4TH EDITION

INTRODUCTION TO BIOPSYCHOLOGY

Andrew P. Wickens

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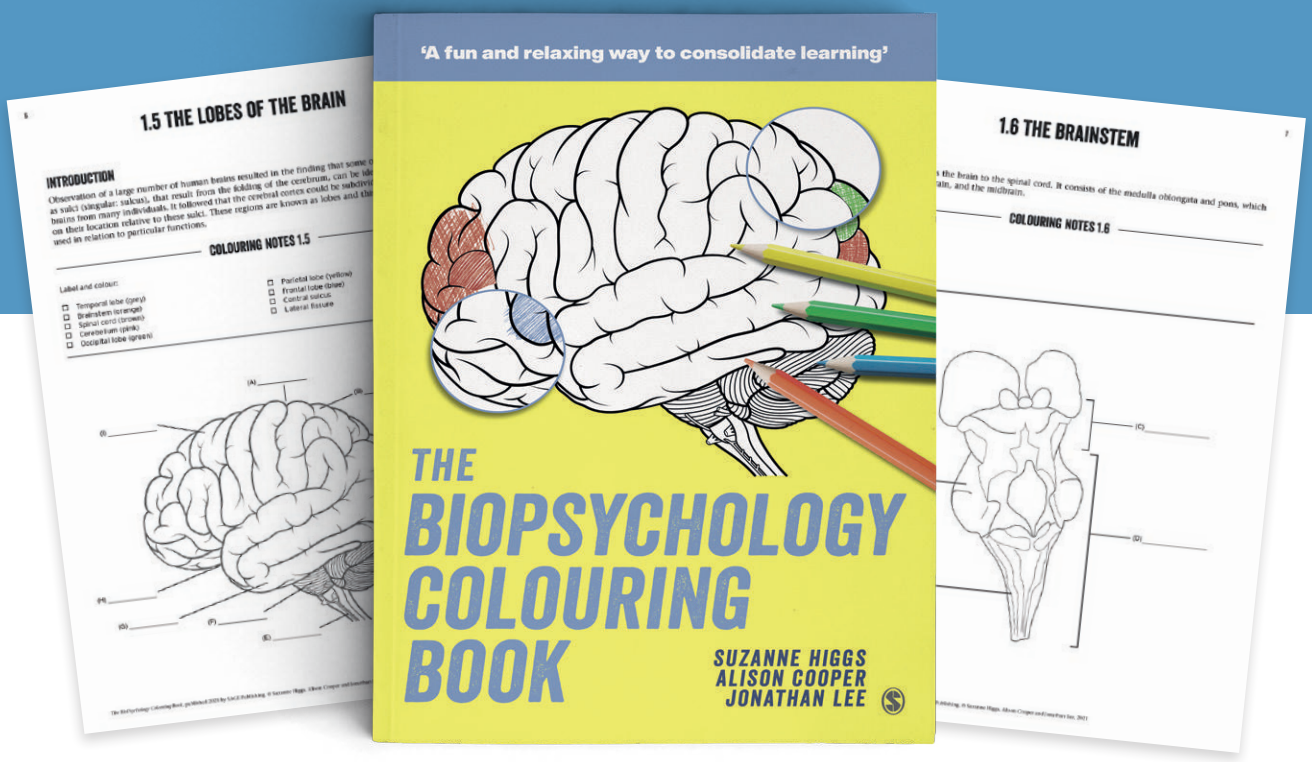

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Andrew P. Wickens

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PREFACE

The human brain is the most complex living object known in the universe. Although an average adult brain weighs only about a kilogram and a half, it contains in the region of 100 billion nerve cells which transmit tiny electrical signals. But this figure is small compared to the trillions of connections between the neurons. These are called synapses – tiny gaps mostly awash with neurotransmitters and chemicals. It is at these sites that the main information processing of the brain is believed to take place. Somehow, the electrical and chemical melee of this activity gives rise to the human mind with its remarkable capacity for behaviour, intentional thought and consciousness. How it achieves this remarkable feat is still largely a mystery, and the conundrum taxes the ingenuity of psychologists, neuroscientists and philosophers alike. Nonetheless, the number of ground-breaking scientific discoveries about the brain increases with every passing year. The aim of this book is to make this ever-growing knowledge both accessible and interesting to the curious person who may not have any previous knowledge of biological psychology. It is also hoped the book will take you on a journey that will fascinate, surprise and give you greater insight into your behaviour and that of others. If you are a student, it will even help you to pass your exams!

This is the new fourth edition and the book has come a long way since its first appearance in 2000. Originally entitled *Foundations of Biopsychology*, it is now entitled *Introduction to Biopsychology* to reflect a much broader scope. It also has a new publisher (SAGE) to spruce things up. When writing the first edition I was conscious of the need to stamp my own style on the book. There were a number of highly respected textbooks already available, and it was not always easy to avoid imitation. But, I hope, I succeeded in writing my own version, and in doing so provide a valuable text for students. One unique feature of the new book is the inclusion of a Key Thinker box in each chapter. I am a great believer in the usefulness of history to teach students about where biological psychology has come from and where it is heading – and these boxes hopefully get across some of the excitement of important discoveries about the brain and the personalities behind them. In addition, the book has individual chapters on degenerative disease and genetics. Looking at other texts, I discovered this is quite an unusual feature, but I feel both are necessary for showing some of the ways in which neuroscience is moving forward. The new edition of the book also has a companion website that is designed to encourage independent learning for students as well as providing a useful resource for lecturers. I would also add that I have tried out every chapter in a two-hour lecture setting – so I know they work in the classroom.

Despite all these improvements, I still like to believe the most important feature of *Introduction to Biopsychology* is its readability. When writing the first edition, I had been lecturing in Biopsychology and Neuroscience for over a decade. Nothing is worse that lecturing to a group of disinterested students. And this soon taught me that the art of

good teaching lay in one's enthusiasm, and making the subject informative and structured in a way that enabled the content to be easily followed and understood. If the lecture followed some sort of narrative – then all the better. These are also the principles I have attempted to incorporate in each chapter of this book. Fortunately, tutor and student feedback has confirmed that my attempts provide an enjoyable and academically rigorous introduction to biopsychology. I hope it continues with this new edition.

Biological psychology is the study of how the brain produces behaviour, and is one of the most demanding subjects of all. A good knowledge of biological psychology requires more than a passing understanding of many other disciplines, including anatomy, physiology, biochemistry, pharmacology and genetics. Thus one might be excused for finding a simpler subject to study. But by doing this one would miss out on a subject that has no equal when it comes to providing powerful and insightful explanations of human nature. The Nobel laureate Gerald Edelman called the subject 'the most important one imaginable' because, in his view, 'at its end, we shall know how the mind works, what governs our nature and how we know the world'. And this is only one of the benefits, because as knowledge progresses, better treatments for a wide range of medical, behavioural and psychological problems will arise. Hence students should never lose sight of the great good which biopsychology can bring to our world.

The past decade or so has seen many exciting advances in biopsychology. For example, the widespread use of functional scanning techniques, such as fMRI, has allowed the cognitive processes of the mind to be visualized for the first time. This has led to a new discipline called Cognitive Neuroscience, which may one day have the power to expose your own private thoughts and emotions to scientific scrutiny. At the other end of the spectrum are advances in genetics, allowing the creation of transgenic animals, so that scientists can work out the function of individual genes and their impact on behaviour and disease. We are also at the beginning of the stem cell revolution, which will undoubtedly bring further remarkable advances. These examples not only help illustrate the broad canvas of biopsychology, they also show we are standing at the threshold of a new age in unravelling the mysteries of the brain. This is an exciting time to study biological psychology.

Inevitably, writing a book of this size will reflect the author's interests and biases. As you will see, this includes a smattering of history and philosophy, which are subjects close to my heart. However, I have also tried to include areas that are likely to be important for the brain scientist in the future. This is one reason why the final chapter is on genetics, which introduces some of the new developments taking place in molecular biology and brain science. Some may argue that the gap between molecular biology and behaviour is too great for it to be relevant to psychologists but I disagree. If you are to be student of the brain, then you must be prepared to expand your academic horizons in a wide variety of new ways. After all, biopsychology is a multidisciplinary subject, and this is one of the reasons why it is such a fascinating one. I hope this book can provide you with a thorough grounding in biopsychology and more. But most of all, I hope it gets across some of the excitement and wonder I feel when contemplating the brain. If this book helps you to pass an exam in biopsychology that is great. And if it stimulates you to go beyond its pages, and develop an ongoing fascination with the brain, then it will have been a greater success. I like to think that, for some of its readers, it will do just that.

Andrew Wickens
January 2021

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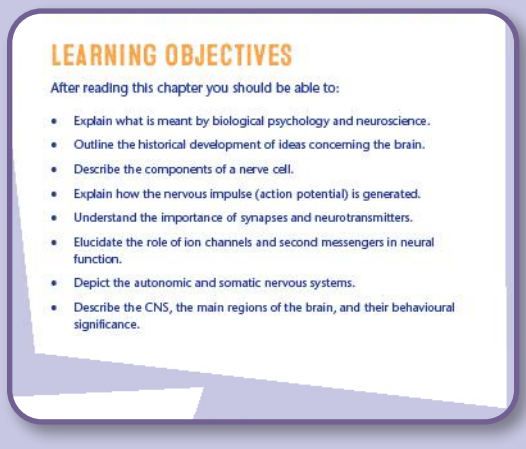
The origins of this new edition of *Introduction to Biopsychology* came about through a meeting with Becky Taylor, a publisher with SAGE, in the refectory at the University of Central Lancashire in early 2018. Although I was in talks with another company at the time, I am grateful to Becky for recommending me to her colleagues, before she left SAGE to become a publishing consultant. As things transpired, I am very happy to have joined the SAGE family! I would also like to thank the Senior Commissioning Editor, Donna Goddard, for making me feel so welcome, and especially Martha Cunneen, who has been the Development Editor for my book. She has helped me every step of the way and been invaluable in reading my scripts and correcting them when necessary. This book has been significantly improved through her efforts. I would also like to thank Rachel Burrows, who has been responsible for overseeing the book through the latter stages of its production, and Audrey Scriven for her Herculean efforts in copyediting my manuscript. Last but not least, I am grateful to my girlfriend Kathy Wright for her continual support and friendship.

HOW TO USE THIS BOOK

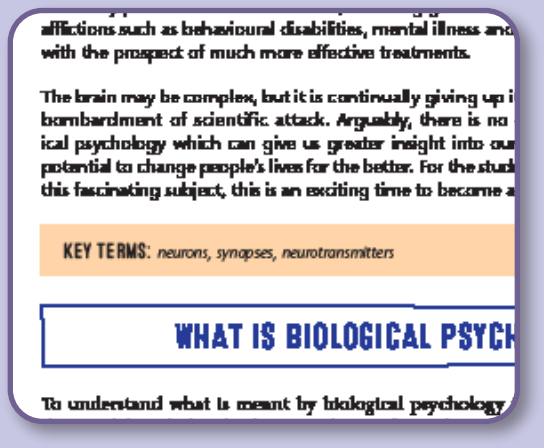


LEARNING OBJECTIVES

After reading this chapter you should be able to:

- Explain what is meant by biological psychology and neuroscience.
- Outline the historical development of ideas concerning the brain.
- Describe the components of a nerve cell.
- Explain how the nervous impulse (action potential) is generated.
- Understand the importance of synapses and neurotransmitters.
- Elucidate the role of ion channels and second messengers in neural function.
- Depict the autonomic and somatic nervous systems.
- Describe the CNS, the main regions of the brain, and their behavioural significance.

Learning Objectives list everything you should achieve and understand by the end of the chapter.



afflictions such as behavioural disabilities, mental illness and
with the prospect of much more effective treatments.

The brain may be complex, but it is continually giving up i
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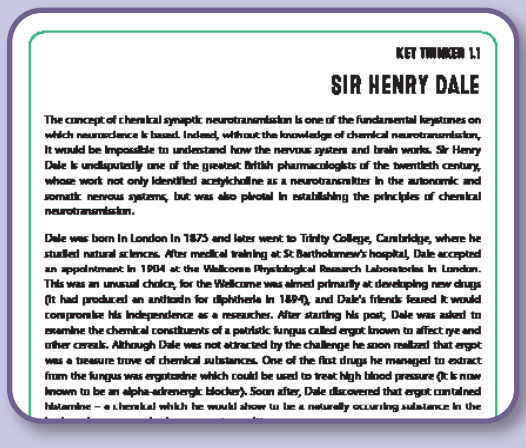
potential to change people's lives for the better. For the stud
this fascinating subject, this is an exciting time to become a

KEY TERMS: *neurons, synapses, neurotransmitters*

WHAT IS BIOLOGICAL PSYCH

To understand what is meant by biological psychology

Key Terms highlight the need-to-know terminology for the chapter.



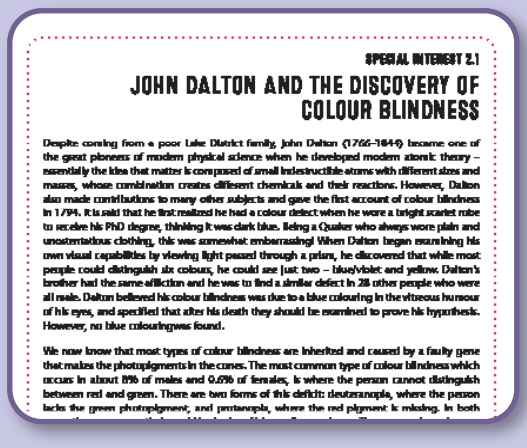
KEY THINKER 1.1

SIR HENRY DALE

The concept of chemical synaptic neurotransmission is one of the fundamental keystones on which neuroscience is based. Indeed, without the knowledge of chemical neurotransmission, it would be impossible to understand how the nervous system and brain works. Sir Henry Dale is undisputedly one of the greatest British pharmacologists of the twentieth century, whose work not only identified acetylcholine as a neurotransmitter in the autonomic and somatic nervous systems, but was also pivotal in establishing the principles of chemical neurotransmission.

Dale was born in London in 1875 and later went to Trinity College, Cambridge, where he studied natural sciences. After medical training at St Bartholomew's hospital, Dale accepted an appointment in 1904 at the Wellcome Physiological Research Laboratories in London. This was an unusual choice, for the Wellcome was aimed primarily at developing new drugs (it had produced an antitoxin for diphtheria in 1894), and Dale's friends feared it would compromise his independence as a researcher. After starting his post, Dale was asked to examine the chemical constituents of a putrefactive fungus called ergot known to affect rye and other cereals. Although Dale was not attracted by the challenge he soon realized that ergot was a treasure trove of chemical substances. One of the first drugs he managed to extract from the fungus was ergotoxine which could be used to treat high blood pressure (it is now known to be an alpha-adrenergic blocker). Soon after, Dale discovered that ergot contained histamine – a chemical which he would show to be a naturally occurring substance in the

Key Thinker boxes spotlight the lives and work of important thinkers and researchers from history to share the story of their discoveries.



