

# The BRAIN

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*Issue Six*

## THE DEVELOPING BRAIN

Back-up systems  
of the brain

When is a brain  
conscious?



CRITICAL  
MILESTONES  
of development

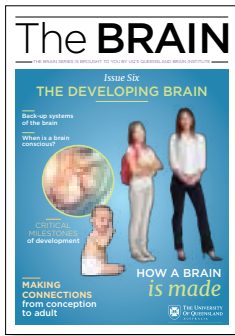


MAKING  
CONNECTIONS  
from conception  
to adult

HOW A BRAIN  
*is made*



THE UNIVERSITY  
OF QUEENSLAND  
AUSTRALIA



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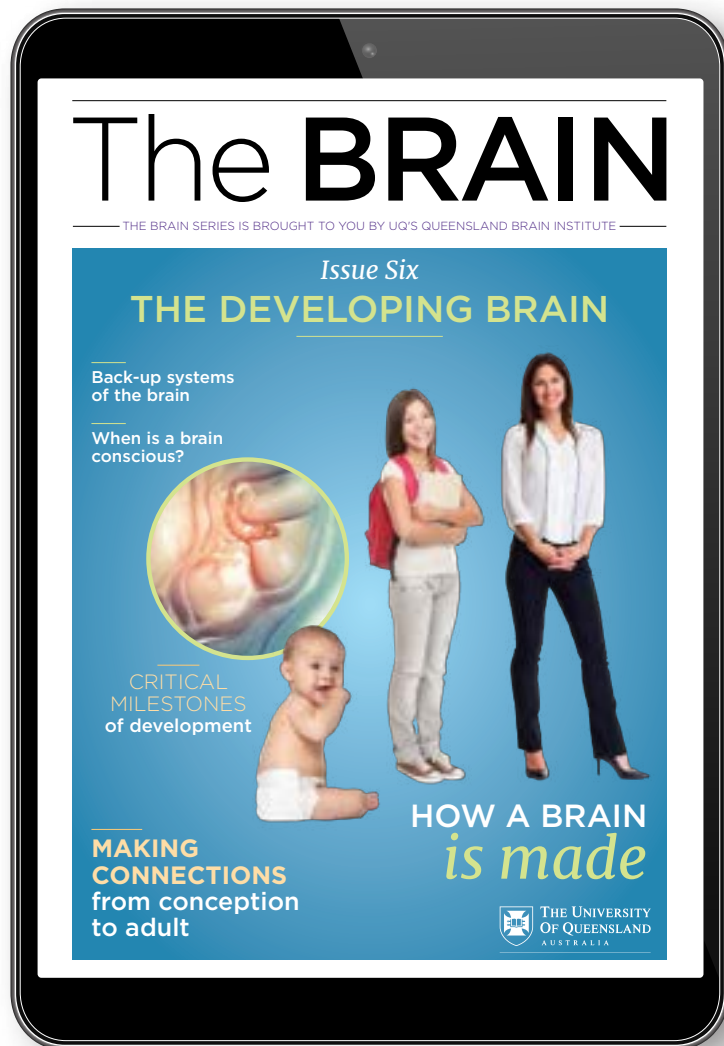


CREATE CHANGE

# SPECIAL REPORT: THE DEVELOPING BRAIN

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## A MESSAGE FROM

# PROFESSOR PANKAJ SAH

DIRECTOR, QUEENSLAND BRAIN INSTITUTE

**Y**our brain is a marvel of complexity, but it starts as a mere sheet of cells in the embryo. How does this transformation happen? This is the core question developmental neuroscientists try to answer. In this magazine—the 6th edition of our BRAIN magazine—we take you on a journey to understand how the human brain is built.

As explained in Chapter 1, scientists use various tools and technologies to understand the developing brain. In the process, we learn more about developmental brain disorders like autism and schizophrenia.

We now know that brain development relies on highly choreographed interactions between the genes that we inherit and the environment (Chapter 2). A symphony of molecular coordination and chemical signalling plays from the moment sperm meets egg until a newborn emerges from the womb.

Even after birth, the brain has more development to do. Exposed to a brave new world, a baby gradually learns to fend for itself (with help from its parents). Chapter 3 covers how the brain matures from birth through adolescence, creating and refining connections between brain cells in a lifelong process of learning that progressively brings skills like movement and language online.

In Chapter 4, we discuss some of the hardships faced by brains as they grow, including infection, poor nourishment, and stress. The brain is remarkably resilient, but sometimes our best defences are overwhelmed.

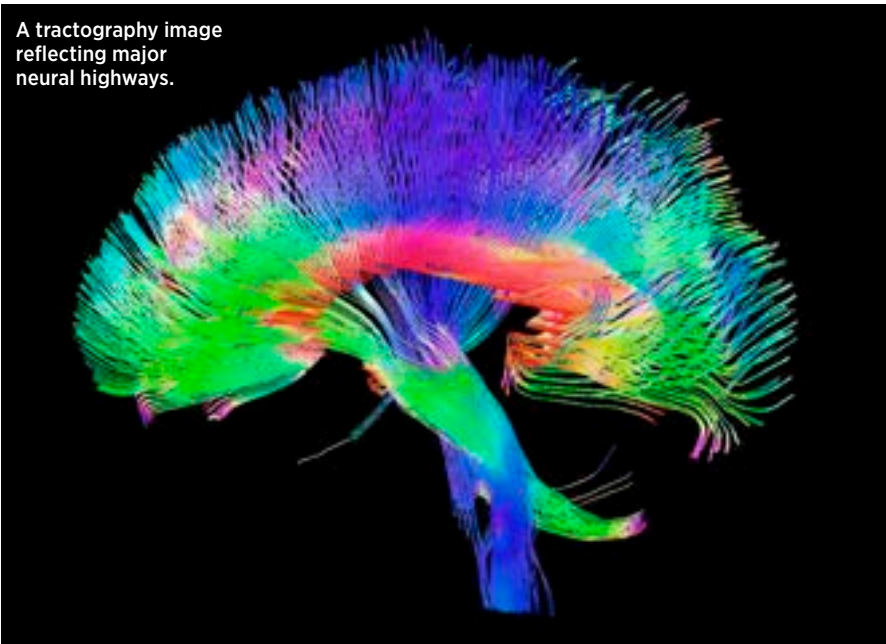


For reasons that we are still trying to understand, this can sometimes trigger psychiatric conditions like depression or schizophrenia.

Finally, in Chapter 5, we touch on some of the outstanding questions in the world of brain development. How do all the right molecules interact to coordinate the brain's development, and how is this shaped by our genetic makeup and individual experiences? How is someone's risk for schizophrenia influenced by the brain's early development? And how do brain cells go from isolated, individual units to densely linked and finely tuned networks? Read on to explore the developing brain. I hope you enjoy our latest issue of The BRAIN magazine.

# THE DEVELOPING BRAIN

A tractography image reflecting major neural highways.



## Why study the developing brain?

Your brain is responsible for nearly everything you do. Because of your brain, you can read, understand and remember this text. You can feel happy, sad, anxious and excited. You can plan your day, move around, eat, sleep, and learn from everything you experience.

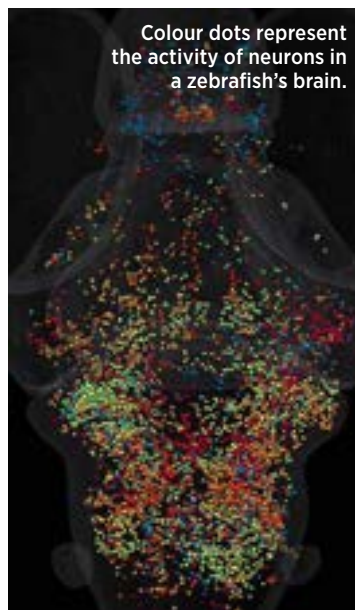
Incredibly, this complex biological machine starts as just a thin sheet of cells in the embryo. By adulthood, it is a 1.4 kg organ composed of about 100 billion cells called neurons, a similar number of supporting glial cells, and around 100 trillion connections called synapses.

Amongst this mass of cells and complexity lies incredible order: for example, distinct brain areas cater for defined functions like movement, sight and language. Different neuron types give rise to many functions, such as movement, memory and sensing external stimuli, and usually, more than one brain region is involved in each. Building a brain is a highly choreographed process.

How does a thin sheet of cells transform into a fully functioning brain? Developmental neurobiologists are trying to understand this.

Answering this question is crucial to understanding developmental brain disorders like autism, attention deficit hyperactivity disorder (ADHD), and intellectual disabilities. In addition, errors or failures in the wiring up of the developing brain can have delayed effects, for example, increasing the risk of developing schizophrenia or bipolar disorder in adulthood. Understanding what goes wrong in the brain during development and the interaction between genes and the environment

Colour dots represent the activity of neurons in a zebrafish's brain.



is vital for preventing or treating such disorders. From a single cell to embryo, infant, teenager and adult, we will guide you through the incredible processes that create your brain.

## How do researchers study the developing brain?

To understand human brain development, neuroscientists use technologies such as brain scans. A challenge in studying human brain development is the length of time that a baby develops—an average of 40 weeks for human pregnancy and then up to 14 years until the brain reaches its full size. Basic molecular and cellular processes governing the development of individual brain regions cannot be studied directly in a human brain because of ethical reasons in accessing the brain of a living person. So, researchers use animals as models. For example, the transparency of the zebrafish embryo allows researchers to study how neuron activity (tracked with fluorescent markers) relates to behaviour. Animals like the fruit fly provide insights into the genes responsible for development, and the use of rodents allows researchers to study similar brain anatomy and circuits to those found in humans.

Model systems include transparent animals like zebrafish.

