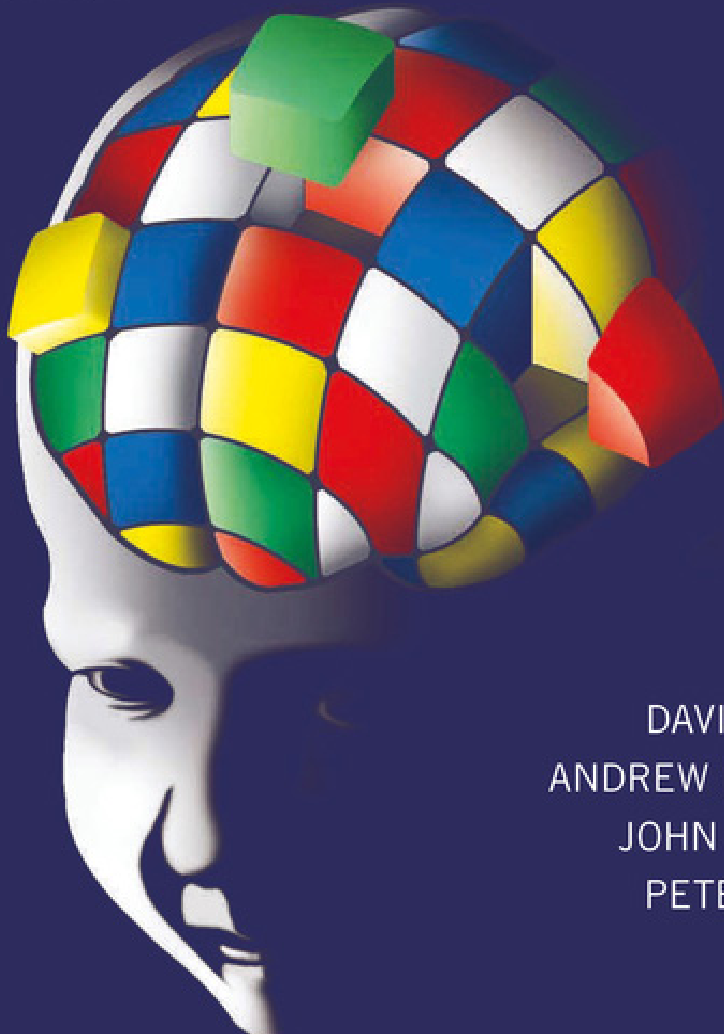
BUILDING BRAINS

AN INTRODUCTION TO NEURAL DEVELOPMENT

SECOND EDITION



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The New York Academy of Sciences

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Building Brains: An Introduction to Neural Development

Second Edition

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UK

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Preface to Second Edition

Many important conceptual and technical advances have improved our understanding of nervous system development over the 6 years that have elapsed since we completed the first edition of Building Brains. In this second edition, we have updated the book to include recent conceptual breakthroughs in specific areas and we have added new descriptions of major technical developments that are likely to have a huge impact in the future. Technical advances include our ability to sequence, rapidly and efficiently, entire genomes and transcriptomes, telling us much more about the genetic control of both normal and abnormal development. Vast quantities of data on the genomes and transcriptomes of normal and abnormal organisms, tissues and cells are becoming available on public databases where they can be analysed by the scientific community using new computational methods. In this second edition, we explain these advances and we stress their potential to enhance our understanding of human development and disease. We complement this with more background on how the human nervous system develops and we draw out the similarities and differences between neural development in humans and other species. We include descriptions of new approaches using human cells in culture, for example to generate brain-like structures in which mechanisms of normal and abnormal development can be modelled and analysed. Advances in transgenic methods, including those for generating mutations in specific cells at specific times, have had a major impact on our ability to understand the molecular mechanisms of development both in human cells and in model organisms. We explain these methods and the opportunities they offer to the experimentalist. We hope that these additions will not only increase the usefulness of our book but will also convey the sense of excitement felt by those of us working in this field. The opportunities to make major contributions to solving the profound mysteries of normal and disordered brain development have never been greater.