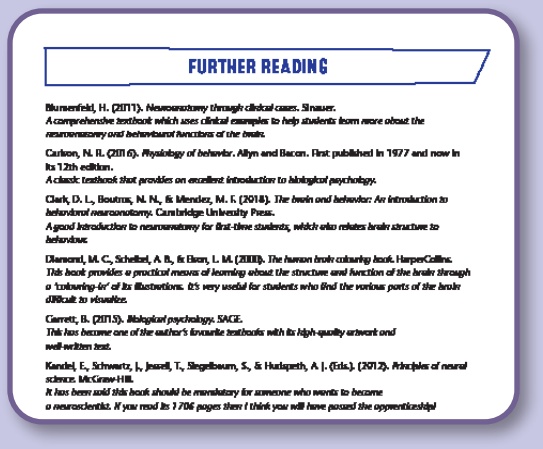
SPECIAL INTEREST 2.1

JOHN DALTON AND THE DISCOVERY OF COLOUR BLINDNESS

Despite coming from a poor Lake District family, John Dalton (1766–1844) became one of the great pioneers of modern physical science when he developed modern atomic theory – essentially the idea that matter is composed of small indestructible atoms with different sizes and masses, whose combination creates different chemicals and their reactions. However, Dalton also made contributions to many other subjects and gave the first account of colour blindness in 1794. It is said that he first realized he had a colour defect when he wore a bright scarlet robe to receive his PhD degree, thinking it was dark blue. Being a Quaker who always wore plain and unostentatious clothing, this was somewhat embarrassing! When Dalton began examining his own visual capabilities by viewing light passed through a prism, he discovered that while most people could distinguish six colours, he could see just two – blue/violet and yellow. Dalton's brother had the same affliction and he was to find a similar defect in 28 other people who were all male. Dalton believed his colour blindness was due to a blue colouring in the vitreous humour of his eyes, and specified that after his death they should be examined to prove his hypothesis. However, no blue colouringwas found.

We now know that most types of colour blindness are inherited and caused by a faulty gene that makes the photopigments in the cones. The most common type of colour blindness which occurs in about 8% of males and 0.6% of females, is where the person cannot distinguish between red and green. There are two forms of this deficit: deuteranopia, where the person lacks the green photopigment, and protanopia, where the red pigment is missing. In both

Special Interest boxes bring biopsychology to life through fascinating discussions related to the chapter. Includes the discoveries of colour-blindness and synaesthesia, the memory of London cab drivers, and a look at why we laugh.



FURTHER READING

Blumenfeld, H. (2011). *Neuroanatomy through clinical cases*. Sinauer.
A comprehensive textbook which uses clinical examples to help students learn more about the neuroanatomy and behavioural functions of the brain.

Carlson, N. R. (2016). *Physiology of behavior*. Allyn and Bacon. First published in 1977 and now in its 12th edition.
A classic textbook that provides an excellent introduction to biological psychology.

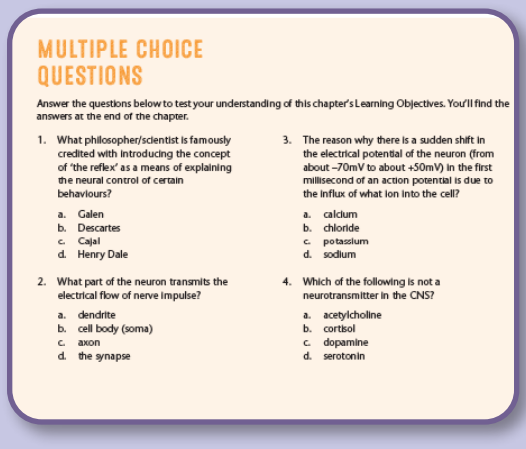
Clark, D. L., Boutros, N. N., & Mendez, M. F. (2018). *The brain and behavior: An introduction to behavioral neuroanatomy*. Cambridge University Press.
A good introduction to neuroanatomy for first-time students, which also relates brain structure to behaviour.

Diamond, M. C., Scheibel, A. B., & Elson, L. M. (2000). *The human brain coloring book*. HarperCollins.
This book provides a practical means of learning about the structure and function of the brain through a 'colouring-in' of its illustrations. It's very useful for students who find the various parts of the brain difficult to visualize.

Garrett, B. (2017). *Biological psychology*. SAGE.
This has become one of the author's favourite textbooks with its high-quality artwork and well-written text.

Kandel, E., Schwartz, J., Jessell, T., Siegelbaum, S., & Hudspeth, A. J. (Eds.). (2012). *Principles of neural science*. McGraw-Hill.
It has been said this book should be mandatory for someone who wants to become a neuroscientist. If you read its 1706 pages then I think you will have passed the apprenticeship!

Further Reading provides suggestions for exploring the subject further to help build your bibliography for assignments.



MULTIPLE CHOICE QUESTIONS

Answer the questions below to test your understanding of this chapter's Learning Objectives. You'll find the answers at the end of the chapter.

1. What philosopher/scientist is famously credited with introducing the concept of 'the reflex' as a means of explaining the neural control of certain behaviours?
   a. Galen
   b. Descartes
   c. Cajal
   d. Henry Dale

2. What part of the neuron transmits the electrical flow of nerve impulse?
   a. dendrite
   b. cell body (soma)
   c. axon
   d. the synapse

3. The reason why there is a sudden shift in the electrical potential of the neuron (from about –70mV to about +50mV) in the first millisecond of an action potential is due to the influx of what ion into the cell?
   a. calcium
   b. chloride
   c. potassium
   d. sodium

4. Which of the following is not a neurotransmitter in the CNS?
   a. acetylcholine
   b. cortisol
   c. dopamine
   d. serotonin

Multiple Choice Questions at the end of the chapter test your comprehension of the chapter themes and learning objectives.

Online tools are available at **https://study.sagepub.com/wickens** to help you further test your understanding of brain and behaviour and revise key concepts and terms. Look out for the icon below

- **Drag and drop** – label diagrams for a fun and interactive way to revise the important brain and sensory systems.
- **Flashcard glossary** – check the definitions of key terms and hear the correct pronunciations.

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- **Test Bank** – test your students' understanding and help them prepare for assessments with this collection of 200 multiple choice and short answer questions.

1

AN INTRODUCTION TO BIOLOGICAL PSYCHOLOGY, BRAINS AND NERVE FUNCTION

LEARNING OBJECTIVES

After reading this chapter you should be able to:

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GO ONLINE

Test your understanding of this chapter and visit **https://study.sagepub.com/wickens** to access interactive 'Drag and Drop' labelling activities and a flashcard glossary.

INTRODUCTION

An isolated human brain is a pinkish-grey mass of tissue which on first sight is not dissimilar in appearance to a giant walnut. If held in the palm of one's hand, it is deceptively heavy (an adult brain weighs about 3.5 pounds or 1.5 kilograms) and feels like hardened jelly to touch. It may not appear to be the most complex object in the universe, but the chances are that it is. Indeed, when holding a brain in our hands, or viewing it from afar, it is difficult not to be moved by what we have in our presence. This odd-looking structure once housed the mind of a human being – their memories, thoughts and emotions – their wishes, aspirations and disappointments – and their capability for consciousness, self-reflection and free will. Somehow this organ has enabled us to become the most dominant species on Earth with all of our many artistic, scientific, medical and technological achievements.

But what exactly is it that is so special about the human brain? Part of the answer is its great complexity. Like any other part of the body, the brain is composed of individual autonomous cells, the most important being **neurons** which are specialized to receive, process and transmit information. Their main purpose is to communicate with each other, and they do so using a mechanism that is not dissimilar to an incredibly fast electrical on-off switch.[1] Although estimates vary (see Herculano-Houzel, 2009), the human brain contains in the region of one hundred billion neurons (100,000,000,000) – a figure so great that if you took a second to count every cell it would take over 3,000 years. Yet, what makes our brain really complex is the way the neurons are arranged and connected. Neurons rarely form connections with each other on a one-to-one basis, but rather a single nerve cell may project up to between 5,000 and 10,000 others. This means that there are literally trillions of connections between neurons, and to make matters even more complicated, their points of contact are not physically continuous or joined but instead exist as **synapses** (these can be envisaged as miniscule gaps), which in the majority of cases rely on chemicals (or **neurotransmitters**) for communication. The number of synapses in the human brain is truly astronomical. In fact, Thompson in his textbook *The Brain* (1993) went so far as to say that the number of possible synaptic connections in the human brain is greater than the number of atomic particles that constitute the entire universe. If you don't fully understand this logic, don't worry, nor does the author of this book – but it is certainly a lot of connections! Yet one thing is for sure: as you read these very words, millions upon millions of tiny electrical signals are being rapidly sent through the neural fibres of your brain which is also awash with a huge variety of fleetingly formed chemical substances at the synapses.

One might be forgiven for thinking the brain is so complex that it defies comprehension, but I hope this book will demonstrate otherwise – at least on a biological level. Neuroscience is one of the most rapidly expanding areas in modern science today, and an important part of this endeavour is psychobiology which attempts to understand how the brain's anatomy, physiology and neurochemistry give rise to human thought, emotion and

[1]It takes about 3–4 milliseconds (thousandths of a second) for a neuron to generate a nerve impulse (or action potential). Thus, neurons can achieve firing rates of up to 300–400 impulses per second.

behaviour. Progress is occurring at an ever-increasing pace. In addition, brain research has many potential benefits for us all, including greater insights into the causes of human afflictions such as behavioural disabilities, mental illness and degenerative diseases, along with the prospect of much more effective treatments.

The brain may be complex, but it is continually giving up its secrets to the unrelenting bombardment of scientific attack. Arguably, there is no other discipline than biological psychology which can give us greater insight into ourselves, as well as having the potential to change people's lives for the better. For the student beginning their study into this fascinating subject, this is an exciting time to become acquainted with your brain.

KEY TERMS: *neurons, synapses, neurotransmitters*

WHAT IS BIOLOGICAL PSYCHOLOGY?

To understand what is meant by biological psychology it is helpful to consider first the word 'psychology'. The term derives from the Greek words *psyche* ('mind') and *logos* ('reason').Thus, 'psychology' literally means the reasoned study of the mind. Few psychologists, however, would unreservedly accept this definition today. The study of psychology first emerged in the nineteenth century as a branch of philosophy concerned with explaining the nature of thought through the technique of introspection (i.e. self-reflection). In fact, the first laboratory dedicated to psychological research was created by Wilhelm Wundt at the University of Leipzig in 1879. But the problem with introspection is that no matter how skilled the practitioner, its findings are subjective and unable to be verified by others. Because of this, a more experimental approach to psychology began to emerge in the early twentieth century that focused on overt behaviour which could be empirically observed and measured (Watson, 1913). This emphasis on experimentation and measurement has continued to the present day and many psychologists would now describe psychology as *the scientific or experimental study of behaviour and mental processes*.

Modern psychology has developed into a wide-ranging discipline concerned with understanding behaviour and mental processes from a variety of perspectives. As the name suggests, biological psychology is the branch of science that attempts to explain behaviour in terms of biology, and since the most important structure controlling behaviour is the brain, biopsychology is *the study of the brain and how it produces behaviour and mental processes*. Implicit in this definition is the assumption that every mental process, feeling and action must have a physical or neural basis in the brain. This is much the same as saying that the mind is the product of the brain's electrical and neurochemical activity. Although there are some philosophical grounds for questioning this viewpoint (Chalmers, 2010; Levine, 2001), even the most hardened cynic of materialism (i.e. the view that the mind is the result of physical processes) would find it hard to disagree that mind and brain are inextricably linked. This assumption is the foundation on which biological psychology is built. Yet the perplexing mystery of how the brain creates the mind remains unsolved (see Goldstein, 2020 for a recent account of how neuroscience is trying to tackle the problem).

To link the brain with behaviour, however, is a daunting task. Indeed, any attempt to do so must first require a very good understanding of the brain's biology. Traditionally, the two disciplines most relevant to the biological psychologist have been neuroanatomy (the study of the brain's neural architecture and pathways) and neurophysiology (the study of how neurons produce action potentials and neural information). However, in the last few decades the study of brain function has expanded greatly and attracted the interest of specialists from many other disciplines, including experts in biochemistry, molecular biology, genetics, pharmacology, psychiatry and artificial intelligence. Not all scientists working in these fields are necessarily interested in behaviour, although their discoveries can sometimes be of great interest to the biological psychologist. Consequently, in recent years, psychologists interested in the brain have become aquatinted with many other areas of biological science that lie outside the traditional domains of their subject. In addition, there is growing interest in how understanding the brain may relate to the philosophy of mind.

A number of different terms have been used to describe the study of brain and behaviour, and these terms at first can be confusing. For much of the twentieth century, the study of brain and behaviour was called physiological psychology because its investigators typically used 'physiological' techniques such as lesioning (the selective removal of small parts of the brain) and stimulation (using either electrical current or direct chemical administration) as their main experimental tools. This approach was complemented by examining human subjects who had suffered brain damage from accidents and stroke etc. – an area known as clinical neuropsychology. Although the terms 'physiological psychology' and 'clinical neuropsychology' are still heard today, there is a growing acceptance that they do not adequately cover many of the newer disciplines and techniques currently being used to examine the brain. Indeed, one notable major change that has taken place in brain research over the last few decades has been the use of computerized brain-scanning techniques to study the brain's activity – an area that has become known as cognitive neuroscience (a term invented by Michael Gazziniga and George Miller in the back of a New York taxi in the 1970s). Although some have suggested the terms 'biological psychology' or 'behavioural neuroscience' to describe today's brain research (Davis et al., 1988; Dewsbury, 1991), perhaps the most satisfactory is 'biopsychology' (Pinel, 2011). Whatever the arguments for and against these terms, they mean roughly the same thing: they attempt to give an appropriate name to the scientific discipline which relates brain function with psychology and behaviour. It is also important to note that biopsychology forms arguably the most important discipline within the much broader field of **neuroscience** – or what is generally regarded as the study of the nervous system in its entirety from molecules to behaviour (Cowan, 1978).

