Potential Developmental Reversibility of Neocortical Malformations

Curing Epilepsy 2007: Translating Discoveries into Therapies

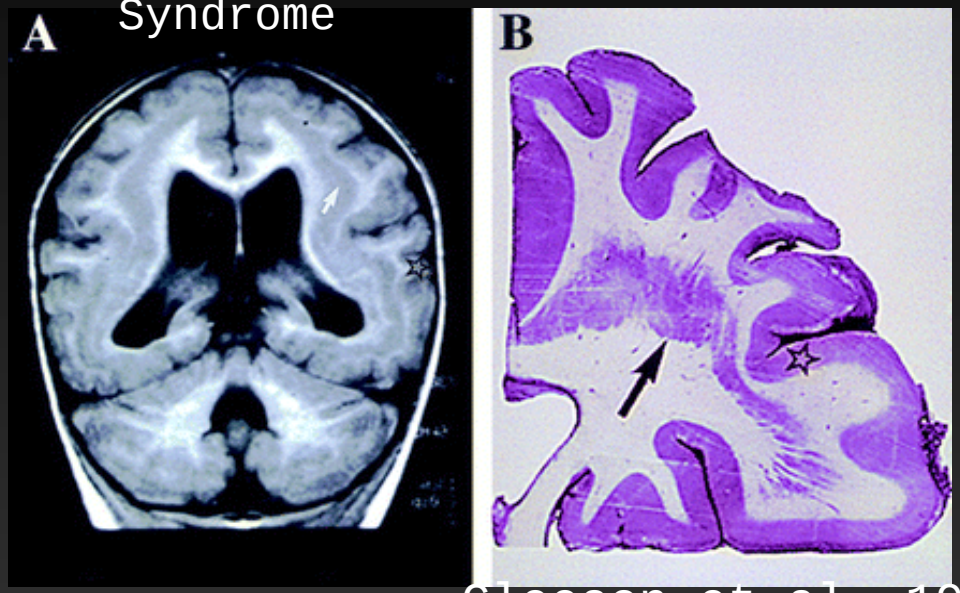
Joe LoTurco
Physiology and Neurobiology
University of Connecticut, Storrs

An alternative and accessible version of this presentation is available at 10:50 am in the Videocast of Day One

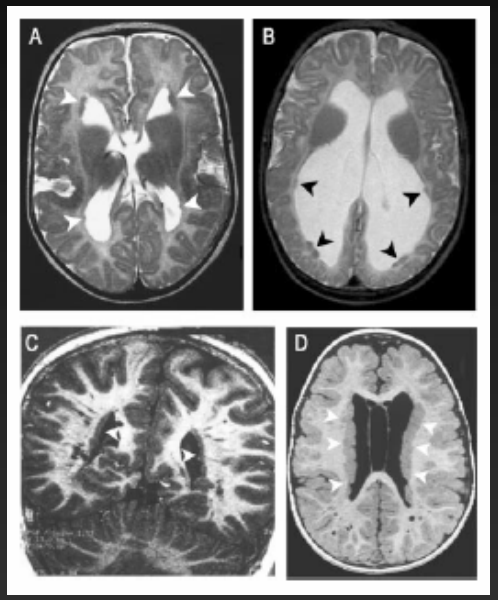
“I do not have significant financial interests related to this conference"

Disruptions in Neuronal Migration Cause Neocortical Malformations

Double Cortex Syndrome



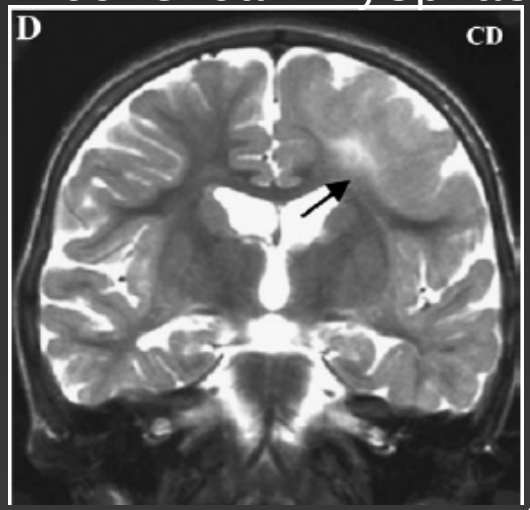
Gleeson et al, 1998

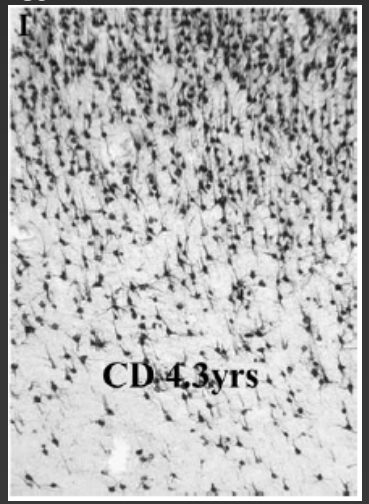


Periventricular Heterotopia (PH)

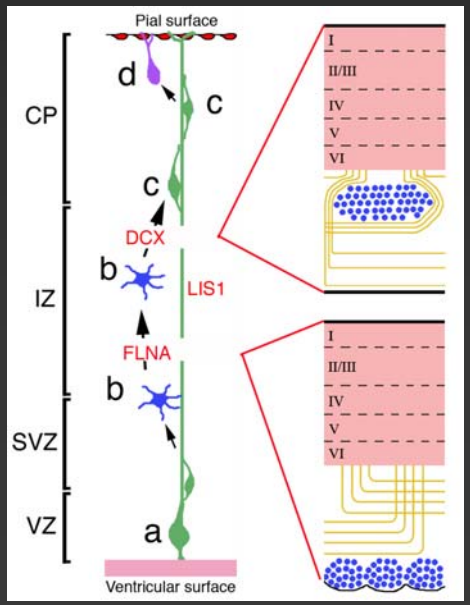
Parrini et al, 2006

ocal Cortical Dysplasia





Andres et al., 2005



LoTurco & Bai, 2006

Animal Models Show a Consistent Causal Link between Cortical Malformation and Hyperexcitability.

1) Multiple mouse knockouts and mutant rat strains have malformations of cerebral cortex and exhibit spontaneous seizures and/or increased cortical excitability.

2) Experimentally induced focal malformations by either embryonic teratogen treatment or perinatal lesion create hyperexcitable neocortical tissue.

Fundamental Questions Regarding Potential Reversibility of Cortical Malformations

- 1) Does more mature cortex permit continued migration?
- 2) Is it possible to re-start migration after neurons have stalled during development?
- 3) If re-started, can stalled neurons reach appropriate positions in neocortex?

