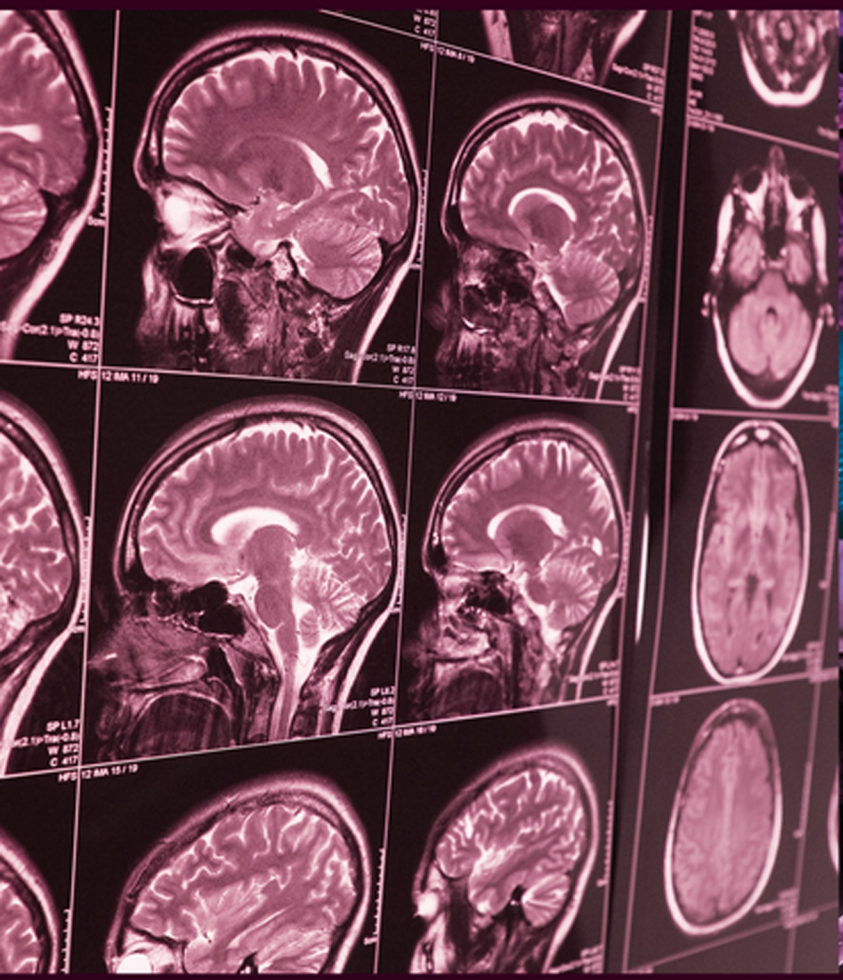
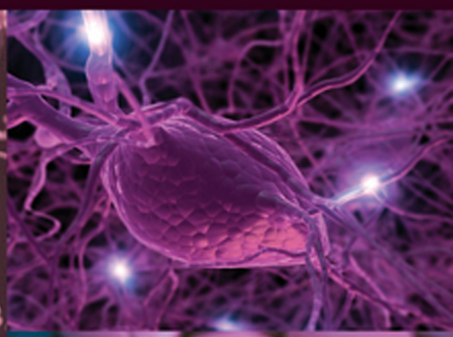
Neuropsychopharmacology and Therapeutics

Ivor S. Ebenezer





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Dedicated to the memory of my mother, Ivy Salome Ebenezer, and my aunt, Ellen Sophia Padayachy.

Contents

Preface

Neuropsychopharmacology is a relatively new subject area in the neurosciences and may be viewed as the amalgamation of the principals of neuropharmacology and psychopharmacology. I have been teaching neuropsychopharmacology to undergraduate and postgraduate students for more than two decades. During this time, I have had difficulty in finding suitable textbooks that I could recommend to my students reading for the MPharm (Honours) degree in pharmacy, BSc (Honours) degree in pharmacology and related medical sciences degrees that adequately covered all the topics I teach. There are a small number of books on neuropharmacology and psychopharmacology, but they tend to cover limited areas of these topics; for example, there may be a good description of a particular central nervous system (CNS) disorder in terms of its pathology and brain dysfunction, but it may be limited in terms of therapeutics, or vice versa. In other cases, the books may only cover a small number of CNS conditions. Therefore, I have to recommend a number of textbooks to my students, as well as giving them numerous handouts to supplement my lectures. My students keep asking me if I can recommend a single textbook that reviews most of the areas covered during their neuropsychopharmacology modules because (i) they do not want to buy or borrow too many books, (ii) they find reading multiple books sometimes difficult or confusing because of different emphases or styles of writing and (iii) they complain about the lack of time when given a large reading list. Thus, many students tend to depend mainly on their lecture material and do not read adequately around the subject area. The impetus to write this book was threefold: to simplify access for undergraduate students, to enthuse them in the neurosciences and to show them how an appreciation of basic and clinical research findings can be translated into therapeutics.

Neuropsychopharmacology and Therapeutics is a textbook that had been written primarily for students reading for degrees in pharmacy, pharmacology and the medical sciences. However, it will also be useful for students on other courses where they study a module on CNS disorders. I have taught such modules to psychiatric/mental health nurses and to students reading for masters' degrees; this book will be suitable for them. The book has eleven chapters. The material covered in Chapter 1 provides an introduction to the subject area that will be beneficial when reading the other chapters. The main psychiatric and neurological disorders that are covered in most undergraduate courses are reviewed in Chapters 2 to 11. They are discussed in terms of their clinical symptoms, epidemiology, pathology, aetiology, underlying neurobiological and neurochemical mechanisms, pharmacotherapy (including information about the drugs and their recommended clinical doses, their mechanism of action, their pharmacokinetics and their adverse effects), adjunctive nonpharmacological treatments and clinical outcomes. Each chapter of the book is a 'stand-alone' chapter and is written in a style that most students will be able to follow and understand. In addition, readers may pick and choose what part of a chapter they want to read or place greater emphasis on. For example, if they are interested in the symptoms and the drug used to treat a CNS condition, then they can read those sections of a chapter. On the other hand, if they are more interested in the aetiology, pathology and the underlying neurobiological mechanisms of a CNS disorder, then they can focus on those sections.