KEY TERMS: *neuroanatomy, neurophysiology, lesioning, stimulation, neuroscience*

ANCIENT HISTORICAL BEGINNINGS

Amongst the first people to realize that the brain was the organ of mind and behaviour were the ancient Greeks. The first person to recognize this appears to be Alcmaeon of Croton (c. 510–440 BC) and it was endorsed by the father of medicine, Hippocrates

(c. 460–370 BC). However not everyone agreed, including the most famous philosopher of antiquity Aristotle (348–322 BC) who believed the heart was the organ of sensation and that the brain merely served to cool blood! In fact the ancient Egyptians were so dismissive of the brain that during mummification they extracted it through the nose with an iron hook and threw it away, unlike other parts of the body which they stored in canopic jars for use in the afterlife. Throughout most of the ancient world, the human body was sacred and autopsies were prohibited – a situation that prevailed until the fourteenth century in Europe – and the first naturalistic drawings of the human brain were not undertaken until Leonardo da Vinci did so around 1480. Nonetheless, the ancient Greeks were aware of the basic form of the brain mainly through animal dissection, and they described its **ventricles** – a series of connected fluid-filled cavities that could be seen when the brain was sliced open. Because the ventricles stood out visually from the rest of the brain, it is perhaps not surprising they were used to formulate early theories about how the brain worked (Wickens, 2015, 2017a).

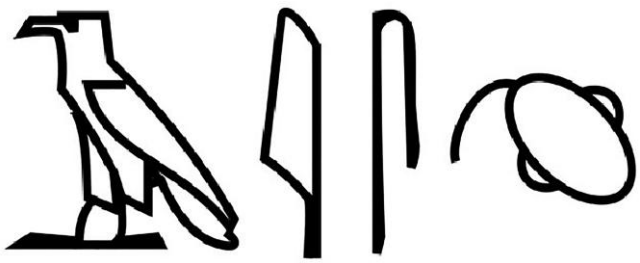


Figure 1.1 The ancient Egyptian hieroglyph for the brain as shown in the Edward Smith papyrus

Source: Said Carnot/Wikimedia Commons

One of the first writers to propose a theory of brain function based on the ventricles was the most important physician of the Roman Empire, Galen (c. 130–210 AD), who is also credited with performing the first experiments on the brain in a variety of animals including monkeys and pigs. From this work he also made many important anatomical discoveries including the cranial nerves that pass between the brain and the body (see later). Galen believed that the heart was the organ of the body that gave the spark of animation to the person because it contained a *vital spirit* necessary for life. This vital spirit was also transported to a large group of blood vessels at the base of the brain called the *rete mirabile* ('wonderful net')where it was mixed with air that had been inhaled through the nose, and transformed into *psychic pneuma*. This was then stored in the brain's ventricles and believed to provide the 'substance' of the mind. When needed for action, the pneuma was said to enter nerves resembling hollow tubes, which passed into the body where it pneumatically moved muscles to produce behaviour. Galen knew that the brain had four main ventricles. The first two are now called the lateral ventricles which form a

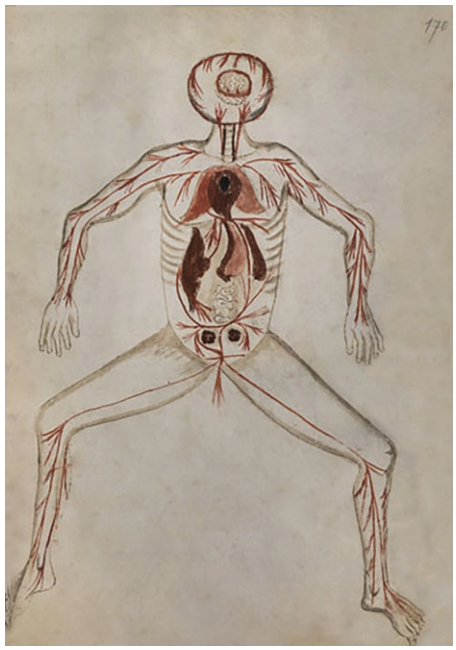


Figure 1.2 One of a series of five drawings found in a number of early medical manuscripts, possibly first drawn in Alexandria c. 300 BC. The insert shows the earliest depiction of the brain

Source: From Sudhoff 1908, plate 2. With permission from the University of Basel (Basel University Library, sign D II, fol 170)

symmetrical pair inside the two hemispheres of the cerebral cortex. Both of these feed into the third ventricle located close to the thalamus, that joins the fourth ventricle in the medulla via a narrow passage called the cerebral aqueduct (see Figure 1.3).

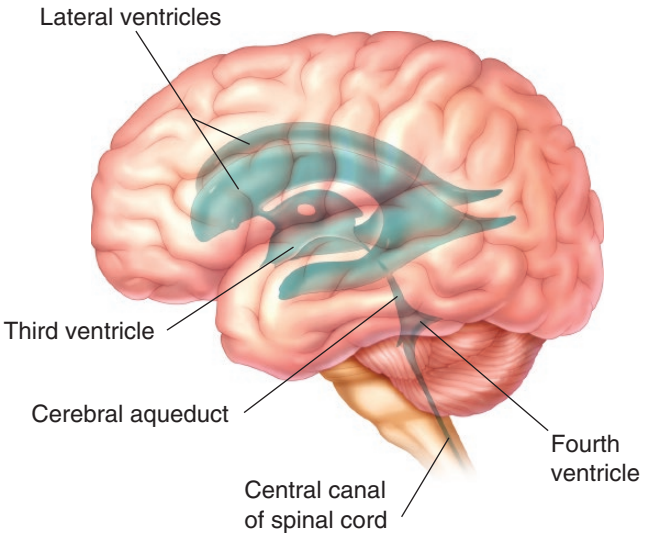


Figure 1.3 The ventricular system of the brain
Source: Garrett and Hough (2021)

Others who followed Galen extended his ideas and gave the ventricles different functions. For example, in the fourth century AD, Nemesius, the Bishop of Emesa, hypothesized that the lateral ventricles were the site of sensory and mental impressions; the third ventricle the site of reason; and the fourth ventricle the site of memory. This theory was also adopted by St Augustine (354–430 AD), who was one of the founding fathers of the Christian religion. With respected spiritual authority behind it, the ventricular concept of psychological function became the most popular theory in the brain's written history and was accepted uncritically for nearly 1,500 years. The first doubts only surfaced in the Renaissance when Vesalius (1543) in his great anatomical work *De humani corporis fabrica* showed that the human brain does not actually contain a *rete mirabile*. It seems that Galen, who had not been allowed to perform human dissection in Rome, had inferred its human existence by observing it in cattle and oxen (Wickens, 2015).

KEY TERMS: *lateral ventricles, third ventricle, fourth ventricle, cerebral aqueduct*

A NEW AGE OF REASON: DESCARTES

Descartes was a French philosopher and mathematician who more than any other person was responsible for the demise of the intellectual assumptions characterizing the Middle Ages. Indeed, his scepticism of all knowledge expressed in his famous

quote *Cogito, ergo sum* ('I think, therefore I am'), which refers to Descartes' doubt of all things except his own mental existence, is widely seen as heralding a new age of reason. The importance of Descartes in the development of psychology lies largely with his attempt at resolving the mind–body problem. Descartes believed, as did many ancient philosophers, that mind and body are two entirely different things (a theory known as dualism), with the body composed of physical matter and the mind being non-physical and a separate entity from the material world. A problem with this position, however, lies in explaining how the soul-like mind can control the physical workings of the body. In his attempt to provide an answer, Descartes proposed that the mind and body interacted in the **pineal gland**. Descartes chose this organ because he believed the soul had to be a unified entity without different parts, and the pineal gland was one of the few structures in the brain that was singular (most other brain areas are bilateral). It also helped that the pineal gland intruded into the third ventricle which put it into contact with the cerebrospinal fluid. Descartes hypothesized that the soul was able induce 'minute movements' in the pineal gland, which caused the flow of animal spirits stored in the ventricles to enter the nerves of the body. In other words, the pineal gland provided the site where the soul could act upon the brain (Lokhorst and Kaitaro, 2001; Mazzolini, 1991).

Yet Descartes realized that a great deal of behaviour was mechanical without the need for mental intervention. He first developed this idea during a visit to the Royal Gardens in Paris as a young man. The gardens exhibited mechanical statues that moved and danced whenever they were approached, caused by hydraulic pressure-sensitive plates hidden under the ground. This led Descartes to speculate that the human body might work according to similar principles. From this premise, he developed the concept of the reflex which occurs, for example, when a limb is quickly moved away from a hot source such as a fire. To explain this response, Descartes hypothesized that a sensory nerve is composed of a hollow tube – which contains small threads or fibrils passing to the ventricles of the brain. Here, they pulled open valves in the ventricular walls that forced or 'reflected' the animal spirits to flow out through the nerves, back to the muscles of the affected limb, thereby causing its withdrawal. The important point was that this response was reflexive: the mind was not involved (although it felt pain and was aware of what had happened) and therefore not a *cause* of behaviour. This idea was truly revolutionary for its time.

Figure 1.4 Descartes and his illustration of the reflex from *L'Homme* (published in 1662)

Source: Anthonyhcole/Wikimedia Commons

Prior to Descartes, it was believed that a soul-like animating force (called the *psyche* by Aristotle) controlled all the actions of the human body, but Descartes appeared to show the body operated according to mechanical principles – not unlike the internal workings of a watch. Nor did it need a soul to make it operate once it had been put into motion. With remarkable foresight, Descartes not only proposed that functions such as digestion and respiration were reflexive, but also included (more controversially) some mental functions including the receipt of sensory input, emotions and memory. He based this idea partly on his observation that animals, which he believed had no soul, were capable of sensory processing along with emotion and memory. Thus, if these processes did not need the involvement of a soul-like force in animals, then why should humans be any different? In other words, they could be regarded as reflexive responses that belonged to the physical or mechanical world. The one exception for Descartes, however, was reasoning and thought, which he held was the exclusive property of the mind and uniquely human.

Descartes' theory laid the foundations for the modern development of physiology and psychology. Although his theory was based on a dualist view of the mind, it helped shift attention towards the practical problem of how reflexes might underlie behaviour without fear of contradicting religious dogma. In addition, it encouraged others to think more deeply about how the brain worked. But perhaps most importantly, Descartes provided a great impetus for experimental research – not least because some of his ideas could be tested. As we have seen, he believed that the nervous system controlling reflexes was a hydraulic system consisting of hollow tubes through which animal spirits flowed from the ventricles to the muscles. If this idea was correct, then it followed that muscles should increase in volume as they 'swelled' with spirit during contraction. When investigators tested this theory by flexing a person's arm in a container of water, however, no increase in its level occurred. Nonetheless, Descartes had paved a way for a scientific and non-secular approach to understanding human physiology that included the brain (Wickens, 2015, 2017a).

KEY TERMS: *dualism, pineal gland, reflex.*

THE DISCOVERY OF 'ANIMAL' ELECTRICITY

In 1791, the idea of animal spirit as the cause of nervous activity was challenged by the Italian Luigi Galvani who undertook a series of experiments on amputated frog legs which included stimulating the exposed ends of their severed nerves. Galvani found that he could induce the frog's leg to twitch in a number of ways (see Figure 1.5) as indeed shown in one famous case where during a thunderstorm, he connected a nerve stump to a long metallic wire that pointed to the sky and obtained strong muscular contractions in the detached leg (arguably the most dangerous experiment in the history of biopsychology!). But perhaps more importantly, he also found that similar movements were produced when he suspended the frog's leg between two different metals. Although he did not know it at the time, Galvani had shown that when dissimilar metals make contact through a salt solution an electrical current is produced. This was, in fact, the first demonstration of the battery later formally

invented by Volta in 1800. These discoveries led Galvani to conclude that nerves are capable of conducting electricity. In other words, what had previously been regarded as some form of 'invisible spirit' was now conceived as being electrical in nature. Galvani called this intrinsic force 'animal electricity'. Its existence was finally proven beyond reasonable doubt in 1820 when the German Johann Schweigger invented the galvanometer (named in honour of Galvani) that measured the strength and direction of an electrical current. Thus, the twitching frog's legs marked the end of hydraulic theories of nervous action and the start of a new chapter in understanding how nerve cells work (McComas, 2011; Piccolino, 1997).

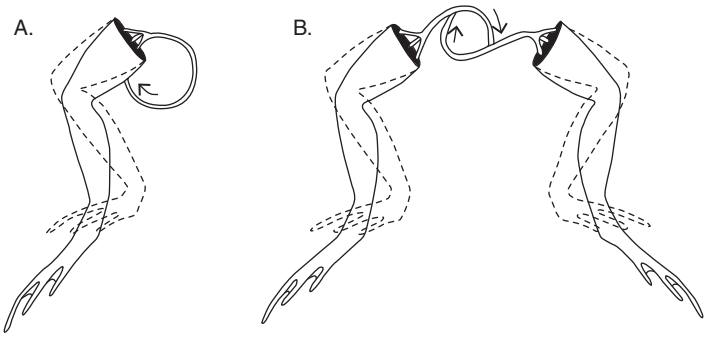


Figure 1.5 Two simple demonstrations (1794 and 1797 respectively) used to show the existence of animal electricity

In both instances muscular contraction occurs without any metallic involvement: (A) when an exposed nerve touches the muscle, the leg contracts; (B) when the right sciatic nerve touches the intact left sciatic nerve, then both legs contract.

Source: Wickens (2009). Images drawn by, and reproduced with permission from, Charlotte Caswell

One question that fascinated neurophysiologists during this time was the speed of the nervous impulse that flowed down the fibre (axon). Although the galvanometer could detect electrical activity, the nerve impulse appeared to be instantaneous and too fast to be measured. In fact, the famous physiologist Johannes Muller wrote somewhat despairingly in 1833 that the speed of the nerve impulse was comparable to the speed of light and would never be accurately estimated. However, Muller was soon proven wrong by the work of Hermann von Helmholtz – in the early 1850s – who managed to extract long motor nerves (some 50–60 mm in length) that were still attached to muscles taken from frog legs. Helmholtz recorded the delay between the onset of electrical stimulation and the resulting muscle twitch, and calculated the speed of the impulse to be about 90 feet (27 metres) per second or around 60 miles (96 kilometres) per hour. We now know that Helmholtz was fairly accurate with his estimation. Moreover, whilst the nerve impulse was fast, it was not comparable with the speed of light. In fact, neurophysiologists have now established that speed of nerve conduction varies depending on the type of **axon** (or nerve fibre), with the impulse being quicker in large diameter axons which are sheathed in an insulating layer of **myelin** (e.g. the fastest neuron can conduct action potentials at a speed of 120 metres per second or 432 km per hour), and slowest in small diameter unmyelinated axons (e.g. 35 metres per second).