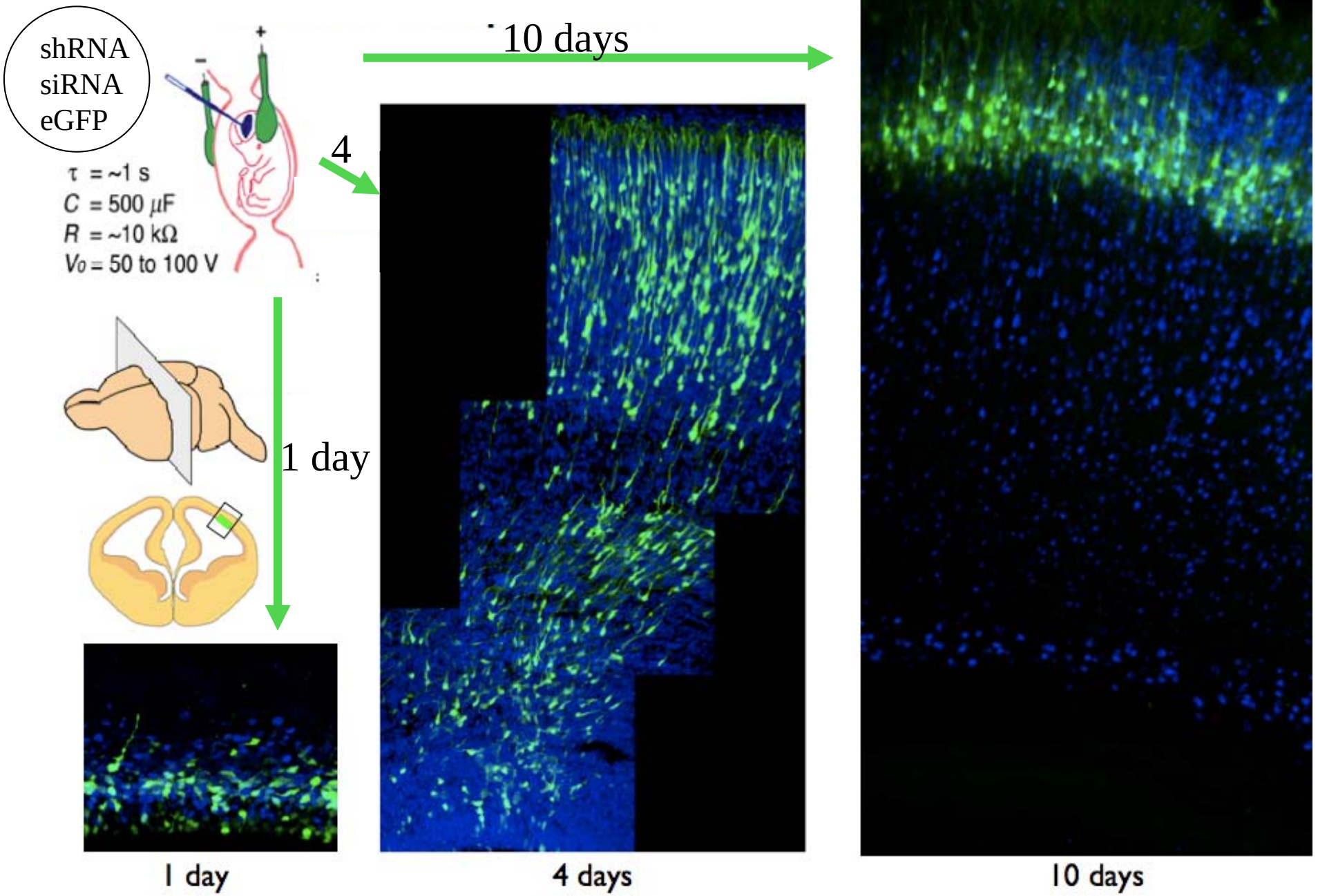
4) Will reversal of migration disruptions reduce circuit hyperexcitability associated with malformations?

5) Can practical therapies be imagined and developed to re-initiate migration after malformations can be detected?

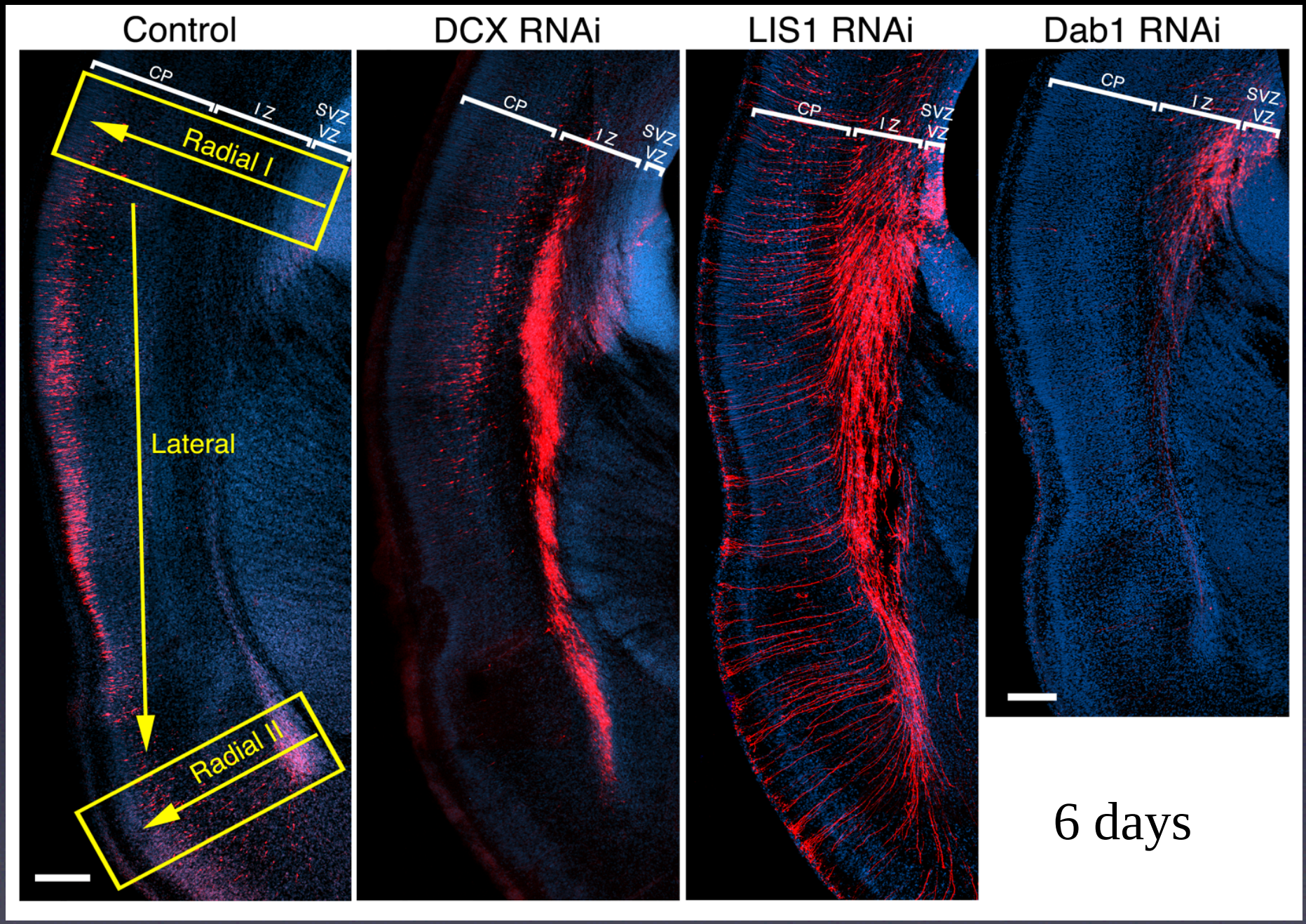
Evidence that migration can continue in brain after the normal developmental period of migration

1) Tansplantation studies of several different neural stem cell types indicate that cells can migration through mature cortex.
2) Significant restructuring after some perinatal insults indicate that migration and associated tissue reformation is possible as the period of normal migration ends.
3) Some endogenous populations of neurons in cerebral cortex, RMS progenitors and dentate granule neurons of the hippocamous, migrate throughout life.

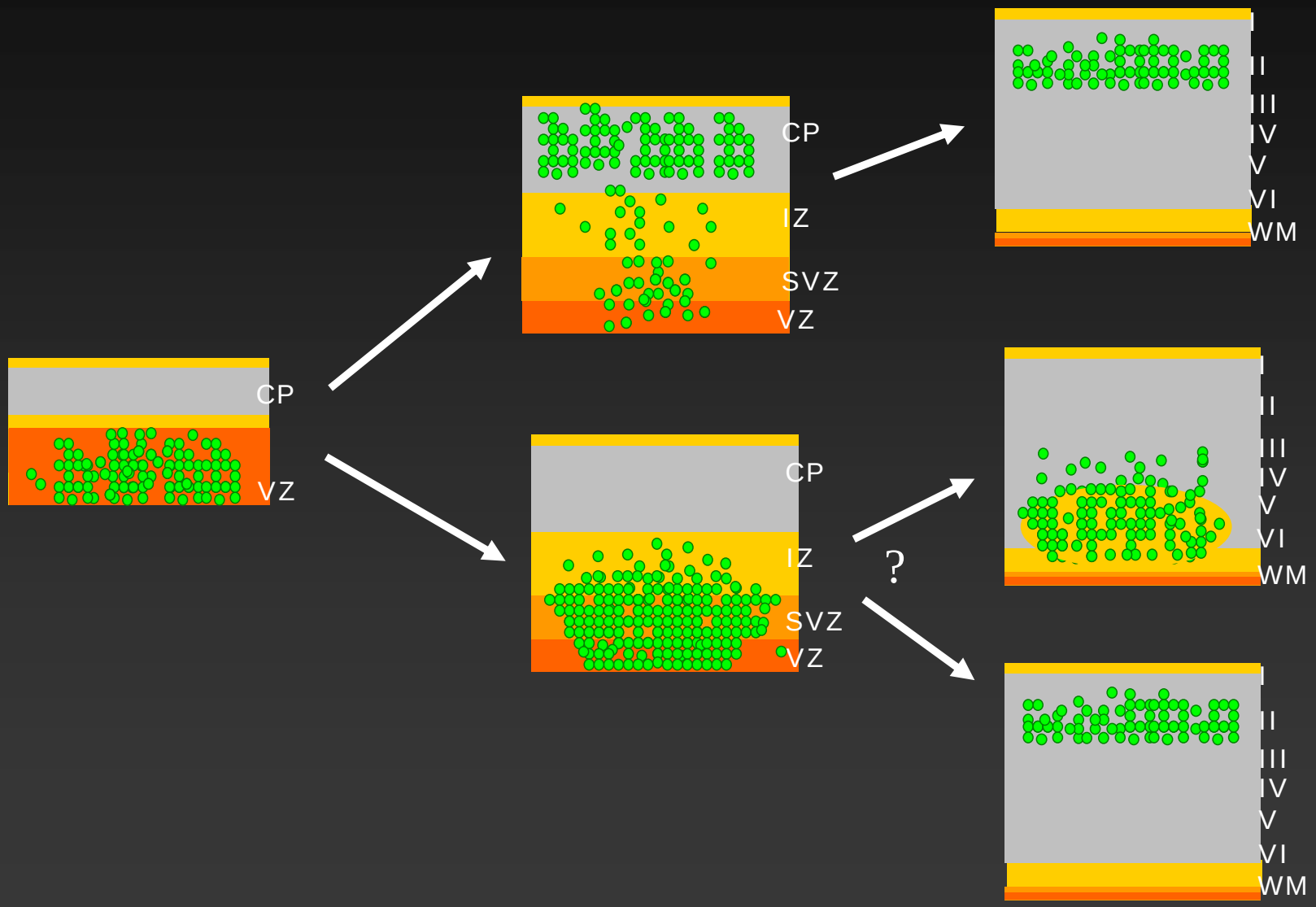
Tracking and manipulating neuronal migration
By electroporation and in utero RNAi