While most texts on psychopharmacology and neuropharmacology deal with the use of drugs in the treatment of CNS conditions, they leave the reader with the somewhat false impression that pharmacological therapy alone will be sufficient to treat the symptoms of the disorder. This may be true in some cases, but with many mental illness and other CNS disorders, psychological and social-based therapies, such as cognitive behavioural therapy and psychoeducation, in conjunction with pharmacotherapy often result in better clinical outcomes. Thus, nonpharmacological treatments that can be used as

adjuncts to pharmacotherapy are discussed to give the reader a more realistic appreciation of treatment and therapeutic outcomes.

I have always been fascinated in the history of science and the manner in which scientific progress is made. As I tell my students, reading about discovery in science is like reading a detective novel. Researchers uncover clues that can lead to discovery. However, in some cases these clues can also lead scientists down blind alleyways and it may take a long time and meticulous research to find an answer to a scientific question or puzzle. This is most evident when one studies the history of psychiatric disorders. I have, therefore, endeavoured to provide brief overviews on the historical evolution of our present-day understanding of CNS disorders and the therapies that are available to treat them.

Finally, I wish to express my gratitude to former mentors and colleagues who helped shape this book by their numerous stimulating scientific discussions and their willingness to share their scientific experiences and expertise with me. In particular, I wish to acknowledge my PhD supervisor, the late Professor John W Thompson, my postdoctoral advisors, the late Professor Ben Delisle Burns, Dr Alison C Webb and Dr Bob Baldwin, my past scientific coworkers and collaborators, Dr Bob Parrott, Dr Sandra Vellucci, Dr James H. Pirch, Dr Geoffrey H. Hall, Professor John F. Golding, Professor C. Heather Ashton and Dr Rasneer S Bains, and the numerous postgraduate and undergraduate students who have worked in my laboratory. I would also like to thank Dr John C Wong, my former colleague and research collaborator, for reading some of the chapters in this book and for his helpful comments, Ms Elizabeth Renwick for convincing me to write this book, Mr Kevin Dunn (copy editor), Ms Durgadevi Shanmughasundaram (project manager), and the editorial team from Wiley, Ms Lucy Sayers, Ms Fiona Seymour, Ms Celia Carden and Ms Audrie Tan, for their help and advice.

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Portsmouth, UK
November 2014

About the Companion Website

This book is accompanied by a companion website:

www.wiley.com/go/ebenezer/neuropsychopharmacology

The website includes:

- PowerPoint slides of all figures from the book for downloading
- PDF copies of all tables from the book for downloading

1

Introduction to Neuropsychopharmacology

All things are ready, if our minds be so.

Henry V, IV, iii (William Shakespeare)

In omnibus negotiis prius quam aggrediare, adhibenda est praeparation diligens.
(In all matters, before beginning, a diligent preparation should be made.)

(Marcus Tillius Cicero)

1.1 Overview

Neuropsychopharmacology is a relatively new subject area in the neurosciences and may be viewed as the amalgamation of the principals of neuropharmacology and psychopharmacology. Neuropharmacology mainly deals with the effects of drugs on neurones, synapses and brain circuits and their interaction with neurotransmitters and other neurochemicals at their receptors and ion channels, both at a molecular and systems level. Psychopharmacology is the study of drugs that have the ability to alter mental states, such as emotional behaviours and cognition. Neuropsychopharmacology is, therefore, a field of study that describes the effects of drugs from the molecular to the behavioural level and requires integration and synthesis of knowledge from various disciplines, including neuroanatomy, physiology, pharmacology, molecular biology, genetics, psychology, psychiatry, sociology, biochemistry and chemistry. The principals of neuropsychopharmacology are important in (i) discovering more about the workings of the brain and the impact on behaviour, (ii) learning about the cellular, receptor and neurochemical changes that accompany brain dysfunctional states and (iii) the development of drugs to treat central nervous system (CNS) disorders and psychiatric conditions.

The authors of most textbooks on neuropharmacology and psychopharmacology presuppose that the reader has almost no knowledge of basic pharmacology, neurotransmitters and neurotransmission, receptor mechanisms, cell signalling, neuroanatomy, the fundamental principals of molecular biology and

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genetics. Therefore, they spend the first few chapters of their books explaining the essential principals of these subject areas. Here, on the other hand, I will assume that the reader of this book has a working knowledge of these subjects. However, a lot of the basic information is covered in the different chapters of this book. In this chapter, some of the useful terms and concepts referred to in subsequent chapters are explained and brief overviews are given of (i) the anatomy and functions of the brain, (ii) important neurotransmitters in the CNS, (iii) some of the CNS depressant and stimulant drugs that are used in the treatment of the disorders that are discussed in subsequent chapters, and(iv) the experimental and clinical techniques that are used to obtain information on brain function.

1.2 A Brief Overview of the Anatomy and Function of the Brain

Reviewed briefly in this section are some of the important structures in the brain and their main functions. More detailed information on the anatomy and function of brain areas pertinent to specific CNS disorders are covered in the relevant chapters.

1.2.1 The Brainstem

The *brainstem* is made up of three structures, the *medulla oblongata*, the *pons* and the *midbrain* (Figure 1.1).

