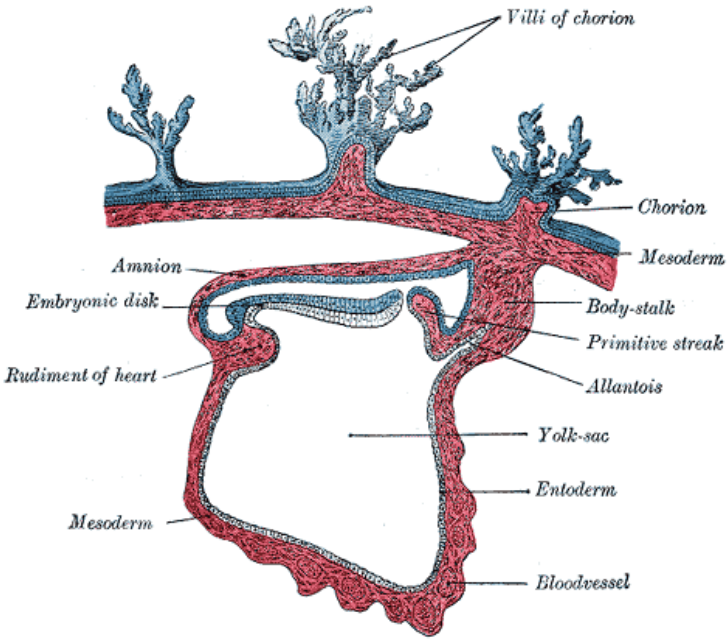
Cognitive Neuroscience

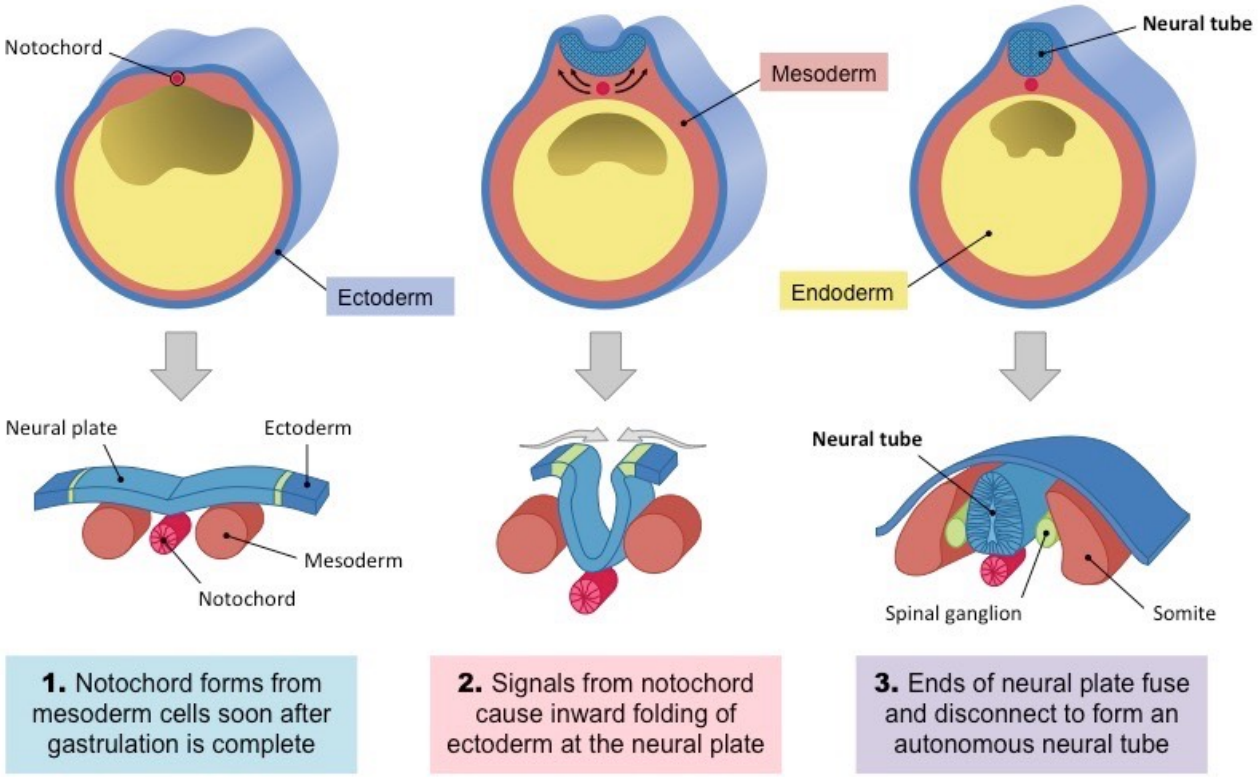
// Early brain development

- ovulation happens on the 14th day of the menstrual cycle
  - fertilised egg travels for a week before implanting into the uterus
    - during the process, a lot of cell division happens
      - **morula**: 16-32 cells
      - liquid accumulates inside, forming the **blastocyst**

