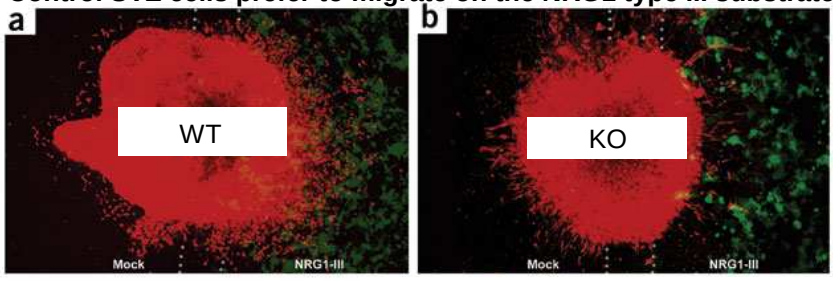
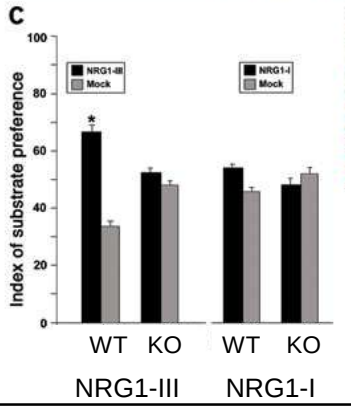
ErbB4 migrazione II parte

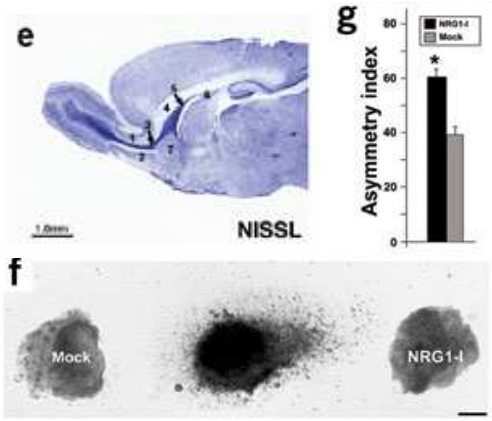
Control SVZ cells prefer to migrate on the NRG1 type III substrate





- the substrate preference of the neuroblasts migrating out of the SVZ explant was evaluated
- SVZ cells had a strong preference for COS cells expressing NRG1 type III, but not for mock-transfected cells or COS cells expressing NRG1 type I
- NRG1 type III at the cell surface may provide a permissive, guidance substratum for neuroblast migration towards the OB

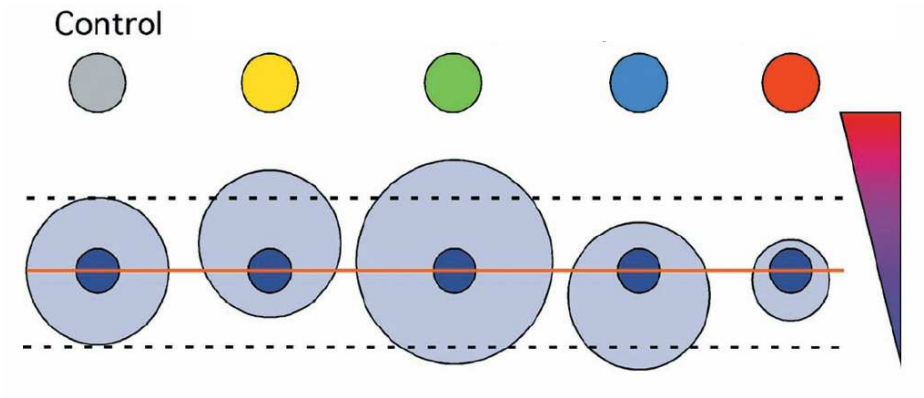
NRG1 type I is a chemoattractant for SVZ cells *in vitro*



- SVZ explants were placed adjacent to COS cell aggregates expressing NRG1 type I or mock-transfected COS cell aggregates
- SVZ cells were attracted towards the NRG1 type I source