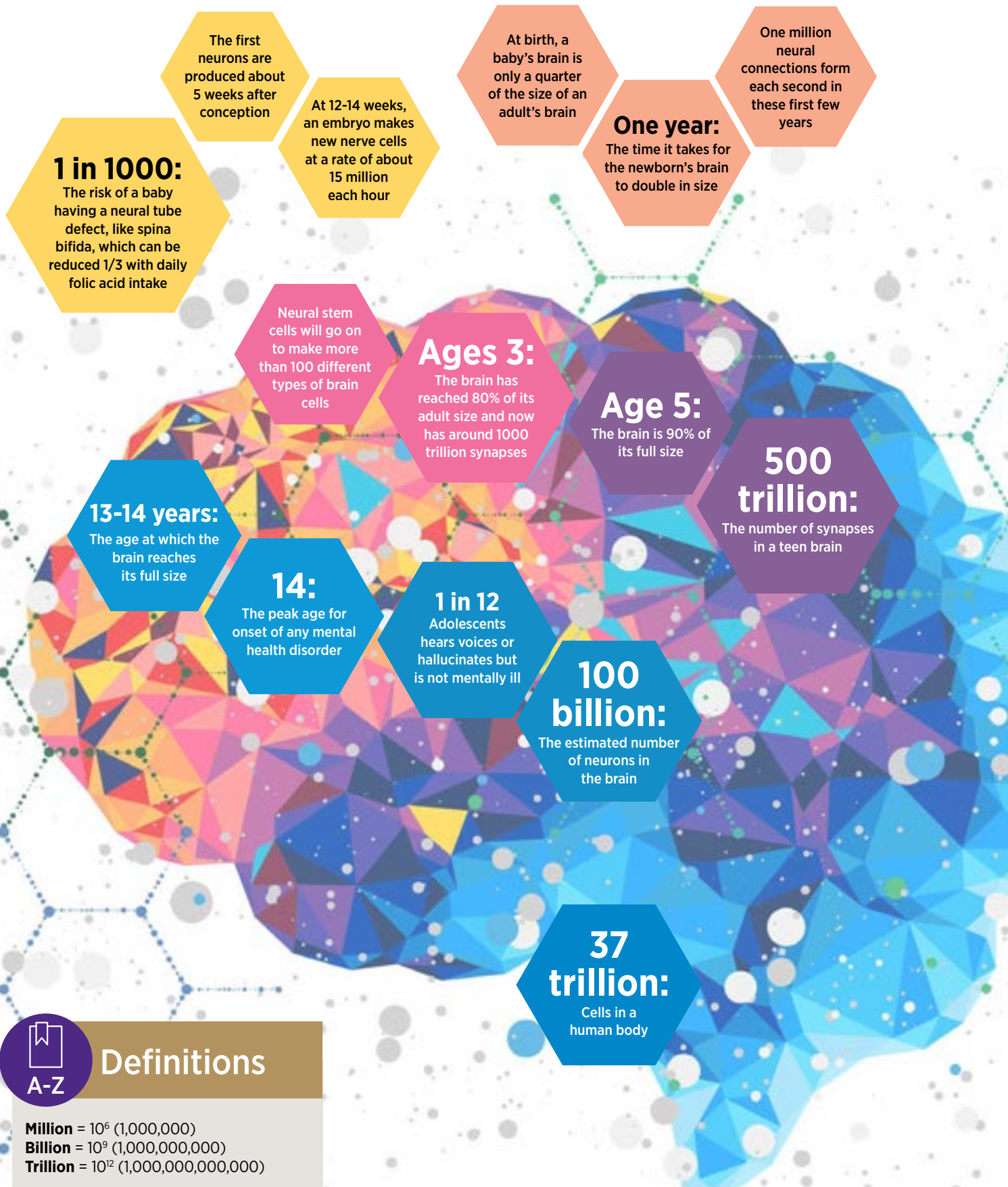


## Definitions

### Developing brain

The developing brain describes the stage from when the brain has its first neurons a few weeks after conception to when it reaches its full size at about 14 years of age.

# Brain development by numbers



## Definitions

**Million** =  $10^6$  (1,000,000)

**Billion** =  $10^9$  (1,000,000,000)

**Trillion** =  $10^{12}$  (1,000,000,000,000)

# Timeline of brain development

**T**he process of building a brain is orderly and complex, and set in motion by genes which orchestrate a cascade of biological processes.

The first sign of anything resembling a brain and spinal cord is seen within the first month of gestation, when a human foetus is barely 6-7 mm long.

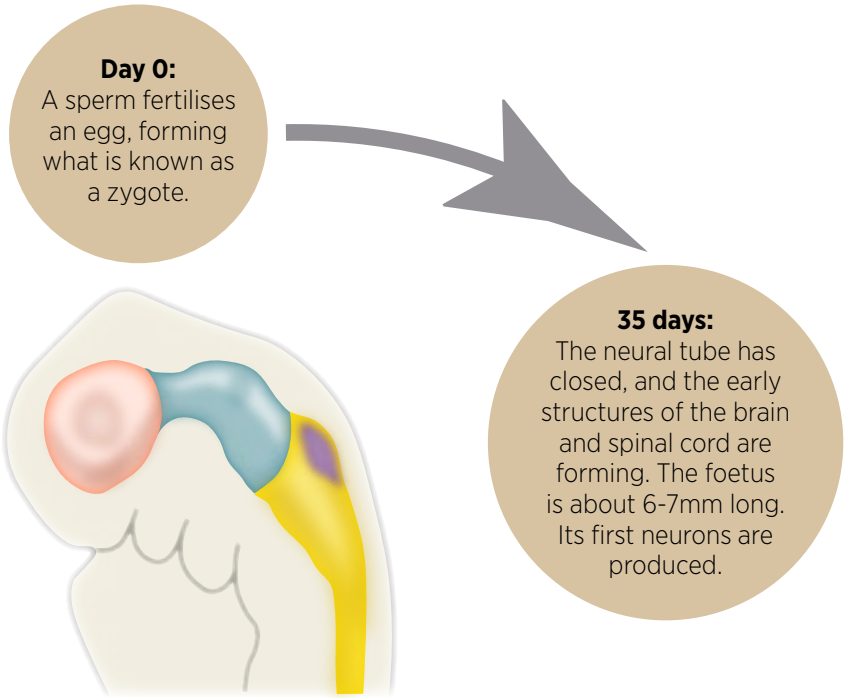
Growth-promoting molecules then initiate the development of specialised areas and the emergence of two symmetrical halves of the early brain, including the two cortical hemispheres.

Once the basic brain structures are established, they are populated with cells. This process is called neurogenesis, which means the birth of neurons. These new neurons are born in specialised regions deep in the brain. Then, guided by molecular cues, they migrate to their final positions in the mature brain.

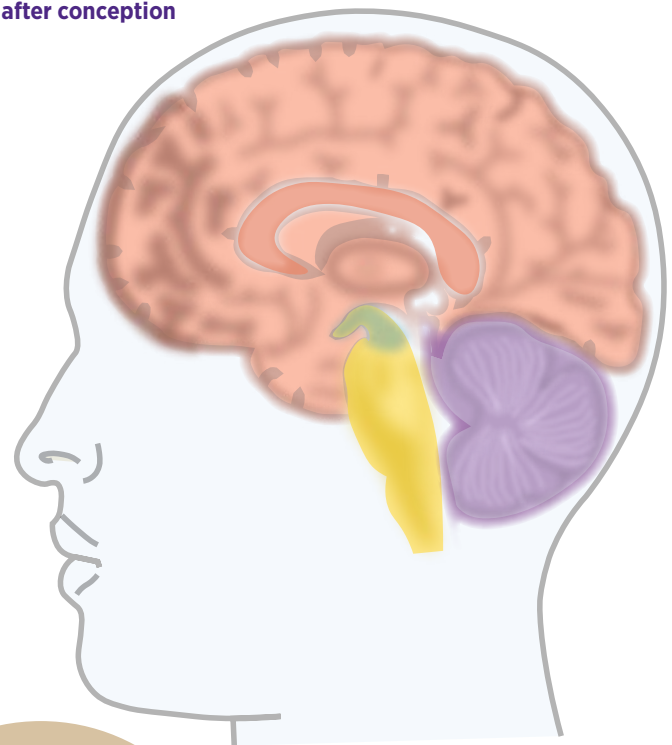
At birth, most neurons have been born, but the brain is only around 25% of its adult weight. This is because the brain's support cells (glia) are only just emerging. Glial cells—which outnumber neurons—perform various activities critical for proper brain function and health, such as maintaining homeostasis and supporting neuronal communication.

By two years, the human brain has grown to 80% of its original size. From this time, neurons and glia work together to refine the newly created synapses and circuits, a process that continues through adolescence.

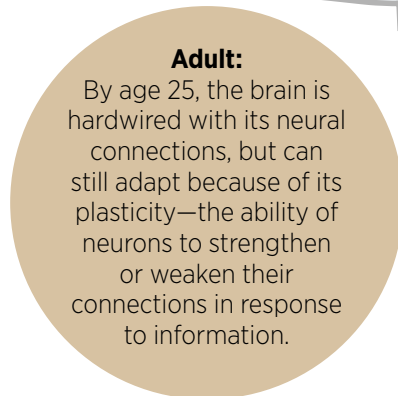
The brain is considered full size around age 14, but circuitry continues to rewire until early adulthood.



**35 days**  
after conception



**Adult**



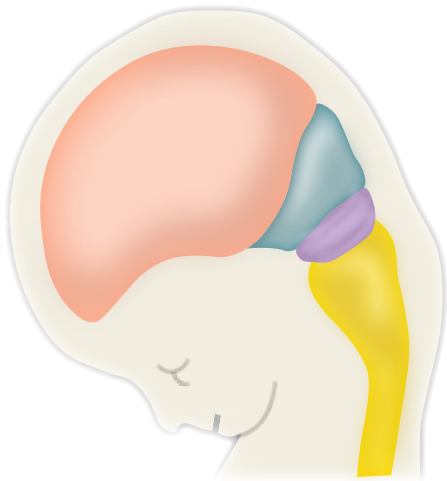
**Definitions**  
A-Z

**Gestation**  
The period from conception until the birth of a baby.

**In utero**  
Latin for inside a woman's uterus (womb).

**Postnatal**  
The period from the birth of a baby to ~6 weeks of age.

DR BELAL SHOHAYEB (GBI), WITH PERMISSION FROM SEMINARS IN CELL AND DEVELOPMENTAL BIOLOGY.

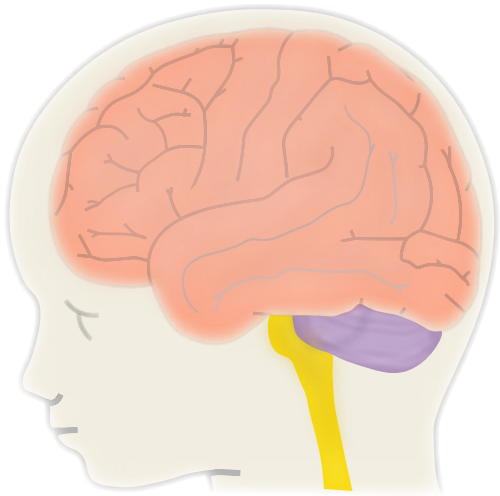


**100 days**  
after conception

**By 100 days:**  
Neurons are born deep in the brain at a rate of about 15 million/hour and then migrate to their final positions, guided by molecular signals. From there, neurons connect with each other, forming networks.

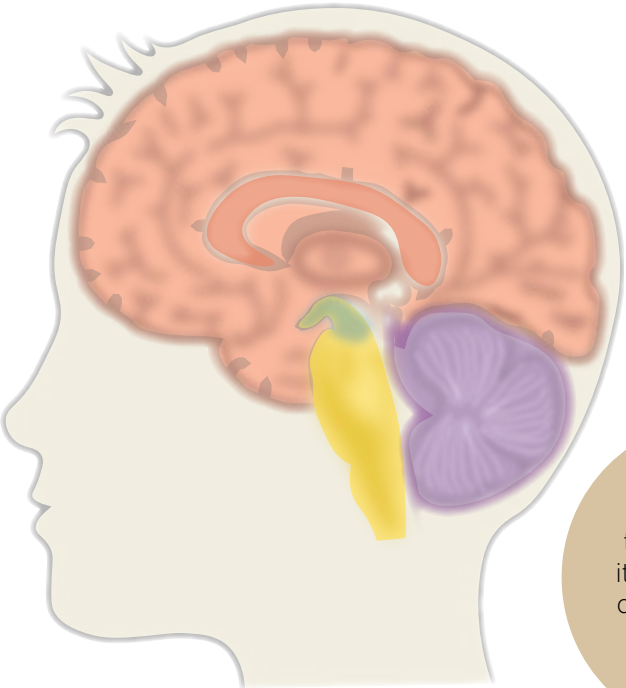
**9 months after conception:**  
At birth, the brain is about ¼ of the size of an adult brain. Now begins a period of huge brain growth. By age 2, the brain is about 80% of its adult size, as neuron circuitry matures and protective glial cells are born.

