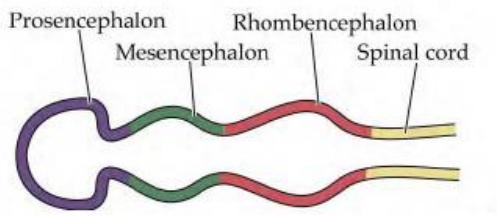
Lecture 3 – Development of the Brain Cortex: Cortical Arealization

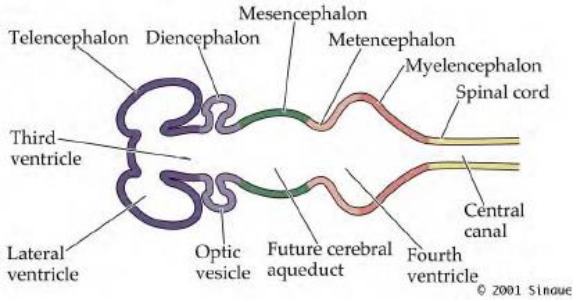
Cortex divided into functional areas – the 4 lobes, each subdivided into more regions

Neural tube morphogenesis + patterning

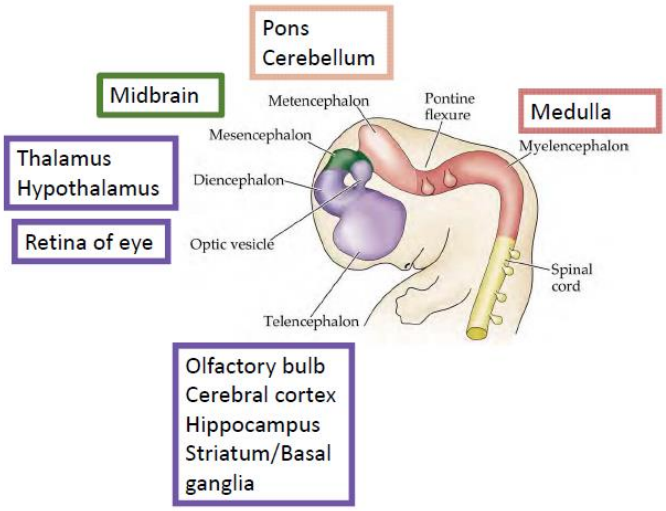
- Closure of neural tube
  - Walls = neuroepithelium
  - Fluid filled central cavity = ventricular system (the neural tube isn't solid)
- Primary brain vesicles (along anterior-posterior axis) – **3 vesicle** stage
  - Prosencephalon (forebrain)
  - Mesencephalon (midbrain)
  - Rhombencephalon (hindbrain)



- Secondary brain vesicles – **5 vesicle** stage
  - Prosencephalon → Telencephalon (cerebral cortex) + Diencephalon
    - Telencephalon forms 2 big vesicles – but remains **1 layer thick** for some time before it starts building its layers (cortex)
  - Mesencephalon (from before – becomes the midbrain)
  - Rhombencephalon → Metencephalon + Myencephalon



- Adult brain structures



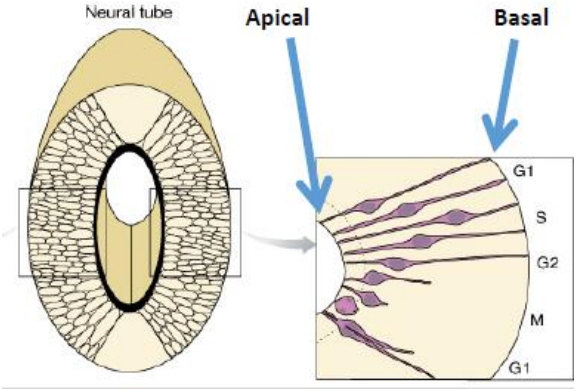
Proliferation + Patterning in the Spinal Cord

By **opposing gradients** of morphogens

Morphogen: Signalling molecule secreted locally, diffuses out into the developing tissue and act directly on cells, producing specific cellular responses depending on its **local concentration**

Functional regions + organisation of the mouse cortex is actually v similar to that of a monkey + human

Expansion is mostly in SA of cortex (gyri) – the grey matter = the cortex proper (thickness remains relatively constant through different species)