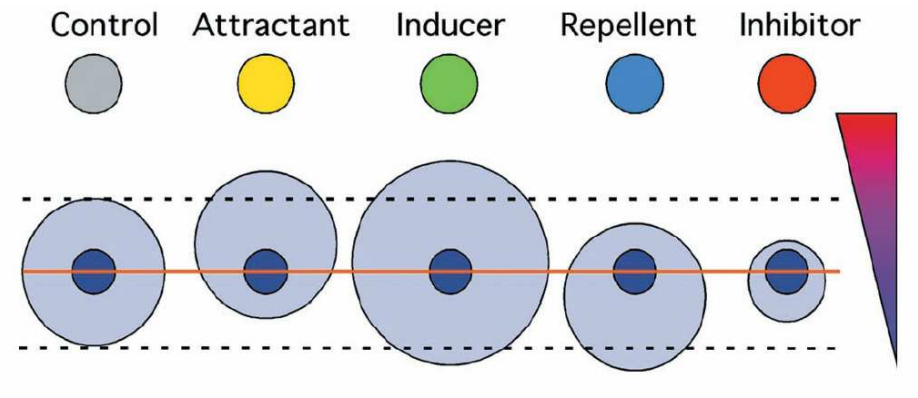
Although the ability to serve as a moderate chemoattractant *in vitro* is notable, the in situ hybridization profiles of NRG1 types I and II do not identify an obvious source for this factor in the OB.

Come definireste le sostanze rilasciate da queste diverse sorgenti?



The *top colored circles* represent aggregates of cells secreting putative regulators of migration. The *small blue circles* represent explants, and the *larger light-blue circles* represent the migrating cells. The size of the circle signifies the number of cells; their location relative to the *inner circle* shows the preferred direction of migration. The *orange line* shows the separation between the distal and proximal hemispheres; the *dashed lines* facilitate the comparison between control and experimental points. The *triangle* on the *right* depicts an expected concentration gradient of the molecules.

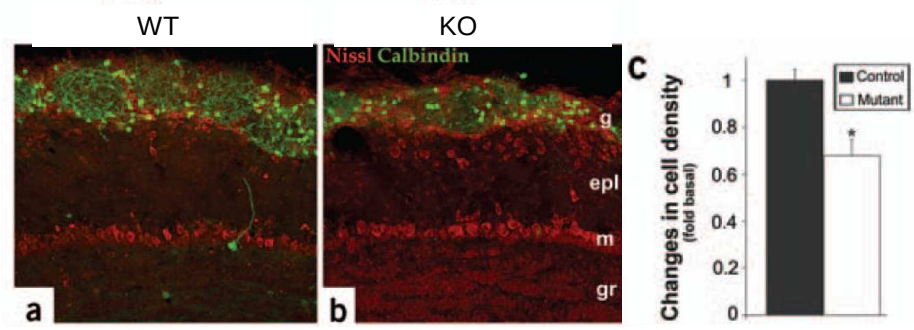
Model of the quantitative and qualitative differences in the effects of attractants, repellents, inhibitors, and inducers on migration from explants



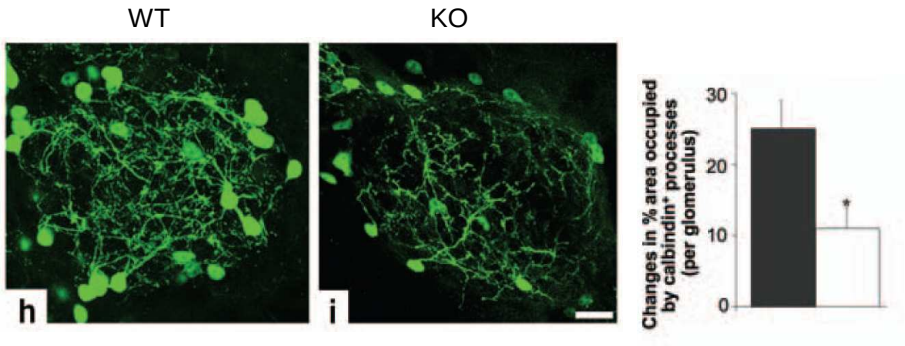
Defects in OB interneurons in ErbB4-deficient mice

• to determine whether the defects observed in the RMS of ErbB4-null mice led to any changes in the generation and placement of interneurons in the OB, the olfactory interneurons present in the mutant mice were characterized, as these cells are believed to arise from SVZ neural stem cells.