- The ***Medulla Oblongata*** (commonly referred to as the *medulla*) is a division of the brain known as the *myelencephalon*. It forms the most posterior or lowest part of the brain and is often considered an extension of the spinal cord within the skull. It is a small structure of about one inch (2.5 cm) in length and lies below the pons. It is composed largely of projection tracts carrying information between the body (via the spinal cord) and the rest of the brain. The medulla also has a network of cells that occupy the core of the brainstem, extending through the pons and midbrain, known as the *reticular formation* (reticulum means 'little net'). The ascending projections from the reticular formation project to the thalamus and cortex and play an important role in arousal and, for this reason, they are also known as the ascending reticular activating system (ARAS) (Chapter 8). Various nuclei in the medulla's reticular formation have diverse functional roles. There are cardiac, vasomotor and respiratory centres that regulate cardiovascular, circulatory and respiratory reflexes, respectively, as well as other nuclei that regulate reflexes, including vomiting, swallowing, coughing and sneezing.
- The ***Pons*** (which means bridge) is a structure, with a characteristic bulge, that lies above the medulla and is considered a 'bridge' between the medulla and the midbrain (which is located above it). Ascending and descending fibre tracts pass through the pons, which is also part of the reticular formation. It is a division of the brain known as the *metencephalon*. It is connected to another division of the metencephalon, the cerebellum (Section 1.2.2), by bundles of transverse fibre tracts. The pons contains centres for reflexes that are mediated by the fifth (trigeminal), sixth (abducens), seventh (facial) and eighth (vestibulocochlear) cranial nerves. The pons also has the pneumotaxic centres that, together with the medulla, control respiration.
- The ***midbrain*** is a division of the brain known as the *mesencephalon* and lies above the pons. Ascending and descending fibre tracts pass through the midbrain and it is also part of the reticular formation. The roof or tectum of the midbrain consists of two pairs of folds called colliculi (meaning 'little hills'); these form the upper part of the midbrain that lies immediately above the cerebellum The two *inferior colliculi* have auditory centres and are involved in auditory function. The *superior colliculi*, which lie in front of the inferior colliculi, have visual centres and are involved in the regulation of pupillary reflexes and eye movements that are mediated by the third and fourth cranial nerves, respectively. Under, or ventral to the tectum, is another subdivision of the midbrain, the tegmentum,

which contains part of the brainstem reticular formation. In addition, it contains a number of other key nuclei: the periaqueductal grey, which is involved in the regulation of pain and species-specific startle reflexes (Chapter 8); the substantia nigra and the red nucleus, which are involved in the regulation of motor movements (Chapter 2); and nuclei that are involved in the regulation of motivation and reinforcement (Chapters 10 and 11).

1.2.2 The Metencephalon

The ***cerebellum*** (meaning 'little brain') is a division of the metencephalon (Figure 1.1). It is a highly convoluted structure that has two hemispheres and is located behind the brainstem, to which it is connected. The cerebellum is the second largest part of the brain after the cerebral cortex and occupies about one-tenth of the brain's volume. It is densely packed with neurones and has more than half the total number of neurones in the brain. It can be divided anatomically into three parts, known as the inferior, middle and superior cerebellar peduncles, which carry nerve fibre tracts between the medulla, pons and midbrain, respectively, and the cerebellum. The cerebellar cortex (outer layer) consists of grey matter (cell bodies) and the central core consists of white matter (myelinated nerve fibres). The cerebellar white matter has nerve fibre tracts that run to and from the thalamus and cortex.

The main function of the cerebellum is the coordination of movement; this operates below the level of consciousness. The cerebellum receives incoming sensory information from the ears (equilibrium receptors), skeletal muscles (proprioceptors), the brainstem and the cerebral cortex. It integrates this information and sends it to the motor cortex and skeletal muscle to coordinate posture, balance and movement. The cerebellum also acts, in conjunction with the cortex, to plan motor movements. In addition, the cerebellum has a role in 'storage' and 'execution' of motor memories, such as riding a bicycle or playing the piano, which once learnt can be carried out reflexively without conscious thought. More recently, there has been evidence to suggest that the cerebellum may also have a role in the regulation of cognitive functions, such as nonmotor learning and attention.

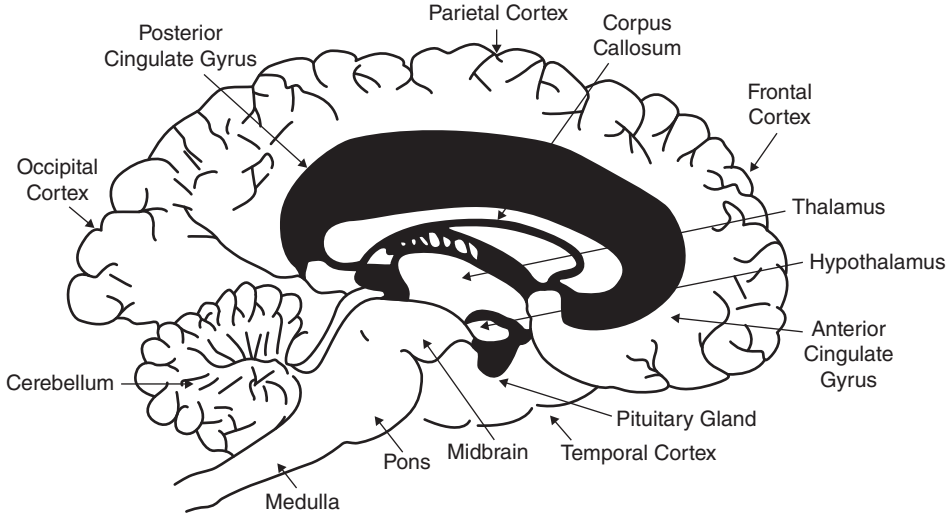

Figure 1.1 *The human brain.*

Damage to the cerebellum, due to haemorrhage, tumours or injury, may result in ataxia (which is loss of muscle coordination), tremor, vertigo (dizziness), slurred speech and an inability to walk. Drugs, such as alcohol, benzodiazepines and barbiturates (Sections 1.6.1 and 1.6.2; Chapters 9 and 11), may depress neural activity in the cerebellum and produce symptoms such as ataxia and slurred speech.

1.2.3 Diencephalon

The *diencephalon* (which means 'between brain') is the division of the brain that is located between the cerebral cortex and the midbrain. The main structures of the diencephalon are the *thalamus* and *hypothalamus* (Figure 1.1). There are other smaller structures, such as the pineal gland (Chapter 9), in the diencephalon.