**Birth**



**9 months**  
after conception

**Adolescent**



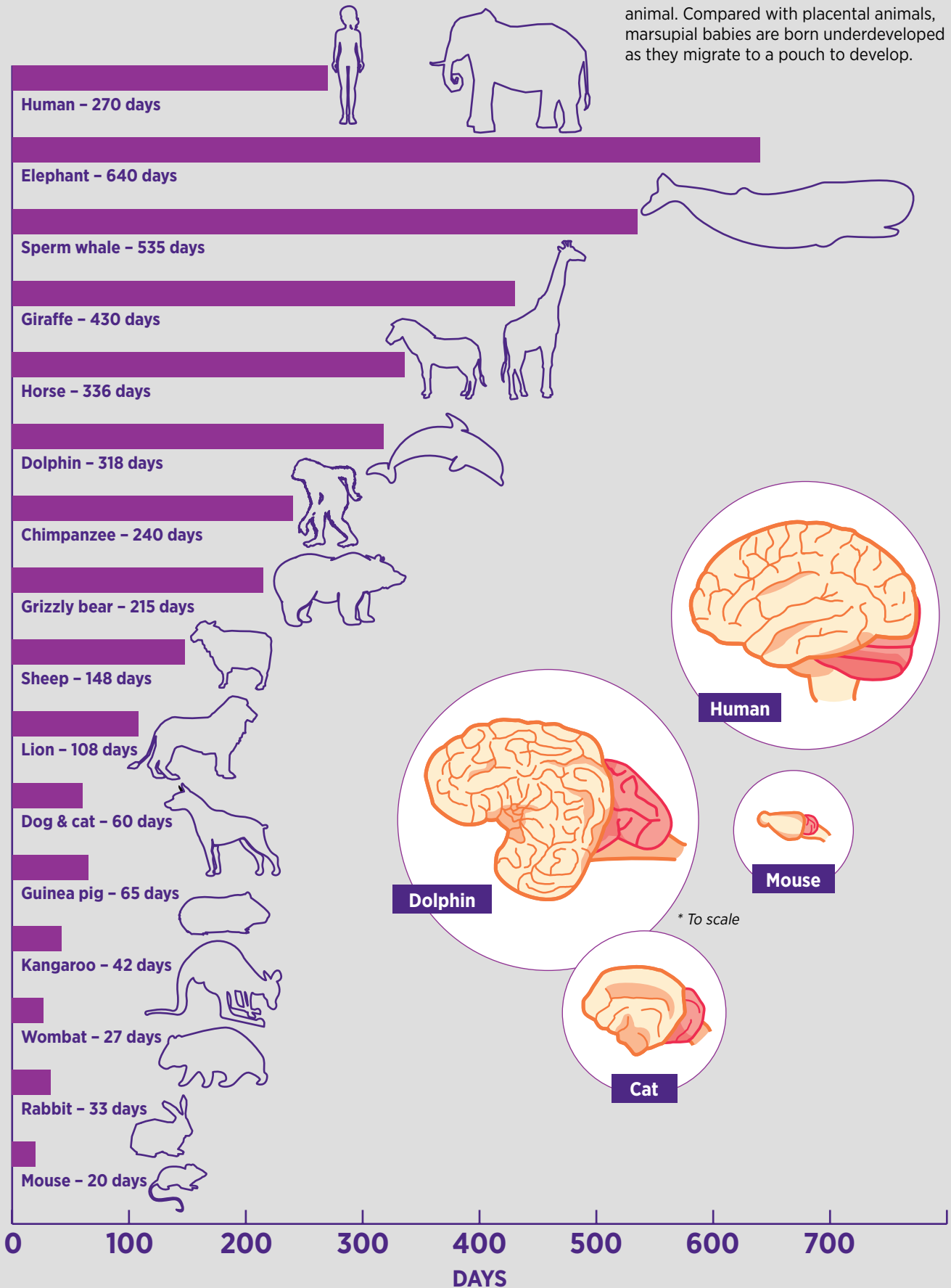
**Adolescent:**  
At age 14, the brain reaches its full size, but the circuitry continues to rewire until early adulthood.

**Legend**

- Forebrain / cortex
- Midbrain
- Hindbrain / cerebellum
- Brainstem and spinal cord

# Gestational times for different animals

The average time it takes for a placental or marsupial baby to develop in the mother's uterus is linked to the size of the animal. Compared with placental animals, marsupial babies are born underdeveloped as they migrate to a pouch to develop.





## CHAPTER 2

# HOW A BRAIN IS FORMED



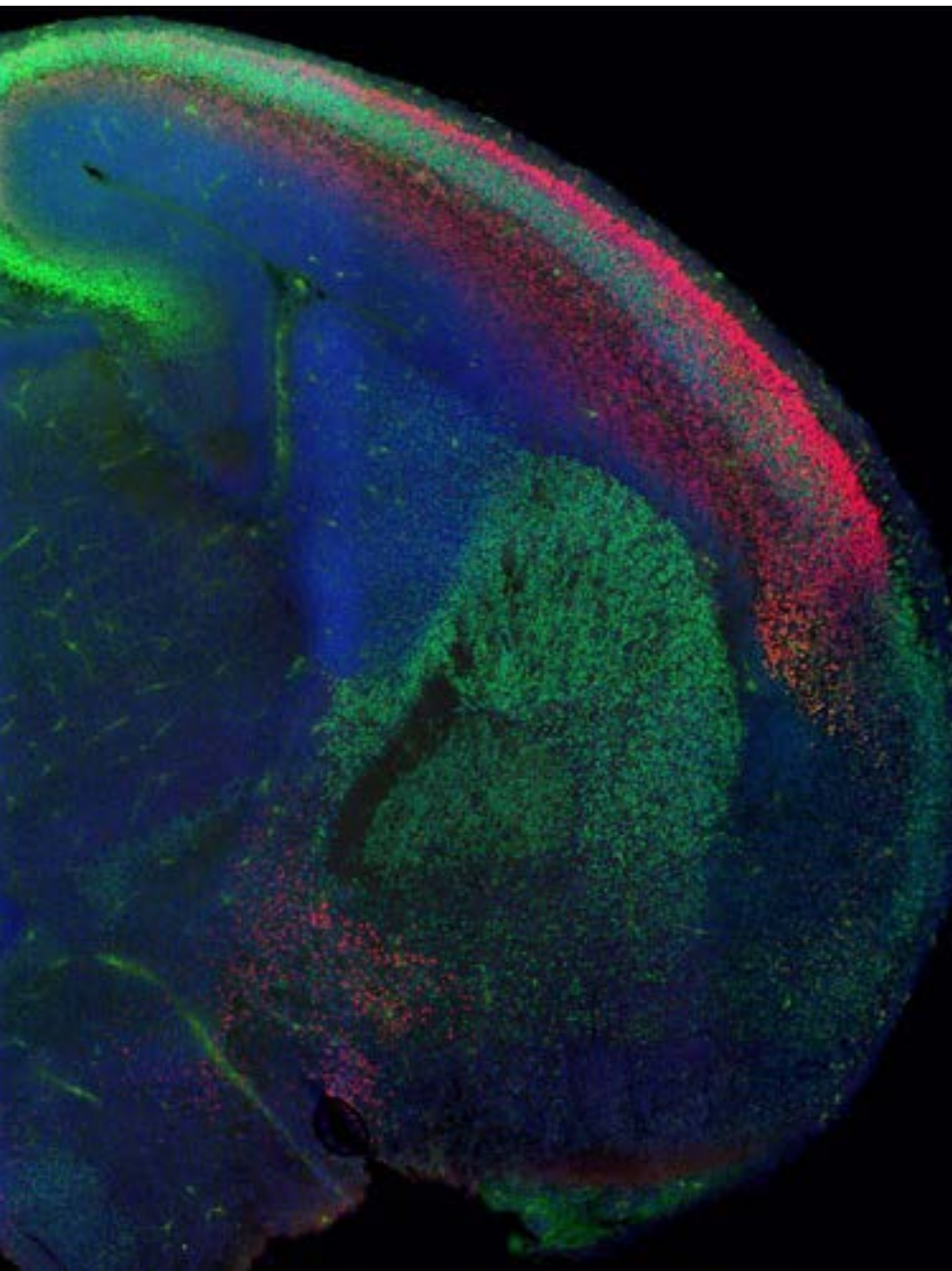
**T**he development of the brain is a complex process that has evolved over millions of years. Our bodies follow basic instructions, first creating the beginnings of the neural tube, then initiating and nurturing the production of neurons and other brain cells, and then connecting the cells.

This process is not straightforward. The precise interplay between genes and the surrounding environment is

crucial in ensuring the proper development of the brain.

If a key gene is mutated or nutrition is lacking, the result can be a developmental brain disorder like spina bifida.

Brain development doesn't proceed according to a simple formula. What makes the brain special—and what makes each of us unique—is the role experience and genetics plays in sculpting our brains. This is especially important once we emerge from the womb.



Specialised neural stem cells (blue) in the developing brain divide to reproduce themselves and/or make new neurons, which then produce the 100 billion neurons in the adult brain. Red and green represent different types of neurons.

## Stem cells: from one cell to billions

**Y**our brain is a collection of billions of cells working together to allow you to breathe, feel and read the words on this page. It all begins with just a single cell.

When a sperm fertilises an egg, forming a zygote, the race is on to create a fully functioning human being. This first cell begins dividing and replicating, over and over. Like blank slates, stem cells become all cell types

in the body, like blood cells, muscle cells and nerve cells called neurons.

With recent technological advances, scientists can now see the brain in its earliest stages of development. We know that a little over two weeks after conception, early brain cells have formed into the neural tube, which then expands into three distinct structures of the early brain. This structure becomes increasingly

complex until, by birth, an infant's brain has most, but not all, of the features found in the adult.

"The neural tube contains the stem cells that produce all the cells of the brain," says Dr Dhanisha Jhaveri at UQ's Queensland Brain Institute.

The variety of neurons produced follows a carefully orchestrated and coordinated plan. This process relies on genetic instructions and is guided by where the cells are in relation to each other and the growth cues produced by the genes or influenced by the environment within the womb. This is why pregnant mums need adequate nutrition (see opposite).

Neural stem cells make more than 100 different types of neuron, eventually allowing us to think and plan movements by sending electrical and chemical signals to each other. Those neural stem cells also create the neurons' support network, made up of billions of glial cells.

By adulthood, neurons have established their final connections. However, a small population of stem cells remain and can be brought to life with exercise to create new brain cells. Researchers like Emeritus Professor Perry Bartlett are trying to establish how we can harness their power to treat a range of neurocognitive disorders with exercise.



A-Z

### Definitions

#### Stem cell

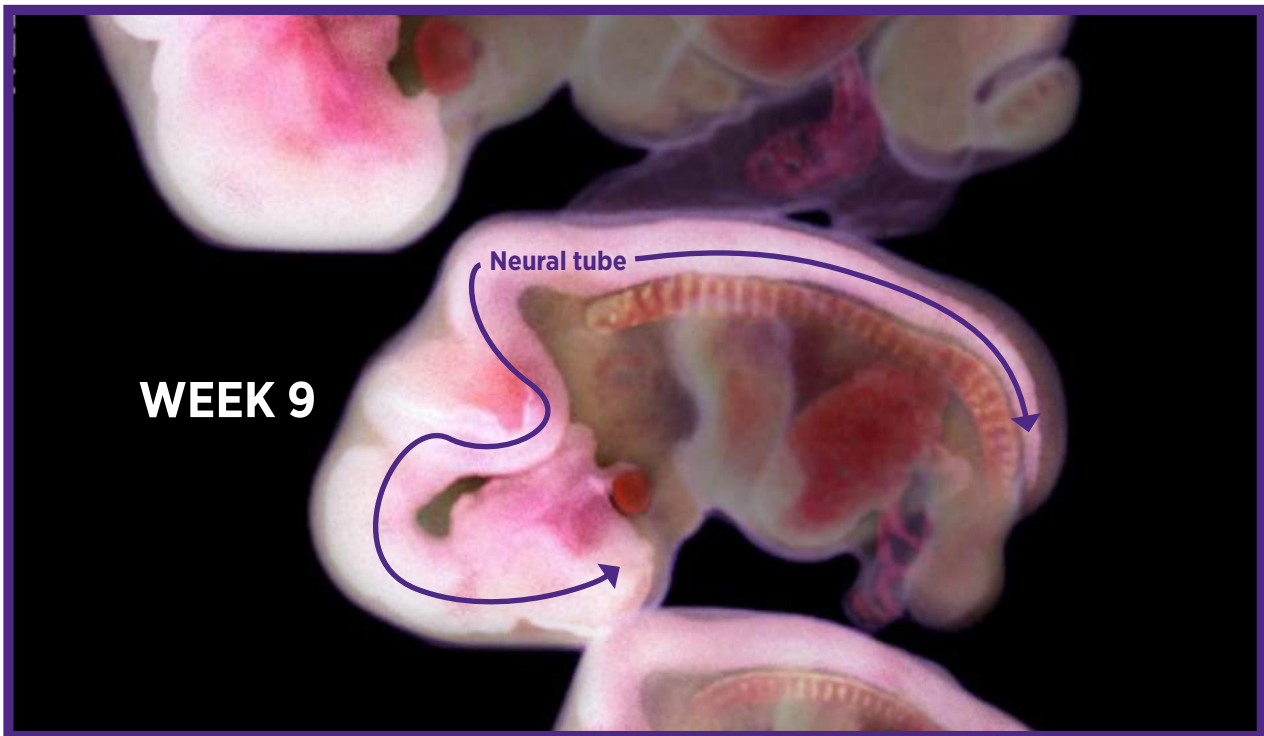
A blank cell that can develop into any kind of cell in the body. A neural stem cell is programmed to produce neurons and can divide to reproduce itself or differentiate into the many neuronal subtypes found in the nervous system.