- the blastocyst implants itself into the uterine wall
  - before implantation, the inner cell mass begins to transform into two distinct epithelial layers
    - they form the **bilaminar embryonic disc**
      - the embryo forms from the **epiblast** (dorsal layer)
      - extra-embryonic structures form from the **hypoblast** (ventral layer)
      - the embryonic disc is sandwiched between two balloons: the primitive yolk sac and the amniotic cavity



- **gastrulation**: cell movements that reorganise the single-layered blastula into a the gastrula: a trilaminar structure (endoderm, mesoderm, ectoderm)
  - epiblast cells get internalised to form the germ layers
    - the **ectoderm** forms the skin and nervous system
    - the **mesoderm** forms muscle, bone and cartilage, the circulatory system, the urogenital system
    - the **endoderm** forms the respiratory and digestive systems
- **neurulation**: neuroectodermal tissue differentiates from the ectoderm and thickens into the neural plate, leading to the formation of the neural tube (precursor to the CNS)
  - the **notochord** is also derived from mesoderm cells
    - it is a site of muscle attachment, a vertebral precursor, and a midline tissue that provides signals to surrounding tissue during development
  - **somites**: surrounding structures from the mesoderm that will form the vertebrae and skeletal muscle
- **sonic hedgehog (SHH)**: a protein originating from the notochord that helps pattern the dorsal-ventral axis of the neural tube
  - it is a **morphogen**: a substance whose non-uniform distribution governs tissue patterning
    - has different effects on the cells of the developing embryo depending on its concentration
  - **bone morphogenetic protein (BMP-4)**: similar to Shh, forming a gradient from the dorsal part (roof plate) rather than ventral part (floor plate) of the neural tube
    - during early development, inhibition of BMP signalling differentiates neuroectoderm from ectoderm



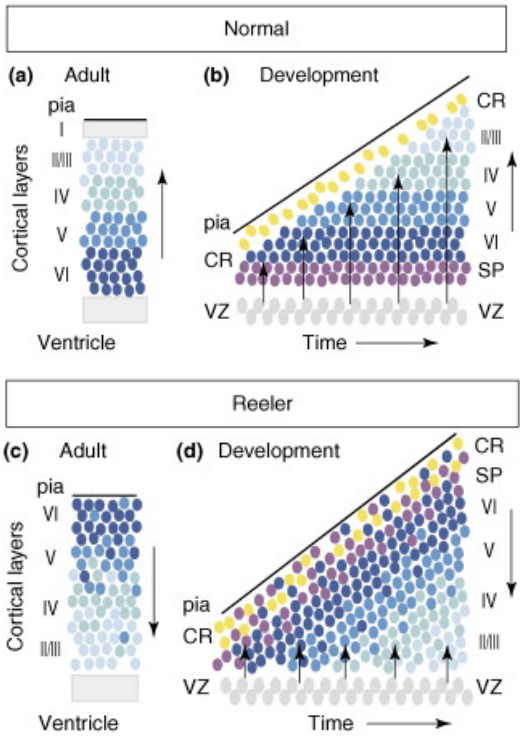
- most highly concentrated BMP areas become the **alar plate** of the spinal cord (sensory neurons)
  - concentrated SHH areas become the **basal plate** (motor neurons)

- as the neural tube continues developing at the most anterior part, there's an early stage of three vesicles
  - **prosencephalon** (forebrain), **mesencephalon** (midbrain), **rhombencephalon** (hindbrain)
  - later development:
    - **forebrain**: telencephalon (cerebrum, olfactory lobes, hippocampus), diencephalon (optic vesicle, thalamus, hypothalamus)
      - also in limbic system: amygdala (emotion), hippocampus (memories)
      - basal ganglia: at base of forebrain; one of the nuclei is the striatum
        - the putamen and caudate nucleus form the dorsal striatum
    - **midbrain**: mesencephalon (substantia nigra & Parkinson's, fibre tracts between anterior & posterior brain)
    - **hindbrain**: metencephalon (pons & cerebellum), myelencephalon (medulla)