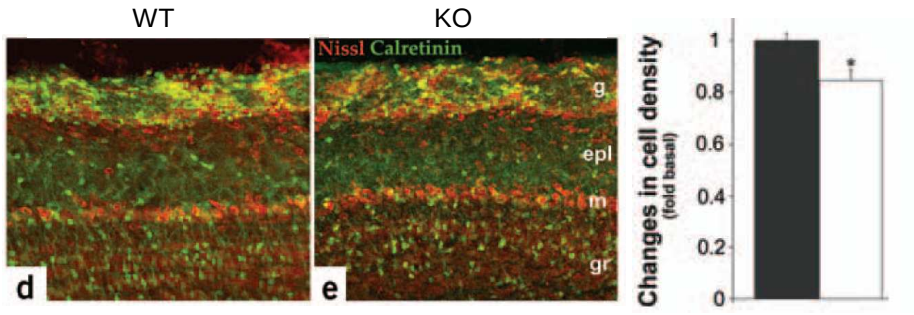
•CALBINDIN serves as a marker for interneurons primarily located in the glomerular region. When compared with controls, KO mice had fewer calbindin expressing neurons, with 35% fewer positive cells detected in the glomerular layer.



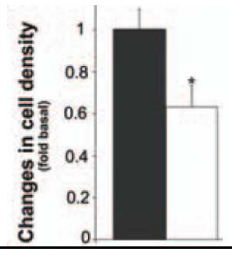
The process arborization of the remaining neurons was retarded, suggesting that these cells may differ functionally from their normal counterparts.



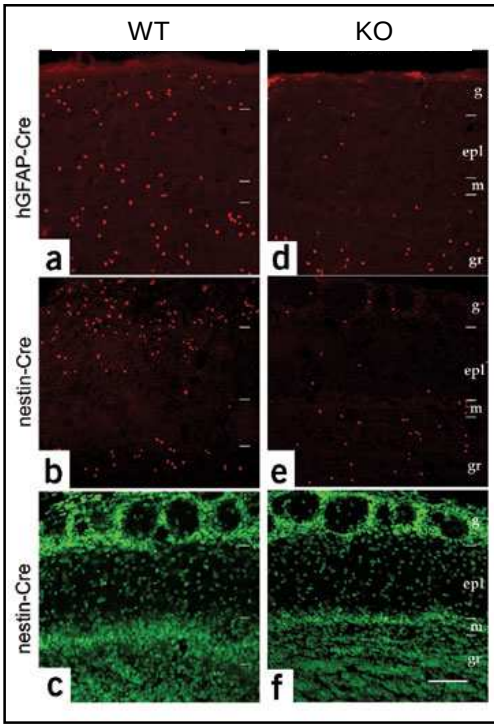
CALRETININ, a calcium binding protein, is another interneuronal marker, less restricted in its laminar expression and normally detected throughout the layers of the bulb. Mutant mice had fewer (15% fewer) calretinine positive interneurons in the glomerular layers.



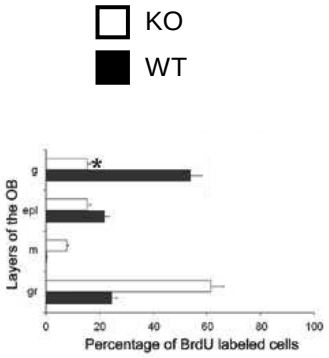
GAD65 is a general interneuronal marker (glutamic acid decarboxylase-65) showing a 37% decrease in the glomerular layer.

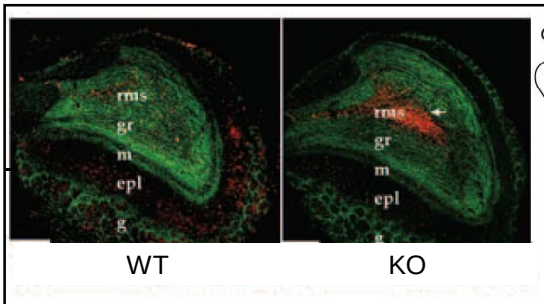


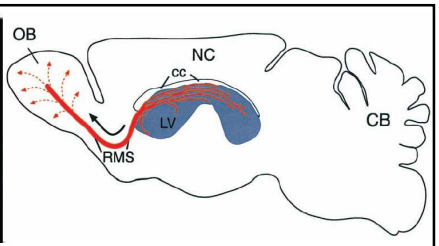
Taken together, these findings suggested that the loss of ErbB4 led to a reduction in specific subset of interneurons.



