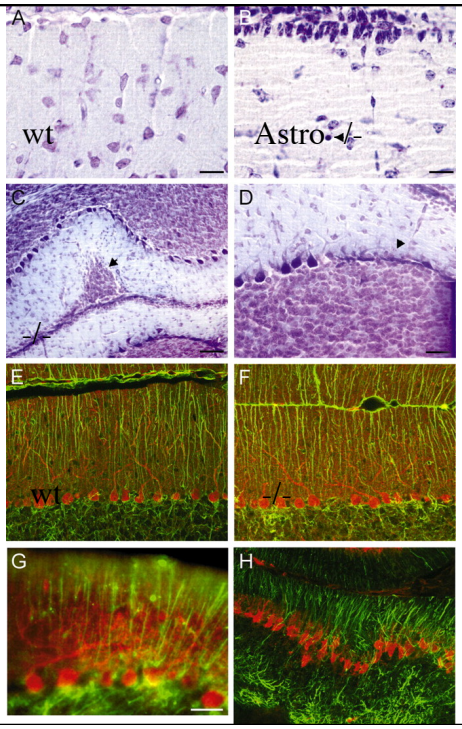


In vitro migration assay shows -/- mice granule cells are slower.



BrdU labeled granule cells migrate more slowly in the astrotactin mutant mice in vivo



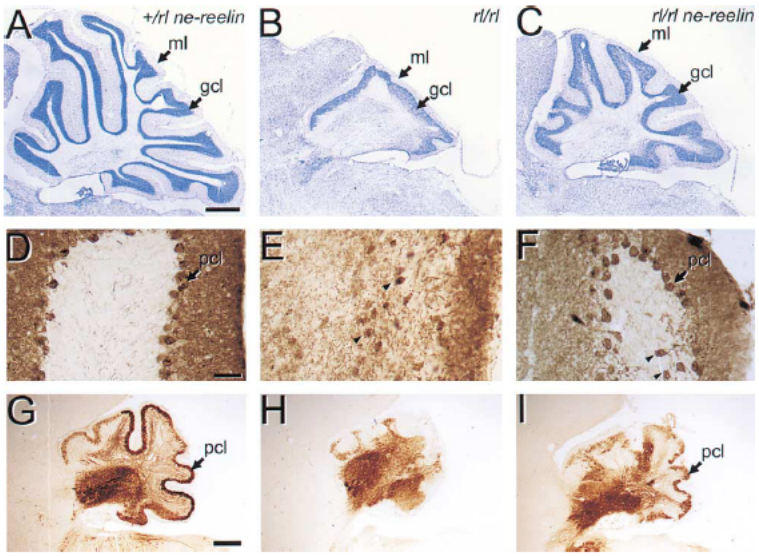


EGL dispersion is delayed in the astro -/- mice

Some factors involved in cerebellar granule cell migration :