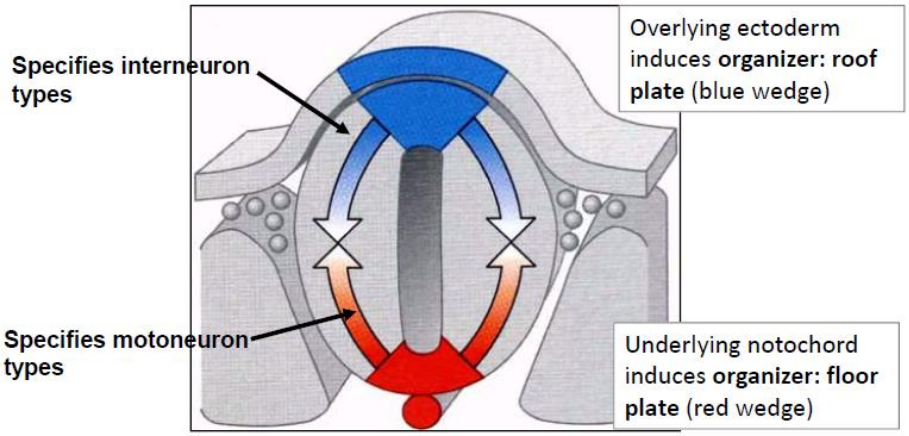


Neuronal Replication

- Neural tube initially consists of **single layer** of neuroepithelium – neuronal precursors (but looks layered)
    - **Pseudostratified** neuroepithelium
- Precursors lose their processes divide on the **apical** edge (closest to lumen)
    - Daughter cells with either still be precursors (expand population) or will become a neuron + migrate to brain surface
    - Lumen is filled with CSF
    - During different phases of cell cycle, the cell body migrates up/down the process
    - Called **interkinetic nuclear migration**
        - Enables **dense packing**
        - Nuclei exposed to particular signals at different cell cycle stages

Patterning (Dorsal-ventral patterning)
Best studied in the spinal cord

- From **patterning centres/organisers** secreting morphogens



- Organisers secrete morphogens (arrows) – form a **concentration gradient**
    - Morphogens induces **transcription factors** (turn them on or off)+ changes the fate of the cells
        - Floor plate makes **sonic hedgehog**
        - Roof plate makes **BMP, Wnt**
    - Transcription factors produced determine **cell fate**
        - Early neural tube – all become neurons
            - Different precursors depending on morphogen → different lineages of neurons (e.g. motor neurons)
        - Later – produce other cells (glia)

Cortical Development

2 initial hypotheses

1. **Protomap Hypothesis** (Rakic, 1988)

   The proliferative ventricular/germinal zone (VZ) have the different areas of the brain **already determined**/mapped via differential patterns of **gene expression**

2. **Protocortex Hypothesis** (O'Leary, 1989)

   The VZ precursors are all the same with **undetermined fates** – have the potential to become anything in the brain. They receive their instructions from **afferents of thalamic nuclei** (**activity-dependent**)

Actual process is a **combination** of both of these

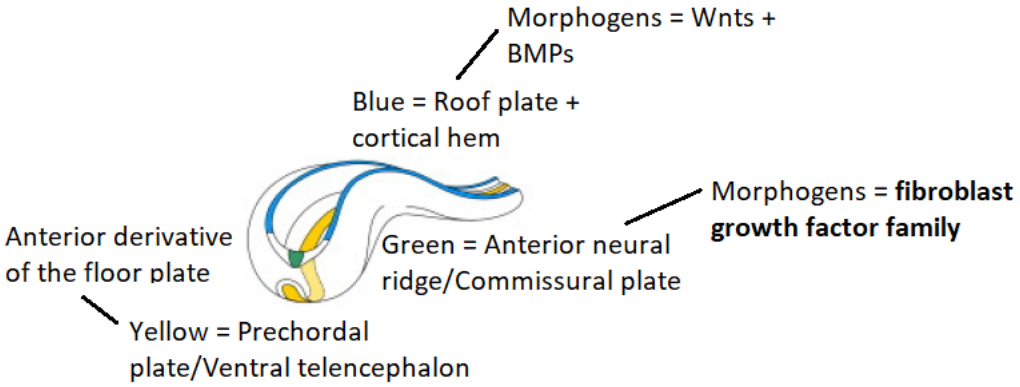
Patterning in the Cortex

Early telencephalic territories (day 8.5-10.5 of 18.5 gestation period in mice)

Early Forebrain Organizers

*The dorsal + ventral morphogens are the same as in the spinal cord (Sonic hedgehog, BMP, Wnt)

