The Nervous System

3

CHAPTER OUTLINE

Learning Objectives

By the end of this chapter you should appreciate that:

- the components of the nervous system have specific functional roles;
- there is regional specialization within the brain;
- nerve cells (neurons) have to use energy to maintain their electrical potential gradients, and that neurons 'fire' through the generation of action potentials which perturb these gradients;
- nerve cells communicate with each other via neurotransmission;
- chemical neurotransmission informs the design of drugs;
- the brain is susceptible to environmental influence;
- neural tissue has limited potential for repair;
- we can study the function of the brain via dysfunction;
- the brain is a type of complex information processing device.

INTRODUCTION

We can study behaviour and thought without necessarily knowing anything at all about the nervous system – or how the behaviour is generated. Cognitive psychologists studying slips of the tongue, for example, may not care whether the brain is made up of rubber bands or of *neurons*. In fact, if you simply count the cells in the brain, neurons are very much a minority group; most of them are non-neuronal, *glial cells*. But rubber bands are rarer still in there.

neuron a nerve cell

glial cells non-neuronal cells in the brain that provide 'support' for the neurons

Nevertheless, our interactions with the world around us depend crucially on the activity of the nervous system. Without it, we not only have no senses and no ability to move; we also have no thoughts, no memories and no emotions. These are the very essence of our selves, yet they can be disastrously changed, and even completely erased, by disorders of the nervous system.

We can very effectively treat some psychological disorders simply by using words to change the ways in which patients think (see chapter 16). But the only generally available palliatives for other conditions, like Parkinson's disease or schizophrenia, are drug treatments. And some

conditions, such as Alzheimer's disease, are currently untreatable.

The more we learn about how the nervous system operates, the better we can understand how it can go wrong. That, in turn, will increase our chances of finding out how to prevent, or even reverse, psychological disorders. If we do not understand the way that the nervous system works, then we, like our forebears throughout humankind's history, are confined to a passive role as observers and documenters of the effects of nervous dysfunction.

HOW YOUR BRAIN PLAYS TENNIS

Imagine you are playing tennis, at match point, waiting to return your opponent's serve. You are on edge, your heart rate is up, but you are totally focused on your opponent's actions. You are thinking about your opponent's strengths and weaknesses and considering your options. Up goes the ball, the racquet flashes down, here comes the serve and your opponent is running in towards the net. You take a quick step, stretch out and hit the ball right in the centre of your racquet's sweet spot, sending your return fast and low, just inside the line but just beyond your opponent's reach. The whole sequence has taken no more than a couple of seconds, and you have won the match. What a feeling! But how did you manage to do it?

DECEPTIVELY SIMPLE . . .

The deceptively simple-looking sequence of behaviour that won you the match depends on some very complex interactions between different parts of your brain, and between your brain and the rest of your body.

As you were waiting, your body posture was being continually monitored and adjusted: you did this by constantly updating *proprioceptive* information from sensors located in your joints and muscles, and combining it with information from your middle-ear balance system, and with visual information.

Ian Waterman is one of only ten people in the world known to have lost this proprioceptive sense, which meant that he became unable to control his movements at all. His arm would unpredictably fly up in the air without his consent. Amazingly he taught himself to walk again, using vision to monitor the position of his limbs. But if someone turns out the lights, he is once again unable to move, or even just stand still normally (Cole, 1995). He is likely to collapse into a dangerously uncontrolled heap on the ground, unable to tell where the different parts of his body have ended up and unable to rearrange himself until the lights are turned on again.

To return to our tennis match, when the ball was served, you probably monitored the initial impact with your opponent's racquet, then moved your eyes to the place where you expected it to bounce. After the bounce, you would have followed the ball with your eyes for a fraction of a second longer to guide your own shot. You did not have to work out consciously how far to extend your racquet, as your brain's motor control systems have learned this in your hours of tennis practice.

. . . IMMENSELY COMPLEX

Your strategic planning and your ability to concentrate on limited, key aspects of your surroundings required *frontal lobe* function – brain function that is mediated by the most anterior portion of the brain. Your feelings of excitement and emotion result partly from the effects of hormones secreted into your bloodstream, in response to instructions originating in your brain (see chapter 6). Some of those hormones not only influence your heart and muscles, but also modify what is happening in your brain. Your elation at winning reflects activity in your brain's reward systems. And throughout the sequence, your memory systems (see chapter 11) were laying down records of what was happening, as well as recalling the information you had already stored about your opponent's strengths and weaknesses, and recognizing familiar tactical situations.

The immensely complex system that underlies all these experiences, actions and abilities depends on interactions between nerve cells. These highly specialized cells are called neurons. Their interactive nature is precisely what is so special about them. Each neuron's activity is controlled not just by its own internal condition, but by the myriad inputs it receives from other neurons, from sensory detection apparatuses (for example, those detectors located in the skin), or from chemical signals in the fluids that surround it. Neurons generate electric potentials. These are modified by the inputs they receive, and are used to send outputs to other neurons, glands or muscles in the body.

Different regions of the brain have their own specialized activities. So a great deal of what we know about brains comes from the study of patients with damage to specific areas of the brain, resulting in startlingly specific deficits. Throughout this chapter – or virtual tour of the nervous system – we take a look at what happens when particular components go wrong.

COMPONENTS OF THE NERVOUS SYSTEM

The nervous system has both central and peripheral components. The central part includes the brain and the spinal cord; the

central nervous system collectively, the brain and the spinal cord

peripheral part includes the nerves through which the *central nervous system* interacts with the rest of the body.

'Nerve' is a familiar word and is used in various ways in ordinary conversation. But in psychology we use it specifically to mean a cord of neuronal *axons* bundled together passing through the human body. We have probably all had the experience of hitting our 'funny bone' – the discomfort is due to the compression of the ulnar nerve. Nerves are typically sensory (afferent) – carrying information to the central nervous system from sensory neurons whose cell bodies are located in the periphery of the body – or motor (efferent) – extending out from the central nervous system to the organs and regulating muscular movement or glandular secretion.

axon the neuronal outgrowth through which the output is transmitted

The support and structure of neurons

Glial cells – more than just glue

The basic unit of the whole of the nervous system is the neuron. Neurons operate alongside various other types of cells, whose activity can be essential to normal neuronal function. Even in the brain, only about 10 per cent of the cells are neurons. Most are glial cells, which fall into several different classes, each with its own function. There are astrocytes, oligodendrocytes (in the central nervous system), microglia and ependymal cells. (The word ending *-cyte* means 'cell'.)

Glial cells were once thought of as the structural glue (that is what *glia* means in Greek) that holds the neurons in place, but their roles are proving to be far more complex. For example, astroctyes, which are the most common class, not only provide physical support to the neurons, but also help to regulate the chemical content of the fluid that surrounds the neurons. Astrocytes wrap closely round some types of *synapses* (the junctions between neurons) and help to remove glutamate (a neurotransmitter substance) from the *synaptic cleft* (the gap between neurons meeting at the synapse) via an active pumping system. If the pump fails, the system can become reversed, so that excess glutamate is released back into the synapse, which can be fatal to nearby neurons.

synapse the highly specialized area at which neurotransmission occurs between neurons; transmitter is released at the pre-synaptic axon terminal and binds to specialized receptors in the membrane of the post-synaptic target neuron

synaptic cleft the gap in the synapse between two adjacent neurons

The three components of neurons

Neurons come in many shapes – or morphologies – which give them their different functions. For example, *projection neurons* have fibres that connect them to other parts of the nervous system. Even within this category, there are many different morphologies, but all projection neurons share some basic similarities.

projection neurons neurons with connections that are not just local (i.e. they connect to other areas)

You can think of the neuron as having three essential components (see figure 3.2). The heart of the neuron is the *cell body*, where the cell's metabolic activities take place. Input from other neurons typically comes via the *dendrites*. These can be a relatively simple tuft of fine, fibre-like extensions from the cell body, or highly complex branches like the twigs and leaves of a tree.

dendrites the input system of a neuron, so called because of its branching structure

The output of the neuron is transmitted via its axon to the dendrites of other neurons, or other targets such as muscles. Axons can be very long, reaching right down the spinal cord, or so short that it is difficult to tell them apart from the dendrites. Nerve cells with such short axons are called *interneurons* rather than projection neurons, because all their connections are local.

interneurons neurons whose output projection targets are all local

Some neurons have just a single axon, although it may still make contact with a number of different target cells by branching out towards its end. Other cells have axons that are split into quite separate axon collaterals, each of which may go to an entirely different target structure.

The peripheral nervous system

Peripheral nerves are just bundles of axons. They appear as *white matter*, because most mammalian axons have a white myelin sheath around them, which helps to speed up nerve conduction. Although many neurons have cell bodies located in the central nervous system, there are clusters of cell bodies in the *peripheral nervous system* too. The simplest type of cluster is called a *ganglion* (plural, ganglia).

white matter those parts of brain consisting mostly of axons rather than cell bodies; the axons' myelin sheaths are very white

peripheral nervous system the autonomic nerves and the somatic nerves that branch out beyond the spinal cord itself (as opposed to the central nervous system)

ganglion a cluster of neuronal cell bodies, especially in the spinal cord

The sensory division of the peripheral system deals with inputs from *receptors* sensitive to pressure on your skin, for example. The motor division deals with outputs, or signals, causing muscles to contract or relax. Together,

receptor the specialized site of action at which neurotransmitters have their effects (e.g. by controlling a membrane ion channel)

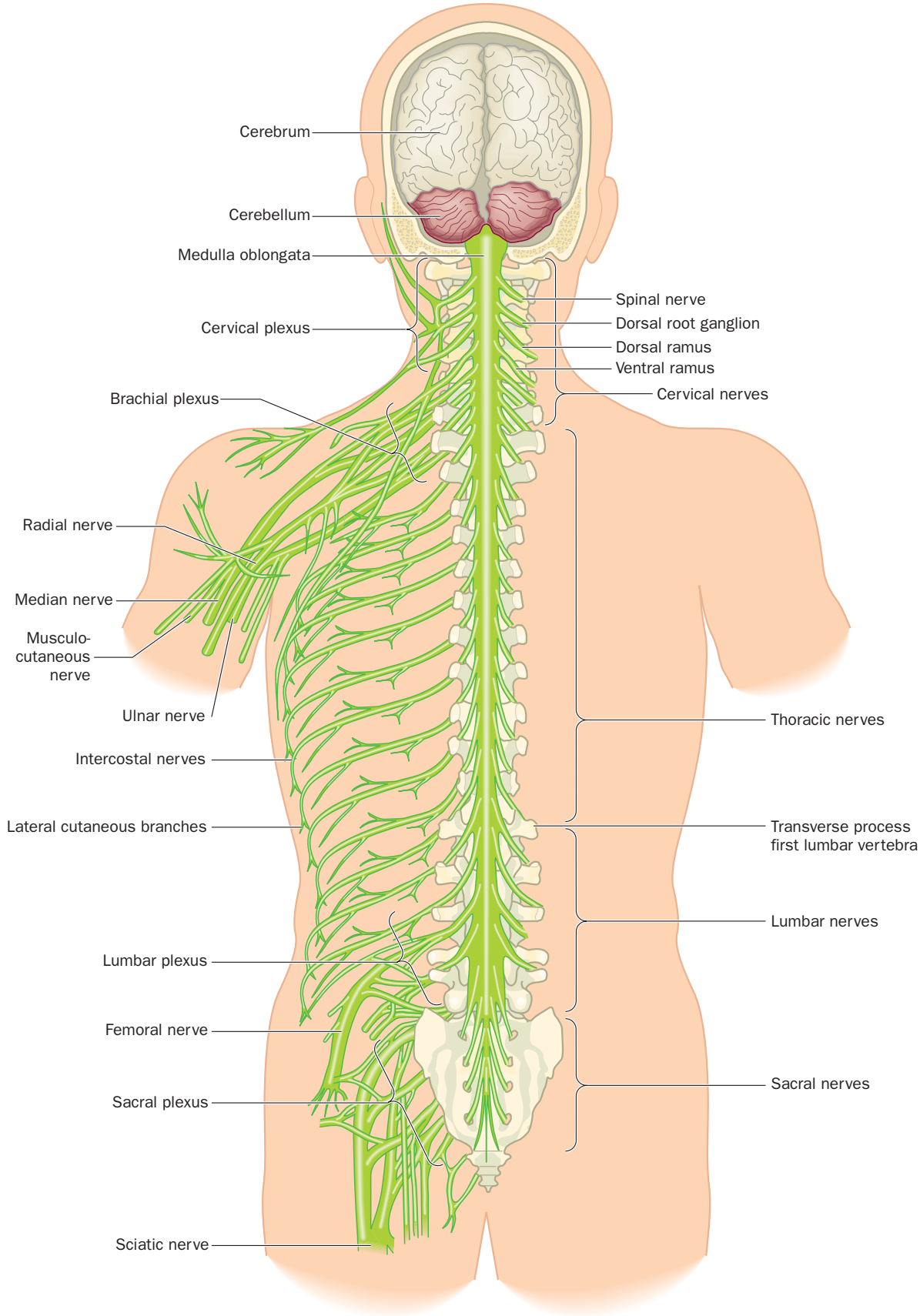

Figure 3.1

The human body and central and peripheral nervous systems. Source: http://publish.uwo.ca/~jkiernan/wholens.jpg

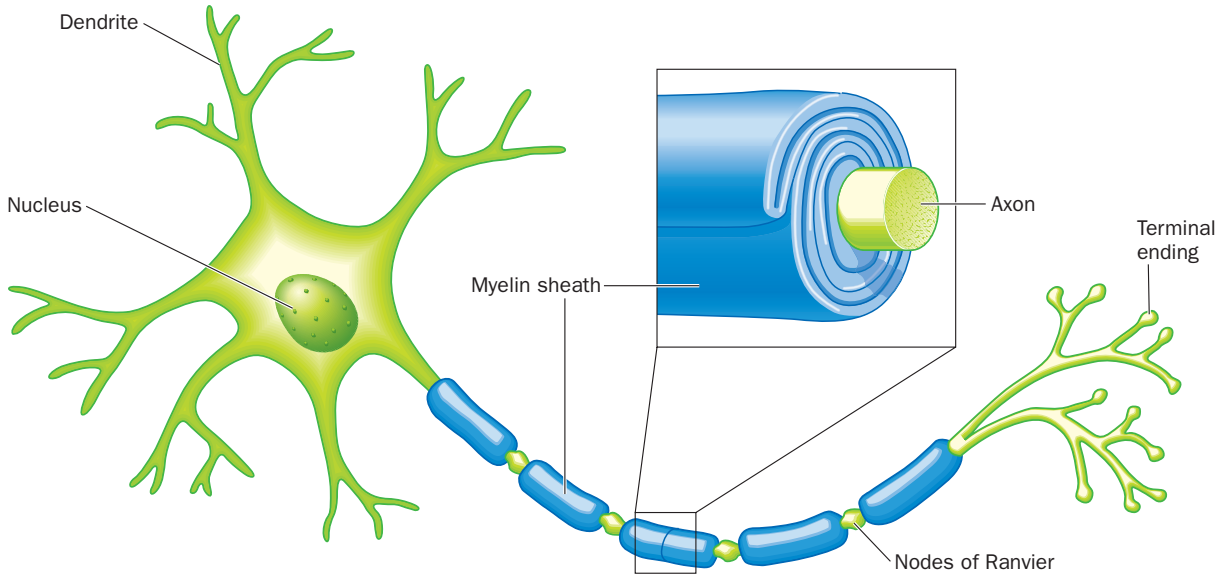

Figure 3.2

Diagram of a neuron. Source: www.msu.edu/course/asc/333/casby/myelin.jpg

somatic nervous system the part of the peripheral nervous system that includes the sensory and motor nerves, but excludes the autonomic nervous system

autonomic nervous system part of the peripheral nervous system, with sympathetic and parasympathetic components that control functions like heart rate and blood pressure

sympathetic nervous system part of the autonomic nervous system that prepares the body for emergency action

parasympathetic nervous system one of the components of the autonomic nervous system, essentially calming in its effects

these divisions make up the *somatic nervous system*, which enables you to interact with your external environment.