#### Neurogenesis

Neurogenesis is the process by which new neurons form in the brain. Neurogenesis is crucial when an embryo is developing but also continues in certain brain regions after birth and throughout our lifespan.

#### Differentiation

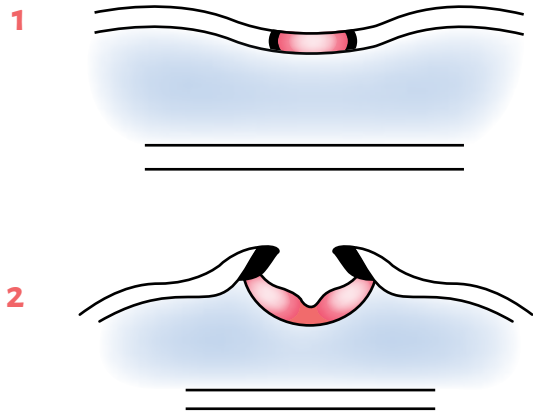
The process whereby a stem cell develops into a specific cell type.



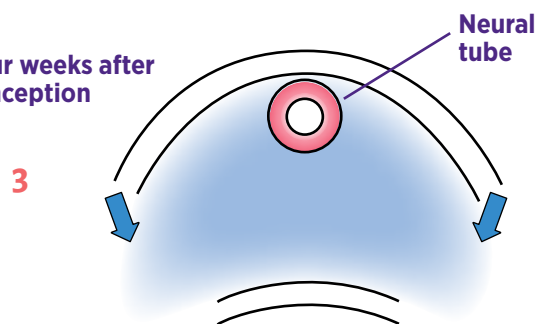
## Neural tube and folate

The human central nervous system (the brain and spinal cord) contains around 100 billion neurons distributed between four main areas: the forebrain, midbrain, hindbrain and spinal cord. A fascinating question immediately arises: what are the embryonic origins of such a complex organ? We now know that the central nervous system begins as a simple sheet of cells, called the neural plate, on the dorsal surface (think the dorsal fin of a shark) of the very young embryo three weeks after conception. Between four and six weeks, the neural plate lengthens along the entire head-to-tail axis of the growing embryo. The plate's edges curl upwards and fuse to form the neural tube, a cylinder comprising stem cells that eventually produce all cells in the central nervous system. Failure of the neural tube to fuse lengthways can result in devastating conditions, such as anencephaly, where the neural tissue bulges from the brain, or spina bifida, where the end of the spinal cord remains open. Neural tube defects occur frequently in the population (~1/1000 pregnancies). The introduction of B vitamin folate, an important ingredient in the production of key metabolic molecules, into the diet of pregnant mothers and women of childbearing age greatly reduces the risk.

### Three weeks after conception



### Four weeks after conception



Between four and six weeks after conception, the neural plate lengthens along the entire head-to-tail axis of the growing embryo (1). Then, the neural plate begins to fold and fuse at the tips (2) to form the neural tube (3). The neural tube contains the neural stem cells that produce all cells in the central nervous system. About 1/1000 pregnancies has a neural tube defect, commonly spina bifida or anencephaly. Taking B vitamin folate reduces the incidence of neural tube defects.

# Early brain structures

The beginnings of the brain and spinal cord, which make up the central nervous system, are seen at various stages of the developing fetus in utero.

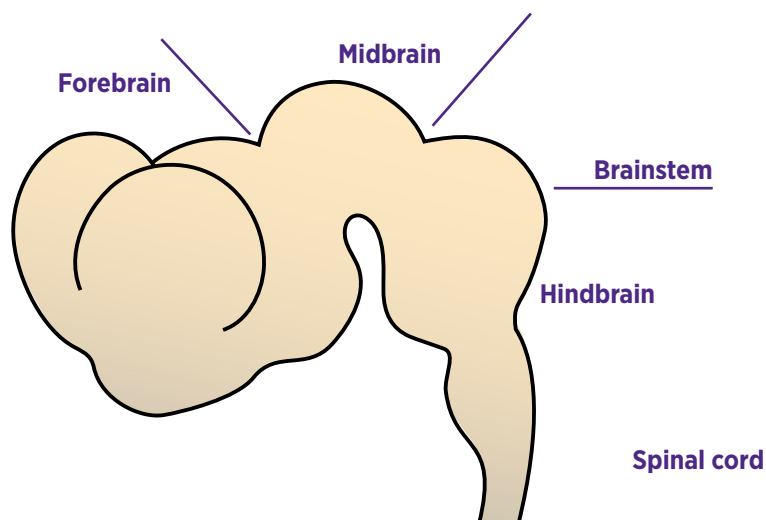


The neural tube (see page 9) is initially straight with little semblance of the functionally distinct areas of the adult human brain. However, even before the neural tube is fully closed, its front part elongates and bends, forming three distinct developmental structures known as primary brain vesicles: the forebrain, the midbrain, and the hindbrain (see illustration). These vesicles then grow and further compartmentalise, giving rise to the functionally distinct areas of the adult brain.

**1)** The forebrain eventually makes up the largest portion of the brain, comprising the cerebral cortex, the basal ganglia, the limbic system (hippocampus, amygdala, hypothalamus), and the thalamus. These areas are responsible for cognitive capacities such as memory, learning, reasoning, and emotions, as well as the processing of sensory information like vision, hearing, touch, smell, and taste.

**2)** The midbrain is the smallest of the three developmental brain regions and is located between the forebrain and the hindbrain. It contains two main areas, the tectum and the tegmentum, which are involved in aspects of visual and

## The primary vesicles of the developing brain



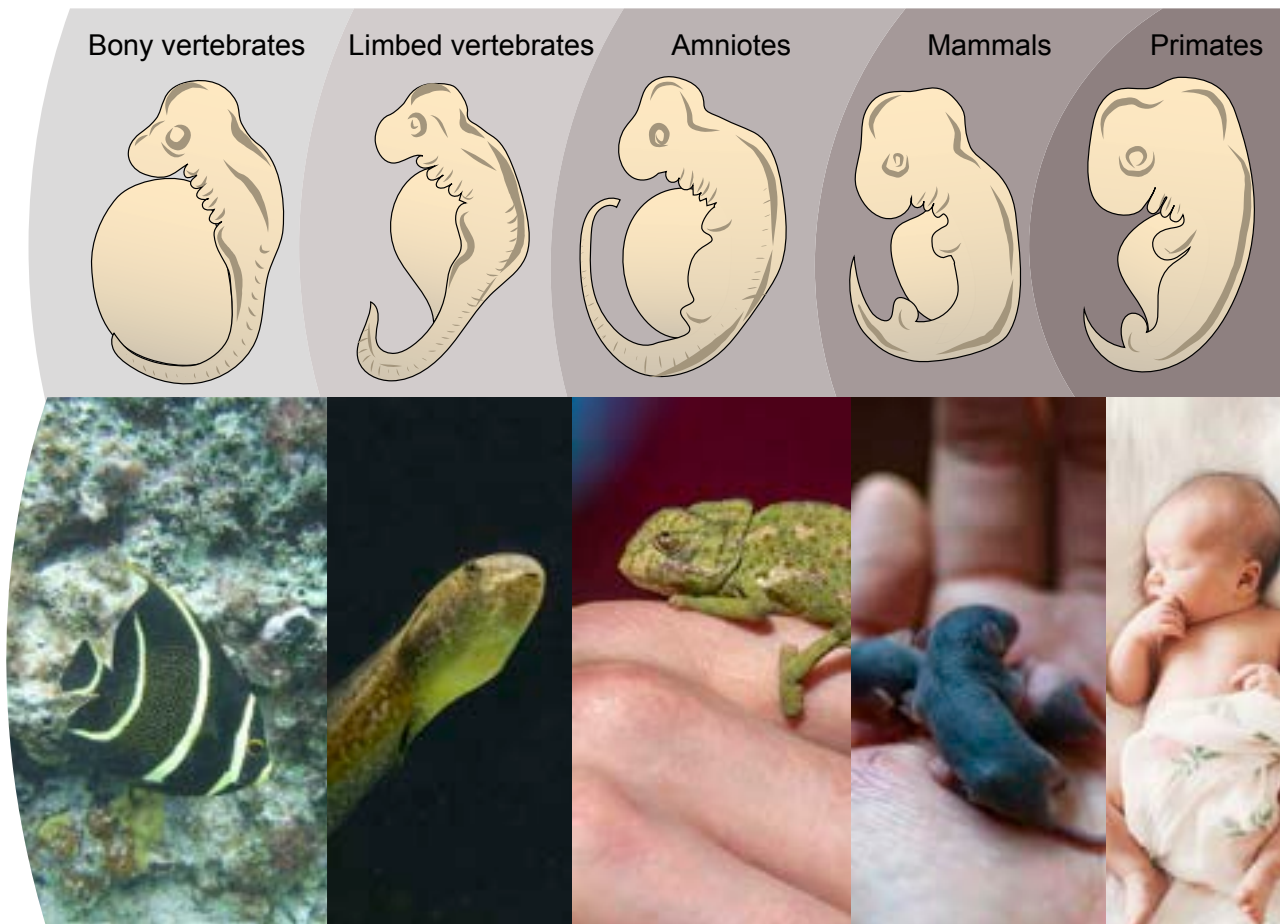
auditory processing (e.g., involuntary eye movements and the pupillary reflex) as well as sleep and attention.

**3)** The hindbrain is located at the lowest part of the brain. When fully developed, the hindbrain consists of the pons, the cerebellum, and the medulla oblongata. Its functions include integrating sensory and motor information to facilitate controlled motor output for balance, posture,

and coordinated movements, as well as vital autonomous bodily functions such as breathing, heart rate, and sleep. The medulla oblongata also acts as the main juncture for nerve signals between the brain and the spinal cord.

Midbrain and hindbrain (not including the cerebellum) are commonly also referred to as the brainstem, i.e., those areas of the brain that govern vital involuntary bodily functions.

# The brain taking shape: an ancient process



**T**he basic developmental stages of the brain and spinal cord – from a simple neural tube (see page 9) to the three main brain regions (forebrain, midbrain, hindbrain) – are common to all vertebrates, from fish to amphibians, to reptiles, birds, and mammals (including humans).