Migration of newly generated cells to the periglomerular layer of the OB is disrupted in ErbB4-deficient mice







• it has been speculated that neuroblasts migrating tangentially in the RMS switch to a radial mode of migration when they reach the OB and start to disperse towards distinct layers

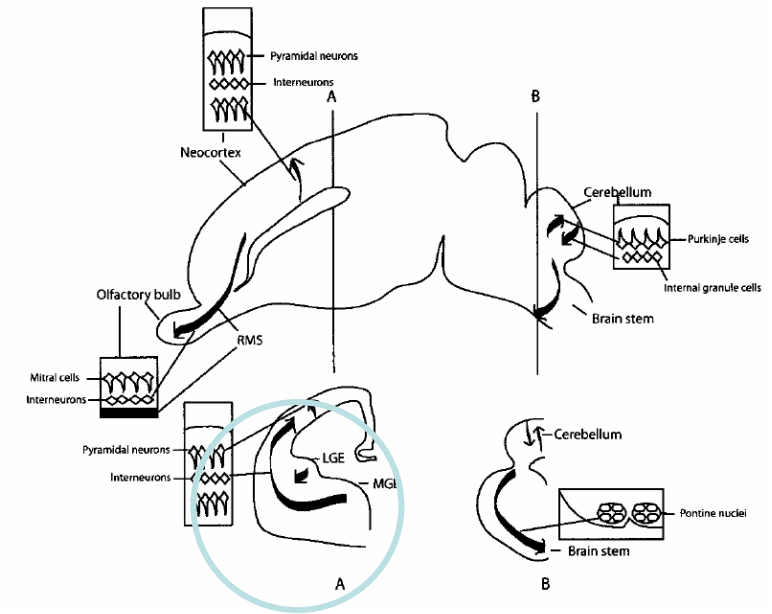
• the accumulation of cells at the centre of OB, near the region where the RMS ends, is consistent with the concept that in the absence of ErbB4 signalling, migrating neuroblasts may have additional deficits in transiting from a tangential to radial mode of migration in the OB

• whether this switch in migratory mode requires radial glial guides is unclear, as the number of radial glia in the adult is very low

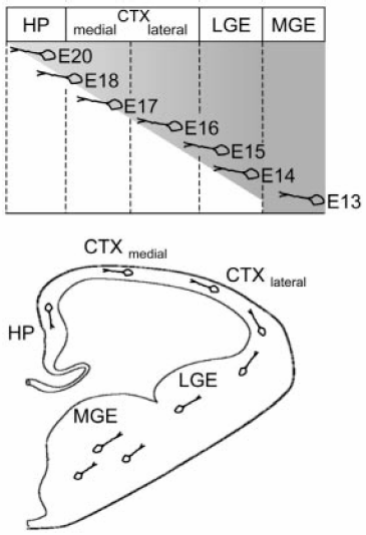
SUMMARY

the protein-tyrosine kinase receptor ErbB4 is expressed by the tangentially migrating neuroblasts in the RMS
• the loss of ErbB4 leads to the formation of an aberrant RMS
• ErbB4 mutant neuroblasts in the RMS have a slower rate of migration and deficits in orientation
• these defects are correlated with an altered distribution and differentiation of interneurons in the mature OB

• these findings imply that ErbB4 has a role in RMS neuroblast migration and olfactory interneuronal placement



Schematic summary of the progression of tangential migration of ErbB4-positive interneurons from the ventral to the dorsal telencephalon of rats during development.



ErbB4-positive cells appear in the MGE as early as E13 and then migrate via the LGE into the lateral parts of the cerebral cortex at E15–E16. By E17, ErbB4-positive cells have reached the medial parts of the cortex. They begin to enter the hippocampal primordium at E18. After E20, they migrate deeply into the hippocampal primordium.

CTX, cerebral cortex;
HP, hippocampus,
MGE, medial ganglionic eminence,
LGE, lateral ganglionic eminence.

