The Female Brain

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London and New York

The Female Brain

Conceptual Advances in Brain Research

A series of books focusing on brain dynamics and information processing systems of the brain.

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This book is for my two Christys,
female brains extraordinaire.

Contents

Series preface

The workings of the brain, including the human brain are a source of endless fascination. In the last generation, experimental approaches to brain research have expanded massively, partly as a result of the development of powerful new techniques. However, the development of concepts which integrate and make sense of the wealth of available empirical data has lagged far behind the experimental investigation of the brain. This series of books entitled Conceptual Advances in Brain Research (CABR) is intended to provide a forum in which new and interesting conceptual advances can be presented to a wide readership in a coherent and lucid way.

The series will encompass all aspects of the sciences of brain and behaviour, including anatomy, physiology, biochemistry and pharmacology, together with psychological approaches to defining the function of the intact brain. In particular, the series will emphasise modern attempts to forge links between the biological and the psychological levels of describing brain function. It will explore new cybernetic interpretations of the structure of nervous tissue; and it will consider the dynamics of brain activity, integrated across wide areas of the brain and involving vast numbers of nerve cells. These are all subjects which are expanding rapidly at present. Subjects relating to the human nervous system as well as clinical topics related to neurological or psychiatric illnesses will also make important contributions to the series.

These volumes will be aimed at a wide readership within the neurosciences. However, brain research impinges on many other areas of knowledge. Therefore, some volumes may appeal to a readership, extending beyond the neurosciences. Books suitable for the series are monographs, edited multiauthor collections or books deriving from conferences, provided they have a clear underlying conceptual theme. In order to make these books widely accessible within the neurosciences and beyond, the style will emphasise broad scholarship comprehensible by readers in many fields, rather than descriptions in which technical detail of a particular speciality is dominant.

The next decades promise to provide major new revelations about brain function, with far-reaching impact on the way we view ourselves. These great breakthroughs will require a broad interchange of ideas across many fields. We hope that the CABR series plays a significant part in the exploration of this important frontier of knowledge.

Preface

In the autumn of 1990, during a seminar on cerebellar-brainstem networks and the control of eye movements, we got onto the topic of physiological factors which can affect neuronal responses. One student asked if the sex of the experimental animal could make a difference. "I don't know," I replied. "I'll find out for next week."

After the seminar I headed to the library, but couldn't find any answers. I completely forgot about the incident until a couple of years later, when another student asked the same question, but about a completely different part of the brain. Again, there was no information to be found. "This," I thought, "is very strange, indeed."

The second time, I didn't forget about it. I filed the strange lack of information on sex differences in brain function in my mental "bottom drawer", that place where strange bits of information and odd, half formed ideas live. Over the next few years, more questions that were never answered (or never asked) went into the drawer. When it was full to overflowing, my curiosity got the best of me. I really wanted some answers, and in the process of trying to find them, I decided to write this book.

Along the way, a number of people have offered enthusiastic support and very practical assistance. Professor Sarah Romans, of the Department of Psychological Medicine here in Dunedin, offered me her files of papers on female brain-related subjects, which formed an invaluable base for many of the literature searches. The members of the Women's Health Research Group have been a constant source of encouragement and moral support. My office "neighbour", Dr. Janice Murray, has kept my energy levels up with her amazing raspberry jam. Janice has also consistently demonstrated an uncanny skill at knowing when it is OK to ask, "How's the book going?" and when it is better to peer out the window and say, "Looks like it's starting to rain again".

And then there's Jaimee. Jaimee King has been my research assistant for the duration of the writing project. She has been involved in just about every aspect of the book preparation: collecting references, convincing librarians to drag archived materials out of warehouses, checking manuscript drafts against the literature for accuracy. Her humorous comments, written in the margins and accompanied by smiley faces, have made the whole process so much more fun.

Finally, Associate Professor Robert Miller, Professor Paul Smith and Max . . . Robert is the editor of this book series. His support, advice, encouragement and humour have been so generously given and so gratefully received. Paul is my husband; fortunately, he's also a great chef. He has done virtually all of the cooking during the final stages

of manuscript preparation. He has also listened endlessly, read drafts continuously, and patiently corrected my very peculiar US-Australia-New Zealand form of English usage. Max is our cat. He has rearranged manuscript pages, chewed the corners of figures, and sailed pencils off the desk. At midnight, when the words just wouldn't work, Paul's cocoa and Max's purrs have been life-savers.

To all of you, thank you.

CD
Dunedin, NZ
2002

1

Introduction

The Major: Strange creatures women . . .
Basil: They do get awfully confused, don't they? They're not thinkers. I see it with Sybil every day . . . no capacity for logical thought.
The Major: Who?
Basil: Women.
The Major: Oh yes, yes . . . I thought you meant Indians.
Basil: No, no, no, no . . . wasn't it Oscar Wilde who said. "They have minds like Swiss cheese?"
The Major: What do you mean – hard?
Basil: No, no – full of holes.
The Major: Really? . . . Indians?
Basil: No, **women!**
The Major: Oh.

Cleese, J. and Booth, C. (1988) The Germans.
The Complete Fawlty Towers,
Methuen, London, pp. 138–189.

For centuries the beauty of the female form has been celebrated by painters, sculptors, song writers and poets. The artist has *his* muse, a real or imaginary woman, who provides inspiration to the creative genius within. But why this celebration of the female form, why a female muse for a male artist? Obviously, because the female body is different from the body of the male. But is this difference so obvious to everyone? Perhaps not.

We have arrived at the beginning of the 21st century, congratulating ourselves upon a century of scientific achievement, but entertaining a rather indeterminate view of female and male physiology. Overt sexual differences aside, the human body is

often viewed as almost androgynous. Ironically, the organ with the greatest reason to differ between the sexes, the brain, is viewed as the most androgynous of all.

The assumption of equivalence between the female and the male brain is even apparent in much of the most recent scientific literature on brain function. Almost by convention, male animals are used in laboratory experiments in neuroscience, but the results of the research are considered applicable to both males and females. Whether it is an anatomical study of the structure of the brain, or a neurophysiological study on memory mechanisms, male animals are generally used. The reason given is often that females tend to be inconsistent in their responses as a result of the oestrous cycle. Even in clinical drug trials in humans, females are often excluded from the early phases of testing. The reason? The risk of pregnancy and . . . females tend to be inconsistent in their responses due to the menstrual cycle. The flaw in the reasoning is enormous: these very results will be applied to females, and yet it is only recently that concern has been expressed by some researchers that research on male brain function may not be so generally applicable to females.

The issue of basic biological differences between the sexes, in terms of brain function, has been clouded by issues of gender. The traditional girl-boy roles engendered in most societies often make it difficult to distinguish biology from culture. The argument is often made that girls have been socially conditioned to perform well at some tasks but not at others. This is true, but it is does not address the basic question of functional differences.

Differences in brain function may arise as a result of different brain structure (in computer terms, different hardware). The differences may also arise from virtually the same brain structures performing in different ways (same computer but running different software). Or, to make things more complicated, and more interesting, slightly different hardware with slightly different software may be the answer. The purpose of this book is to address the question of structural and functional differences between the female brain and the male brain. Are there differences? How good is the evidence? Where do the differences lie, literally and figuratively? Are there differences in the neuroanatomy of females, and if so, where? Do females and males process information differently, and if so, how?

This book is divided into nine chapters. In this introductory chapter, Chapter 1, some of the background information necessary for understanding the contents of the remaining chapters will be introduced. This chapter is meant to serve as a guide, and a reference point, for the remainder of the book. For readers who already have a background in the physiological sciences, some sections will be redundant. Just skip them. For readers who do not have such a background, Chapter 1 should be something you can refer back to as needed.

Chapter 2 is about the history of the study of the female brain. Needless to say, it is short. It is really intended to put the current lack of knowledge into some kind of historical perspective; to try to provide an answer to the inevitable question, "How could this kind of intellectual neglect come about?"

Chapters 3 through 8 explore specific aspects of brain structure and function. These are the chapters which review the empirical evidence relevant to the different aspects of brain structure and function. By necessity, these chapters contain scientific detail that will be difficult for some readers. Hopefully, the explanations provided with the

material in the chapters and in Chapter 1 will make the reading easier. Chapter 3 looks at the evidence for structural differences between the female brain and the male brain. Chapter 4 examines the evidence for functional differences in terms of neurotransmitters and their receptors. In many cases it is difficult, if not impossible, to separate structure from function, so the division between the chapters is somewhat arbitrary. Chapter 5 is about laterality, the functional asymmetry of the brain, the left brain-right brain distinctions and how they differ between females and males. In Chapter 6, the evidence for differences in perception and cognition are examined. How and why males and females apparently process memories differently is discussed. In Chapter 7, female/male differences in neurological and psychiatric disorders are discussed. In Chapter 8, we examine the treatment strategies for those disorders and the role that hormones may play. For Chapters 4 through 8, one of the important factors always under consideration is the menstrual cycle: how abilities and symptoms change with fluctuating hormones; and how treatment strategies may need to consider cyclic changes. The effects of hormone replacement therapy are also discussed.

Chapter 9 contains the summing up and conclusions. It is very much a "where do we go from here?" chapter. Hopefully, some readers may use it as a road map to inspire their own research into the female brain.

The background

> What I mean is that to tell a story you must first of all construct a world, furnished as much as possible, down to the slightest details. If I were to construct a river, I would need two banks; and if on the left bank I put a fisherman, and if I were to give this fisherman a wrathful character and a police record, then I could start writing, translating into words everything that would inevitably happen. What does a fisherman do? He fishes (and thence a whole sequence of actions, more or less obligatory). And then what happens? Either the fish are biting or they are not. If they bite, the fisherman catches them and then goes home happy. End of story. If there are no fish, since he is a wrathful type he will perhaps become angry. Perhaps he will break his fishing rod. This is not much; still, it is already a sketch.
>
> Eco, U. (1980) *The Name of the Rose*, Harcourt, Orlando, p. 512.

There are a number of different kinds of information that may be helpful to different readers. Some of the information is in the form of background information for different chapters. Other information is in the form of general guidelines, "rules for reading". The background information in this chapter includes the anatomy of the brain, neurotransmitters and their receptors, hormones and the menstrual cycle. The "rules" include the use of terminology, abbreviations (including a list of common abbreviations) and referencing (what material is referenced to specific literature and what is not).

Hormones

The place to start the background discussions has to be with hormones. Hormones and their regulation have to be one of the most complicated systems of the body. In order to keep this discussion even moderately brief, and to keep the length of this book to one volume, it is necessary to place strict limitations on the hormones and actions to be discussed. For further information a textbook of endocrinology or *Essential Reproduction* by Johnson and Everitt (1995) is recommended.

The major hormonal players that we are going to consider are oestrogen and progesterone for females and testosterone for males. Interestingly, oestrogen can be produced from testosterone, so although it is considered a "female" hormone, it is also of importance to males. These three hormones are synthesised from cholesterol via several different pathways (Figure 1.1). There are 3 forms of oestrogen: 17β-oestradiol, oestrone and oestriol. Progesterone is a progestagen, as are 17α-hydroxyprogesterone

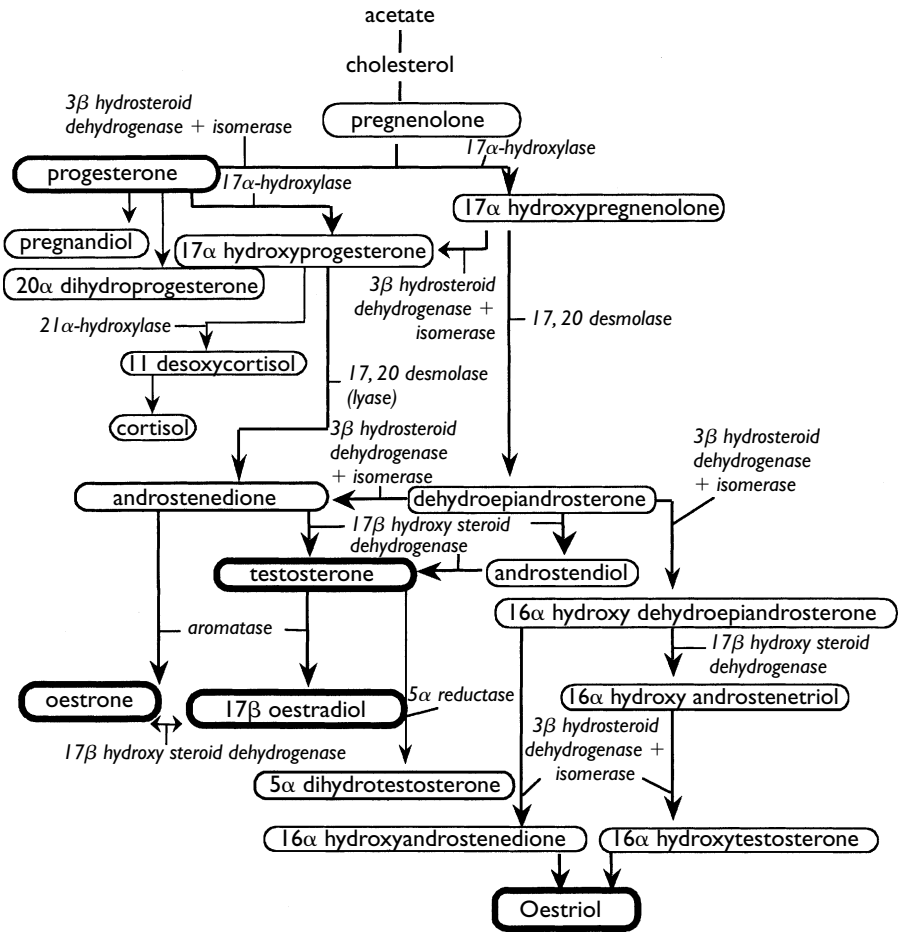

Figure 1.1 The synthesis pathways for the production of oestrogen, progesterone and testosterone. Adapted from Johnson and Everitt (1995).

and 20α-hydroxyprogesterone. The release of oestrogen, progesterone and testosterone is controlled by the hypothalamus (see next section) via the secretion of gonadotrophic-releasing hormone which acts on the anterior pituitary gland to stimulate the release of follicle-stimulating hormone and leutinising hormone. In males, these two hormones regulate spermatogenesis and the production of testosterone. In females, follicle-stimulating hormone and oestrogen control the development of the follicle and leutinising hormone regulates the secretion of oestrogen. A peak in the release of leutinising hormone triggers ovulation. Oestrogen is synthesised from androstenedione by the follicle of a mature oocyte. Hence, when the supply of oocytes is exhausted, menopause occurs and the supply of oestrogen ceases. Progesterone is produced by the corpus luteum, a structure formed by the ruptured follicle after the oocyte has been released. The corpus luteum also releases oestrogen; however, after about 12 days it begins to deteriorate (regress) and the secretion of progesterone and oestrogen decline.

The levels of oestrogen and progesterone in the circulating blood fluctuate across the menstrual cycle in the human female (Figure 1.2). Similar fluctuations can be

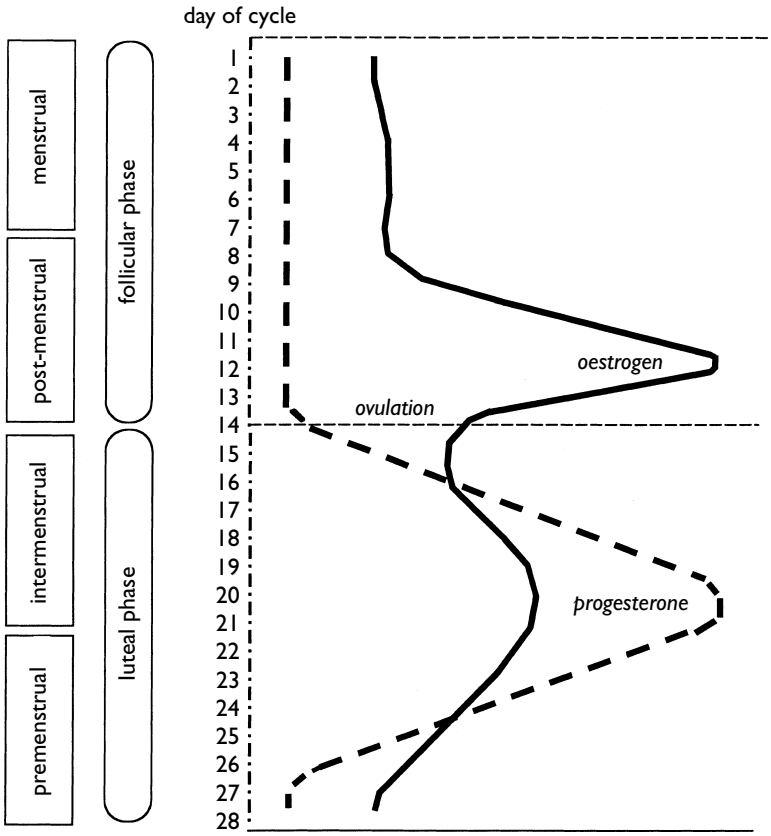

Figure 1.2 Schematic representation of the menstrual cycle showing relative levels of oestrogen and progesterone. The phases of the menstrual cycle are shown at the left of the figure.

observed during the oestrous cycle in female rats. In terms of the menstrual cycle, oestrogen rises during the early part of the cycle (released by the mature follicle) and peaks just before ovulation. After ovulation the level begins to drop, but there is another, lower, peak before it drops sharply towards the end of the cycle. During the time leading up to ovulation, oestrogen acts on the endometrium (the lining of the uterus), causing it to thicken and become enriched with blood vessels in preparation for implantation of a fertilised ovum. After ovulation, progesterone, released by the corpus luteum, begins to rise. If fertilisation does not occur, progesterone causes the enriched, but not required, endometrium to shrink and detach from the uterus. Towards the end of the cycle, and by the start of menstruation, the levels of both oestrogen and progesterone are low (Walker, 1997).

It is the cyclic rise and fall of hormone levels that distinguishes female physiology. Males produce testosterone at a fairly constant rate (ignoring circadian rhythms), although there is some decline in testosterone production in old age. Circulating oestrogen in males, which has been synthesised from testosterone, will also remain at a fairly constant level. For females, from puberty to menopause, the hormonal milieu is constantly, though predictably, changing. So, for research in females, there are 28 (assuming a 28 day menstrual cycle) possible hormonal states to take into consideration. Ideally, all research in which the menstrual cycle is a variable would use blood analysis to determine hormone levels exactly. However, due to practical constraints (such as finances) blood analysis is often not an option. Many researchers instead rely on their experimental subjects keeping an accurate record of their menstrual cycles. The researchers then plan their experimental testing for particular phases of the cycle. The two most common divisions of the menstrual cycle are the 2-phase cycle and the 4-phase cycle (Figure 1.2). From Figure 1.2, it is easy to see that the 2-phase cycle only provides information on what happens when progesterone is present or absent. The 4-phase cycle allows for some distinction between the effects of oestrogen and progesterone. In addition, the "normal" cycle length is between 26 and 32 days. Ovulation does not always occur on day 14 (or even at all) and in some cycles, for some reason, progesterone does not rise normally.

Another important characteristic of hormones, for experimental purposes, is that they are present in the blood circulation only in very small concentrations. Some, for example, are present in concentrations of approximately 10^{-9} molar, that is, there is one gram of the hormone in 1,000,000,000 litres of blood. Understandably, hormones at this concentration are very difficult to detect in the blood or other tissue by standard chemical analysis. The use of high-performance liquid chromatography has made the analysis of very low concentrations of hormones and neurotransmitters much more accurate, however, the problem of the constantly changing levels remains.

Hormone researchers have a very direct solution to this problem. Animals used in hormone research have their gonads (ovaries in females, testes in males) removed prior to testing. The age at which the animals are gonadectomised will depend upon the questions being asked by the study. If, for example, the study is looking at receptor binding during infancy, then rat pups may be operated on right after birth. If, on the other hand, the study is intended to look at receptors in the fully developed adult, then the procedure may be performed a short time, e.g. 1 week, before the binding study takes place. To study the "natural" presence of the receptors, a most unnatural

condition is created. In females, the process of removing the ovaries is called, not surprisingly, ovariectomy and female animals which have had the procedure are referred to as "OVX females" or just "OVX".

> A great deal of misapprehension arises from the popular use of maps on a small scale. As with such maps you are able to put a thumb on India and a finger on Russia, some persons at once think that the political situation is alarming and that India must be looked to. If the noble Lord would use a larger map – say one on the scale of the Ordinance Map of England – he would find that the distance between Russia and British India is not to be measured by the finger and thumb, but by a rule.
>
> Salisbury, R. (1877) Hansard
> 11 June, Col. 1565. In *The Oxford Dictionary of Quotations*, Oxford University Press, Oxford, p. 554.

The central nervous system

After hormones, the next background section has to be about the brain. The following section gives a very basic description of the brain and spinal cord. For more detailed descriptions and information, *Principles of Neural Science* by Kandel *et al.* (2000), the "bible" of neuroscience, is highly recommended.

The central nervous system (CNS) is composed of the brain and spinal cord, not just the brain as many people assume. The spinal cord connects the brain to the peripheral nervous system and allows sensory information to be transmitted to the brain, and behavioural responses (motor commands) to be transmitted to the muscles and glands. Between sensory input and motor output, the brain analyses the sensory signals for meaning, integrates this information with other sensory inputs and information stored in memory, and generates a motor command which causes the appropriate response to occur. The process of receiving sensory information and generating an appropriate response may be available for conscious analysis or it may be completely unconscious, depending upon the kind of information received and the type of response required. So, for example, we will consciously decide to take a piece of chocolate cake but will be completely unaware of our body's responses to the associated increase in blood sugar. Sometimes, however, we may have access to the results of the brain's capacity for unconscious processing. Most of us have had the experience of seeing a familiar face but not being able to remember the person's name. Then, some time later, after the incident has been "forgotten", not only do we suddenly remember the person's name but often many other details about them as well. Such experiences have given rise to the well-worn joke, "I can't tell you right now, but I'll ring you at three in the morning when I remember".

In terms of gross anatomy, the brain can be divided into four regions: the *cerebral hemispheres* (including the cerebral cortex); the *diencephalon* ("the between brain"); the *brainstem*; and the *cerebellum* (Table 1.1) (Figure 1.3). These four main regions are connected by bundles of nerve fibres which carry information to and from the different areas of the brain and to the spinal cord. These complex networks of interconnections

Table 1.1 The major divisions of the brain and some of their functions

Division/subdivisions	*Function*
Cerebral Hemispheres	
cortex:	
frontal lobe	emotional, behavioural "control"
temporal lobe	language
parietal lobe	language, balance, hearing
occipital lobe	vision
basal ganglia*:	motor control, cognition
globus pallidus, putamen,	
caudate nucleus (globus pallidus +	
putamen = *lenticular nucleus*)	
(putamen + caudate nucleus = *striatum*)	
limbic system*:	memory and emotion
amygdala, cingulate,	
hippocampus, septum	
Diencephalon	
thalamus	sensory, motor processing and relay
hypothalamus	control of homeostasis
Brainstem	
tegmentum	autonomic control
reticular formation	arousal
midbrain:	
periaqueductal grey	pain perception
superior colliculus	eye-head coordination
substantia nigra	motor control
inferior colliculus	auditory reflexes
pons and medulla:	
nuclei of cranial nerves	sensory and motor function
inferior olive	cerebellar relay
Cerebellum	fine motor control

* There is some disagreement about which nuclei should be included in these divisions.

allow the activities of the different brain regions to be coordinated smoothly and efficiently. For a comprehensive coverage of the structure of the human brain, Kandel *et al.* (2000) and Diamond *et al.* (1985) are recommended.

The cerebral cortex is the outermost area of the top and sides of the brain. Viewed from the outside, the cortex appears as a wrinkled and folded surface covering the rest of the brain. When the cortex is cut to expose a cross section, thick layers of neatly ordered cells can be seen. These layers are indeed folded into deep grooves and wrinkles which cover the cortical surface. In phylogenetic terms, the cerebral cortex is the newest part of the brain. That is, it is the most highly evolved area and is the site of the highest levels of cognitive function. The folding of the cortical surface is an important

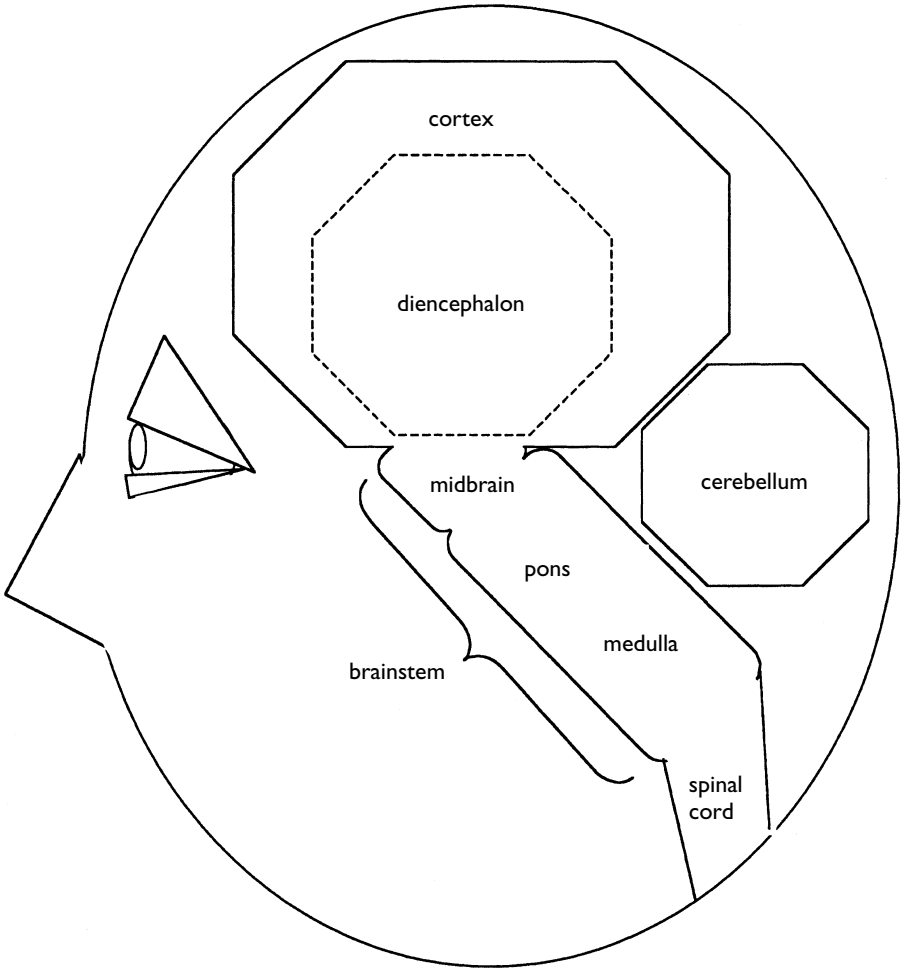

Figure 1.3 Schematic representation of the five divisions of the brain.

aspect of brain evolution. The deep folds allow for greater surface area in each cortex and, therefore, a greater number of cells and greater capacity for information processing. The cortex of a mouse or rat, for example, has fewer and shallower folds than the cortex of a primate, such as a lemur, which in turn has fewer folds than the cortices of humans.

The hemispheres, including the cortex, are paired. The left and the right hemispheres have different functional specialities, often described as logic and creativity, respectively. The areas of each cortex are further distinguished anatomically by very deep folds, known as sulci, which loosely define the boundaries of 4 lobes: frontal, temporal, parietal and occipital, and are named for the bones of the skull which cover them (Figure 1.4). Areas of the cortices are also organised functionally into primary, secondary and tertiary regions. The primary regions are those areas most concerned

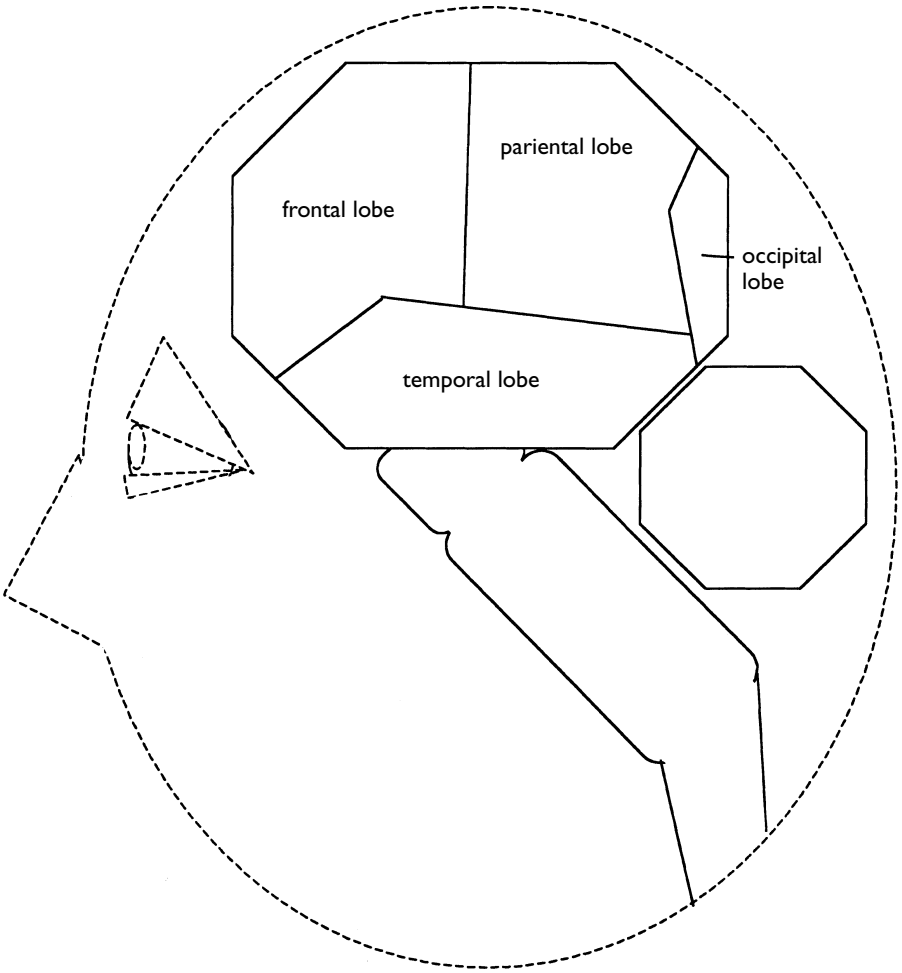

Figure 1.4 Schematic representation of the lobes of the cerebral cortex.

with our interactions with the world. So the primary sensory areas are those which receive sensory information mainly from a single sensory system via the peripheral nervous system, for example, the visual system. The primary motor cortices are those areas which send the commands for action directly to the spinal cord to produce appropriate behavioural responses. The secondary and tertiary regions surround the primary regions and conduct complex processing which may include information on several aspects of the sensory signal being processed. One of the cortical regions best understood in terms of the increasing complexity of sensory information processing is the visual cortex. In 1965 Hubel and Wiesel won the Nobel Prize for their work in which they identified rows and columns of neurones in the visual cortices of cats which processed increasingly complex aspects of a visual stimulus.