We have also taken this opportunity to improve the clarity of aspects of the book that readers found difficult in the first edition. We are grateful to all of you who have given us suggestions and pointed out errors. We thank the undergraduate students taking our course at Edinburgh, who offered extensive feedback. In particular, Natasha Anstey gave detailed comments far beyond our expectations – thank you! We also thank Natasha Price for helping us make movies explaining trickier topics (you can use the QR codes in to find them on the companion website) and for original drawings of some organisms used in Chapter 1. We are indebted to all at Wiley who helped produce this book, in particular Mindy Okura-Marszycki, Rebecca Ralf and Ramprasad Jayakumar.

David J. Price
Andrew P. Jarman
John O. Mason
Peter C. Kind
June 2017

Preface to First Edition

A few years ago we started teaching a new course at the University of Edinburgh aiming to stimulate undergraduates in the middle years of their studies to think about the challenges and excitement of trying to understand how nervous systems are built. We did not set out to cover all possible topics equally. Instead, we selected areas that we thought provided the best understood or the most intriguing examples of how developmental events are controlled by genetic instructions combined with information from other cells and from the developing organism's environment. We used examples taken from all stages of neural development from its earliest beginnings in the embryo to its refinement as a mature functioning structure. We selected research on vertebrates and invertebrates to illustrate key findings that provide the greatest insight into developmental mechanisms and that can be extrapolated to many or even all species of animal. One of our main reasons for writing this book was to gather together the material that we teach into a single text that might appeal to students taking similar courses elsewhere.

We also teach a variety of other students about these topics: some are in their final undergraduate year, some are in the middle year of a medical degree and some are taking courses that are components of a postgraduate degree. Although these students are at more advanced levels, many of them have received little or no training in one or more of several crucial subjects such as embryology, neuroscience, genetics and molecular biology. Increasingly, many students enter developmental neurobiology with backgrounds in mathematics, physics or computer science. We have, therefore, to teach our topics without assuming a great level of biological knowledge, and so another of our reasons for writing this book was to provide an accessible but rigorous introduction to mechanisms of neural development for students with little or no prior knowledge in this or related fields.

A third reason for writing this book was to provide students with many memorable, colourful illustrations of developmental mechanisms and the experiments that have led to their discovery. Neural development is a highly visual branch of biology: experiments are often made on structures that can be seen without great technical difficulty. The real problem with neural development, as pointed out by one of our students, is the need to understand genetics, molecular biology, biochemistry and physiology, and then apply it all in four dimensions. In this book we have tried to tackle this admittedly daunting task by depicting the essential three-dimensional anatomy of developing embryos early in the book, and then using this information to help orient the reader throughout the remaining chapters.

Most of all, we hope that the reader will find our book clear and interesting, and we hope that it succeeds in conveying some of the enthusiasm we feel for this subject. If the reader is inspired to go deeper, for example by reading one of the more detailed books on neural development that are available, then one of our major aims is achieved.

We thank the many people who helped us. A number of reviewers, some anonymous, made very constructive comments: in particular, we thank Patricia Gaspar, Frank Sengpiel, Ian Thompson, Tom Pratt, Alex Crocker-Buque, Valentin Nagerl and David Willshaw. We thank our undergraduate students who gave us invaluable feedback. We thank Gillian Kidd, Julie Robinson, Anna Price and Natasha Price for help with the illustrations; Gillian's expert work on the cover illustration is greatly appreciated. We thank Siân Jarman for her help and insight and Nicky McGirr and our publishers for their patience and support.

Finally, we would like to hear what you think works well and what could be improved so talk to us on the Building Brains page on Facebook.

David Price
Andrew Jarman
John Mason
Peter Kind
August 2010

Conventions and Commonly used Abbreviations

Naming conventions for genes and proteins

The conventions for naming genes and their protein products are complicated and vary from species to species. We have taken the following pragmatic approach. We hope that in most (if not all) places where a gene or protein name is used, the context will provide all the information that the reader needs, but just in case …

Genes
In many cases this will be roman non-italic if the gene is named after its protein (e.g. the follistatin gene). Cases where the gene was named before the protein are usually italicized, for example *reeler*.

Gene abbreviations
These are italicized and have an initial capital, for example *Pax6, Hoxb4*. This is the convention for the mouse. Frog, chick and zebrafish have a variety of conventions for gene abbreviations, but here we have mostly followed the mouse.