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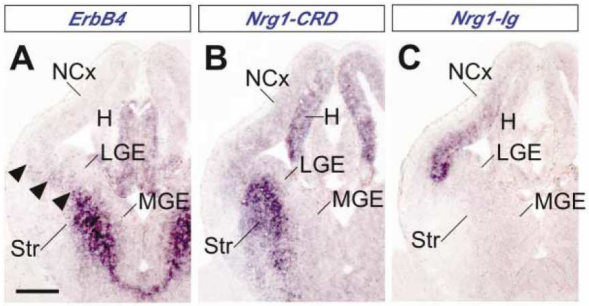
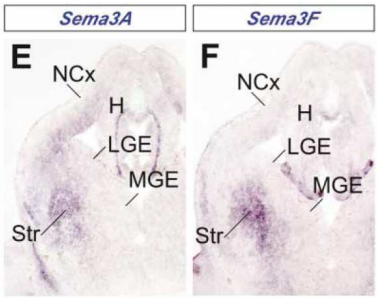
Short- and Long-Range Attraction of Cortical GABAergic Interneurons by Neuregulin-1

Nuria Flames,[1] Jason E. Long,[2]
Alistair N. Garratt,[3] Tobias M. Fischer,[4]
Martin Gassmann,[5] Carmen Birchmeier,[3] Cary Lai,[4]
John L.R. Rubenstein,[2] and Oscar Marín[1,*]

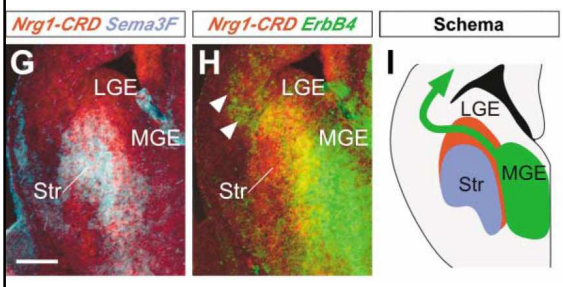
Complementary expression of *Nrg1* isoforms and *ErbB4* in the developing telencephalon during the period of interneuron migration to the cortex (E 13.5)



- *Nrg1-CRD* is expressed throughout the LGE, from the subventricular zone to the developing striatal mantle
- the developing cortex - the target of the migrating ErbB4^{+} interneurons - specifically expressed the diffusible form of the *Nrg1* gene, *Nrg1-Ig*
- the analysis of adjacent sections revealed that the tangentially migrating *ErbB4*$^{+}$ cells follow a corridor through the LGE that is *Nrg1-CRD*$^{+}$ (and lacks *Semaphorin* expression)



- *Semaphorin3A* (*Sema3A*) and *Semaphorin3F* (*Sema3F*) were found to be expressed in the striatal mantle where they create an inhibitory territory that migrating cortical interneurons avoid in their way toward the cortex

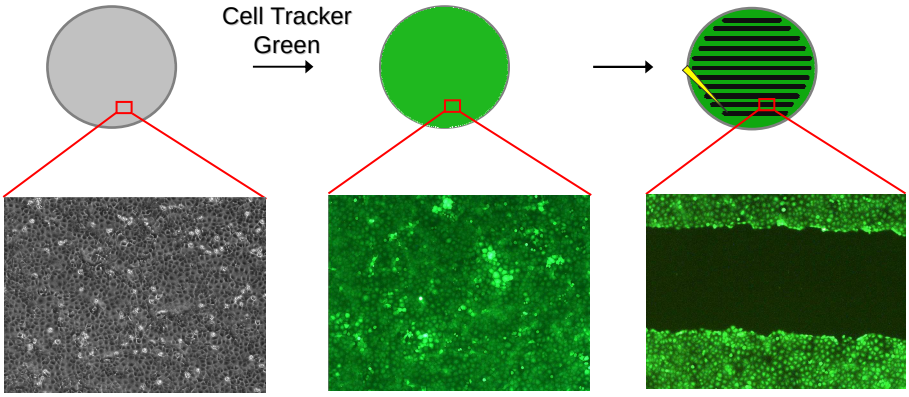


- ***ErbB4*-expressing interneurons** reach the cortex through a cellular corridor expressing ***Nrg1-CRD*** avoiding the striatal mantle due to **Sema3A/3F**-mediated chemorepulsion