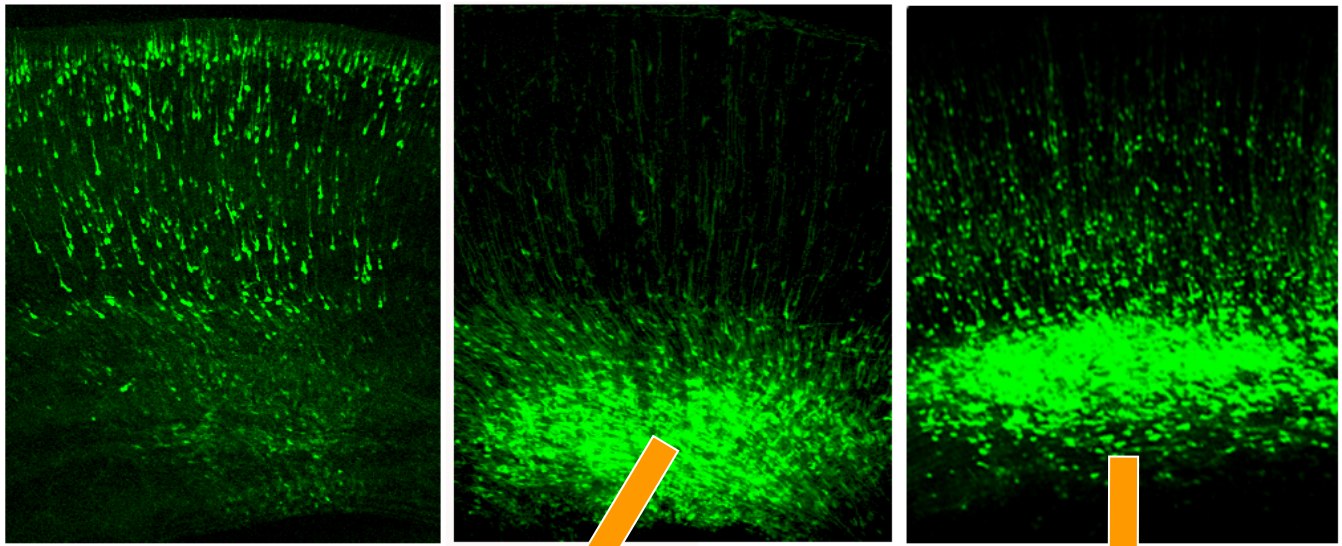
In utero RNAi Creates Neuronal Migration Disru



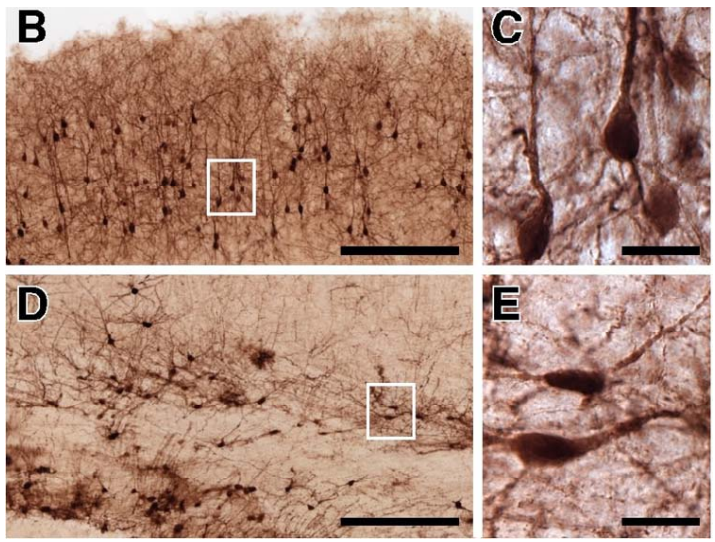
Do malformations ever reverse after they begin to form?