Names of gene families do not necessarily follow these rules and we follow the prevailing conventions in each field, for example Hox genes and SMAD genes, but *Sox* genes.

Species-specific exceptions

Human
The same as above, except gene abbreviations are italic, all capitals, for example *PAX6*.

Drosophila
Genes and gene abbreviations are italicized.

If mutation of the gene is recessive, for example *hedgehog* (*hh*), then all the letters are lower case.

If mutation is dominant (e.g. *Krüppel* (*Kr*)) – or if the gene is secondarily named after the protein (e.g. *Dscam*) – then the initial letter is a capital.

C. elegans
Gene abbreviations are lower-case italic and include a hyphen, for example *ced-7*.

Proteins (all species)
Proteins are generally in lower-case roman, for example follistatin and reelin, but may have an initial capital letter in cases that might otherwise be ambiguous or odd in a sentence, for example Dishevelled, Sonic hedgehog.

Proteins named after a gene abbreviation are given the gene name in roman letters, all capitals, for example PAX6, SOX1, HOXB4 and SMADs.

Commonly used abbreviations

We have tried to minimize the use of abbreviations. We have defined abbreviations where they are first used and in some cases repeatedly in multiple locations where we thought it would be helpful to remind the reader. Here is a list of some of the more commonly used abbreviations.

AIS	axon initial segment
AMPA	α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate
AP	anteroposterior
BDNF	brain-derived neurotrophic factor
bHLH	basic helix–loop–helix
BMP	bone morphogenetic protein
BMPR	BMP receptor
BrdU	bromodeoxyuridine
CAM	cell adhesion molecule
cDNA	complementary DNA
CNS	central nervous system
CP	cortical plate
CR cells	Cajal–Retzius cells
CSPG	chondroitin sulphate proteoglycan
CS	Carnegie stage
DiI	1,1′-dioctadecyl-3,3,3′,3′-tetramethylindocarbocyanine perchlorate
dLGN	dorsal lateral geniculate nucleus
DNA	deoxyribonucleic acid
DV	dorsoventral
ECM	extracellular matrix
EGL	external granule layer
EPSP	excitatory post-synaptic potential
ES cells	embryonic stem cells
FGF	fibroblast growth factor
G protein	guanine nucleotide binding protein
GABA	γ-amino butyric acid
GAP	GTPase activating protein
GDNF	glial cell derived neurotrophic factor
GEF	Guanine–nucleotide exchange factor
GFP	green fluorescent protein
GMC	ganglion mother cell
HES	hairy/enhancer of split
HSN	hermaphrodite specific neuron
HSPG	heparan sulphate proteoglycan
IPC	intermediate progenitor cell
iPSC	induced pluripotent stem cell

IPSP	inhibitory post-synaptic potential
ISO	isthmic organizer
ISVZ	inner subventricular zone
LGE	lateral ganglionic eminence
LTD	long-term depression
LTP	long-term potentiation
MAP	microtubule-associated protein
MAPK	mitogen-activated protein kinase
MD	monocular deprivation
mEPSP	miniature excitatory post-synaptic potential
mIPSP	miniature inhibitory post-synaptic potential
ML	mediolateral
mRNA	messenger RNA
MZ	mantle zone
NCAM	neural cell adhesion molecule
NGF	nerve growth factor
NMDA	*N*-methyl-D-aspartic acid
NMJ	neuromuscular junction
OD	ocular dominance
oRG	outer radial glial cell
OSVZ	outer subventricular zone
PIP3	phosphatidylinositol (3,4,5)-trisphosphate
PKA	protein kinase A
pMN	progenitor domain of the motor neurons
PNS	peripheral nervous system
PSD	post-synaptic density
r1–8	rhombomeres 1–8
RA	retinoic acid
RGC	retinal ganglion cell
RNA	ribonucleic acid
SOP	sense organ precursor
SVZ	subventricular zone
TCA	thalamocortical axon
TS	Theiler stage
TTX	tetrodotoxin
UAS	upstream activating sequence
VEP	visually evoked potential
Vp0	progenitor domain of the V0 interneurons
VZ	ventricular zone
ZLI	zona limitans intrathalamica