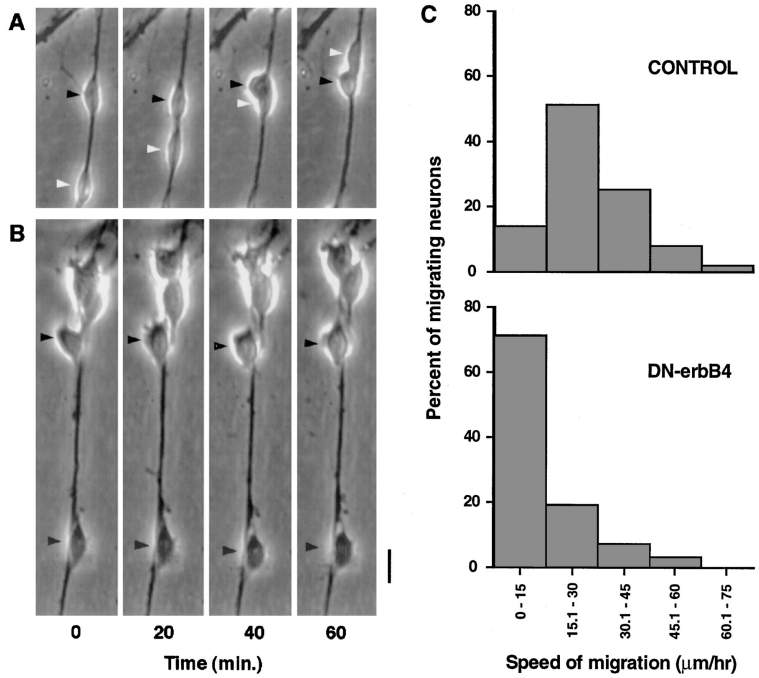
- Astrotactin
- Neuregulin
- reelin

Reelin mice also have cerebellar defects

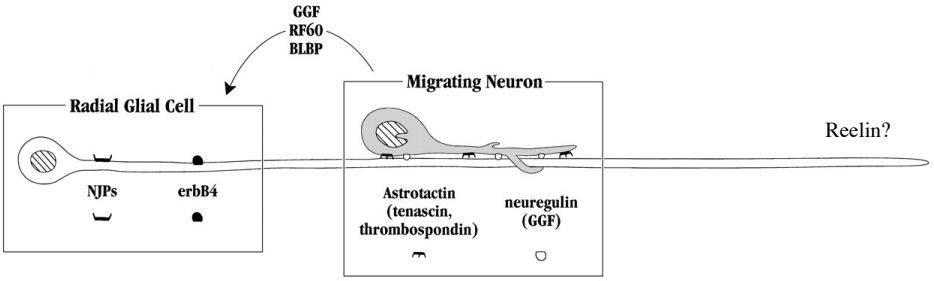


Some factors involved in cerebellar granule cell migration :

- Astrotactin
- Neuregulin
- reelin



Multiple mechanisms in cerebellar migration



Ca+2 channels and granule cell migration

- Ca+2 changes during migration
- GIRK mutation responsible for weaver
- Ca+2 channel blockers inhibit migration
- NMDA receptor mutants have migration defects

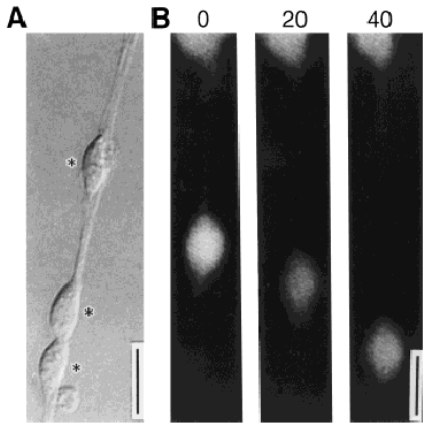


Figure 5 Granule cell migration in cerebellar microexplant cultures. (A) Typical migrating granule cells from a microexplant culture of postnatal 2-day-old mouse cerebella. Migrating neurons (asterisks) in this assay display characteristic leading and trailing processes. (B) A migrating granule cell loaded with the cell-permeant, acetoxymethyl ester form of 1 μM Fluo-3 shows changes in fluorescence intensity over the time indicated in minutes at the top of each photograph. Bars = 10 μm.

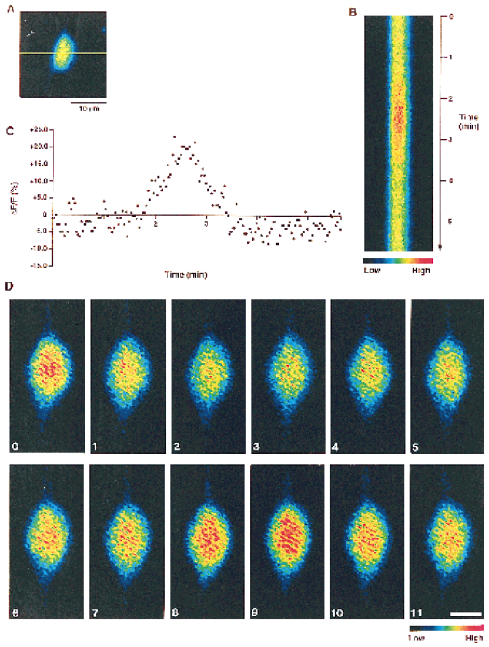


Figure 6 Spontaneous intracellular Ca^{2+} elevations in migrating granule cells. (A) Pseudocolor frame image of $[Ca^{2+}]_i$ in a migrating cell loaded with 1 μM Fluo-3. The yellow line indicates the equator of the cell soma. (B) Pseudocolor line scan image of $[Ca^{2+}]_i$ obtained