The *autonomic nervous system* is the manager of your internal environment. It controls activity in structures like your heart and your gut and some endocrine glands (which secrete regulatory hormones), and it governs sweating and the distribution of blood flow.

The autonomic nervous system is itself divided into the *sympathetic* and *parasympathetic nervous systems* (see figure 3.3), which have essentially opposite functions. The sympathetic system prepares you for emergency action. It redirects blood from your skin and your gut to your muscles, raises heart rate, dilates air passages to your lungs and increases sweating. These changes help you to run faster or fight more vigorously, and explain why people sometimes go white when they are really angry.

The parasympathetic system calms you down: it slows heart rate, increases blood flow to the gut to facilitate digestion, and so on. Your bodily state in part reflects the balance between these two systems.

The central nervous system

cerebellum the brain region important in skilled movement (in Latin, *cerebellum* means 'small brain')

The brain sits at the top of the spinal cord like a knotted end on a string or a walnut on a stick, with a smaller knot at the back (the *cerebellum* – Latin for 'little brain') which plays a key role in making movement smooth and efficient.

The spinal cord, made up of both axons and ganglia, gives us some essential reflexes. You can withdraw your hand from a fire before the information from your fingers has reached your brain: the spinal circuitry is complex enough to go it alone. It is also complex enough to contribute to other motor sequences, like those involved in walking.

Mammalian brains are made in two halves – or hemispheres – again like a walnut. The brain surface as viewed from the side or above is deeply wrinkled (see figure 3.4). This outer layer is the *cortex* (plural cortices), which comes from the Latin word meaning 'bark of a tree'. What this view hides are the numerous subcortical structures (see figure 3.5). These process sensory input and relay it to appropriate areas of the cortex, or process motor output before relaying it to the spinal cord and from there to the peripheral nervous system.

cortex structure made of a layer of cell bodies, especially neocortex, the multi-layered outside of the brain (*cortex* means 'bark' in Latin)

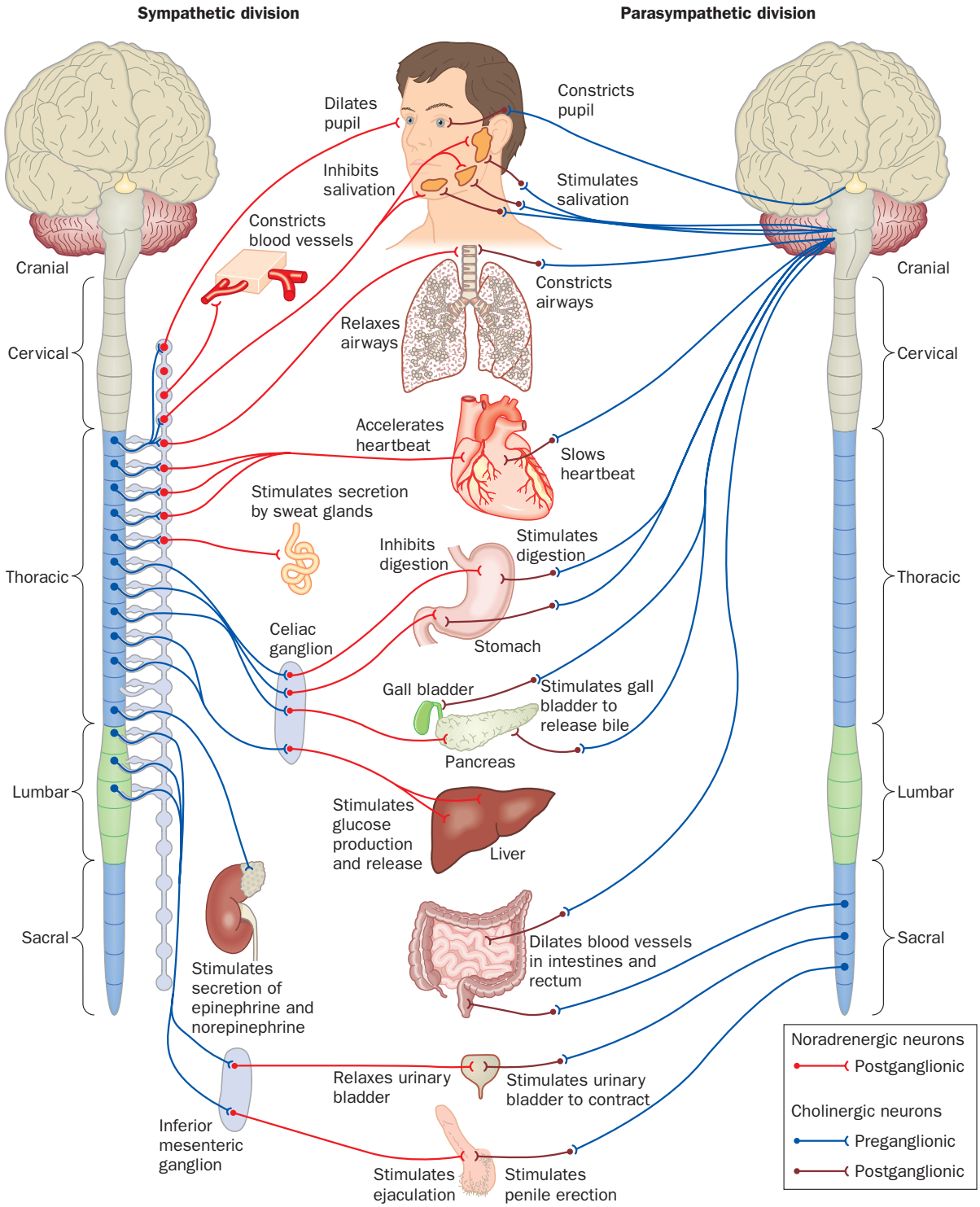

Figure 3.3

Sympathetic and parasympathetic nervous systems. Source: http://home.swipnet.se/sympatiska/anatomi.jpg

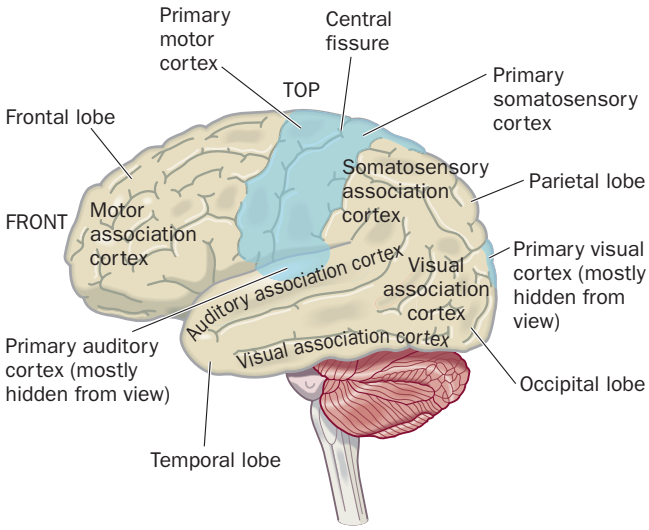

Figure 3.4

Surface view of the brain from the side. Source: Carlson (1981).

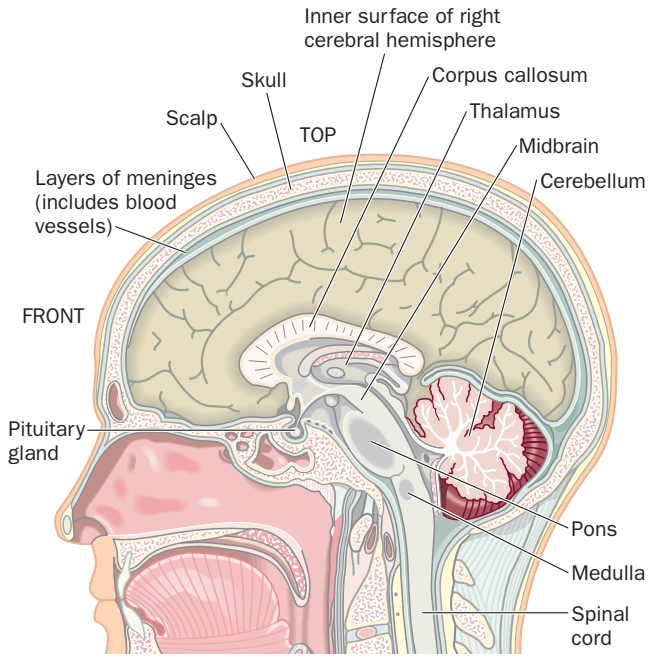

Figure 3.5

A view of the brain that has been sliced through the midline. Source: Carlson (1981).

But the brain should not be thought of as a sort of cognitive sandwich, with sensory information as the input, motor responses as the output, and cognition as the filling. Brain function is much more highly integrated than that. The motor and sensory systems are interactive, and each can directly modify activity in the other, without having to go through a cognitive intermediary.

A cluster of cell bodies in the brain might form a blob, or *nucleus* (plural, nuclei), or be organized into an extended layer like the cortex. These nuclei are often connected by clusters of axons, called fibre bundles.

nucleus a cluster of cell bodies in the brain (as opposed to a cortical layer)

If you cut into a nucleus, or into the cortex, the exposed surface does not appear white, but grey. The term *grey matter*, sometimes used colloquially, refers to areas that are composed primarily of cell bodies rather than axons.

grey matter parts of the brain that consist mostly of neuronal cell bodies rather than axons

Regions within the brain

Basic functions

The surface of the underside of the brain (looking up the string) is much smoother. If we work upwards from where the spinal cord joins the brain, at the *brain stem*, the first structure is the *medulla*. This is not just a relay station for incoming and outgoing communications; it also contains nuclei that control basic functions like breathing and heart rate.

brain stem a grouping of brain structures generally taken to include the medulla, pons, midbrain, hypothalamus and thalamus

medulla the nearest part of the brain stem to the spinal cord, where some vital control systems influencing heart rate and respiration are located

The brain stem also includes the *pons*. A variety of motor system connections are routed through the pons, and it includes some of the nuclei that seem to be important in sleep and arousal.

pons located just above the medulla, the pons has a role in arousal, autonomic function and sensory relays between the cerebrum and cerebellum

Sensory communication and motivation

Next we reach the midbrain (or *mesencephalon*). There are important early sensory relays here, particularly for the auditory system. The *substantia nigra*, which is the critical area lost in Parkinson's disease patients, is also in this region.

mesencephalon the mid-brain

substantia nigra part of the brain containing the cell bodies for the dopamine-containing projection to the striatum, which degenerates in Parkinson's disease (the Latin name means 'black substance')

The midbrain merges with the thalamus, under which is the *hypothalamus* (*hypo-* means 'under'). The thalamus contains major sensory relays to and from the cortex, but should not be thought of as

hypothalamus brain structure important in motivation and homeostatic regulation, located beneath the thalamus

Figure 3.6

An obese mouse with hypothalamic damage.

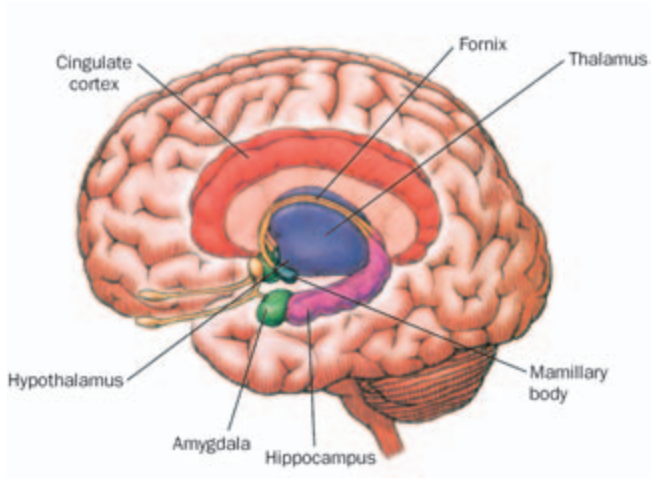

Figure 3.7

The limbic system. This system is made up of a number of subcortical structures, including the limbic lobe (consisting of the fornix, hippocampus, cingulate cortex and mamillary bodies); the thalamus; the hypothalamus; the basal ganglia; and the amygdala. Source: Gleitman, Fridlund and Reisberg (1999).

an exclusively sensory-processing structure; for example, specific nuclei of the thalamus are involved in important functional capacities such as memory.