KEY TERMS: *axon, myelin*

SPECIAL INTEREST 1.1

THE NOBEL PRIZE IN PHYSIOLOGY OR MEDICINE

As a student of biopsychology, the most coveted award you can aspire to achieving is the Nobel Prize in Physiology or Medicine. As a recipient of this award, you will have been judged to have made '*discoveries*' conferring '*the greatest benefit on mankind*', and will enjoy instant recognition, celebrity and unrivalled authority. At the time of writing, some 216 persons have been given this accolade in 'physiology or medicine', with about 50 of those individuals making contributions that can be considered relevant to neuroscience. Put simply, if one is ingenious enough to win the prize, then one will belong to a very select band of scientists whose fame will be eternal in the annals of physiology and medicine.

Alfred Bernhard Nobel was born in 1833 in Stockholm, Sweden. The son of an engineer, he moved in his childhood to Russia, where his father made a fortune making explosives and military equipment. At the age of 17, Nobel studied chemistry in Paris and worked for a time in the USA before returning to Sweden in 1859. In 1866, he invented nitro-glycerine. Unfortunately, an explosion at his factory was to kill Nobel's younger brother Emil and four other workers in 1864. In an attempt to make a safer explosive he invented dynamite in 1867. This was to establish Nobel's fame world-wide as it was widely used to blast tunnels, cut canals and build railways and roads. By the time Alfred Nobel died in 1896, he had made a massive fortune, and in his will left instructions that most of his money (which amounted to 94% of his total assets, or 31 million Swedish kronor) should be used to give prizes that honoured people from all over the world for outstanding achievements in physics, chemistry, medicine, literature and peace. Although the will was strongly contested, the first awards were made in 1901 on the fifth anniversary of Nobel's death.

The first Nobel Prize in Physiology or Medicine was awarded in 1901 to Emil Adolf von Behring, for his work on developing a vaccine against diphtheria. But the first person of interest to psychologists to become a Nobel Laureate was Ivan Pavlov in 1904. Despite this, his prize was in recognition of research on the physiology of digestion and not for his experiments which followed on the elucidation of conditioned reflexes. In fact, the first 'proper' brain researchers to obtain the award were Camillo Golgi and Santiago Ramón y Cajal, in 1906, for their work describing the neuroanatomy of the central nervous system. The award ceremony, however, was not without some acrimony, as during their acceptance speeches Golgi and Cajal gave opposing views on whether neurons were joined together or separated by synapses. Golgi, who believed that nerves were joined together in a reticulum, accused his rival of not having any 'firm evidence' to support his claims of neurons being independent units. However, it was Cajal who was correct. There have also been other controversies. For example, in 1949 Egas Moniz won the prize for introducing the frontal lobotomy to treat mental illness – a procedure that often resulted in many harmful side effects. Protests from over 250 scientists were also raised about the 2000 Nobel Prize (awarded to the neuroscientists Avrid Carlsson, Paul Greengard and Eric Kandel) for the non-inclusion of Oleh Hornkiewicz who has been noted for his work on Parkinson's disease. Another controversy was the omission of Rosalind Franklin in the 1962 award for the discovery of DNA. Although she was the first to take an X-ray picture of DNA, shown to Crick and Watson, without her permission, and vital in their deductions of determining the structure of the DNA molecule, Franklin is often forgotten for her work.

Table 1.1 Nobel Prize winners in areas related to Biopsychology and Neuroscience

Date	Nobel Laureate	Nationality	Area of work
1904	Ivan Pavlov	Russian	Digestion
1906	Camillo Golgi Santiago Ramón y Cajal	Italian Spanish	Structure of the nervous system
1914	Robert Barany	Austrian	Vestibular apparatus of the ear
1932	Charles Sherrington Edgar Adrian	British British	Function of neurons
1936	Henry Dale Otto Loewi	British German	Chemical nature of the nerve impulse
1944	Joseph Erlanger Herbert Gasser	American American	Research on single nerve fibres
1949	Egas Moniz Walter Hess	Portuguese Swiss	Lobotomy Functions of the hypothalamus
1961	Georg von Békésy	Hungarian	Functions of the cochlea
1963	Alan Hodgkin Andrew Huxley John Eccles	British British Australian	Ionic basis of neural transmission
1967	Ragnor Granit Haldan Hartline George Wald	Finnish American American	Visual processes of the eye
1970	Jules Axelrod Bernard Katz Ulf von Euler	American German/British Swedish	Release of neurotransmitters in the synapse
1973	Konrad Lorenz Nikolaas Tinbergen Karl von Frisch	Austrian Dutch Austrian	Ethology and animal behaviour
1977	Roger Guillemin Andrew Schally	French Polish	Discovery of neuropeptides
1979	Herbert Simon	American	Cognitive psychology
1979	Godfrey Hounsfield Allan MacLeod	British South African	Invention of CAT scanning
1981	David Hubel Torsten Wiesel Roger Sperry	Canadian Swedish American	Visual cortex Functions of the cerebral hemispheres
1986	Rita Levi-Montalcini Stanley Cohen	Italian American	Discovery of neural growth factors
1991	Erwin Neher Bert Sakmann	German German	Ion channels in nerve cells

(Continued)

Table 1.1 (Continued)

Date	Nobel Laureate	Nationality	Area of work
1994	Alfred Gilman Martin Rodbell	American American	G proteins and their role in signal transduction
1997	Stanley Prusiner	American	Discovery of prions
2000	Arvid Carlsson Paul Greengard Eric Kandel	Swedish American American	Discoveries related to synaptic neurotransmission
2003	Paul Lauterbur Sir Peter Mansfield	American British	The development of magnetic resonance imaging
2004	Linda Buck Richard Axel	American American	The discovery of odorant receptors
2007	Mario Capecchi Sir Martin Evans Oliver Smithies	Italian British British-American	The genetic modification of stem cells
2014	John O'Keefe May-Britt Moser Edvard Moser	American-British Norwegian Norwegian	Brain mechanisms of spatial navigation
2017	Jeffrey Hall Michael Rosbash Michael Young	American American American	Discoveries concerning the molecular basis of circadian rhythms

THE DISCOVERY OF THE NERVE CELL

Although Galvani had shown that nervous energy was electrical in nature, there was still much to learn about nerves and the nervous system. For example, up until the early nineteenth century there was no accurate idea of what a nerve looked like, other than they had some sort of body (sometimes called a globule) and long thin projections. In fact, many believed that nerves were joined together in much the same way as blood vessels are interconnected (i.e. through a system of connecting tubes) which was called a reticulum by neuroanatomists. These beliefs persisted despite the invention of the microscope in 1665 by Robert Hooke, who coined the word 'cell' after examining a slither of cork, and the subsequent work of Anton Von Leeuwenhoek, who used it to examine biological tissues. Unfortunately, the early microscopes did not reveal neural structure in great detail, and it wasn't until around 1830 when chromatic lenses were developed that they provided stronger and clearer magnification. Even so, there was the problem of how to prepare the tissue for microscopic work so that nerve cells could be distinguished from other types of material. Although by the 1800s, histologists had found new ways to stain nerve tissue, their methods stained all neurons indiscriminately. This meant that the only way to visualize a neuron was to remove it from the mass of tangled cells in which it was embedded. Since neurons were far too small to be seen with the naked eye, this proved extremely difficult and rarely successful.

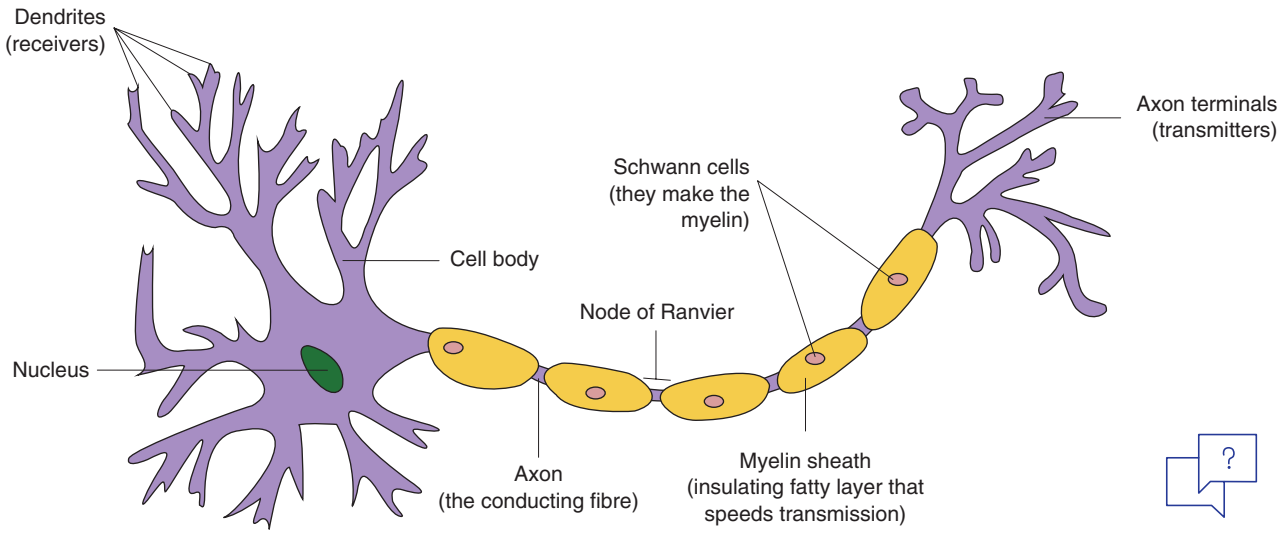


Figure 1.6 The main components of a typical brain neuron

Source: Higgs et al. (2020); Quasar Jarosz/Wikimedia Commons

In 1875, however, a major breakthrough occurred when the Italian anatomist Camillo Golgi (1843–1926) discovered a new stain that allowed individual nerve cells to be observed. By serendipity, he found that when he exposed nervous tissue to silver nitrate, this caused nerve cells to turn black, enabling them to stand out in bold relief so they could be clearly be seen under a microscope. But more importantly, Golgi's technique only stained around 2% of the cells in any given slice of nervous tissue. This was a great advance as it made individual neurons and all their various components such as **dendrites** and **axons** more clearly observable (see Figure 1.6). This method soon proved indispensable for examining the wide variety of cells in the brain. Indeed, much of the basic terminology which we now use to describe nerve cells was introduced by anatomists around this time (c. 1880).

The person who put the Golgi stain to its greatest use, however, was the Spaniard Santiago Ramón y Cajal (1852–1934) who many regard as the father of modern neuroscience. Cajal not only improved upon Golgi's method by double staining to give more reliable results, but he also spent many hours peering down a microscope to describe and draw the neural anatomy of the brain with the technique. The number of his important neuroscience discoveries is probably unmatched by any other researcher. He showed, for example, that the brain contains a great variety of cells with different characteristics. Although some cells had short axons that projected to cells within the same structure (i.e. interneurons), others had long axons that formed pathways that projected to distant brain regions. Cajal further showed that the brain was not a random morass of nerve cells as had been widely assumed, but a highly organized structure with clearly defined regions and groups of nuclei composed of cell bodies (see Figure 1.7). Cajal even guessed the direction of information flow though neurons. For example, his observations led him to realize that neurons received much of their input via their dendrites (from the Greek *dendron* meaning tree) and that they sent information along their cable-like pathways called axons. Thus, he was one of the first to see that there is a preferred direction for transmission from cell to cell – something he called dynamic polarization (Finger, 2000).

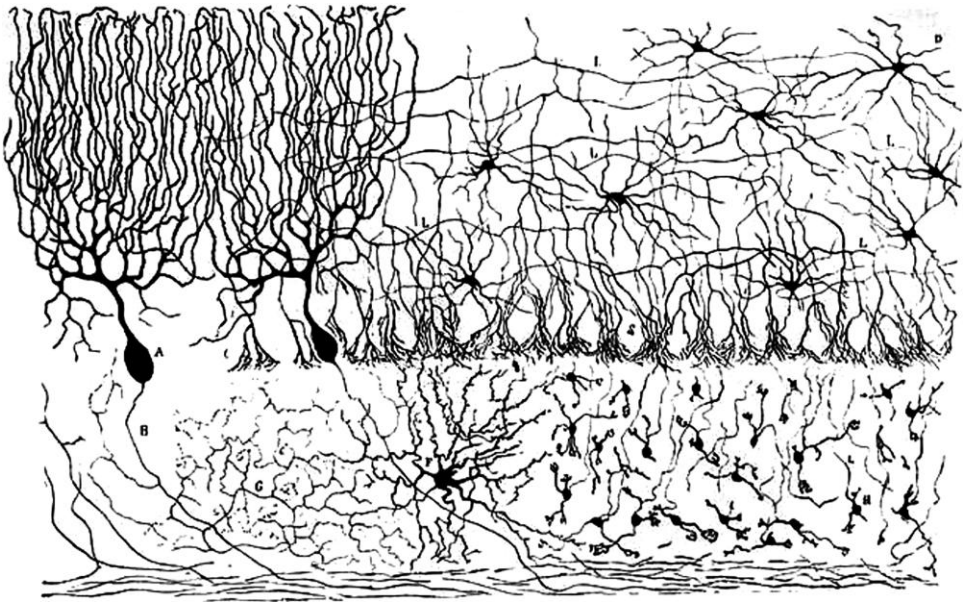


Figure 1.7 Cajal's depiction of neurons in the cerebellum using the Golgi stain
Source: Santiago y Ramon Cajal, public domain

Yet perhaps Cajal's most important contribution to neuroanatomy was his discovery that nerve cells were individual units which became known as **neurons** (a term first used by Wilhelm Waldeyer in 1891). Put another way, the nervous system was composed of cells much like any other part of the body. Previously, it had been believed that nerves were joined together in a network of tubes called a reticulum by Golgi who was a vociferous supporter of this theory. However, Cajal showed that nerve cells are not physically joined or connected. Rather, the axon terminals end very close to the neurons – normally by innervating their dendrites. In other words, each neuron is an individual unit that is not joined to its neighbours – and in some cases they can be seen to be separated by a small gap (see Figure 1.9). These points of contact were called 'synapses' in 1897 by the British neurophysiologist Charles Sherrington who derived the term from the Greek synapsis which means 'to clasp'. This discovery raised many new questions, not least how nerve cells sent information across the synapse, and how this transmission was able to generate a new electrical signal in the postsynaptic neuron.

Following Golgi's discovery many other staining techniques were developed that enabled investigators to examine nerve cells in more detail. For example, some techniques were able to selectively stain cell bodies, called the soma, whereas others highlighted the axons by staining their myelin covering – which allowed neural pathways in the brain to be traced. In other instances, staining techniques were combined with lesioning methods to provide useful information (e.g. neural pathways can be traced by staining degenerating axons that arise from a structure after it has been experimentally destroyed). By the turn of the century the study of neuroanatomy had become an established discipline. It also provided one of the foundation stones on which physiological psychology was based, for without knowledge of brain structure and organization, very little can be said about how it functions to produce behaviour (Rapport, 2005; Shepherd, 1991).