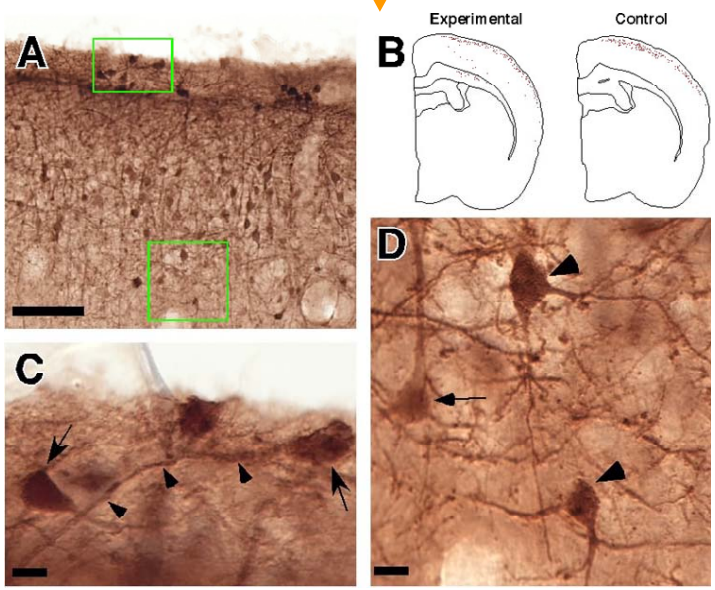


Some RNAis cause migration delay with minimal permanent malformation



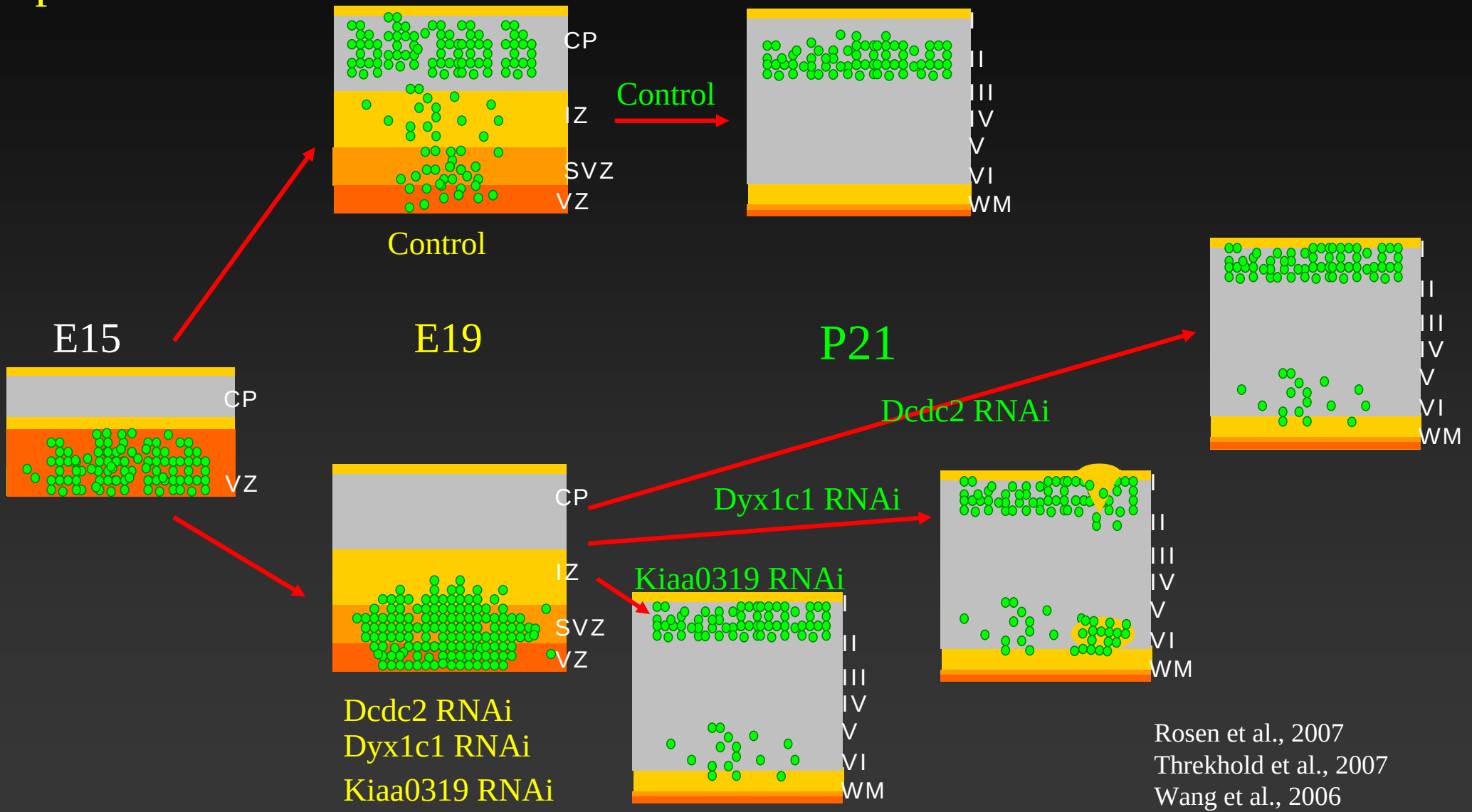
4 days after start





30 days after start

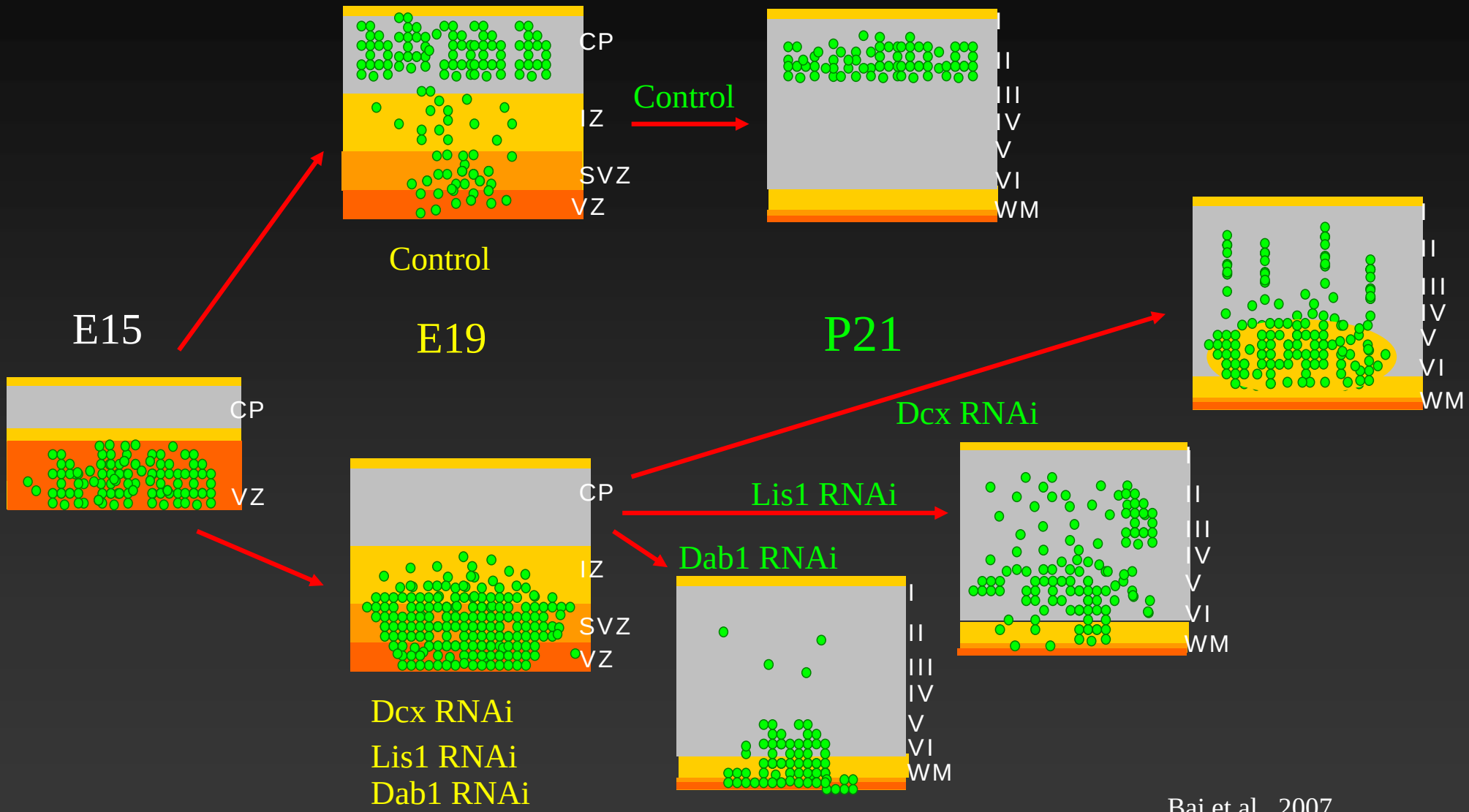
Some RNAis can cause Migration Delay with relatively minimal permanent malformation.



Rosen et al., 2007
Threkhold et al., 2007
Wang et al., 2006

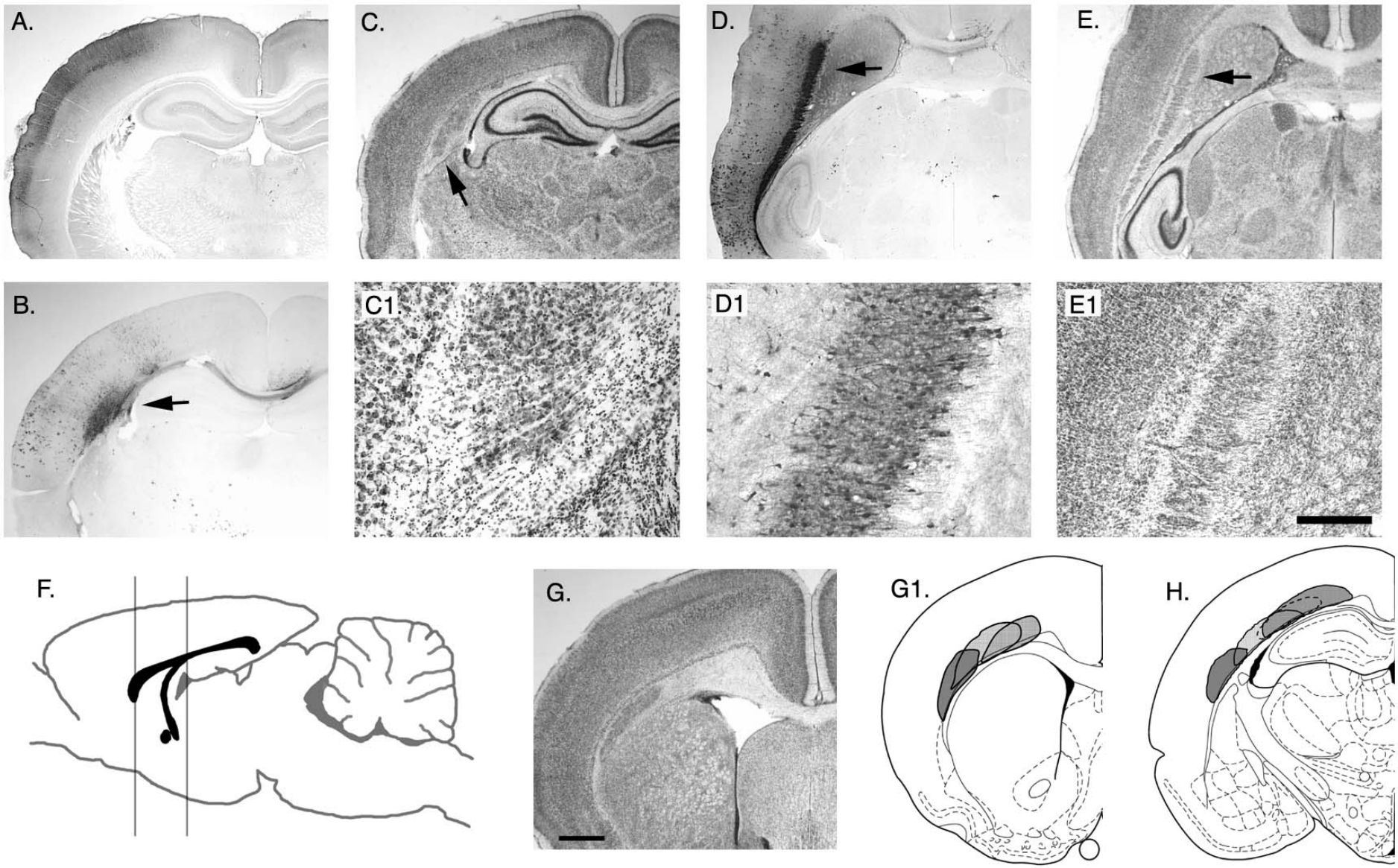
Implication:
At least some developmentally stalled neurons can restart and migrate to appropriate positions in cortex.