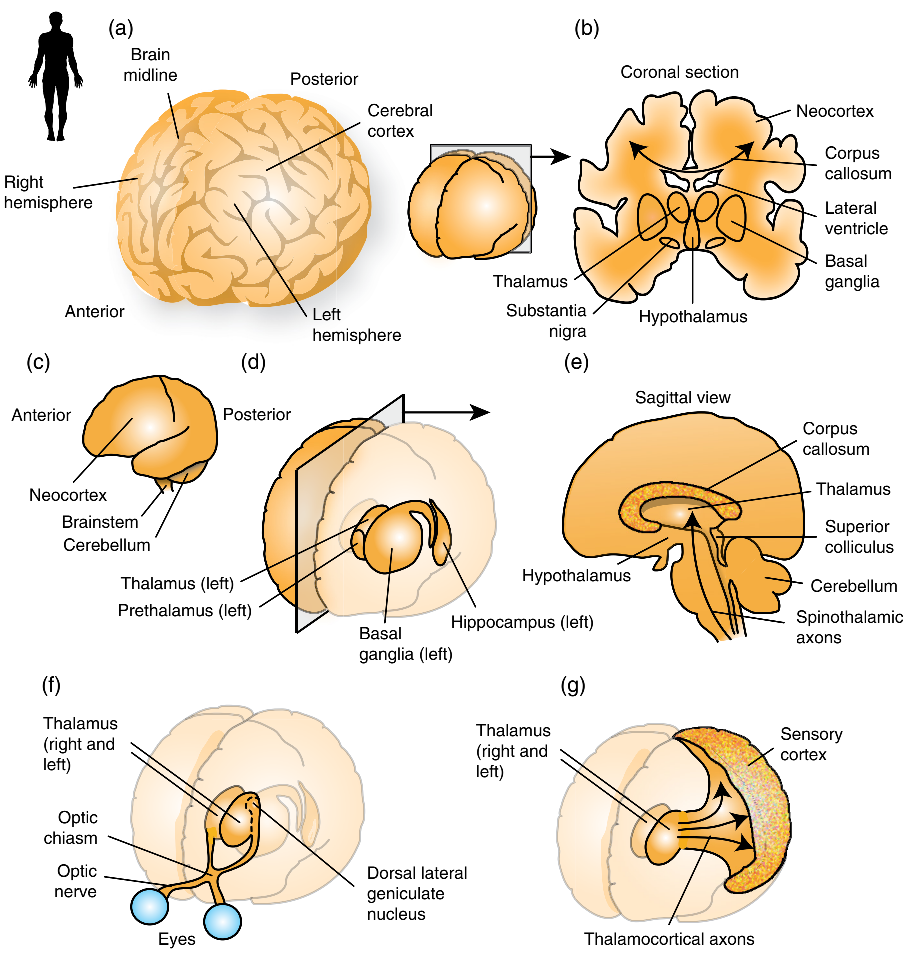
Significance of bold and blue bold terms

All terms that are shown using a blue bold typeface are defined in the margin close to their appearance in the text and also in the Glossary section at the end of the book. All terms that are shown using bold lettering are defined in the Glossary. The terms are not shown as bold every time they appear, just the first time or in other places where their emphasis might be helpful. The Glossary also contains some additional terms that are not given a bold type face in the text but whose definition might be helpful.

Introduction

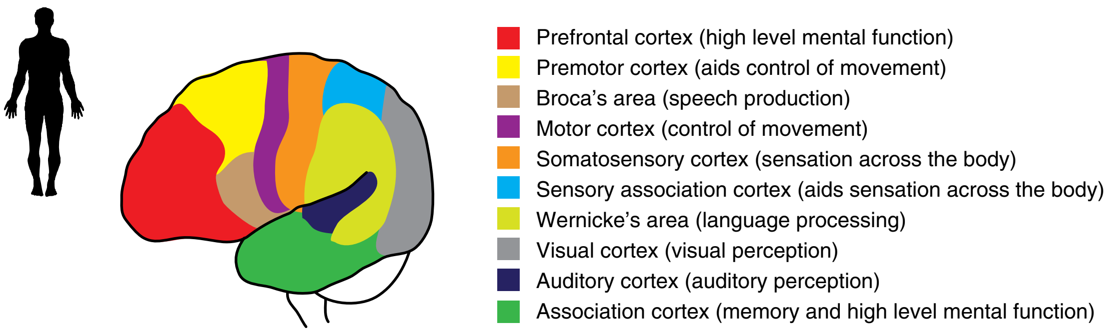
Major Components of the Adult Human Brain

Although the brain is extremely complex, you will be relieved to hear that you need only a relatively simple understanding of its anatomy to learn about its mechanisms of development. The following diagrams map the locations of major brain structures described in this book; we shall refer back to them at the appropriate places.