- The ***thalamus*** is a structure consisting of two large lobes that are situated on each side of the third ventricle (Section 1.2.6) and joined together by the massa intermedia that extends through the ventricle. Fibre tracts carrying sensory and other information from the spinal cord, the brainstem, cerebellum and parts of the cortex synapse in the thalamus. This information is processed in the thalamus and then sent to various areas of the cortex. The thalamus is, therefore, a major relay station in the brain. The thalamus consists of many pairs of nuclei. Some of these are specific sensory relay nuclei that receive information from sensory receptors, such as those for touch, temperature, pressure, pain, vision and sound, process them and then transmit them to appropriate sensory areas in the cortex. Thus, the lateral and medial geniculate nuclei of the thalamus are important for processing visual and auditory inputs, whereas the ventral posterior nuclei play a role in processing somatosensory information. In fact, within the thalamus, impulses from sensory receptors can produce conscious recognition of the crude sensations of pain, temperature and touch. There are also association nuclei in the thalamus, where signals of different sensory modalities are integrated and sent to association areas in the cortex for further processing. In addition, the thalamus plays an important role in mechanisms involved in alertness and attention (Chapter 9), emotions (Chapters 6, 7, 8, 10 and 11) and complex motor and reflex movements (Chapter 2).
- The ***hypothalamus*** is located below the anterior portion of the thalamus and above the midbrain and the pituitary gland (Figure 1.1). The hypothalamus, which is about the size of a peanut in the human brain, consists of several nuclei that regulate diverse bodily functions:
  - It regulates autonomic functions in both the sympathetic and parasympathetic divisions of the autonomic nervous system.
  - It plays a major role in the control of endocrine functions. Axons from the hypothalamus secrete releasing-hormones that act on the pituitary gland to regulate the secretion of various hormones into the bloodstream, including growth hormone and other hormones that, in turn, act on the adrenal gland, the sex glands and thyroid gland to elicit the release of the adrenal hormones, sex hormones and thyroid hormones, respectively. For example, corticotrophin hormone (CRH), released from axons in the hypothalamus, acts on secretory cells in the anterior pituitary gland to secrete a hormone called adrenocorticotrophin hormone (ACTH) into the blood stream. ACTH then acts on cells in the adrenal cortex, situated above the kidneys, to cause the release the hormone cortisol (Chapter 6; Figure 6.5).
  - The hypothalamus plays an essential role in the regulation of eating and drinking. Neurones in the ventromedial nucleus and lateral nucleus of the hypothalamus are involved in the regulation of food intake and energy homeostasis, while neurones in supraoptic and paraventricular nuclei of the hypothalamus are involved in the control of water intake and water balance.
  - The hypothalamus also plays an important role in the sleep–wake cycle by modulating arousal mechanisms (Chapter 9).

- The hypothalamus has an important functional role in regulating body temperature, which has to be maintained within very narrow limits to prevent damage to cells and cellular processes. By regulating autonomic output and somatic centres in the brain, the hypothalamus can cause vasoconstriction and shivering if body temperature falls below a certain limit, and vasodilation and sweating if body temperature increases beyond a certain limit.

Thus, the hypothalamus plays a crucial role in almost all bodily function by virtue of its endocrine, autonomic and other functional roles, and is a target for drugs to treat obesity, anorexia, sleep disorders (Chapter 9), fever and hormonal disorders (Chapter 6).

1.2.4 The Telencephalon

The *telencephalon* is the division of the brain that is involved with higher brain functions, including learning and memory, voluntary actions, interpretation of sensory information and making judgements. The *cerebrum*, the largest part of the brain, consists of two cerebral hemispheres, the right and left hemispheres. The two hemispheres are connected together by bundles of nerve fibres known as the *corpus callosum*. The cerebral hemispheres are covered by a thin layer of grey matter (consisting of neuronal cell bodies) approximately 2–4 mm thick, known as the *cerebral cortex*. The interior of the cerebrum consists mainly of white matter fibre tracts made up of the myelinated axons of the neurones that descend from and ascend to the cerebral cortex. However, buried deep within the white matter of the cerebrum are nuclei of grey matter that form structures collectively known as the *basal ganglia* and the *limbic system*.

- The ***basal ganglia*** (BG) consists of three main nuclei, the caudate nucleus, the putamen and the globus pallidus (Figure B2.1). The BG is part of the extrapyramidal system and plays an essential role in voluntary motor responses and in the fine-tuning of motor movements. Degeneration of a pathway from the substantia nigra in the midbrain (Section 1.2.1) to the BG results in Parkinson's disease, which is characterized by tremor, rigidity and slowness of movement. This topic is discussed in more detail in Chapter 2. The BG also plays an important role in conjunction with the premotor and supplementary premotor areas of the cerebral cortex (Figure 5.1A) in the planning of motor activity. Abnormalities in the circuits from the cortex to the BG may result in the hyperactivity that is characteristic of attention deficit hyperactivity disorder (ADHD) (Chapter 5).
- The ***limbic system*** plays an important role in the control of emotional (Chapters 6 and 8) and motivated (Chapter 11) behaviours. It comprises a circuit of structures that circles the thalamus and includes the cingulate cortex, the hippocampus, the amygdala, the fornix and septum (Figure 5.1B). The amygdala is an almond-shaped structure located in the anterior temporal lobe in front of the hippocampus; it is involved in the physiology of fear, apprehension, anxiety and aggression (Chapter 6). The hippocampus (which means 'seahorse' because it resembled this creature to early neuroanatomists) is involved with learning and memory (Chapter 3). The fornix is an important white fibre tract connecting different parts of the limbic system and circles from the hippocampus around the thalamus to the septum (located at the tip of the anterior cingulate cortex and connected to the fornix with the corpus callosum) and the mammillary bodies (located on the inferior (bottom) surface of the hypothalamus near the pituitary gland and is involved in relaying information between the fornix and thalamus). The cingulate cortex is part of the cerebrum and, in association with the prefrontal cortex, plays a major role in the regulation of selective attention and other forms of behaviour (Chapter 5).
- The ***cerebral cortex*** (commonly referred to as the *cortex*) is the outermost covering of the brain and is the largest part of the brain in humans. The cortex has six layers. Layer I, nearest the surface of the brain, has relatively few cell bodies and consists mainly of axons and dendrites. Layer II and layer IV

consist mainly of stellate cells (which are cortical interneurones with star-shaped cell bodies and short axons). Stellate cells are also found in layers I, III, V and VI. Pyramidal cells (which are large cortical neurones with a pyramid-shaped cell body, long axons and apical dendrites) are found mainly in layer V but also in layers II, III and VI. The stellate cells receive information from subcortical and cortical areas; for example, the stellate cells in layer IV receive sensory information from the thalamus. On the other hand, the pyramidal cells mainly relay information from the cerebral cortex to subcortical regions, but also relay information between cortical regions largely via their apical dendrites. In fact, each stellate and pyramidal cell connect to many thousands of other cells in the cortex, thus allowing a huge amount of information to be processed. As skull size is limited, the cerebral cortex in humans is deeply convoluted (consisting of 'furrows' and 'ridges' or, in layman's terms, 'valleys and hills'), so that a greater area of tissue may be contained within the skull without a significant increase in cortical volume.