Finally, there are the association areas. In the association areas all of the information necessary for the planning and initiation of movement and other responses is

integrated. Information from the sensory systems is combined with information retrieved from memory about: previous encounters with the particular stimulus; previous responses; new information which may have changed the meaning of the stimulus since the last time it was encountered; and finally, the desirability of different response outcomes. It is from the association areas that the commands to initiate the chosen behaviours are sent to the tertiary motor areas and ultimately to the primary motor area where the movement command is issued.

The two other areas of the hemisphere of particular interest are the basal ganglia and hippocampus (Figure 1.5). The basal ganglia (and here there is some disagreement over what specific nuclei should be included) are important in movement control and they also play a role in cognitive function. The limbic system (again, somewhat controversial in terms of what should be included), composed of the hippocampus and amygdala, cingulate and septum, is said to be the "emotion control centre" of the brain. It plays a role in control of the autonomic nervous system, and indirectly modulates some hormone levels in the body. The hippocampus is also intimately involved in memory.

Underneath and between the cerebral hemispheres is the diencephalon. This area includes principally thalamus and the hypothalamus. The primary function of the hypothalamus is to maintain homeostasis, a state of physiological balance, which

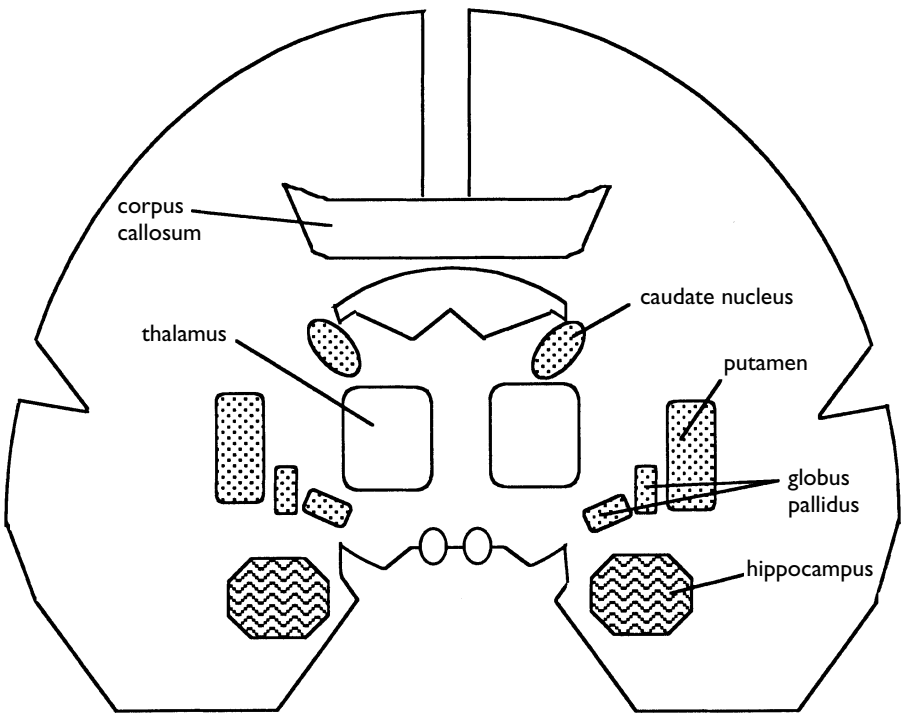

Figure 1.5 Schematic representation of a coronal section of the brain, approximately at the level of the junction of the frontal and parietal lobes. Dotted areas represent the basal ganglia, wavy lines indicate the hippocampus.

includes optimal body temperature, blood pressure, heart rate and respiration. The thalamus is the relay centre for information being sent to the cerebral hemispheres. Some of the information relayed through the thalamus is almost unchanged from the original sensory signal but other information undergoes processing in the thalamus before it is relayed to the cortex.

The hypothalamus is the major CNS control centre for the endocrine system, the hormonal system of the body, which is essential for the control of homeostasis. The hypothalamus controls hormonal activity throughout the body by synthesising and releasing hormones from secretory cells directly into the bloodstream and also by neuronal activity transmitted by neurones in the hypothalamus. This type of dual control allows the hypothalamus to have both slow, and long lasting, control of hormone levels as well as rapid, neuronal responses. With these two distinct types of response, long term changes, such as the menstrual cycle, and short term changes, such as the "fight or flight response" to danger, can be accurately maintained.

The hormones released from the hypothalamus regulate the release of other hormones from the pituitary gland (Table 1.2). Through a number of complex feedback mechanisms, the hypothalamus closely regulates and monitors hormone secretion to ensure the correct hormonal balance throughout the body. In addition to the synthesis and release of hormones, there are a number of other functions which the hypothalamus also controls or regulates. These include: the balance of salt and water (electrolytes) in the body; the autonomic nervous system; appetites including thirst and sexual desire; body temperature and respiration; emotions; and the maintenance of a number of biological rhythms. Not surprisingly, it is in the hypothalamus that scientists first looked for differences in brain structure between females and males.

The cerebellum sits at the back of the brain, behind and below the cerebral hemispheres. Like the cortex, it is composed of precisely organised layers of neurones folded into deep ridges. The cerebellum is essential for almost all aspects of fine motor control, including eye movements, balance and posture. All highly skilled movements, for example, tap dancing or playing the piano, are dependent upon the cerebellum for precision and accuracy.

After the cerebral hemispheres, the diencephalon and the cerebellum, the brainstem is what is left over. It is an elongated structure which extends along the lower

Table 1.2 Hypothalamic regulation of the release of pituitary hormones

Target	*Hormone*
anterior pituitary	growth hormone-releasing hormone
	thyrotropin-releasing hormone
	adrenocorticotrophic hormone
	gonadotrophin-releasing hormone
	growth hormone release-inhibiting hormone
	prolactin release-inhibiting hormone
posterior pituitary	antidiuretic hormone
	oxytocin

surface of the brain from just behind the diencephalon to under the cerebellum, where it continues without interruption to form the spinal cord. Phylogenetically, the brainstem is the oldest part of the brain, and this part of the human brain is remarkably similar not only in mammals, but also in non-mammalian species. Loosely speaking, the rest of the brain has evolved on top of the brainstem. This is the area where the control centres for vital functions such as cardiovascular and respiratory control are found. The area closest to the diencephalon, the midbrain, is involved primarily in motor control. Behind the midbrain, the pons is also involved in motor control but, in addition, acts as a relay between the cerebellum and the cerebral hemispheres. It is through the pons that the cerebellar signals necessary for the fine tuning of movements are relayed to the motor areas of the cortex. Behind the pons is the medulla. Together with the pons, the medulla contains the centres for the control of breathing and cardiovascular function, including the control of blood pressure. All three areas of the brainstem also contain a neuronal network, known as the reticular formation, which is important for the modulation of arousal, the overall state of awareness of an individual.

The spinal cord continues downward from the medulla and carries signals from the brain to the nerves of the peripheral nervous system. The cord is arranged into ascending tracts which carry information from the peripheral nervous system to the brain, and the descending tracts which carry motor commands from the brain to the peripheral nervous system (Figure 1.6). Between these areas are groups of neurones which function within the spinal cord itself and mediate spinal reflexes such as the "knee jerk" response to a tap of the patellar tendon. The spinal cord is encased in the vertebrae of the spinal column which act as a coat of armour, just as the skull protects the brain. This extensive form of protection is necessary because breaks in or damage to the spinal cord result in a loss of sensation and/or motor control below the level of the lesion.

The nerves supplying different parts of the body exit from the spinal cord to the peripheral nervous system at very specific positions so that the area of the body affected by damage to the spinal cord can be accurately predicted from the known location of a lesion. The nerves leave the spinal cord between the vertebrae and vertebrae are numbered according to their position in the cervical, thoracic, lumbar or sacral portion of the spine. So, for example, a complete lesion of the spinal cord at the level of thoracic vertebrae 4 (T4) will consistently result in a complete loss of sensation and motor control below the mid-chest level.

The entire brain and spinal cord are surrounded by three layers of membranes, the *meninges*, which form a protective sac. Within this protective sac, and also within cavities within the brain, *cerebrospinal fluid* (CSF) circulates. CSF is essential to the function of the brain. In addition to providing a fluid cushion to prevent the brain from being damaged by knocking against the inside of the skull, the CSF bathes the brain in nutritive substances and also carries away waste products. In patients with suspected neurological diseases, analysis of the CSF is an important tool in the diagnostic process. Small quantities of CSF may be extracted by inserting a needle into a space at the bottom of the spine and withdrawing a small amount of fluid in a procedure known as a lumbar puncture. While not generally viewed as a patient's favourite life experience, the procedure can provide potentially lifesaving information on the type

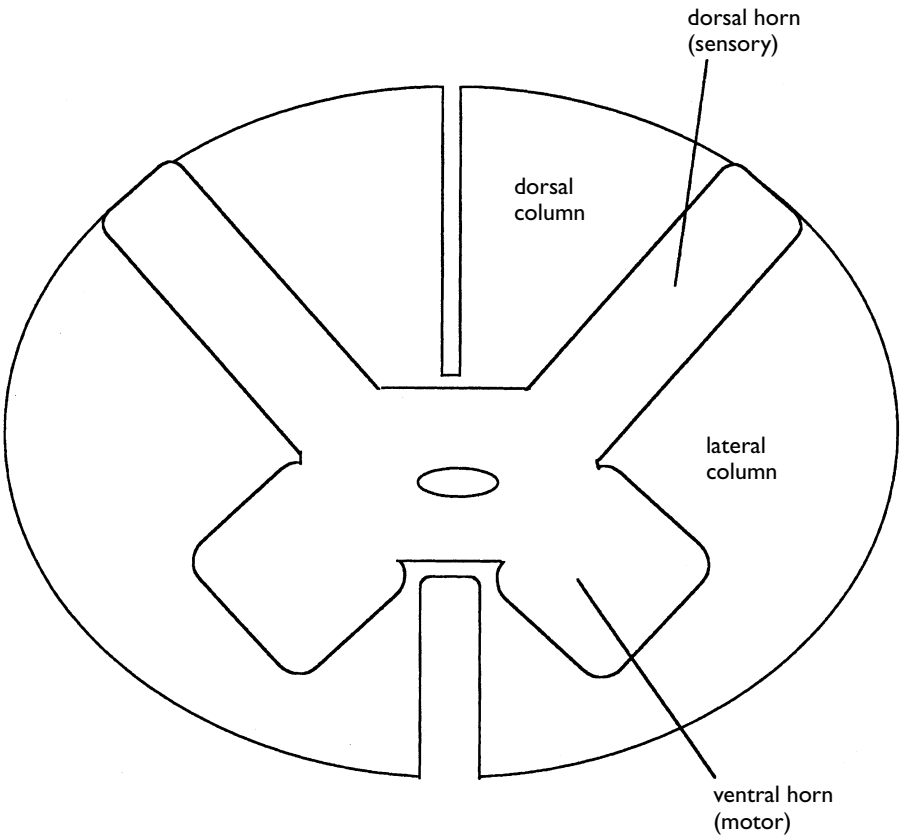

Figure 1.6 Schematic representation of the spinal cord in cross-section. The dorsal column relays sensory information from the peripheral nervous system to the brain. The lateral and ventral columns carry both sensory and motor information.

of disease present. In the case of bacterial meningitis, for example, the strain of bacteria causing the infection can be identified and the appropriate antibiotic treatment initiated. Another protection for the brain is the *blood-brain barrier*. The blood-brain barrier refers to the arrangement of the cells in the walls of capillaries in the brain. The epithelial cells are positioned so that there is very little space between them ("tight junctions"), which prevents the movement of many substances from the blood into the brain. There are isolated areas of the brain, the *periventricular* organs, located on the margins of the ventricles, where the epithelial cells do not have tight junctions. Some substances can reach the brain via the periventricular organs.

There are several different types of cells found in the brain and spinal cord but the principal type of cell is the *neurone*, the cell type with the capacity to transmit and receive information. It is the communication between neurones which constitutes the activity of the brain. Although neurones have many variations in shape and size, there is a general anatomy of neurones that allows a generic neurone to be described (Figure 1.7). A neurone may be divided into three areas based upon the function of

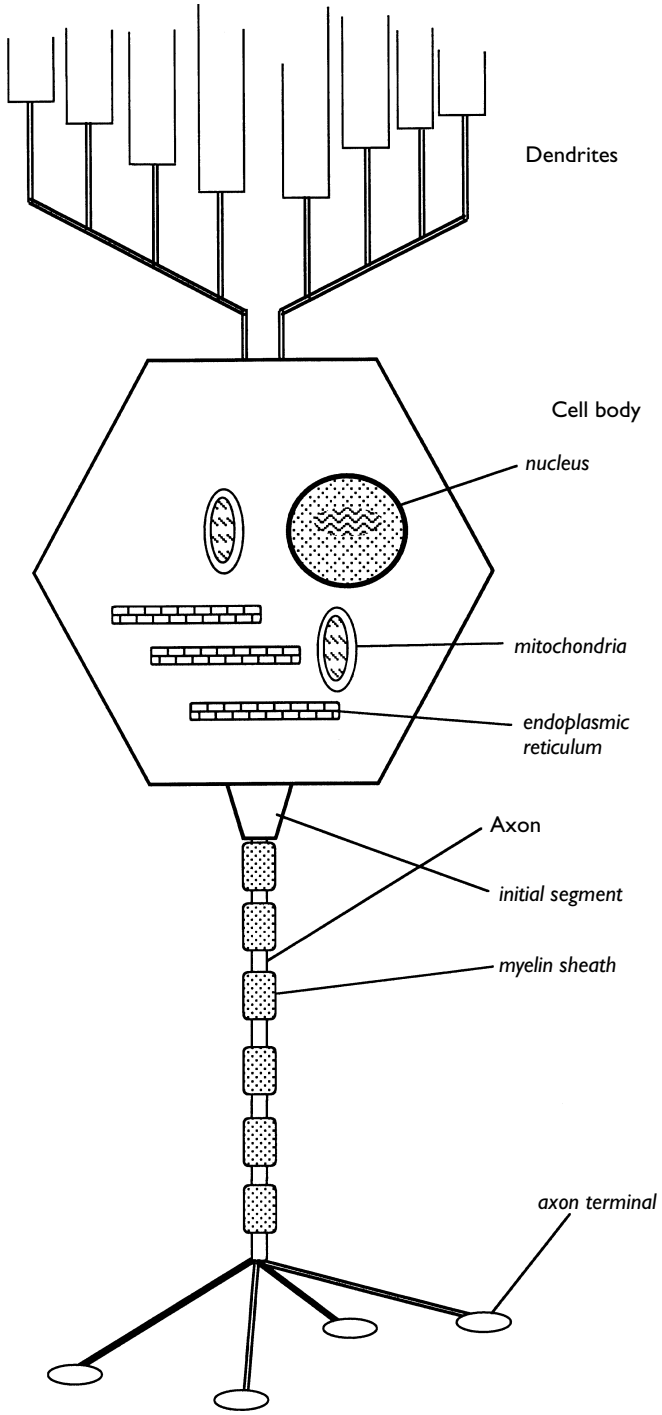

Figure 1.7 The generic neurone.

each area. The dendrites are the areas where information from other neurones is received. The dendrites are often described as branching like trees and they may spread quite widely to maintain contact with a large number of other neurones. The axons of other neurones may make synaptic contact with the dendrites and/or the cell body. The cell body (soma) is the information processing centre for the neurone. All of the different inputs arriving via the dendrites are processed and integrated to produce an appropriate response by the neurone. If the majority of the incoming signals received are excitatory, the neurone will respond by producing an electrical signal which will travel down the axon and cause the release of neurotransmitter at the synapse. If, on the other hand, the majority of signals received are inhibitory, the neurone will not produce an electrical signal and the neurotransmitter will not be released.

The soma contains the internal organs of the neurone which maintain the neurone's health and function by manufacturing new proteins to replace worn parts, generating energy to support the neurone's activities, and by manufacturing and releasing neurotransmitters and/or neuromodulators. Extending from the cell body, usually on the side approximately opposite to the dendrites, is the axon. The axon carries the electrical signals (the action potentials) generated by the cell body to the synaptic terminals where the neurone makes contact with the dendrites or cell bodies of many other neurones. The neurones being contacted may be within the same part of the brain or they may be located at a great distance from the signalling cell. Axons which must travel over large distances often travel together in bundles known as fibre tracts. One of the major fibre tracts is the corpus callosum, which conveys information back and forth between the two cortical hemispheres. When the corpus callosum is cut, one side of the brain literally does not know what the other side is doing. Some axons consist of a single fibre with few branches, but other types of axons may branch repeatedly allowing access to a large number of neurones and even different brain regions. The axon endings consist of synaptic terminals which make contact with the dendrites and in some cases the somata or axons of other neurones. The point of contact is known as the synapse and the physical space between the synaptic terminal and the other neurone is known as the synaptic cleft. Neurotransmitters released from the synaptic terminal cross the synaptic cleft and bind to receptors on the dendrites or cell bodies which are located in regions known as synaptic densities (Figure 1.8). In this way signals are conveyed from one neurone to another.

The majority of axons are wrapped in an "insulating" sheath called myelin which allows the signals to travel faster along the axon. In the CNS, myelin is formed by cells known as oligodendrocytes which wrap themselves around the axons to form a sheath. Damage to the oligodendrocytes, as in multiple sclerosis, causes disruption of the myelin sheath and slows the signals travelling along the axon. When this occurs in a number of axons, communication between neurones may be severely disrupted.

Neurotransmitters are the chemicals released by the axon terminals of neurones. There are certain characteristics of neurotransmitters which define a "classical" neurotransmitter (Kandel *et al.*, 2000). First, the chemical must exist in the presynaptic terminals. Second, the chemical must be released from the presynaptic terminal. Third, when the chemical is applied experimentally, it must have the same effect as the naturally occurring chemical. Fourth, there must be a mechanism for breaking down or

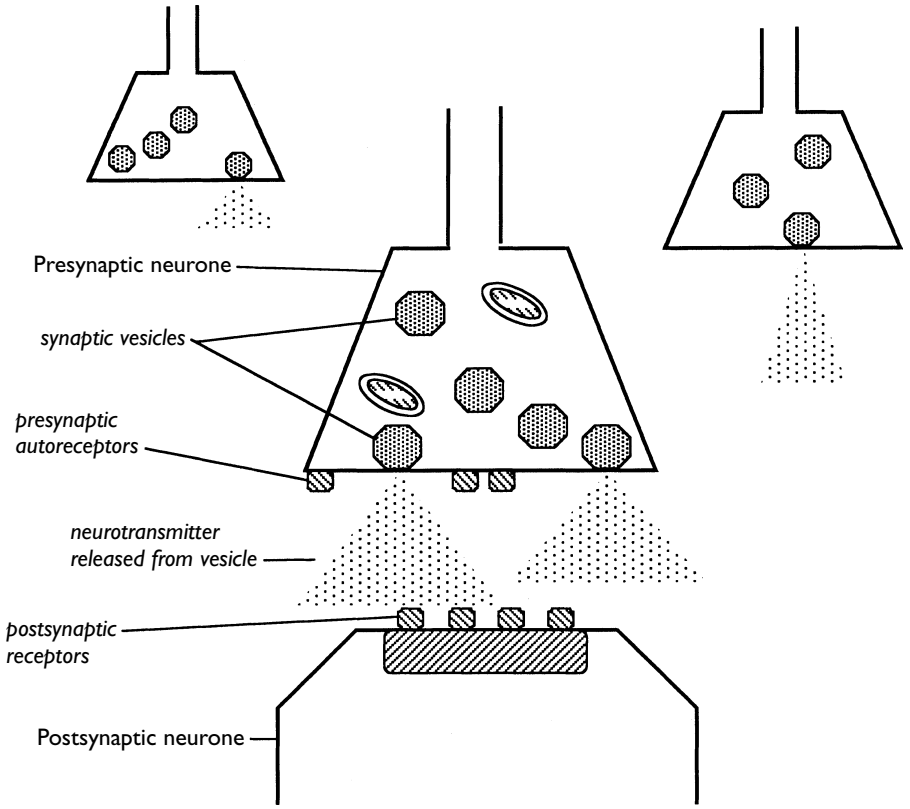

Figure 1.8 The generic synapse.

removing the chemical from the synapse. Fifth, an *antagonist*, a substance which blocks the action of the naturally occurring chemical, must also block the action of the experimentally applied chemical. Twenty years ago a discussion of neurotransmitters was easy. There were a small number of known neurotransmitters which had a few different subtypes of their respective receptors. Now there are numerous substances which are known to act as neurotransmitters and for which there are a number of receptors and subtypes (Table 1.3). In addition, it is now known that a number of substances which are not classical neurotransmitters (for example, hormones and nitric oxide) can act as modulators of neurotransmitter systems.

Receptors are the sites where neurotransmitters released into the synaptic cleft bind, to convey information from the presynaptic neurone to the post-synaptic neurone. Receptors are specific structures, made of proteins, which span the cell membrane and convey information from outside the neurone to the intracellular space where the process of responding to the neurotransmitter begins. Different types of receptors function in different ways. However, there are some basic principles of receptor function (Figure 1.9). First, receptors do not respond to any neurotransmitter that happens to drift by. Their responses are specific to a particular type of neurotransmitter. This response specificity is termed "selectivity". Second, there is the principle

Table 1.3 Examples of some "classical" neurotransmitters and their receptors

Neurotransmitter	*Receptors*	*Actions*
GABA	$GABA_A$	increase Cl^- conductance
	$GABA_B$	decrease cAMP
		increase Ca^{2+} conductance
	$GABA_C$	increase Cl^- conductance
Glycine		increase Cl^- conductance
Glutamate	AMPA	increase Na^+ conductance
	$GLU_{(1-4)}$	increase Na^+ conductance
	$GLU_{(5-7)}$	
	NMDA	increase Ca^{2+} conductance
	$mGLU_{(1-7)}$	decrease cAMP
		increase IP_3/DG
Acetylcholine	nicotinic	increase K^+ conductance
		increase Na^+ conductance
		increase Ca^{2+} conductance
	muscarinic	
	$mACh_{(1,3)}$	increase IP_3/DG
	$mACh_{(2,4)}$	decrease cAMP
		increase K^+ conductance
Dopamine	$D_{(1,5)}$	increase cAMP
	D_2	decrease cAMP
		increase K^+ conductance
		decrease Ca^{2+} conductance
	D_3	?
	D_4	?
Noradrenaline	α_{1A-D}	increase IP_3/DG
	α_{2A-C}	decrease cAMP
		increase K^+ conductance
		decrease Ca^{2+} conductance
	β_{1-3}	increase cAMP
Serotonin	$5\text{-}HT_{1A-F}$	decrease cAMP
		increase K^+ conductance
	$5\text{-}HT_{2A-C}$	increase IP_3/DG
	$5\text{-}HT_3$	increase K^+ conductance
		increase Na^+ conductance
	$5\text{-}HT_4$	increase cAMP
	$5\text{-}H_{6 \text{ and } 7}$	increase cAMP

Modified from Hardman *et al.* (1996). cAMP, cyclic adenosine monophosphate; Ca^{2+}, calcium; Cl^-, chloride; IP_3/DG, inositol triphosphate, diacylglycerol; K^+, potassium; Na^+, sodium.

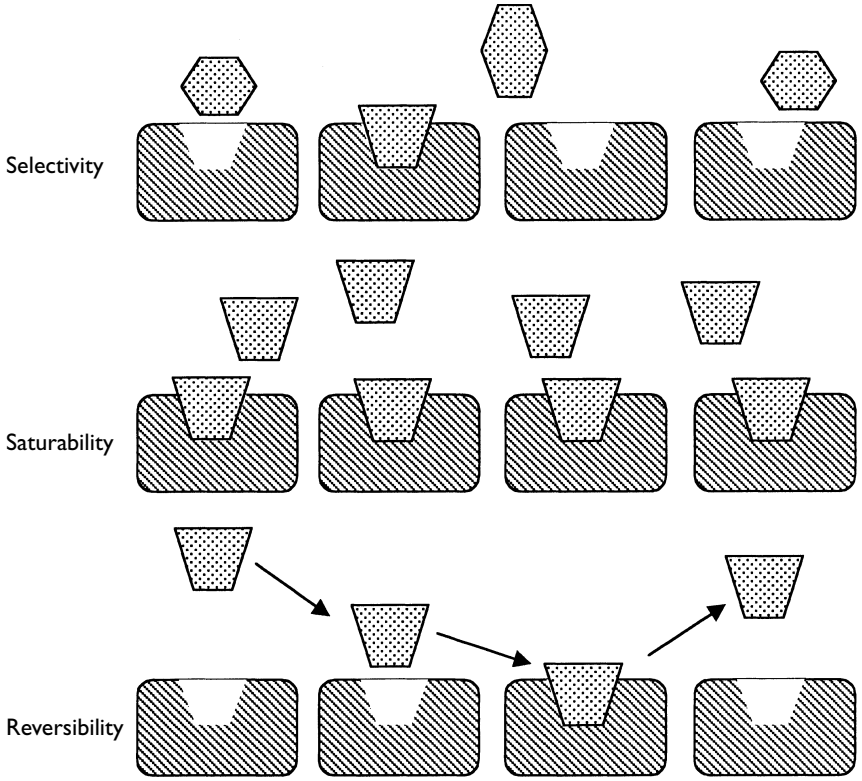

Figure 1.9 Schematic representation of the characteristics of receptor binding.

of "saturability". There are a finite number of receptors and once they are occupied then no more binding can take place. In receptor binding studies, it is important to establish saturability in order to demonstrate that what may seem to be binding is not just the drug or neurotransmitter being absorbed by other tissue. Third, receptor binding usually displays reversibility. This is necessary in order to act as an effective signalling system. The message is conveyed via neurotransmitter binding, then the neurotransmitter dissociates from the receptor. The release of the neurotransmitter serves two important functions; it signals "message over" and it allows the neurotransmitter to be broken down and recycled.

However, and this is a rather big "however", the responses of specific types of receptors may be modified by substances other than their specific neurotransmitters, e.g. drugs. The neurotransmitter GABA (gamma-aminobutyric acid), for example, causes an inhibitory response when it binds to a specific subtype of GABA receptor. When GABA binds to the "A" subtype of the GABA receptor (the $GABA_A$ receptor), it will cause a decrease in the activity of the cell on which the receptor is located. But, the $GABA_A$ receptor, in addition to the binding site for GABA, also has a number of other binding sites which recognise different types of drugs, including alcohol, steroids, barbiturates and benzodiazepines. When, in addition to GABA, there is one of these drugs present (and bound to its binding site), the action of GABA on the

receptor will be modified. Binding sites on receptors, which modify the actions of the neurotransmitter, are known as allosteric binding sites.

The presence or absence of allosteric binding sites on receptors is one way in which the action of a particular neurotransmitter may be made more specific. Another way specificity of action is achieved is by the distribution of the different receptor types, and subtypes, throughout the CNS. The number and types of neurotransmitter receptors present on neurones varies widely throughout the brain. Some neurotransmitter receptors are located only in very discrete brain regions while other receptor types are widespread.

Interactions between hormones and neurotransmitters

It is now known that hormones and neurotransmitters interact at the receptor level (Chapter 4). One fascinating area where this interaction appears to be particularly important is in the development of the brain. This is also an area which is, by necessity, completely outside the scope of this book. For readers interested in the role that hormones and neurotransmitters play in the developing nervous system, there are two excellent reviews, one by Kawata (1995), the other by Döhler (1991), that are highly recommended.

Neuroscience methods

There are many standard methods used in neuroscience research and it is not possible (within reason) to cover them all in this chapter. There are, however, two relatively new methods, based on recent advances in genetic research, which may be unfamiliar to the reader.

The first method is RT-PCR. It is a biochemical method which is now widely used to examine the effects of various drugs or other variables on the activity of the neuronal nucleus which leads (under most conditions) to the expression of new protein. "RT-PCR" stands for "reverse transcriptase polymerase chain reaction", which is a high-resolution method for determining the extent to which a particular gene has been expressed. When a gene is activated, messenger RNA (mRNA) is produced from DNA in a process called "transcription". The mRNA template then travels to the ribosomes to produce the corresponding protein in a process known as "translation". In RT-PCR, the enzyme "reverse transcriptase" is used to make corresponding double-stranded complimentary DNA (cDNA). This is the reverse of the process that usually occurs during transcription. The PCR part of the technique relates to identifying and amplifying enough of a specific gene so that it can be quantified. Because DNA has a double-helical structure, it has the capacity to unwind and reform double-helices. The PCR method uses repeated temperature changes (thermal cycling) to do this. When DNA is heated to 95°C, the strands separate. Partial DNA sequences (*oligonucleotides*) for the gene of interest are synthesised and these oligonucleotide primers bind or *hybridise* to complementary sequences in the single-stranded DNA. With large amounts of DNA polymerase, the partial DNA sequence of the primers will be "filled in" to complete the sequence. The process is then repeated thousands of times. Each time the separated DNA strands serve as a template for the construction of the DNA sequence or

gene of interest. The gene expression can then be quantified using gel chromatography or by measuring the amount of a fluorescent probe inserted into the primer.