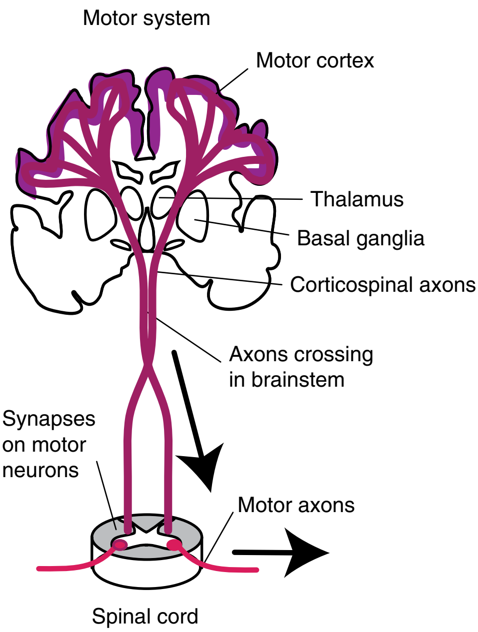


The structures depicted here have the same names, are in the same relative positions and have similar functions in other mammals, even those with smaller and simpler brains. (a) The **cerebral cortex**, lying just beneath the skull, is spread across two hemispheres and looks like a giant walnut. The visible cortex is **neocortex** ('neo' meaning new, in evolutionary terms, to distinguish it from more primitive cortical regions such as the hippocampus; see (d)). Cortical ridges are called gyri (singular, gyrus) and the valleys between them are called sulci (singular, sulcus). Cortex with wrinkles like this has a very large surface area if you stretch it out. (b) Slicing through the brain reveals its internal structures (the plane here is called coronal). The **lateral ventricles** are fluid-filled cavities. They are continuous with other fluid-filled cavities running through the centre of the CNS, which are not seen in this plane (they are the 3rd and 4th ventricles, which are in the brain, and the central canal of the spinal cord). The **thalamus**, which is in the centre of the vertebrate brain, transmits sensory input to the cerebral cortex; see (j). The **basal ganglia** are large groups of neurons lying under the cerebral cortex responsible for the control of movements; one of these is the **substantia nigra**, a layer of grey matter in the midbrain. The **hypothalamus** regulates hormone secretion and controls many autonomic functions. The **corpus callosum** is a massive bundle of axons connecting the cerebral hemispheres along their anterior to posterior length. (c) A side view of the brain. The **cerebellum** regulates a range of functions including motor control, attention and cognition. The **brainstem** is the posterior region of the brain of vertebrates consisting of the medulla oblongata, pons and **midbrain**. (d) The left thalamus, **prethalamus**, basal ganglia and **hippocampus**, which is associated with learning and memory, seen through a translucent left hemisphere. (e) The brain is cut in half in the plane shown in (d), which is called sagittal. You are looking at the inner surface of the right hemisphere. Many of the structures mentioned above are marked. The **superior colliculus** is a region of the midbrain that receives visual input from the retina. **Spinothalamic axons** transmit sensory signals arising mainly from the skin (e.g. about touch, temperature and so on) from the spinal cord to the thalamus, from where they are relayed to the cerebral cortex (this is referred to as the **somatosensory** system, 'soma' being Greek for body; see also (j). (f) The inputs from the eyes to the brain: axons from each retina run through the **optic nerve** to the **optic chiasm**, where some cross to the other side of the brain and others stay on the same side, and connect with neurons in a region of the thalamus called the **dorsal lateral geniculate nucleus**, which connects to the visual cortex. (g) **Thalamocortical axons** relay sensory signals from the thalamus to the sensory regions of the cortex, which are in its back (or posterior) part; see also (j). (h) The neocortex is regionalized into many areas with different functions. (i) The motor system: corticospinal axons from the motor cortex run down the spinal cord to control muscles on the opposite side of the body. (j) Somatosensory information is relayed to the opposite cortex via sensory nerves, spinothalamic axons and thalamocortical axons.