The hypothalamus has major roles in motivation. Hypothalamic damage in one location can lead to gross over-eating (*hyperphagia*) and obesity (see figure 3.6), while damage at a different hypothalamic site can result in potentially fatal under-eating. The hypothalamus controls aspects of hormonal function: it can directly control hormone release from the *pituitary gland*, which lies just beneath the hypothalamus outside the brain itself. Pituitary hormones can themselves control hormone release from other endocrine glands, like the adrenal gland next to the kidneys, whose own hormones can in turn modify both peripheral function and brain function. So the brain and the endocrine system interact.

hyperphagia pathological overeating

pituitary gland an endocrine gland, located just outside and below the brain

Memory and emotion

Further up still, we reach some of the crucial motor system nuclei in the basal ganglia. We also encounter limbic structures, like the *hippocampus* – crucial for normal memory function – and the *amygdala*, which appears to play a key role in aspects of emotion, especially fear (see figure 3.7). Animals with amygdalar damage are less frightened than normal animals by signals of impending shock (LeDoux, 1992). Humans with amygdalar damage cannot recognize facial expressions of emotion, particularly fear and anger (Young et al., 1995), or angry or fearful tones of voice (Scott et al., 1997).

hippocampus brain structure important in memory processing, whose shape was thought to resemble a seahorse (*hippocampus* means 'seahorse' in Greek)

amygdala a group of nuclei in the brain, important in emotional processing, whose shape was thought to resemble an almond (*amygdala* means 'almond' in Latin)

Visual processing and other specialized functions

Beyond the hippocampus, which is the simplest example of a cortical layered structure we come to, there are various transitional cortical regions with increasingly complex layered structures, before we reach the neocortex, the most complex of them all. The neocortex has specialized motor areas, sensory processing areas and more general purpose association areas. Some of these are shown in figure 3.8.

Within each area there may be further, more specialized, modules. In the visual system, for example, separate modules for colour, form and motion speed up visual processing by handling all these attributes in parallel. This high level of specialization means that damage restricted to particular cortical regions can have very precise effects. For example, people with a condition called *prosopagnosia* are unable to recognize particular people's faces, despite other visual abilities remaining quite normal.

prosopagnosia a neurological condition in which the capacity to recognize individuals by their faces is lost, although other visual discriminations are unimpaired

High-level processing – the cortex

Sometimes people think of the cortex as the most important part of the brain because it evolved later than other parts, and because of its complexity and its roles in high-level processing and

Research close-up 1

Prosopagnosia

The research issue

The patient in this study has prosopagnosia. He has probably suffered brain damage in the posterior right hemisphere (McCarthy & Warrington, 1990). His visual acuity is good, but he cannot recognize the faces even of very close friends. He may have learned to recognize friends by the way they walk, and he can easily identify them by their voices, but he cannot identify them from their face. Yet, at the same time, his skin conductance response (the sort of response that is used in lie detectors) does discriminate between familiar and unfamiliar faces (De Haan et al., 1992).

Design and procedure

The patient is tested on a visual task. He looks at pictures of a variety of different objects, and then a picture of a close friend followed by a picture of a stranger. In each case, he is asked to identify the object or person. The neuropsychologist who is testing him studies traces on a machine which records skin conductance.

Results and implications

The patient recognizes the objects without difficulty, easily spotting very small details in the pictures. But when presented with a picture of a close friend and asked to identify them, he does not know who it is, any more than he recognizes the total stranger.

And yet the neuropsychologist notes a clear difference in the galvanic skin response to familiar and unfamiliar faces. This suggests that the patient implicitly recognizes his friends, even though he cannot explicitly recognize them.

De Haan, E.H., Bauer, R.M., & Greve, K.W., 1992, 'Behavioural and physiological evidence for covert face recognition in a prosopagnosic patient', *Cortex*, 28, 77–95.

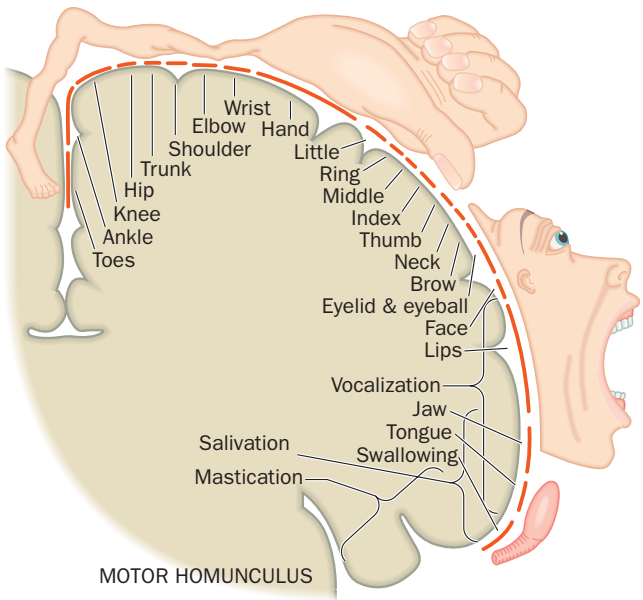

Figure 3.8

The motor homunculus. Source: Gleitman, Fridlund and Reisberg (1999).

Pioneer

John Hughlings Jackson (1835–1911) was a co-founder of the famous journal *Brain*. He is sometimes referred to as the father of British neurology. His wife suffered from epilepsy, and perhaps his most important inferences about brain function derived from his observations of the consistency of the patterns of epileptic seizures.

Jackson saw that in at least some patients the first signs of an impending seizure were twitchings of particular muscles. In the case of his wife, the seizures would start at one of her hands, then extend to include the arm, then the shoulder and then her face, eventually including her leg (all on the same side) after which the seizure would end. Jackson deduced that this kind of pattern could occur if the epileptic seizure was always initiated at the same point in the brain, from which it spread to related areas, assuming that each motor region of the brain had its own specialized function. He further suggested that the seizures were caused by electrical discharges in the brain, and that the condition might be treated by surgically removing the epileptic focus. In doing this he played an important role in the advance of neurosurgery.

Everyday Psychology

Studying and manipulating the living brain

It is one thing to study structures in the brain using post mortem techniques on either laboratory animals or humans, but is quite another thing to study structure and function in the living brain, or to manipulate the living brain. Techniques that allow this have been developed, and used more widely, only quite recently. There are several such techniques, each with its own advantages and disadvantages (see Owen, Epstein & Johnsrude, 2001).

The first technique that reliably and non-invasively showed up brain tissues in a living brain was the CAT (computerized axial tomography) scan. This uses X-rays, but complex computer programs allow a much clearer image to be constructed. More recently, two much more sophisticated methods have emerged – magnetic resonance imaging (MRI) and positron emission tomography (PET).

MRI relies on signals derived from putting the head into intense magnetic fields. Structural MRI gives a picture with a resolution in the cubic millimetre range.

Functional MRI (fMRI) – as you might expect – measures brain function. When a particular part of the brain increases its activity, the blood flow to that area increases as well. Changes in blood flow, and blood oxygen levels, change the fMRI signal. So we can now identify the different areas of brain that are active when we are thinking in different ways.

PET scanning can also detect blood flow changes, but with less precision than fMRI. Its advantage is that it can also show which areas of brain take up particular drugs or chemicals, so giving a map of specific neurochemical systems.

These functional imaging methods have high spatial resolution, the best being capable of remarkably finely detailed images showing structures as small as a millimeter across. But they do not have particularly good temporal resolution. They cannot show the brain's changing patterns of activity from second to second, let alone from millisecond to millisecond.

Neuronal activity occurs over a matter of milliseconds, but a single PET scan may take two minutes to complete. And fMRI has similar problems, with the local blood flow changes on which it relies taking some 7–10 seconds to reach their maximum.

The two non-invasive procedures with the best temporal resolution are electroencephalography (EEG), which records tiny electrical currents on the scalp resulting from the activities of the neurons within the brain (Mangun, 1995), and MEG (magnetoencephalography), which detects the tiny magnetic fields generated by neuronal activity. These give good temporal resolution but do not have the spatial resolution of fMRI.

Some laboratories and hospitals are now trying to get the best of both worlds by combining two techniques to follow information processing as it moves from structure to structure in the human brain.

Moving from the study of structure and function to the possibility of *manipulating* the brain, how can we study the ways in which changes in brain activity affect behaviour and cognition? The classic lesion method causes damage in the structure

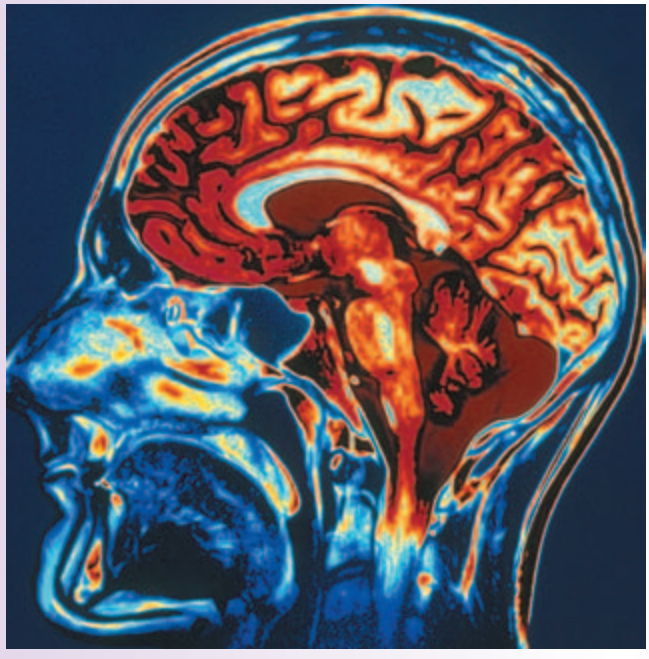

Figure 3.9

Structural MRI of a slice through the middle of the whole head.

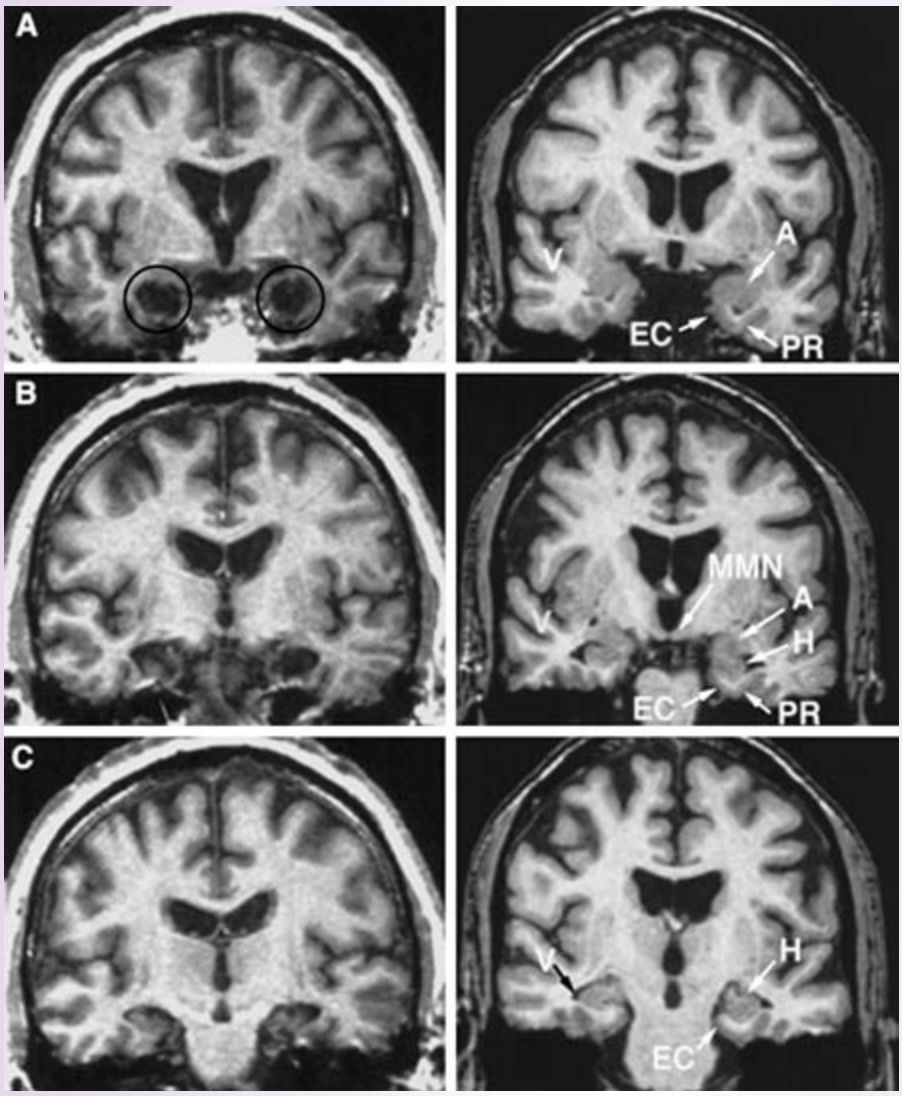

Figure 3.10

Structural MRI of patient H.M.

A = amygdala; H = hippocampus; EC = entorhinal cortex (a key input area for hippocampus); PR = perirhinal cortex. All these areas have been, at least partially, damaged in H.M.

of interest. Lesions can be made in a variety of ways: the most sophisticated cytotoxic lesions use microinjections of tiny volumes of chemicals (perhaps one ten thousandth of a millilitre) that kill particular types of neurons while leaving others unaffected. The effects of these lesions can be highly selective: rats with hippocampal lesions show clear deficits in spatial memory, while remembering individual objects perfectly well (Rawlins et al., 1993). Since single unit recording experiments have shown that some neurons in the hippocampus are active whenever the rat is in a particular place, it has been suggested that the role of this structure is to form and store maps of our spatial surroundings (O'Keefe & Nadel, 1978). Such conclusions are always more convincing when they are derived from different lines of converging evidence, as in the present example. Clinical studies of patients with hippocampal damage also show memory deficits, but they extend beyond just spatial memory. It is not yet clear whether this is because the brain damage in the patients is less selective than in the rats, or because hippocampal function is different in humans and in rats, or because it is difficult to find equivalent memory tests for humans and for rats.