Several RNAis cause migration delay and persistent malformation

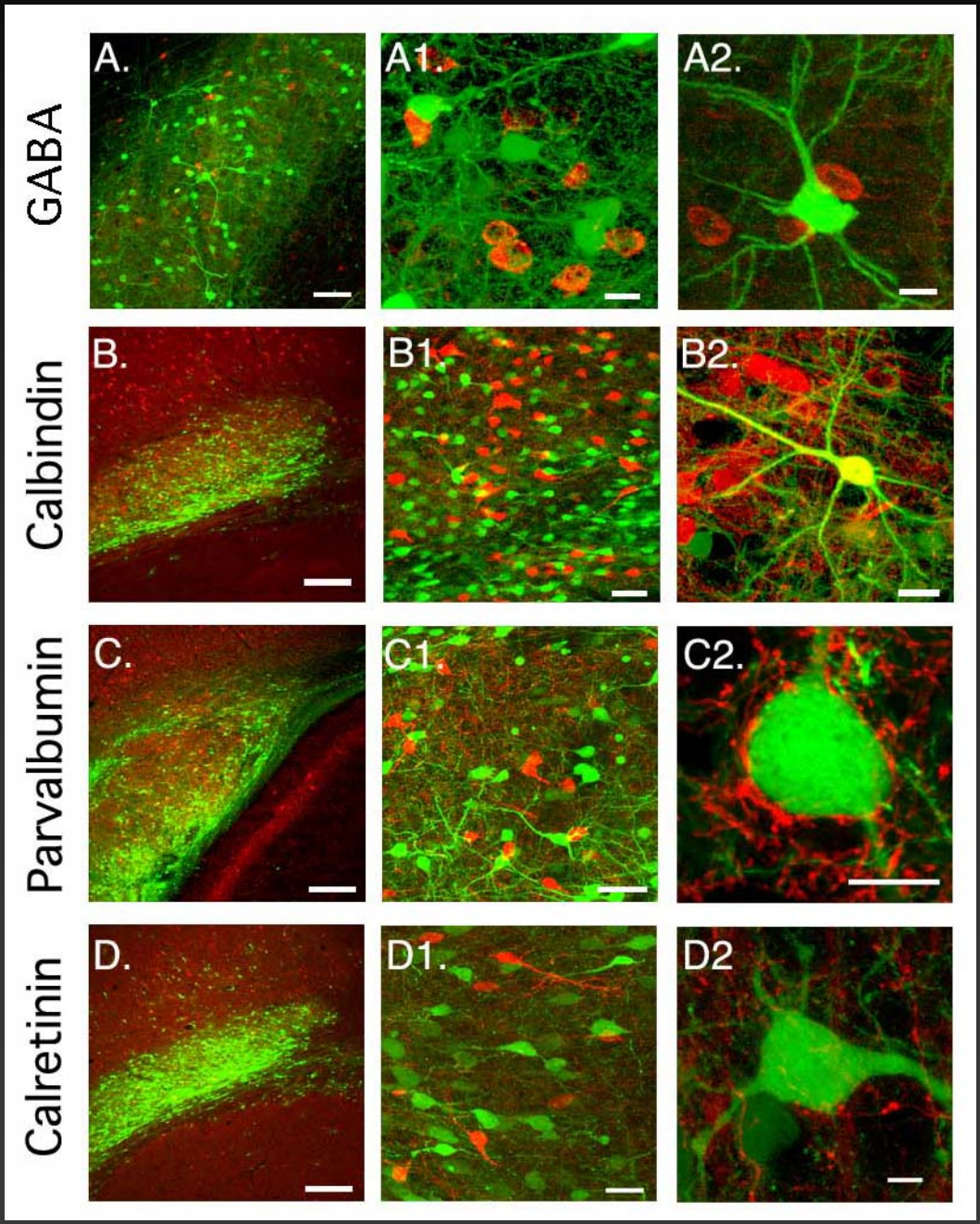


Bai et al., 2007
Ramos et al. 2006
Bai et al. 2003

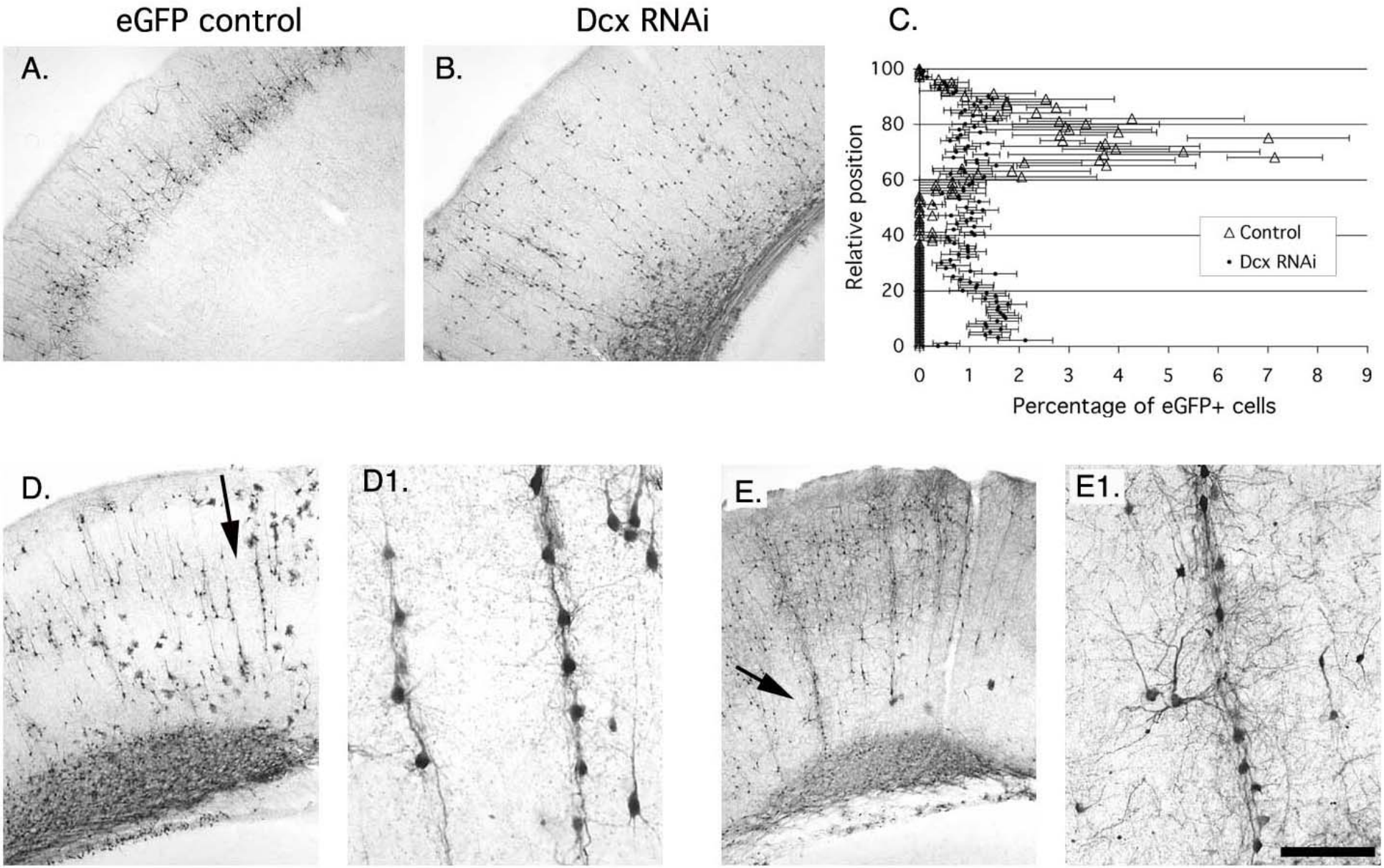
The RNAi model of double cortex syndrome