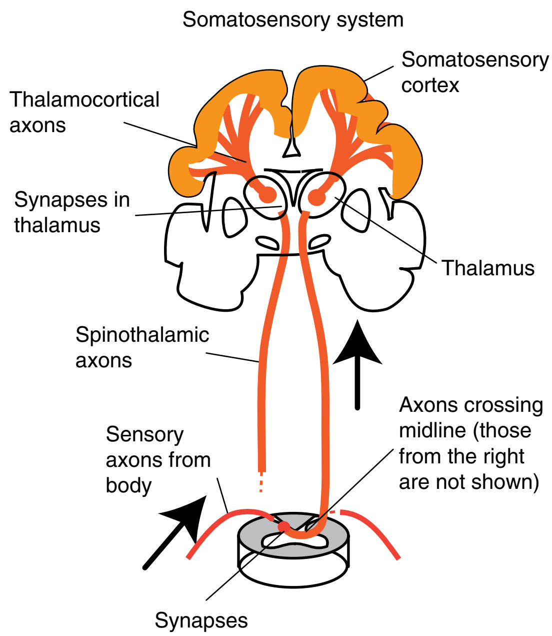
(h)


Prefrontal cortex (high level mental function)
Premotor cortex (aids control of movement)
Broca's area (speech production)
Motor cortex (control of movement)
Somatosensory cortex (sensation across the body)
Sensory association cortex (aids sensation across the body)
Wernicke's area (language processing)
Visual cortex (visual perception)
Auditory cortex (auditory perception)
Association cortex (memory and high level mental function)

(i)


Motor system
Motor cortex
Thalamus
Basal ganglia
Corticospinal axons
Axons crossing in brainstem
Synapses on motor neurons
Motor axons
Spinal cord

(j)


Somatosensory system
Somatosensory cortex
Thalamocortical axons
Synapses in thalamus
Thalamus
Spinothalamic axons
Axons crossing midline (those from the right are not shown)
Sensory axons from body
Synapses

About the Companion Website

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There you will find valuable material designed to enhance your learning, including:

- **Videos**
- **All the figures in this book**

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Models and Methods for Studying Neural Development

1

1.1 What is neural development?

Neural development is the process by which the nervous system grows from its first beginnings in the embryo to its completion as a mature functioning system. The mature nervous system contains two classes of specialized and closely interacting cells: **neurons** and **glia**. Neurons transmit signals to, from and within the brain: their axons transmit electrical signals and they communicate with other cells via **synapses**. There are many types of neuron with specialized shapes and functions, with cell bodies that vary in diameter from only a few micrometers to around 100 micrometers and with axons whose lengths vary from a few micrometers to more than 1 meter. There are also different types of glial cell. The interactions between neurons and glia are very precise and they allow the nervous system to function efficiently. Figure 1.1 shows a beautiful example of the complex structures created by interacting neurons and glia, in this case a microscopic view of a labelled node of Ranvier, which allows rapid signalling in the nervous system.

The great molecular, structural and functional diversity of neurons and glia is acquired in an organized way through processes that build on differences between the relatively small numbers of cells in the early embryo. As more and more cells are generated in a growing organism, new cells diversify in specific ways as a result of interactions with pre-existing cells, continually adding to the organism's complexity in a highly regulated manner. The development of an organism is a bit like the development of human civilization (allowing for the obvious difference that organismal development repeats over and over again). In both, population size and sophistication (be it humans on earth or cells in an organism) grow hand-in-hand, each stage adding further layers of complexity to previously generated structures, functions and interactions. The mechanisms that regulate cellular actions and interactions during development are often described using terms commonly applied to human activities. We shall highlight this at several places throughout the book where analogies might be helpful.