KEY TERMS: *cell, dendrites, axons, soma, interneurons.*

THE DISCOVERY OF CHEMICAL NEUROTRANSMISSION

One of the most important questions following Cajal's work concerned the nature of the message crossing the synapse from the presynaptic neuron (the neuron before the synapse) to the postsynaptic neuron (recipient neuron). From the time of Galvani, it was known that neurons transmitted messages using electrical energy, but how did this principle extend to synapses? For example, did an electrical current jump across the synapse, or was there another form of communication? As early as 1877 the German physiologist Emil Du Bois-Reymond had suggested that chemical transmission might be the answer. And in 1904, the Cambridge researcher Thomas Elliott lent support to this idea by showing that adrenaline stimulated the activity of bodily organs that were innervated by the body's autonomic nervous system. Indeed, Elliott made what is now regarded as the first clear statement about the feasibility of neurotransmission. Indeed, Elliott made what is now regarded as the first clear statement about the feasibility of neurotransmission by stating: 'Adrenaline might then be the chemical stimulant liberated on each occasion when the impulse arrives at the periphery.' But, arguably, the most important experiment to confirm chemical transmission was performed by Otto Loewi in 1921. According to Loewi's memoirs, this discovery began on the night of Easter Saturday when he awoke from a sleep and wrote down the details of an experiment that had come to him in a dream. Loewi then went back to sleep, but on waking again, was unable to decipher his notes. The next night he awoke at 3 am with the experiment back on his mind, and this time he immediately cycled to his laboratory to perform it (see Figure 1.8). Two hours later, the chemical nature of synaptic transmission had been established (Zigmond, 1999).

In his experiment, Loewi used frog hearts which are similar to our own in that they are innervated by two different autonomic nerves: the sympathetic branch that excites the heart and makes it beat more rapidly, and the parasympathetic branch (also called the vagus nerve) which slows it down. Loewi used two hearts: one with the sympathetic and vagus nerve intact, and the other with nerves removed. He then placed the intact heart in a fluid bath and stimulated its vagus nerve, causing its beat to slow down. Loewi

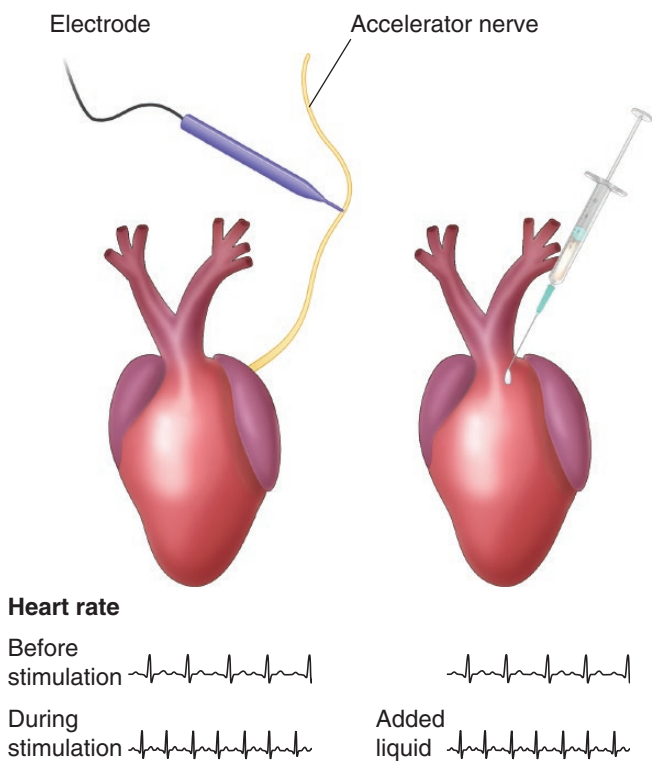


Figure 1.8 Loewi's experimental set-up showing that nerves send messages by releasing chemical substances

Source: Garrett and Hough (2021)

collected the fluid surrounding this heart and applied it to the second one – and found that its intrinsic beat also began to decrease. This indicated that the fluid must contain a substance that had been secreted by the stimulated vagus nerve. Later analysis by Sir Henry Dale and his colleagues showed this chemical to be acetylcholine, which is now recognized as an important neurotransmitter in the peripheral and central nervous systems (Wickens, 2019a).

Although electrical synapses are known to exist, it is now accepted that the vast majority of nerve cells in the body, including the central nervous system, communicate by releasing neurotransmitters from their axon terminals into synapses. The series of events that produce this transmission can be described simply as follows:

1. The axon terminals of the 'first' or *presynaptic neuron* receive an electrical impulse called an **action potential** and in response they typically secrete a *neurotransmitter*.
2. This chemical diffuses into the synapse and binds to adjacent specialized sites on the 'recipient' *postsynaptic neuron* called **receptors**.
3. Receptor binding leads to changes in the *postsynaptic neuron*, which either directly or indirectly (i.e. via second messengers) cause the opening of ion channels in its cellular membrane. This, in turn, allows positively or negatively charged ions to enter the neuron, which increases (excites) or decreases (inhibits) its internal resting electrical voltage.
4. If the neuron is excited past a certain level (i.e. by about –15mV) at its axon hillock, the increase in voltage generates an action potential (nervous impulse) that is conducted down the axon to its terminals, leading to neurotransmitter release.

Much of the subsequent chapter discusses these steps in greater detail.

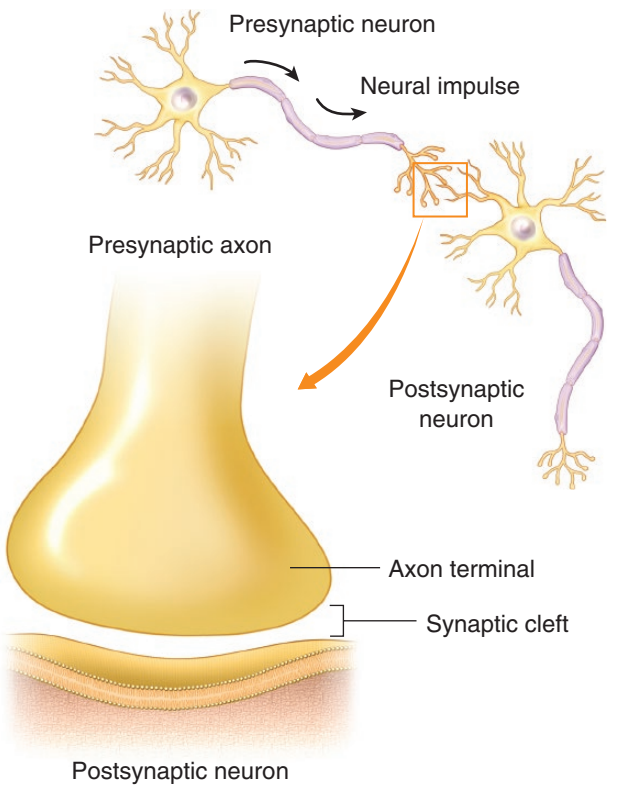


Figure 1.9 The synapse between a presynaptic and postsynaptic neuron

Source: Garrett and Hough (2021)

It is now recognized that the brain contains dozens of different neurotransmitters. The first to be confirmed was **acetylcholine** (Loewi was awarded a Nobel Prize for his discovery along with Sir Henry Dale in 1936). This was followed by **noradrenaline** in the 1940s, **dopamine** and **serotonin** in the 1950s, and gamma-Aminobutyric acid (GABA), **glutamate** and glycine in the 1960s. All of these chemicals are synthesized and stored in the nerve endings. In the 1970s, a new group of transmitter substances called neuropeptides composed of amino acids were discovered which included opiate-like substances (endorphins). These are synthesized in the cell body. More recently, it has been found that certain gases such as nitric oxide also have a neurotransmitter function. To make matters more complex, neurons do not necessarily release a single neurotransmitter as was once thought (known as Dale's Law) but secrete two or more substances together. Many of these 'secondary' chemicals act primarily as neuromodulators whose function is to 'modify' the effect of other neurotransmitters. These substances, which include the endorphins (natural opioid-like substances), prostaglandins and endogenous cannabinoids, tend to affect groups of neurons in a generalized diffuse manner (see Hyman, 2005).

Table 1.2 The main neurotransmitters found in the central nervous system

Neurotransmitter	Function
Acetylcholine	Transmitter at muscles; in brain, involved in learning, etc.
Monoamines	
Serotonin	Involved in mood, sleep and arousal, aggression, depression, obsessive-compulsive disorder, and alcoholism.
Dopamine	Contributes to movement control and promotes reinforcing effects of food, sex, and abused drugs; involved in schizophrenia and Parkinson's disease.
Norepinephrine	A hormone released during stress. Functions as a neurotransmitter in the brain to increase arousal and attentiveness to events in the environment; involved in depression.
Epinephrine	A stress hormone related to norepinephrine; plays a minor role as a neurotransmitter in the brain.
Amino Acids	
Glutamate	The principal excitatory neurotransmitter in the brain and spinal cord. Vitally involved in learning and implicated in schizophrenia.
gamma-Aminobutyric acid (GABA)	The predominant inhibitory neurotransmitter. Its receptors respond to alcohol and the class of tranquilizers called benzodiazepines. Deficiency in GABA or receptors is one cause of epilepsy.
Glycine	Inhibitory transmitter in the spinal cord and lower brain. The poison strychnine causes convulsions and death by affecting glycine activity.
Neuropeptides	
Endorphins	Neuromodulators that reduce pain and enhance reinforcement.
Substance P	Transmitter in neurons sensitive to pain.
Neuropeptide Y *Gas*	Initiates eating and produces metabolic shifts.
Nitric oxide	One of two known gaseous transmitters, along with carbon monoxide. Can serve as a retrograde transmitter, influencing the presynaptic neuron's release of neurotransmitter. Viagra enhances male erections by increasing nitric oxide's ability to relax blood vessels and produce penile engorgement.

Source: Garrett and Hough (2018)

The discovery of chemical transmission by Otto Loewi, Henry Dale and others, leading to the discipline of psychopharmacology, is one of the greatest scientific achievements of the twentieth century. It not only opened up new ways of understanding brain function, it also raised the possibility of modifying behaviour by the use of drugs that targeted the action of neurotransmitters. This advance has since been realized in many ways, with the development of drugs that can be used to treat various types of mental illness such as depression or schizophrenia, or neurodegenerative disorders such as Parkinson's and Alzheimer's disease. It is also now recognized that many of the drugs acting on the brain do so either by mimicking the action of a neurotransmitter at its receptor site (known as an **agonist**) or by blocking the receptor from working (known as an **antagonist**). In addition, histochemical advances have enabled neurotransmitters in nerve endings to be visualized, enabling chemical pathways in the brain to be traced and mapped out (Hökfelt, 2009; Snyder, 2009).

KEY TERMS: *presynaptic neuron, postsynaptic neuron, neurotransmitters, receptors, ion channels, agonist, antagonist*

NEURAL CONDUCTION

By the early part of the twentieth century, neurophysiologists knew that neurons were capable of generating electrical currents, but they did not know the finer details of how this energy was being created or conducted along the axon. The main difficulty lay in trying to record from the neuron during these events. Although physiologists had at their disposal recording electrodes with very fine tips, along with oscilloscopes and amplifiers that greatly magnified the tiny electrical charges, neurons were too small to enable this type of work to take place. This remained the case until 1936, when Oxford biologist John Z. Young discovered a neuron located in the body of a squid (*Loligo pealii*) which had an axon nearly 1 mm in diameter (about 100 to 1,000 times larger than a typical mammalian axon). Not only was this axon large enough to allow the insertion of a stimulating or recording electrode, but it could also be dissected from the animal and kept alive in a bath of salt for several hours. This allowed both the electrical and chemical properties of the neuron to be examined in great detail.

Almost everything we know about how neurons generate impulses has been derived from research on the giant squid axon. Because it is accepted that all nerve cells, no matter what size or type of animal they come from, work according to the same principles, the giant squid neuron has provided an invaluable means of understanding neural function. The use of this technique was largely pioneered by two physiologists at Cambridge University called Alan Hodgkin and Andrew Huxley,[2] who published their main findings in a classic landmark set of papers in 1952 (although important work was also undertaken by Kenneth S. Cole and Howard J. Curtis in America). Hodgkin and Huxley not only developed a technique enabling recording electrodes to be positioned inside and outside the neuron without causing it damage, but they also found a way of 'squeezing' cytoplasm from the axon so its chemical composition

[2]Huxley's grandfather was the famous biologist Thomas Huxley who was also known as 'Darwin's bulldog' for his support of evolutionary theory.

KEY THINKER 1.1

SIR HENRY DALE

The concept of chemical synaptic neurotransmission is one of the fundamental keystones on which neuroscience is based. Indeed, without the knowledge of chemical neurotransmission, it would be impossible to understand how the nervous system and brain works. Sir Henry Dale is undisputedly one of the greatest British pharmacologists of the twentieth century, whose work not only identified acetylcholine as a neurotransmitter in the autonomic and somatic nervous systems, but was also pivotal in establishing the principles of chemical neurotransmission.

Dale was born in London in 1875 and later went to Trinity College, Cambridge, where he studied natural sciences. After medical training at St Bartholomew's hospital, Dale accepted an appointment in 1904 at the Wellcome Physiological Research Laboratories in London. This was an unusual choice, for the Wellcome was aimed primarily at developing new drugs (it had produced an antitoxin for diphtheria in 1894), and Dale's friends feared it would compromise his independence as a researcher. After starting his post, Dale was asked to examine the chemical constituents of a patristic fungus called ergot known to affect rye and other cereals. Although Dale was not attracted by the challenge he soon realized that ergot was a treasure trove of chemical substances. One of the first drugs he managed to extract from the fungus was ergotoxine which could be used to treat high blood pressure (it is now known to be an alpha-adrenergic blocker). Soon after, Dale discovered that ergot contained histamine – a chemical which he would show to be a naturally occurring substance in the body and now recognized as a neurotransmitter.

But Dale's most important discovery came in 1913 when he identified a substance called acetylcholine in ergot. This chemical had effects on the body, mimicking the activation of the parasympathetic nervous system which included slowing heart rate and respiration. Dale would not only go on to prove that acetylcholine was a natural constituent of the body (he did this by obtaining 71 pounds of ox spleen tissue from the local abattoir from which he extracted one-third of a gram of acetylcholine), but would also show that it mimicked the drugs muscarine and nicotine at different sites of the body. Although this did not confirm chemical neurotransmission at the time, it was nevertheless strong evidence that different receptors for acetylcholine existed in the body. In fact, we now know that muscarinic receptors exist in the autonomic nervous system whereas nicotinic receptors are found at the neuromuscular junction. Both receptor types are also found in the brain.