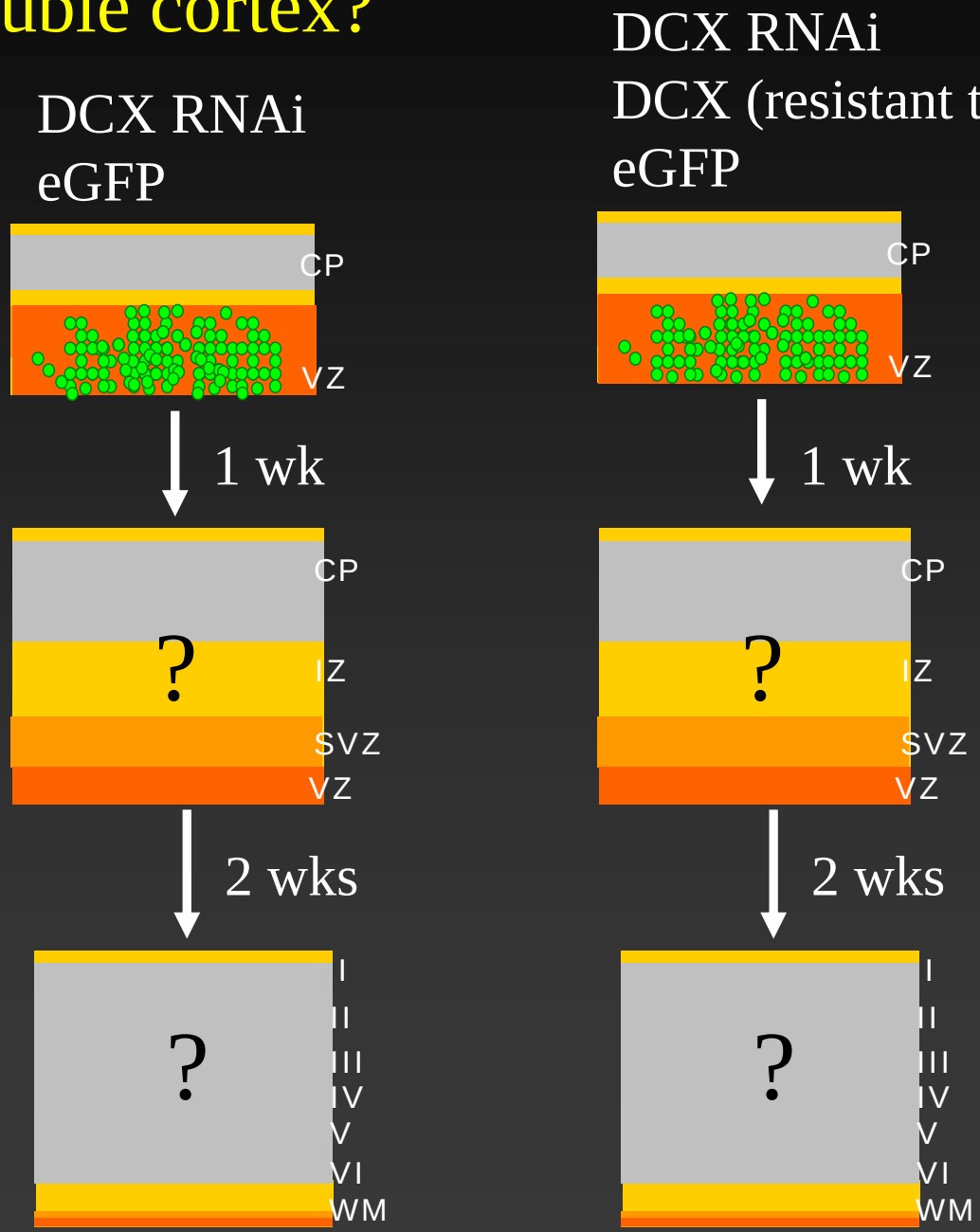
Interneurons are present in double cortex malformations b
Non-cell autonomous recruitment into the heterotopia



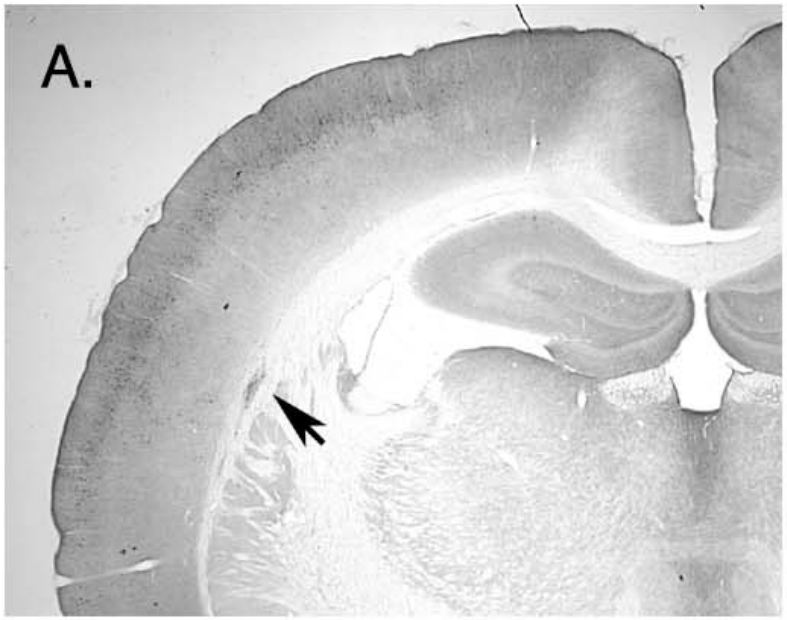
Some transfected neurons migrate out of heterotopia