Manipulative studies can also simply inactivate a target structure, rather than destroying it. This can be done by temporarily cooling a region, or by injecting drugs, or by passing small electrical currents into an area, so as to take over control of the activity of the neurons there. A recent procedure for temporary inactivation in humans uses intense magnetic fields, rather than electrical currents. These magnetic fields can pass through the scalp and skull, to control the activity of the neurons beneath. This transcranial magnetic stimulation (TMS) can be used to interrupt the normal activity of a target structure just below the skull to reveal how that structure contributes to normal information processing (Walsh & Cowey, 2000). If TMS was used to activate your visual area, then you would see 'phosphenes': little glowing patches of light. If the

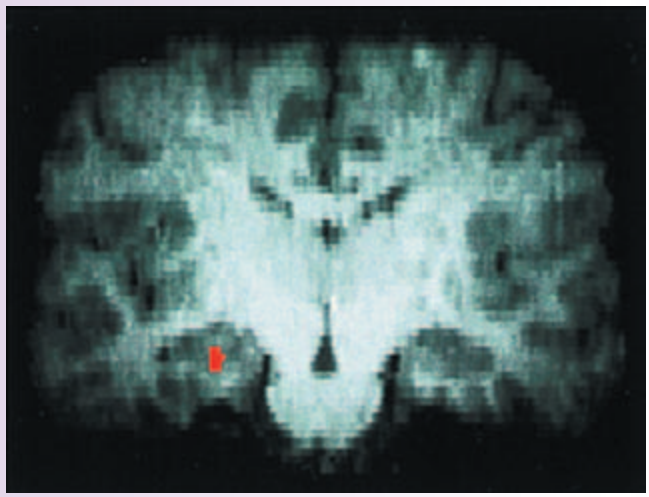

Figure 3.11

Hippocampal activation in learning. Source: Ploghaus et al. (2000).

area underlying motion perception is activated, then these phosphenes are typically moving. Although it is not possible selectively to activate deeper structures in the brain using this method, so its application is inevitably restricted, this advance has made a classic manipulative approach available for the study of brain function in healthy humans.

Owen, A.M., Epstein, R., & Johnsrude, I.S., 2001, 'fMRI: Applications in cognitive neuroscience' in P. Jezzard, P.M. Matthews & S.M. Smith (eds), *Functional MRI: An Introduction to Methods*, New York: Oxford University Press.

human faculties. But a good deal depends on what you mean by 'important'.

If you ask neuroscientists whether they would prefer to lose a cubic centimetre of cortex or a cubic centimetre of some subcortical region, they would probably choose to give up some cortex. This is because damage to the subcortex tends to be more profoundly disabling. For example, the loss of neurons in the small subcortical region called the substantia nigra results in Parkinson's disease, which eventually causes almost complete motor disability.

The functions of the different areas of the cortex have, until recently, been determined either by experimental studies of monkeys (which have a much more highly developed neocortex than animals like rats) or by neuropsychological studies of the effects of brain damage in clinical patients. The development of *functional neuro-imaging* methods has given us a new way to study the roles of different brain areas in cognition in healthy humans by allowing us to observe which brain regions are active.

functional neuro-imaging methods for observing which brain regions are active

THE STRUCTURE OF THE HUMAN BRAIN

Why did the cortex evolve later?

Imagine an animal with a simple brain made up of a big blob of neurons. How could such a brain develop, allowing space for extra neurons? It cannot just grow larger. The bigger the blob, the harder it is to sort out all the input and output axons for the cells in the middle. Somehow, all those connections have to find their way through gaps between all the new neurons on the outside of the blob.

The alternative solution is to arrange cell bodies in layers. The most complicated structure, the *neocortex*, is actually made up of six layers of cells (see figure 3.12). This allows all the inputs and outputs to run neatly along in a layer of their own. Fibres divert upwards to contact other cell bodies as needed, facilitated by the cortex being organized into columns.

Further development of the brain becomes much easier with this arrangement. You can simply add more columns, or 'bolt on' more modules, rather like plugging in a new component on your computer. You would not need to reorganize any pre-existing connections. You can also place cells that need to interact alongside each other, forming cortical modules that minimize inter-cell communication distances. This speeds up communications and saves space. Much the same arrangement is used for laying out printed circuit boards.

The wrinkles in the brain, which make it look like an outsized walnut, are all folds in the cortex. A valley, where the cortex is folded inwards, is called a *sulcus*, while a ridge is called a *gyrus*. This development enables the maximum

sulcus the inward folds in the wrinkled cortical surface

gyrus outgoing fold in the wrinkled cortical surface

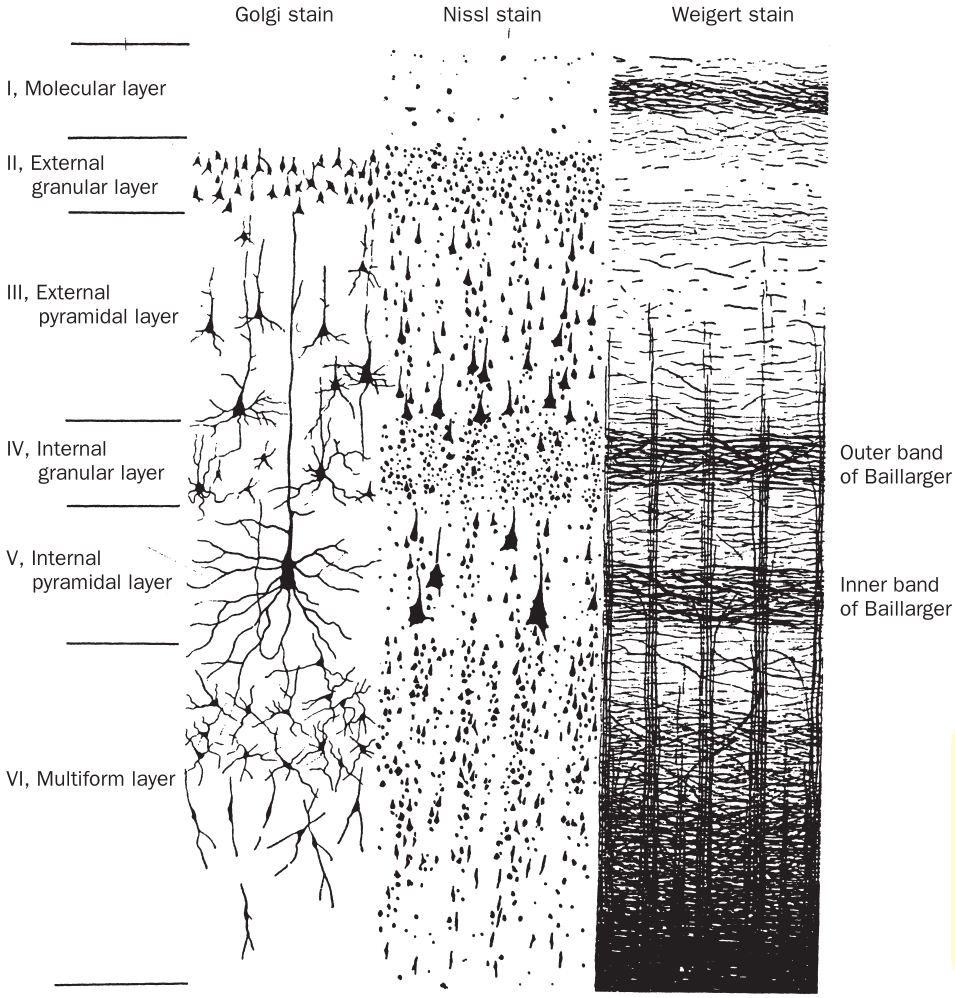

Figure 3.12

The six layers of the neocortex, as revealed by three different tissue stains. Golgi stains (left column) can show the whole neuron, from dendrites to axons; Nissl stains (middle column) show the cell bodies of the neurons; Weigert stains (right column) stain the myelin sheath that surrounds axons. Source: Nolte (1993).

cortical area to fit into a volume with minimal outside skull dimensions, just like crumpling up a newspaper to fit it into a small wastepaper basket. The volume and surface area of the newspaper are actually unchanged, but it fits into a neater space.

Is size everything?

The neurons that make up the human brain are essentially the same as those making up the brains of other animals. So how do we explain our extraordinary capacity for complex, abstract thought?

If you were to flatten out a human cortex, it would cover about four pages of A4 paper, a chimpanzee's would cover a single sheet, and a rat's would cover little more than a postage stamp. So we have big brains . . . but size is not everything. In mammals, brain size correlates with body size: bigger animals have bigger brains. But this does not make large animals more intelligent than smaller ones. Adaptable, omnivorous animals like rats are a favourite experimental subject for psychologists partly because they so readily learn new behaviours. Their opportunist lifestyle may well lead to greater behavioural flexibility, compared to larger but more specialized animals like the strictly herbivorous rabbit, whose food keeps still and does not need to be outwitted.

Nonetheless, there is something special about human brain size. Our brains are disproportionately large for our body weight, compared to our primate relatives (Jerison, 1985). This overdevelopment is especially marked in the most general purpose regions of the cortex, the association areas (though the cerebellum is disproportionately enlarged, too). It is possible that at least some of this enlargement provides extra processing facilities that support the human capacity for abstract thought.

Hemispheric differences

The two halves of our brains have different cognitive processing specialities. In most humans, language processing takes place in the left hemisphere. Damage on this side of the brain (see figure 3.13) can leave people unable to speak (aphasic), though quite capable of understanding spoken language. Paul Broca (1861) was the first to describe a condition known as Broca's *aphasia* and to identify the key area of damage responsible for it.

aphasia loss of speech ability

Just a few years later, Wernicke (1874) reported that damage at a different point of the language system in the left hemisphere

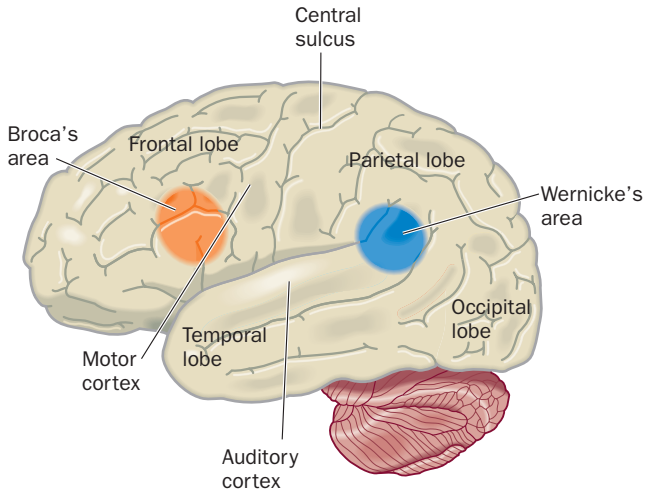

Figure 3.13

Broca's area and Wernicke's area.
Source: http://uhaweb.hartford.edu/lboudreau/wernipic.gif

leaves people with a different kind of speech problem, Wernicke's aphasia. These patients speak perfectly fluently, but what they say makes no sense, and they do not appear to understand what is said to them.

hemi-neglect a neuropsychological condition leading the patient to ignore one side of the world, including one side of their own body

Other neuropsychological conditions are typically associated with right rather than left hemisphere damage. For example, severe *hemi-neglect* often results from damage to the right parietal lobe. Patients with hemi-neglect may ignore the entire left half of the world, so that they eat only the food from the right side of their plates, shave only the right side of their face, and, when dressing, pull their trousers on to their right leg only. Some patients will even try to throw their left leg out of bed, since they do not consider it as being their own!

Neglect of the right-hand side of the world, resulting from left hemisphere damage, is much rarer. The underlying reasons for this are not yet certain, but it suggests that the right hemisphere might be able to support bilateral spatial attentional processes, whereas the left hemisphere (perhaps because of its own specialized allocation to language processing) can only support unilateral spatial attention. This would mean that when the left hemisphere is damaged, the right takes over processes that would normally depend on the left hemisphere. But when the right hemisphere is damaged, the left presumably continues to support its usual processing of events in the right half of the world, but cannot take over processing of events on the left.

corpus callosum massive fibre system of axons connecting the two hemispheres

split brain occurs when the corpus callosum has been cut (e.g. in order to prevent the spread of epileptic seizures)

The two hemispheres are joined together below the surface by the *corpus callosum*, a massive fibre pathway. *Split brain* patients have had their corpus callosum cut, for example to stop the spread of epileptic seizures from one side of the brain to the other. This disconnection can have startling consequences.

If a split brain patient sees a word briefly flashed up so that it falls on the part of the eye that is connected to the right hemisphere, then the patient cannot read out the word. This is because

Research close-up 2

Hemi-neglect

The research issue

When a patient with hemi-neglect tries to fill in the numbers on a clock face, he writes the numbers in the correct order but places them all on the right hand side of the circle (see figure 3.14).

Similarly, when presented with a paper that has a large number of short lines on it and asked to cross off each of the lines, he crosses off all the lines on the right half of the sheet, leaving the lines on the left side untouched. The subject confirms that the task is finished. Is this because he simply cannot see anything on the left?

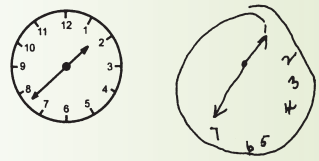

Figure 3.14

Typical response of a hemi-neglect patient attempting to draw a clock face. Source: Adapted from Sterling (2002).

Design and procedure

A neuropsychologist asks the patient to imagine that he is standing in a town square that he knows well, facing the main building of the square. (This finding was originally reported for the cathedral square, the Piazza del Duomo in Milan.) She asks him to tell her what he would be able to see from that viewpoint. Later, she asks him to imagine he is standing with his back to the main building, and, again, to tell her what he would be able to see.