- **fibroblast growth factor (Fgf)**: morphogen at the most anterior/rostral part of the brain
  - the 3D combination of expression of different molecules (Fgf, Wnt/Bmp, SHH) helps establish the differentiation of neurons (their identity and where they project to)
- generation of neurons tends to happen in the ventricles (most interior part of neural tube)
  - they migrate to different cell layers using **radial glia scaffolding**
    - radial glial cells are bipolar-shaped cells whose fibres extend radially
    - they also serve as primary progenitor cells, generating neurons, astrocytes, and oligodendrocytes
- the neocortex is formed of six layers of neurons
  - it has an **inside-out** development: early neurons are located in deeper layers
    - later neurons migrate across them to reach upper layers
    - the upper layers end up being involved in intra-cortical communication and connections

- species with extended periods of cortical development end up with more neurons on the outside, resulting in gyrification

- cells that migrate via glia scaffolding are:
  - projecting / glutamatergic nuerons
    - glutamate is the brain's most prominent neurotransmitter
  - pyramidal cells
  - excitatory in the neocortex
- there are also neurons that undergo **tangential migration**
  - **interneurons** / inhibitory cells
  - express GABA instead of glutamate
    - GABA is the brain's main inhibitory neurotransmitter
  - usually don't project in a long range
    - form local circuits
    - aren't produced in cortex
    - generated at the bottom of the forebrain, in **ganglionic eminences**
      - migrate tangentially to terminate in the different layers of the cortex
  - cholinergic neurons (producing ACh; found even lower in forebrain) migrate tangentially as well



- **transitory cells**: there is a *transient* population of neurons that helps pattern the cortex
  - disorders in the production of these cells disrupt the proper organisation of the brain
  - e.g., Cajal-Retzius (CR) cells produce **Reelin** in the pial (external) surface, which is important for inside-out development in the cerebral cortex
    - Reelin mutants show an inverted, outside-in development

- **axon guidance**: navigation of the axon as it grows to a very precise location
  - brain circuits are highly specific, and regulated during development
  - there are both negative and positive signals in axon guidance
- **growth cone**: the very tip of the axon
  - a motile structure, constantly moving and sensing the environment
  - has a central and a peripheral domain
    - expression of different proteins helps it navigate
    - microtubules in central domain and actin filaments in the peripheral domain
- movement / steering of the growth cone is the result of **asymmetric** modification of microtubules
  - receptors in the growth cone membrane respond to repulsive or attractive cues
    - receptors transduce the signal, dictating whether proteins should elongate or shorten the microtubules

- there are many different kinds of cues in axon guidance
  - **extracellular matrix adhesion**
    - a group of proteins forms a matrix
    - as the growth cone navigates, it adheres to the matrix to receive a signal

- **cell surface adhesion**
  - a population of cells in surrounding tissue has membranes with signals
  - growth cone attaches to the surface of the cells
- **fasciculation**
  - the growth cone associates with an axon that has already been formed (**pioneer neuron**)
- **chemoattraction & chemorepulsion**
  - molecules secreted from cells guide the growth cone
- **contact inhibition**
  - like cell surface adhesion, but the growth cone is repulsed

- the formation of the corpus callosum exhibits the use of different cues
  - cerebral cortex neurons fasciculate along pioneer axons to cross onto the other cortex
  - glial cells express chemo-repellent and chemo-attractive molecules

- **electrical activity** plays a role in the formation and development of circuits in the brain
  - that is why substances affecting electrical activity (e.g., alcohol, epilepsy medication) affect the development of a fetus when a mother consumes them
- Spitzer (2006): **calcium spikes** affect the **differentiation** of neurons
  - suppressing the production of spontaneous Ca spikes results in the body compensating by increasing the number of neurons expressing excitatory transmitters, and decreasing the number of neurons expressing inhibitory transmitters
  - increasing the frequency of Ca spikes reverses the effect, making neurons inhibitory where they should have been excitatory
- Mire et al. (2012): removed thalamus cells and grew them *in vitro*
  - observed **axonal growth**
  - spontaneously adding potassium chloride increased neuron activity since it helped depolarise the cells
    - this resulted in longer axons
  - the **Kir2.1** gene codes for a potassium channel that works as a silencer
    - its presence makes the axons much shorter
- Yamada et al. (2010): **axonal branching** is also disrupted when spontaneous activity is silenced

- Ming et al. (2001): electrical activity affects **growth-cone response** to guidance cues
  - **Netrin** is known to be a chemorepellent
    - electrical activity can make the growth cone treat it like a chemoattractant
    - therefore, no molecule has the intrinsic quality of being a repellent or attractant
      - everything depends on the situation