Genetic modification is another new technique which, with the rise of the biotechnology industry, is rapidly becoming accessible to many researchers (providing that they have the necessary funds to buy the materials). Mice may be genetically modified to express an extra copy of a gene or to express a new gene (*transgenic mice*). Conversely, mice may be genetically modified so that they do not express a particular gene at all (*knockout mice*). Production of genetically modified mice seems amazingly straightforward, but the technology involved would have dazzled mid-twentieth century science fiction writers (and the success rate, at present, is only about 10%). A section of cDNA is produced which has been modified to either delete the sequence containing the gene being studied, or to include a new or additional sequence of a particular gene. The truly amazing part is that once the section of cDNA has been produced, it is simply injected into a fertilised mouse ovum. The ovum is then implanted into a surrogate mother along with unmodified ova from the same source. When the litter is born, it consists of the experimental, genetically modified animals, and their normal (wild-type, WT) littermates.

The rules

Rt. Hon. James Hacker: "...I don't want to look a gift horse in the mouth?"

Sir Humphrey Appleby: "I put it to you, Minister, that you are looking a Trojan horse in the mouth."

Rt. Hon. James Hacker: "You mean that if I looked closely at this gift horse I'd find it's full of Trojans?"

Mr. Bernard Wooley: "If you had looked a Trojan horse in the mouth, Minister, you would have found Greeks inside.

Well, the point is, it was the Greeks who gave the Trojan horse to the Trojans, so technically, it wasn't a Trojan horse at all but a Greek horse."

Jay, A. and Lynn, J. (1980) "The Bed of Nails",
Yes, Minister, BBC Television.

In writing a book of this type it is very difficult to decide upon, and adhere to, a particular set of rules for terminology and usage. Consider the use of the term "female". There are a number of ways to indicate that you are referring to the non-male members of the human species. In addition to being "females", they can be "women", "ladies", "gals", "sheilas" or even "the girls". When the aim is to maintain consistency throughout nine chapters, it is important to make the decision early and stick to it. In this case, "female" has been chosen and is used throughout the book. Sometimes, it sounds a little awkward and sometimes it sounds contrived. However, overall, it works and, at least, it is accurate.

Also, for the sake of accuracy, it is tempting to spell out every single term and to distinguish between every possible form of a drug or chemical. For the sake of readability, it is necessary to decide upon an accurate, but palatable, usage of scientific names and terminology. Consider, for example, a discussion of the two hormones, oestrogen and progesterone. It is accurate to say, "The hormones 17β-oestradiol,

oestrone, oestriol, progesterone, 17α-hydroxyprogesterone and 20α-hydroxyprogesterone have been demonstrated to fluctuate across the menstrual cycle of the human female but there is no oestrous cycle in the ovariectomised female rat". It is much more comfortable (and for most purposes) just as informative to say, "The hormones oestrogen and progesterone fluctuate across the menstrual cycle of the human female but there is no oestrous cycle in the OVX rat."

In this book, when the important message is that an oestrogen is involved in a particular process, the term "oestrogen" will be used. If, however, the particular form of oestrogen is important to the discussion, for example, in the case of a behavioural study comparing the actions of 17β-oestradiol and oestriol, then the type of oestrogen will be specified. This same rule applies to the name "progesterone" and to certain classes of drugs, e.g. benzodiazepines.

A similar rule has been applied to the referencing of scientific data. It is essential that experimental results and the ideas regarding their interpretation be referenced to the appropriate author. It is often the case, however, that several authors report similar results over a number of years. To reference all of the literature, for every chapter, would create a huge bibliography that would be of little interest or use to the majority of readers. Instead, I have adopted the following policy: when a particular result has been published by a number of authors, then very recent work which cites the previous publications is used as the reference. When it is the case that early work is relevant to a particular section, then that work will be cited, often in addition to a recent review. In the case of general material, for which a very wide literature exists, then a general reference source, usually a textbook, is cited. Finally, there are a number of areas which, while extremely interesting and important, are outside the scope of the book. For these, recent reviews have been recommended.

As far as possible, the use of abbreviations has been avoided. To read and understand a paragraph riddled with acronyms is difficult for a person who knows what they mean, but it is almost impossible for a person who is not familiar with them. Sometimes, however, it is awkward and impractical not to use abbreviations. This is particularly true in the case of subtypes of neurotransmitter receptors. For example, the choice is between spelling out the entire name, e.g dopamine receptor subtype 3, every time it appears (which may be several times in a single sentence) or using the standard receptor shorthand, D_3. The rule is this: when one or more letters appear followed by a subscript number and/or letter, it specifies a neurotransmitter receptor subtype. There are some standard abbreviations that appear routinely in the scientific literature and because of their common usage have virtually become terms in themselves, for example, "CSF" for cerebrospinal fluid. Although every abbreviation is identified the first time it is used, a table of commonly used abbreviations is provided as a reference, if needed (Table 1.4).

Table 1.4 Commonly used abbreviations

Abbreviation	*Meaning*
ACh	acetylcholine
AMP	adenosine monophosphate
cAMP	cyclic adenosine monophosphate
BBB	blood-brain-barrier
CNS	central nervous system
CSF	cerebrospinal fluid
CT	computerised tomography
D (followed by subscript)	dopamine receptor
DNA	deoxyribonucleic acid
E	oestrogen
EEG	electroencephalography
GABA	gamma-amino-butyric acid (when used alone)
	gamma-amino-butyric acid receptor (when followed by subscript numbers and/or letters)
Glu (followed by subscript)	glutamate receptor
HRT	hormone replacement therapy
5-HT (followed by subscript)	serotonin receptor
MRI	magnetic resonance imaging (anatomical information)
fMRI	functional magnetic resonance imaging (functional information)
NA	noradrenaline
mRNA	messenger ribonucleic acid
OVX	ovariectomy
RT-PCR	reverse transcriptase polymerase chain reaction

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2

An historical perspective

> Gnostic creation myths of the early Christian era were still telling versions in which the female principle was pre-eminent, which is why they were declared uncanonical. "In his madness," Jehovah claimed to be the only God, because he had forgotten the mother who brought him into being, according to one source. The Mother of Gods was angry that he had impiously sinned against her, and against her other children, the male and female Immortal Ones. These were the *elohim* of the Book of Genesis. God grouped himself with them, calling the group "us" (Genesis 3: 22). But Bible revisions tended to erase earlier deities, especially female ones. After the centuries of choosing and revising canonical books, nearly every trace of female divinity had been eliminated from Christian literature.
>
> Walker, B.G. (1983)
> *The Woman's Encyclopedia of Myths and Secrets*,
> Harper, San Francisco, p. 184.

Taking an historical perspective on the study of the female brain is a little like pursuing the dog that didn't bark in the night. The real significance is what *did not* happen. To make the task of identifying causes even more difficult, it is not one but several things that did not occur. Certainly, the greatest omissions have occurred in the last 100 years, but the social perspectives, which led to these omissions, have developed over centuries.

In any society the areas chosen for research and development will reflect the needs, desires and perspectives of the members of the society. Opportunity and resources will usually only be available for the development of priority areas of concern. Only in times of great wealth and excess can a society afford the luxury of the pursuit of knowledge just for the pleasure of knowing. The kinds of areas developed will depend in part upon the education and skills of the people doing the

research and the personal interests and biases of those individuals. It follows that the present lack of knowledge of the female brain must stem from a number of circumstances where decisions were made which did not favour such interests. Since study of this type, until very recently, was almost exclusively the domain of physicians, the role of females in medical science will be an important aspect of the discussion.

Since ancient times females have been cast in the role of caregivers. We know that the Neanderthals cared for their sick and elderly, but we do not know whether the caring role was exclusively for females. We do know that by the time females developed agriculture around 8000 BC and farming communities began to emerge, females were the farmers and caregivers while males were the hunters. It seems likely, at least in the early social orders, that females developed the role of healers.

At some stage, the ability to heal became endowed with mystical connotations and, not surprisingly, became a source of power. It was probably at that time that males began to take on the roles of healers. We do not know whether in the very early human societies males and females had equal social stature. We do know, however, that by around 1450 BC, the females in Mesopotamia had become the "other sex" and were under the control of males. A Mesopotamian female was obedient to her father, her husband, her father-in-law and eventually, even to her sons.

The earliest female healers in recorded history were the female physicians of Ancient Egypt (Brooke, 1993). In 1900 BC the Kahun papyrus, a record of diseases of females and children, was written as a guide for female physicians. Female patients were treated only by female physicians and medical specialities were well established. Isis was the "healing goddess" of the Egyptians and the Temples of Isis were houses of healing. Within the temples, in special birth houses, the patients were cared for by female obstetricians and midwives. Hatshepsut (1503–1482 BC) championed female physicians and established three medical schools, although her brothers happily claimed the credit for her work. During this time, priestess-healers, trained in pharmacology, supervised the growing of medicinal herbs and the preparation of medications. In Greek literature of the 8th century BC, there were several mentions of female healers called "leeches". In the Illiad, Agamede, the daughter of Angea was said to have cared for soldiers wounded in the battle of Troy. In the Odyssey, an Egyptian woman known as Polydamma was credited with supplying illicit drugs to Helen, daughter of Zeus. "Into the bowl in which their wine was mixed, she [Helen] slipped a drug that had the power of robbing grief and anger of their sting and banishing all painful memories" (Homer, c. 800 BC, Book 4: 220–226). The female dynasty of Egyptian queens began around 400 BC. The Queens themselves were physicians and they enthusiastically promoted all manner of medical and scientific practice. The medical schools flourished. The physicians of classical Greece received their education in Egypt, particularly in the medical school in Alexandria. The end of the female dynasty saw the decline of the role of females in medical practice and the rise of male priests and healers in Egypt.

In Greece, the Athenian wife was seen as the child bearer and chief domestic servant. She had no independent status and could not own property, with the exception of clothing, jewellery and slaves. It was even up to her husband to decide whether or not to keep a newborn child. Some were taught to read and write but it is often said that during this era, the most intellectually advanced Athenian females were prostitutes.

In 445 BC, Periclese scandalised Athenian society by replacing his wife with Aspasia of Miletus. Aspasia was the proprietress of a house of young prostitutes who were renowned for their intellect as well as their beauty. By around 340 BC Greek girls were educated in gynacaea (female only schools) where they were taught the skills necessary for successful household management. Despite the low general status of females, however, there was a tradition of female healers. Theano, for example, was the wife of Pythagoras and after his death took over the running of his school, teaching philosophy and medicine. Pythias, the wife of Aristotle, co-authored a number of her husband's works for which he claimed credit, calling her his "assistant". It is clear that some Greek females were allowed to study and practise medicine, but it seems to have been with the mentorship (and probably protection) of a prominent male, usually a husband or father. One area where females did out-perform males was in the Roman slave markets, where a healthy female often cost 50 times the price of a healthy male. Several important texts were written during this era. A gynaecology and obstetrics text written by another Aspasia in the first century AD was the standard text until the work of Trutula Platearius, in the 12th century. Cleopatra (not the Egyptian queen, AD 129–201) wrote a gynaecology text that was in use until the 16th century (Brooke, 1993).

Around 200 BC Greek physicians, both male and female, began practising in Rome and females had relatively free access to the profession until around 100 BC. During the first century BC, the status of the females in Rome was somewhat better than the status of Greek females. Roman females could own property and a dowry was not mandatory. However, the Roman males were generally much better educated than their wives. Around 7 BC, a carpenter's wife named Mary gave birth to a son in Bethlehem and a whole new era began.

For a comprehensive discussion of the role of female healers in ancient Egypt and classical Greece, *Women Healers Through History* (Brooke, 1993) is highly recommended.

> As in all the churches of the saints, the women should keep silence in the churches. For they are not permitted to speak, but should be subordinate, as even the law says. If there is anything they desire to know, let them ask their husbands at home. For it is shameful for a woman to speak in church.
>
> First Letter of Paul to the Corinthians, 14: 34–36
> *The Holy Bible*, Standard Revised Version (1952).

The rise of Christianity has often been blamed for the denial of education to females. This accusation, while partially true, is certainly not a complete explanation. As Christianity became the dominant religion, Christian females became physicians. One such female, Fabiola, (who died in AD 399) was a physician who dedicated her life and practice to the care of the poor and opened the first hospital for the poor in Rome. By AD 385, four monasteries had been established at Bethlehem. Three were for females and the head of one of them, Eustochrum, was well educated, had learned Hebrew and edited Jerome's translation of the Bible.

There were problems for female scholars, however. In Alexandria, a female academic at the University of Alexandria was killed by a Christian mob in 415, her scholarly position being viewed as against Christian dogma.

Starting around AD 300, European society slid into the era of the "Dark Ages". Schools and libraries were destroyed and the study of medicine, mathematics and philosophy ceased. Religious orders took over the practice and preservation of healing skills. The exception was in Celtic Britain where the study and practice of medicine continued and female physicians became part of the folklore of the British Isles. Morgan le Fay is remembered in Arthurian legend as the high priestess and healer of Avalon.

The situation in the Middle East was somewhat different. In 610, the newly founded Muslim faith decreed that both females and males should receive secular and religious education. The medical school at Baghdad had 6000 male and female students.

The end of the dark ages around AD 1000 saw the return of scholarship to Europe. Solerno became famous as a healing centre and the medical school was deemed to be the best in Europe. The school was open to males, females, Jews and Muslims. The 1100s saw the publication of two medical books by female authors. *Diseases of Women*, by Trotula Platearius, a Professor of Medicine at the medical school of Solerno, became the major gynaecology text in use for the next 7 centuries. The *Book of Simple Medicine*, by Hildegarde von Bingen, a German abbess, identified 47 diseases and 300 medicinal herbs. In addition to the *Book of Simple Medicine*, Hildegarde wrote medical and scientific papers and songs. She was also an accomplished painter. It seems clear that up until the twelfth century, despite occasional lapses, the Christian movement generally supported education and scholarship for females.

Two events occurred, however, which severely curtailed the educational prospects of females. In 1229 the Inquisition of Toulouse forbade the reading of the Bible by lay persons. This ban effectively placed European education in the monasteries and made it, therefore, available only to males. In England, the tradition of female academia within convents remained until 1534 when Henry VIII closed all convents and schools. The closure lasted for 50 years and when the ban was lifted, England had been effectively deprived of its female teachers and scholars.

The first universities appeared around 1200 in Bologna, Paris and Oxford, and were established as training grounds for the clergy. The teachings from classical Greece were rediscovered and formed the basis for most of the teaching and scholarship. As females could not enter the clergy, they were virtually banned from the universities. Although, at that time, females could still obtain an education within the convent system, the university ban effectively prevented females from having access to philosophy and mathematics, the foundations of modern science. In addition, because the clergy were not permitted to marry, potential woman scholars were denied access to educated male mentors (Wertheim, 1995). The ban on females in universities lasted for almost 700 years.

The rise of modern science

Sir Humphrey Appleby: "Oh, Minister, Sarah Harrison is an excellent civil servant. And a bright hope for the future, but she is our most junior secretary and I cannot and will not recommend her promotion to deputy secretary."

Rt. Hon. James Hacker: "I think you're a sexist."

Sir Humphrey Appleby: "Ah (laughs), Minister, how could you say such a – I'm very pro women. Wonderful people women. And Sarah Harrison is a dear lady and I'm one of her greatest admirers. But if the cause of women is to be advanced, it must be done with care, tact and discretion. She is our only woman contender for a top job. We must not push her too fast. Women find top jobs very difficult, you know."

Rt. Hon. James Hacker: "Can you hear yourself?"

Sir Humphrey Appleby: "Minister, if women were able to be good permanent secretaries, there would be more of them, wouldn't there? It stands to reason."

Rt. Hon. James Hacker: "No, Humphrey!"

Sir Humphrey Appleby: "I'm not anti-feminist! I love women. Some of my best friends are women, Uh-h, my wife, indeed. (pause) But Sarah Harrison is, as yet, very inexperienced. Her children are still of school age. They might get mumps."

Rt. Hon. James Hacker: "You might get shingles, come to that, Humphrey!"

Sir Humphrey Appleby: "I might, indeed, Minister, if you continue in this vein. What if her children caused her to miss work all the time?"

Rt. Hon. James Hacker: "Oh, is it likely? Would she have reached the rank of undersecretary if her children kept having mumps? No, she is the best person for the job."

Sir Humphrey Appleby: "Now, Minister, if you're going to promote women just because they're the best person for the job, you will create a lot of resentment throughout the whole civil service."

Rt. Hon. James Hacker: "Not from the women in it anyway."

Sir Humphrey Appleby: "Well, that hardly matters."

Rt. Hon. James Hacker: "Hardly matters, Humphrey?"

Sir Humphrey Appleby: "There are so few of them."

Jay, A. and Lynn, J. (1980) Equal Opportunities. *Yes, Minister*, BBC Television, London.

Sir Francis Bacon is often cited, at least by British and American authors, as being the father of modern scientific method. In the same breath, he is also often cited as the originator of the view of science as a masculine pursuit (Keller, 1985). In his writings, Bacon used a number of metaphors for science (the male) and nature (the female). Although there is some disagreement in the literature concerning the extent of Bacon's belief in "masculine science", his true thoughts are in some ways immaterial. Bacon has served as an icon of scientific method for 400 years, widely respected and quoted. To attribute a view of "masculine" science to him has probably been, at least on some occasions, very convenient. It has also probably been used in a particular, flawed form of logical argument known as "argument from authority". Argument from authority can be a useful, and often successful, means of supporting a dubious position ("It has to be right, X said so").

What is clear is that in Bacon's time empirical investigation of scientific questions was coming into its own. By the mid-1600s the microscope was accepted as a useful scientific tool. Physiology and biology blossomed. By the end of the century, red blood cells, capillaries and various microrganisms had been discovered. In 1662 the Royal Society was established. The Society, with its publication *Philosophical Transactions*, offered a forum for the discussion and publication of experimental results.

In the latter half of the 1700s, the foundations for the modern discipline of

neuroscience were being laid. When in 1766, Albrecht von Haller discovered the structure and function of nerves and their connections to the brain, he uncovered the physiological foundation for the connection of the "mind" to the body. The establishment of this connection had far-reaching consequences, although ironically, even today there are philosophers and psychologists who will argue for the "mind" as a separate entity. One of the most important advances of this time was the establishment of the first insane asylums in France and the recognition of insanity as an illness rather than a derangement of the soul or possession by demons. Also, around this time, anaesthetics were discovered, giving a much more humane perspective to the practice of medicine.

In 1810, Franz Gall published the first of 4 volumes on the structure and function of the nervous system. Much of his work was later shown to be correct. He identified the function of the grey and white matter and made a systematic analysis of the different parts of the brain. His work was sophisticated and insightful and should stand as a milestone in the study of neuroanatomy. Unfortunately, Gall went off on a tangent and tried to develop a discipline of neural analysis based upon the shape and location of bumps on the skull, "phrenology". It is sad that it is for this diversion that Gall is generally remembered.

By the middle of the 1800s, the formula for female neglect was well established. Few females had the education or support and encouragement to pursue any kind of science, let alone a scientific investigation on the qualities of the female brain. Females who did receive medical training often worked in areas catering to the care of females and children or the poor. In many cases, this was probably by choice, but in at least some cases, these were clearly the only areas where they were allowed to practise medicine. As the study of the brain became a legitimate scientific pursuit, more and more physicians, anatomists and physiologists began the systematic study of its structure and function. At the same time, the pursuit of scientific knowledge left the privately funded laboratories adjoining the homes of researchers, where some females, at least, had had access to the facilities. The development and maintenance of research facilities became the domain of universities and hospitals. Females, without formal scientific education were relegated to the roles, if any, of cleaners and technicians. The few females who were qualified to conduct research would have faced an additional hurdle. When research became institutionalised, the acquisition of funding for research and the provision of facilities became competitive. Hospital or university administrators reviewed the requests for research support. They granted funds and facilities to those individuals and projects that they considered worthy of such investment. It is doubtful that a board of university administrators in the 1800s would have voted a research proposal on the structure and function of the female brain worthy of pursuit. Even today it can be difficult to convince granting bodies of the worthiness of such questions. If membership in learned societies is used to gauge female acceptance into the scientific community, then it is worth noting that the first female member of the National Academy of Sciences in the United States was elected to membership in 1925. It took the Royal Society another 20 years to allow the election of female Fellows.

It is probably the case that in the earliest stages of brain research, even if females had been academically involved, the questions of sex differences would not have arisen. The essential questions were related to understanding very basic aspects of structure and function. It must not have been long, however, before behavioural differences between

male and female laboratory animals became apparent, and confounding, factors in brain research. The behaviour of male animals did not vary because of a breeding cycle. Female animals were in a constant, albeit predictable, state of change. Female scientists would probably have realised the significance of these behavioural differences and, just maybe, a parallel study of male and female neuroscience would have developed. Unfortunately, there were few female scientists in the laboratories, at least not in positions of authority, to pursue these crucial observations. The fluctuating nature of female physiology became just another laboratory problem to be overcome. The solution to the problem was easy, males became almost exclusively the experimental subjects, while females were relegated to the role of "breeders". After all, it made good financial sense. A small number of males and their harems could keep the laboratories supplied with male animals for experimentation. It is ironic that the females of experimental species followed the plight of human females, valued for their capacity to reproduce but generally barred from other activities, even participation in an experiment.

> When I make myself imagine what it is like to be one of those women who live at home, faithfully serving their husbands – women who have not a single exciting prospect in life yet who believe that they are perfectly happy – I am filled with scorn. Often they are of quite good birth, yet have no opportunity to find out what the world is like. I wish they could live for a while in our society, even if it should mean taking service as attendants, so that they might come to know the delights it has to offer.
>
> Shonagon, S. (c. AD 994)
> *The Pillow Book of Sei Shonagon*.
> Morris, I. (Translator and Editor)
> Penguin, London (1967), p. 39.

Another point for consideration was the "suitability" of females as research subjects. Females, as the weaker, "fairer" sex, were not considered robust enough to be the subjects of scientific research. Their mythical physical frailty suggested they would be more at risk from dangerous drug side effects, or more easily exhausted by the rigours of psychophysical experiments. The "well-recognised" weakness associated with the menstrual cycle introduced an inconvenient variable. The problem of possible pregnancy was an even greater hurdle. At a time when pregnancy tests did not exist, any female of reproductive age was suspect. There were, in fact, two issues relating to pregnancy: willingness to administer experimental drugs to a pregnant female and ruling out pregnancy before including females. If it had been the case that the drugs being tested (or other drugs for that matter) were not administered to pregnant females, exclusion might have been justified. However, once testing was complete, the drugs were generally administered to females, pregnant or otherwise. Even as late as the 1960s, for example, in England drugs such as barbiturates were administered to treat hypertension in pregnancy.

To be fair, many of the laws governing medical experimentation were formulated during the time when the Nazi atrocities of World War II were a recent memory. In addition, several cases of unethical research were uncovered in the United States. The resulting public outcry led to the formulation of laws to protect the subjects of medical

research. The problem was that, in an effort to protect, the structure of the laws actually led to the exclusion and disadvantage of the "minorities" that they were originally designed to protect.

With the development of the pharmaceutical industry, the policy restricting research to male animals moved from neglectful to ridiculous. Drug development and research in male laboratory animals was followed by testing using human males. This routine was so well established that the oestrogen-based female contraceptive pill was tested on males! The rationale used for screening drugs in human males was delightfully illogical; females were not suitable test subjects because of their changing hormonal levels during the menstrual cycle and there was always the risk of producing birth defects. True, however, these very drugs were usually destined for use by both females and males. Ironically, when a drug-induced disaster (thalidomide in the 1960s) did occur, it was pregnant females and their children who were the victims.

Both Plato and Aristotle observed the brain of the human male to be larger than the brain of the female. Aristotle also held that the structure of the male brain was more complex, in order to allow for better "ventilation". In the 1800s, the eminent neuroanatomists, Broca and Crichton-Browne, debated whether the difference in brain size could be accounted for by the general difference in body size between males and females. By the final quarter of the 20th century, substantial experimental evidence had accumulated to suggest difference in brain function between females and males. From experimental psychology came research demonstrating differences in perceptual skills and motor performance (Chapter 6). From psychiatry came evidence of female–male differences in responses to antipsychotic drugs (Chapter 8). It seemed that the scientific community should have been poised to start investigating the differences.

Interestingly, it was the long overdue feminist movement that may have actually impeded progress. As feminism gathered strength and support, the emphasis was on closing the gaps between females and males in education, employment, and civil liberties. At last, opportunities for females in all aspects of life were becoming available. But the new opportunities were hard won and many prejudices were lurking, just waiting for an invitation to resurface. It was not a politically opportune time to promote research on the very differences that so many dedicated individuals (both female and male) were striving to overcome.

> Come writer and critics
> Who prophecise with your pen
> And keep your eyes wide
> The chance won't come again.
> And don't speak too soon
> For the wheel's still in spin
> And there's no tellin' who
> That it's namin'
> For the loser now
> Will be later to win
> For the times they are a-changin'
>
> Dylan, B. (1963) The Times They Are A-Changin'.
> *Bob Dylan*, Warner Bros, New Jersey (1974).

Since the early 1980s, one particular researcher has pursued the question of sex differences and behaviour. Over the past 20 years, Kimura has published on a number of areas where she has observed female–male differences including language (Kimura and Harshman, 1984), performance of spatial tasks (Hampson and Kimura, 1988) and the effects of hormone replacement therapy in protecting cognitive function after menopause (Kimura, 1995). For the interested reader, "Sex Differences in the Brain" published in *Scientific American* (Kimura, 1992) and *Sex and Cognition* (Kimura, 1999) are highly recommended.

In the 1990s two initiatives by the U.S. National Institutes of Health (NIH) signalled positive change for female health and health research. In 1991, the U.S. government approved the NIH Women's Health Initiative, a 14 year, US$625 million research project. The aim of the Initiative was to conduct multicentre studies of issues relating to the health of post-menopausal females over the period 1993 to 2007 (Thaul and Horta, 1993).

In 1993, the NIH Revitalisation Acts were passed (Mastroianni *et al.*, 1994a,b). There were several stimuli for the implementation of the Acts. Pressure from "minority" groups including females, homosexuals and people with HIV to be included in research initiatives had become intense. In addition, a government audit of the NIH revealed that a 1986 policy of greater inclusion of females in research had not been successfully implemented and females were still "under-represented".

The Revitalisation Acts include wide-ranging recommendations for the inclusion of females in all aspects of medical research. The following are only some of the recommendations:

1. NIH is to establish a register of its research activities which includes information on participants including sex and ethnic representation.
2. Medical and health research must benefit all people regardless of sex, race or age.
3. Volunteers for medical research must be allowed to participate without prejudice because of sex, race or age. In addition, the researchers must ensure that anyone who may benefit from the research, is enrolled in suitable numbers to allow meaningful results. Financial concerns are not a valid reason for failure to do so.
4. Researchers must design experiments to avoid gender bias and NIH must encourage females of all ethnic groups to pursue careers in scientific research.
5. Researchers must not exclude males or females of reproductive age, or pregnant or lactating females, from studies of drugs or procedures which will ultimately be used by these groups.

Conclusions

Females were, most likely, the original healers. However, the power associated with healing ultimately led to the males, in most societies, claiming the roles of healers. It is probably this change in power base which led to a lack of research into female health interests generally, and the female brain, in particular. The points for consideration from this chapter are:

1. Historically, females have been excluded from medical research on various grounds of "unsuitability" including frailty, the menstrual cycle-associated fluctuations in physiology and behaviour, and the risk of pregnancy.

2. Despite the exclusion of females from research, results obtained in males have been assumed to apply equally to females.
3. Recent NIH research initiatives have provided a legal basis for including females in all aspects of medical research.

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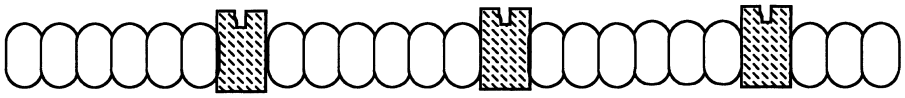
3

Brain structure: The architecture of difference

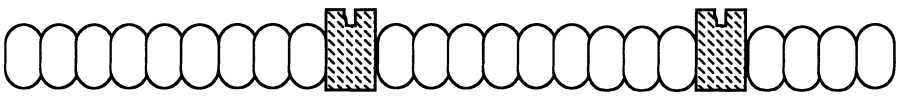
> The formal study of the philosophy of science had its origins in the writings of the early Greek philosophers, who attempted to fit a logical structure and method of observation to the study of nature. Over the centuries, as layer upon layer of scientific discoveries were built upon those early naturalistic observations, questions about the nature of the sciences themselves arose. Human-eye observation of leaves, clouds, and body parts was superseded by microscopic and macroscopic methods of observation, the red blood cell and the craters on the moon became accessible to the appropriately equipped observer. Moreover, with this accessibility came questions about the nature of the laws governing the objects and processes observed at these different levels. Do, for example, the same laws of physics apply to a brain cell and a spacecraft? Can you logically use the same kinds of scientific terms, in this case, the terms of physics, to give satisfactory explanation of both objects? If the answer you decide upon is "yes", then you are arguing for the philosophical position known as Reductionism. If, on the other hand, you say "no", then you are faced with the responsibility of defining the extra level of explanation that is required. This is not an easy task.
>
> C.D.

The exploration of a physical system can proceed in several ways. For the Structuralist, the exploration will include detailed examination and recording of all of the physical features available to observation. For the neuroanatomist, for example, the examination may begin with the gross anatomy, holding the preserved brain in gloved hands and inspecting the surface, then move to the microscopic anatomy, the study of cell structure using light or electron microscopy. Finally, at the molecular level, techniques such as gel chromatography can analyse the protein composition of cells, or even parts of cells.

a. Numerous receptors are present before drug administration.



b. Receptor down-regulation, by loss of receptors, may occur after one dose.



c. Down-regulation continues with repeated doses until few, if any, receptors are left to respond to the drug.

Figure 3.1 Receptor down-regulation: A functional change occurs as a result of a physical change.

For the Functionalist, the challenge is to understand the processes performed by the structure. The neurophysiologist also uses macro- and micro-techniques in the exploration. The pupillary reflex can be observed with the naked eye. The activity of single neurones in the reflex pathway can be recorded using glass electrodes with microscopic tips. Finally, the neurotransmitters released by activity in the reflex pathway can be identified using microdialysis techniques.