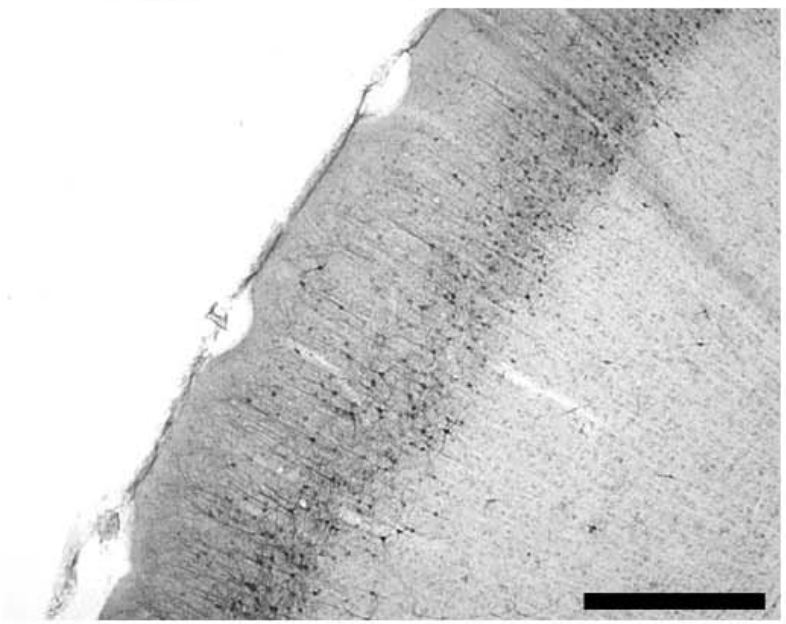


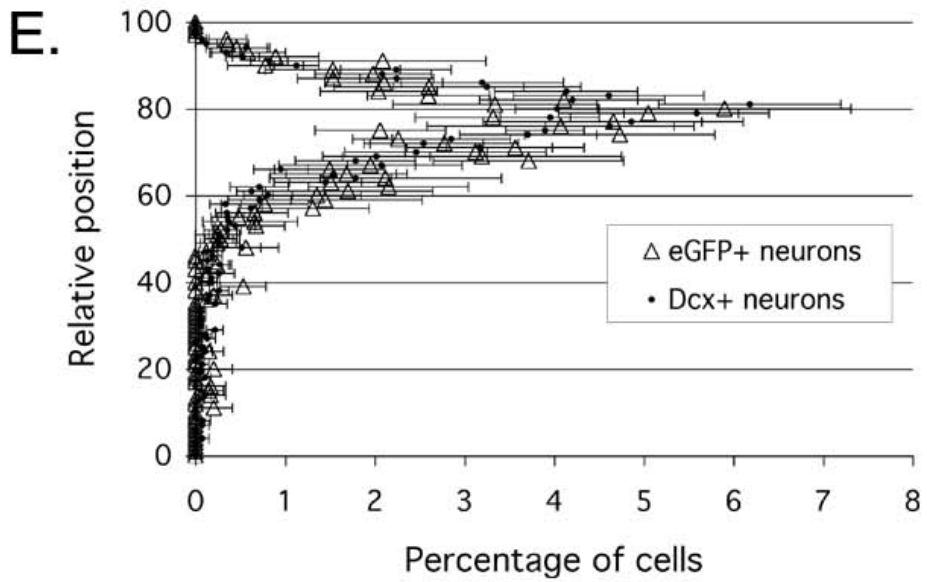
Can induced DCX expression prevent formation of double cortex?

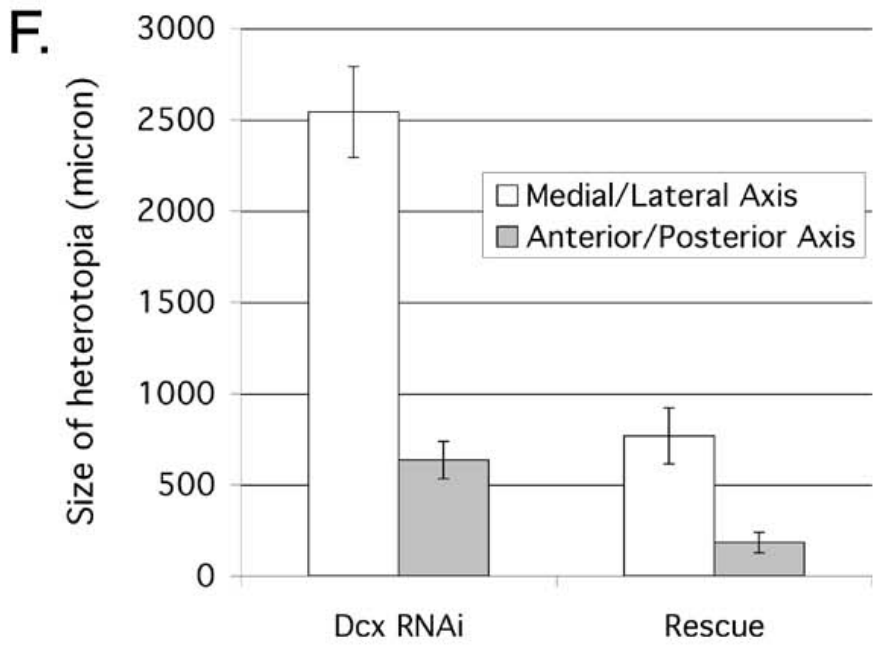


Restored neuronal position and near elimination of double cortex 3 weeks after transfection.