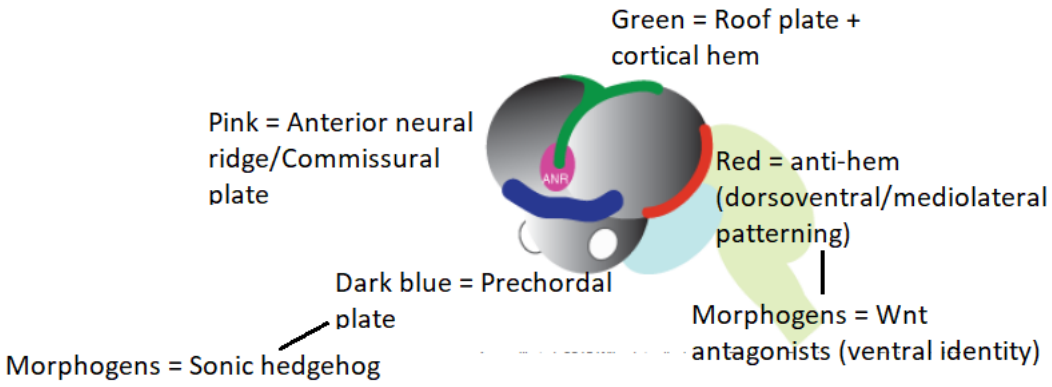
But the organisers look different:



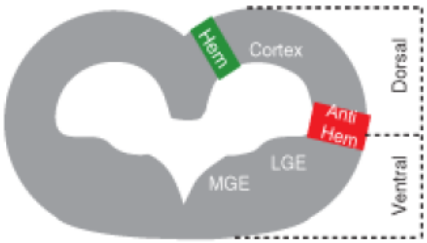
Secondary Organisers

(day 11-13.5)

Then as the vesicles continue to grow + expand… get involvement of **secondary organizers** (anti-hem – get the pallial-subpallial boundary)



Neuroepithelial cells become **committed to cortical fate** – different transcription factors



Ngn2
Pax6 (A>P)
Emx2 (P>A)

Transcription factors for dorsal (pallial) identity

Ascl1
Dlx 1,2,5

Transcription factors for ventral (sub-pallial) identity

Upper half becomes the cortex

Lower half becomes the striatum/basal ganglia

Therefore, the brain needs patterning for…

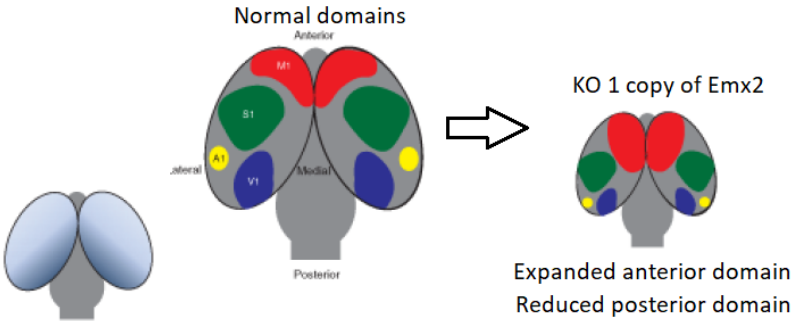
- Medial-lateral
- Front-back
- Top-bottom

<u>Transcription Factors</u>

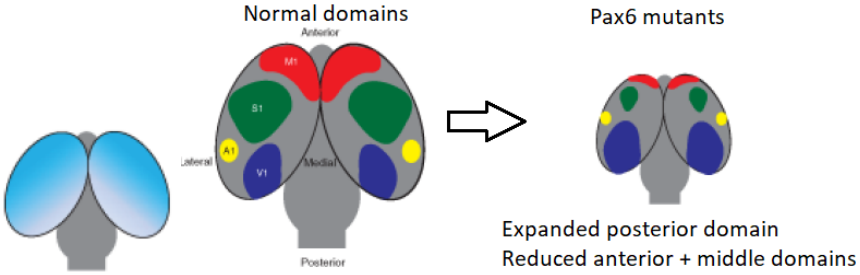
In dorsal telencephalic neuroepithelium, induced by morphogens of secondary organisers

Identified using KO mice

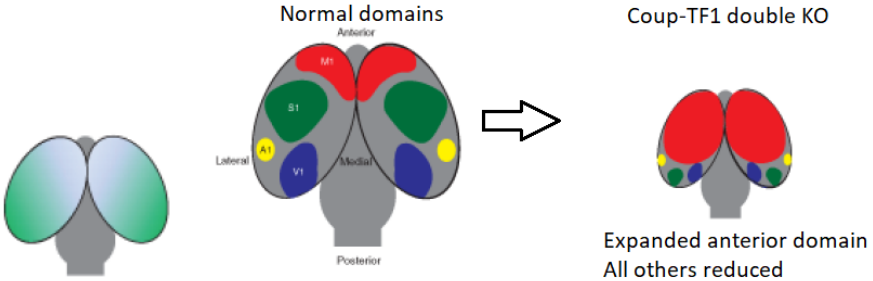
- **<u>Emx2</u>**: Expressed most highly medially + posteriorly