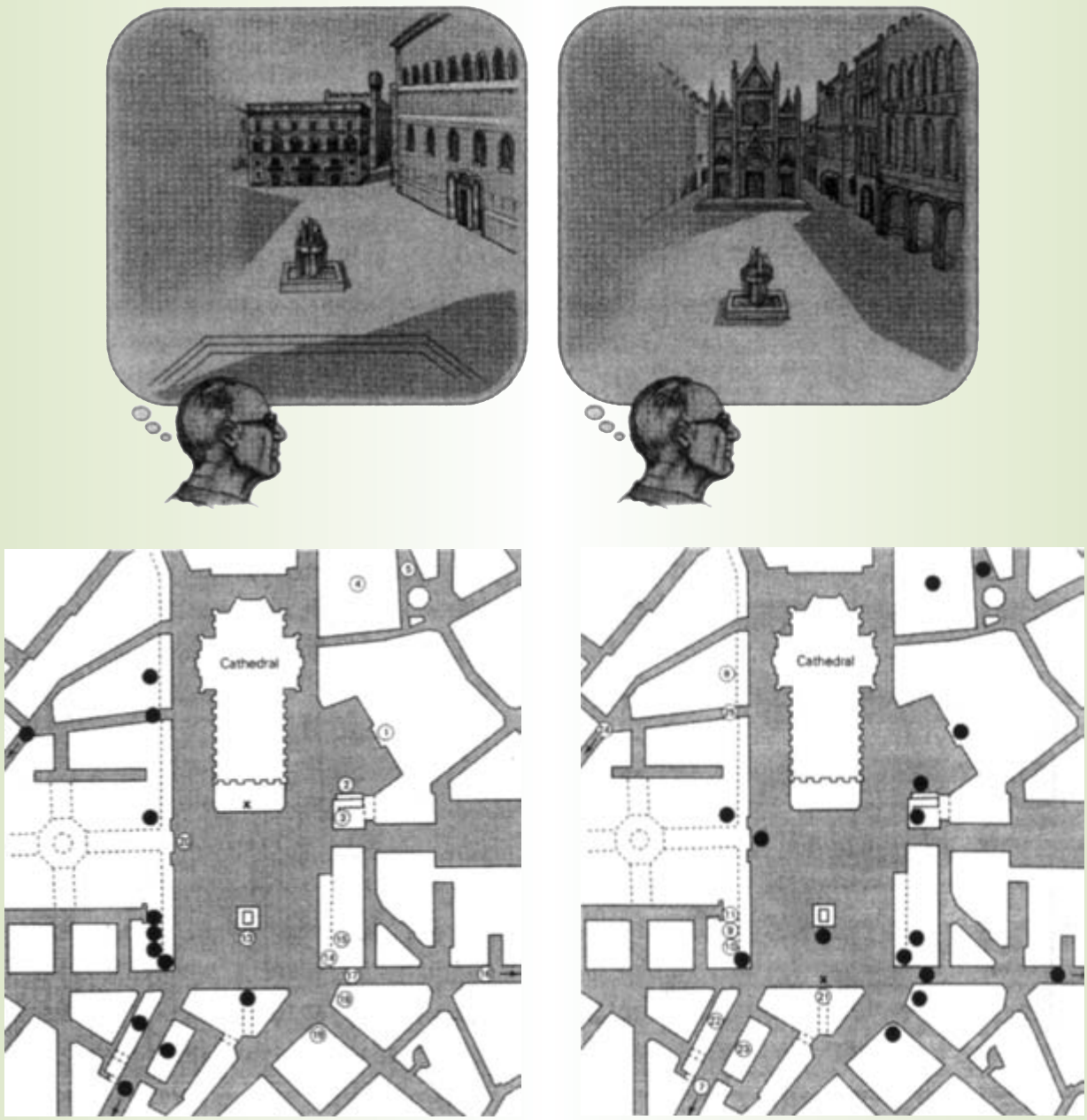

Figure 3.15

An illustration of the effects of hemi-neglect on spatial attention. Source: Bisiach and Luzzatti (1978).

Results and implications

The patient describes a number of buildings and landmarks, all on the right of his imagined viewpoint. Eventually he cannot think of any more.

Imagining his back turned to the main building, he again describes the buildings and landmarks on his right, but now he is naming the buildings that he omitted in the first part of the test, and this time omitting the buildings that he had named before (Bisiach & Lazzatti, 1978).

It is therefore clear that he knew about the buildings on both sides of the square, even though from each imagined viewpoint he only reported what lay in half of the physical space. So this kind of hemispatial neglect cannot simply be a visual defect.

Bisiach, E., & Luzzatti, C., 1978, 'Unilateral neglect of representational space', *Cortex*, 14, 129–33.

the visual information has not reached the left hemisphere, and so cannot be processed properly as language. But it is fascinating to see that if the word is the name of an object, the patient can use their left hand (which is connected to the right hemisphere) to select that object from among a variety of others. The patient may even be able to demonstrate how the object is used, but until they touch it with their right hand, they will remain unable to say what it is called (see Sperry, 1974).

NEURAL INTERACTION

What do neurons look like?

Until the nineteenth century, we really had no idea what neurons looked like. Early workers were only able to stain the neurons' cell bodies: until the axons and dendrites could be seen, neurons looked not so very different from liver or muscle cells.

This changed in 1862, when a cell staining method was developed (largely by accident) that enabled the structure of a single neuron to be seen clearly through a microscope. Camillo Golgi's staining method was a bit hit and miss: sometimes no cells at all might be stained; at other times all the cells in a particular section of brain might be so densely stained that the whole section looked black and individual cells could not be distinguished at all. But sometimes just a few cells would be darkly stained, and their *morphology* could then be established. It soon became clear that there are many different kinds of neurons.

morphology the shape or form of a neuron

The great brain anatomists like Ramón y Cajal ([1892] 1968) and Lorente de Nó (1934) used these kinds of techniques to examine, describe and draw the structures of the brain at a level of detail that would previously have been inconceivable. Nowadays you can inject a dye directly into a cell, so that it alone is filled; you can then visualize the neuron in its entirety. Where such studies are combined with functional studies recording the activity of that cell and the other neurons most intimately connected with it, the relationship between form and function can be established with great rigour.

We also discover where each neuron's incoming connections originate, and where their own outputs go, by injecting anatomical *tracers*. These are substances that are absorbed by cell bodies, or by axon terminals, and then transported through the cell. This, coupled with electrophysiological studies in which we stimulate activity in one area and determine its effects in others, enables us to identify how neurons interconnect and interact. Neuronal interaction is what the brain is all about.

tracers substances used in neuroanatomy that are taken up by neurons (e.g. at the axon terminals) and transported along them (e.g. to the cell body), allowing the neurons' connections to be identified

Pioneer

Santiago Ramón y Cajal (1852–1934) was born in the Spanish village of Petilla. His father, at that time the village surgeon but subsequently the Professor of Dissection at the University of Zaragoza, found him a difficult teenager, and apprenticed him first to a shoemaker and later to a barber. The young Ramón y Cajal himself wished to become an artist, but eventually went to medical school, graduating in 1873. He entered academic life in 1875, but his great life's work began when, in 1887, he was shown brain sections stained by Camillo Golgi's silver method. Ramón y Cajal was captivated. Thereafter he studied and drew the nervous system in great detail. His observations led him to propose that the nervous system is made up of vast numbers of separate nerve cells: the 'neuron doctrine'. He shared the Nobel Prize with Golgi in 1906.

Electrical activity

Neurons are integrators. They can have a vast number of different inputs, but what they produce is a single output signal, which they transmit to their own targets. How is this done?

The key lies in the electrical potentials they generate. There is a small voltage difference between the inside and the outside of the neuron. The inputs are tiny amounts of chemical *neurotransmitters*. The target cell has specialized receptor sites, which respond to particular neurotransmitters by subtly changing the cell's electrical potential for a short time. If enough signals come in together, then the total change can become big enough for the target cell to 'fire' – or to transmit an output signal along its axon to modify the activity in its own target cells.

neurotransmitters chemical messengers used for communication between neurons, released from specialized sites at the axon terminal and affecting specialized receptor sites across the synaptic cleft

So our first task is to find out how neurons produce electric potentials. Then we can see how these potentials change in response to inputs. Once we understand that, we can look at the way this same electrical potential system produces a fast and reliable output from the cell.

The resting potential

The outside of a neuron is made of a highly specialized membrane. Within the neuron, much of the chemical machinery is made up of large, negatively charged protein molecules, which are too big to leak out through the membrane. Outside the membrane, in the gaps between neurons, lies the extra-cellular space, which contains fluid with electrically charged ions dissolved in it.

What does this mean? Well, common salt, for example, also called sodium chloride, is a compound of two elements – sodium

and chlorine (giving a chemical formula of NaCl). When it is dissolved in water, it dissociates into a positively charged sodium ion (Na^+) and a negatively charged chloride ion (Cl^-). Potassium chloride also dissociates into its ionic constituents – potassium (K^+) and Cl^-.

Mobile, positive ions are electrically attracted to the negatively charged proteins held within the neurons, but although the neuronal membrane lets potassium ions through, it is relatively impermeable to sodium ions. So potassium ions are pulled into the cell and held there by the electrical charge on the intracellular proteins. As potassium levels within the cell rise above those outside it, this inward flow of charged ions reduces, because there is now a concentration gradient tending to pull potassium *out* of the neuron.

Equilibrium is reached (with the inside of the neuron more negative than the outside) when the opposing pulls of the concentration gradient and of the electrical gradient balance each other. There is also an active pumping of ions across the neuronal membrane: for example, some sodium leaks into the neuron and is actively pumped out. These processes give neurons their characteristic electrical charge – the *resting potential* (see figure 3.16).

resting potential the potential difference across the neuron's membrane when it is neither activated nor inhibited (roughly 70 millivolts)

Some ions have their own channels that let them pass through the cell membrane. These can be opened or closed, selectively altering membrane permeability. Some pumps move ions inwards and others move them outwards. Neurotransmitters use these different *ion channels* to manipulate the cell's membrane potential – a complicated balancing act.

ion channel specialized opening in the neuron's outer membrane, which lets electrically charged ions flow through, so changing neuronal potentials

These activities consume a lot of energy. Your brain is only 2.5 per cent of your body weight, but uses some 20 per cent of your resting energy. This increases when the nervous system is actively processing signals. When a region increases its energy consumption, its blood supply needs to increase as well. This can be detected by functional neuro-imaging systems to help us identify which parts of the brain are activated during particular kinds of mental processing.

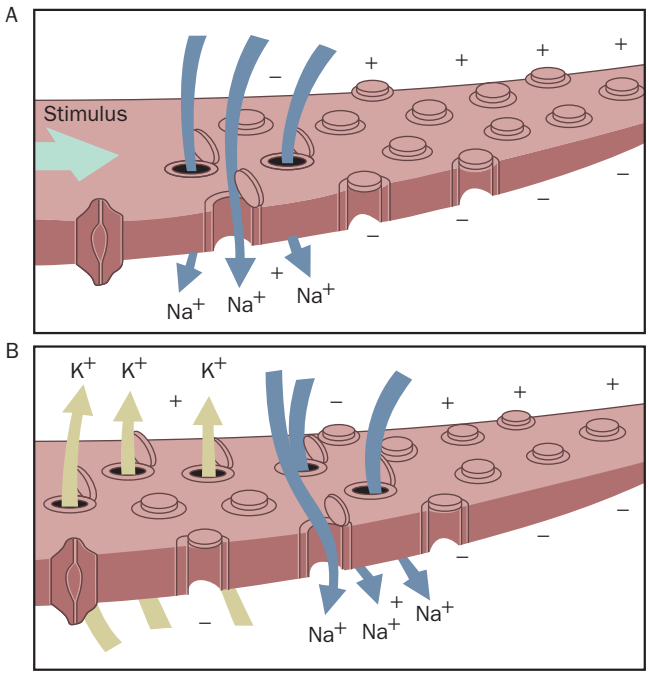

Figure 3.16

Ion flows across the neural membranes. The white area in the upper part of (A) and (B) is extracellular fluid, and the white in the lower part of each diagram is the cell interior.
Source: Gleitman, Fridlund and Reisberg (1999).

The action potential

When a neuron is activated by its input, the potential across the cell membrane changes. This is because when a neurotransmitter binds to its receptor, it can open channels that let particular ions go through the membrane.

Say we open a sodium channel. Positive Na^+ ions will flow through the membrane into the cell for two reasons:

- The resting potential keeps the inside of the cell negatively charged, so positive ions are attracted in.
- There is an attracting concentration gradient for sodium, because there are many more Na^+ ions outside the cell than inside it.

The resulting influx of positive ions makes the inside of the cell less negative, reducing the resting potential. This is called depolarizing the cell.

If the cell is depolarized from its resting potential of around minus 70 millivolts to its *threshold potential* of about minus 55 millivolts, an abrupt change is seen. This is called an *action potential* (see figure 3.17). It has been studied with great precision by controlling the membrane potential directly using electrical stimulation. The potential across the cell membrane suddenly flips radically from the normal state, in which the inside is negative relative to the outside, to a transient state in which, for a millisecond or so, the inside becomes positive relative to the outside.

threshold potential the voltage at which depolarization of a cell leads to generation of an action potential

action potential the all-or-nothing electrical output of a neuron

The normal direction of polarization is rapidly restored once the stimulation stops. In fact, the neuron becomes *hyperpolarized* for a few milliseconds, which means that its inside becomes even more negatively charged than

hyperpolarization increasing neuronal membrane potential to more than its usual resting potential (making it harder to induce the cell to produce an action potential)

Pioneer

Lord Adrian (1889–1977) was a physiologist who initiated single neuron recording methods. He was the Nobel Prize winner in 1932, shared with Sir Charles Sherrington. Adrian pioneered the use of then state-of-the-art electronics to amplify the signals he recorded and display them on an oscilloscope. This was a crucial technological advance that allowed him to monitor activity in single nerve fibres. One of his key findings was that intensity of sensation was related to the frequency of the all-or-nothing action potentials of constant size – so-called 'frequency coding', as opposed to 'intensity coding'.

Adrian also studied the sensory homunculus in different species. He reported that in humans and monkeys both the face and the hand have large areas of the sensory cortex devoted to them, whereas in pigs, the greater part of sensory cortex dealing with touch is allocated to the snout. So the richness of sensory representation can be related to the typical needs and activities of the species concerned. Subsequently, Adrian moved from work on the peripheral nervous system to study the electrical activity of the brain itself, opening up new fields of investigation in the study of epilepsy and other types of brain injury

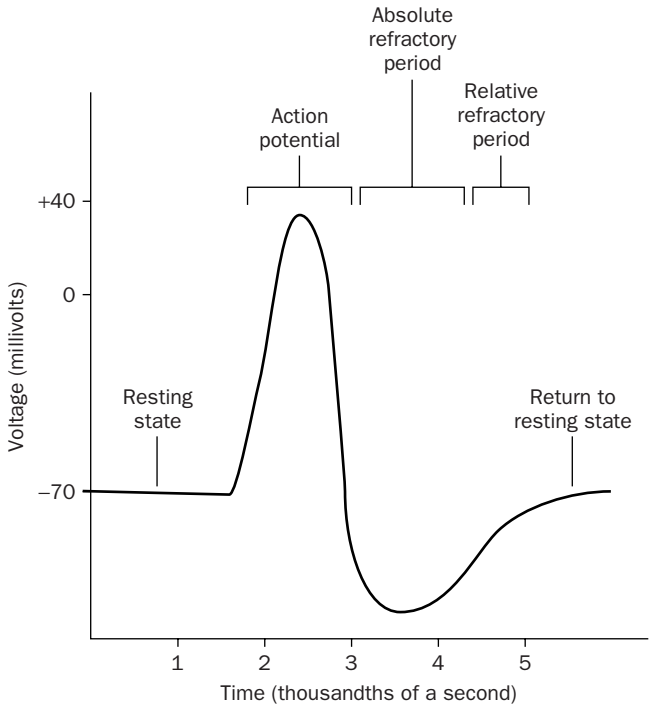

Figure 3.17

The action potential. Source: http://psychology.uww.edu/305ww/neuron/action%20potential.jpg

refractory period a brief period following the generation of an action potential, during which a neuron is hard to re-excite

usual. During this time – the *refractory period* – the hyperpolarized neuron is less readily able to respond to further input. So a single, relatively small, stimulation pulse can produce a radical change in the neuron's electrical state.