Not all animals have convoluted cortices. Rats and mice have smooth cerebral cortices, while dogs, cats and monkeys have convoluted ones. It appears that the degree of convolution may depend on body size, at least in mammalian species, and not necessarily on intellectual capacity. The furrows are referred to as fissures, if they are large, and sulci (or sulcus – singular), if they are small. The ridges are referred to as gyri (or gyrus – singular). The fissures and gyri on the surface of the cerebral cortex are used by neuroanatomists to describe different regions of the structure.

The cerebral cortex consists of four lobes (Figure 1.1 and Figure 5.1A in Chapter 5): the frontal lobe (also referred to as the frontal cortex), the parietal lobe (also referred to as the parietal cortex), the occipital lobe (also referred to as the occipital cortex) and the temporal lobe (also referred to as the temporal cortex). The anterior portion of the frontal lobe (known as the prefrontal cortex) has areas that are responsible for planning, judgements, the capacities to multitask, analyse and evaluate complex problems, stay focused on a particular task despite external distractions, suppress urges governed by emotions, inhibit inappropriate behaviours and delay gratification for needs, such as sex, money, influence or food, by balancing future goals in relation to short-term and long-term rewards (Chapter 5). The posterior portion of the frontal lobe has the areas involved in the planning (premotor cortex and supplementary motor cortex) and execution of motor activity (motor cortex). The control of motor activity is discussed in Chapter 2. The parietal lobe has areas where somatosensory information (such as touch, pressure, pain, heat and cold) is consciously experienced. The occipital lobe has areas that are concerned with vision. The temporal lobe is involved in auditory and olfactory functions.

Each of the senses – visual, auditory, olfactory, somatosensory, gustatory – are processed in selective regions of the cortex. The way the cerebral cortex processes and interprets sensory information involves three important stages. (i) There are ***primary*** cortical areas where sensory information is received. For example, separate sets of neurones in the primary visual cortex (which is located in the occipital lobe) will fire in response to different shapes of lines (straight line, curved lines, horizontal lines, vertical lines and so forth). So, if a person is looking at a face, different sets of neurones in the primary visual cortex will respond to the different shapes of lines that make up the face. (ii) Adjacent to the primary cortical areas are ***association*** areas that are responsible for connecting the various bits of information together to make sense of them. For example, the visual associative cortex will put together the various bits of information (different shapes of lines) and interpret them as a face. (iii) There are ***integrative*** areas in the cerebral cortex that integrate the information from the association areas with other information, so that it becomes meaningful. For example, the visual integrative area will provide information that the face is female, is someone that the person recognizes and links a name to the face. Impairments in the visual integrative area may result in a person, for example, being able to be able to recognize a face but not being able to put a name to the face.

There are areas in the cerebral cortex that are dedicated to speech and language. In the second half of the nineteenth century, Pierre Broca discovered an area (referred to as Broca's area) located in the left frontal cortex that is a premotor area for speech. Its output is to the face and tongue regions of the motor cortex. In the late nineteenth century, Karl Wernicke described a sensory area in the temporal lobe

in the left hemisphere (referred to as Wernicke's area) that was responsible for understanding language. Wernicke's area is connected to Broca's area by bundles of fibres. People with damage to Broca's area can understand speech but are unable to form coherent speech (Broca's aphasias). On the other hand, people with damage to Wernicke's area have trouble comprehending speech but can produce fluent speech that is a meaningless jumble of words that lacks any meaning (Wernicke's aphasia).

The cerebral cortex is also the brain division where leaning occurs and memory is stored. As mentioned above, the hippocampus, in association with the cortex, is also involved in the physiological control of learning and memory. The role of the hippocampus and cortex in learning and memory is discussed in Chapter 3.

It is important to note that the right hemisphere controls functions on the left side of the body and the left hemisphere controls functions on the right side of the body. For example, the movement in the right hand is under the control of the left motor cortex and vice versa, and the visual pathway from the right eye crosses over to the left visual cortex and vice versa. In addition, brain functions are also divided between the two hemispheres. Thus, as mentioned above, the speech and language areas are located in the left hemisphere. Damage to one hemisphere may produce a condition known as *unilateral neglect*, where the patient displays unusual behaviour, such as only shaving on one side of the face or eating from one side of the plate and ignoring food on the other side.

1.2.5 The Cerebral Ventricles and Cerebrospinal Fluid

Within the brain there are four fluid-filled spaces called *ventricles.* The ventricles contain cerebrospinal fluid (CSF) that is similar to blood plasma but without the plasma proteins. One ventricle is located under the right hemisphere and another under the left hemisphere of the cerebrum. They are known as the ***lateral ventricles***. The CSF from both lateral ventricles drains into the ***third ventricle*** via the *interventricular foramen* (also known as the foramen of Monro). The CSF seeps into the ***forth ventricle*** via the cerebral aqueduct (also known as the aqueduct of Sylvius). Some of the CSF drains from the fourth ventricle into the *cisterna magna* (which is a space behind the medulla that is continuous with the subarachnoid space that surrounds the brain and cord). The CSF circulates in the subarachnoid space and then is absorbed into venous blood.