Stripe Choice Assay

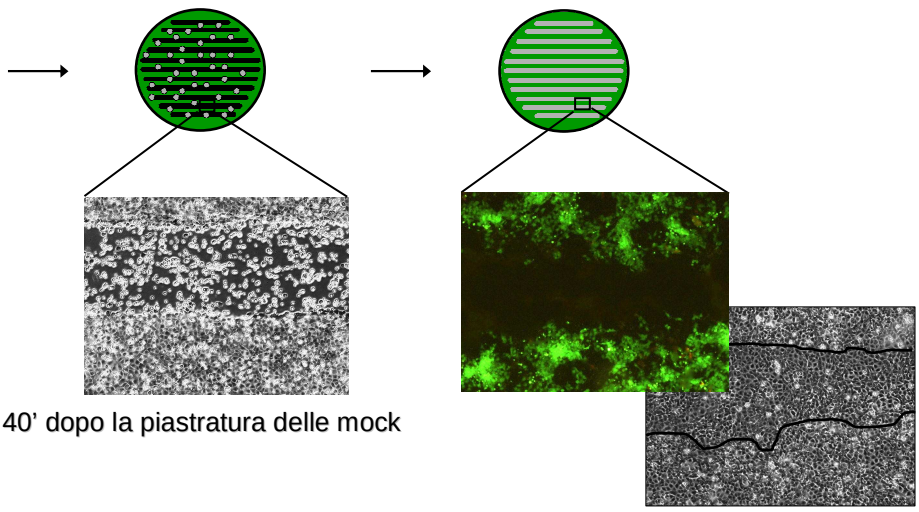
Piastre confluenti di cellule esprimenti la NRG1-III-β3

Cell Tracker Green



graffi ogni 2 mm

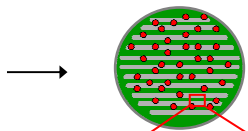
mock

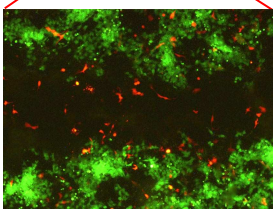


40’ dopo la piastratura delle mock

24h dopo la piastratura delle mock

MGE
explants
+RFP



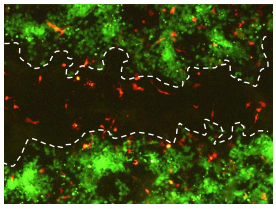


24h dopo la piastratura delle cellule MGE

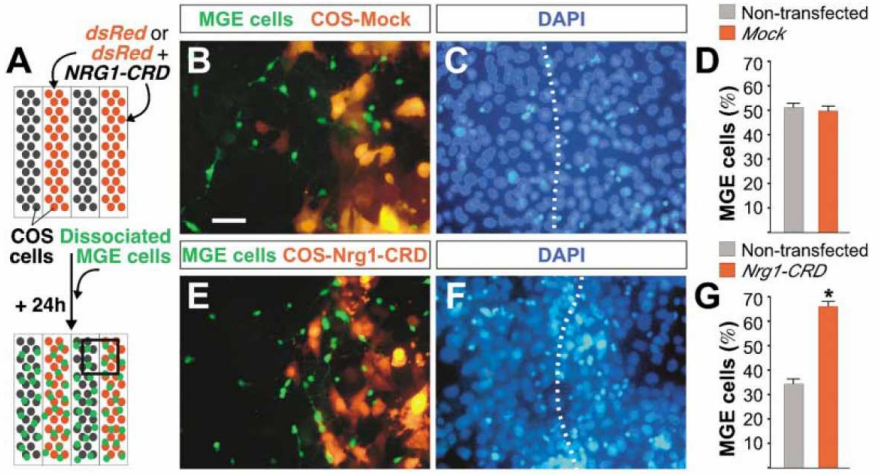
Quantificazione:

A: numero cellule rosse (MGE) /
Area cells verdi (NRG1-III-β3)

B: numero cellule rosse (MGE) /
Area cells incolori (mock)