How does this happen? The crucial mechanism lies in the way that the different ion channels are controlled. While some are controlled by neurotransmitter receptors, others respond to the electrical potential across the cell membrane. When the cell has been depolarized all the way to the threshold potential, additional sodium channels suddenly open. More sodium ions pour into the cell through these channels, because there is still both a concentration gradient and an electrical gradient to attract them. This drives the depolarization further downwards, leading to further opening of sodium channels. So depolarization proceeds very rapidly.

If we are to restore the original resting potential, ready for the next action potential, we have to reverse this current flow as quickly as possible. This is achieved by an outflow of positively charged potassium ions from the cell, combined with a process that deactivates sodium flow. Although the full picture is much more complicated than this, and involves many more different ions and channel types, an understanding of the sodium and potassium currents conveys its essence.

Once an action potential has been generated, it will rapidly travel along the cell's axon, changing membrane permeability as it goes. This active, self-regenerating method of spreading makes the classical action potential a very effective and reliable way to transmit information. If the neurons' signals were conducted passively, in the way that heat is conducted along a wire, the signals would get weaker and weaker the further they had to go. If you use a long enough poker you can safely stir the red hot embers of a fire without your hand getting burnt. The hotter the fire, the longer the poker you need to use. But if heat were propagated actively, like an action potential, you would have to wear asbestos gloves, however long the poker.

The action potential is the same size whether the depolarizing stimulus is only just strong enough to reach threshold or depolarizes well beyond threshold. This all-or-nothing property often leads people to liken action potentials to the digital signals in a computer. But this vastly underestimates the complexity of the nervous system and the potential subtlety of its responses. As we shall see, the propagation of the action potential may be all or nothing, but its effect can be very subtly graded.

Neurotransmission

We know how electrical signals are generated – but how do they activate neuronal targets? If we compare neurons to electrical circuits, then the answer is clear. Each wire in a circuit connects to the next wire in a circuit and current flows uninterrupted through all of them.

But very few neurons are connected together in this way. Instead, communication between neurons usually relies on neurochemical transmission.

The limitations of gap junctions

Where there are points of structural continuity between neurons, current can flow from one neuron to the next, just as it would from one wire to another that has been soldered to it. The electrical potential in one neuron then directly affects the electrical potential of the next, depolarizing the target neuron as though it were no more than an extension of the neuron in which the signal originated.

gap junction extremely close contact between two neurons allowing direct flow of electrical current between them

Such connections – or *gap junctions* – do have some advantages. The signal is passed on at the maximum possible speed, and activity amongst groups of neurons is more easily synchronized, which can have its own advantages. But if all the neurons in our nervous system were interconnected in this way, whatever happened to one neuron would affect all the others and would at the same time be affected by all the others. This would radically reduce the system's capacity for information processing. If all the neurons end up doing exactly the same thing, you might as well have only one neuron and be done with it.

So to get the most out of each neuron, you want them to be able to operate to some extent independently. In particular, you may not want the activity of the target neurons to determine the activity of their own inputs. This problem of how to keep neurons independent and ensure that information flows in the right direction is solved by chemical neurotransmission.

The advantages of chemical neurotransmission

Chemical neurotransmission takes place at the synapse, across a very narrow gap called the synaptic cleft, where the axon of the input neuron most closely approaches its target (see figure 3.18). Both the axon terminal region and the post-synaptic membrane (i.e. the membrane on the target cell's side of the synaptic cleft) are highly specialized. The axon's terminal region contains small *vesicles* – packages filled with neurotransmitter. The neurotransmitter is released from the axon terminal, crosses the synaptic cleft and binds to specialized receptors in the membrane of the target neuron. For chemical neurotransmission to be fast, the chemical messengers need to be made of rather small molecules. The classical synapse in the brain is where an axon makes contact with the dendrites of its target neuron, although contacts from axon to axon and dendrite to dendrite are also known to occur.

vesicle subcompartment of a neuron in which neurotransmitter is stored prior to release

When an action potential reaches the axon terminal, some vesicles fuse with the external cell membrane of the neuron, and the neurotransmitter chemical they contain is released. Because the distance across the synapse is very small, the neurotransmitter rapidly diffuses across to the post-synaptic neuron, where

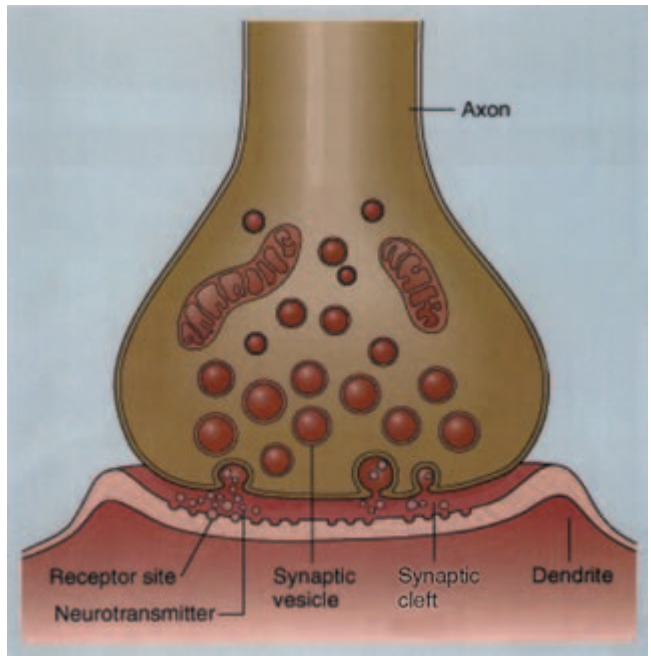

Figure 3.18

The synapse, showing transmitter release.
Source: www.usm.maine.edu/psy/broida/101/synapse.JPG

it binds to its receptor sites. Stimulation of different receptor subtypes produces different physiological effects. For example, the classical acetylcholine receptor opens sodium ion channels, leading to a Na^+ influx that depolarizes its target cells, as described earlier.

Once a neurotransmitter has been released, two more events must occur. First, more of the transmitter chemical is synthesized in the cell body and transported along the axon to the terminal region, ready for the next output signal. Second, the effects of the neurotransmitter in the target cell must be turned off again. Otherwise, a single input would depolarize its target forever, and no more information could be passed that way. A muscle, for example, would be left in a permanent state of contraction, whether it received a single impulse or a whole series of them.

There are several mechanisms for deactivating neurotransmitters. The molecule might be degraded into a form that has no physiological effects. In the case of acetylcholine, this is done by the action of the enzyme cholinesterase, which completes the job within a millisecond. It can also be done by reabsorbing the neurotransmitter back into the axon terminal that released it, or by absorbing the neurotransmitter into an adjacent glial cell.

Neurons as integrators

You know by now that neurons' output signals are all-or-nothing action potentials, and that a neuron must be depolarized beyond

its threshold to generate an action potential. How are the neuron's many different inputs combined?

Input axons typically connect to target dendrites. The branching dendritic trees of some neurons may have as many as one hundred thousand synapses on them. At any moment, each of those synapses may be either active or inactive. Each active excitatory input will to some extent depolarize the target cell membrane around its synapse. But unless the target cell is depolarized all the way to its threshold potential, so that an action potential is generated, that individual excitatory input will not lead to any output from its target. The more inputs there are, the more sodium ions flow into the target cell, and the more likely it becomes that threshold potential will be reached.

So the eventual activity of the cell depends on the overall pattern of activity of its many inputs. This means that, although neurons have all-or-nothing outputs, those outputs cannot control their targets in an all-or-nothing way. The effect on the target depends on the signals coming in at the same time from all its many inputs. In this way, neurons are effectively integrating their own inputs.

Disrupting the system

Neurotransmission mechanisms are open to disruption. We can manipulate the receptors, or the transmitter release system, or the transmitter inactivation mechanisms. By designing drugs that affect the system in these ways, we can alter brain function.

Antagonists – blocking the goal

Curare is an Amazonian plant product. It paralyses movement by binding to the acetylcholine receptor on the muscles, and prevents acetylcholine released from motor nerves from reaching its intended target. Unlike acetylcholine, curare does not depolarize muscles, so the motor nerves can no longer cause muscle contractions. This loss of movement includes breathing. This is an example of an *antagonist*. Antagonists block the effects of neurotransmitters, often by occupying the transmitter's receptor site.

antagonist neurotransmitter antagonists prevent or reduce the normal effect of a neurotransmitter

Curare was first used by South American Indians as a poison for hunting, but its synthetic derivatives are nowadays widely used in surgery. It can be very valuable for the surgeon to be able to control muscle movement and maintain respiration through artificial ventilation.

Another way to produce essentially the same effects would be to block acetylcholine release. Botulinus toxin (from the bacterium *clostridium botulinum*, which sometimes grows in preserved foods that have been imperfectly sterilized) has this effect. It is one of the most lethal poisons known. You could kill off the entire human population of close to six billion people with about 28 grams of toxin. Nowadays it is sometimes used in cosmetic surgery to reduce brow wrinkles by paralysing the muscles under the skin.

Neurotransmitter antagonists also have an important role in psychiatry. The hallucinations and delusions in schizophrenia are often treated using dopamine receptor antagonists like haloperidol. Unfortunately, prolonged use of these drugs sometimes induces movement disorders as an unwanted side effect, by blocking the action of dopamine in the *nigrostriatal* pathway. This is the pathway damaged in patients with Parkinson's disease (see below).

nigrostriatal the pathway from the substantia nigra to the striatum, which degenerates in Parkinson's disease

Agonists – keeping signals switched on

Neurotransmitter *agonists* are chemicals that have the same kind of action as the neurotransmitter itself. If their action is irreversible, or much more powerful than the natural compound whose place they usurp, then they are just as dangerous as powerful antagonists. They can equally disrupt function, by keeping signals permanently switched on.

agonist neurotransmitter agonists mimic or enhance the effect of a neurotransmitter

This can be done in several ways. Nicotine is a very widely used acetylcholine receptor agonist. It acts both centrally and peripherally. The lethal dose of nicotine for a human adult is 40–60 mg. There can be this much nicotine in just two or three cigarettes, but smoking leads to much lower nicotine absorption than eating.

There are also *indirect agonists*, which work by inducing greater than normal neurotransmitter release, or preventing re-uptake. Amphetamine is a somewhat unselective, indirect dopamine agonist, which effectively increases dopamine release. Amphetamine abuse can lead to hallucinations and delusions – essentially the opposite of the effect of haloperidol, described above.

indirect agonists substances increasing neurotransmitter effects, typically by inducing additional neurotransmitter release

Direct neurotransmitter agonists also have an important role in neurology. Parkinson's disease results from loss of dopamine neurons in the nigrostriatal system. One way to help restore normal movement in these patients is to boost dopamine function in the nigrostriatal pathway. This can be done by giving apomorphine – a direct dopamine agonist, which simulates the effects of the missing dopamine. Or we can give a dopamine precursor, L-DOPA, which helps the surviving neurons to synthesize more dopamine. Too much L-DOPA can lead to terrible hallucinations. So clinical manipulations of dopamine activity need to manage some tricky balancing acts.

Preventing neurotransmitter deactivation

A third way to increase neurotransmitters' effects in the synapse is to disrupt deactivation mechanisms. So, although neurotransmitter is released perfectly normally, its period of effective action

is abnormally prolonged. The result is similar to the effect of a direct neurotransmitter agonist.

Cholinesterase inhibitors, which stop cholinesterase from performing its usual job of breaking down acetylcholine into inactive fragments, work in just this way. They are found in a number of plants and are widely used as insecticides. (They also form the basis of some of the most deadly nerve gases.) So the direct acetylcholine agonist, nicotine, and the cholinesterase inhibitors are both synthesized by plants – presumably because they both make the plants toxic by overactivating the cholinergic systems of animals that consume them. But they achieve this effect by two, quite different, biochemical routes.

These kinds of mechanisms can offer therapeutic benefits as well. Psychiatrists have for many years used monoamine oxidase inhibitors to treat depression. These drugs neutralize the enzymes that normally deactivate monoamine transmitters (noradrenaline, dopamine and serotonin). This increases the effectiveness of monoamine neurotransmission, leading to clear clinical improvements after a few weeks of treatment.

Although these drugs are still in clinical use, it is now more usual to treat depression with newer compounds that use a rather different mechanism aimed at prolonging the actions of monoamine neurotransmitters. Perhaps the best known is Prozac (fluoxetine). This is a specific serotonin re-uptake inhibitor (or SSRI). It reduces the re-uptake of a particular monoamine, serotonin, into the neuron from which it has been released. Once again, this means that whenever neurotransmitter is released, its effects on its targets are longer-lasting (see chapter 16).

Inhibitory neurotransmission

So far we have considered only excitatory neurotransmission – how one cell induces an action potential in a target. But there is much more to chemical neurotransmission than signal amplification and one-way information flow. There are also *inhibitory neurotransmitters*, which reduce the excitability of a cell. If a cell has a constant but low level of incoming stimulation that keeps it firing at a regular rate, an inhibitory transmitter can reduce that firing. And if a target cell is quiescent, an inhibitory neurotransmitter can prevent it from being excited.

inhibitory neurotransmitters neurotransmitters that make their target cell less excitable, so it becomes harder to induce an action potential

The classic inhibitory neurotransmitter is GABA (gamma-amino-butyric acid). GABA works by increasing chloride ion flow into the interior of the cell. Since chloride ions are negatively charged, they increase the cell's negativity. This is called hyperpolarization. It is harder to excite an action potential in a hyperpolarized cell.

Just as some drugs are designed to disrupt excitation, others work on inhibitory transmission to modify neuronal activity. Enhancing inhibition has much the same effect as disrupting excitation: both reduce neuronal activity. Yet because these two approaches depend on different chemical neurotransmitters, they can have rather different side effects.

Among the various subtypes of GABA receptors is $GABA_A$. This is a particularly interesting one, because it includes the site of action of the very widely used benzodiazepine minor tranquillizers – the class to which Librium and Valium belong. These drugs increase chloride flow into the cell. Alcohol and barbiturates act on other components of the $GABA_A$ receptor to have much the same effect, so in some ways they also act like inhibitory neurotransmitters.