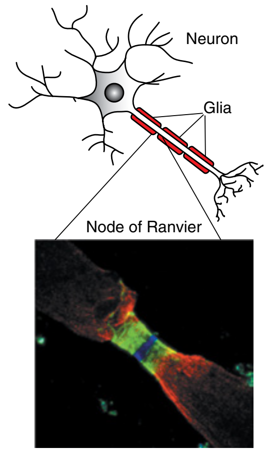

Figure 1.1 A node of Ranvier: these highly organized structures, formed as a result of interactions between axons and glia, are essential for speeding up the transmission of electrical signals along axons. In this single fibre from the mouse spinal cord, sodium channels (blue) are sandwiched between the regions where axons and glia form junctions (called axoglial junctions) (green), which are, in turn, flanked by potassium channels (red). This picture is courtesy of Peter Brophy and Anne Desmazieres, University of Edinburgh, UK.

Building Brains: An Introduction to Neural Development, Second Edition.
David J. Price, Andrew P. Jarman, John O. Mason and Peter C. Kind.

Companion website: www.wiley.com/go/price/buildingbrains2e

To understand how organisms develop we need to know how cells in each part of the embryo develop in specific and reproducible ways as a result of their own internal mechanisms interacting with an expanding array of stimuli from outside the cell. Many laboratories around the world are researching this area. Why?

1.2 Why research neural development?

1.2.1 The uncertainty of current understanding

One reason for researching neural development is that we still know relatively little about it. In this book we shall try to explain some of the main events that occur during neural development and, in particular, the mechanisms by which those events are brought about, in so far as we understand them. It is important, however, to appreciate that much of what we present, particularly our understanding of molecular mechanisms, is best thought of as continually evolving hypotheses rather than established facts. The biologist Konrad Lorenz once stated that 'truth in science can be defined as the working hypothesis best suited to open the way to the next better one'; this is highly appropriate in developmental neurobiology.

Some of our understanding is incomplete or may be shown by future experiments to be inaccurate. We have tried to highlight issues of particular uncertainty or controversy and to indicate the limits of our knowledge, since it is at least as important and interesting to acknowledge what we do not know as it is to learn what we do know. Much of the excitement of developmental neurobiology arises from the mystery that surrounds Nature's remarkable ability to create efficiently and reproducibly neural structures of great power.

One reason that we still know relatively little about the mechanisms of neural development is the sheer size and complexity of the finished product in higher animals. During the development of the human brain, for example, about 100 billion cells are generated with about 1000 trillion connections between them; if this number of connections is hard to visualize then consider that it might roughly equal the number of grains of sand on a small beach. Although cells and connections with similar properties can be grouped together, there is still great variation in their molecular make-ups, morphologies and functions throughout the nervous system. In reading this book you will see that many of our hypotheses about neural development are formulated at the level of tissues or populations of cells rather than individual cells and their connections, particularly in higher mammals. Only in very simple organisms containing a few hundred neurons (e.g. in some worms) do we fully understand where each cell of the adult nervous system comes from and even then we do not know for sure what mechanisms determine how each cell and its connections develop. We still have a long way to go to gain a profound understanding of the molecular and cellular rules that govern the emergence of cells of the right types in the right numbers at the right places with the right connections between them functioning in the right ways.

1.2.2 Implications for human health

Just because we do not know much about a subject is not sufficient reason to want to invest time and resources in researching it further. However, there are many practical reasons for wanting to know more about the ways in which the nervous system develops. A better understanding should help us to tackle currently incurable diseases of the nervous system. Many congenital diseases affect neural development[1] but their causes are often unknown; some examples of such diseases will be given later in this and in subsequent chapters. Numerous relatively common psychiatric and neurological diseases, such as schizophrenia, intellectual disabilities, autisms and some forms of epilepsy (Figure 1.2), are now thought to have a developmental origin, but the mechanisms are poorly understood. Knowledge of how cancers form should be helped by a better understanding of normal development; the uncontrolled growth of cancer cells is often attributed to abnormalities of the same molecules and mechanisms that control growth during normal development. Regarding the development of