Presented in this way, the distinction between structure and function seems clear. However, consider what happens with the development of drug tolerance. Following prolonged or repeated exposure to a particular drug, the system becomes less sensitive to the drug so that a larger dose is required to achieve the effect previously obtained by the smaller, original dose. This process may occur in several ways: the affinity of the receptor for the drug may decrease so that the drug is less likely to bind to the receptor; or the drug may bind with the same affinity but produce a smaller effect; or the number of receptors may decrease so that the same amount of drug has fewer binding sites and therefore, produces less response (Figure 3.1). In all of these cases, a structural change underlies the functional change and the structure/function distinction breaks down.

The focus of this chapter will be primarily on the structure of the brain, and how it differs between the sexes. The next chapter will concentrate on the functional differences between the brains of males and females, in terms of neurochemistry. Both chapters will, of necessity, stray into the areas where the distinction breaks down and the placement of a topic in one chapter or the other becomes arbitrary.

Development of the brain

> Since the seed is residue, and is being moved in the same movement as that with which the body grows . . . when it comes to the uterus it constitutes and moves the female's residue in the same movements in which it itself is actually

> moving . . . It even contains potentially the sort of parts whereby there is a difference between male and female. For just as the offspring of deformed animals are sometimes deformed and sometimes not, so that of a female is sometimes female and sometimes not – but male. For the female is as it were a male deformed, and the menses are seed but not pure seed; for it lacks one thing only, the source of the soul.
>
> Aristotle (384–322 BC)
> In Ackrill, J.L. (Translator and Editor) (1987)
> *A New Aristotle Reader*, Princeton
> University Press, Princeton, pp. 248–249.

The potential for structural differences between the female and the male brain develops early in gestation when testosterone in the developing male foetus causes the differentiation of the sex organs and forms the foundation of the female/male differences that will endure throughout life.

Human cells may exist in two states, as haploids, which carry a single set of chromosomes, and as diploids, which carry a double set of chromosomes. Cell proliferation, and therefore growth, usually occurs by mitosis, the division of the parent cell to produce two identical daughter cells. The two daughter cells each divide to produce two more cells and so the cycle continues. However, for cells specialised for sexual reproduction, gametes, the process is different. Gametes are haploid cells: The oocyte, contributed by the female, is a nonmotile cell, containing a single X chromosome. The female always contributes an X chromosome; the female chromosomal pattern is XX, therefore, the parent cell will produce X containing gametes (Figure 3.2). In contrast to the oocyte, the sperm is a small, highly motile cell which may contain either an X- or a Y-patterned chromosome. The male parent cell, which divides to produce the individual sperm, contains an XY chromosome pattern. When the cell divides, the gametes will be either X or Y. Whether the fertilised oocyte becomes an XX, female, or an XY, male, depends entirely upon which sperm reaches and successfully penetrates the cell membrane first. At conception, the sex of the zygote (strictly speaking, it becomes an embryo at 3 weeks and a foetus at 9 weeks) is determined by the chromosomal pattern as either genetic female (XX) or genetic male (XY) (Alberts *et al.*, 1994).

It is the presence or absence of the Y chromosome that determines whether the gonads, which are undifferentiated at the time of conception, will develop to be male or female. If only X chromosomes, or even only one X chromosome, are present then the gonads will develop into ovaries. It is only if a Y chromosome is present that the gonads will develop into testes. In other words, the foetus will be female unless proven otherwise.

Until gestational week 6, the gonads are identical in both females and males. Two sets of genital ducts are present, the Müllerian ducts, which have the potential to differentiate into the female genitalia, and the Wolffian ducts, which have the potential to differentiate into male genitalia.

At post-conception week 6, under chromosomal control, the gonads in the male begin to differentiate into testes, and these developing testes secrete testosterone. It is the presence of testosterone that causes the differentiation of the embryo into a male. Testosterone stimulates the Wolffian ducts to further develop into the internal sex

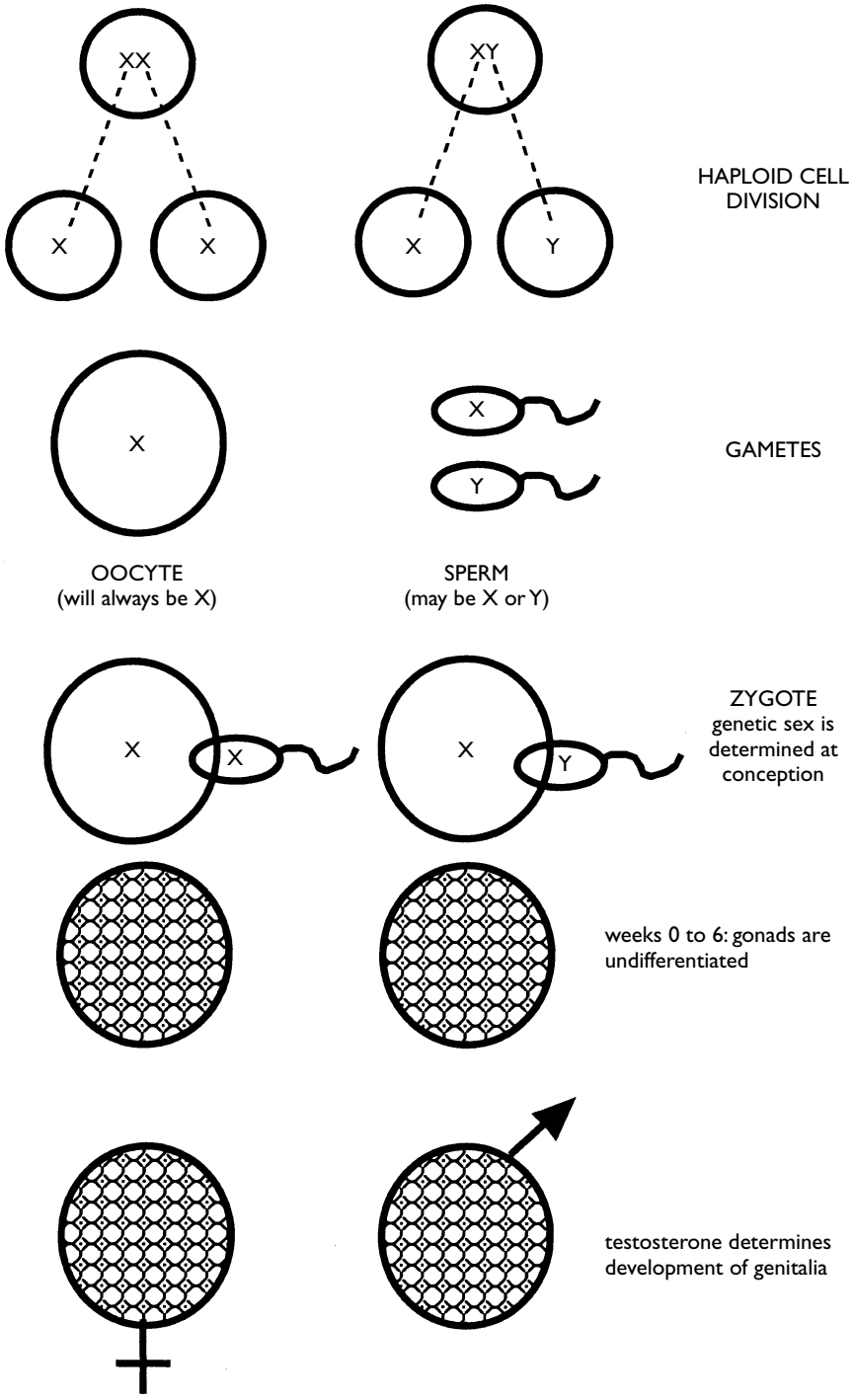


Figure 3.2 Sexual determination of the foetus.

organs, while at the same time, the peptide hormone, Müllerian inhibiting factor, also secreted by the testes, suppresses the development of the Müllerian ducts. At the same developmental time, without the addition of testosterone, the undifferentiated gonads in the female begin to differentiate into ovaries and the Müllerian ducts begin developing into female sex organs. At this stage, in both female and male, the external genitalia are also undifferentiated, and androgens secreted by the testes cause the differentiation into male genitalia. Here the role of chromosomes in sexual development finishes.

Sexual dimorphism in the CNS

> **dimorphism 1.** (in biology). The existence of two distinctly different types of individual within a species. An obvious example is *sexual dimorphism* in certain animals, in which the two sexes differ in colouring, size, etc. *Dimorphism* also occurs in some lower plants, such as mosses and ferns, that show an alternation of generations.
>
> *Concise Science Dictionary*, Oxford University Press (1991).

The sexual differentiation of the CNS is a much slower process than the development of the sex organs. Research suggests that the development of sexual dimorphism continues well beyond birth, with spurts of development taking place at different times and in different brain regions, depending upon the sex of the individual. Indeed, it has been suggested (Swaab and Hofman, 1995) that in one region specifically related to sexual behaviour, the sexually dimorphic nucleus of the preoptic area, the changes continue throughout life. The variables that contribute to sexual dimorphism in the brain have been the subject of some disagreement. Until fairly recently, the general assumption has been that, as with the development of the sex organs, the presence of testosterone is the stimulus for differentiation into a male brain, and absence of testosterone results in development of a female brain. Recently, however, this idea has been challenged and evidence now suggests that the presence of oestrogen and/or progesterone, not just the absence of testosterone, is necessary for the differentiation of at least some of the sexually dimorphic brain regions (Patchev *et al.*, 1995; Wagner *et al.*, 1998). Hormones alone, however, are not totally responsible for sexual differences, and in Chapter 4 we will explore the interactions of neurotransmitters and neuromodulators with the hormones present in the brain.

Although research on sexual dimorphism in the animal brain has arisen relatively recently, the literature on human brain dimorphism goes back about 2000 years. As discussed in Chapter 2, both Plato and Aristotle observed that the brain of the human male was larger than the brain of the female. Now, in the 21st century, there is still debate over whether there are real size differences in the brains of females and males, and what, if anything, such differences might mean. A number of authors writing on the subject state flatly that there is a 10% difference in the size of the female brain relative to the male brain and cite a 1978 study (Dekaban and Sadowsky, 1978) to support the claim. Other, more recent, studies have reported that with adjustment for body size, female and male brains are roughly the same size. Blatter *et al.* (1995) have compiled tables of normative volumetric data using the MRI scans of 194 healthy

adult brains of individuals ranging in age from 16 to 65 years. The authors presented the data in two forms: as volumetric estimates corrected for differences in total intracranial volume; and as uncorrected data, shown in both instances as mean volumes sorted by decade of life and sex. The authors report that age-related changes in cerebrospinal fluid volume were observed for both males and females. However, when the data were corrected for differences in total intracranial volume, most, but not all, of the sex-related differences in the volume of brain tissue disappeared. Falk *et al.* (1999) collected similar data from 44 female and 39 male rhesus monkeys. From their data, the authors concluded that, even when adjustments were made for body weight, male macaques had larger brains than females of equivalent weight (Falk *et al.*, 1999).

Whether or not there are differences in total brain volume between male and female humans, there is certainly evidence to suggest that there are differences in the volume of particular brain regions of males and females. A recent study by Reiss *et al.* (1996) used MRI scans from 85 children, aged between 5 and 17 years. There were 64 females (mean age 11 years) and 21 males (mean age 11 years). Handedness was matched between the two groups with 83% of the subjects being right-handed, 15% left-handed and 2% having no hand preference. A subset of the female (n = 57, mean age 11 years) and male (n = 12, mean age 10 years) subjects were also tested for IQ. The mean IQ for the two groups was 113 for the females and 105 for the males. All of the participants were in good health and had no known psychiatric or neurological disorders.

The scans were analysed to determine the volume of grey matter, white matter and CSF. After correction for intracranial volume, the results of the study revealed significant differences in brain volume attributable to sex. The total cerebral volume (grey matter + white matter + CSF) was approximately 10% larger in males than in females. The difference was primarily due to an increased volume of cortical grey matter in males (and, to a lesser extent, to a larger volume in the lateral ventricles). There were no differences in the volume of the caudate nucleus, lenticular nucleus (i.e. the putamen + the globus pallidus) or thalamus (Table 3.1). Although there were no significant differences directly attributable to age, the authors comment that with increasing age, there was a trend for decreasing volume of grey matter and increasing volume of white matter. Further analysis of the data revealed that the volume of grey matter in the prefrontal regions was related to the IQ of the subjects.

In a similar study, Giedd *et al.* (1996) used MRI to study the brain structure of 104 children aged between 4 and 18 years. The authors report that males had significantly larger cerebral (9%) and cerebellar (8%) volumes than females. Regional analysis showed a larger putamen and globus pallidus in males but a relatively larger caudate nucleus in females. Also, in agreement with the previous study, no age-related changes in the cerebral or cerebellar volumes were observed. However, several regional changes were seen to occur with age. In males only, a significant increase in the volume of the lateral ventricles and a significant decrease in the volumes of the caudate and putamen were observed, suggesting that sex-specific maturational changes in the volume of specific brain regions were occurring.

Andreasen *et al.* (1993) looked for correlations between brain volume, gender and IQ in adults. The subjects for the study were 67 normal, healthy adults recruited

Table 3.1 Brain volume estimates in children using MRI

Measure	*Result*
Absolute brain volume	m > f
right hemisphere volume	m > f
left hemisphere volume	m > f
Total grey matter volume	m > f
cortical grey matter	m > f
caudate nucleus grey matter	m = f
lenticular nucleus grey matter	m = f
thalamus grey matter	m = f
White matter	m > f
CSF	m = f
CSF outside ventricles	m = f
CSF in lateral ventricles	m > f

Adapted from Reiss *et al.* (1996) p. 1766.

through newspaper advertisements. There were 30 female subjects (mean age 38 years, mean height 168 cm) and 37 males (mean age 38 years, mean height 181 cm). Regional and total brain volumes were measured using MRI; intelligence was measured using the Wechsler Adult Intelligence Scale – Revised (WAIS-R). The WAIS-R is an instrument for assessing adult intelligence which gives an overall IQ score, as well as individual scores for Performance IQ and for Verbal IQ. The mean full-scale IQ for all subjects was 116, mean verbal IQ was 114 and mean performance IQ was 114. There were no significant differences between female and male IQ. The MRI scans were analysed for the volume of different brain regions, with discrimination made between grey matter, white matter and CSF. The MRI data, corrected for body height differences, were then compared to the IQ data for correlations between regional volumes and IQ.

The results of this study showed that, for both male and female subjects, there was an overall positive correlation between brain volume and IQ, with all of the differences being attributable to the volume of the grey matter. In addition, there were male–female differences in the correlations of the volume of specific brain regions and Verbal and Performance IQ. For females, there were correlations between Verbal IQ and total brain volume, the volumes of the cerebellum, the cerebral hemispheres, the left and right temporal lobes and the hippocampi. Performance IQ, on the other hand, was correlated only with the volume of the cerebellum, the right temporal lobe and the left hippocampus. Results for the male subjects showed correlations between Performance IQ and the total brain volume, and the individual volumes of the cerebral hemispheres, the cerebellum and the left hippocampus. For Verbal IQ the only correlations were for the volumes of the right temporal lobe and the cerebellum (Table 3.2).

This study is interesting for several reasons. First, there is a clear indication that "the larger the brain, the higher the IQ" (p. 132) although, as the authors are quick to point out, the differences are "modest". Therefore size is only one of a number of factors contributing to IQ. More interesting, however, is the finding that the correlation

Table 3.2 Correlations between brain volume and IQ

Structure	*Sex*	*V/IQ*	*P/IQ*	*FS/IQ*
total cranium volume	m	–	*	*
	f	*	–	*
right hemisphere volume	m	–	*	*
	f	*		*
left hemisphere volume	m	–	*	*
	f	*	–	*
right temporal lobe volume	m	*	–	*
	f	*	*	*
left temporal lobe volume	m	–	–	–
	f	*	–	*
cerebellum volume	m	*	*	*
	f	*	*	*
right hippocampus volume	m	–	–	–
	f	*	–	*
left hippocampus volume	m	–	*	*
	f	*	*	*

From Andreasen *et al.* (1993). FS/IQ, full scale IQ; P/IQ, performance IQ; V/IQ, verbal IQ.
* Indicates significant positive correlation.

between volume of different brain regions and particular types of IQ, Performance or Verbal, differs between females and males.

Regional differences

Differences between females and males have been reported for several cortical structures. A postmortem study of the language-associated cortical areas of the brains of 11 females and 10 males has reported that the volume of the superior temporal cortex was 18% larger in females than in males. The overall difference in volume was accounted for primarily by differences in the planum temporale (mostly the auditory association cortex), which was 30% larger in females (Harasty *et al.*, 1997).

A cytoarchitectural study of the planum temporale in females and males has reported particularly interesting results (Witelson *et al.*, 1995). This study offers some especially useful information because although it used tissue obtained post-mortem, not only was the cause of death well understood but the subjects were also known to have had normal cognitive function in life. The subjects for the study were 5 females and 4 males suffering from metastatic cancer. At the time the subjects were recruited for the study they were free from obvious symptoms of their disease. The subjects gave their consent for their brains to be examined at autopsy. At the time of recruitment, they underwent extensive medical and neuropsychological testing. In addition, they developed no neurological or psychiatric complications as the disease progressed. All subjects were predominantly right-handed. The mean age at death was 49 years for the males and 54 years for the females.

Following death, the brains were removed and fixed for histological analysis. The time between death and tissue fixation was on average 3.5 hours for the males and 7.2 hours for the females. The variables measured were the total cortical depth, the number of neurones per 1 mm^2 of cortical surface and the number of neurones per unit volume (the density of cell packing). Neither the cortical depth nor the number of cells differed between females and males. The number of neurones per unit volume, however, was significantly greater in females (by 11%) than in males. The authors point out that this is almost the same difference as the difference in total brain volume generally reported between females and males. They suggest that reported overall difference in brain volume may simply be because cells are packed more densely in the female brain than in the male brain. A similar suggestion has been made by Gur *et al.* (1999) who have reported, using MRI, that females have a higher percentage of cortical grey matter while males have a higher percentage of cortical white matter. They suggest that the increased density of grey matter in females could compensate for the smaller overall volume. By contrast, Rabinowicz *et al.* (1999) have reported significantly higher neuronal density and higher estimated neuronal numbers in males than in females.

Despite superficial appearances, the brain is not symmetrical around its longitudinal axis. This asymmetry has been shown to apply to both structure, discussed in this chapter, and function (Chapter 5). Many studies have demonstrated that the brains of normal individuals are asymmetrical, with the right hemisphere larger than the left, and that this asymmetry is evident in the newborn child. This normal asymmetry is so well documented, in fact, that individual variations in asymmetry may be indicative of brain pathology such as schizophrenia (Chapter 7). It is also reported that the female brain is more symmetrical than the male brain. The asymmetry is reported to differ most between females and males in areas related to language function and to handedness (Chapters 5 and 6).

A number of recent studies have demonstrated that, in people who are right-handed, the frontal areas of the brain tend to be larger on the right side. Paus *et al.* (1996) have reported frontal lobe differences in an MRI study of 105 right-handed individuals (Table 3.3). In their study, these authors report that the volume of grey matter in the anterior cingulate sulcus and in the superior-rostral sulcus was larger in the right hemisphere than the left hemisphere, while the volume of grey matter in the

Table 3.3 Estimated frontal lobe asymmetry using MRI

Region	*Asymmetry*
volume of grey matter, anterior cingulate sulcus	R > L, f and m
volume of grey matter, posterior cingulate sulcus	L > R, f and m
volume of grey matter, paracingulate sulcus	L > R, f and m
sex differences in asymmetry:	
cingulate sulcus	f > m
paracingulate sulcus	m > f

From Paus *et al.* (1996).

posterior cingulate sulcus and paracingulate sulcus was greater on the left. The cingulate sulcus was significantly larger in females than in males and the paracingulate sulcus was significantly larger in males. However, an imaging study by Bullmore *et al.* (1995) has demonstrated that these differences are not nearly so clear cut when you consider handedness as a variable. In their study, the only consistent pattern of asymmetry was for right-handed males. As the authors point out, their result is consistent with the idea that the female brain is more symmetrical than the male brain. On the other hand, Reiss *et al.* (1996), in a study of children, report that the brain asymmetry, with greater volume in the right cortical areas, was the same for boys and girls. Although the proportion of left-handed to right-handed children was balanced between the two groups (15% were left-handed), the results were not analysed for differences in handedness.

One area where clear size and shape differences have been noted is in the fibre tracts that connect the cerebral hemispheres. These fibre crossings are known as commissures or decussations, depending upon their location. The largest of the commissures is the corpus callosum (Figure 3.3), which relays information between the two cerebral hemispheres. Most fibre tracts in the human brain and spinal cord are bilaterally crossed and symmetrical (Figure 3.4). Sensory information from one side crosses to the opposite side and is relayed to the cerebral cortices for processing. The corpus callosum has generally been reported to be larger in females, and some authors have attributed sex differences in the lateralisation of cognitive and language functions to this size difference (Chapter 6). Some studies, both histological (de Lacoste-Utamsing and Holloway, 1982) and MRI (Allen *et al.*, 1991), have suggested that the previously reported sex differences may be due to a different *shape* in females rather than a difference in the overall size of the corpus callosum. The anterior commissure, which

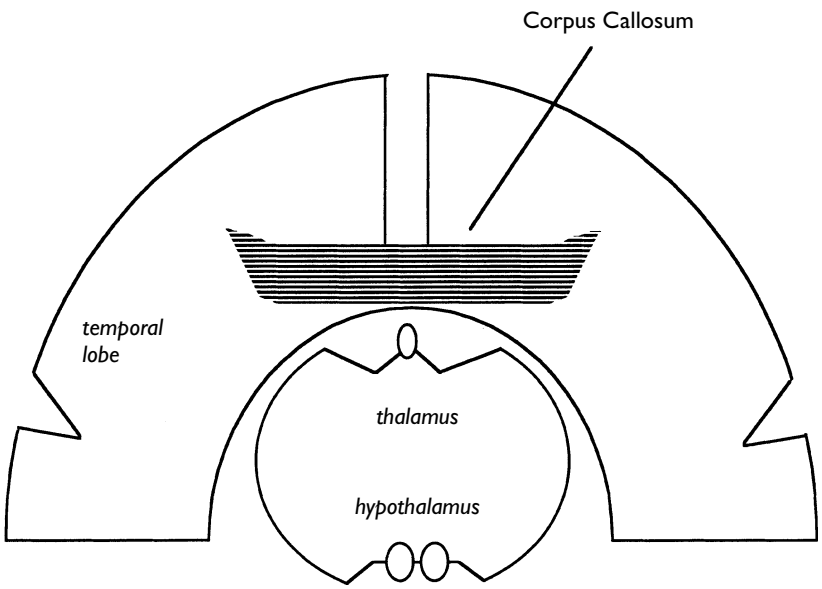


Figure 3.3 The corpus callosum connects the two cerebral hemispheres.

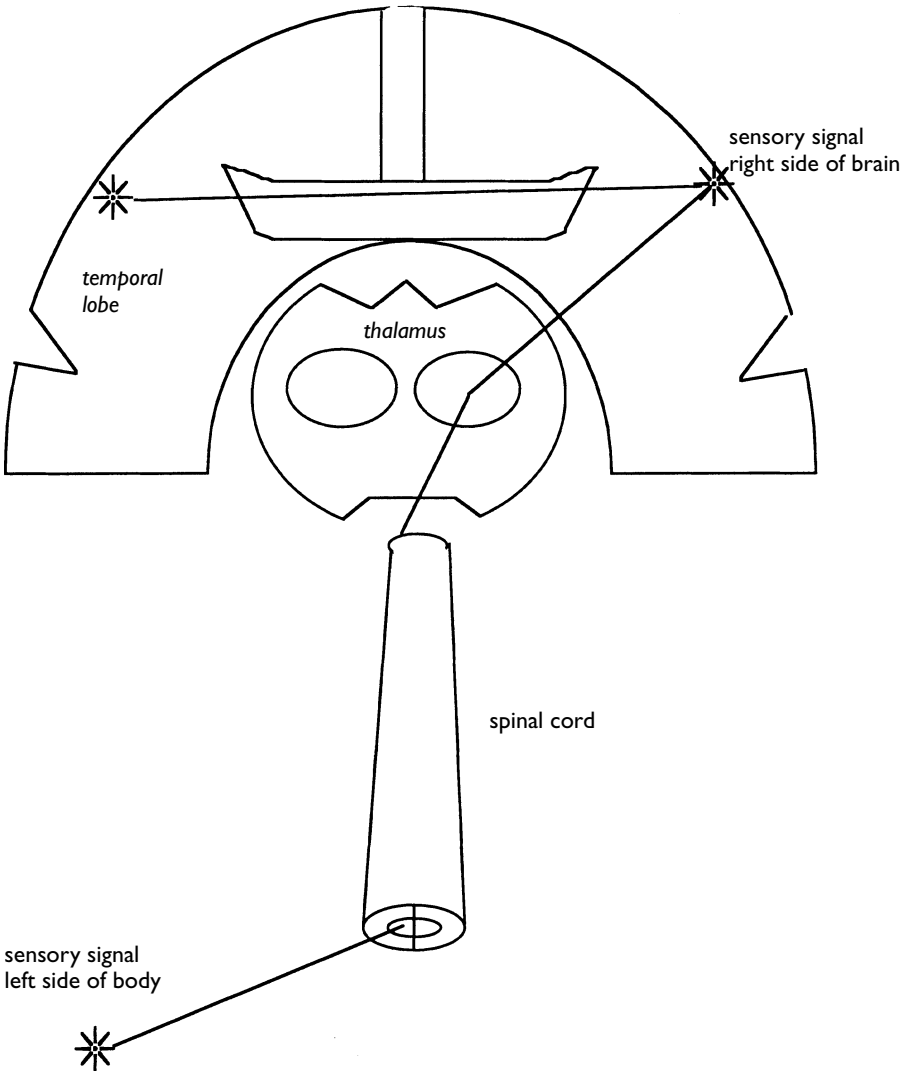


Figure 3.4 Sensory information, for example, touch, from one side of the body is relayed, via the thalamus, to the opposite side of the brain. The information is then "shared" via the corpus callosum with the other side of the brain.

crosses the deep diencephalon, near the hypothalamus, contains axons that primarily connect the two temporal lobes. In a study of autopsy material from 100 human females and males it has been reported that the anterior commissure is approximately 12% larger in females than in males (Allen and Gorski, 1991).

The hypothalamus is known to play a role in sexual behaviour and reproduction. Not surprisingly, it was one of the first regions to be systematically examined for sexual dimorphism. The hypothalamus may be divided into a number of distinct

regions, based upon the function of the neurones located in each different area. The preoptic area is classified as a part of the hypothalamus by some authors and as a separate nucleus by others. However, the two areas are so intimately linked that to consider them together is probably the logical option, at least for our purposes (Figure 3.5).

Sexual dimorphism in the human preoptic nucleus was first reported in 1985 by Swaab and Fliers. In that study both the size and the total number of neurones in particular regions of the preoptic nucleus were reported to be significantly larger in

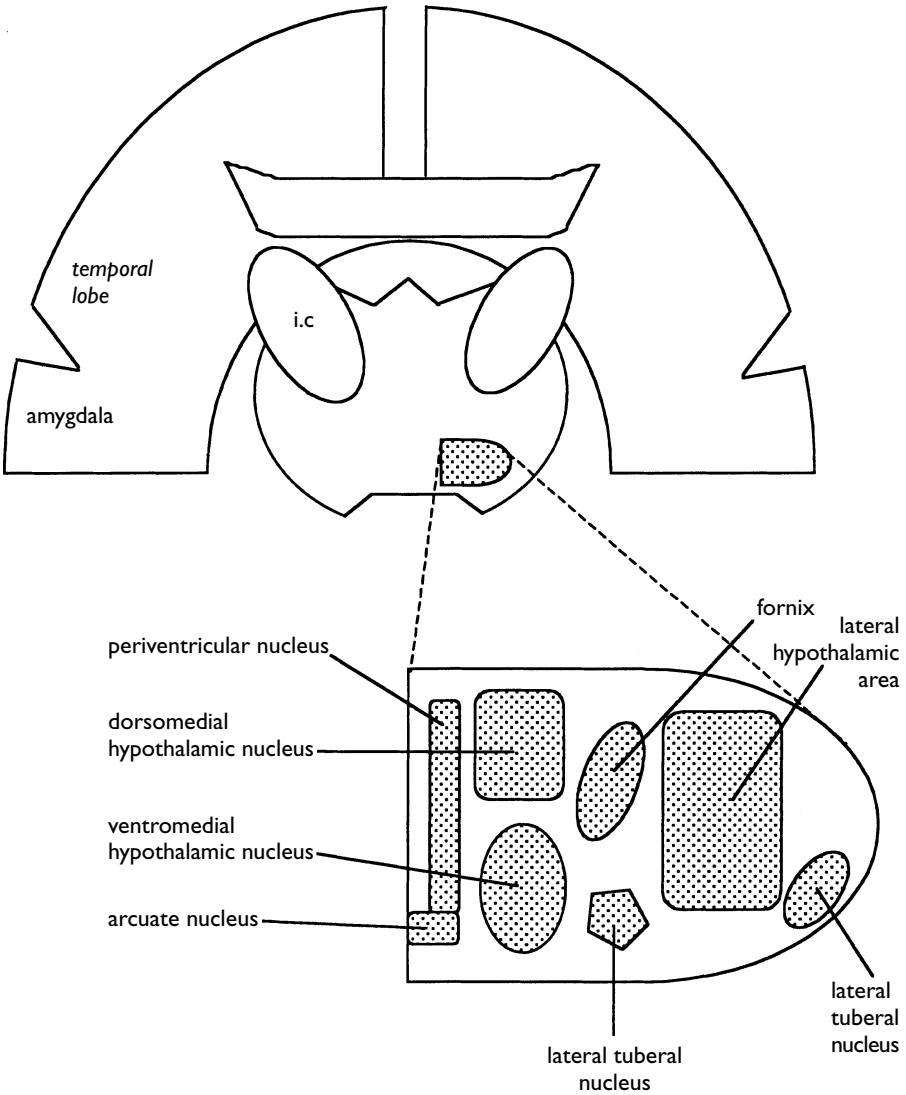


Figure 3.5 Schematic representation of the subregions of the human hypothalamus. Shaded region represents approximate location of enlarged area. i.c, internal capsule.

males than in females. The volume of the bed nucleus of the stria terminalis in males has also been reported to be approximately twice the volume in females (Allen *et al.*, 1990; Zhou *et al.*, 1995). The evidence for sexual dimorphism in the hypothalamus was reviewed by Swaab and Hofman (1995). In their article, the authors note that the nucleus is the same size in females and males at birth, but is smaller in adult females relative to adult males because the size decreases with maturity in females. Another area where the female/male size relationship changes with development is the amygdala. At birth, it is the same size in females and males, but by the age of around 8 years it has grown to a larger overall size in males. At around 10 years, however, the volume has begun to decrease in males, but continues to increase in females so that from about the age of 20 onward, the volume of the amygdala is greater in females than in males (Goldstein *et al.*, 1999).