It is an easy mistake to think of inhibitory neurotransmitters as simply inhibiting thought or action. But in a complex network of neurons, in which inhibitory projections may inhibit other inhibitory cells, it is hard to predict the eventual outcome of inhibiting neuronal activity. Nonetheless we can generalize about the effects of blocking inhibitory GABA transmission. Drugs that do this tend to produce epileptic seizures. Equally, drugs that enhance inhibitory transmission can be used to prevent epilepsy. If a patient has been treated for a long time with drugs that increase GABA transmission and that treatment is suddenly stopped, there is a risk that the patient may suffer from epileptic convulsions.

So at some very general level, inhibitory transmitters do damp down the excitability of the brain. Some of the most horrific poisons, like strychnine, produce their effects by preventing inhibitory transmission (in this case at glycine-dependent inhibitory interneurons in the spinal cord).

Further intricacies

Autoreceptors

We have so far described transmitter being released by the pre-synaptic neuron, crossing the synaptic cleft, binding to post-synaptic receptors, and shortly afterwards being deactivated. In fact, by no means all receptor sites are located on the post-synaptic membrane. Surprisingly, some axons have receptors for their own neurotransmitter – *autoreceptors*.

autoreceptor a neurotransmitter receptor located on a neuron so as to be activated by that neuron's own release of neurotransmitter

For example, there are dopaminergic cells with dopamine autoreceptors on their axons. These can be activated by the dopamine that their own cells release, to provide a local, negative feedback loop, which can inhibit the cell from further firing. So input neurons can modify their own activity while activating their post-synaptic targets.

Paracrine effects

Target neurons can also have receptors located outside the specialized synaptic region. They are presumably activated either by neurotransmitter that escapes from the synaptic cleft, or perhaps by a transmitter that is itself released outside specialized synaptic regions.

paracrine non-classical effects of neurotransmitters that may not be released at the synapse, and/or whose receptors are not located at the synapse

neurocrine classical neurochemical action of transmitters that are released at the axon terminal to affect specialized receptor sites across the synaptic cleft

These extra-synaptic routes for chemical communication are sometimes called *paracrine* systems, as opposed to the more classical *neurocrine* routes. Their existence adds yet further subtleties to neuronal activity. It is possible that, under certain neuronal conditions, overflow from the synaptic cleft becomes more likely. This overflow could then differentially activate these non-classical paracrine communication routes, potentially producing qualitatively different actions on the target structures.

Neuromodulators and hormones

A still further level of complexity is provided by non-classical neurotransmitter substances. Some of these are released by neurons like the conventional neurotransmitters already described, but they can have longer-lasting actions and (like paracrine neurotransmitters) act at greater distances from their release sites. Some may have no directly measurable effects on their targets, but they may change the target neuron's responsiveness to its other classical neurotransmitter inputs.

neuromodulators neurochemicals that indirectly affect neuronal activity, usually by modifying response to other chemical neurotransmitters

There is a more or less indefinable boundary between these substances – often called *neuromodulators* – and hormones. For example, cholecystokinin (CCK) is a peptide that is released as a hormone by the duodenum (part of the digestive tract), but is also released like a neurotransmitter from dopaminergic neurons in the brain, where it modifies the responses of dopamine autoreceptors. So the same molecule can operate as a neuromodulator in the brain and as a hormone in the gut.

Hormones are molecules that are released into the bloodstream from specialized endocrine glands (such as the pituitary gland or the adrenal gland) and can therefore, in principle, act anywhere in the body. For hormones, specificity of action results from the presence of chemically specific receptors on the target structures that are bathed by the bloodstream. The hormonal receptors are activated when the hormones pass by in the blood. Hormones can affect neuronal function in a similar way to neuromodulators, changing sensitivity to other inputs and altering the release of neurotransmitters.

EXPERIENCE AS A MODIFIER

LTP and LTD

Although there are many ways to modulate neuronal function, they are not usually linked to specific psychological functions. But there is one form of synaptic modifiability that has led researchers to make striking and specific claims, presenting it as a possible neural basis for some forms of learning or the ability to lay down new memories (see Andersen, 1983; Bliss & Lømo, 1973; Morris et al., 1986).

The first crucial observation was made by electrophysiologists studying the responses of cells in the hippocampus, a structure that is crucial in memory processing. They found that the size of the neuronal response to a single pulse of electrical stimulation at a given intensity could be increased, in a long-lasting way, by giving a relatively brief burst of high frequency stimulation (Bliss & Lømo, 1973; Lømo, 1966). By comparing the size of the response to a single pulse before and after this high frequency series of pulses, researchers showed beyond doubt that neuronal responsiveness had increased (see figure 3.19). This change is called *long-term potentiation*, or LTP.

long-term potentiation (LTP) a long-lasting increase in a target neuron's response to a given level of activity of its input neurons

It is now clear that LTP can be seen in many structures in the brain, and not only those thought to be associated with memory. It is highly likely, though, that LTP always reflects experience-dependent changes in neuronal functioning, whether in the sensitization produced by painful stimuli, or in perceptual development in the visual cortex, or in the laying down of memory traces in the brain.

It has also become clear that there is a complementary process – *long-term depression*, or LTD – which describes a decrease in neuronal response. The ability either to increase or to decrease synaptic connectivity as appropriate offers maximum flexibility for adjusting neuronal function.

long-term depression (LTD) a long-lasting reduction in a target neuron's response to a given level of activity of its input neurons

Pioneers

Tim Bliss (1940–) and **Terje Lømo** (1935–) first reported the phenomenon of long-term potentiation. The plausibility that a strengthening of synapses might underlie memory storage increased tremendously when the phenomenon of long-term potentiation (LTP) was discovered by these two researchers. In the 1970s, Bliss and Lømo noticed that if they applied a few seconds of high frequency electrical stimulation to certain neurons in the rabbit hippocampus, synaptic transmissions to those neurons would increase in amplitude. More surprisingly, this enhancement seemed to be long-lasting, sometimes persisting for weeks (Bliss & Lømo, 1973). This phenomenon has since been termed long-term potentiation, or LTP. In the twenty years since its discovery, a great debate has raged among neuroscientists about whether this LTP might be the crucial mechanism underpinning learning and memory.

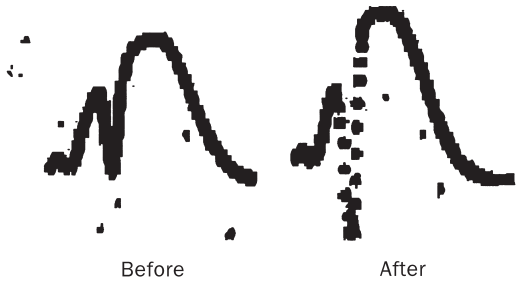

Figure 3.19

LTP: field potentials before and after potentiation.

The NMDA receptor

NMDA receptor a subtype of glutamate receptor

One key element in LTP is a particular subtype of glutamate receptor, the *NMDA receptor*. Calcium entry into the cell is one of the triggers for the development of LTP. The NMDA receptor controls a calcium ion channel that is both transmitter dependent and voltage dependent. This means that even when the NMDA receptor is activated by glutamate, no calcium will pass into a cell through the NMDA-controlled channel unless the target cell has also recently been depolarized. So NMDA-dependent LTP can only develop in a cell that has been depolarized and then receives a further input – exactly the conditions that apply during a burst of high frequency stimulation.

The mechanism underlying this dual sensitivity to neurotransmitter levels and voltage levels is remarkably simple. It turns out that in cells at their normal resting potential, a positively charged magnesium ion is held in the channel by the electrostatic gradient across the cell membrane. If the NMDA receptor is activated, so that the channel could, in principle, be opened, the inflow of calcium is blocked by the magnesium ion. Once the cell is depolarized, nothing holds the magnesium ion in place, so it can diffuse into the extracellular fluid. If the NMDA receptor is again activated at this point, the ion channel opens and, with the magnesium block removed, calcium can pour into the cell, triggering the series of events that leads to LTP. Of course, as the cell repolarizes, the magnesium ion is drawn back into position once more.

The LTP system, particularly in the hippocampus, has been a focus of intense research activity. Rat experiments have shown the blockade of the NMDA receptor by the drug AP5 prevents the development of LTP, and at the same time appears to prevent the normal operation of hippocampus-dependent spatial memory (Morris et al., 1986). More recently still, psychological studies of 'knockout' mice, genetically engineered so they can no longer show LTP in the hippocampus, have also shown striking failures of hippocampus-dependent spatial memory tasks, that neatly parallel the effects on LTP (e.g. Reisel et al., 2002). If we can combine these new techniques in molecular biology with sophisticated behavioural analysis, we will have ways to study the relation between brain and cognition at a finer level of detail than has ever been possible before.

So we have seen that the adult nervous system is highly modifiable: our brains change in accordance with our experiences. Is the development of our brains modified by the environment too?

THE GROWTH OF THE CENTRAL NERVOUS SYSTEM

Neonatal brain development

When mammals are born, they have to pass through a narrow birth canal, which places a practical limit on neonatal head size. But this does not necessarily limit ultimate brain size, so long as further brain development can take place after birth.

This is not too much of a problem for human infants, whose particularly helpless state at birth is made feasible by parental care. Small animals like rats can hide their young safely away in holes. So, like humans, the young can be born immature without incurring excess risk. In contrast, herbivores that inhabit open grassland may need to be able to run with the herd within minutes, or at most a few hours, of their birth. Such creatures could not afford a long postnatal period of general brain development. This problem has been solved in a different way by the kangaroo, which is born very early in its development but remains protected in the safety of its mother's pouch, where it continues to develop until it is capable of independent movement.

Our own protracted postnatal development not only allows us to grow a bigger brain (the adult brain is around four times the size of a new-born baby's brain). It also ensures that our brain continues to develop while we are interacting with our environment. So each person's brain will, to a certain extent, be adapted to the circumstances of their lives.

Survival of the most useful

The first sign of what will become the brain appears very early in human gestation. By the end of the second week, a neural plate made up of precursor neurons can be identified. By the end of the first month, a primitive brain has already formed.

Like other parts of the body, the brain develops when cells migrate to the appropriate place. Those cells have to know how to differentiate into the right kinds of eventual cell types, and when to stop differentiating. But brain development requires more than cells simply knowing how to get to the right place and what to do when they are there. For this particular organ, a high level of competitiveness is involved.

During development, connections in the brain respond to what is going on. We start off with many more potential neurons than will eventually survive. Neurons compete to make connections with their targets, and it is the connections that are actually used which seem to have a better prospect of survival. Unsuccessful neurons die, through a process of programmed cell death, called *apoptosis*. If one set of neurons fails to make its normal connections, then another set of opportunist neurons may colonize the vacant space.

apoptosis genetically programmed self-destruction of a neuron

The capacity for neural regeneration

So the eventual wiring of the adult brain in part reflects experiences during the long period of brain development that takes place after birth. And, to some extent, the brain responds to those experiences by making structural changes. However, once the mammalian brain is fully developed, the capacity to form new neurons is drastically reduced, though not totally lost (see below). Even before full development is reached, a lack of input during a critical stage can lead to a permanent loss of appropriate connection.

For example, covering one eye during development can distort visual connections, leading to persistent impairment of adult vision that depends on that eye (Mitchell, Murphy & Kaye, 1984; Murphy & Mitchell, 1986). As little as two weeks of occluded vision can induce these effects in human infants. This has implications for eye surgery procedures in children – for example, placing a patch over the eye after surgery could significantly impair the efficient wiring of the visual system.

In this respect, the central nervous system differs from the peripheral nervous system, in which regeneration occurs regularly after injury. Areas of axonal loss can be reinnervated (i.e. the neural connections can be re-established) under some circumstances, to afford a complete recovery of function. But in the central nervous system, spinal cord damage, for instance, leads to permanent paralysis. Christopher Reeve, once the star of *Superman* films, is now confined to a wheelchair due to spinal cord damage sustained during a riding accident.

It is possible that this difference between the central nervous system and the peripheral nervous system lies in the non-neuronal cells that are found alongside neurons. In the central nervous system, these are glial cells; in the peripheral nervous system, they are schwann cells. These non-neuronal cells provide the environment for the neuron, and can clearly secrete a variety of bioactive signalling substances. When peripheral nerves are cut, the portion of axon lying beyond the injury is cleared away, partly by the schwann cells, which form into cylindrical guides along the original path of the axon. New axon processes sprout and spread from the remaining stump, and if one of these processes enters the schwann cell guide tube, then its growth rate increases and it is led along the tube towards the nerve's original target. Central nervous glial cells do not seem to have this ability to guide regenerating axons.

CAN WE REPAIR DAMAGED BRAINS?

The question of whether it might be possible to induce the central nervous system to regenerate has taken a new turn since the early 1970s. At this time, it became clear that adult neurons can sometimes form new connections. If one input to a target area is lost, the remaining inputs sometimes send out new branches from their axons to colonize the vacant space (Raisman & Field, 1973).

This is not necessarily an advantage. If normal function of the target area depends partly on interactions between two inputs, it may be worse off having a double signal from only one of them than having a normal signal from one and no signal from the other.

How can we encourage the right kind of regeneration in response to injury?

Neural grafting

One way is to transplant into the damaged brain a new supply of neurons of the missing kind. If the transplanted neurons are themselves taken from a brain at the right stage of development, they will grow in an adult host brain and form new connections, leading at least to a partial restoration of normal function.

This has been most convincingly demonstrated in the dopamine system running from the substantia nigra to the caudate-putamen at the base of the forebrain. Destruction of this dopaminergic pathway leads to movement disorders in rats, and to Parkinson's disease in humans (Hornykiewicz, 1973; Ungerstedt, 1971). Transplants of dopamine cell bodies lead to a clear restoration of some motor functions in the rat (Dunnett et al., 1981), and alleviate some of the symptoms of Parkinson's disease in human patients (Hagell et al., 1999).

If the transplant is made into the site in the substantia nigra where the original dopamine cell bodies would have been located, it will not grow its axons to the original target for the dopamine pathway. So the transplant has to be made into the caudate-putamen. This means that the incoming connections to the original dopamine cell bodies will not be made to the transplanted dopamine cell bodies, as these are not where the original cells were located.

How do we explain the success of this transplanting procedure? The most plausible explanation is that the implanted dopamine cells make synaptic connections where they can release dopamine in appropriate amounts, although this dopamine release will not be controlled normally by the activities of the remainder of the brain. The success of this procedure also illustrates the key role of dopamine – to enable other neurons in the motor system to operate normally, rather than carrying some specific signals of its own. The dopamine system itself does not seem to give instructions about which muscle to move next.