In 1936, Dale won the Nobel Prize (along with Otto Loewi) for his work on the chemical transmission of the nerve impulse. At the time it still remained an open question whether chemical neurotransmission occurred in the central nervous system, with some, including the notably strident Australian John Eccles, believing it was electrical. This situation led to much hotly contested debate and argument at various scientific meetings in the 1940s and early 1950s in what has become known as 'the soup versus sparks debate'. Dale argued strongly for chemical neurotransmission and would be proven right in 1952, when Eccles himself provided irrefutable proof that his own theory was wrong (see Wickens, 2019b).

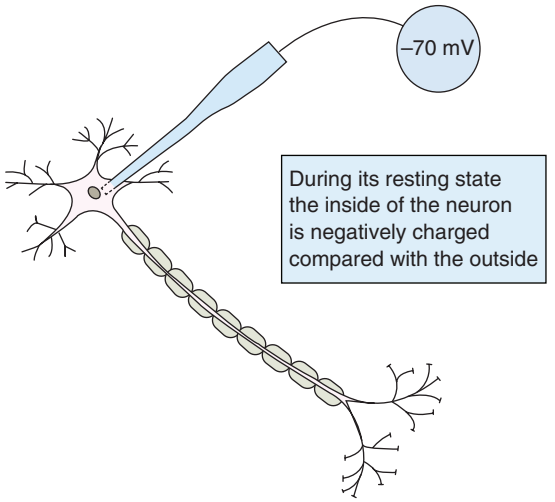


Figure 1.10 Measurement of the resting potential of the nerve cell using a micro-electrode

Source: Wickens (2009)

could be examined. This was an important step in allowing Hodgkin and Huxley to deduce how the neuron produced an electrical impulse (Wickens, 2019b).

One of the most important discoveries made by Hodgkin and Huxley (c. 1939) was that the giant squid axon exhibited a **resting potential** (Figure 1.10). That is, if a recording electrode was inserted into the neuron when it was at rest, and its voltage compared to that just outside the cell, a small but consistent difference between the two electrodes was found. Crucially, this voltage difference is around –70 millivolts (mV) with the interior of the neuron always negative compared to the outside. The difference is roughly one tenth of a volt or about 5% as much energy as exists in a torch battery. This may not appear to be very much, but it is a huge energy differential for a tiny nerve cell to maintain, and it is this voltage difference that holds the secret to understanding how it generates electrical current in the form of action potentials.

To explain why the voltage difference of –70mV occurs, it is important to understand that the intracellular and extracellular environments of the neuron, when it is at rest, are different in their concentrations of ions. An ion is simply an electrically charged atom, or particle, that has lost or gained an electron which gives it a positive or negative charge (see Figure 1.11). As any school pupil should know, an atom is composed of a nucleus containing positively charged (+) protons and neutrons, surrounded by tiny negatively charged (–) electrons that orbit around it. In the atom's normal state, the opposite charges of protons and electrons cancel themselves out, making it neutral. However, if the atom loses an electron, then it will have one less negative charge, and the result is it becomes a positively charged (+) ion. Alternatively, if the atom gains an extra electron it becomes a negatively charged (–) ion. Although only a few types of ion exist in the nervous system, they play a crucial role in the production of the nerve impulse. These include sodium ions (NA^+) and potassium ions (K^+) that have lost an electron and as a result become positively charged, and chloride (Cl^-) and organic anions (A^-) that have gained an electron and become negatively charged.

One of Hodgkin and Huxley's most important discoveries was that the concentrations of ions differed between the interior and exterior of the cell when it was at rest (see Wickens, 2015). For example, they showed positive sodium ions (NA^+) to be more highly concentrated outside the neuron than inside (at a ratio of around 14:1), along with negatively charged chloride ions (a ratio of around 25:1). In contrast, positive potassium ions (K^+) were found predominantly inside the neuron (at a ratio of around 28:1), as were negatively charged anions (which are actually large protein molecules confined to the inside of the neuron). When the positive and negative charges of the ion concentrations were added up by Hodgkin and Huxley it explained why the resting potential inside the neuron was about –70mV. In short, the intracellular fluid of the cell contains more negatively charged ions, whereas the extracellular fluid is dominated by positively charged (sodium) ions.

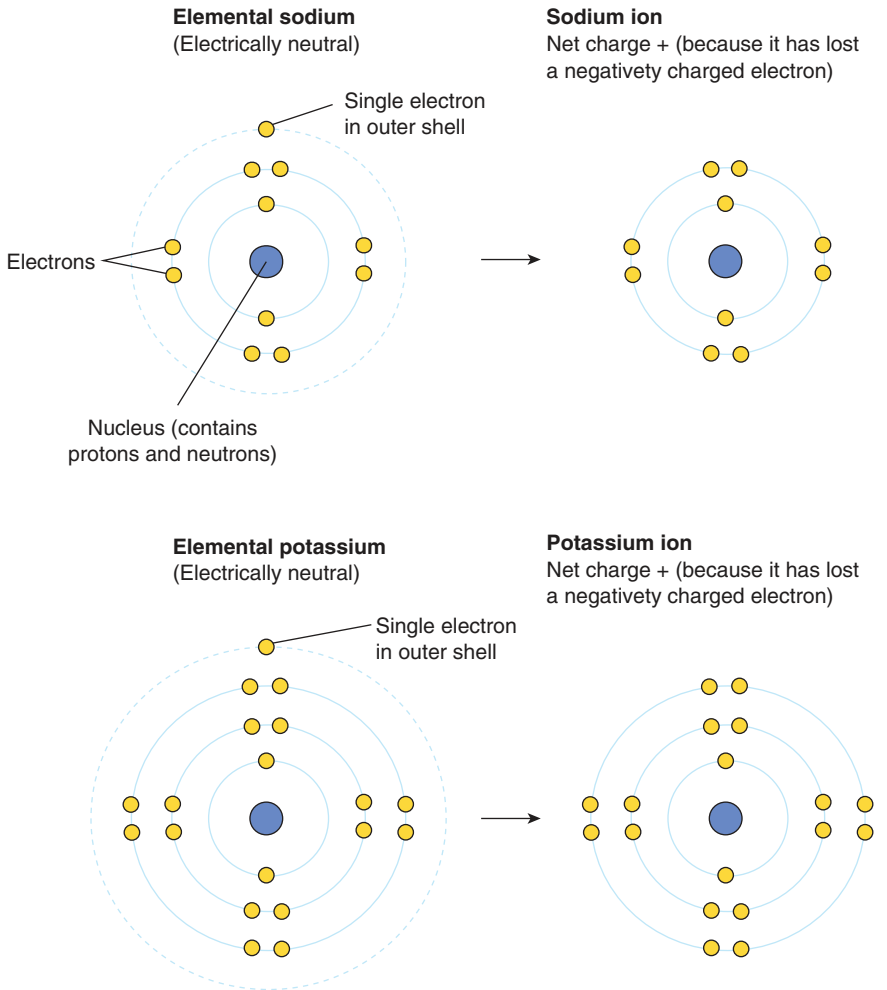


Figure 1.11 How sodium and potassium ions are formed

Source: Wickens (2009)

KEY TERMS: *resting potential, sodium ions (NA^+), potassium ions (K^+)*

Table 1.3 The concentration of ions inside and outside the axon when it is at rest expressed in millimoles (mM)

	Concentration of ions in axoplasm (mM)	Concentration of ions outside the cell (mM)
Potassium (K^+)	400	10
Sodium (Na^+)	50	450
Chloride (Cl^-)	40	560
Organic anions (A^-)	345	0

HOW DOES THE NEURON MAINTAIN ITS RESTING POTENTIAL?

Because of the uneven distribution of ions, a state of tension always exists between the inside and outside of the nerve cell. This occurs because positively charged ions are strongly attracted to negative ones, or vice versa (a force known as the electrostatic gradient), and because high concentrations of ions are attracted to areas of low concentration, or vice versa (a force known as the diffusion gradient). Consequently, when an unequal distribution of ion concentrations occurs between the interior and exterior of the cell, strong electrical and diffusion forces are produced. This means that the extracellular sodium ions will be attracted to inside of the nerve cell by electrostatic and diffusion forces, produced by the cell's negative resting potential and its relative lack of sodium. Similarly, the intracellular positively charged potassium ions will be attracted to the extracellular fluid, albeit more weakly, by diffusion forces.

If this is the case, then why don't ions simply pass down their respective electrostatic and diffusion gradients to correct the ionic imbalance and cancel the negative resting potential in the neuron? The secret lies with the nerve cell's outer coating, or membrane, which consists of a double layer of lipid (fat) molecules. This acts as a barrier to ion flow. However, embedded in the membrane are a number of specialized protein molecules that act as ion channels. These are tiny pores that can open to allow certain ions to flow into, or out of, the neuron. There are two main types of ion channel which we will discuss in more detail later: ligand-gated ion channels that are opened by ligands (i.e. chemicals) attaching themselves to receptors, and voltage-gated ion channels opened by voltage changes occurring inside the neuron. However, ion channels are also 'leaky'. In fact, when the neuron is at rest, the membrane is about 100 times more permeable to potassium ions than sodium – largely because potassium is more able to leak through its own channels. Thus, potassium moves in and out of the cell more freely than sodium.

This brings us to another important question: if ions are in constant motion across the neural membrane, how can it be that the resting potential of –70 mV is maintained? Clearly, if physical forces are simply left to operate, the flow of potassium to the extracellular fluid will quickly cause the resting potential inside the neuron to become neutral – and the flow of sodium towards the cell's interior, even at a slower rate of infiltration, will help to do the same. The answer is that the neuron maintains the intra- and extracellular balance of ions by a specialized protein located in its membrane which acts as a **sodium/potassium pump** – a molecule that transports three sodium ions out of the cell for every two potassium ions it takes in. This requires considerable energy with about 20% of the cells' energy spent on this pumping process (Dudel, 1978). Such is the importance of maintaining the negative resting potential. Without it, the neuron would be unable to generate action potentials.

KEY TERMS: *electrostatic gradient, diffusion gradient, ligand-gated ion channel, voltage-gated ion channel, sodium/potassium pump*

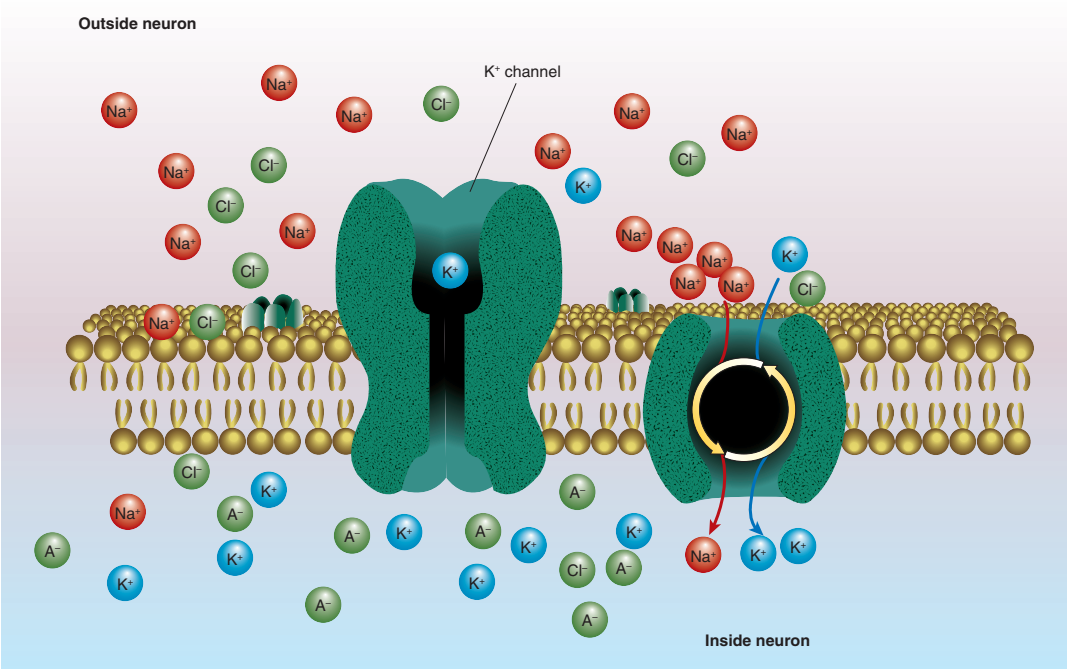


Figure 1.12 An illustration showing a potassium (K^+) channel and a sodium/potassium pump
Source: Higgs et al. (2020), adapted from Garrett (2011)

THE ACTION POTENTIAL

It was established over a century ago by Emil du Bois-Reymond that the nerve impulse is a brief pulse of electrical excitation which flows down the axon. He called this the action current, which later became known as the action potential. But how does the neuron produce this electrical excitation in the first place? By undertaking a large number of experiments on the giant squid axon, Hodgkin and Huxley demonstrated that the electrical pulse was caused by the sudden back and forth movement of sodium and potassium ions, which act as tiny electrical charges, through their respective ion channels in the neural membrane (see Wickens, 2015). They also showed the triggering event for this process was initiated when the neuron's resting potential (–70 mV) became more positive by about +15 mV. That is, the resting potential has to increase to around –55 mV, otherwise known as its threshold potential. But what exactly causes this event to happen?

As we have seen, the neuron is like a tiny biological battery with the negative (–70mV) pole inside the cell and the positive one outside. And it goes to great lengths with the sodium-potassium pump to maintain this polarity. But this also puts the neuron's resting potential under strain – not least because of the electrostatic and diffusion pressures acting to force ions in and out of the cell. In fact, the cell's resting potential is not stable at –70 mV, even with the help of the sodium potassium pump. One reason for this lies with other neural input whose activity causes the release of neurotransmitter that constantly targets the receptors of the neuron. One effect of this receptor activation is the brief opening of tiny pores in the cell's membrane, called ligand-gated ion channels, which enables small amounts of ions to flow into

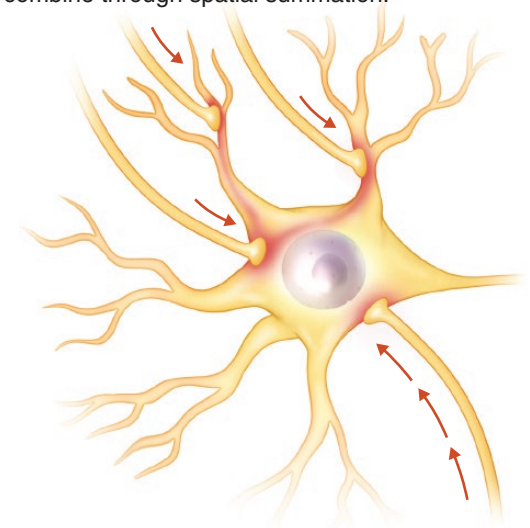


Figure 1.13 Spatial and temporal summation in the neuron

Source: Garrett and Hough (2021)

the cell – which then cause small changes to the neuron's resting potential. Some neurotransmitters such as glutamate make the resting potential more positive by increasing the membrane's permeability to positive ions, whereas others such as GABA make it more negative by allowing the influx of negative ions (see Hille, 2001).