CSF circulates in the subarachnoid space around the brain and spinal cord and fills the spaces within the brain and the central canal of the spinal cord. CSF is formed by the separation of the plasma-like fluid from blood by a network of blood capillaries known as the *choroid plexuses*. CSF is made in the lateral ventricles and the roof of the third ventricles. The main functions of CSF are to (i) keep the surface of the brain and spinal cord moist, (ii) provide a protective cushion against injury to the brain, (iii) afford a medium for providing oxygen and nutrients to brain tissue, and (iv) provide a means of ridding the brain of waste products.

1.3 Important Neurotransmitters

Some of the important neurotransmitters that are involved in brain function and dysfunction are shown in Table 1.1. Their functional roles are discussed in the different chapters of the book. The synthesis, release, action and termination of action for many of these neurotransmitters are also discussed. In this chapter, the actions of the two principal amino acid neurotransmitters in the CNS are discussed, namely *γ-aminobutyric acid* (GABA) and *glutamate*.

1.3.1 GABA and GABA Receptors

GABA (γ-aminobutyric acid) is an amino acid and is the main inhibitory neurotransmitter in the brain. It plays a key role in reducing neuronal excitability throughout the CNS. It is found in about 60% of brain

Table 1.1 *Some important neurotransmitters in the CNS.*

Neurotransmitter	Receptors	Receptor Type
Acetylcholine (ACh)	Two main ACh receptors: Muscarinic (m) and nicotine (n) ACh receptors. (There are various subtypes of the mACh and nACh receptors.) The mACh receptor is a metabotropic receptor and the nACh receptor is a ligand-gated ionotropic receptor.	Both ionotropic and metabotropic. [Ionotropic receptors open ion channels when activated; metabotropic receptors are linked to G-proteins and 2nd messengers.]
Noradrenaline (NA)	Alpha adrenoceptors and beta adrenoceptors. NA receptors (various subtypes).	Metabotropic
5-Hydroxytryptamine (5-HT)	Seven 5-HT receptors [5-HT_1–$5HT_7$ receptors] with each of the 5-HT receptors having a number of subtypes, e.g. $5HT_{1A}$, 5-HT_{1B}, 5-HT_{1D} and 5-HT_{1E}.	Metabotropic, with the exception of 5-HT_3 receptors, which are ionotropic receptors.
Dopamine (DA)	Five DA receptors [D_1–D_5 receptors]. The DA D_1 and D_5 receptors belong to the family of D_1-like receptors; the D_2, D_3 and D_4 receptors belong to the family of D_2-like receptors.	Metabotropic
Histamine	Four histamine receptors [H_1–H_4 receptors].	Metabotropic
Adenosine	Three adenosine receptors [A_1, A_2 and A_3 receptors]. Some have multiple subtypes.	Metabotropic
Neuropeptides	Various neuropeptides act as neurotransmitters and neuromodulators with the CNS, e.g. orexin, dynorphin, galanin, cholecystokinin and angiotensin.	Metabotropic
Glutamate (Glu)	There are two classes of glutamate receptor: the ionotropic receptors and the metabotropic receptors. The glutamate ionotropic receptors are (i) NMDA receptor, (ii) AMPA receptor and (iii) Kainate receptor. There are eight subtypes of the metabotropic receptors [mGlu1–mGlu8].	Both ionotropic and metabotropic
Gamma-aminobutyric acid (GABA)	Two main types of GABA receptors: $GABA_A$ receptors (ionotropic) and $GABA_B$ receptors (metabotropic). There is also a third type, $GABA_C$ receptors (ionotropic). However, some investigators classify it as a subtype of the $GABA_A$ receptor.	Both ionotropic and metabotropic

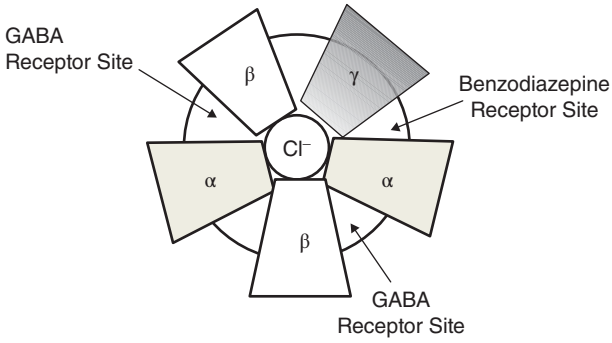

Figure 1.2 *The $GABA_A$ receptor complex comprises five subunits arranged around a central chloride ion channel. The $GABA_A$ receptor binding site is located between the α and β subunits. Benzodiazepines do not bind to the same receptor site on the $GABA_A$ receptor complex as GABA but bind to distinct benzodiazepine binding sites situated at the interface between the α and γ subunits.*

synapses and mediates effects by acting at two pharmacologically distinct receptor subtypes, namely the $GABA_A$ receptor and the $GABA_B$ receptor. There is also a third receptor, known as the $GABA_C$ receptor, but many investigators believe that it should be classified as a subtype of the $GABA_A$ receptor. Dysfunctions in GABAergic signalling lead to a host of neurological and psychiatric disorders, including epilepsy (Chapter 4), schizophrenia (Chapter 10), depression (Chapter 6), bipolar disorders (Chapter 7), anxiety disorders (Chapter 8) and Parkinson's disease (Chapter 2).

The $GABA_A$ receptor is a ligand-gated ionotropic receptor (Figure 1.2). The endogenous ligand is GABA and when GABA acts on its binding site it opens chloride ion channels that cause the influx of chloride ions through its central chloride ion channel, resulting in hyperpolarization of the membrane. In other words, the membrane becomes more difficult to depolarize. The $GABA_A$ receptor complex is a pentametric transmembrane receptor that comprises five subunits arranged around a central chloride ion channel. Two molecules of GABA have to bind to the GABA binding sites on the receptors situated between the α and β subunits (Figure 1.2) to open the central chloride ion channel. The $GABA_A$ receptor has a number of allosteric sites that bind benzodiazepines, barbiturates, ethanol and various steroid molecules. Figure 1.2 shows the allosteric binding site for the benzodiazepines; it is located between the γ and α subunits. When benzodiazepines bind to this site, they enhance the inhibitory effects of GABA on the $GABA_A$ receptor by opening more chloride ion channels (Section 1.6.1). Muscimol is a $GABA_A$ receptor agonist drug and will mimic the effects of GABA at the $GABA_A$ receptor. On the other hand, bicuculline (Section 1.5.2.2) is a competitive antagonist at the GABA receptor. Interestingly, the $GABA_C$ receptor is also linked to chloride ion conductance, but is bicuculline insensitive. Most investigators believe that it should be classed as a bicuculline-insensitive subtype of the $GABA_A$ receptor rather than as a separate type of GABA receptor.