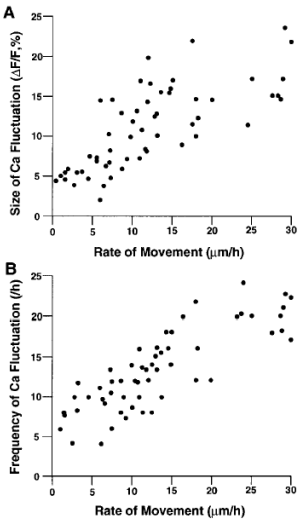
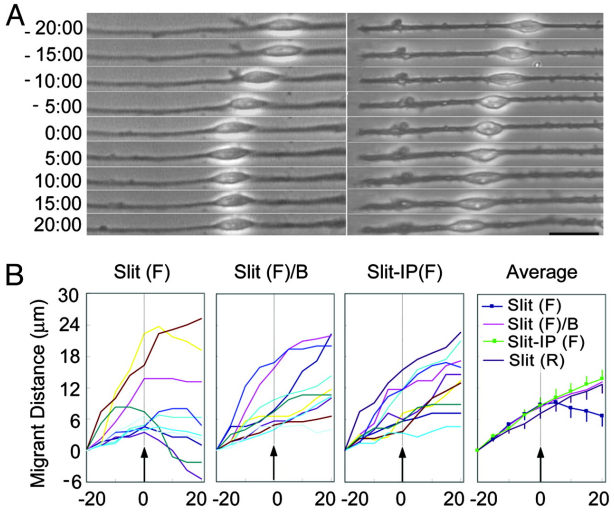


Figure 9 Positive correlation between the amplitude component of Ca^{2+} fluctuations and the rate of cell movement (A), and between the frequency component of Ca^{2+} fluctuations and the rate of cell movement (B). Each point displays either the size or frequency of Ca^{2+} fluctuations in relation to the rate of cell movement of a single neuron. (From Komuro and Rakic, Neuron **17**:275–285, © 1996 Cell Press, reprinted with permission.)

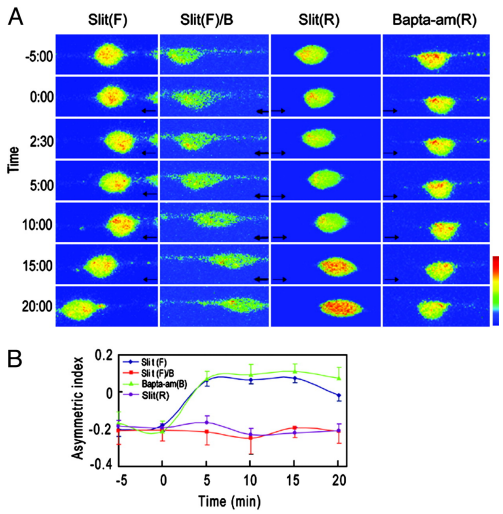
Fig. 2. Regulation of granule cell migration by Slit2



Xu, Hua-tai et al. (2004) Proc. Natl. Acad. Sci. USA 101, 4296-4301

PNAS

Fig. 4. Calcium signaling in migrating granule cell



Xu, Hua-tai et al. (2004) Proc. Natl. Acad. Sci. USA 101, 4296-4301

PNAS

Neuronal Migration

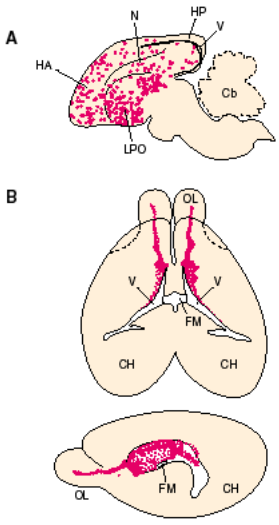
Cerebral cortex

Cerebellar cortex

Rostral migratory stream

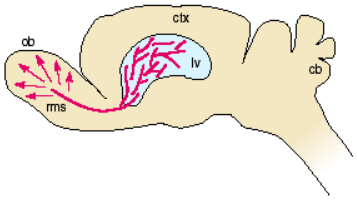
Subcortical tangential migration

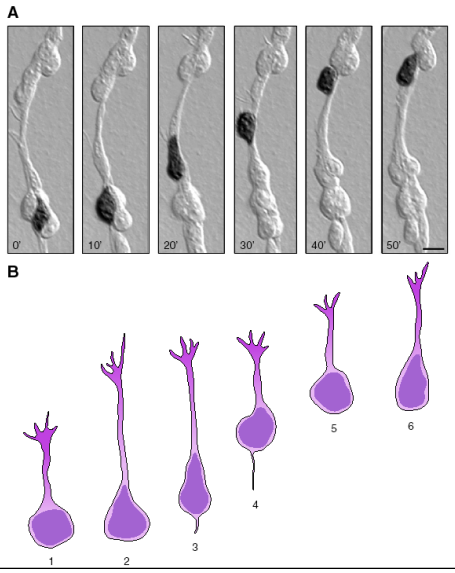
In the early 80s, Fernando Nottebohm reported that neurogenesis continues throughout life in songbirds.