Although a few molecules of neurotransmitter binding to a receptor will probably have a negligible effect on the cell's resting potential, it must be remembered that a neuron is likely to have thousands of receptors (and ion channels) spread over its dendrites and soma. A significant number of these receptors will also be subjected to both excitatory and inhibitory neurotransmitters impinging upon them at any moment. Consequently, the 'summation' of all this stimulation, at a given point in time, may produce a significant change in the cell's resting potential. In fact there are two types of summation: spatial summation where inputs from widely distributed neural sources impinge on the neuron at once, or temporal summation where a high frequency of inputs occur at a single or smallish location (see Figure 1.13). If the summation, spatial or temporal, causes the voltage inside the cell to become more positive it produces what is known as **excitatory postsynaptic potential** (EPSP). If the internal voltage of the cell becomes more negative it is called an **inhibitory postsynaptic potential** (IPSP).

KEY TERMS: *action potential, summation, excitatory postsynaptic potential, inhibitory postsynaptic potential*

The change in resting potential produced by the flow of ions into the cell following neurotransmitter stimulation normally begins in the dendrites, with the voltage change (i.e. an EPSP or IPSP) spreading down into the cell body. But how does a change in resting potential lead to an action potential? The answer lies with a specialized part of the neuron called the **axon hillock** located at the junction between the cell body and axon. Like the rest of the neuron, this area normally has a resting potential of around –70mV. But if the voltage at this site is increased to reach its threshold value of –55 mV, then a rapid sequence of events occurs that causes an action potential, or nerve impulse, to be produced and move down the axon.

As Hodgkin and Huxley showed, if a recording electrode is placed into the axon hillock during the formation of an action potential, it reveals some remarkable events (see Figure 1.14). Firstly, there will be a sudden increase in voltage from about –55mV to about +30mV in less than one thousandth of a second (msec)! This is

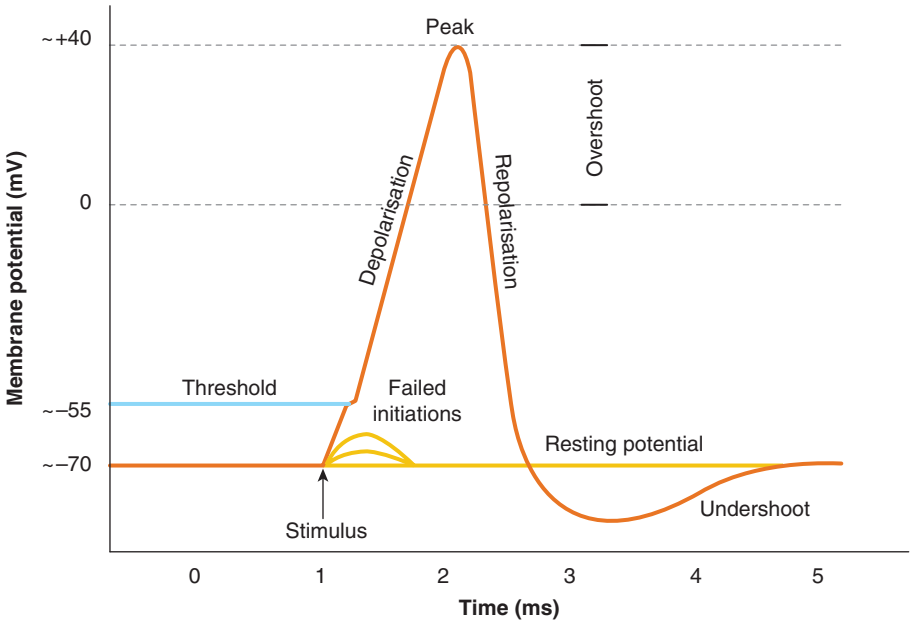


Figure 1.14 The action potential

Source: Higgs et al. (2020); Chris 73 and Diberri/Wikimedia Commons

known as depolarization (Chen & Lui, 2020). However, this huge reversal from negative to positive does not last long. Almost immediately, the voltage will show a sudden decline, falling from +30mV to –80mV, before returning to –70mV. This fleeting drop below the resting potential of –70mV is called the refractory period and during this interval the neuron is inhibited from firing again. But, since this whole process takes place in just 4 or 5 msecs, it means it is possible for a neuron to fire over a hundred times a second. The depolarization at the axon hillock is the origin of the nervous impulse that begins its journey down the axon.

It follows that the axon hillock is the critical site where the integration of excitatory and inhibitory postsynaptic potentials has to take place before an action potential can be generated. This response is 'all-or-nothing' as the neuron either fires or doesn't (e.g. there is no in-between or graded response). However, once the action potential is formed, it travels down the nerve fibre to reach the axonal endings where the stores of neurotransmitter are located ready to be released into the synapse. But here lies a physiological difficulty: axons are long spindly projections, and if the action potential passively moved down the fibre, its energy would decay before getting very far. Thus the axon must have some way of actively moving the charge down its length. The secret of how it does this lies with a fatty sheath called myelin which covers the axon and is not dissimilar to the rubber coating that surrounds an electrical cable. Unlike an electrical cable, however, the myelin contains short gaps along its length called nodes of Ranvier, and it is here renewal of the action potential takes place. At each node, the action potential is amplified back to its original intensity. In effect, the impulse 'jumps' down the axon. This process is called **saltatory conduction** (from the Latin *saltare* meaning 'to jump') and explains how the action potential can travel long distances without weakening. If you imagine a neural impulse going from a giraffe's brain to its back legs, then you will realize the necessity of such a process.

KEY TERMS: *axon hillock, depolarization, all-or-nothing response, saltatory conduction*

THE IONIC BASIS OF THE ACTION POTENTIAL

How does the neuron bring about the sudden change in depolarization (e.g. from –55 mV to around +30mV) to generate an action potential? The answer lies with the sodium and potassium ions – or rather, the opening and closing of their respective voltage-gated ion channels embedded in the neural membrane (Bean, 2007). As we have seen, large numbers of sodium ions exist in the extracellular fluid, and these are attracted to the cell's interior by strong electrical and concentration forces. Yet the cell's membrane acts as a barrier to sodium, and if ions infiltrate into the neuron, they are removed by the sodium-potassium pump. However this fine balance is changed when the threshold potential (–55mV) is reached. When this moment occurs, the membrane's sodium channels open, and and as if a door is thrown open, sodium ions flood into the cell propelled by electrostatic and concentration forces. It has been estimated that up to 100,000,000 ions can pass through a channel per second (although they only remain open for a fraction of this time), and it is this large influx of sodium (N^+) current into the cell that changes its negative resting potential into a positive depolarization (see Figure 1.15).

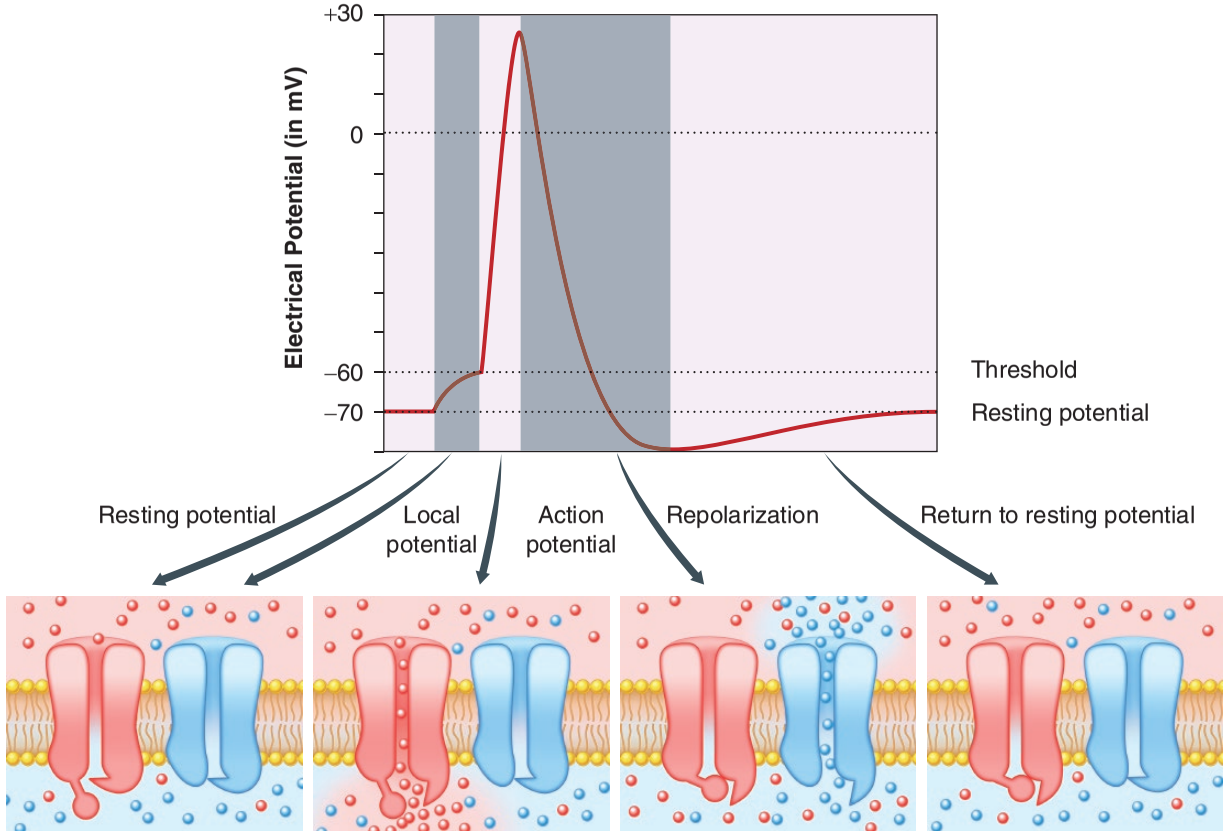
At the peak of this sodium flow (1 or 2 milliseconds after the ion channels have opened) the permeability of the membrane changes again. The neuron now closes the sodium channels and opens its potassium channels (in fact, these began to open just after the onset of the sodium influx). Because the inside of the cell at this point is now positively charged (around +30mV) due to the higher concentration of sodium, the positively charged potassium ions are pushed out of the neuron by electrostatic (as occurs with a magnet, two positive forces repel each other) and diffusion forces. This not only causes the cell's resting potential to become –70mV again, at which point the potassium channels close, but also the flow of potassium ions to the outside of the neuron is so strong, that its internal voltage drops further to about –80mV. This is called the refractory period and it is only after this event has occurred that the cell's resting potential returns to normal with the sodium-potassium pump restoring the ionic balance.

A similar pattern of ion movements in and out of the cell also occurs along the axon's length during saltatory conduction. As the electrical energy generated by the action potential spreads down the axon, it causes the opening of voltage-gated sodium channels in the nodes of Ranvier. This causes a sudden burst of sodium ions into the axon and a re-charging of the action potential. As this energy passes to the next node, there is an outflow of potassium ions at the node left behind restoring the axon's resting potential. As this cycle is repeated, the electrical signal is conducted down the full length of the axon without a loss of strength (Levitan & Kacmarek, 2015).

KEY TERMS: *voltage-gated ion channels, sodium channels, potassium channels*

NEUROTRANSMITTER RELEASE

When the action potential reaches the end of the axon, it passes through a large number of smaller axon branches ending in slightly swollen boutons otherwise known as synaptic



(a) Sodium channels (red) and potassium channels (blue) are closed and the membrane is at resting potential. Arrival of a local potential partially depolarizes the membrane but does not cause the channels to open unless it reaches threshold.

(b) As the local potential reaches the neuron's threshold, the sodium channels' activation gates open. Sodium ions (red) rush in, producing an action potential. The membrane in that area depolarizes and overshoots to positive.

(c) Sodium channels' inactivation gates close. Potassium channels' activation gates open; potassium ions (blue) move out, repolarizing the membrane. Polarity overshoots beyond resting potential.

(d) Potassium channels close. The 'excess' displaced ions drift away and the potential returns to resting level. (The sodium channel gates will return to their original state later.)

Figure 1.15 Ion movement and voltages during the nerve impulse

Source: Garrett and Hough (2021)

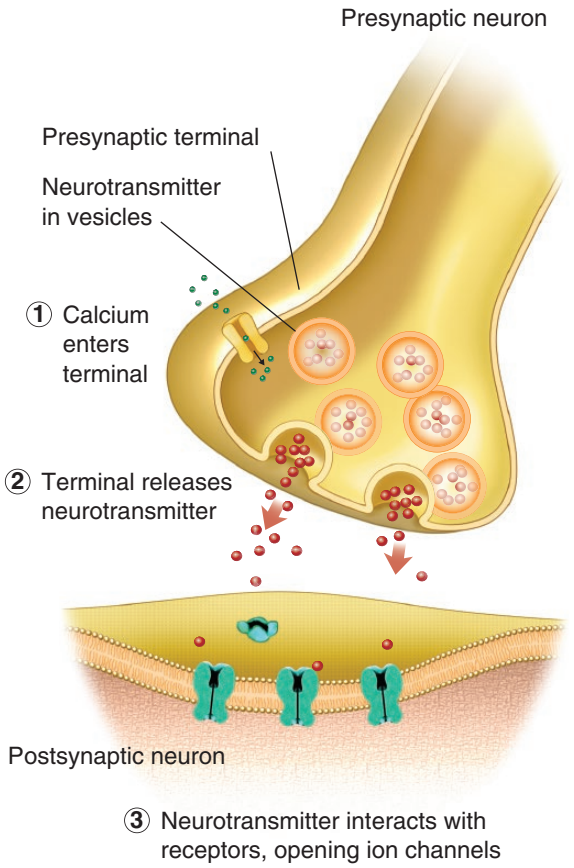


Figure 1.16 The release of chemical neurotransmitters across the synapse
Source: Garrett and Hough (2021)

terminals. Stored within these terminals are large numbers of **synaptic vesicles** each containing a few hundred molecules of neurotransmitter. As the action potential arrives at the terminal, it causes a different type of ion channel to open – namely the voltage-controlled calcium channel which allows positively charged calcium ions (Ca^{++}) to enter the bouton. This leads to a process known as **exocytosis** in which the vesicles fuse with the presynaptic membrane, releasing their contents into the synapse (Liang et al., 2017). In fact, vesicles are continually fusing with the axon terminal membrane resulting in the secretion of small amounts of neurotransmitter, although the action potential markedly speeds up this process. Consequently, the higher the number of action potentials, the greater the influx of calcium ions into the synaptic terminals with more neurotransmitter release.