> Traffic roared amid the towers of Capital City, just beyond the sealed crystal dome of the official palanquin. But no sound penetrated to disturb the bureaucrat of Cost and Caution, who concentrated only on the holo-image of a small planet, turning slowly within reach of one down-covered arm. Blue seas and a jewel-bright spray of islands came into view as the bureaucrat watched, sparkling in the reflected glow of an out-of-view star. *If I were one of the gods spoken of in wolfling legends* . . . the bureaucrat imagined. Its pinions flexed. There was the feeling one had only to reach out with a talon and seize . . .
>
> Two downy aides fluttered quietly nearby, preening the bureaucrat's feathers and bright torc for the appointment ahead. They were ignored. Aircars and floater barges darted aside and regimented lanes of traffic melted away before the bright beacon of the official vehicle. This was status normally accorded only royalty, but within the palanquin all went on unnoticed as the bureaucrat's heavy beak lowered toward the holo-image.
>
> Brin, D. (1987) *The Uplift Wars*, Orbit, London, p. 1.

Evidence from other species

The majority of animal studies on sexual dimorphism in the brain have come from studies on the laboratory rat, although monkeys, ferrets, gerbils and squirrels have also had their day. In general, the results of the experimental studies are consistent with the results obtained in humans. For this reason, this section will give only a brief overview of the animal literature.

Sexual dimorphism has, not surprisingly, been clearly demonstrated in the hypothalamus. One particular region of the preoptic area has been reported to be five to six times greater in volume in male rats than in female rats (Gorski *et al.*, 1978). This region was named the "sexually dimorphic nucleus of the preoptic area" by Gorski *et al.*, who first reported the size difference. Another part of the preoptic area, the anteroventral periventricular nucleus of the preoptic area, shows the opposite pattern of sexual dimorphism: the area is substantially larger and more densely packed with neurones in the female than in the male.

Brain regions where anatomical dimorphism has been observed are summarised in

Table 3.4. This table is not meant to be a comprehensive listing of the literature, it is meant only as a list of examples. In most cases, the difference reported seems to be a larger area in the male. One area which has been deliberately omitted from the list are the song-related nuclei which show distinct differences in a number of bird species. The song-related nuclei play an important role in the sexual behaviour of many birds. The song of the male is part of an elaborate courtship display necessary to seduce the female. While human males may indeed use song as part of their courtship display (have a look at Mick Jagger in action), anything even close to the song-related nuclei is yet to be discovered in the brain of the human male.

In the cerebral cortex, differences have been reported in regions related to vision, motor control, sense of smell, and emotion. In the visual cortex, there are more neurones in males than in females and the dendrites of some neurones are larger in males. Sex-based differences have been reported in the hippocampus and amygdala. In the

Table 3.4 Examples of studies reporting regional brain differences in rat

Region	*Difference*	*Reference*
amygdala	volume, m > f	Mizukami *et al.*, 1983
bed nucleus	volume, m > f	Collado *et al.*, 1990
olfactory tract	cell count, m > f	
corpus callosum	unmyelinated axons, f > m	Mack *et al.*, 1995
	myelinated axons, m > f	
hippocampus	granule cell number, m > f	Roof, 1993
	CA3 pyramidal cells, proximal dendrite	
	volume, f > m; distal dendrite volume, m > f	Juraska *et al.*, 1989
hypothalamus:		
anterior ventral	volume, f > m	Simerly *et al.*, 1985
periventricular	cell count, f > m	
preoptic area		
arcuate nucleus	volume, m > f,	Leal *et al.*, 1998
	density denditric branching and spines, f > m	
medial preoptic area	volume, m > f	Gorski *et al.*, 1978
locus coeruleus	noradrenaline neurones	Guillamon *et al.*, 1988
	number, f > m	
	volume, f > m	
neocortex	volume, m > f	Reid and Juraska, 1992b
bed nucleus stria terminalis	volume, m > f	De Vries *et al.*, 1994
striatum	GABA neurones	Ovtscharoff *et al.*, 1992
	number, f > m	
suprachiasmatic nucleus	spine synapses	Guldner, 1982
	m > f	
visual cortex	volume, number of neurones	Reid and Juraska, 1992a
	m > f	

hippocampus, which is clearly divided into layers composed of different types of neurones, the granule cell layer is larger in males than in females. The amygdala is also larger in males and receives, in males, a greater number of axons from neurones in the hypothalamus carrying the hormone vasopressin. Differences have also been noted in the striatum and the locus coeruleus. In both of these regions, neurones containing the major neurotransmitter of the region (noradrenaline in the case of the locus coeruleus, and GABA in the case of the striatum) are more numerous in females than in males. In addition to areas containing neuronal cell bodies, a number of animal studies have also reported size differences in the corpus callosum and the anterior commissure, similar to those already discussed in humans.

The CT scan is a multiple x-ray method which provides a snapshot of brain structure at a given point in time. The machinery is rotated around the head of the subject, taking x-rays at every degree of rotation. By summing the density of the image, for each individual exposure, for individual co-ordinates throughout the brain, a 3-dimensional representation of the brain structures can be created which distinguish grey matter and white matter, as well as CSF and blood. The advent of CT was a major step forward in providing anatomical analysis of the human brain. It allowed visualisation of individual brain structures without the distortion associated with anatomical studies of fixed tissue. It was also a breakthrough as a diagnostic tool, providing accurate localisation (about 1 mm resolution) of tumours and lesions.

An early CT study of 75 males and 41 females reported a significantly greater ratio of ventricles to brain volume in males than in females, with larger sulci and fissures in the males (Jacobson, 1986). An MRI study in 1999 presented similar results. In this study, which measured volume of grey matter, white matter and CSF, females had a higher percentage of grey matter than males. The males, on the other hand, had a higher percentage of white matter and CSF. There were no hemispheric asymmetries in females. However, grey matter percentage was higher in the left hemisphere of males, while CSF was higher in the right (Gur *et al.*, 1999).

MRI, like CT, also uses computerised analysis of sequential brain images to produce a 3D image of the brain. "Magnetic resonance" refers to the oscillations observed in the nuclei of elements with odd atomic numbers (e.g. hydrogen, H) when they are exposed to a magnetic field. The oscillating nuclei align themselves with the magnetic field. Once the nuclei are aligned, a burst of radio waves will disrupt the alignment. When the radio waves stop, the nuclei will "snap back" into their alignment with the magnetic field, and in doing so will emit a radio signal of their own. This radio signal may be recorded, using the same multiple exposure, rotating-image protocol, to build up a three dimensional image of the object. The human body is ideal for this kind of imaging because the different structures have quite different chemical compositions and different water (H_2O) content. Bone, for example, contains little water so there are few H nuclei to oscillate, producing a very weak signal. White matter, on the other hand, has a higher water content, and produces stronger signals. The result is a high-resolution image (about 0.1 mm). Because changes in water content accompany neuropathologies such as tumours or multiple sclerosis, MRI is a much better diagnostic tool than CT.

MRI has proved to be a valuable tool in studying the effects of ageing on the living brain. The corpus callosum (CC), because of its importance to the transfer of

information between the hemispheres, has received a good deal of attention. Probably the most interesting result to come out of these studies is the demonstration that while the CC has a tubular shape in males, in females it has a clearly bulbous shape at the posterior end (Allen *et al.*, 1991). The volume of the CC has also been demonstrated to decrease with age in females. Cowell *et al.* (1994) have reported that the frontal and temporal lobes have a greater volume in males than in females, with the right volume being the greatest. The study of 130 subjects, 70 males and 60 females, included an age range from 18 to 80 years. The frontal and temporal lobes have also been reported to decrease with age, with greater age-related reductions in females than males (Cowell *et al.*, 1992).

Conclusions

Alhambra: view of the Lion Court

The Lion Court palace, a work dating from the heyday of the Nasrid sultanate, was built by Muhammad V during the second half of the 14th century. The Lion Court itself forms the heart of a self-contained palace, which is in turn composed of a number of self-containing living-quarters. In this sense, it corresponds closely to the classical Andalusian patio; however, the patio theme is subjected here to extraordinarily subtle variations. The oblong court, formerly a garden, is surrounded by a cloister-like colonnaded gallery, of the sort previously reserved for particular façades, but never used for enclosing whole courtyards or gardens, in other words, open-air spaces . . . The graceful columns surrounding the courtyard are arranged singly, doubly or in threes. These compositions, seemingly arbitrary at first sight, obey a subtle rhythm, in which various axial systems interlock, giving the patio a harmonious visual perspective.

Barrucand, M. and Bednorz, A. (1992)
Moorish Architecture in Andalusia,
Taschen, Cologne, p. 196.

When you consider the vast amount of data available on neuroanatomy, both in humans and experimental animals, the literature on female–male differences seems meagre indeed. There are a number of possible explanations for the scarcity of hard evidence; perhaps the most compelling explanation is in terms of the technology required to find consistent structural differences in brain tissue.

It must be assumed that the differences in question will be fairly small and discreet by the standards of gross anatomy. If they were not, head sizes could be expected to differ radically between the sexes (all that extra volume would have to go somewhere) or at least head shape would differ. It is really only in the last 20 years that scanning techniques for examining living tissue have become readily available, and even more recently that such techniques have been accessible for research purposes. Before the advent of scanning techniques, neuroanatomists were dependent upon techniques using preserved brain tissue which, particularly in the case of human brain, may have undergone structural changes, especially shrinkage, before and during the preservation procedure. In such conditions, subtle differences could be difficult to find.

Another possibility is that few researchers actually looked for sex differences. As discussed in the two previous chapters, sex differences in neuroanatomical studies may have been "averaged out" by pooling data from a mixed sex population of experimental animals, or excluded initially by using only one sex. Systematic studies comparing tissue from a number of brains have, until the advent of histological video analysis in the 1990s, been time consuming, eye-straining work. In older studies where sexual dimorphism has been reported in areas where it would not be expected, you can only assume that painstaking work by dedicated anatomists revealed unexpected results. It is also possible that in some cases, sex differences were observed but not reported simply because they were beyond the scope of the particular study.

Despite the relative shortage of data in this chapter, it has been established that some reliable differences in architecture do exist between the brains of males and females. This architecture forms the foundation for the next chapter, in which the evidence for functional differences in terms of neurotransmitters, neuromodulators and their interactions with hormones will be examined.

The following summarises the main points to be drawn from Chapter 3:

1. There are structural differences between the brains of females and males in areas not directly associated with sexual function or behaviour.
2. Structural differences in cortical areas may provide the foundation for observed differences in some cognitive abilities.
3. The brains of both females and males are normally asymmetrical and there are sex differences in the extent of this normal asymmetry.

A final note: When most authors discuss the functional significance of sex differences in brain structure they conclude that the structural differences probably underlie the observed functional differences. DeVries and Boyle (1998) have offered an alternative view. Perhaps, they suggest sexual dimorphism in brain structure allows females and males to display similar behaviours despite their physiological and neurochemical differences.

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4

Functional differences: Neurotransmitters and neuromodulators

Morocco to Tunisia . . .
There are two crossing points between the two countries: between Oujda and Tlemcen not far from the coast in the north, and between Figuig and Beni Ounif 300 km to the south.

Although relations between Morocco and Algeria have been strained at times, things have been fairly stable in the last few years. However, as long as the war in Western Sahara continues, with Algeria supporting the Polisario movement, the border situation could change.

Oujda-Tlemcen
The strange quirk with this border post is that it is not possible to cross on foot if you are entering Algeria from Morocco. It is possible, however, if you are going in the opposite direction, from Algeria to Morocco. It is a ridiculous situation and may change but, for the meantime, check the situation in Oujda before heading out to the border.

Crowther, G. and Finlay, H. (1989)
Morocco, Algeria & Tunisia: a survival kit,
Lonely Planet, New York, p. 204.

This chapter begins on the other side of the arbitrary dividing line between structure and function described in Chapter 3. The distinction between structure and function is blurred when the topic for discussion is receptors, the binding sites for neurotransmitters and hormones. The receptors themselves are structures, complexes of protein units embedded in the plasma membrane of the cell. However, receptors are by nature plastic. They may change in number, distribution or sensitivity depending upon the physiological state of the organism as well as previous exposure to drugs, hormones and neurotransmitters. Because of their constantly changing nature, even descriptions of the structural components of receptors are more suited to a chapter on function.

Receptors are the functional units of action for neurotransmitters, hormones and drugs. Brain cells are well protected, self-contained units. The plasma membrane separates the intracellular space from the extracellular space, isolating the cellular machinery from environmental (extracellular) events. For a drug to influence the activity of a cell, it must have access to the intracellular signalling mechanisms, and, for the majority of drugs, the receptor is the point of access. It is logical that the investigations of drug actions in the brain begin with the search for, and identification of, drug-specific receptors. The study of hormone actions in the brain is no exception.

In 1968 McEwen *et al.* (1968) discovered that when minute doses of radioactively-labelled steroids were injected into the bloodstream of rats, the steroids were selectively taken up by certain regions of the brain. The resulting areas of radioactivity indicated the presence of specific binding sites, receptors, for the steroids. This experiment changed forever our perspective on sex differences in the brain. The discovery of steroid receptors, in this case for corticosteroids and progesterone (McEwen *et al.*, 1968), meant that the hormones normally found in the circulating blood of females and males could cross the blood brain barrier and act directly on brain cells. Changes in circulating hormone levels could, potentially, be reflected in changes in neuronal activity and, therefore, behaviour.

Long before the search for the steroid/hormone receptors began, certain areas in the brain associated with sexual function had been identified. Some of these early studies were crude. Electrical stimulation, using metal electrodes implanted in the area of interest, was used to study the effects of "activating" a specific area on the behaviour of the animal. Alternately, specific areas were lesioned, using either electric current or surgical techniques, and the effect on behaviour observed. As a result of this early work, many of the regions of the brain associated with sexual function were identified. These areas, particularly the hypothalamus and limbic system, served as the starting point in the search for hormone receptors.

In the 10 years following McEwen's initial experiments, many other studies confirmed and extended the original results (see McEwen *et al.*, 1986 for a review). Binding sites for corticosteroids, androgens, oestrogens, and subtypes of each were identified. As the different types of receptors were characterised, it became clear that they had very different patterns of distribution within the brain. By the early 1990s, comprehensive maps of steroid receptor binding sites in the rat brain had been published. Not surprisingly, the greatest density of oestrogen binding sites was identified in the amygdala and areas associated with control of reproduction, the preoptic area, the bed nucleus of the stria terminalis and the hypothalamus. The distribution of binding sites for progesterone was very similar to the distribution of oestrogen binding sites. The greatest density of testosterone receptors has been shown in the hypothalamus, preoptic area, the bed nucleus of the stria terminalis, amygdala, septum and the hippocampus. In addition, binding sites for both hormone types have been demonstrated, albeit in very low density, in other brain regions including the brainstem and cerebellum.

Oestrogen, androgens and their receptors in the CNS

An interesting characteristic of steroids is their ability to cross cell membranes. In the majority of cases, drugs and neurotransmitters will not cross the plasma membrane.

Effects upon the activities of the cells must therefore be mediated by a receptor which relays information on the extracellular environment into the cell. In the case of steroid hormones, this extracellular/intracellular distinction is not maintained. It is generally accepted that when steroid hormones are present in the extracellular fluid they may move through cell bodies and back into the extracellular space. It is only when the circulating steroid encounters an appropriate receptor complex that its actions affect cellular activity. The receptor complexes for steroids are usually found in the cytoplasm or in the nucleus of the cell, where their primary action is to alter gene transcription. The receptors in the nucleus are associated with specific DNA sequences known as "promoters" (Figure 4.1). When the receptors in the cytoplasm or nucleus are

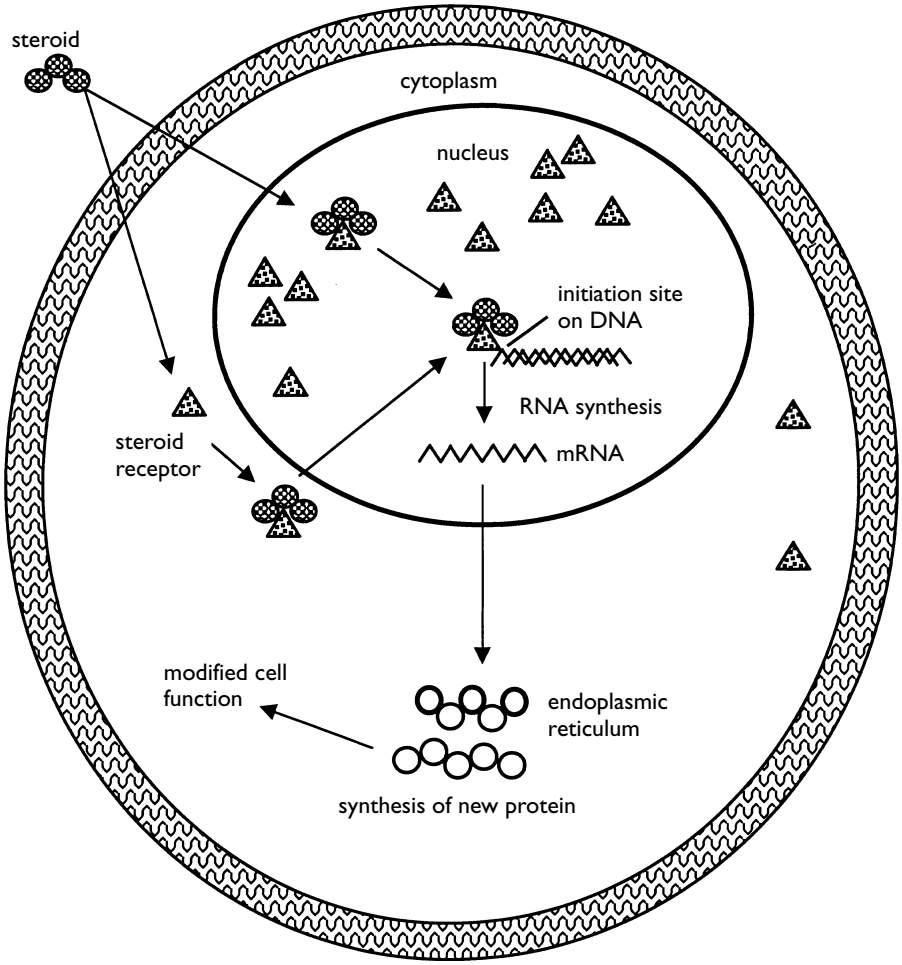

Figure 4.1 Classical view of steroid actions. Steroids cross the plasma membrane and bind to steroid receptors in the cytoplasm or the nucleus of the cell. The steroid-receptor complex attaches to the initiation site on the DNA, stimulating RNA synthesis and ultimately leading to the synthesis of new protein.

activated by hormone binding, they form complexes which move into the nucleus of the cell and bind to the promoter sequences. In both cases, it is the activation of the promoter sequences that results in the synthesis of new protein by the cell. In the adult brain, protein synthesis may have a number of functions including the production of new receptors or the synthesis of neurotransmitters or hormones. The effect on the ongoing activity of the cell will be transient (minutes to hours), depending upon the amount of time required for protein synthesis to occur.

Methods for identifying receptors in the CNS

> Eye of newt, and toe of frog,
> Wool of bat, and tongue of dog,
> Adders fork, and blind-worm's sting,
> Lizard's leg, and howlet's wing,
> For a charm of powerful trouble,
> Like a hell-broth boil and bubble.
>
> Shakespeare, W. (1606)
> Macbeth, Act 4, Sc.1.1.14.
> *The Complete Works of*
> *William Shakespeare*,
> Collins, London.

There are 2 prerequisites for the identification and localisation of receptors. First, it is necessary to attach a marker molecule to the receptor so that the receptor can be visualised or counted in some way. Second, the labelled receptors need to be localised to specific brain regions.

In the first instance, the "grind and bind" method, brain tissue is homogenised to allow maximum exposure of the receptors to the labelled drug. The homogenate is then centrifuged to separate the protein which contains the receptors, and incubated with the labelled drug. Following incubation, the receptor-drug complexes are separated from the unbound drug. The final drug-receptor complex product can then be analysed and characteristics such as B_{max} (an estimate of the number of binding sites) and K_D (a measure of the affinity of the receptor for the drug) can be determined. The main drawback of this type of analysis is that direct receptor localisation is limited by the amount of tissue that can be dissected out for analysis. This second requirement, receptor localisation, is best achieved using thin sections of brain tissue where receptors can be visualised directly. These sections of brain tissue are mounted on glass slides and incubated in medium containing the labelled drug. Following incubation, the extra medium is removed and glass coverslips are placed on the slides to protect the tissue. The slides are then analysed visually or by computer. The receptor sites can be localised in fine detail. The drawback is that the binding characteristics of the receptor are difficult to determine. Ideally, the two methods are used together to give detailed localisation of the receptors, as well as their binding characteristics.

Oestrogen receptors

Two types of oestrogen receptors (ERs) have now been cloned and sequenced. The first ER, which was cloned from rat uterus by Koike *et al.* in 1987, is a member of a much larger family of receptors, "ligand-dependent nuclear transcription factors" (Koike *et al.*, 1987; Simerly *et al.*, 1990). This family includes other steroid receptors as well as receptors for vitamin D, thyroid hormone and retinol. All of the receptors in this family have an active region, the DNA-binding domain, which enables the receptor to bind to the "promoter" sequence on the DNA. The DNA promoter sequence, which recognises the ER binding domain, has been shown to be present in DNA in a number of brain regions. It has also been demonstrated that this binding domain is identical in rat and human (Koike *et al.*, 1987). The cloning of the receptor was a significant step forward for oestrogen researchers, because it meant that for the first time, there was a highly specific target for studying oestrogen binding sites in the brain. Instead of looking for the uptake of radioactively-labelled oestrogen in brain cells, and then assuming the existence of receptors in those locations, it was possible to design probes that would bind specifically to the amino acid sequence of the oestrogen receptor. Using these histochemical methods it soon became clear that the ERs identified by Koike *et al.* could not account for all the oestrogen binding observed in the brain. In 1996, Kuiper *et al.* cloned a second type of ER. The new receptor, found in rat prostate and ovary, was named ERβ, making the earlier identified receptor ERα.

The 2 ER types have subsequently been identified in a number of brain regions. There is a general consistency in the literature on the distribution of the two types of ERs (Table 4.1). Both types of receptor are predominantly distributed in areas associated with the limbic system: the amygdala, septum and hypothalamus. ER distribution is generally sparse in other regions such as the brainstem and cerebellum, although there is evidence for moderate numbers of ERα in selected brainstem nuclei, including the periaqueductal grey, locus coeruleus and area postrema. A recent study (Laflamme *et al.*, 1998) characterised ERα and ERβ in intact female and male rats. Laflamme *et al.* reported that overall there was a greater expression and wider distribution of ERαs than of ERβs. Interestingly, there was little difference in the number or distribution of receptors between female and male rats. Little is known about the function of the two

Table 4.1 Characteristics of two types of oestrogen receptors

ERα	*ERβ*
Distribution: predominantly in amygdala, septum, hypothalamus also in periaqueductal grey, locus coeruleus, area postrema	Distribution: predominantly in amygdala, septum, hypothalamus, olfactory cortex
greater expression than ERβ	less expression than ERα
number and distribution: F = M	number and distribution: F = M
genomic action	genomic action
membrane-bound receptors	membrane-bound receptors also may act on MAP kinase pathway

types of ERs. Recently, however, it has been demonstrated that 17β-oestradiol causes rapid and sustained activation of the microtubule-associated protein (MAP) kinase signalling pathway, a second messenger pathway activated by membrane bound receptors (Toran-Allerand *et al.*, 1999). Because the action on the MAP kinase pathway occurs in ERα knockout mice (see below), it has been suggested that this action is mediated by other oestrogen receptors, such as the ERβ receptor.

The genomic actions of ERs have been characterised in a number of species including rat, mouse, monkey and human. The primary genomic action of oestrogen binding to the ER is to alter gene expression via action on DNA. There is, however, evidence that in some cases, oestrogen can alter the turnover of mRNA (Simerly *et al.*, 1990). Functionally, little is known about the ER's actions. The presence of receptors in areas associated with reproduction is to be expected, although even in those regions, their actions are not understood. The presence of ERs in other brain regions provides a foundation for oestrogenic modulation of a number of non-reproductive functions.

Recently, steroid binding sites have been observed on the extracellular membrane (Ramirez *et al.*, 1996) and on classical neurotransmitter receptor complexes suggesting that, in addition to their longer term effects on protein transcription, steroids are also able to produce or modulate rapid changes in synaptic activity. Membrane-bound receptors for both oestrogen, progesterone and testosterone have been identified and characterised. Evidence suggests that the action of one type of membrane-bound oestrogen receptors is G-protein coupled (Mermelstein *et al.*, 1996). It has also been demonstrated that one of the membrane-bound oestrogen receptors corresponds to a subunit of proton ATP synthase (see below).

Zheng and Ramirez (1999) have suggested another possibility for rapid acting, non-genomic oestrogen receptors. Using a preparation from rat brain consisting of mitochondrial material, the authors isolated a protein which bound 17β-oestradiol, the ligand for the ERs discussed above. Using the sequencing methods described in Chapter 1, the authors were able to identify the protein as a subunit of the mitochondrial enzymes ATP synthase/ATPase which are essential for the production of adenosine triphosphate (ATP). ATP is the basic unit of energy, produced by the mitochondria and essential for biological function throughout the body. If the binding of oestrogen to this protein can alter the energy metabolism of the cells, this provides a pathway for rapid changes in brain activity associated with oestrogen.

"The knockout model"

A novel way of looking at the functional importance of specific receptor types is to look at the effects of genetically modifying an animal so that it does not express the receptor. These animals, usually mice, are known as "knockout" animals. In 1999, Rissman and colleagues reported interesting behavioural anomalies in male and female ERα knockout (ERαKO) mice. Given the importance of oestrogen and its receptors in development, it probably came as something of a surprise to many researchers that ERαKO mice could survive the gestation period and be born alive. But survive they did, and they matured to adulthood looking very much like their wild-type (WT; not genetically modified) littermates. Probably the most obvious, and expected, differences in the adult ERαKO mice were in their sexual behaviour. Neither the adult

females nor the adult males displayed normal sexual behaviour and both females and males were infertile. Perhaps the most interesting differences, at least for our purposes, were the differences between the ERαKO and their WT littermates in the ability to learn spatial orientation tasks.

The Morris water maze is a tool long used by experimental psychologists to examine an animal's ability to learn tasks that depend upon the animal's memory for spatial orientation (Figure 4.2). The water maze itself is a pool with a movable platform located just below the surface of the water. Often powdered milk is added to the water to make it opaque and ensure that the animal cannot see the platform. The animal is trained over a number of trials, to swim to the platform and wait to be removed from the pool (escape). Most animals learn the task easily and the latency to reach the platform decreases over trials. The ERαKO mice that Rissman *et al.* (1999) tested learned to escape from the water maze just as well as their WT littermates. The ERαKO females showed the same pattern of learning as the untreated females, and their latency to find the platform decreased over trials. Both types of female mice were then treated with high doses of oestrogen. However, WT females treated with oestrogen failed to learn the task and the latency to find the platform and escape did not decrease with practice. In this case, it appears that high levels of oestrogen, acting via the ERα, disrupted the learning process. We will return to the question of oestrogen and learning in Chapter 6.

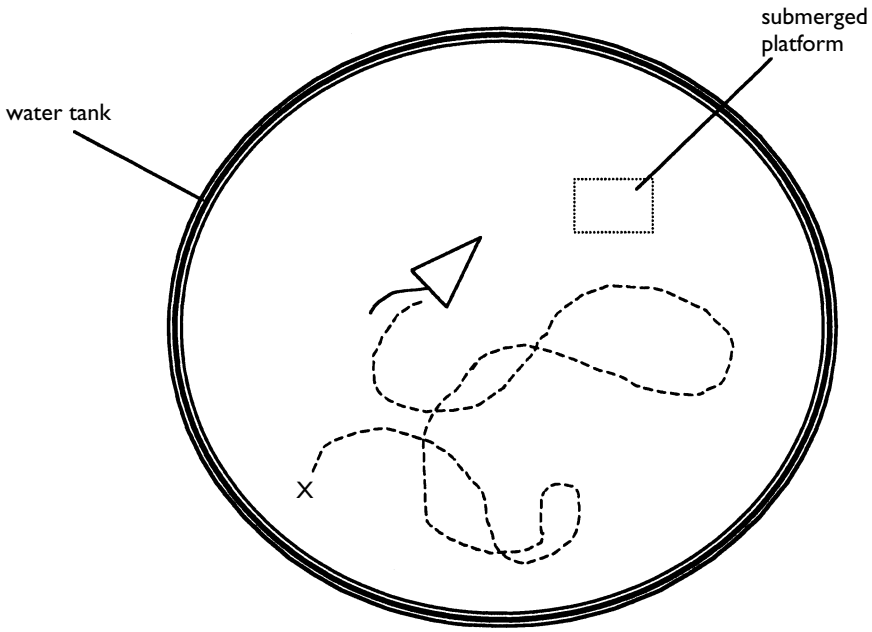

Figure 4.2 Schematic representation of a water-maze. The rat is placed in the maze at point "X" and must swim to the submerged platform to escape. Over repeated trials the rat learns to swim directly to the platform. The time taken to reach the platform and/or the distance travelled may be measured.

In addition to the action of oestrogen alone on CNS neurones, the ability of oestrogen to interact with neurotransmitter systems is now well documented. The neurotransmitters to receive the greatest attention in terms of oestrogen interactions are GABA, serotonin and dopamine. Interestingly, these three neurotransmitter systems are implicated in the aetiology of anxiety, depression and psychosis, disorders where sex differences have been well established.