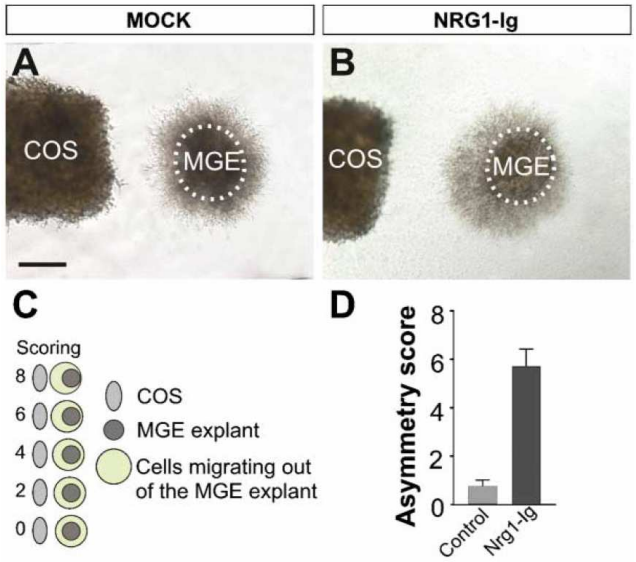


MGE-Derived Cells Prefer a *Nrg1-CRD*-Expressing Substrate in the Stripe Choice Assay



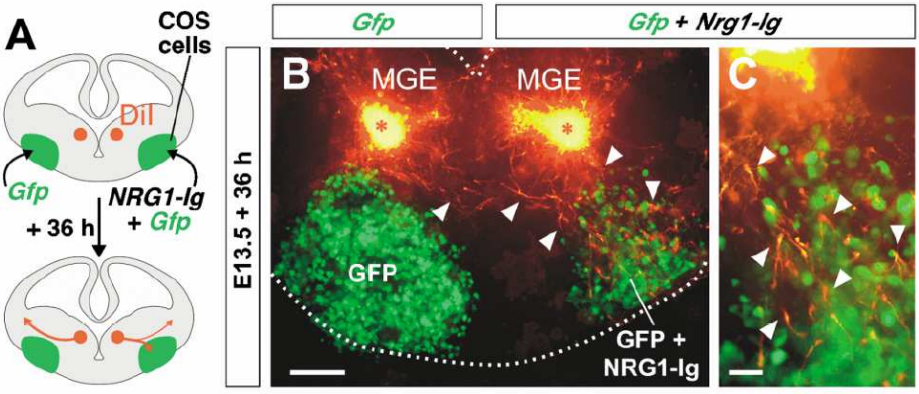
Slides were coated with alternating stripes of nontransfected COS cells (dark gray dots) and either mock-transfected or Nrg1-CRD-transfected COS cells (red dots). Dissociated E13.5 MGE cells (green dots) were plated on top of the stripe carpets, and their distribution was studied 24 hr later.

NRG1-Ig is a chemoattractant for MGE-derived neurons



Medial ganglionic eminence (MGE) explants from the telencephalon of E13.5 embryos were cultured in Matrigel adjacent to mock-transfected (A) or *Nrg1-Ig*-transfected (B) COS cell aggregates.

ECTOPIC EXPRESSION OF NRG1-Ig REDIRECTS THE MIGRATION OF MGE-DERIVED CELLS IN SLICE CULTURES



Coronal slice through the telencephalon with cell aggregates formed with control (left) and *Nrg1-Ig* (right) transfected COS cells. DiI-labeled cells (arrowheads) from both the ipsilateral and contralateral MGE (asterisk) migrate ectopically in a ventrolateral direction towards the COS cell aggregate expressing NRG1-Ig.

- different isoforms of neuregulin-1 are expressed in the developing cortex and in the route that migrating interneurons follow toward the cortex, whereas a population of the migrating interneurons express *ErbB4*, a receptor for neuregulin-1

- the different isoforms of neuregulin-1 - type III and type I- act respectively as short- and long- range attractants for migrating interneurons

- perturbing ErbB4 function in vitro decreases the number of interneurons MGE that tangentially migrate to the cortex

- *in vivo*, loss of neuregulin-1/ErbB4 signalling causes an alteration in the tangential migration of cortical interneurons

- these observations provide evidence that neuregulin-1 and its ErbB4 receptor directly control neuronal migration in the nervous system