The $GABA_B$ receptor is a metabotropic receptor formed by the heterodimerization of two 7-transmembrane (7-TM) subunits referred to as $GABA_{B1}$ and $GABA_{B2}$. $GABA_B$ receptors are distributed widely in the CNS and regulate both pre- and postsynaptic neuronal activity. $GABA_B$ receptors mediate their actions by two mechanisms. Firstly, they are linked to potassium ions channels via G-proteins and the action of GABA on $GABA_B$ receptors is to activate the opening of potassium ions channels, causing hyperpolarization of the cell membrane. This prevents action potentials from firing, voltage sensitive calcium ion channels from opening and, as a result, inhibits neurotransmitter release. Secondly, activation of $GABA_B$ receptors with GABA also reduces the activity of adenylate cyclase activity and decreases cellular conductance of calcium ions. The main agonist at the $GABA_B$ receptor is baclofen

and the effects of GABA or baclofen on $GABA_B$ receptors may be blocked with the $GABA_B$ receptors antagonists saclofen or CGP35348.

1.3.2 Glutamate and Glutamate Receptors

Glutamate is an amino acid that is widely distributed in the CNS. Until fairly recently, it was assumed that the presence of vast amounts of glutamate in the brain was due to the fact that it plays an important role in central metabolic functions and is also an amino acid that is a component of many brain proteins. However, about four decades ago, it was demonstrated that glutamate also acts as a central neurotransmitter, and it is now recognized to be the major mediator of excitatory neurotransmission in the mammalian CNS. Glutamate receptors are found in over 90% of neurones in the brain and glutamate acts on its various receptor subtypes to control most aspects of normal brain function, including synaptic plasticity, cognition, memory, learning, brain development, motor function, nociception and various other sensory functions. While glutamate is an important neurotransmitter in regulating many physiological functions, excess release of glutamate is toxic to both neurones and glia, causing neuronal atrophy and cellular death. Glutamatergic dysfunction may result in a number of neurological and psychiatric conditions, including schizophrenia (Chapter 10), Parkinson's disease (Chapter 2), Alzheimer's disease (Chapter 3), affective disorders (Chapter 6 and 7), cerebral ischaemia, multiple sclerosis, pain, stroke, epilepsy (Chapter 4) and addictive behaviours (Chapter 11).

Like GABA, glutamate also acts on two main groups of receptors: ionotropic and metabotropic receptors (Table 1.1). The ligand-gated ionotropic glutamate receptors are associated with an ion channel pore that opens when glutamate binds to the receptor. There are three ionotropic glutamate receptors subtypes, known as the NMDA (N-methyl-D-aspartate), AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole proprionic acid) and kainate receptors. They have been named according to chemical substances that were shown to be potent and selective agonists for these receptor subtypes. On the on the hand, the metabotropic glutamate receptors (mGluRs) are linked to G-proteins and may indirectly activate ion channels on the neuronal membrane through a signalling cascade. There are eight mGluRs, divided into three groups: Group 1 ($mGluR_1$ and $mGluR_5$) increases calcium ions levels in the cytoplasm and increases potassium ions efflux from cells; Group 2 ($mGluR_2$ and $mGluR_3$) inhibit adenylate cyclase and inhibit cAMP production; Group 3 ($mGluR_4$, $mGluR_6$, $mGluR_7$ and $mGluR_8$) activate calcium ion channels to allow more calcium ions to enter the cell.

The ligand-gated ionotropic glutamate receptors are normally postsynaptic receptors that work together to modulate the excitatory effects of glutamate. The AMPA and kainate receptors act to open sodium ion channels on the cell membrane to mediate rapid excitatory neurotransmission. On the other hand, the effects of glutamate on neurotransmission mediated by NMDA receptor are slower. This is because the receptor is both ligand gated and voltage gated. Figure 1.3 shows an illustration of the NMDA receptor in the resting state. There is a glutamate binding site, a glycine allosteric site and an ion channel. For glutamate to activate the opening of the channel to allow the entry of calcium and sodium ions, the following must occur. Firstly, glutamate must bind to the glutamate receptor binding site. However, glutamate cannot open the ion channel in the absence of glycine or D-serine. It has been found that there is an absolute necessity for glycine or D-serine to bind to the glycine allosteric site to activate the opening of the ion channel. However, when the channel opens, magnesium ions rapidly enter and block the channel (Figure 1.4), thus inhibiting further influx of calcium and sodium ions. It has been found that magnesium ions are expelled from the channel when the membrane potential is above –30 mV. Therefore, depolarization has to occur to allow the membrane potential to increase so that the magnesium ions can be expelled. The actions of glutamate on its other receptors causes depolarization of the membrane, so the NMDA channel can open and allow the influx of calcium ions. Thus, three events have to happen to activate the NMDA receptor: (i) glutamate must act on its binding site; (ii) glycine or D-serine must act on the glycine allosteric site; and (iii) glutamate, acting thought its other receptors, must depolarize the membrane to expel magnesium ions from the channel. Drugs that block