The synaptic gap between neurons is around 50 nanometres across, which is equivalent to 0.00005 millimetres, and each neuron has anywhere between a few hundred to hundreds of thousands of synaptic connections (Caire et al., 2020). On one side is the presynaptic neuron with its axon ending, and on the other side is the postsynaptic neuron. When a neurotransmitter is released, it diffuses across the synapse, and binds to receptors on the postsynaptic neuron where it may exert several effects (see next section). But this is not the full story regarding the neurotransmitter's fate. Neurotransmitters must be quickly deactivated and broken down into inert chemicals, otherwise they will continue to exert a receptor effect, or block the receptor from receiving further input. Because of this, a number of processes have evolved to limit the life of a neurotransmitter in the synapse. One mechanism is to remove the transmitter from the synapse by means of a reuptake pump which recycles it back into the presynaptic axon terminal. This process is particularly important for the monoamine neurotransmitters such as noradrenaline, dopamine and serotonin. An understanding of reuptake also has important clinical implications, since drugs that block this process for either noradrenaline (e.g. Imipramine) or serotonin (e.g. Prozac) are useful in the treatment of depression and other types of mental illness (Stahl, 2013). Another important process involves chemical breakdown (i.e. enzymatic degradation). For example, acetylcholine is rapidly broken down into inert choline and acetate by the enzyme acetylcholinesterase (AchE) found in the synapse. Inhibitors of this enzyme have also been used to increase brain levels of acetylcholine in Alzheimer's disease. Another enzyme, this time present in axon terminals and glial cells, is monoamine oxidase (MAO) which degrades noradrenaline, serotonin and dopamine. Some antidepressant drugs such as Marsilid work by inhibiting this enzyme.

KEY TERMS: *synaptic vesicles, calcium channels, exocytosis, reuptake pump*

RECEPTORS

In 1905, the Cambridge physiologist John Langley first used the term '**receptor**' to refer to a site he believed must exist on muscle and neurons which were sensitive to chemicals released by the nervous system. We now know that Langley was correct and that neurotransmitters produce their effects by interacting with protein receptor molecules – many of which, but not all (see next paragraph), are found on the postsynaptic cell's membrane. The receptor and its neurotransmitter can be likened to a lock and key. In the same way it takes a specific key to turn a lock, a given neurotransmitter will only bind to its own type of receptor. Once this occurs, changes in the conformation of the receptor protein will initiate a series of events, typically leading to the opening of certain ion channels, with the subsequent ion flow instigating a change in the cell's internal voltage (i.e. an EPSP or IPSP). Interestingly, there are often several types of receptor for each neurotransmitter. For example, there are two different types of receptor for acetylcholine (muscarinic and nicotinic); two for noradrenaline (alpha and beta); five for dopamine (designated D-1 to D-5); and seven different classes with various subtypes for serotonin (designated 5HT-1 to 5HT-7). In effect, this means that a neurotransmitter can exert a different cellular response depending on the receptor it interacts with. This subject is of interest to neuropharmacologists who try to develop drugs with highly specific affinities for certain types of receptors in their attempts to better treat various conditions (see Feldman et al., 1997).

Table 1.4 Some of the main receptor subtypes found in the central nervous system

Neurotransmitter	Types of receptor
Acetylcholine (ACh)	Muscarinic and nicotinic
Dopamine (DA)	D-1, D-2, D-3, D-4 and D-5
gamma-Aminobutyric acid (GABA)	GABA-A and GABA-B
Glutamate	NMDA, APPA and kainate
Histamine	H-1, H-2 and H-3
Noradrenaline	Alpha (α) and beta (β)
Opioid	Mu (μ), delta (δ) and kappa (κ)
Serotonin (5HT)	5HT-1, 5HT-2, 5HT-3, 5HT-4, 5HT-5, 5HT-6 and 5HT-7

Although most receptors are located on dendrites, which make up most of the neuron's surface area, and to a lesser extent the cell body, they can also be found in some other places. For example, certain specialized receptors are found on the axonal endings, where they modulate neurotransmitter release, normally by a process called presynaptic inhibition. In this instance, stimulation of the receptor might cause less neurotransmitter to be released. GABA-A receptors, for example, are important in producing presynaptic inhibition, and when stimulated they reduce the inflow of calcium ions into the axon terminal, thereby slowing down exocytosis. Other types of

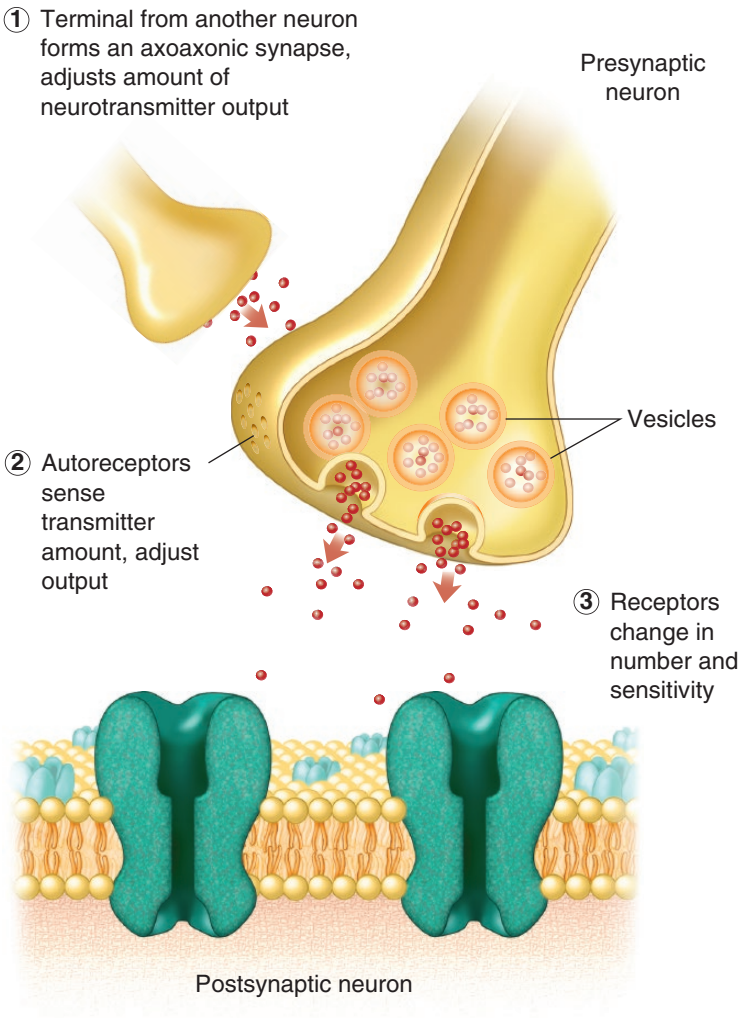


Figure 1.17 Regulating activity at the synapse
Source: Garrett and Hough (2021)

receptors are found at the axonal endings which react to neurotransmitters released by their own neuron. These 'feedback' receptors are called **autoreceptors** and they normally act to inhibit further neurotransmitter release. It is now known that a number of neurotransmitters have presynaptic autoreceptors that serve this function, including noradrenaline, dopamine, serotonin and GABA. To complicate matters further, receptors are not static entities but can change in number and sensitivity.

KEY TERMS: *receptors, acetylcholine, dopamine, noradrenaline, serotonin, presynaptic inhibition*

CHEMICAL EVENTS IN THE POSTSYNAPTIC NEURON

Whilst many types of neurotransmitter receptor exist in the central nervous system, they all alter the voltage of the neuron by opening ion channels in the neural membrane.

But how can receptor activity alter ion channels? There are two basic ways. In one situation, the receptor and ion channel form part of the same molecular unit. That is, the receptor is actually located on the ion channel and it directly influences its opening. These are called ionotropic receptors. In the other situation, the receptor and ion channels are separate entities which are not physically joined together. These are known as metabotropic receptors.

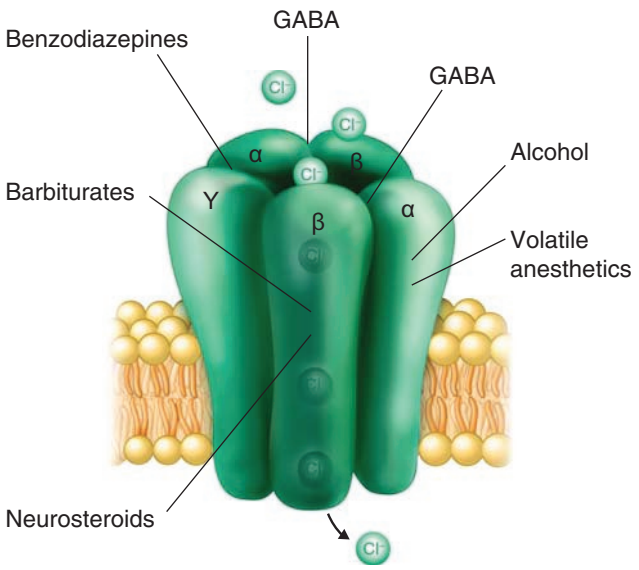


Figure 1.18 The GABA-A receptor complex
Source: Carolina Hrejsa/Body Scientific Intl. in Gaskin (2021)

In the case of ionotropic receptors, the binding of the neurotransmitter to its receptor will directly cause a conformational change in the protein molecules making up the ion channel, thereby causing it to open for a brief period of time. However, metabotropic receptors are very different. Here, the receptor activates a type of specialized protein located on the inner aspect of the cell membrane called a **G-protein**, which acts as a molecular switch to instigate a cascade of intracellular chemical processes involving various enzymes and **second messengers**. One effect of these chemical events is to activate other effector proteins to open the ion channel.

An example of a ionotropic receptor, sometimes called a ligand-activated channel, is the GABA-A receptor (see Figure 1.18). This consists of a long polypeptide chain which is shaped in such a way that it forms five elongated units, arranged in the shape of a cylinder, that pass through the neural membrane. These units are tightly held together. However, if GABA binds to a receptor site on the surface of this complex, they briefly change their shape, which creates a channel that allows the influx of negative chloride ions (Cl^-) into the cell. The GABA-A receptor is also notable for having separate binding sites for barbiturates such as Pentobarbital, and benzodiazepines such as Valium, which increase the chloride current. Thus, both Pentobarbital and Valium enhance inhibitory activity in neurons with GABAergic receptors. Another example of a ligand-activated channel is the cholinergic nicotinic receptor found at the neuromuscular junction. This receptor also contains five units in the shape of a cylinder that pass through the membrane. When acetylcholine binds to part of this site, an influx of positively charged sodium ions (NA^+) enters the cell. A distinguishing feature of ligand-gated channels is the rapidity with which they open, and for this reason they are involved in the fastest forms of synaptic transmission which take only a few milliseconds to occur.

KEY TERMS: *ionotropic receptor, metabotropic receptor, G-protein, second messenger*

Most receptors in the brain are of the metabotropic variety – which includes muscarinic acetylcholine receptors, GABA-B receptors, and several types of monoamine receptors. In these cases, when a neurotransmitter binds to its receptor, it causes an

alteration in the G-protein to which it is attached. There are many types of G-proteins with wide-ranging intracellular actions. One of the best known effects occurs when certain G-proteins increase the activity of an enzyme called **adenylate cyclase** that converts ATP, a substance used by the cell to provide energy, into cyclic adenosine monophosphate (cAMP) (see Figure 1.19). This chemical acts as a **second messenger** (the first messenger being the neurotransmitter) by diffusing through the cell's cytoplasm to open ion channels by the process of protein phosphorylation (a fancy term for changing the configuration or 'shape' of a protein). This mechanism is believed to underlie the action of noradrenergic beta receptors and dopaminergic D-1 receptors. It should also be noted that cAMP can affect many other chemical processes within the cell and not just those associated with ion channel function.

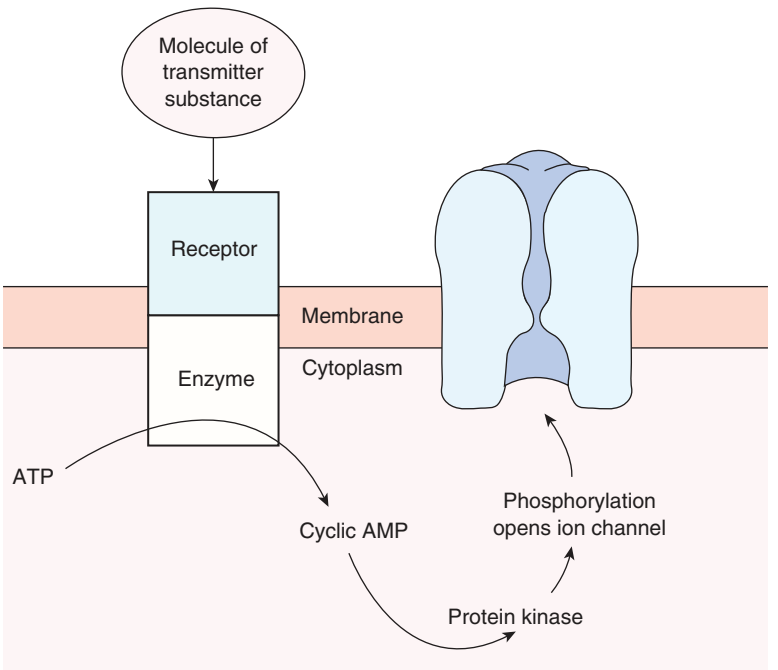


Figure 1.19 Diagram showing the main steps in the cAMP second messenger system
Source: Wickens (2009)

In recent years, much attention has focused on another second messenger system which involves G-protein stimulation of an enzyme called phospholipase C. This enzyme generates two second messengers: diacylglycerol (DAG) and inositol triphosphate (IP3). DAG activates the enzyme protein kinase C which can phosphorylate ion channel proteins, whereas IP3 acts to release stores of calcium ions within the cell which alters the excitability of the neuron. Some serotonergic receptors along with the histamine H-1 receptor use these second messenger systems. In addition to opening ion channels, certain types of second messenger can enter the cell's nucleus where they influence the activity of genes. Such a mechanism, for example, may allow changes in the physical alteration of dendritic synapses that underlie long-term memory.

Second messengers may at first sight appear to be a complex way of going about opening ion channels, but this process actually gives the cell far greater adaptability.