This similarity of the early stages of brain development across species is an example of ‘evolutionary conservation’ – a key theme in evolutionary and developmental biology. Only as development progresses do the specialised structures become more distinct across different vertebrate species.

However, regions derived from similar early brain structures, i.e., fore-, mid-, or hindbrain, still correspond to similar, increasingly complex functions. For example, as in humans, the hindbrain controls basic functions like breathing, reflexes and fine movements. The midbrain plays key roles in sensory perception and attention. The forebrain controls higher-order cognitive functions, like learning, memory, and sensory processing.

There is clear functional importance for different brain regions growing to different sizes and shapes, with larger and more complex areas usually indicating more specialised functions. For example, species in which the

sense of smell (olfaction) is more important, such as pigs, also have relatively larger brain areas dedicated to the processing of olfactory information. On the other hand, species that rely more on visual cues, like humans, have enlarged brain areas dedicated to vision.

Humans also have a uniquely enlarged cerebral cortex (the wrinkly surface covering most of the brain) thought to be the key to our remarkable cognitive abilities.

Thus, refinements in the shaping of a shared basic brain plan across vertebrates underlie the astounding diversity of form and function between brains of different species.

# Wiring up the brain

Higher-order cognitive attributes, such as consciousness, creativity, language, sensory perception and memory, arise from different populations of neurons relaying and processing information via neuronal connections between functionally distinct brain areas in a highly synchronised manner.

Neurons communicate via long wire-like extensions, called axons, and much shorter dendrites, both of which form connections known as synapses (see illustration). Some axons can be up to a metre long, for example, those extend from the adult brain into the spinal cord. In contrast to the axon, the dendrites of a neuron are highly branched, like a tree. The high number of dendrites allows neurons to form networks, the prerequisite for differential neuronal integration from many different sources of information, i.e., the brain areas.

Neural circuits (or networks) are established during embryonic development as newborn neurons acquire mature characteristics and migrate to their final locations during brain development.

One of the earliest steps in the formation of the neurons making up the central nervous system is the extension of a single axon from the cell body of the newborn neuron. As the axon grows, the growth cone at its tip continually reassesses the local environment, determining the correct pathway among the maze of possible routes to find its final target neuron (see opposite page).

How do axons know which path to follow? They follow a predetermined road map defined by chemical cues called axon guidance molecules. Detected by the axon growth cone via specific receptors, these cues act in concert to guide its growth direction. Axon guidance molecules are produced by cells along the pathway in the axon's local environment and form concentration gradients that act as either attractants or repellants, reorienting the direction of the axon's growth.

Remarkably, the types of axon guidance molecules are very similar across many animal groups, from invertebrates like insects and worms to vertebrates like fish and mammals

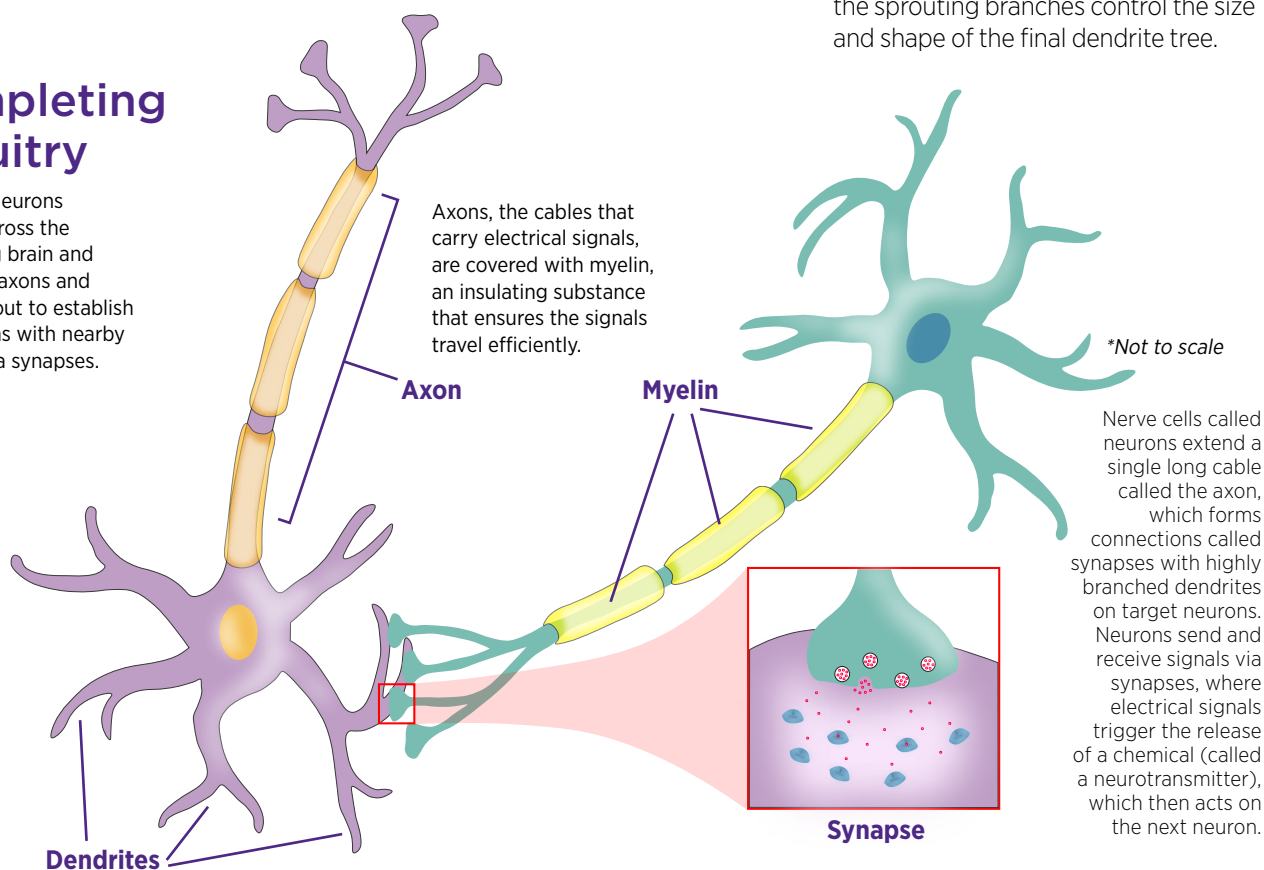
– including humans. This suggests that these mechanisms arose very early in animal evolution, which allows researchers to study these mechanisms in model organisms such as worms and flies.

Dendrite formation occurs by a slightly different process, thought to be driven by genes controlling calcium-regulated transcription factors. Early dendrites appear as thick strands with few spines (small protuberances) extending from the cell body. As dendrites mature, the number and density of spines increase, which in turn increases the chances that a dendrite will contact a neighbouring axon. Connections between dendrites and axons are the basis for synaptic connections between neurons, which, as we will describe below, is essential for brain function.

The architecture of the dendritic tree is unique to each type of neuron, and its geometry is influenced by growth cues which trigger the sprouting of branches at predetermined points along the dendrite. Then, guidance molecules in the local environment of the sprouting branches control the size and shape of the final dendrite tree.

## Completing circuitry

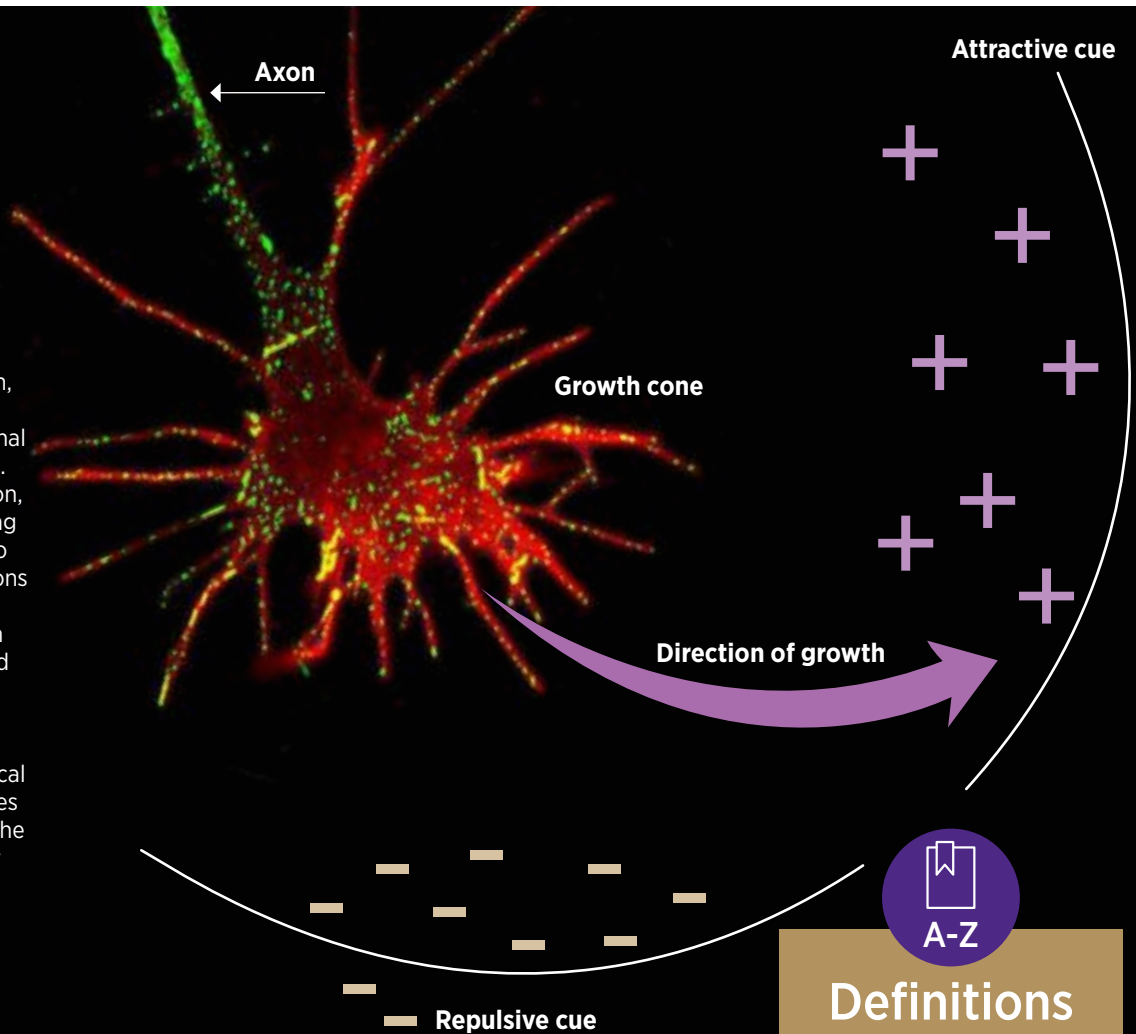
Newborn neurons migrate across the developing brain and send their axons and dendrites out to establish connections with nearby neurons via synapses.



## Growing neurons

In the developing brain, neurons are born and then migrate to their final destination in the brain. Once at their destination, they extend out the long cable called the axon to start forming connections with other neurons.

The direction of axon migration is determined by the response of the growth cone at the tip of the growing axon to chemical cues in the local environment. These cues guide the direction of the growing axon by either attraction or repulsion.



## Definitions

### Differentiation

The process whereby a stem cell develops into a specific cell type.

### Axon

The long, thin, cable-like structure of a neuron. Electrical impulses are sent along the axon to the dendrites of a nearby cell.

### Growth cone

This highly sensitive, dynamic and pathfinding tip is essential for growing neurons and rewiring circuits after nerve cell damage.

### Dendrite

These small branch-like projections of a neuron receive information sent via the axon.