> As the shuttle accelerated toward the redness, details slowly emerged through the thick gloom of space. Gradually, Lister made out the thousands of tiny pin-pricks of windows and a tooth floss-thin line of light ringing the ship: the vessel's metro system.
>
> A huge, shadowy carbuncle jutted out a mile or so from the red monster's belly – a small moon, torn out of orbit, had flung itself into the ship's solar plexus, and was now embedded in the hull, hanging there like a giant stone leech.
>
> As the shuttle swung out to align itself for docking, the red ship's nose-cone loomed into view . . . For a tantalising moment, between a huge mosque-shaped dome and a line of industrial chimneys, the tiny blue light that was Earth winked and flickered invitingly in the glow of the distant Sun, then just as suddenly was gone, as they swooped towards the yawning doors of the docking bay.
>
> Naylor, G. (1989) *Red Dwarf*, Penguin, London, pp. 39–41.

GABA

Gamma-amino-butyric acid (GABA) is an amino acid neurotransmitter with inhibitory actions. GABA receptors are widely distributed throughout the brain. The GABA receptor is a transmembrane receptor complex either with an associated ion channel or a G-protein. The receptors are composed of a number of basic subunits that may be arranged in different configurations to produce different receptor sub-types with specific binding characteristics. There are three main sub-types of GABA receptors, $GABA_A$, $GABA_B$, and $GABA_C$ (Table 4.2). In addition, there are numerous sub-types of $GABA_A$ receptors, approximately 14, which are made up of different combinations of

Table 4.2 Characteristics of GABA receptors

Receptor subtype	*Characteristics*
$GABA_A$	ligand-gated ion channel
	chloride influx
	post-synaptic inhibition
$GABA_B$	G-protein-coupled
	inhibition of adenylate cyclase
	pre-synaptic inhibition, decreased post-synaptic inhibition, increased potassium influx
$GABA_C$	ligand-gated ion channel
	chloride influx

the subunits. Binding of GABA to the GABA site on the $GABA_A$ receptor complex causes an influx of chloride ions through the associated ion channel. When this occurs, the probability that the cell will produce action potentials decreases and the overall effect is a temporary suppression of cellular activity. Binding of GABA to the $GABA_B$ receptor complex activates a G-protein decreasing cAmp, which also results in inhibition.

It is the $GABA_A$ receptor that is the target of drugs which depress CNS activity, such as alcohol and sedatives. In fact, the $GABA_A$ receptor complex contains binding sites for alcohol, barbiturates, benzodiazepines *and* steroids (Figure 4.3). The preoptic area of the limbic system is rich in receptors for oestrogen, progesterone and testosterone. It also contains large numbers of GABA-containing neurones. The first documentation of an interaction between oestrogen and GABA in the CNS was in 1983. Sar *et al.* (1983) reported that radioactively-labelled oestrogen was taken up by GABA-containing neurones in the preoptic region. Since that time, the interactions between oestrogen and GABA have been widely studied, using more and more sophisticated techniques. It is now known that about 20% of neurones in this region that contain GABA (as measured by glutamic acid decarboxylase (GAD) reactivity) also contain oestrogen receptors. Administration of oestrogen has been demonstrated to increase the extracellular concentration of GABA, but not apparently through the increased synthesis of GABA by GAD. Recent evidence, as reviewed by Herbison (1997), suggests that the increased extracellular concentration of GABA in the preoptic region may be due to an oestrogen-stimulated increase in the activity of GAT-1, the GABA transporter. This is not necessarily the case for all GABA-oestrogen interactions in the brain. For

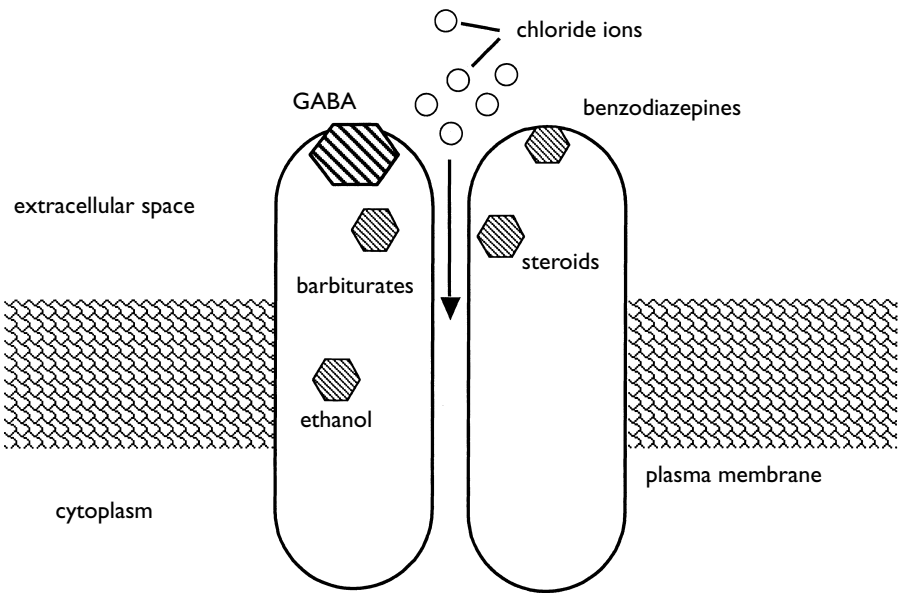

Figure 4.3 Schematic representation of the $GABA_A$ receptor. In addition to the GABA binding site, the receptor also contains allosteric binding sites for barbiturates, benzodiazepines, ethanol and steroids.

example, Weiland (1992) has demonstrated that in the hippocampus, both oestrogen and progesterone modulate GAD activity, and, therefore, the concentrations of GABA. Interestingly, it has been demonstrated in the preoptic area and in the ventromedial nucleus of the hypothalamus that the level of activity of GABA-containing neurones in male rats is twice that of female rats (Grattan and Selmanoff, 1997).

The $GABA_A$ receptor has been demonstrated to be a target for direct actions by hormones via the steroid binding site (see Majewska, 1991 for a review) (Figure 4.3). The naturally occurring steroids that bind to this site include androsterone, tetrahydrodeoxycorticosterone and the progesterone metabolite, tetrahydroprogesterone. It has been demonstrated in a number of studies, using biochemical and electrophysiological techniques, that the binding of these steroids to the allosteric binding site on the $GABA_A$ receptor prolongs the neural response to GABA. For example, steroid binding has been demonstrated to increase the duration of the Cl^- influx through the $GABA_A$ receptor ion channel and to prolong GABA-mediated inhibitory postsynaptic potentials (Majewska, 1991). This is particularly important because results of this type clearly distinguish a membrane receptor action from a genomic effect.

It has also been demonstrated that two anabolic steroids, stanozolol and 17α-methyltestosterone, when bound to the $GABA_A$ receptor, modulate the binding of benzodiazepines to the benzodiazepine binding site on the $GABA_A$ receptor, and that the effects differ between females and males (Masonis and McCarthy, 1995). This result will be further discussed in Chapter 8.

Serotonin

In contrast to the widespread distribution of GABA in the brain, serotonin- (5-hydroxytryptamine, 5-HT) containing neurones are found in discrete regions in the midbrain and brainstem. All of the brain's serotonergic projections arise from these two areas (Figure 4.4). There are at least 16 subtypes of serotonin receptor and the effect of serotonin will depend upon the receptor subtype to which it binds. The effect may be inhibitory or excitatory and may involve increases or decreases in cAMP, increased potassium conductance or activation of phosphoinositide-related second messenger pathways. Although it is a gross simplification, serotonin is often said to be the neurotransmitter associated with depression, migraine and the action of hallucinogenic drugs such as "magic mushrooms" and LSD. In fact, serotonin is involved in a wide range of neural functions including sleep, pain and various endocrine actions. Probably one of the most publicised actions of serotonin is in the mediation of depression. Fluoxetine (Prozac), paroxetine (Aropax) and other drugs in the selective serotonin reuptake inhibitor (SSRI) family act by increasing the time that serotonin (as well as noradrenaline) remains in the synapse.

There is a long (but not entirely consistent) history of studies showing sex differences in serotonin levels and actions, dating from the 1950s (Table 4.3). From a number of animal studies, it appears that during times when oestrogen and progesterone are naturally high, serotonergic activity is decreased. In ovariectomised female rats, where the effect of oestrogen application may be more directly observed, both serotonin levels and receptor binding are modulated by oestrogen. On first observation, the results of the various studies appear inconsistent and confusing. However,

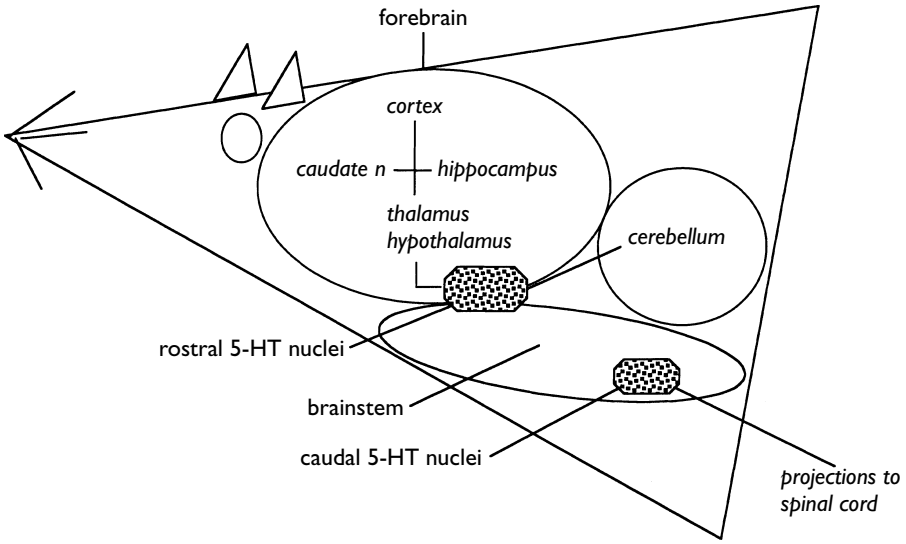

Figure 4.4 All 5-HT projections arise from two 5-HT neurone-containing regions (shown in dotted areas ▒) in the midbrain and brainstem, respectively.

Table 4.3 5-HT and oestrogen interactions

5-HT_1 receptor binding (rat)	decreased with high oestrogen
extracellular 5-HT (OVX rat)	increased by oestrogen in: suprachiasmatic nucleus, median eminence, dorsal raphe decreases by oestrogen in: cortex, medial preoptic nucleus, anterior hypothalamus
5-HT_1 receptor binding (OVX rat)	increased by oestrogen in: midbrain, hypothalamus decreased by oestrogen in cortex
5-HT_2 receptor binding (OVX rat)	increased by oestrogen in: cortex, nucleus accumbens, dorsal raphe
5-HT synthesis (human)	m > f

when broken down by brain region and receptor type, a pattern begins to emerge. There is an increase in extracellular serotonin in the suprachiasmatic nucleus, the median eminence and the dorsal raphe (a region containing serotonergic neurones) following oestrogen injection, but a decrease in the cortex, medial preoptic nucleus and anterior hypothalamus. When the results of the receptor binding studies are organised in a similar manner, binding to 5-HT_1 receptors appears to decrease in the cortex but increase in the midbrain, and, in the majority of reports, in the hypothalamus. Binding of serotonin to 5-HT_2 receptors increases in the cortex, nucleus accumbens and dorsal raphe. Rubinow *et al.* (1998) published a comprehensive review of

the literature on interactions between oestrogen and serotonin, which covers both human and animal studies. For readers who would like to pursue this area further, this review is an excellent place to start. There is little direct evidence available on serotonin levels in the human. However, a PET imaging study of healthy females and males has shown that in many areas of the brain, females synthesise less serotonin than their male counterparts. Overall, the rate of synthesis was found to be 52% higher in males (Nishizawa *et al.*, 1997).

Dopamine

Dopamine, like serotonin, is found only in neurones in discrete brain regions. The dopaminergic pathways, which arise from these regions, are anatomically and functionally distinct (Figure 4.5). The nigrostriatal pathway projects from the substantia nigra to the striatum. This pathway contains about 75% of the brain's dopamine. Loss of dopaminergic neurones in the substantia nigra occurs in Parkinson's disease, depriving the striatum of its dopaminergic input. The mesolimbic and mesocortical pathways project from the dopamine-containing neurones in the ventral tegmental area to parts of the limbic system and the neocortex. Excessive dopamine activity in this pathway is associated with the development of psychosis, and modulation of the activity of the dopamine receptors is one of the chief strategies for the treatment of schizophrenia. The third dopamine pathway, the tuberoinfundibular pathway, projects

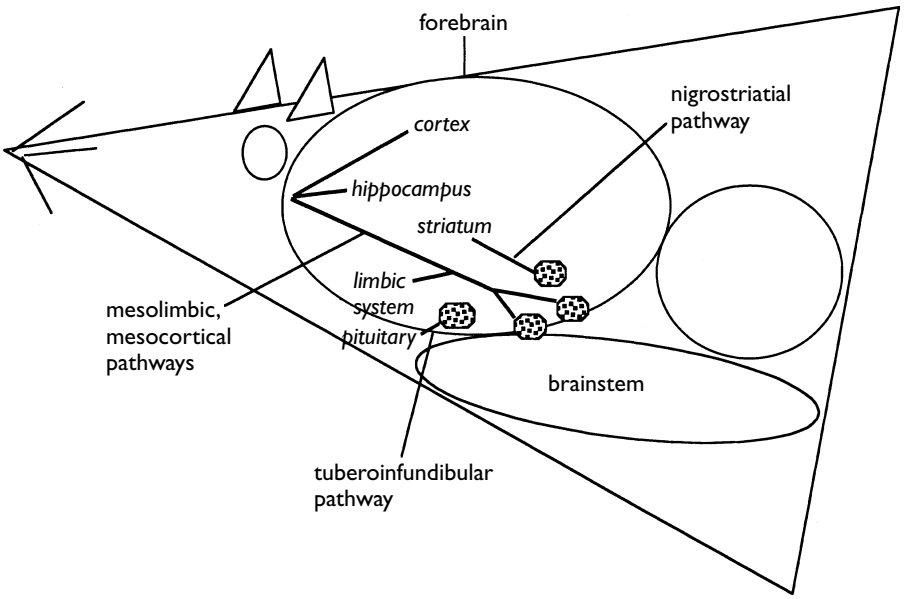

Figure 4.5 The 3 dopaminergic pathways are the nigrostriatal pathway arising from the substantia nigra *par compacta*, the mesolimbic/mesocortical pathways arising in the ventral tegmental area, and the tuberinfundibular pathway arising from the hypothalamus. Dotted areas ⁘ represent the regions of dopamine containing neurones.

from the arcuate nucleus of the hypothalamus to the pituitary gland. This pathway plays a central role in the modulation of prolactin release. As with the other neurotransmitters discussed so far, there are a number of dopamine receptor subtypes. The D_1, D_2 and D_4 receptors are the subtypes primarily associated with the treatment of psychosis.

Dopamine has a well-established role in female reproductive functions. Via the tuberoinfundibular pathway, dopamine released from neurones in the hypothalamus acts on dopamine receptors on lactotrophs (prolactin-secreting cells) in the anterior pituitary to modulate prolactin release. In this sense, dopamine may be classed as a hormone as well as a neurotransmitter. The effect of dopamine on lactotrophs is to reduce prolactin secretion. Administration of oestrogen over a long period induces increased prolactin secretion and a condition known as hyperprolactinaemia. It has been suggested that oestrogen may reduce the sensitivity of the dopamine receptors on the lactotrophs, resulting in decreased inhibition in response to dopamine binding and therefore, increased prolactin secretion (see Johnson and Everitt, 1995 for a review).

The striatum is an area crucial for motor control. Dopamine released from neurones in the substantia nigra pars compacta inhibits GABA-containing neurones in the striatum, which project to the cortex by way of the thalamus. The nigro-striatal pathway forms the foundation for a complex and essential network for motor control. The importance of this system is clearly demonstrated when disease causes a disruption of the network. Both Parkinson's disease (where the dopamine is lost) and Huntington's disease (where GABA is lost) are characterised by profound and irreversible disruptions of motor control.

There is a good deal of experimental evidence demonstrating that oestrogen affects striatal dopaminergic activity. For example, using the OVX rat model, it has been demonstrated that a single injection of 17β oestradiol (but not progesterone) increased the binding of dopamine in the striatum by 24% while leaving the affinity unchanged (Morissette *et al.*, 1990a) (Table 4.4).

It has also been demonstrated that the density of striatal dopamine receptors changes during the oestrus cycle in female rats. The density of D_1 receptors has been demonstrated to be greatest on diestrous II. In OVX rats, the density of D_1 receptors decreased by 17%. It is interesting in these two studies to note that the variable that changes is the actual density or number of sites, but not the affinity of the dopamine receptor (Levesque *et al.*, 1989). By contrast, the affinity of the D_2 receptor has been reported to change within 15 minutes of 17β-oestradiol administration (Levesque,

Table 4.4 The effect of oestrogen on dopamine receptors

Variable	*Effect*
binding DA, OVX rat	increased 24% in striatum by E
density of D_1 receptors, OVX rat	decreased by 17%
density of D_1 receptors, I/F rat	greatest diestrous II (high P/low E)
affinity D_2 receptor, OVX rat	altered within 15 min of E administration
affinity D_2 receptor, I/F rat	fluctuated during oestrous cycle

DA, dopamine; I/F, intact female; OVX, ovariectomised female; E, oestrogen; P, progesterone.

Di Paolo, 1988). It has also been demonstrated that the D_2 receptor affinity also fluctuates during the rat oestrus cycle (Di Paolo *et al.*, 1988) (Table 4.4).

Not only has oestrogen been demonstrated to alter the characteristics of dopamine receptor binding, but it has also been reported to alter dopamine metabolism in the striatum. A study using the OVX rat model has demonstrated that a single injection of 17β-oestradiol, progesterone or a combination of the two, caused an increase in dopamine metabolites (including homovanillic acid) which peaked 15–60 minutes after the injection. However, the concentration of dopamine itself increased only following progesterone or progesterone combined with oestradiol (Morissette *et al.*, 1990b) (Table 4.5).

Homovanillic acid (HVA) in plasma or urine is commonly used as a measure of brain dopamine metabolism. A study of HVA at different stages of the menstrual cycle in healthy women failed to find any significant changes (Abel *et al.*, 1996). However, a study of HVA levels in the CSF of OVX monkeys and post-hysterectomy women showed significant increases in HVA (Di Paolo *et al.*, 1989).

The acute administration of amphetamine to rats or mice causes a dose-dependent increase in the release of dopamine in the striatum. Because of the reliability of the effect, "amphetamine-stimulated striatal dopamine release" is an animal model frequently used to study the interactions of drugs and other neurotransmitters with dopamine. A number of studies have demonstrated that amphetamine-stimulated

Table 4.5 Dopamine and the oestrous/menstrual cycle

Variable	*Effect*
Dopamine metabolism, OVX rat	HVA increased by E, P, E + P
Dopamine metabolism, human F	no cycle-related changes HVA
Dopamine metabolism, OVX monkey, hysterectomised human	increased HVA
Amp stimulated DA release, I/F rat	greatest oestrus (low E)
Amp stimulated DA release, OVX rat	decreased, but restored by E
DA transporter, OVX rat	decreased striatum, nucleus accumbens, not restored by E
DA transporter mRNA, OVX rat	no change after 2 weeks (in short term animals) increased after 2 weeks (in rats 3 months post-OVX) modulated by E, substantia nigra no effect E, ventral tegmental area
TH immunoreactivity, OVX monkey	decreased dorsolateral prefrontal cortex, restored by HRT.
DA β-hydroxylase, OVX monkey	increased dorsolateral prefrontal cortex, modulated by HRT.

Amp, amphetamine; DA, dopamine; I/F, intact female; HRT, hormone replacement therapy; HVA, homovanillic acid, a DA metabolite; OVX, ovariectomised female; E, oestrogen; P, progesterone; TH, tyrosine hydroxylase.

dopamine release can be modulated by administration of oestrogen or progesterone. Female rats exhibit the greatest response to amphetamine on the day of oestrus. This increased response includes greater striatal dopamine release, metabolism and concentration compared to other days of the cycle. In OVX rats, the response to amphetamine is greatly decreased but returns with oestrogen replacement. Results of this kind suggest a role for oestrogen in modulating dopamine release, but give no insight into possible mechanisms of action.

One area of interest has been the dopamine transporter (DAT). Following release, dopamine is removed from the synaptic cleft by binding to the DAT and being taken up into the presynaptic terminals. A study of the effects of OVX on DAT (Bossé *et al.*, 1997) has yielded particularly interesting results. Three groups of rats were used in the study: long-term OVX rats which were tested 3 months after OVX; short-term OVX rats, which were tested after only 2 weeks; and control rats which received no operation. Half of the animals in each group received 17β-oestradiol for 2 weeks. The other half received vehicle injections. The two-week treatment protocol meant that the short-term animals were treated from the time of OVX while the long-term animals were treated for the last 2 weeks of the 3-month period. At the end of the experimental time, the animals' brains were removed and prepared for analysis. DAT mRNA expression in the substantia nigra *pars compacta* and the ventral tegmental area was measured using in situ hybridisation. DAT levels in the striatum and nucleus accumbens were measured using autoradiography.

The authors report that DAT levels decreased in the striatum and nucleus accumbens following OVX and that treatment with 17β-oestradiol did not restore it (Table 4.5). The expression of DAT mRNA was unchanged in the short-term animals but was increased in the long-term animals. In the long-term animals, 17β-oestradiol treatment partially restored the mRNA levels in the substantia nigra but had no effect in the ventral tegmental area. This latter result is particularly interesting because it suggests that the effect of oestrogen replacement may differ between the dopamine systems in humans. While motor control systems (the nigro-striatal pathway originating in the substantia nigra *pars compacta*) may benefit from hormone replacement, the mesocortical/mesolimbic systems may be more resistant to treatment.

The mesolimbic dopamine pathway has often been associated with the aetiology of psychosis. Hyperactivity in this pathway, resulting in excessive dopamine release, is thought to be associated with the development of cognitive/affective disorders (Goldstein and Deutch, 1992). Oestrogen has long been thought to play a protective role, but there has been little direct evidence to support this belief. Recently, however, Kritzer and Kohama (1998) demonstrated that in adult female rhesus monkeys, OVX decreased immunoreactivity for tyrosine hydroxylase in the dorsolateral prefrontal cortex (which would effectively decrease dopamine levels). The tyrosine hydroxylase levels could be restored by hormone replacement. The authors then went on to demonstrate (Kritzer and Kohama, 1999), using immunocytochemistry for dopamine β-hydroxylase, choline acetyltransferase, and serotonin, that the levels were also altered by OVX. Now this is the really interesting part. While there was a small decrease in choline acetyltransferase, there was a pronounced increase in immunoreactivity for dopamine β-hydroxylase and serotonin. When the authors looked at the effects of hormone replacement, they found that oestrogen alone and oestrogen

combined with progesterone normalised choline acetyltransferase and dopamine β-hydroxylase activity. However, it was the oestrogen plus progesterone therapy that was most effective in normalising serotonin. In their discussion, the authors propose that oestrogen and progesterone may be important modulators of neurotransmitter actions in the prefrontal cortex. Another interesting aspect of dopamine function is its role in neurotoxicity. 6-hydroxydopamine (6-OHDA) has frequently been used to lesion the striatum in an effort to produce an animal model of Parkinson's disease. When 6-OHDA lesions are produced in OVX rats, oestrogen treatment has been demonstrated to reduce the extent of the lesions compared to vehicle-treated controls. Similarly, oestrogen replacement has also been demonstrated to be protective against MPTP-induced neurotoxicity. We will return to the discussion of oestrogen as a neuroprotectant in Chapter 8.

> The night sky is interesting. There are patterns there. Without even trying, you can imagine pictures. In the northern sky, for example, there is a pattern, or constellation, that looks a little ursine. Some cultures call it the Great Bear. Others see quite different images. These pictures are not, of course, really in the night sky; we put them there ourselves. We were hunter folk, and we saw hunters and dogs, bears and young women, all manner of things of interest to us . . . If the constellations had been named in the twentieth century, I suppose we would see bicycles and refrigerators in the sky, rock-and-roll "stars" and perhaps even mushroom clouds – a new set of human hopes and fears placed among the stars.
>
> Sagan, C. (1981) *Cosmos*,
> Abacus, London, pp. 59–60.

Measures of global function

The techniques for measuring global brain function are gross compared to the methods discussed in the previous section. Immunohistochemistry can identify specific neurotransmitters in individual axons. An MRI, on the other hand, provides a measure of neuronal activity for entire brain regions. The responses of individual neurones are far too small to be seen individually, but sum to produce images representing activity in an entire region.

There are 3 types of global measures to consider (Table 4.6). The visual imaging techniques, positron emission tomography (PET) and functional MRI, provide anatomical localisation of activity. Electroencephalography (EEG) provides activity patterns but with only gross anatomical localisation referenced to scalp surface electrodes.

EEG measures neural activity, "brain waves", by recording the patterns of electrical activity from an array of electrodes attached to a person's scalp. The placement of the electrodes is standardised to skull landmarks using an international protocol known as the "10–20 International System". Each electrode in the 21-electrode array is numbered, odd numbers on the left, even numbers on the right (Figure 4.6). A letter preceding the number indicates the scalp region. So, O1 is the electrode on the left side of the occipital region, while T4 refers to an electrode over the right temporal region. Adoption of the 10–20 International System has allowed a standardisation of EEG recording between individuals and in a single individual across time (Neidermeyer

Table 4.6 Methods of measuring global brain activity

Method	*Information*
EEG	ongoing, event-related, electrical activity
	cortical activity only
	gross signal localisation
PET	functional brain image
	measures regional uptake of radiolabelled isotope
	resolution, 4–8 mm
functional MRI	functional brain image
	sensitive to changes in tissue structure
	high resolution, 0.1 mm

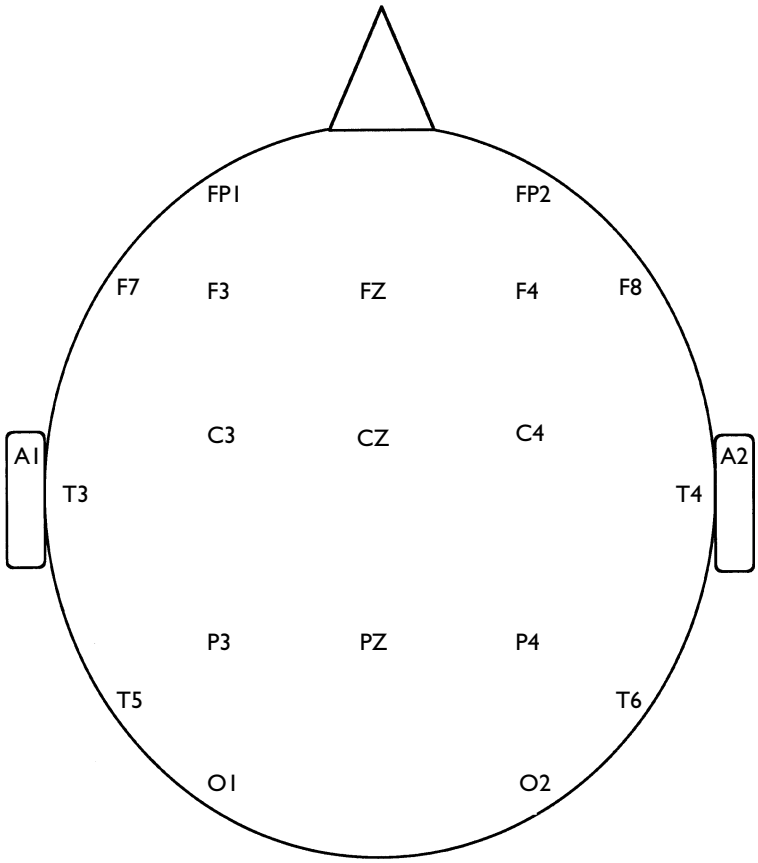

Figure 4.6 Standard electrode array for EEG recording. Odd number indicates left side, even number indicates right side. A, auricle; C, central; CZ, vertex; F, frontal; FP, frontal pole; FZ, frontal midline; O, occipital; P, parietal; PZ, parietal midline; T, temporal. From Niedermeyer and Lopes da Silva, 1993.

and Lopes da Silva, 1993). The activity measured from any given electrode is a sum of the activity in the region of cortex below the electrode. Specifically, it is thought to be the summation of post-synaptic potentials in the area recorded by the electrode. While EEG cannot give information about the ongoing activity in deep brain structures, it provides a valuable insight into the patterns of cortical activity. It is a valuable diagnostic tool, particularly in the case of epilepsy. It is also a research tool for studying the changes in cortical activity associated with the performance of different tasks or the administration of drugs.

When recording from normal individuals, the EEG will be a complex wave form, made up of individual frequencies of potentials ranging from 0.1 to 70 Hz. Frequency analysis of the EEG component wave forms usually reveals 4 frequency components characteristic of cortical activity (Table 4.7). The wave form associated with wakefulness, alpha waves, has a frequency range of 8–13 Hz. Alpha waves are recorded over the posterior regions of the brain. They are usually recorded while the person relaxes with closed eyes, hence the term "relaxed wakefulness". Alpha waves can be temporarily blocked by an arousing stimulus, e.g. opening the eyes, or by performing a task such as mental arithmetic. Recordings of alpha waves are generally agreed to be asymmetrical, with the highest voltages recorded over the non-dominant hemisphere. Beta waves range from 13–35 Hz and are associated with high levels of activity, such as performing difficult mental arithmetic. Beta waves are recorded from the frontal and central regions. Beta recordings from the central electrodes can be blocked by motor activity or tactile stimulation. Some drugs, such as barbiturates, have been demonstrated to increase both the quantity and voltage of beta activity. Delta waves (<3.5 Hz) and theta waves (4–7 Hz) are associated with sleep. Theta, named for its origins in the thalamus, is important in infancy and childhood, but in adults is primarily associated with sleep. A normal, awake adult EEG will show only a small amount of activity on the theta band and no organised "theta rhythm". This is in marked contrast to the theta rhythm recorded in rodents, which is recorded during alertness and has been suggested to be a measure of "emotion".