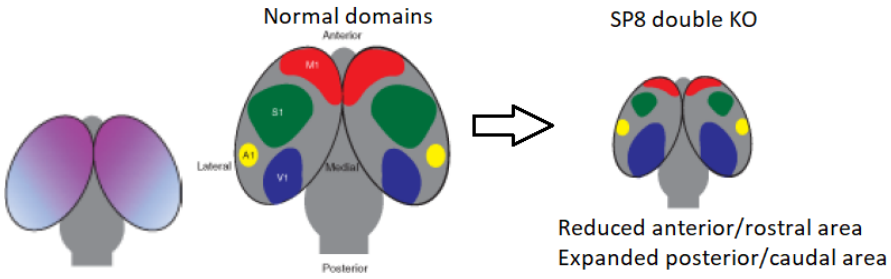
- **<u>Pax6</u>**: Highest laterally + anteriorly (opposite of Emx2)



- **<u>CoupTF1</u>**: Highest laterally + posteriorly

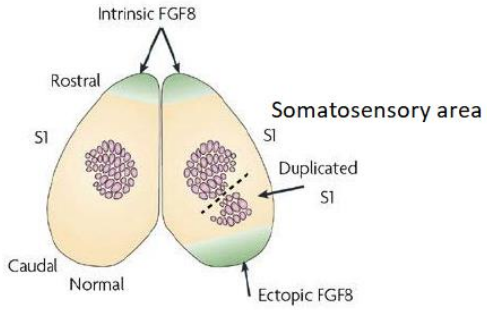


- **<u>Sp8</u>**: Highest anteriorly + medially

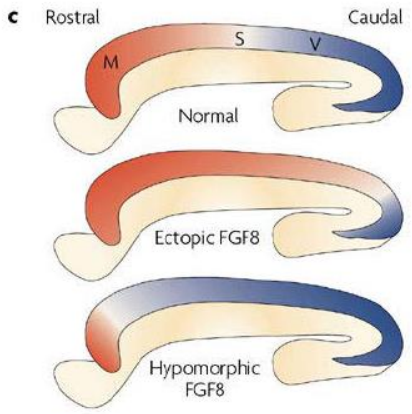


Experiment: Manipulating FGF8 (fibroblast growth factor 8) levels
Made by anterior neural ridge/commissural plate

1. Introduced some FGF8 on the caudal end = Made another somatosensory region (S1)



2. Introduced extra FGF8 in different locations along the rostral-caudal axis



Somatosensory region forms in the middle of red/blue

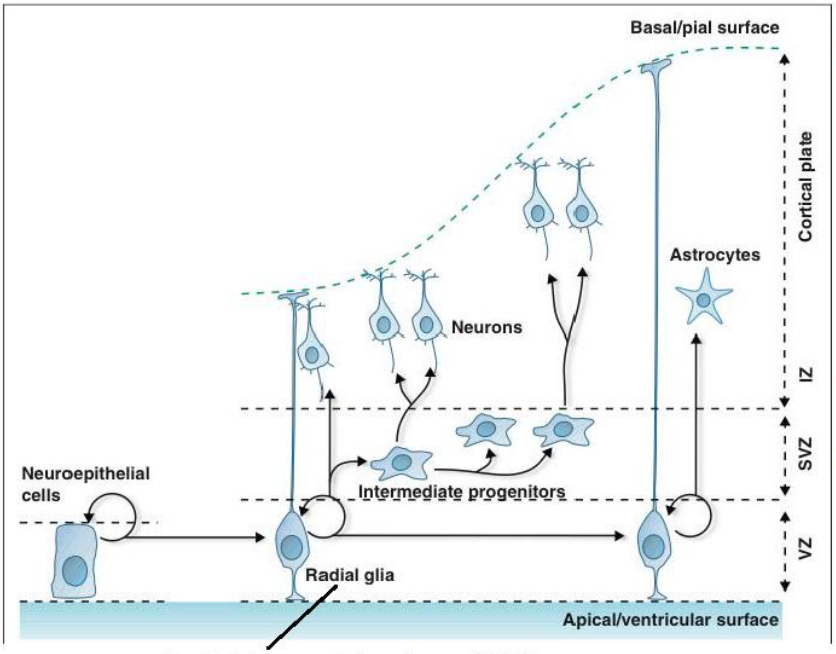
Red = motor region
Blue = visual region

Too much FGF8 at the front = motor region takes over almost everything - visual regions much smaller