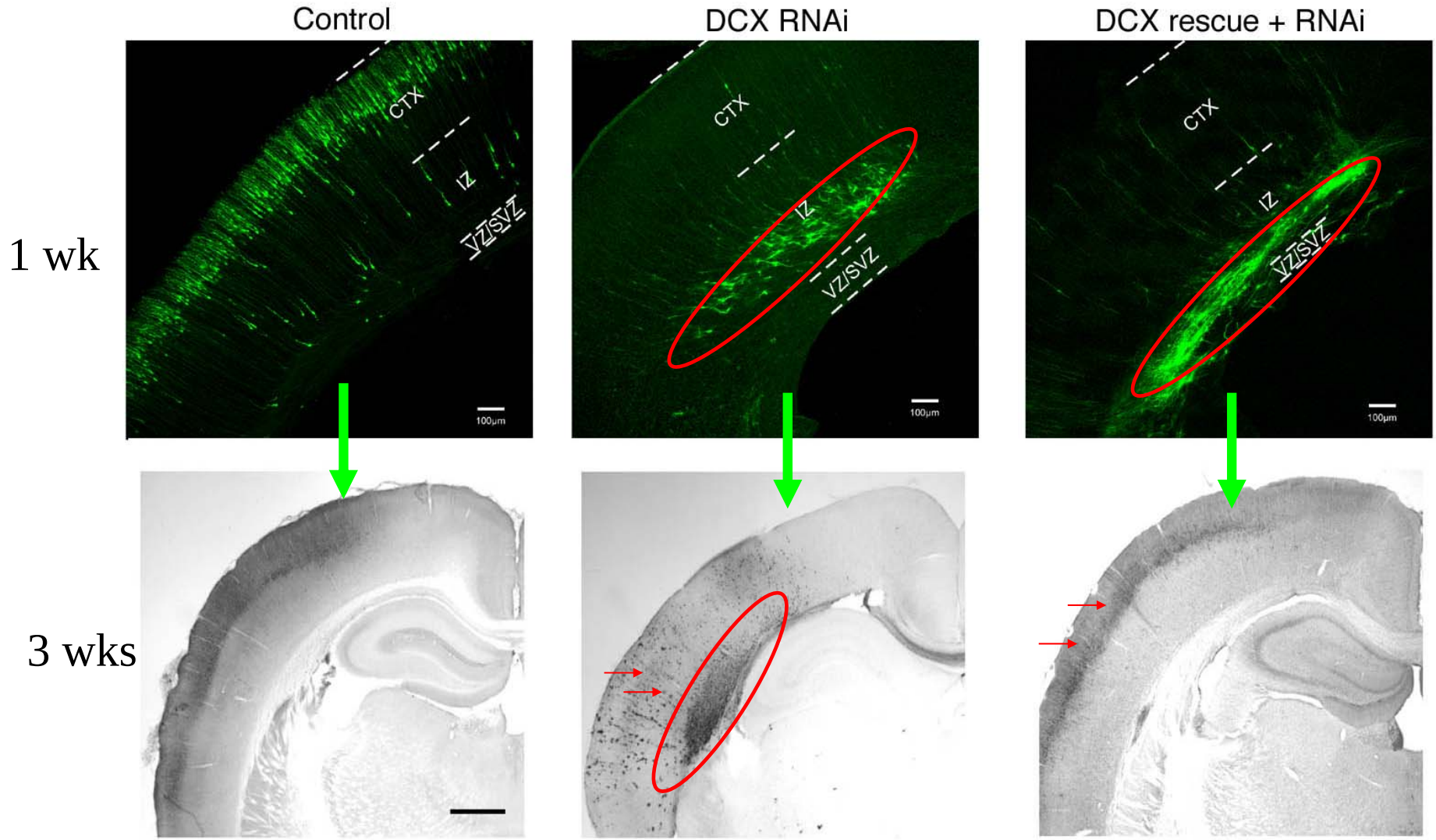


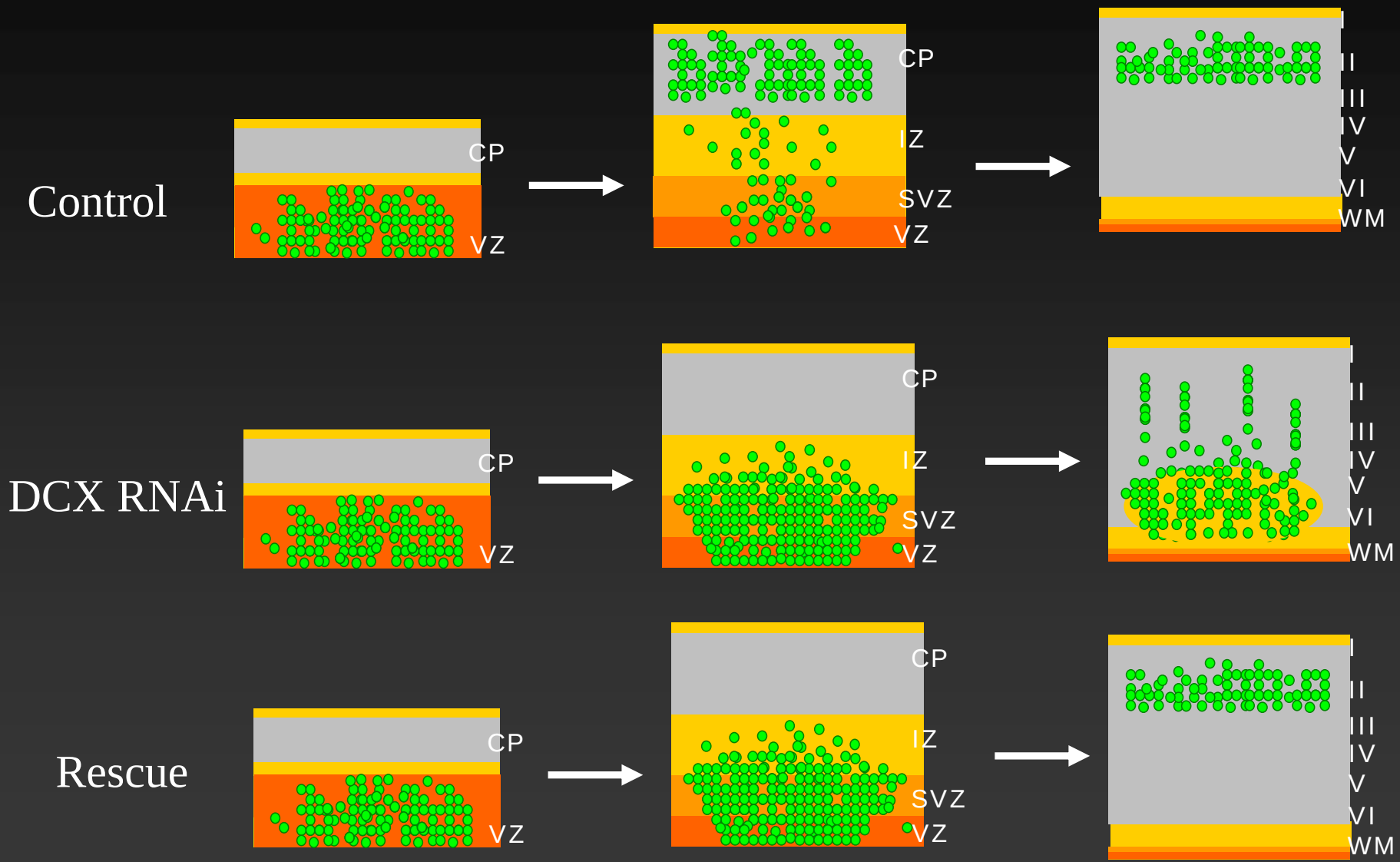




Ramos et al. *Cerebral*

Initially migration is stalled, but over time normal migration is restored and double cortex is eliminated.




Control
CP
VZ
CP
IZ
SVZ
VZ
I
II
III
IV
V
VI
WM
DCX RNAi
CP
VZ
CP
IZ
SVZ
VZ
I
II
III
IV
V
VI
WM
Rescue
CP
VZ
CP
IZ
SVZ
VZ
I
II
III
IV
V
VI
WM

Conclusions, Next Questions and Outlook

1) Neurons can migrate to their appropriate positions even if significantly delayed.
2) Neuronal migration can restart even in the perinatal period?

3)What are the temporal limitations of re-starting Does delayed migration rescue or attenuate hyperexcitability normally associated with malformations?
4) Can other malformation models be rescued after malformations begin to form?

6) Other possible approaches and technologies that may restart migration in identified malformations.
a) Gene therapy to reintroduce or compensate for defective gene function in stalled neurons within malformations.
b) Pharmacological intervention to enhance signaling systems implicated in neuronal migration.
c) Transplantation of stem cells may cooperatively re-initiate migration in stalled neurons.

University of Connecticut Lab

Current

Yu Wang
Jean-Bernard Manent
Faez Sidiqi
Yoonjeung Chang
Murugan Paramasivam
Chris Fiondella

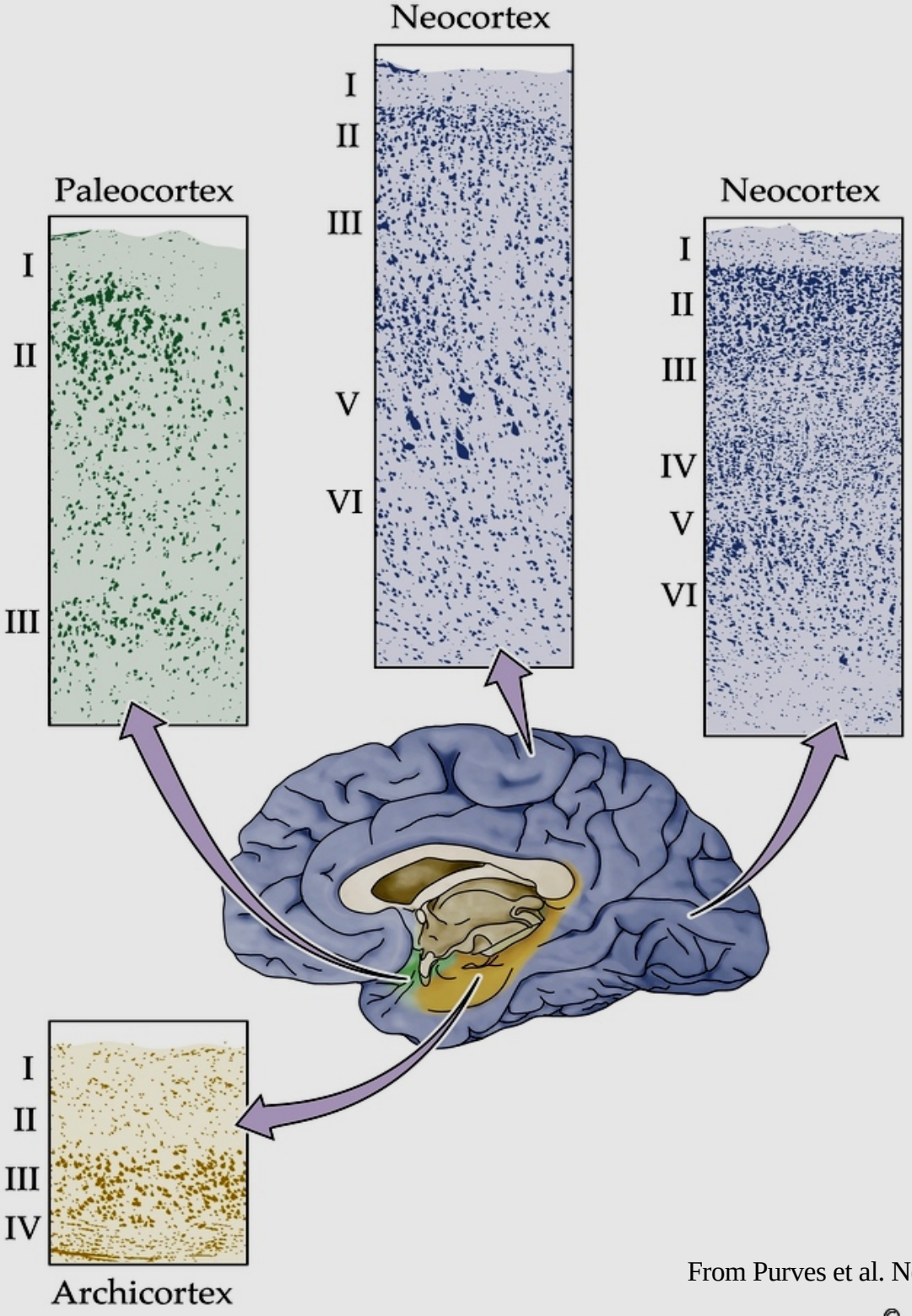
Past

Jilin Bai
James Ackman
Raddy Ramos
Richard Lee
Ankur Thomas

Collaborators:

Jeff Gruen, Yale
Al Galaburda, BIDMC, Harvard
Glenn Rosen, BIDMC, Harvard
Tony Monaco, Oxford
Sylvia Parrachini, Oxford
Juha Kere, Karolinska

Supported by NIH/NIMH and NIH/NICHD



From Purves et al. Neuroscience, 2nd Addition, Sinauer

Plasticity in the Developing Cortex