Studies using EEG may measure and analyse several different variables for a single

Table 4.7 Characteristics of EEG frequencies in humans

Frequency	*Characteristics*
Alpha	8–13 Hz
	relaxed wakefulness
	highest over non-dominant hemisphere
Beta	13–35 Hz
	high level mental activity
	frontal and central regions
Delta	<3.5 Hz
	sleep
Theta	4–7 Hz
	sleep, drowsiness

Niedermeyer and Lopes da Silva (1993).

recording period. First, the EEG can be analysed for the presence or absence of the different component wave forms. Initially, this kind of analysis was performed by passing the signal through an assortment of filters to physically remove different frequencies of activity. Now, computer analysis allows on-line Fourier analysis of the EEG into the component frequencies. Further analysis may be used to determine the amplitude of the wave form (in μV), the total amount of time in which the wave form occurs in the recording period, and the timing of the wave form recorded from different electrodes (in-phase or out-of-phase).

The usual condition for measuring EEG, lying down or sitting quietly with the eyes closed, is assumed to measure EEG activity when the brain is alert but resting. However, it is impossible to know exactly what the brain is doing during that "resting" time. Most people find it nearly impossible to think of "nothing" while remaining alert. At least some portion of the variability in resting EEGs is probably attributable to the thought processes of the subjects. One way of adding an element of control to the EEG recording is to record the EEG following the presentation of a specific stimulus. Evoked potentials are EEG recordings of activity following a specific event. For example, auditory-evoked potentials may be recorded following a "click" stimulus delivered to the ear through headphones. When the activity in the period immediately following each click is recorded and averaged over a number of clicks, a distinct pattern of activity emerges. The resulting pattern will consist of a series of positive and negative components (peaks) which represent different stages of processing in the auditory pathway (Figure 4.7). An interesting aspect of evoked potentials is that the

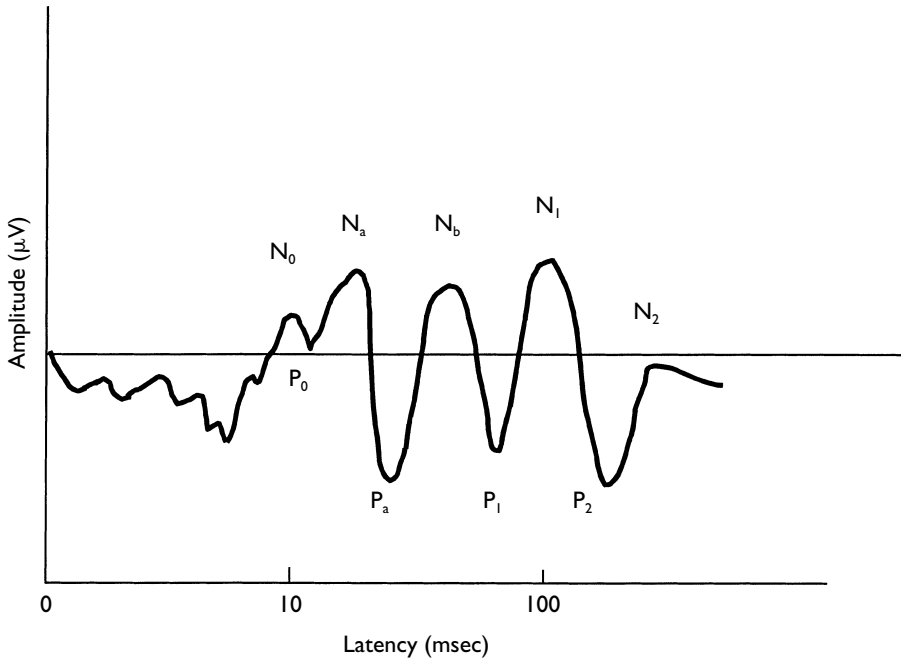

Figure 4.7 Schematic representation of an auditory-evoked potential. Signals are averaged over a number of trials to produce the characteristic wave forms.

amplitude of the potential that is recorded is correlated with the size of the person. For this reason, a necessary step in the analysis of evoked potentials is to normalise the data with respect to body size. Many of the early evoked potential studies did not include this form of correction and so the data must be considered cautiously.

PET and functional MRI differ from CT by providing images of brain function at a given point in time. PET is similar to CT in its use of sequential, rotating images. But it differs in the sense that the signals being detected by the scanning equipment are of the distribution of positron-emitting (radioactive) isotopes in the brain tissue (resolution 4–8 mm). Positron-emitting isotopes can be bound to a number of biologically-active substances to give a wide range of possibilities for functional analysis. For example, by binding an isotope to 2-deoxyglucose, the metabolism of glucose (an indicator of neuronal activity) can be measured. In addition to labelling glucose, neurotransmitters and drugs can also be labelled and imaged. Functional MRI uses the same equipment and methods as MRI scanning used for anatomical localisation. The difference with functional MRI is that the scans are taken while the subject performs a specific task, for example mental arithmetic. The question with functional MRI is "How does the image change when the subject performs the task instead of resting quietly?"

> Static in radio broadcasts was proving a rather intractable problem. Radio transmission for the first forty years after Marconi's discovery . . . was carried out by systematically altering the amplitude (the height of the waves) of the carrier signal to match the variation in the amplitude of the sound waves being transmitted. This was called amplitude modulation, or AM.
>
> Unfortunately, thunderstorms and electrical appliances also modulate the amplitude, doing it randomly and producing the irritating noise of static.
>
> Asimov, I. (1990)
> *Asimov's Chronology of Science and Discovery*,
> Grafton, London, p. 540.

Evidence from EEG studies

One of the earliest reports of sex differences in EEG recordings was made at the 1967 meeting of the Central Association of Electroencephalographers. Giannitrapani and Snekhaus (Small, 1967) reported that while conducting an EEG study of laterality, they noted that in some brain areas, differences in activity seemed to be associated with the sex of the subject. As a result of this observation, the authors conducted a study looking specifically at sex differences and the relationship between the activity of specific EEG electrode pairs. The EEGs of 15 males and 15 females were recorded and the authors reported that in-phase activity was decreased in male subjects during a psychomotor task, but was unchanged in females. The cortical areas in which the differences occurred were the left compared to the right prefrontal areas, the right prefrontal area compared to the right frontal areas, the right frontal area compared to the right motor areas and the right motor area compared to the right parietal areas.

Since 1967, it has been demonstrated in a number of studies that there are sex differences in EEG activity which can be seen in childhood and which continue into old

age. For example, Matsuura *et al.* (1985) analysed the alpha, beta, theta and delta wave activity of 1416 people ranging in age from 6 years to 39 years. Analysis was made for 3 regions: frontal, central and occipital. The greatest sex differences were for beta waves, for which the percentage of time during which beta could be recorded was greater for females for all 3 regions at all ages. The amplitude of the beta waves was also greater in females than in males after the age of 21 years. Alpha waves recorded in the occipital region were of greater amplitude in females compared to males after the age of 21, but the percentage of alpha time in the occipital region was greater in males than in females after age 17. The percentage of time for theta activity was higher in the frontal and central regions for females compared to males until age 25. No differences were reported for delta waves. The authors concluded that their results support the view that EEG matures faster in males than in females. However, they also suggest that because the differences in theta were small and no differences were found in delta, sex differences are not important in interpreting routine EEGs. This comment is a little surprising given that theta and delta are associated with sleep in adults and routine EEG recordings are made in awake, resting people.

In elderly people (aged 60–87 years), differences in central recordings of alpha, beta and theta have been reported. The mean frequency of beta was reported to be increased in females, while alpha and theta frequency were decreased in females relative to males. The reported differences were specific to sex, independent of age. In their conclusions, the authors suggest that consideration of sex is an important issue in EEG analysis, at least for the elderly population (Brenner *et al.*, 1995).

EEG changes that correlated with the different phases of the menstrual cycle have been reported by several researchers. The results of these studies, as summarised by Niedermeyer and Lopes da Silva (1993), are represented in Figure 4.8. The most consistently reported changes are in the frequency and percentage of alpha activity. At first glance, the pattern of EEG changes in relation to absolute hormone levels seems inconsistent. However, if one considers the EEG in relation to the female changes in hormone levels, a pattern begins to emerge. Alpha frequency is decreased during the menstrual phase, but increases when oestrogen rises in the preovulatory phase. During the postovulatory phase, when oestrogen decreases and then rises slightly, alpha frequency decreases. Finally, when oestrogen drops during the premenstrual phase, alpha frequency increases again. At the start of the next cycle, oestrogen is still low and alpha frequency decreases until another change occurs, and the cycle repeats.

Evidence from evoked potential studies

The above studies measured the EEG in people resting with their eyes closed. Event related potentials measure EEG activity associated with the occurrence of a particular stimulus, for example a flash of light (visual evoked potentials) or a specific sound (auditory evoked potentials).

Visual-evoked potentials stimulated by a flash of light have been reported by Kaneda *et al.* (1996) to have a greater peak-to-peak-amplitude in females than in males. This study is particularly interesting for two reasons. First, a large number of subjects, 100 females and 100 males, were tested. Second, the data were normalised to the body size of the subjects. This is an important factor in evoked

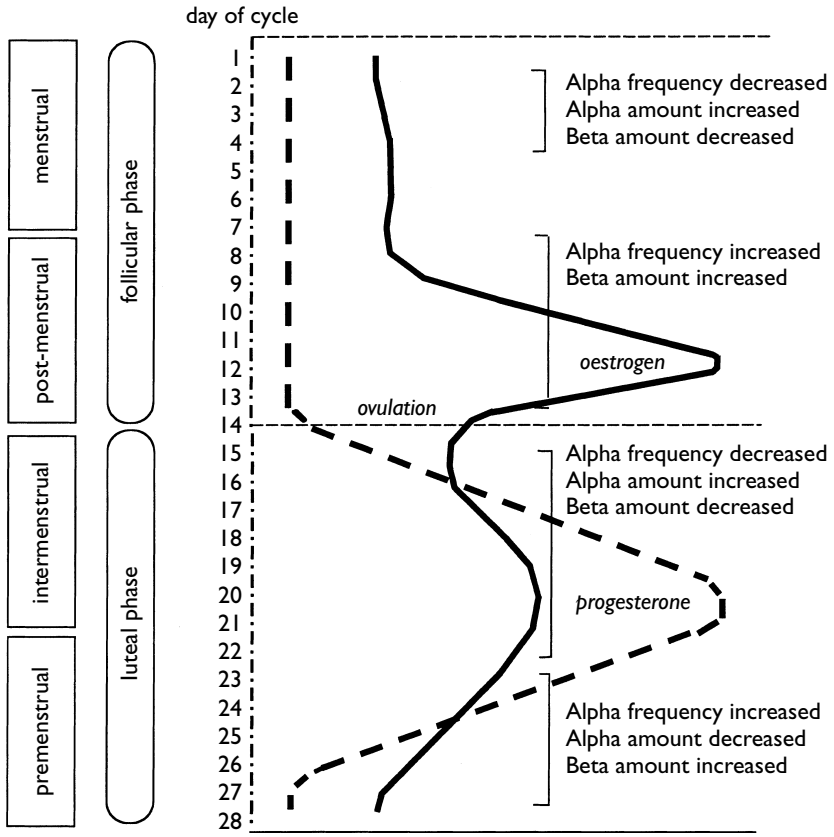

Figure 4.8 Changes in EEG frequency across the menstrual cycle. Adapted from Niedermeyer and Lopes da Silva, 1990, p. 135.

potential recordings which, at least in the past, has often been overlooked. Because people with smaller bodies usually have proportionally smaller brains, the evoked potentials have less distance to travel and the latency will appear to be shorter. Initially, female/male differences were observed on several of the measured variables. However, when the body size adjustment was applied, the only remaining difference was in peak-to-peak-amplitude. In looking at their female subjects alone, after adjustment for body size, the peak-to-peak-amplitude of the P5 to N7 component was significantly greater during the luteal phase of the cycle than in the follicular phase. Interestingly, differences in latency, both between females and males, and between the luteal and follicular phases in females, disappeared when the body size adjustment was made.

Other studies relating visual-evoked potentials to the menstrual cycle have yielded mixed results, possibly because adjustments for body size were not made during data analysis. The P300 wave has been reported to increase in amplitude with high progesterone, increase in latency at ovulation, decrease in latency at ovulation or not change at all. Interestingly, a subsequent study by Kaneda *et al.* (1997) of 44 females, with data normalised for body size, reported no significant differences overall between the

luteal and follicular phase for either latency or amplitude of any of the visual evoked potential components. The majority of studies using auditory or somatosensory evoked potentials also report no differences in latency or amplitude related to the menstrual cycle. Latencies, however, have been reported to be significantly shorter for females than for males.

> Tromp l'oeil stone blocks
> As pattern to break up uninterrupted areas of blank wall, fake stone blocks and even painted brickwork have been used for centuries. They evoke the romantic effect of stone walls with none of their inconvenience and are especially suitable for halls where "natural" material links inside with outside, and any other area where a "hard" material seems appropriate. The principles of simple tromp l'oeil painting are easily grasped, and the effect works best on a limited area. It is important to be consistent with the imagined light source.
>
> Sutcliffe, J. (1996)
> *Paint: Decorating with Water-based Paints*,
> Frances Lincoln, London, p. 54.

Evidence from scan studies

Several studies using PET have looked for differences in the levels or patterns of brain activity between females and males (Table 4.8). For example, a study measuring cerebral blood flow during a series of cognitive tasks (Espisto *et al.*, 1996) reported that the rate of blood flow during the various tasks was higher in the female subjects than in the males. A study of glucose metabolism failed to find differences in overall glucose utilisation (Azari *et al.*, 1992). However, the authors did find differences in the patterns of interaction between cortical areas (a similar idea to looking for synchronous and non-synchronous EEG activity). The correlations in activity between different cortical areas were more positive for females than for males. The areas where correlations were more positive for females were the left frontal and sensorimotor areas, while the correlations were higher for males in the right sensorimotor and occipital

Table 4.8 Summary of results from human studies of global function

PET:	
blood flow during cognitive tasks	f > m
5-HT synthesis	f < m
5-HT_2 receptor binding	f < m, frontal, cingulate cortices
D_2 receptor binding affinity	f < m, L striatum
μ-opioid receptor affinity	follicular = luteal -ve correlation with E at follicular phase, hypothalamus, amygdala
functional MRI:	
Visual cortex activation	m > f; m, R > L; f, L = R

E, oestrogen; L, left; R, right.

areas. This study is interesting from the perspective of functional laterality (Chapter 6). Although there are differences in processing between the two cerebral hemispheres in males and females, the same amount of energy is still used. Another PET study found a significantly higher rate of metabolism in females in the cerebellum only (Volkow *et al.*, 1997).

PET imaging has also been used to look for neurotransmitter differences between females and males. It has been demonstrated that the rate of serotonin synthesis is 52% greater in the brains of males than females and that the binding capacity of the $5HT_2$ subtype of serotonin receptor is greater in males in the frontal and cingulate cortices (Biver *et al.*, 1996). The dopaminergic system has also been reported to differ, with D_2 receptors in the striatum of females showing a lower affinity for the radioactively-labelled ligand, raclopride, than striatal D_2 receptors in males (Pohjalainen *et al.*, 1998).

A PET study of opioid receptors failed to show any differences in the affinity of μ-opioid receptors between the follicular and luteal phases (Smith *et al.*, 1998). However, the study did show a significant negative correlation between plasma oestrogen levels and μ-receptor binding in the hypothalamus and amygdala during the follicular phase.

A number of studies have used functional MRI to study brain function during particular tasks such as reading and mental arithmetic (Chapters 5 and 6). A final study worth noting is a study of the effects of visual stimuli on brain activity as evaluated by MRI (Levin *et al.*, 1998). Eight females and 8 age-matched males were tested using blood-oxygen-level-dependent functional MRI. The subjects received alternations of 30 second periods of dark followed by 30 seconds of visual stimulation. The stimulus was delivered via goggles with light emitting diodes, which flashed at a frequency of 8 Hz during the "stimulus on" periods. Responses were recorded from the left and right primary visual cortices. Analysis of the results showed that overall, the level of activation of the brains of the females was 38% less than the response of the males. In addition, the activation in the female subjects was symmetrical between the left and right areas, while the response in males was significantly greater on the right.

Conclusions

In conclusion, the happy and now famous formula, "The medium is the message," proves ambiguous and pregnant with a series of contradictory formulae. It can, in fact, mean:

1. The *form* of the message is the real content of the message (which is the thesis of avant-garde literature and criticism);
2. The *code*, that is to say, the structure of a language – or of another system of communication is the message (which is the famous anthropological thesis of Benjamin Lee Whorf, for whom the view of the world is determined by the structure of the language);
3. The *channel* is the message (that is, the physical means chosen to convey the information determines either the form of the message, or its contents, or the

> very structure of the codes – which is a familiar idea in aesthetics, where the choice of artistic material notoriously determines the cadences of the spirit and argument itself).
>
> Eco, U. (1986)
> *Travels in Hyperreality*,
> Picador, London, p. 234.

The following summarises the main points to be drawn from Chapter 4:

1. Oestrogen receptors are present in the brains of males and females. Activation of oestrogen receptors may produce genomic responses, or non-genomic responses via membrane-bound receptors.
2. There is substantial evidence for interactions of oestrogen with GABA, 5-HT and dopamine systems. The nature of the interactions varies between brain regions and receptor populations.
3. Global measures of brain function have demonstrated female–male differences. EEG activity in females changes across the phases of the menstrual cycle and there is evidence for differences between females and males.

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5

Perception and cognition

In the early days of experimental psychology, B.F. Skinner gave us the "black box" of behaviourism (Skinner, 1969). In the world of Skinner, the stimulus and the response were everything. The black box, the organism doing the responding, was simply a processing mechanism. The sensory systems were important for perceiving the stimulus, motor systems were necessary for generating a response. Cognitive elements were simply not an issue of interest. The black box was not required to think.

It did not take long for the cracks in this radical form of behaviourism to begin to appear. In animal learning laboratories, researchers observed that rats, when unable to make the conditioned response, would come up with novel ways of obtaining their reward. In one particularly amusing example, the tension on the lever in the Skinner box was increased until it was difficult for the rat to depress it far enough to receive the reward. Rats, previously trained to bar-press for food reward, were placed in the Skinner box. The animals' attempts at responding were recorded as they tried in vain to earn their reward. One particular rat solved the problem. After a period of furious, frustrated attempts at bar pressing, the rat turned around, backed onto the apparatus and using both hind legs depressed the lever far enough to receive his reward (Champion, R., personal communication). It is difficult to argue that some form of cognitive processing had not occurred in the rat's brain.

The processes involved in sensation, perception and cognition are the domain of experimental psychology and psychophysics. The experimental psychologist faces some of the greatest challenges in the world of scientific experimentation. Good experimental design requires rigorous control of the experimental conditions. For example, a "simple" chemistry experiment to establish the boiling point of a liquid, e.g. a sugar solution, requires that a number of observations be made under the same conditions. This is an apparently straightforward requirement, at least until you think about how to go about it. First, consider the materials and methods. You will need a

heat source, a container for the liquid and a method of measuring the temperature of the liquid. These must be the same for every measurement that is made. The conditions in the laboratory must also be identical. Ambient temperature and humidity must be controlled. Atmospheric pressure must also be considered; not only do the experiments have to be conducted at the same altitude but also under identical weather conditions. There is the experimental "subject", the liquid to be measured. If the liquid is mixed fresh before each measurement, all of the mixing procedures must be carefully controlled and the constituent parts must come from the same source. If the liquid is to be stored between measurements, then variability can be introduced through ageing or contamination. Either way, keeping the experimental subject constant can be difficult.

Now, imagine the complexity of the experiment multiplied a billion-fold. Instead of a simple sugar solution, make the subject a 34 year old human female. She has a 34 year plus 9 month (approximate gestation period) history of development and maturation that is unique to her. She also has her own genetic make up (unless she is a monozygotic twin) and 34 years of experience of the world. She really is a "one-of-a-kind" subject. But, if she takes part in an experiment, she will become one of the *x* number of subjects whose results will be pooled to yield descriptive statistics such as means and standard deviations. The kind of experimental rigour required for psychophysical experiments is staggering, and has become a trademark of experimental psychology.

The material covered in this chapter comes from a range of psychophysical experiments including studies of sensory systems, cognitive processes, learning and memory. We will start with the area of visual psychophysics known as "visual perception".

Visual perception

> The function of picture frames is also related to the psychology of figure and ground. The frame as we know it today developed during the Renaissance from the façade-like construction of lintels and pilasters that surrounded the altarpieces. As pictorial space emancipated itself from the wall and created deep vistas, a clear visual distinction became necessary between the physical space of the room and the world of the picture. This world came to be conceived as boundless – not only in depth, but also laterally – so that the edges of the picture designated the end of the composition, but not the end of represented space. The frame was thought of as a window, through which the observer peeped into an outer world, confined by the opening of the peephole, but unbounded in itself.
>
> Arnheim (1974) *Art and Visual Perception: A Psychology of the Creative Eye*, University of California Press, Berkeley, p. 239.

One of the earliest visual perception tasks to reveal female–male differences in spatial ability was the "rod and frame" task described by Witkin *et al.* in 1954 (referenced in Silverman *et al.*, 1973). This is a simple task, requiring only the adjustment of a rod within a frame to earth vertical (Figure 5.1). Intuitively, it should be easy. The subject sits in a darkened room with only an illuminated frame and rod visible. The rod and

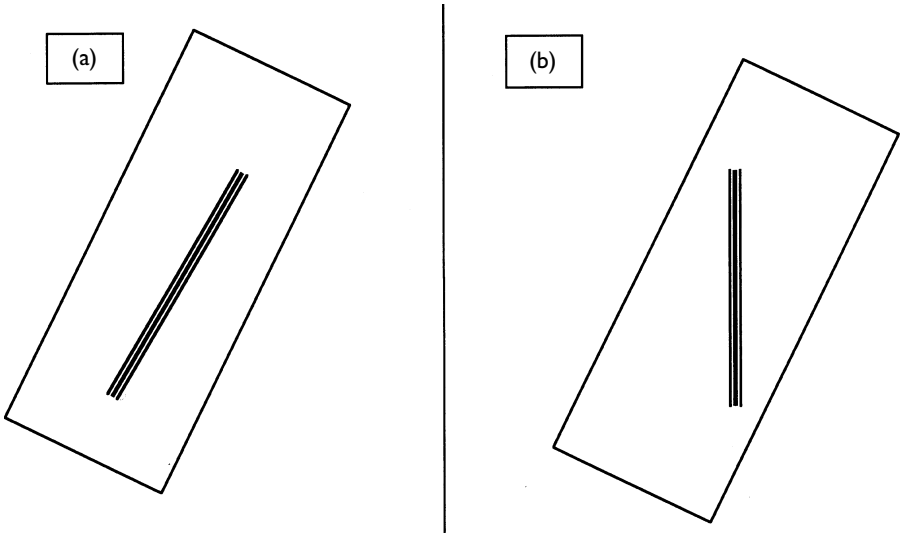

Figure 5.1 Schematic representation of the Rod and Frame Test. The subject is instructed to position the rod vertically within the tilted frame. (a) unsolved task; (b) correct solution.

frame may be moved independently so that they can be tilted in the same direction away from vertical or may be tilted in opposite directions from vertical. Usually, the trials are a randomised mix of same and different directions of tilt. Silverman *et al.* (1973) tested 15 female and 15 male university students, aged between 18 and 22. Their subjects were seated in a darkened room and instructed to set the rod to be parallel with the walls of the room. The subjects' heads were fixed in a vertical position using a padded headrest. The results of 8 trials were averaged to give a mean error score. The error scores for the females were significantly higher than the error scores for the males.

Another area of visual perception where females have traditionally performed less well than males is in tasks involving mental rotation of images. These tasks usually employ a target image, often composed of blocks (Figure 5.2). The subject is required to match the target image to a test image, a rotation of the target image, which is presented with other test images such as mirror images of the target, which have been rotated in 3-dimensional space. In order to complete the task, experimental subjects apparently perform a mental rotation of the target, looking for a match to a test image. In 1995, Desrocher *et al.* measured event-related potentials (ERPs) associated with mental rotation performance. The subjects were university students, 10 females and 10 males, with mean ages of 21 years and 22 years, respectively. All of the subjects were right-handed. Two kinds of images were used in the study, letters and simple abstract designs, presented on a computer screen. The subjects were instructed to look at a target image on the left side of the computer screen and to judge whether or not the image on the right side of the screen was a rotation of the target image. They signalled their decision by pressing a button with their index finger (the hand for "same" and "different" varied across subjects). In order to ensure the accuracy of the subjects'

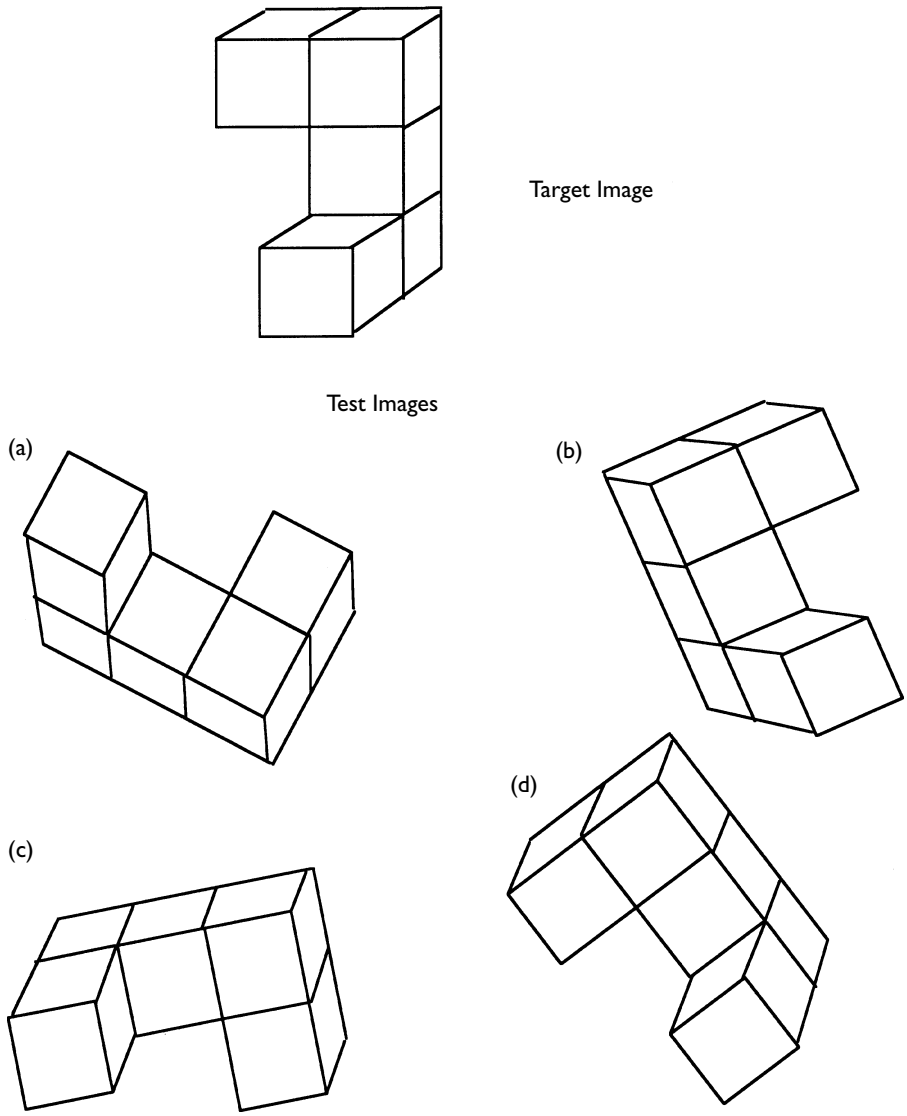

Figure 5.2 Mental rotation. The subject is required to choose the two test figures which are rotations of the sample figure. Correct answers: (a) and (d).

responses, they were given 80 practice trials before the experimental trials (160) began. Although there were no reaction time (RT) differences between females and males, several other differences in processing emerged. The female subjects began their analysis earlier, as indicated by a shorter latency for the N400 wave. In addition, females showed a greater positivity than males in the wave-forms between approximately 400 and 800 ms, which are associated with the later stages of stimulus evaluation and the early stages of mental rotation. Finally, the timing of the processing in

the female subjects differed for the abstract designs and the letters. When the target was an abstract design, processing began earlier if the amount of rotation was large (i.e. a large angle) than if the test figure had only been rotated by a small amount. For letters, however, large angle processing began later than small angle processing. This difference between real and abstract images seems to be an important issue and we will return to it later.

Silverman *et al.* (1993) conducted a series of 4 experiments examining the relationship of performance on a similar mental rotation task to phases of the menstrual cycle. The subjects were recruited mostly from a student population. However, the mean ages of the different groups are not specified. In the first of the 4 experiments the subjects included 158 females and 105 males. The menstrual cycle testing was conducted as a between-subjects design. The female subjects were divided into 3 groups: 1) not on the contraceptive pill (n = 101); 2) currently taking the pill (n = 42); 3) taking the pill but in the "off" (menstrual) phase of the pill cycle (n = 15). The performance of the male subjects was significantly better than the performance of the female subjects. Female pill users also performed significantly better than non-pill users. When this result was broken down further, it was found that the performance of pill-users in the "off" phase was equivalent to the performance of the male subjects. In the second experiment, a within subjects design, female contraceptive pill users (n = 27) were tested during their "on" and "off" phases. Female non-pill users (n = 23) were tested during their menstrual phase and during the luteal phase (days 16–23 for the majority of subjects). The performance of the menstrual phase/"off" pill subjects was significantly better than the performance of the luteal phase/"on" pill subjects. The aim of experiment 3 was to determine if the results obtained in experiments 1 and 2 were specific to the mental rotation task or could also be found using other tests of cognitive function. In this experiment the results on the mental rotation task were compared to the results on two "control" tasks, Digit Symbol, which measures a number of variables including visual-motor coordination, and anagram solving. The effects found in experiments 1 and 2 were replicated for the mental rotation task only. Finally, experiment 4 used a variation of mental rotation, the space relations task, to examine further the mental rotation effects found in the first 3 experiments. The space relations task required the subject to look at a two dimensional target pattern and decide which of a number of target three dimensional objects could be constructed by folding the test pattern. One hundred and sixty two subjects took part in the experiment; males (n = 42), females (menstrual/"off" phase, n = 26) and females (luteal/"on" phase, n = 94). In both tasks the males performed significantly better than the females. For the mental rotation, menstrual/"off" phase females performed significantly better than luteal/"on" phase females (Figure 5.3). The responses of the two groups of females were equal for the space relations task. Another study of mental rotation and the menstrual cycle yielded similar results (Moody, 1997). Males performed better than females overall. The female subjects scored significantly better during the menstrual phase than during the luteal phase, and the performance of females in the menstrual phase was not significantly different from the performance of the males.