In the late 60s, Joe Altman reported that in the hippocamp and the subventricular zone, neurogenesis continues in adul animals.

Chain migration





Neuronal Migration

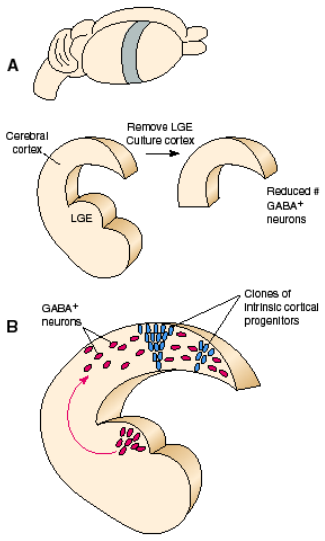
Cerebral cortex

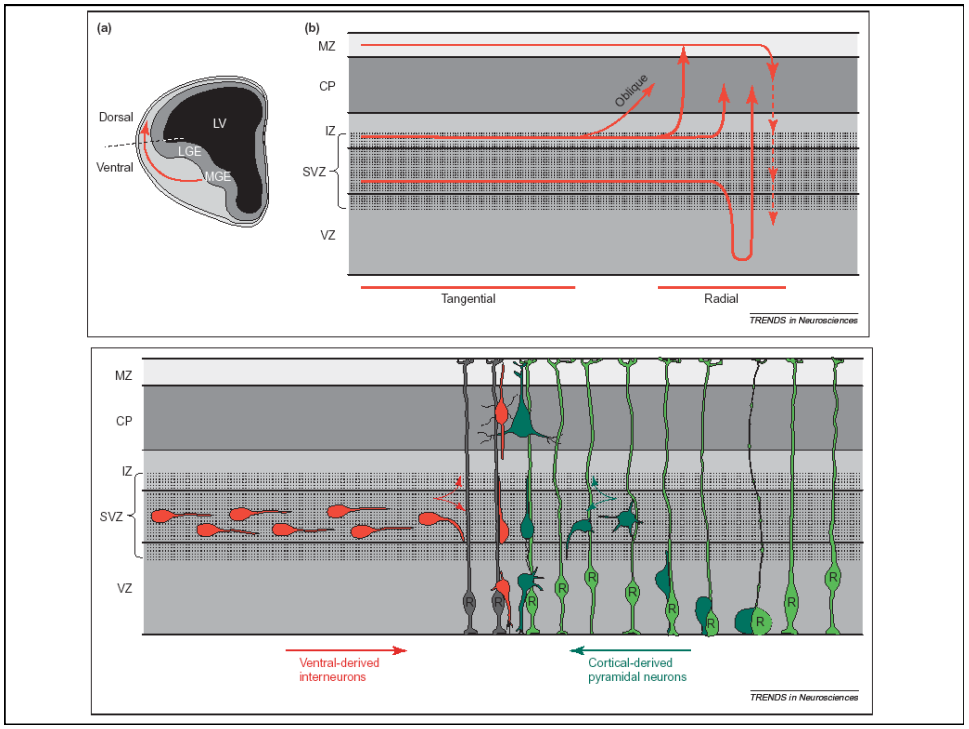
Cerebellar cortex

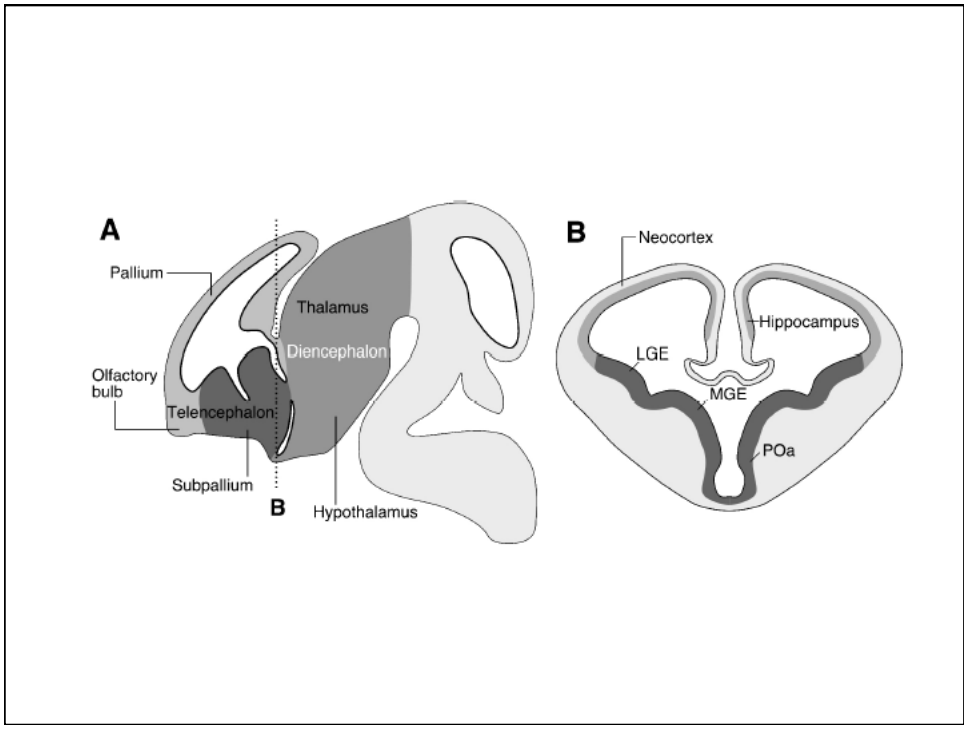
Rostral migratory stream

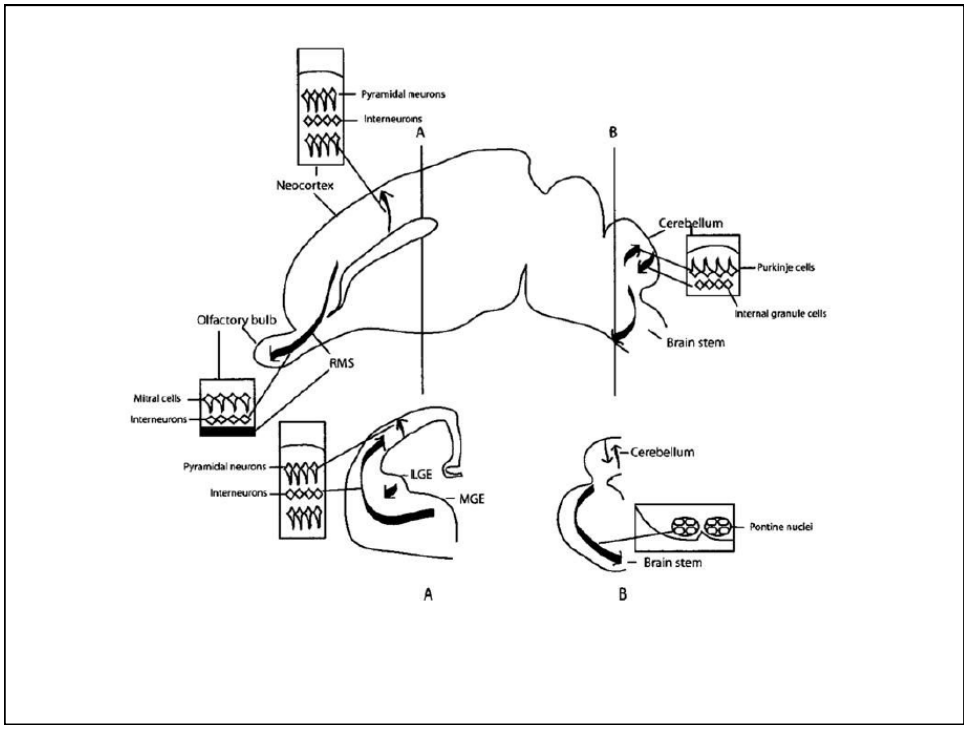
Subcortical tangential migration

Cortical interneurons
Are generated in the
Ganglionic eminence
and migrate tangentially




(a)
Dorsal
Ventral
LV
LGE
MGE
(b)
MZ
CP
IZ
SVZ
VZ
Oblique
Tangential
Radial
TRENDS in Neurosciences
MZ
CP
IZ
SVZ
VZ
R
Ventral-derived interneurons
Cortical-derived pyramidal neurons
TRENDS in Neurosciences


A
Pallium
Thalamus
Diencephalon
Olfactory bulb
Telencephalon
Subpallium
B
Hypothalamus
B
Neocortex
Hippocampus
LGE
MGE
POa


Pyramidal neurons
Interneurons
A
B
Neocortex
Cerebellum
Purkinje cells
Internal granule cells
Olfactory bulb
RMS
Brain stem
Mitral cells
Interneurons
Pyramidal neurons
Interneurons
LGE
MGE
Cerebellum
Pontine nuclei
Brain stem
A
B