The capture and transmission of more specific information by transplanted neural tissue has been demonstrated in retina transplant experiments. A retina is transplanted so as to make connections with the brain of a developing rat. In adulthood, the rat can learn to respond to illumination of the transplanted retina as readily as it responds to illumination of its own natural retina (Coffey, Lund & Rawlins, 1989).

While these kinds of transplant procedures in no way reconstruct the original circuitry in its entirety, more recent developments offer some hope of coming much closer to this ideal. In these procedures, instead of neurons that have already differentiated into a particular neuronal variety, neuronal stem cells are transplanted. These neuronal precursors have the potential to develop into any kind of neuron. So when they are transplanted into a damaged brain, they migrate to the areas in which cells are missing and form new structures that become integrated into the host brain (Lundberg et al., 1997). It is possible that this kind of technique will result in a far more complete recreation of the missing circuitry (Svendsen & Smith, 1999).

Research close-up 3

Temporal lobe amnesia

The research issue

A patient known as H.M. had surgery for the treatment of epilepsy in 1953. The surgeon removed the inner face of the temporal lobe in each hemisphere, including the hippocampus, the amygdala and the rhinal cortex.

Since then, H.M. has remembered almost nothing new, though he still remembers clearly events in his life before the operation. His other cognitive skills are unaffected. He is clearly capable of learning new motor skills, like mirror drawing, and perceptual skills, like completing pictures (figure 3.20), although he does not remember doing so.

In fact his IQ went up slightly after his operation, which successfully reduced the frequency and severity of his epileptic seizures.

Design and procedure

Before testing begins, H.M. talks with the neuropsychologist for a few minutes, having not met her before. The neuropsychologist asks him what he had for breakfast that day: he does not remember. Testing begins.

The neuropsychologist has a collection of photographs of faces. She shows some to H.M., who studies them all carefully. A few minutes later he cannot identify which faces he has just seen and which ones he has not. The same sort of thing happens with a list of words. The neuropsychologist then shows him a very rudimentary line drawing and asks him if he recognizes it. He correctly identifies it as an aeroplane. He is also able to repeat a string of six numbers immediately after hearing them.

Figure 3.20

Example from Gollin's (1960) incomplete drawing test. Source: McCarthy and Warrington (1990).

The neuropsychologist then shows him another very rudimentary line drawing (like the top panel illustrated to the left) and asks him if he recognizes it. He has seen all the drawings before, in previous test sessions, and now correctly identifies the fish even from seeing only the least complete version of the drawing.

The neuropsychologist leaves the room, and H.M. waits with the nurse. Twenty minutes later the neuropsychologist returns. The patient clearly does not recognize her, gets up, and politely introduces himself.

Results and implications

amnesia a clinical problem, often with underlying neurological damage, involving chronic and serious memory problems

H.M. is a particularly 'pure' *amnesic* patient with a highly selective memory loss. His short-term memory is intact, and he still recalls events from his pre-operative childhood, but his memory for everyday events is disastrously impaired. It was initially suggested that his damage left him specifically unable to consolidate (store) new memories, because he can clearly retrieve memories laid down before his surgery and also registers new events in short-term memory. However, we now know that he can learn new skills and perform implicit memory tasks. He learned to identify the line drawing as a fish following training with all five versions of the drawing in the panel. Initially he would not have 'seen' what the top panel was, but once having learned it he continues to give the right answer, even though he cannot remember his training sessions themselves. This persisting new learning makes it unlikely that a consolidation failure accounts for his symptoms.

So some fifty years after his surgery, neuroscientists still do not agree on exactly why he shows profound memory loss. Nonetheless, his case has focused attention on the hippocampus as a core memory structure, and this has proved to be a crucial step in developing neurobiological theories of information storage in the brain.

Scoville, W.B., & Milner, B., 1957, 'Loss of recent memory after bilateral hippocampal lesions', *Journal of Neurology, Neurosurgery and Psychiatry*, 20, 11–21.

Is it possible for brains to regenerate?

In some birds, the brain region related to memory (the hippocampus) varies in size according to demand. In the Americas, cowbirds parasitize other birds' nests in the same way that the European cuckoo does, by laying eggs in them to be brought up by foster parents. Successful brood parasites need to know where the hosts' nests are, and how the egg laying is going in each nest. It is not much use laying your egg after the host's eggs have been incubated, giving them a head start in the race to hatching, nor is it a good idea to lay your egg before the host has laid any eggs at all. Cowbirds therefore need to keep careful track of what is going on during the breeding season. It is now clear that at this time the cowbird hippocampus increases in size relative to other structures in the brain.

In one species of cowbird, only the female keeps track of nest development. In this species, the female's hippocampus increases in relative size during the breeding season and decreases again afterwards, but the male's does not. In another species, both male and female keep track of nests, and the hippocampus in both sexes increases for the breeding system. A third species of cowbird is not a brood parasite at all, and in this species the hippocampus shows no sign of growing or shrinking (Reboreda, Clayton & Kacelnik, 1996).

In humans, hippocampal damage leads to such a profound amnesia that the patient is more or less incapable of living an independent life. Yet birds appear to need a hippocampus only some of the time. At other times they get rid of it, even though they will have to regrow it next year. Why? It has been suggested to me (by my colleague Professor Sir John Krebs) that the answer lies in energy saving, since the brain uses a great deal of energy, and a reduction in energy load may be vitally important. Small birds in cold climates can lose a significant proportion of their body weight overnight, so even a marginal saving could make a vital difference. Whatever the reason, the bird's ability provides a striking example of the potential for reforming circuitry in adult brains.

Neurogenesis in adult mammals

The potential for neural replacement (*neurogenesis*) is almost completely absent in the adult mammalian brain – but not entirely absent (Gage, Ray & Fisher, 1995). Intriguingly, one of the two areas of the adult mouse brain that show neurogenesis lies in the dentate gyrus (part of the hippocampus). Elderly mice living in enriched environments show an increase in the numbers of new neurons formed, as well as increased numbers of surviving dentate granule cell neurons (Kemperman, Kuhn & Gage, 1997). Perhaps the mammalian brain more closely parallels the avian brain in its potential for reconstructing central nervous circuitry than we have tended to assume.

Recent work shows evidence of neurogenesis in the adult hippocampus of primates, including humans (Eriksson et al., 1998; Kornack & Rakic, 1999). A structural imaging experiment has shown that London taxi drivers – whose job demands an extraordinary knowledge of London streets – have a relatively larger posterior hippocampus compared to age-matched controls (Maguire et al., 2000). The extent of the increase in size correlated with the length of time spent as a taxi driver.

It is thus conceivable that constant use of a spatial navigation system has led to growth of the adult human hippocampus, or at least to selective protection from age-related hippocampal shrinkage. One day we may be able to take advantage of this potential, and use it for clinical therapy.

Modular processing

The brain can solve immensely difficult computational problems. We can judge distances, we can identify objects, we can walk through complex environments relying solely on vision to guide us. These abilities are way beyond the capacities of current computers, even though their processing elements operate very much faster than our neurons.

So, how do we solve complex problems of visual geometry so rapidly? The key lies in the brain's parallel processing capacity (see figure 3.21). In principle, different aspects of a visual stimulus

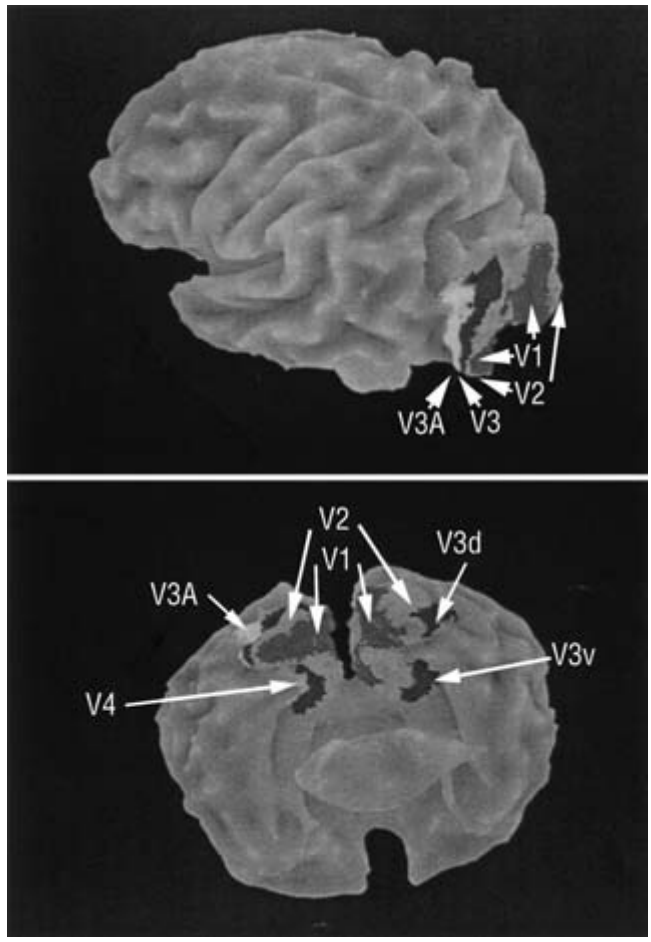

Figure 3.21

Visual processing modules of the brain.
Source: http://ahsmail.uwaterloo.ca/kin356/ventral/v2.jpg

are analysed by different modules in the brain. One module may deal with form, another with motion, and another with colour. By splitting up the task in this way, it is possible to solve complicated problems rapidly.

There might also be an evolutionary explanation for modularity in the brain. To add a new perceptual analysis feature to our existing perceptual analysis systems, the simplest route would be to leave the existing analysis systems unchanged and simply 'bolt on' a new feature. The alternative would be to rewire and reconfigure all the existing systems to add the mechanisms for the new analysis. It is harder to imagine how this might happen without the risk of radically disrupting the pre-existing systems.

A computational stratagem like this poses new problems, however. There needs to be some way of ensuring that the different aspects of a stimulus, although processed separately, are nonetheless related to each other. A cricket ball heading towards you is red, shiny, round and moving. You need to know that these separate attributes all refer to the same object. How does our brain solve this problem? It is possible that the different brain regions analysing different aspects of the same stimulus show synchronized oscillations, which act to link these structures together (e.g. Gray et al., 1989).

The visual processing modules are in some senses independent, but not completely so. Identifying a shape or form, for example, sometimes depends on solving the problem of colour or reflectance. A uniformly coloured, curved surface, lit from above, may emit different wavelengths of light from different points on the surface. We perceive it as being a single colour partly because we are also seeing it as a curved surface. And our perception of it as being curved equally depends partly upon light intensities and/or wavelengths reaching us from different points on the surface. So form and reflectance need to be solved simultaneously, and the solutions are, to some extent, interdependent. Although parallel processing is still an appropriate way to explain how the brain solves problems, as so often seems to be the case, things are a bit more complex than that.

FINAL THOUGHTS

We have just completed a very brief tour of the nervous system. The brain has sometimes been referred to as the most complex entity in the known universe. The human brain contains some 100 billion neurons – the individual units from which this system is built. Each of these may have up to 100,000 synapses providing inputs from other neurons. Those facts alone would be enough to make the brain a system of awesome complexity. Over and above this, there are many different kinds of neurons. Each can have its own responsiveness subtly adjusted by the many and varied chemical inputs it receives. The operations of a vast network, built of individually variable components, are bound to be extraordinarily difficult to unravel and understand.

An introductory chapter can do no more than sketch some of the outlines of neuroscience's achievements so far, and identify a few of the prospects that lie ahead. This chapter aims to give a sense of how the nervous system operates, so that you will not be constrained to thinking of the brain as a series of rather arbitrarily named boxes, each in some unspecified way connected to others. Thinking about why the brain is organized in the way that it is, and appreciating the many ways in which we – and our environments – can alter brain function for good or ill, make behavioural and cognitive neuroscience not only more comprehensible, but far more exciting too.

Summary

- The nervous system is built of individual neurons. The human brain contains some 100 billion neurons, of many different kinds. Each neuron may have up to 100,000 synapses providing inputs from other neurons. Inputs come via the dendrites, and outputs are sent along the axons.
- Neurons maintain electrical potentials, which change in response to inputs from other neurons. When a neuron 'fires', it sends a rapid action potential along its axon, which is 'insulated' by myelin sheaths.
- Neurons interact using chemical transmitters. There are many different neurotransmitters in the brain. Each neuron can have its own responsiveness subtly adjusted by the many and varied chemical inputs it receives.
- The significance of chemical neurotransmission between neurons is revealed in the design of effective therapeutic drugs for neurological illnesses such as Parkinson's disease and schizophrenia.
- The human nervous system has many different components and levels of organization, each element having being fine-tuned through millennia of evolution to serve its current role (e.g. the peripheral nervous system vs. the central nervous system; the cerebral cortex vs. the subcortex; the left cerebral hemisphere vs. the right cerebral hemisphere).
- The nervous system comprises distinct 'modular' components but nevertheless (unless damaged or depleted) operates as a functional integrated whole.
- Some brain regions have highly specific functions. This allows parallel processing of information, to speed up our computations, but also means that very restricted brain damage can produce profound but selective deficits (e.g. the loss of colour vision, or loss of the ability to identify individuals from their faces, while other visual processing remains intact).
- The human nervous system forms many of its connections after birth. This helps to match our brain's development and organization to our interactions with our environment.
- The brain is highly plastic: some connections remain modifiable, and at least some new brain cells can be created, even in adulthood. This might offer long-term avenues for brain repair.

REVISION QUESTIONS

1. How does the peripheral nervous system differ from the central nervous system?
2. What is special about the cortex?
3. Why do nerve cells have to use energy to maintain their electrical potential gradients?
4. How are action potentials generated?
5. How do nerve cells communicate with each other?
6. What are the advantages of chemical neurotransmission? How can it be exploited in drug design?
7. Does our environment influence the structure of our brains?
8. Can damaged brains be repaired?
9. What are the advantages of modularity in the brain?
10. Should we think of the brain as operating like a digital computer?
11. What, if anything, is special about the human brain?
12. Why might neurons with different integrative functions have different morphologies?
13. How have advances in neuroscientific research methods contributed to our ability to understand structure and function in the brain?
14. Can we understand normal function by studying dysfunction?
15. How can different approaches to studying brain function be combined so as to complement one another?

Further Reading

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