### Synapse

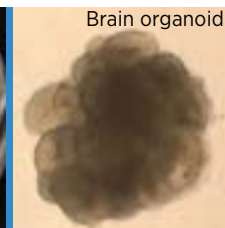
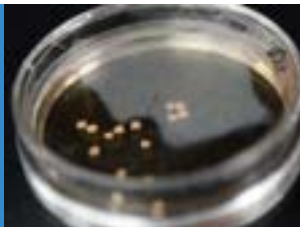
The junction between the axon of one neuron and the dendrite of another, through which the two neurons communicate.



## Brains in a dish

For researchers to understand how the brain works and how it malfunctions in diseases and injuries, they study the brain in a setting as close as possible to its natural environment. To some extent, researchers can do this by taking slices of brain tissue to briefly study the biology of neurons while the cells are alive.

Neurons and glial cells can also be separated and studied individually in a laboratory dish. Recently, researchers like Professor Ernst Wolvetang from UQ's Australian Institute for Bioengineering and Nanotechnology have been creating a more realistic three-dimensional environment using mini-brain-like organs called brain organoids. These are miniature models with similar cellular make-up and architecture as a developing human brain, mimicking many aspects of early development and enabling researchers to discover the multiple cellular mechanisms involved in brain formation.



Organoids are made by taking adult human cells from the skin, hair follicles or blood and culturing them in a special growth medium to create stem cells which, after exposure to the correct growth factor, generate neural stem cells. These cells can then be triggered to produce self-organising structures called organoids, which contain many populations of neurons and exhibit a basic architecture similar to that seen in a developing brain.

Studying organoids will allow researchers to understand the progressive molecular and cellular changes that may occur in several developmental disorders and potentially screen existing, new and emerging medicines for efficacy and possible side effects. Organoids are also now being used to study neurodegenerative diseases such as Alzheimer's disease.

## CHAPTER 3

## THE MATURING BRAIN

**B**rain development is very different to the development of other organs. At birth, the heart, lungs and kidneys are fully developed. The newborn brain, however, is not.

At birth, a baby has only rudimentary sensory, motor and cognitive capacities. Without care, attention and the protection of its caregivers, the baby could not survive. The reason the brain is underdeveloped at birth is precisely the reason it is so incredible: it must learn from and adapt to its experiences of the world.

While still in the womb – cocooned in safety, conveniently fed by its mother, and with only limited scope for sensory input – a human baby is not exposed to the world, and its brain does not have a large role to play in movement, learning, or processing of sensory information.

After birth, we need to make sense of the world, interact with objects and people, plan actions and predict their consequences, learn from our successes and failures, and store experiences away for future reference: this takes time.

To make sense of all this new information, the brain makes new and refines existing synaptic connections between neurons throughout childhood and adolescence, in the process, gradually expanding our cognitive capacities. In this chapter, we explore when and how brain functions ‘come online’. We also look at what makes the teenage brain particularly susceptible to some of the challenges we face during this stage of life.



Babies begin to sense their surrounding world as their five senses develop

## Leaps and bounds of the developing brain

**D**uring the first two years of life, the brain experiences remarkable growth as babies become more independent. Many changes occur in the brain, and a baby hits many new developmental milestones. For example, perceiving

something they were not capable of perceiving before or learning to do new things seemingly overnight.

With the first milestones, babies begin to sense their surrounding world as their five senses develop. As vision improves, they can now perceive

their carers’ facial expressions and develop a ‘social smile’ - an intentional gesture of warmth.

At about six months, reflex responses start to make way for a growing awareness of the outside world and increasing control





*The reason the brain is underdeveloped at birth is precisely the reason it is so incredible: it must learn from and adapt to its experiences of the world.*

over their own bodies. They can now crawl, sit upright, and easily manipulate objects with their hands (and get them to their mouths).

They also begin to respond to their own name and understand short sentences like “it’s time to eat” or “we are going out.” Between six and 12 months, development of those parts of the brain that control social and emotional skills accelerates, making this period an important stage for forming bonds with caregivers. Similarly, elevated activity in regions involved in memory and language allows babies to rapidly learn new words.

Continuously increasing levels of myelination – an insulating layer that covers neurons and axons in the central nervous system and speeds up nerve signal transmission – allows increasingly well-coordinated movements so that by 12-18 months, most babies take their first steps.

Unfortunately, tantrums and frustrations also commonly happen at this age, as the developing pre-toddler brain still lacks control of feelings and emotions that also cannot be well-communicated because of its still limited language abilities.

## Leaps and bounds of the developing brain

In the first few years of a baby’s life, there are huge changes in the size of the brain and what a baby is capable of. There are recognised leaps or milestones, particularly in the first one to two years, which usually happen around these times.

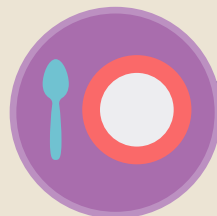
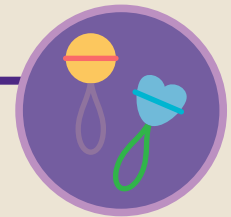


### 1 month

The visual system is developing, and babies can start to focus beyond 20-30 cm. Babies begin to be interested in the world around them and will smile for the first time.

### 2 months

Automatic reflexes like jerking when the head moves back have faded by now. A baby has the motor development to find and clutch their hands. They can recognise familiar faces.



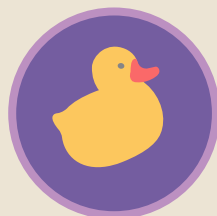
### 4 months

Babbling begins. A baby will mimic facial expressions and communicate hunger or tiredness with crying. They may begin to roll.



### 6 months

Responds to their name. Bring things to their mouth. Begins to sit without support.



### 9 months

Starts pointing. Copies sounds and gestures. Loves peek-a-boo. Can grasp small items with fingers. Pulls up to stand. Begins crawling. Understands object permanence (knows a hidden object is still there).



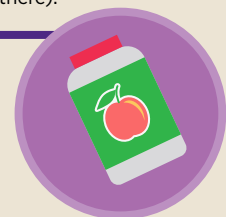
### 12 months

Responds to simple directions. Can use basic body language like shaking head for ‘No.’ Can put things into containers. Can drink from a cup. Starts to walk.



### 18 months

Branches out to explore with a caregiver close by. Can say some basic words. Can start to pretend play. May have tantrums.



### 2 years

Copies other adults and children. Shows defiant behaviour (showing their own mind). Can use basic 2-4-word sentences. Easily find hidden things. Can sort shapes and colours. Can use blocks to build. Names items like ‘cat’ or ‘ball’ in books. Can kick a ball and run.



# What can the developing brain do?

**D**uring childhood and into early adulthood, the brain undergoes more changes than any other body part. These changes happen in stages, each profoundly affecting our abilities and behaviour. Most of these developments happen in the first five years of life.

## In the womb

The brain starts to develop within four weeks of conception. In the first two trimesters of pregnancy, development is about producing neurons, establishing brain architecture and wiring up the circuitry. Toward the end of gestation, the foetus can hear sounds and feel sensations, which begin to shape the brain.

## Birth to age 6

Although all five senses begin to function before birth, the somatosensory cortex, which controls voluntary movements, reasoning and perception, becomes active between two and three months after birth.

Between six months and one year, activity in the frontal lobes triggers the development of emotions, attachments, planning, working memory and attention.

A sense of self develops as the frontal lobe circuits become more integrated at around 18 months. At around age 3-4, important psychological concepts begin to emerge such as the 'theory of mind', in which a child begins to understand that other people have their own minds. At this stage, the brain is about 80% of its adult size.

By age five, the brain is 90% of its adult weight. At this age, children start to apply logic to their thought processes.

A child undergoes more than a decade of rapid growth and development, in which every experience contributes to the person they will become. By the teenage years, the brain is full size but continues to mature its circuitry into early adulthood. Connections continue to be made, pruned, and remade throughout life.



A-Z

## Definition

### Central Nervous System

Refers to all parts of the brain and spinal cord



## When is a brain conscious?

**B**efore we get to the question of when consciousness may begin, first, we must consider what consciousness is.

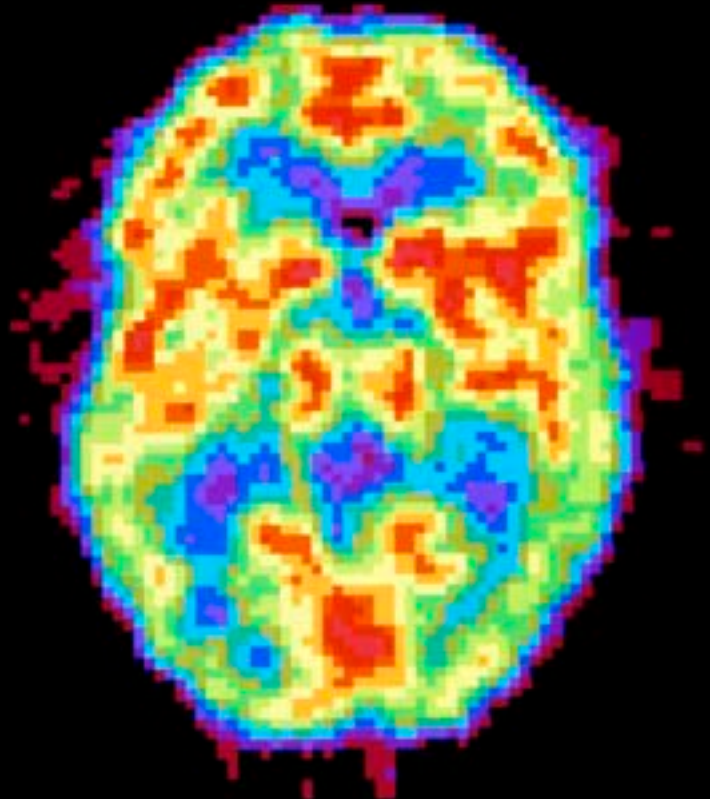
Consciousness appears to develop in sync with rapid eye movement (REM) sleep, during which we have our most vivid dreams, says Professor Bruno van Swinderen. He says this suggests REM sleep is not just about dreaming but is part of becoming conscious: where we consolidate and curate the predictive models we build of the world, like expecting pain from touching a hot stove. These predictive models help us understand how we interact

and fit with the world – they are part of the conscious mind.

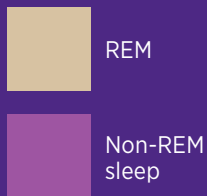
Having discovered that fruit flies might experience something similar to REM sleep, the van Swinderen lab is using this genetic model to better understand the evolution of consciousness in animals with simple brains.

“We know that during development in the womb, babies experience REM sleep,” says Professor van Swinderen. “This may be the origins of the consciousness we experience later in life. Understanding the complex way consciousness evolves may also help us better understand cognitive disorders.”

A coloured Positron Emission Tomography (PET) scan of the human brain during REM sleep. Colour coding depicts active cerebral brain areas (red) through to inactive areas (blue). During the REM sleep phase, the brain is active and dreaming, showing similar activity when awake. In the non-REM phase of sleep, the brain is in a deeper, less active sleep.