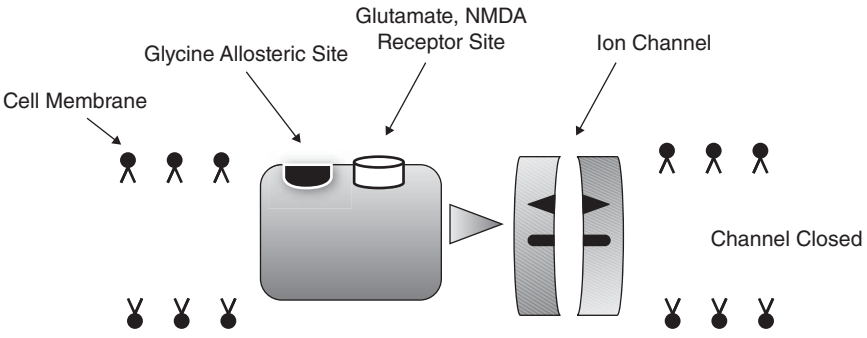

Figure 1.3 *The glutamate NMDA receptor in the resting state.*

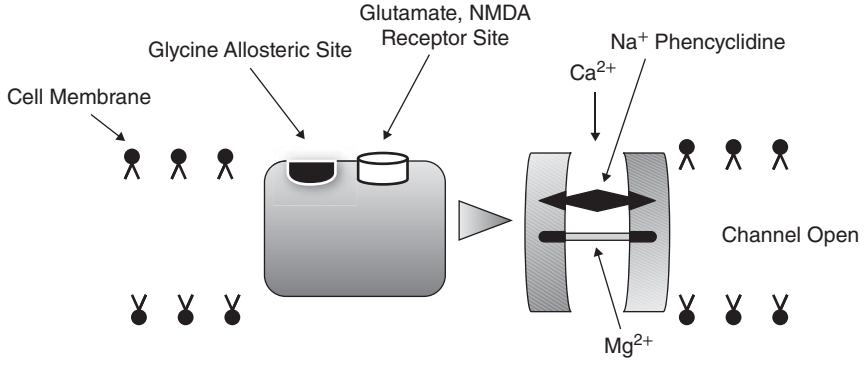

Figure 1.4 *The glutamate NMDA receptor when it is activated by glutamate. The ion channel opens when (i) glutamate acts on its receptor site and (ii) glycine binds to its allosteric site. Note that magnesium ions (Mg^{2+}) block the channel at membrane potentials below –30 mV. Glutamate, acting thought its other receptor subtypes, must depolarize the membrane to expel magnesium ions from the channel. There is also a phencyclidine binding site within the ion channel on which drugs, such as phencyclidine and ketamine, can act to block the ion channel.*

the NMDA receptor ion channels and inhibit NMDA receptor function are phencyclidine (Chapter 10), ketamine (Chapters 6, 7 and 10) and memantine (Chapter 3)

1.4 Central Nervous System Stimulant and Depressant Drugs

It is well known that when you are tired and at a low level of arousal (Chapter 9) your performance in a physical or mental task will be poor. When you are awake and alert, then your performance in such tasks will be almost optimal. However, if you are very stressed about something, then you become overaroused and you will find it difficult to perform adequately in both mental and physical tasks. In 1908, two American psychologists, Robert Yerkes and John Dodson, demonstrated that performance in a given task is related to level of arousal by an inverted U-shape curve (Figure 1.5). This relationship between performance and arousal is known as the *Yerkes–Dodson law.* They demonstrated that performance increases with arousal until it reaches some optimal level. Thereafter, as arousal increases further, performance

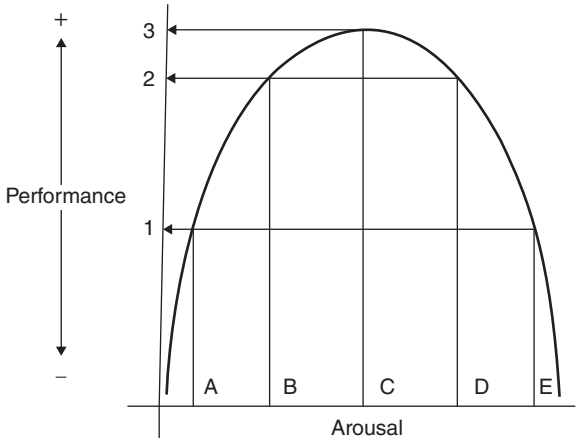

Figure 1.5 *The inverted U-shaped curve relating level of arousal to performance.*

begins to decreases (Figure 1.5). It has been found that different tasks need different levels of arousal for optimal performance.

Stimulant drugs, such as amphetamine (Section 1.5.1.1), increase level of arousal in a dose-dependent manner, whereas depressant drugs, such as the benzodiazepines (Section 1.6.1), reduce level of arousal in a dose-dependent manner. However, the effects of stimulant or depressant drugs on performance in a given task will depend on the baseline level of arousal of the subject when the drug was administered and on the dose of the drug (Figure 1.5). Thus, for example, imagine a subject (we shall refer to him as Graham) who is very tired and is, therefore, at a very low level of arousal (arousal level: A in Figure 1.5). If Graham is given some simple mathematical problem to solve, his performance in this task (performance level: 1) will not be very good as he is tired and, therefore, finds it difficult to focus his attention on the problem. He is then given a low dose of a stimulant drug. The effects of the drug will increase his level of arousal to B in Figure 1.5 and his performance in the task will improve considerably (performance level: 2). If, on the other hand, Graham is given a higher dose of the stimulant drug when he was feeling tired, his level of arousal will increase to C in Figure 1.5 and his performance in the task will become optimal (performance level: 3).

Now imagine that Graham is at the level of arousal (arousal level: C) for optimal performance (performance level: 3). If he is given a small dose of the stimulant drug, his level of arousal will increase to D in Figure 1.5 and his performance in the task will decrease (performance level: 2). If he were given a higher dose of the stimulant drug, then his arousal level will increase to E in Figure 1.5 (in other words, he will become overaroused) and his performance (performance level: 1) will be no better than when he was tired. Thus, a stimulant drug can both increase or decrease performance in a given task depending on the baseline level of arousal of the subject and the dose of drug administered.

As depressant drugs decrease arousal, if Graham is given a low dose of a depressant drug when he is performing optimally on the task (arousal level: C; performance level: 3), his level of arousal will decrease to point B in Figure 1.5 and his performance on the task will also be reduced (performance level: 2). However, if Graham is very stressed or anxious or excited (Chapters 6 and 8), his baseline level of arousal will be high (arousal level: E). In this case, a low or high dose of a depressant drug will decrease his level of arousal to D and C, respectively, and his performance on the task will improve. Thus, a depressant drug can also increase or decrease performance in a given task depending on the baseline level of arousal of the subject and the dose of drug administered.