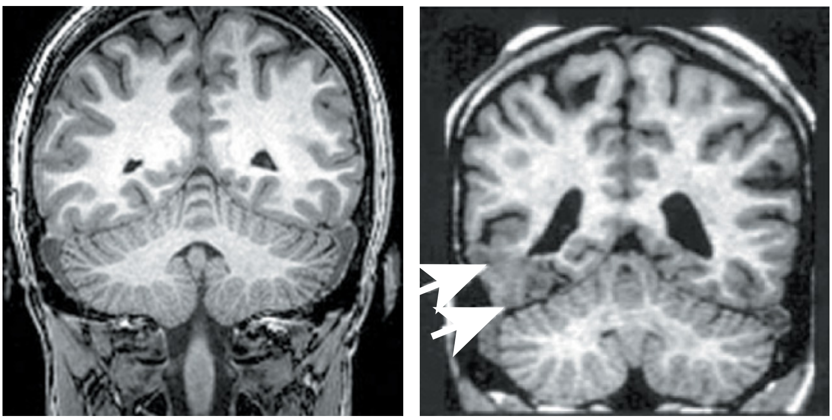

Figure 1.2 Schizophrenia, intellectual disabilities, autisms and epilepsies are neurological disorders affecting about 3–7% of people. Based on epidemiological and neurobiological evidence, schizophrenia is now believed to be a neurodevelopmental disorder with a large heritable component. Many possible susceptibility genes have been identified, but how abnormalities of these genes cause the symptoms of the disease is unknown. Similarly, autism spectrum disorders and intellectual disabilities are highly heritable and many of the known genetic causes seem to regulate the formation of synapses. Malformations of cerebral cortical development are among the commonest causes of epilepsy. Some are large defects that would be obvious to the naked eye whereas others would only be seen at a microscopic or molecular level. They are a consequence of a disruption of the normal steps of cortical formation, for example defective migration of neurons, and can be environmental or genetic in origin. A large number of malformations of cortical development have been described, each with characteristic pathological and clinical features. An example of a large congenital defect causing epilepsy is shown in the scan of a patient's brain on the right (between the arrows): for comparison, a scan of the brain of a normal person is shown on the left. This picture is courtesy of Professor John S. Duncan and the National Society for Epilepsy MRI Unit, UK.

[1] For a comprehensive compendium of human genes and genetic diseases, see http://omim.org/about. For an interesting review of neurodevelopmental disease and its impact, try Stoeckli, E.T. (2012) What does the developing brain tell us about neural diseases? European Journal of Neuroscience, 35, 1811–1817.

possible new treatments, it has been suggested that a diseased brain might be repaired by replacing dysfunctional genes or implanting new cells into the nervous system. Implanted cells would need to recapitulate a developmental programme allowing their survival and functional integration into the nervous system and its circuitry. How this might be achieved is currently unclear, but research on normal developmental mechanisms might help.

1.2.3 Implications for future technologies

Another, perhaps unexpected, motivation for understanding how the brain develops comes from the drive to revolutionize computer technology, to improve robotics and to generate autonomous machines able to make decisions. The application of current manufacturing methods to build much more complex computers than exist at present will need to overcome exponential increases in the production cost of ever smaller and faster circuits. In contrast, evolution has produced brains of enormous computing power that self-construct with great efficiency. Can lessons learned from studying the way the brain constructs itself be used to invent new, more efficient ways of generating computers by having them self-construct? Maybe this sounds like science fiction, but international organizations are taking it seriously enough to put large amounts of money into research aimed at establishing whether it might be possible.[2]

1.3 Major breakthroughs that have contributed to understanding developmental mechanisms

The twentieth century saw breakthroughs that have added greatly to our knowledge of how the nervous system develops. Most notable were the discovery of the structure of DNA and the development of methods for manipulating the functions of genes. We assume that the reader is familiar with the structure and function of DNA; methods for manipulating gene function will be outlined later in this chapter.

Another critically important advance in the twentieth century was the realization that, although animal species differ hugely in size and structure, the mechanisms by which their development is controlled are remarkably highly conserved. Many of the genes that control the development of relatively simple invertebrates have clear **homologues** in higher mammals, including primates. This means that by studying the mechanisms controlling the development of simple experimentally tractable organisms we can learn much of relevance to human development, which cannot be studied extensively for practical and ethical reasons.

homologue a gene or structure that is similar in different species since it was derived from their common ancestor during evolution.

A small handful of animal species, referred to as **model organisms**, are used in most developmental neurobiological research because each has

[2] See Douglas, R. (2011) Constructive cortical computation. *Procedia Computer Science*, 7, 18–19, which links to a recording of an interesting lecture on this topic.