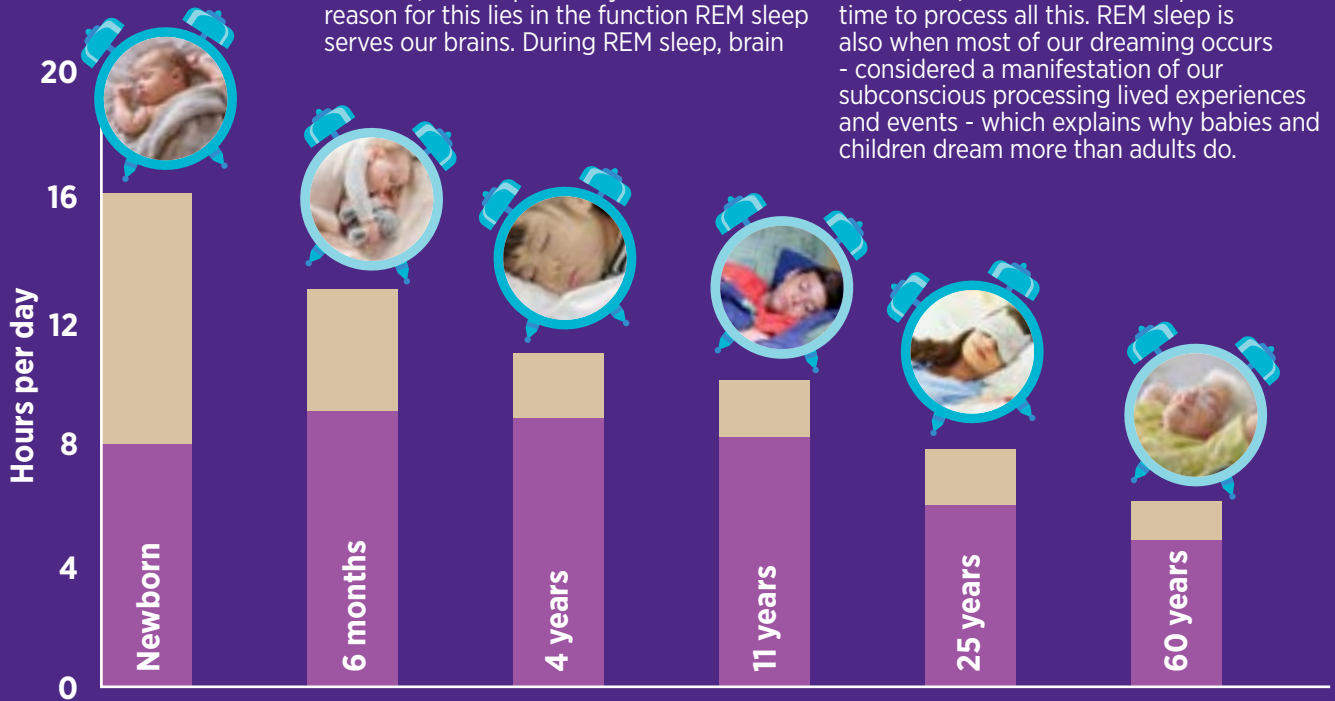


## Sleep through a lifetime



As we age, we sleep less. But that is not all; we also change how we sleep. The largest decrease in sleep duration is due to a reduction of the portion of REM (rapid eye movement) sleep. In newborns, REM sleep accounts for up to 50% of all sleep. In adults, this drops to only about 10%. The reason for this lies in the function REM sleep serves our brains. During REM sleep, brain

activity increases to allow the processing of new information and the reinforcement of memories and learning. The brains of newborns and young children are exposed to relatively more new information through never-before-seen or experienced things and events, and their brains require more time to process all this. REM sleep is also when most of our dreaming occurs - considered a manifestation of our subconscious processing lived experiences and events - which explains why babies and children dream more than adults do.



## The appearance of mental illnesses

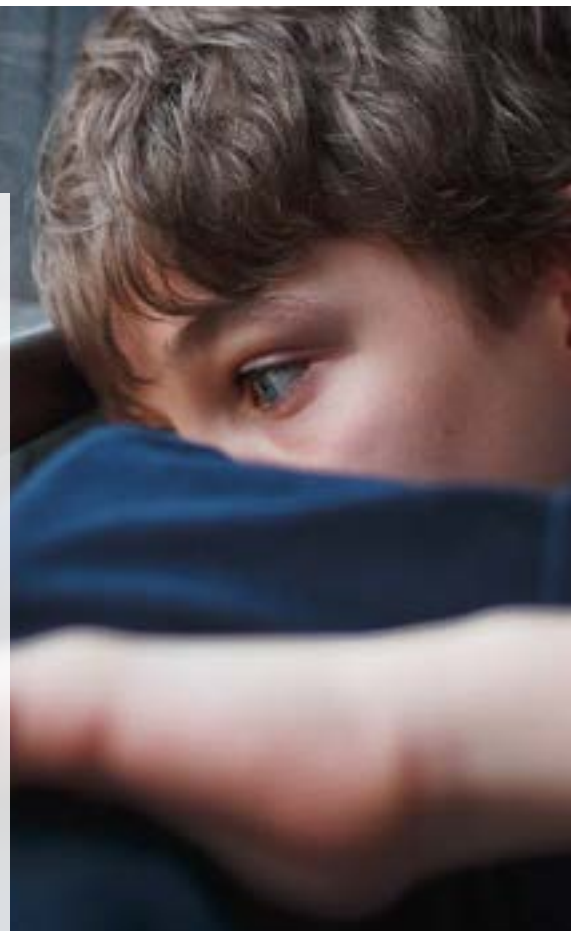
According to a National Comorbidity Survey in the United States, surveying more than 9,000 people, the peak age of onset for having any mental health disorder is 14. Anxiety, bipolar disorder, depression, eating disorder, psychosis (including schizophrenia), and substance abuse disorders begin during adolescence.

Although the exact biological reasons why the teenage brain may be vulnerable are unknown, this period represents a time of substantial changes in:

- hormone production
- synaptic remodelling
- axon myelination (insulating a neuron's transmission cables)
- changes to grey matter (supporting cells and the branches of neurons).

These changes are usually beneficial and optimise the brain for future challenges, but they may also make it more vulnerable to external stimuli.

Many neurons have receptors for male and female hormones, like testosterone and oestrogen. When these receptors are activated, this can affect neurotransmitter release and the size and shape of neurons. Moreover, early alterations in the teenager's brain have been linked with later progression to an adult psychiatric condition. Early intervention to block these changes and slow or stop the onset of psychiatric symptoms is now an active research area.





## The teenage brain

**O**ur brain reaches its full size in early adolescence. However, its wiring is still a work in progress and will continue – albeit to a lesser extent – even throughout later life.

Brain development during the first months and years of life is characterised by an overproduction of neurons and connecting synapses. This provides the developmental plasticity needed to adapt to and learn from the avalanche of new information that infants and young children receive. In contrast, brain development from late childhood through adolescence is dominated by processes that remove neurons and synapses. While this may seem unintuitive or even detrimental, it is an integral part of brain maturation and key to the behavioural, emotional, and cognitive changes that occur during the transition to adulthood.

While the death of excess neurons is pre-programmed, the reduction of synaptic connections – a process called synaptic pruning – is subject

*... as teenagers grow into adults, they acquire a greater cognitive ability to plan, organise and prioritise tasks*

to experience. Frequently used connections, say those used when playing a musical instrument, are reinforced and become hardwired. Unused connections are removed. Teenagers lose about 1% of their grey matter every year until their early twenties. Meanwhile, the amount of white matter increases.

But these changes do not affect all brain areas simultaneously. The sensory and motor areas mature first, followed by regions involved in language and spatial orientation, and then those involved in higher-order cognitive processes and executive functions, such as flexible thinking, reasoning, and self-control. The last to mature is the dorsolateral prefrontal cortex at the very front of the frontal lobe. This area is involved in planning, judgement and decision making, and it also processes emotional information sent from the amygdala - the *fight or flight centre* of the brain. This delay in maturation may help explain typical risky, short-sighted teenage behaviour and the often-apparent lack of control over impulses and emotions.

During this period, the adolescent brain remains highly malleable and still acts like a sponge for learning. Yet lacking impulse and emotional

control makes teens vulnerable to stress and mental health problems.

Epidemiological studies have shown that about half of all lifetime mental disorders start by the mid-teens and three-quarters by the mid-twenties. QBI researchers are exploring how the brain changes during these critical periods of growth.



A-Z

### Definitions

#### Grey matter

Tissue composed of neuron cell bodies, glial cells, and unmyelinated axons, where most processing occurs.

#### White matter

Areas of the central nervous system containing mostly myelinated axons and only a few neuron cell bodies. Its main function is signal transmission between grey matter areas.

#### Epidemiological studies

Epidemiological studies track the prevalence and course of a disease or condition in population groups over time, helping to define the disease or condition's development and outcomes, determine risk factors and identify targets for prevention or treatment.

# ADAPTING TO CHALLENGES

**T**he trajectory of an individual's developing brain is unique. The embryonic and newborn brain is a complex product of the genes inherited from its parents and the environment encountered in utero.

Little can be changed about the genetic make-up of the developing brain. For instance, genetic abnormalities, like DiGeorge syndrome or Fragile X syndrome, frequently lead to early neurological and often later psychiatric conditions.

During pregnancy, a mother may also experience stressful events of varying severity, or a developing foetus exposed to prolonged hypoxia (lack of oxygen), toxins (foetal alcohol syndrome), viral or bacterial infections or nutritional deficits. As we describe in this chapter, the placenta, to a large extent, can buffer the developing brain against such adversities, and the brain is good at adapting to challenges. However with more severe or prolonged exposures, these embryonic defences can become overwhelmed.





## Major threats to the developing brain

**T**here is strong epidemiological evidence linking insults to the developing brain during pregnancy – for example, when the expecting mother experiences stress, malnutrition, or exposure to toxins (e.g., alcohol) or disease-causing pathogens – to a higher risk of the child developing neurological or psychiatric disorders. However, most children whose mothers experienced such insults do not develop such conditions. Nevertheless, unlikely does not mean impossible. So, what can impact a developing brain and how?

### Stress

Stress, for example, due to emotionally difficult life events, as well as anxiety and depression experienced by a mother during pregnancy, affect the brain development of the unborn baby and increase its risk of developing behavioural, emotional, or cognitive

problems, such as ADHD (attention deficit hyperactivity disorder), anxiety or depression, later in life. The exact mechanisms are still not fully understood, but changes in the mother's balance of stress hormones, such as cortisol and glucocorticoids, with subsequent changes to the fetal environment, appear to play a role.

### Nutritional deficiencies

Adequate nutrition during pregnancy and after birth is essential for healthy brain development. Periods of malnutrition have different negative effects depending on the period's timing. For example, nutritional deficiencies during the second trimester of pregnancy result in a reduction in the number of neurons, whereas nutritional deficiency during the third trimester results in a reduction in the number of glial cells. It also matters which nutrients are deficient. For example, iron and

certain vitamins, such as vitamin B9/ folate and vitamin D (see page 21), are particularly important.

### Infections

Bacterial or viral infections can induce a cascade of inflammatory factors that can have profound effects on the function, connectivity and survival of developing neurons.



## Definitions

### Plasticity

The ability of the brain to change and adapt to new information. Synaptic plasticity is change that occurs at synapses, the junctions between neurons that allow them to communicate. It controls how effectively two neurons communicate with each other.

## Toxins

Certain drugs and other chemicals may damage developing neurons. Among the most common developmental neurotoxins is alcohol. Surprisingly, the damaging effects of alcohol on unborn babies and specifically their developing brains were first scientifically reported just 50 years ago. It is now well established that maternal alcohol consumption during pregnancy can cause severe, persisting developmental disorders, including cognitive impairment.

## Oxidative damage

Every newborn faces a 'hyperoxic challenge' as it transitions from life inside the womb to self-sustained life outside. Under normal conditions, the newborn brain is well equipped to combat the damaging potential of oxygen radicals that form during this

transition. Premature babies, however, are vulnerable to oxidative damage as their brains still have only low levels of antioxidants. Oxidative damage to the developing brain can cause several severe disorders, including epilepsy. The risk for it to occur is increased by factors that enhance the risk for premature birth, such as infection, alcohol or drug abuse, and age.