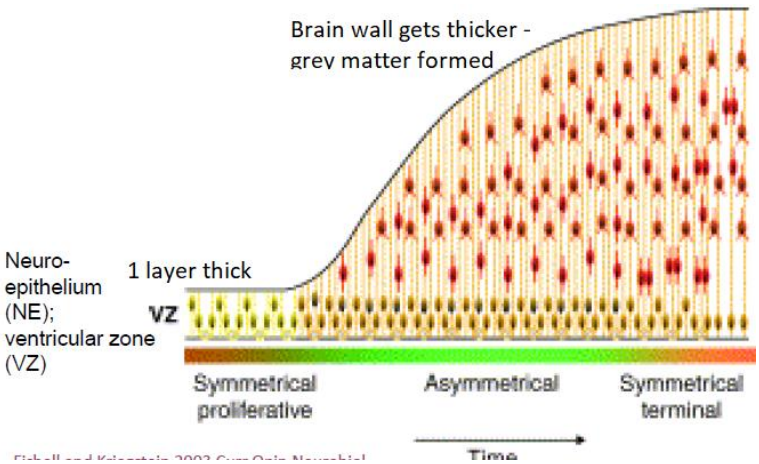
Reduce FGF8 at the front = expanded visual region, tiny motor region

This provides evidence for the **'protomap' model** – altering these transcription factors affects determined 'proto-areas'

Neural Expansion



Radial glia aren't just for scaffolding - they're also precursors producing neurons



When the precursors migrate along the radial glia to the surface of the cortex, they **preserve spatial relationships** as seen in the ventricular zone

Supports the radial unit (protomap) hypothesis:
Neurons migrate radially – intrinsic patterning that has been set up by the graded morphogens/TF to be kept

Thalamic neurons then send their processes down + synapse with these

Supports the protocortex hypothesis:
Neurons final form isn't determined until they get afferent input from the thalamic afferents
i.e. the early molecular map made by graded morphogen expression is **refined** by thalamic input

These (different nuclei of **dorsal thalamus – thalamocortical axons/TCA**) transmit different **sensory modalities** (e.g. from eye → LGN in thalamus → visual cortex)

They differentially affect the **proliferation rate** in the developing cortex + contribute to the different **cytoarchitectural features** of different areas

Experiment: Depleting embryonic LGN axons

= Reduced primary visual area 17
Evidence for the protocortex model (**activity-dependent refinement**)

The size/territory of the visual area depends on size of the LGN

Experiment: Manipulated TCA in mice

- Genetic KOs that removed some TCAs – the mice **didn't survive** to see the maturation of the circuits
- If you modified the TCA projections in the **late embryonic/neonatal stage** it **didn't** result in major changes in gene expression patterns in the cortical plate

= Intrinsic patterning mechanisms are mostly responsible for cortex regions established in **embryogenesis**

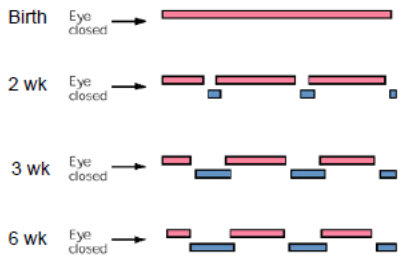
BUT postnatal thalamic innervation is also important!
e.g. in the inputs for both eyes during critical development period – **ocular dominance columns**

Experiment: Ocular dominance columns in cats

Labelled retinal ganglion cell with radioactive tag in one eye
→ thalamus → thalamic afferent going into the cortex
→ **layer IV** of developing **V1** region

Zebra striped pattern in layer IV – **ocular dominance columns**

These are established **postnatally** in **critical period** (first 6 weeks), driven by **visual sensory input**
Eye needs to open + receive sensory information



The less time one eye is closed during the **critical period**
= **less effect** closing it has on ocular dominance columns

Summary of protomap vs protocortex hypotheses

Protomap:

- Proliferative ventricular zone of forebrain shows mapping determined by **graded morphogens**
  - Turn on region/zone-**specific** transcription programs (also exhibit a gradient)
  - Drives **neurogenesis**
- Relative positions of primary **sensory** regions + secondary **association** regions are **preserved** by **radial migration** + columnar organisation
  (after neurons are derived from precursors in the ventricular zone)

Protocortex:

- Can transplant parts of neuroepithelium to other places + allow them to acquire some characteristics of where you put them
    - The protomap is **plastic**
- Boundaries of regions are refined by thalamic input (activity-dependent)
- Functional maturation provided by thalamic input (activity-dependent)