// Postnatal brain development

- one of the first things that happens in the brain of a baby is the **proliferation** of neurons
  - neurons then **migrate** and position themselves in their respective layers
  - **synaptogenesis**: neurons extend their axons and establish synaptic contacts
  - there is an initial **exuberance** (overproduction) of synapses
    - the weakest, least-used synapses are **pruned**
      - e.g., babies initially have poor vision and difficulty focusing their eyes
      - during the first few months, they start focusing more and fixating their gaze

        - the result of refinement of connections (pruning) in the visual system
- the **gray/white matter** volume ratio decreases during childhood and adolescence
  - however, gray matter density actually increases
    - there is not a loss of gray matter; the neuron bodies simply become more packed together

- synapse formation and plasticity involve **structural remodelling** of both axonal boutons and dendritic spines
  - when synapses are very active, the involved structures will grow and become very established
  - when synapses are not active, the structures will recede and be eliminated
- during the formation of brain circuits, there is initial activity that is not necessarily functional
  - e.g., flexor and extensor muscles have to alternate activation to allow movement
    - we have to learn to coordinate the muscles
    - while the embryo is developing, before you can even see movement, there are signs of muscle activation
      - at first, the muscles are activated at the same time, setting base for muscle development
      - as the motor circuits mature, the muscles start to activate alternatively

- the visual cortex receives thalamic input corresponding to each eye in an alternating pattern
  - the **lateral geniculate nucleus (LGN)** is a relay centre in the **thalamus** for the visual pathway
    - it receives major sensory input from the retina
    - it is the central connection for the optic nerve to the occipital lobe (particularly the primary visual cortex)
- **ocular dominance columns**: stripes of neurons in the visual cortex that respond preferentially to input from one eye over the other
  - the development of these ocular columns depends on early visual experience
    - monocular deprivation causes the columns to degrade
    - the non-deprived eye assumes control of more of the cortical cells
  - after 6 weeks post-birth, however, monocular deprivation does not have any effect since the columns have already been strongly established
- Penn et al. (1998) inhibited electrical activity in developing eyes to understand the mechanism behind the termination of axons in ocular columns
  - found that electrical activity is very relevant for the formation of the circuits
    - since the eyes are competing for reaching the LGN, if one eye is deprived, the second eye will take over the first's regions
    - inhibiting activity in both eyes results in more overlapping

- in the developing eye, there are spontaneous waves of activity moving from one side to the other
  - Xu et al. (2011) introduced a mutation in mice that affected the **coordinated response** of neurons
    - inhibited the propagation of the wave without affecting the firing of individual neurons
    - they found that this inhibition strongly affects the formation of distinct regions in the LGN
      - leads to much more overlapping of axons between one eye and the other

- when **oscillations** exhibit high frequency activity, the number of cycles per second is high
  - e.g., 10 cycles per second = 10Hz
  - the **gamma** range of frequencies is roughly between 30-50Hz

    - related to perception
        - if a participant is exposed to an ambiguous image (a blurry shadow), then has a percept (sees the face of a lady), there is an increase in gamma activity
- during the first week of postnatal development, there is a lot of gamma activity in the brain
    - this activity of fast gamma oscillations is important for establishing circuits in the cortex

- Suarez et al. (2014): the importance of **balanced cortical activity** for the correct targeting of the **corpus callosum**
    - removing whiskers from one side of a mouse's face leads to axon projections not forming
    - when removing whiskers from both sides, the projections were formed again
        - it's not necessarily the amount of activity that is important, but the fact that both sides are receiving similar amounts of activity
        - as long as the two hemispheres receive the same treatment, connections will form
- follow-up experiment removed whiskers in either a symmetrical or asymmetrical manner
    - e.g. only upper rows of whiskers in both sides, or upper row in one side and lower in the other
        - asymmetrical cauterisation lead to projections not forming
        - symmetrical cauterisation allowed for projection
        - means that activity between hemispheres is being compared somehow
            - when both are similar, circuits are formed normally

- **Hebbian plasticity**: cells that fire together wire together
    - strength of synaptic connections depends on the synchrony of two neurons' action potentials

- in the cortex, there is an organisation of the sensory fields that corresponds to the **spatial organisation** of the fingers
    - that representation is plastic
        - overstimulation of fingers 2&3 (below) leads to a larger part of the cortex being dedicated to receiving input from those fingers
        - under-stimulation leads to a loss of representation
- interesting: for blind people who learn to read with their fingers, you find a large part of the touch system represented in the visual cortex
    - demonstration of rearrangement of the wiring of the brain based on the input that it receives