## The role of the placenta

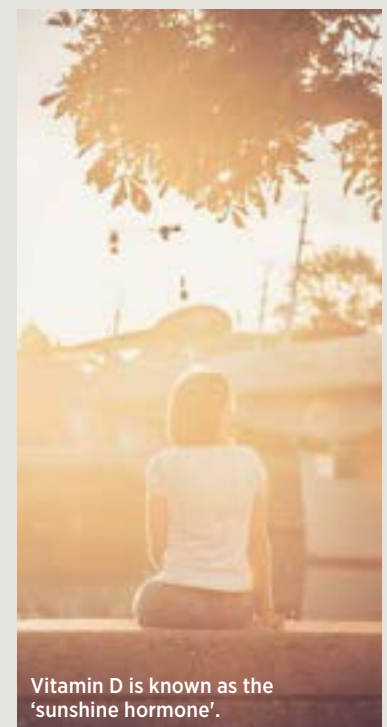
Although the developing brain is vulnerable to various threats, in a way, it has its guardian angel. The placenta acts as a protective barrier between mother and baby by keeping their bloodstreams separate. This way, few viruses and bacteria can infect the baby. The placenta is also effective at removing certain potentially harmful toxins. However, this is not completely failsafe.

## Vitamin D in the developing brain

Vitamin D, also called the 'sunshine hormone' because it is synthesised in the skin upon exposure to sunlight, is probably best known for its role in calcium uptake and bone formation. However, research conducted at QBI over the past 20 years has shown that vitamin D is also important for brain development. When maternal vitamin D levels are low, the risk for a newborn to develop psychiatric conditions such as schizophrenia or autism later in life doubles in comparison to the general population.

In animal models, a vitamin D deficient maternal diet resulted in the offspring's brain undergoing subtle changes in certain structures and altered levels of expression of genes involved in brain development. Another role of vitamin D associated with the above consequences is its involvement in maintaining levels of dopamine, an important neurotransmitter. Dopamine dysfunction is a central feature of the biology of schizophrenia and, to a lesser extent, autism.

Luckily, some (but not all) of the detrimental effects of vitamin D deficiency are reversible when treated with vitamin D supplements.



Vitamin D is known as the 'sunshine hormone'.



For some time now, scientists have known that certain psychiatric conditions are more common in one sex. For example, autism, attention deficit hyperactivity disorder and schizophrenia are more common in males, and depression and anxiety disorders are more common in females. The question is why.

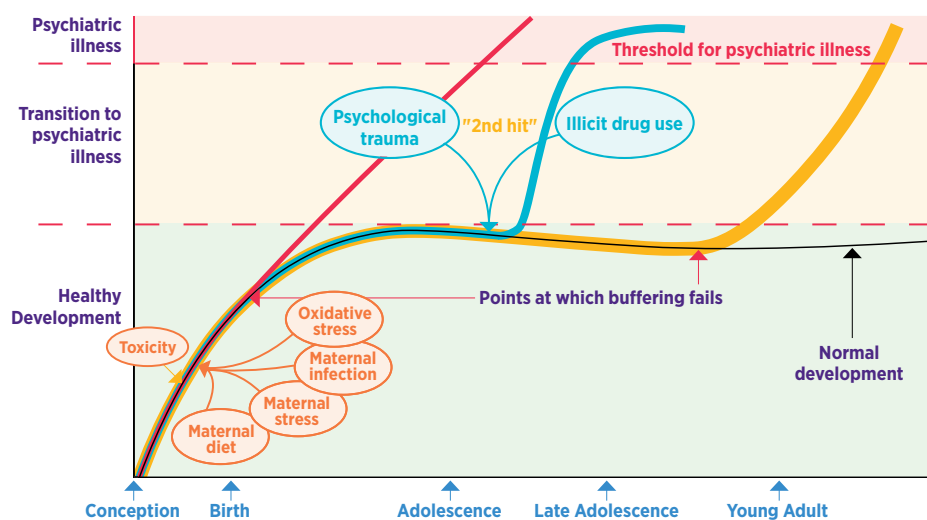
The study of sex differences in psychiatric and neurodevelopmental disorders is complicated due to several interacting biological, psychological, and social factors. This may be compounded by a bias towards one sex in the diagnosis of certain disorders. However, even controlling for such factors cannot fully account for the much higher incidence in one sex, such as that found in autism, which is four to five times more likely to be diagnosed in males.

The role that male and female sex steroids, such as testosterone and oestrogen, play in puberty is

outwardly a process of physical transformation. Less appreciated is the effect these same hormones have on the developing brain. In primates, there is a surge of these hormones in the second trimester of pregnancy that appears to drive hormonal effects in the developing brain. The effect of sex steroids on brain development has been extensively studied in lab rodents. In particular, neuron and immune cell numbers are quite different between male and female rodents in the hypothalamus and the cerebellum (brain regions involved in energy sensing and balance, respectively).

Indeed cross-talk between sex steroids and immune systems is emerging as a major research interest in how the brain develops. Timing is also critical as there are certain developmental 'windows' outside of which varying the sex hormone levels does not affect brain development and later behaviour.

## Developmental trajectory to psychiatric illness



## Psychiatric conditions: when the brain can't cope

While brains can, to some extent, adapt to environmental and genetic challenges during development in the womb, we showed on the previous pages that in some cases, exposure to toxins, pathogens and other threats leads to the development of psychiatric conditions during childhood or adulthood. Researchers propose that this occurs when the level of developmental insults reaches a certain threshold beyond which the developing brain can no longer adapt to the detrimental impacts it faces. The infographic above illustrates three main pathways thought to lead to the emergence of psychiatric conditions.

**1)** If adaptation fails before birth—for example, if the individual was genetically less resilient to insults—childhood psychiatric conditions such as autism or ADHD can emerge (indicated by the red line).

**2)** Alternatively, in cases where insults before birth were deflected, the use of illicit drugs, highly stressful life events, or a significant psychological trauma—for example, during adolescence—may trigger psychiatric conditions many years after the original insult occurred. This is the

so-called 'two-hit' model, in which later stressors trigger a transition to psychiatric illness that had otherwise initially been successfully avoided by the developing brain's buffering capacity (blue line).

**3)** A third possibility is that the effects of early events are initially masked by the developing brain's ability to adapt but that this adaptation does not last forever. So, when brain circuits mature and become 'hardwired', an unintended consequence is that early adaptations to those early events become unmasked, crossing the threshold towards psychiatric conditions such as schizophrenia or bipolar disorder (yellow line). Hormonal surges during puberty can also impact this wiring process. Moreover, research conducted in the laboratory of QBI's Professor Darryl Eyles is contributing to the idea that the brain may also overcompensate - i.e., by creating a toxic process that itself cannot be buffered at later developmental stages.

QBI researchers are now focusing on how such early impacts on the growing cells and circuits in the developing brain may help us discover pathways to psychiatric disorders.

## Disruptions in cortical development

The cortex is the outermost wrinkly layer of the brain and is the command and information processing centre responsible for consciousness, creativity, language, sensory perception and memory. Disruptions to the normal development of the cortex can happen at any embryonic stage and are caused by defective genes or disruptive or toxic environmental factors. Alterations occur during a time when the brain is rapidly producing new neurons and as the new-born neurons migrate to different parts of the maturing brain. When this highly regulated process goes awry, too many or too few neurons are produced (micro- or macrocephaly, respectively), neurons cluster in the wrong place, or incorrect neuronal connections form, thereby disturbing neural circuitry and brain function.

The effects can be mild, with the brain adapting to this challenge, or can be severe, resulting in seizures, intellectual disability, significant impairment to movement and even contribute to neuropsychiatric disorders such as autism.

Researchers in the lab of Professor Helen Cooper at QBI study cortical disorders to discover why sometimes the correct number of neurons are not generated from stem cells, and why they fail to migrate to their specified brain region and establish functional circuitry.

Cortical development disorders can also disrupt the normal wiring of neurons in the developing brain. Once migrating cells reach their correct location, they then must wire properly for the brain to function well. Researchers like Dr Laura Fenlon and Dr Rodrigo Suarez study this process and how it goes wrong—for example, in disorders of the corpus callosum, the bridge of neurons connecting the left and right cerebral hemispheres. The symptoms are highly variable but can include sensory and motor problems and language and reading difficulties.



# FUTURE RESEARCH



## The big questions

**D**espite everything we know about the processes of brain development, neuroscientists are still trying to unravel the details of the biggest question of all: how exactly does a tiny collection of embryonic stem cells produce a functioning human brain containing around 100 billion correctly wired neurons?

We have come a long way from discovering how stem cells function. Neuroscientists now have a working knowledge of the fundamental processes underpinning brain development, including neuron birth, differentiation, migration and the wiring of complex circuitry. We also know that

when these processes fail, devastating consequences may impact a person.

But we do not know how all the intricate and essential processes needed to build a functioning brain are precisely coordinated during development. What guides the integration of molecular and cellular activities – within genetic and environmental influences – to ensure each process occurs how, where and when it needs to?

We also have much to learn about why genetic and environmental risk factors can adversely affect development in some people and not others. For example,

most babies exposed to prenatal maternal smoking experience no developmental problems, but in a small minority, it can cause growth retardation and later psychiatric conditions. Similarly, we do not understand why exposure to the same environmental risk can produce different developmental outcomes, causing autism in some and not others. What makes some embryos resilient to adverse environments and others not? And why do the same risk factors produce different outcomes?

These are some of the questions QBI researchers are striving to answer.

The Queensland Brain Institute (QBI) is one of the world's leading neuroscience institutes.

## On the horizon

As we have explored throughout this magazine, understanding how a brain develops is an enormous but incredibly important challenge. We are currently at the tip of the metaphoric iceberg for understanding brain development. Each new study gives us more information that expands our knowledge about the brain and helps in preventing, managing and treating the diseases and disorders that can afflict it.



Helen Cooper



### How do stem cells become neurons?

The Cooper lab is unravelling the molecular mechanisms underpinning brain development. What molecules direct a stem cell to become a certain type of neuron or guide axons to follow a predetermined route? Recently, their work has linked genes controlling these molecules to mutated genes in autism and schizophrenia, suggesting possible clues about the molecular bases of neuropsychiatric disorders. Their goal is to explore these links further, as well as learn more about the molecular processes directing brain development.



Darryl Eyles



### Development origins of schizophrenia

The Eyles lab is making exciting progress in understanding the developmental roots of schizophrenia with a focus on dopamine systems, showing that alterations to maternal nutrition, and exposure to prenatal hypoxia or infection all change how early dopamine neurons develop. Now, they are investigating whether these environmental factors converge to affect dopamine release in the striatum region of the brain and how pharmacological control of dopamine release could offer a new approach to treating or even preventing schizophrenia.



Karen Thorpe



### Tracking the impact of early educational experiences on human brain development

Early care and education services are attended by 1.3 million Australian children each week, spending up to 10,000 hours in these services before school entry. These hours coincide with the most critical time in human synapse formation, a process entrained by early cognitive and social learning experiences that potentiates a child's ongoing trajectories of learning and behaviour. The Thorpe Lab applies longitudinal tracking of children from early childhood throughout schooling to inform policy and practice to support human learning.



Bruno van Swinderen



### Understanding sleep and consciousness

The tiny fruit fly is offering key insights into brain development. The van Swinderen lab uses flies to study consciousness and sleep. We know rapid eye movement (REM) sleep is critical during development, but we do not know why. QBI researchers believe it might be key to how we become conscious. By understanding this mysterious process first in flies, they believe that one day they will be able to understand it in humans.

# Own the unknown at the Queensland Brain Institute

QBI developmental neuroscientists are striving to understand how the brain develops and the many interactions between the genes we inherit and our environment. Be part of this incredible challenge by supporting QBI discovery research today. [qbi.uq.edu.au/discovery](http://qbi.uq.edu.au/discovery)





CREATE CHANGE

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