A number of variables in the experimental design of mental rotation tasks, including the nature of the target objects and the instructions to the subjects, have been studied. It has been suggested that the nature of the test objects (real or abstract) may

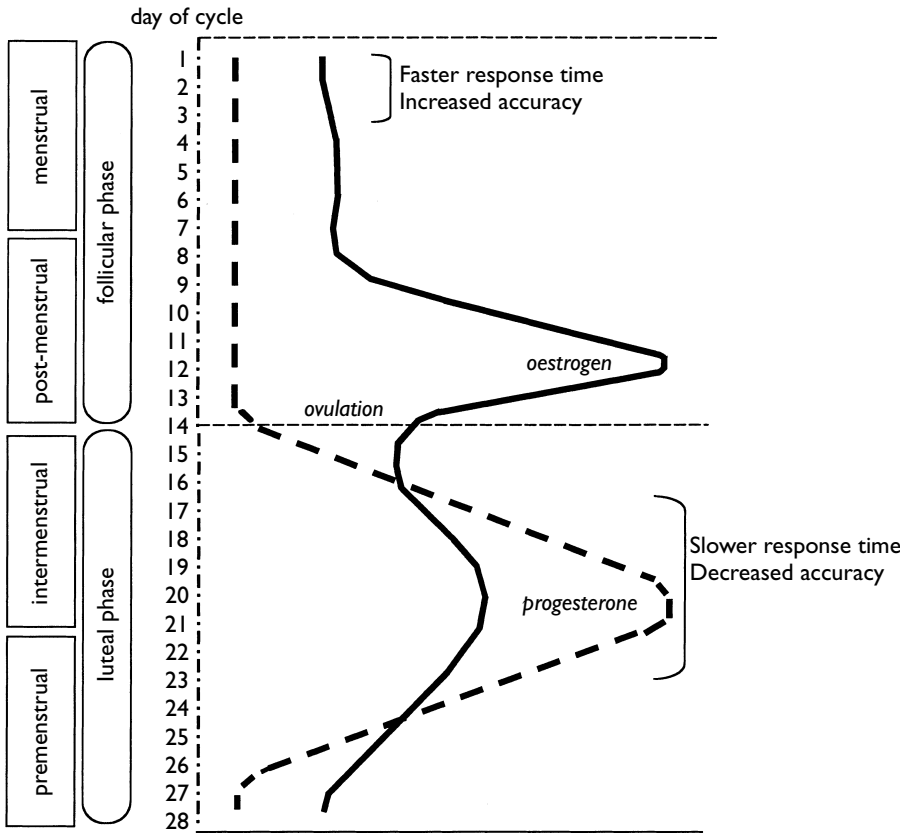

Figure 5.3 Mental rotation and the menstrual cycle.

be important. One study used pictures of mannequins, dressed either as females or males, instead of abstract shapes, as the test figures (Richardson, 1994). Each mannequin had a black disk in one hand and a white disk in the other hand. The mannequins were presented at different orientations and the task of the subject was to determine whether the black disk was in the mannequin's left or right hand. When the male mannequins were presented to one group of females and one group of males, the task was labelled as a "test of spatial ability". When the female mannequins were presented to two different groups of females and males, the task was labelled as a "test of personal empathy". On both tasks the males performed better than the females. In contrast, the instructions given to participants in another mental rotation task significantly changed the performance of the subjects (Sharps *et al.*, 1994). Using the standard target and test figure paradigm, half of the 36 females and 36 males, were given instructions which emphasised the spatial nature of the task while the other participants were given instructions which did not mention spatial ability. When the results were analysed, the subjects in the "spatial task" condition showed the usual male-better-than-females response pattern. However, the performance of the female and male subjects who received the "non-spatial" instructions were the same.

It has been suggested that the difficulty of 3-dimensional rotations might create a performance bias in favour of males. The results of a study comparing 2-dimensional (hard and easy) and 3-dimensional figures revealed that males performed better on all three tasks, although there was less male advantage on the "easy" 2-dimensional task (Collins and Kimura, 1997). Interestingly, when the task employed real, 3-dimensional models of the printed 3-dimensional figures used in most mental rotation tasks, the sex difference disappeared (McWilliams *et al.*, 1997).

In another type of spatial task, this time remembering locations in space, females showed a definite advantage (McBurney *et al.*, 1997). The performance of 46 females and 57 males, mean age 20 years for both groups, was compared on a standard mental rotation task and a spatial memory task. The spatial memory task used a commercially available board game which required players to remember the location of previously viewed images. As expected, the males performed significantly better on the mental rotation task; however, the females were superior to the males in remembering spatial locations. The authors suggest that superior location memory may be related to "evolutionary adoptedness". In a hunter-gatherer society, it was essential for the female gatherers to remember the location of food.

Another experimental result, which could conceivably relate to different strategies for the hunters and the gatherers, has been reported for geographic knowledge and directions (Dabbs *et al.*, 1998). One hundred and four females and 90 males completed a series of tasks measuring geographical knowledge and the ability to give directions from a map. The results of the direction-giving part of the experiment were particularly interesting. While the males gave directions in Euclidian space including compass points and distances, the females gave more personal directions including left and right turns and landmarks. With a slight stretch of the imagination, one can envisage how Euclidian directions would advantage the long-distance hunter, while the "stay-near-camp" gatherer would benefit more from references to turning directions and landmarks.

From the material presented above, it is clear that females do not perform as well as males on some tests of spatial ability. Does this mean that there are some areas of performance, for example, jobs requiring high spatial ability, which are unsuitable for females? This is, not surprisingly, a question of great interest to institutions such as the Air Force. Interestingly, this question was addressed, and answered, in 1982 (McCloy and Koonce, 1982). A group of 103 U.S. Air Force Academy Cadets (52 female, 51 male) were included in the study. The cadets were given a battery of tests which included spatial orientation as well as other aspects of cognitive and motor functioning. The males performed significantly better than the females on the mental rotation task as well as the psychomotor and flight simulator tasks. A year later, the cadets who were still at the Air Force Academy were retested. This time, the test procedure required the cadets to reach a specified performance criterion on each task. The females required more trials to reach criterion but the same standard of performance was achieved. The authors suggest that in designing tests to predict performance of certain skills, such as flying a high performance aircraft, the sex of the test subjects will be an important variable to be included in the test design.

The Stroop task is a visual task that requires both reading and colour recognition. The task, until one has tried it, appears quite straightforward. The names of colours, for

example, red and green, are displayed to subjects in letters coloured either to match the named colour ("green" in green letters) or in a colour different from the named colour ("green" in red letters). The task of the subject is to press a button corresponding to the named colour or to press a button corresponding to the colour of the letters and ignore the colour name. Instead of a button press, a verbal response may be used. The variables measured are accuracy and reaction time (RT). The "Stroop effect", the interference caused by non-matching words and letter colours, is apparent as increased RT and decreased response accuracy. The literature on female–male differences in the Stroop task performance is mixed. Some authors find a difference, some do not. The following two studies are representative of the types of contradictory results found in the literature. A study of 8 female and 8 male undergraduates has reported that although the response (a button press) accuracy was equal for females and males, RT for males was longer (Mekarski *et al.*, 1996). A larger study of 69 females and 59 males, also undergraduates, has reported that when the task, which required a verbal response, was completed in a "relaxed" atmosphere, RT for females was longer than for males, but the responses of the females were more accurate (von Kluge, 1992). However, when the conditions of the task were changed and the importance of performance was stressed, the results changed. The RT of the females decreased to match male RT, but the greater accuracy of the female subjects was maintained.

Weekes and Zaidel (1996) designed a series of studies to try to determine which factors are most important in testing the Stroop effect. The factors included in the experiments included: 1) mode of visual presentation, bilateral or unilateral; 2) mode of response, verbal or manual; 3) separation of colour and word; 4) phase of menstrual cycle, menstrual or mid-luteal. The subjects were 146 right-handed, native English speakers. Equal numbers of females and males were used for each experiment. The females were aged between 20 and 35 years, the age range of the male subjects is not stated. The authors report that factors 2 and 3 were not crucial to the experimental outcome, although the Stroop effect was somewhat weaker for manual rather than verbal responses. There was a clear hemispheric advantage, or disadvantage, with the left hemisphere showing a greater response decrement (Stroop interference) than the right hemisphere. In addition, there was an interaction with the day of the menstrual cycle. When the left hemisphere effects were further analysed, the difference was significant only for males and for females in the menstrual phase, when oestrogen was low (Weekes and Zaidel, 1996). Menstrual cycle effects have also been reported by Lord and Taylor (1991) who tested 50 female subjects every 7 days for 4 weeks. The authors report that the accuracy was low during the menstrual phase, peaked at mid-cycle, then dropped again as the next menstrual phase approached (Figure 5.4).

Object recognition tasks use a more "natural" form of stimulus which may or may not have some kind of emotional value for the viewer. The objects presented can range from images of faces and babies to garden implements and pieces of furniture. The variables measured will be either RT and/or accuracy. In a chair recognition task, for example, following the tachistoscopic presentation of chair images, the subjects were required to select the previously presented chairs from an array of chairs (Bibawi *et al.*, 1995) The accuracy was the same for females and males. For males, the accuracy of their choices was also the same for left visual field (LVF) and right visual field

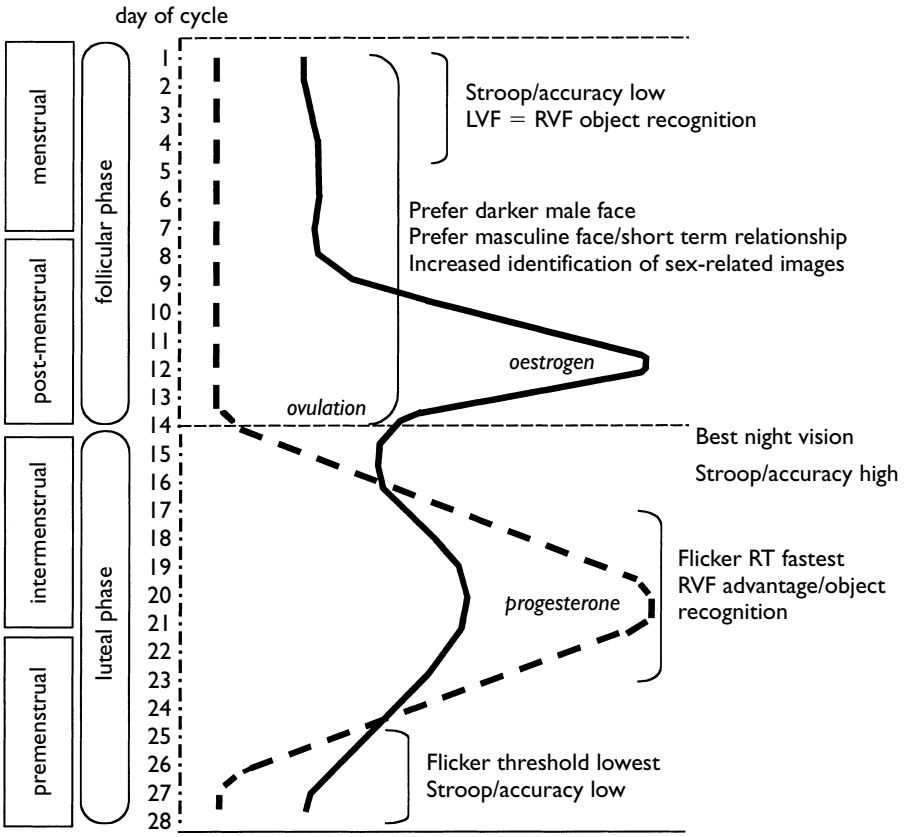

Figure 5.4 Visual perception and the menstrual cycle.

(RVF) presentations. For females, however, LVF and RVF were equal only during the menstrual phase. During the mid-luteal phase there was a significant RVF advantage. In another study, photographs of urban scenes familiar to the subjects were used (Hamel and Ryan-Jones, 1997). All of the scenes were viewed on a computer screen. For some of the presentations, the scenes were high resolution photographs. On other presentations, the scenes were distorted to reduce the amount of detail. The male subjects identified the photographic and the distorted scenes with equal accuracy. For the female subjects, their accuracy for the photographic images was significantly greater than their accuracy for identification of the degraded images.

The human face raises some particularly interesting issues in object recognition. Overall, the faces of females and males differ in appearance. The facial skin of females tends to be lighter than for males. The skin also has a different texture. In the mature male, partial regrowth in shaved areas, the "5 o'clock shadow", also provides additional coloration to the face. The overall shape of the face also differs between females and males, with smaller featured, symmetrical shapes being seen as more feminine. The responses of females and males to viewed faces also differ. For a study on skin tone preference (Feinman and Gill, 1978), the subjects, 482 female and 549 male,

white undergraduates were asked to indicate their preferred skin colour for the opposite sex. The female subjects reported a significantly greater preference for darker skin tones, while for males, the preference was for lighter skin tones. In another study the female subjects were asked to make a preferred face choice (skin tone was the variable) at different phases of the menstrual cycle: subjects in the follicular phase showed a significant preference for darker male faces. Subjects in the luteal phase did not show a preference for face colour, nor did women taking oral contraceptives (Frost, 1994).

In 1999, it was suggested that the preference for facial characteristics changes with the probability of conception (Penton-Voak *et al.*, 1999). In a study of 39 women with a mean age of 21 years, the subjects with the greatest probability of conception (days 5–14) preferred the most masculine faces in a stimulus array. In a second experiment, 65 subjects were allowed to use a computer program to manipulate images of male faces making them more or less masculine. The subjects were asked to indicate which face they preferred for a long-term relationship and which face they preferred for a short-term sexual relationship. There was no difference between the phases of the menstrual cycle for the "long-term relationship" preference. However, for the short-term sexual relationship, the more masculine face was preferred when the probability of conception was high.

The meaning of the stimulus has also been shown to affect response patterns across the menstrual cycle. A study of 16 female subjects used tachistoscopic presentations of images with different meanings; sex (nude males), maternal (babies), body care (for example, a hair brush), and neutral (nonsense syllables) (Krug *et al.*, 1994). The subjects were tested at 3 stages of their menstrual cycles, menstrual, pre-ovulatory and mid-luteal. The ability to recognise nonsense syllables did not change across the menstrual cycle; however, the ability to recognise meaningful stimuli did. In the pre-ovulatory stage, there was an increase in the ability to identify stimuli in the sex category. There was also an increase in the number of incorrect identifications of sex stimuli. In the mid-luteal phase, there was an increased sensitivity to babies. Sixteen women taking oral contraceptives were tested in the same study. Their responses to pictures did not change across the cycle, however, their overall performance was less accurate during the menstrual phase. In an evoked potential study using similar stimuli, it was reported that only the P300 wave changed across the menstrual cycle, increasing in response to babies and males in the mid-luteal phase. (Johnston and Wang, 1991). The response to babies and males was highest in the mid-luteal phase. When the subjects were asked to rate the pleasantness of the slides they had just seen, the highest ratings for pleasantness were given during the pre-ovulatory phase.

Other changes in visual function across the menstrual cycle have also been reported. Generally, visual acuity has been reported to vary across the cycle; night vision has been reported to be best at mid-cycle, response to light flicker has the shortest latency in the luteal phase and the threshold frequency to detect flicker has been reported to be lowest pre-menstrually (Figure 5.4; see Walker, 1997, for a review).

Other sensory systems

> Money is like a sixth sense without which you cannot make a complete use of the other five.
>
> Maugham, W.S. (1915) *Of Human Bondage.*
> In *Oxford Dictionary of Quotations*,
> OUP, New York (1996) p. 454.

The visual system is not the only sensory system where sex differences have been found. The visual system is only one of 6 sensory systems and although vision receives the most attention, the other sensory systems are also vital for cognitive function. The auditory system is the second most-studied sensory system. Studies of auditory psychophysics range in complexity from measuring the ability to detect a single tone to the analysis of complex musical pieces.

A study of 24 female and 24 male undergraduates examined the subjects' ability to distinguish tones and series of tones presented binaurally or as a dichotic listening task (McRoberts and Sanders, 1992). Half of each group were music majors or people with formal musical training (experienced), the other half of each group were people with no formal musical training (naïve). The subjects were given 3 tasks. The first task, the Seashore Pitch Discrimination Test, required the subject to listen to 50 pairs of tones and after each pair to report whether the second tone was of higher or lower pitch than the first tone. The second test, the Seashore Tonal Memory Test, required subjects to listen to 30 pairs of tonal sequences ranging in length from 3 to 5 tones per sequence. In each pair of sequences one note was different. After listening to each pair, the subject had to report which tone (first, second, third, fourth or fifth) was different. The third test was the Fundamental-Frequency Contour Test. For the test the subjects listened to a continuous tone with changing pitch (contour). The pitch of the tone could rise, fall, rise then fall, or fall then rise. The subjects had to decide which contour occurred on each trial. The presentation of tasks was either binaural or dichotic, with the subject instructed to attend to the tone presented to either the right or left ear. Analysis of the results showed that the musically experienced subjects performed better than the musically naïve subjects. For the binaural tasks, the males were more accurate than the females. Overall, there was a left ear advantage for the dichotic tasks and females and males performed equally.

Still on the musical theme, there is evidence to suggest there are sex differences in the perception of loudness which vary depending upon whether you ask the listeners to rate "loudness" or "annoyance" (Fucci *et al.*, 1994, 1997). Young adult subjects were first asked to rate how much they liked or disliked rock music. The subjects then listened to 10 second samples of rock music presented binaurally. There were 9 samples ranging in amplitude from 10 dB to 90 dB above the individual subject's hearing threshold. The samples were presented in random order and the subjects were instructed to rank the intensity of each sample by assigning a number. Fucci *et al.* (1994) asked their subjects to estimate the "loudness" of the music. They reported that the perceived loudness of the rock music was directly related to the females' musical preference. Females reporting that they "definitely dislike" rock music rated the music louder than females reporting that they "definitely like" rock music. Fucci *et al.* (1997) repeated the experiment with only one procedural difference. Instead of rating

"loudness", the subjects were asked to rate "annoyance". This time it was the males who showed the greatest effect. The males who had reported that they "definitely dislike" rock music rated the music as more annoying than males who had reported that they "definitely like" rock music.

A number of studies have looked for differences in olfactory sensitivity between females and males. The results of these studies have been mixed. Although it is often reported that females are generally superior to males in olfactory function, the literature does not consistently support this view. As well as a generally greater sensitivity in females, some have reported differences in sensitivity to particular odours, while other studies have reported no differences for the same stimuli. Methodological problems may account for many of the discrepancies, especially in the early studies. For example, odours are particularly difficult stimuli to deliver and remove, they diffuse easily and can remain for long periods. Or, if your subjects smoke, or have recently been in the company of smokers, their sensitivity may well be altered. Koelega (1994) conducted a study of olfactory sensitivity designed to overcome some of the design problems of previous studies. One hundred and twelve subjects with a mean age of 20 years participated in the experiment. There were 57 females (30 non-smokers and 27 smokers) and 55 males (26 non-smokers and 29 smokers). Five odourants were used: amyl acetate (banana oil), n-butanol iso-valeric acid (pungent, unpleasant), pentadecanolide (musky, scent of angelica root oil), and oxahexadecanolide (Exaltolide, also musky). Subjects were presented with a series of 4 odourants in small glass bottles and were asked to indicate which odour was different from the other three. After a 60 second interval, the next array of bottles was presented. There were 4 test sessions separated by 24 hours, with 7 trials per session. Analysis of the results revealed 2 sex differences: females were more sensitive than males for musk and banana oil. Although there was a trend towards decreased sensitivity in smokers, the difference was not significant.

Olfactory event-related potentials (OEPs) are, as the name suggests, evoked potentials in response to a particular odour. Olfactory acuity and OEPs were recorded from 33 subjects ranging in age from 18 to 83 years (Evans *et al.*, 1995). Eighteen subjects were female, 15 subjects were male. The olfactory stimulus, amyl acetate (banana oil), was presented to the right nostril in different concentrations. Although the ability to detect the odour diminished with increasing age, there were no female–male differences in sensitivity. There were, however, significant differences in the N1-P2 amplitudes between females and males. The amplitudes for the female subjects were 60 to 90% larger than the amplitudes for the male subjects. A study using 40 odourants, the University of Pennsylvania Smell Identification Test, also demonstrated that olfactory sensitivity decreases with increasing age (Ship and Weiffenbach, 1993). However, this study of people aged between 19 and 95 years, 221 males and 166 females, also found a gender difference in sensitivity, with females demonstrating greater sensitivity than males. From as early as 1935, olfactory sensitivity has also been reported to vary across the menstrual cycle. It has been reported that in the pre-ovulatory phase, females are more sensitive to musk and rose. Pre-menstrual females have been reported to be more sensitive to benzene, coffee and camphor (Figure 5.5; see Walker, 1997, for a review).

Although there is a lot of anecdotal evidence suggesting that cravings for sweets,

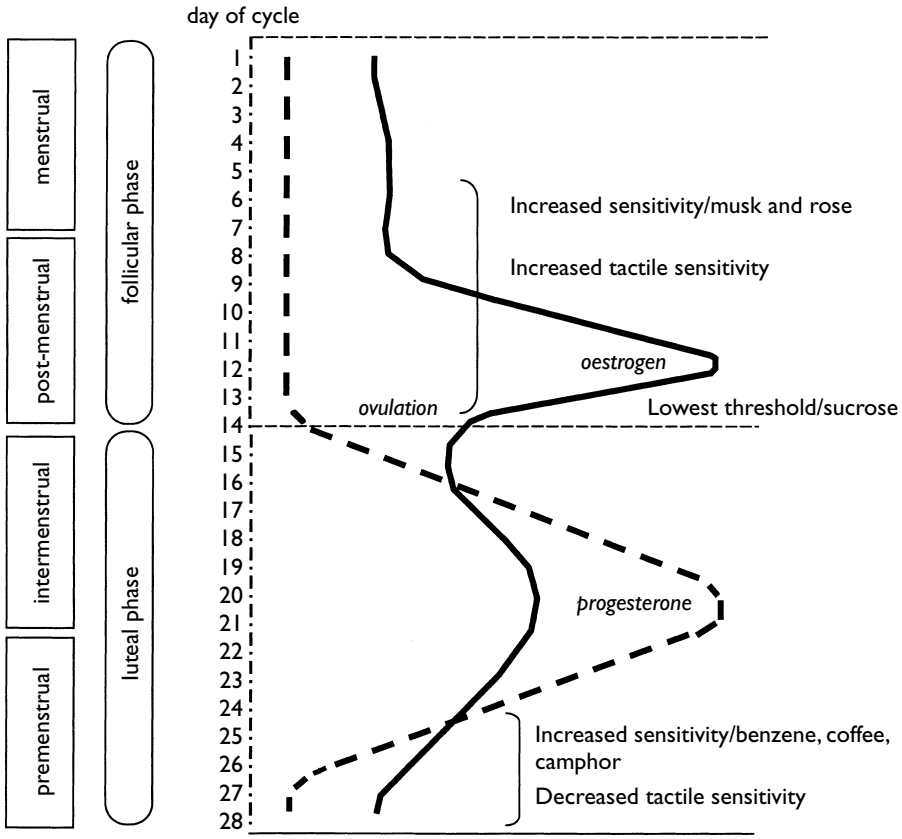

Figure 5.5 Sensation/perception and the menstrual cycle.

and chocolate in particular, occur more frequently in the pre-menstrual phase, little work has been done on taste preference and the menstrual cycle. The threshold to detect sucrose has been reported to be lower in the pre-ovulation phase (Than *et al.*, 1994). A pre-menstrual increase in the intake of high-fat, high-carbohydrate foods has also been reported (Rogers and Jas, 1994). Finally, and this seems like a good place to leave the discussion of taste, it has been reported that females prefer the taste of "expensive" brands of chocolate chip ice cream while males prefer the taste of the cheaper brands (Kunz, 1993).

Tactile sensitivity is not an area that has been greatly researched. The threshold to detect vibrations delivered to the palm of the hand has been reported to be the same in females and males, although females report vibrations above the threshold as "more intense" than males (Verrillo, 1979). A study applying a tactile stimulus (also vibration) to the tongue, failed to find a similar difference in judgements of above-threshold stimuli (Petrosino *et al.*, 1988). It has also been reported that tactile sensitivity is greatest in the pre-ovulatory phase and lowest pre-menstrually (Walker, 1997).

Numbers and sums

> We have "a priori" knowledge when we know something to be the case without this knowledge being grounded on experience. It seems that we have knowledge of this sort in mathematics, and perhaps in other areas as well; the fact that we do have such knowledge has often seemed puzzling to philosophers. How is it that we are able to know with certainty, apart from observation, measurement, etc., that the angles of an Euclidian triangle all together equal 180 degrees, and that 8 plus 7 always and invariably equals 15?
>
> Alston, W.P. (1964)
> *Philosophy of Language*,
> Prentice-Hall, N.J., p. 4.

The ability to manipulate numbers is frequently used as a general measure of cognitive function. This ability may be tested in a variety of ways but one of the more popular methods (particularly for screening job applicants) is some form of the "serial addition" task. This task requires the person to add one number to another, speak or write the answer, add a number to that answer, speak or write the new answer, etc., etc., etc. Usually the process is timed or paced and both speed and accuracy are measured. The test requires more cognitive skills than just simple addition. It is necessary to do the arithmetic, make the response, listen for the next number to be added to the last answer, and not confuse the numbers in the present addition with those in any of the previous sums. Furthermore, a timer is ticking away or the new numbers to be added are simply arriving at a fixed rate, e.g. 1 every 2 seconds.

Wiens *et al.* (1997) used the Paced Auditory Serial Addition Test (PASAT) to measure the performance of 821 adults (672 males and 149 females). The PASAT uses a pre-recorded set of 50 single digit numbers presented in random order. The task of the subject is to add each new number to the previous total and speak the new total. There are 4 trials, each with a different set of randomised numbers, the only difference between the trials is that the rate at which the numbers are presented increases across the trials (2.4, 2.0, 1.6, 1.2 seconds between numbers, respectively). The variable measured is the number of correct responses. In this study, the performance of females and males was equal for the first 3 trials, however, on trial 4 (one number every 1.2 seconds), the accuracy of the males was significantly greater than the accuracy of the females.

Another test of cognitive function which uses number skills is the "Mental Dice Task". This task requires the subject to produce a series of "random" numbers using numbers from 1 to 6 only, "as if throwing dice". As with serial addition, the task requires more than just number manipulation. To generate the response, the subject must overcome the natural tendency to count, either forwards or backwards, or to repeat a pattern of presentation, e.g. 3 odd, 3 even. One particular advantage of this task is that the subjects do not know what response is expected of them. There is no "correct" answer. There is, however, a similarity with the Stroop test. In order to respond appropriately, the subject must suppress an "automatic" response, in this case counting. Brugger *et al.* (1993) tested 20 right-handed females (mean age, 30 years) during the preovulatory phase (days 8–13) and during the premenstrual phase (days 23–28). The subjects were instructed to imagine that they were rolling dice and to call

out their imaginary numbers at a rate of 1 number per second. A series of 66 numbers was recorded in this way. When the numbers generated by the subjects were compared to a real series of dice throws, there was evidence of too much counting and, interestingly, too few repetitions at both test times. When comparing the responses between the two phases of the menstrual cycle, there was significantly greater counting in the premenstrual phase than in the preovulatory phase. If you consider this result as indicating a reduced suppression of an automatic behaviour then the result is consistent with the Stroop results of Lord and Taylor (1991).

Memory

> Mais, quand d'un passé ancien rien ne subsiste, après la mort des êtres, après la destruction des choses, seules, plus frêles mais plus vivaces, plus immatérielles, plus persistantes, plus fidèles, l'oedur et al. savur restent encore longtemps, comme des âmes, à se rappeler, `a atendre, à espérer, sur la ruine de tout le reste, à porter san fléchir, sur leur gouttelette presque impalpable, l'édifice immense du souvenir.[1]
>
> M. Proust (1913) *Du côté de chez Swann*, Folio Classique, Gallimard, 1988, p. 46.

It is difficult to talk about memory as a separate entity. All of the types of cognitive function covered so far in this chapter rest on a firm foundation of memory. Learned and remembered skills are required for the successful completion of some tasks (mental rotation, giving directions) or need to be suppressed for the successful completion of others (Stroop, mental dice). What distinguishes the papers covered in the following section from those discussed above is their focus on the memory processes required for the cognitive task, rather than task performance per se.

A good place to start this discussion is with a return to the question of the hunters and the gatherers. Males are better at mental rotation of objects but women are better at remembering where hidden objects may be found. What is it about the object location task that gives females the advantage? James and Kimura (1997) approached this question by presenting subjects with a visual array composed of drawings of 27 objects. After studying the original stimulus array, the task was to identify objects in a test array which had exchanged location with another object (condition 1) (Figure 5.6) or moved to a new location without exchange (condition 2). The stimuli were presented either on printed pages or on a computer screen. The experimental subjects were 174 undergraduate psychology students aged between 18 and 27 years.

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1 "But when from a long-distant past nothing subsists, after the people are dead, after the things are broken and scattered, taste and smell alone, more fragile but more enduring, more immaterial, more persistent, more faithful, remain poised a long time, like souls, remembering, waiting, hoping, amid the ruins of all the rest; and bear unflinchingly, in the tiny and almost impalpable drop of their essence, the vast structure of recollection." M. Proust (1913) *Swann's Way*, Translated by Moncrieff and Kilmartin, Vintage Classics, 1996, p. 54.

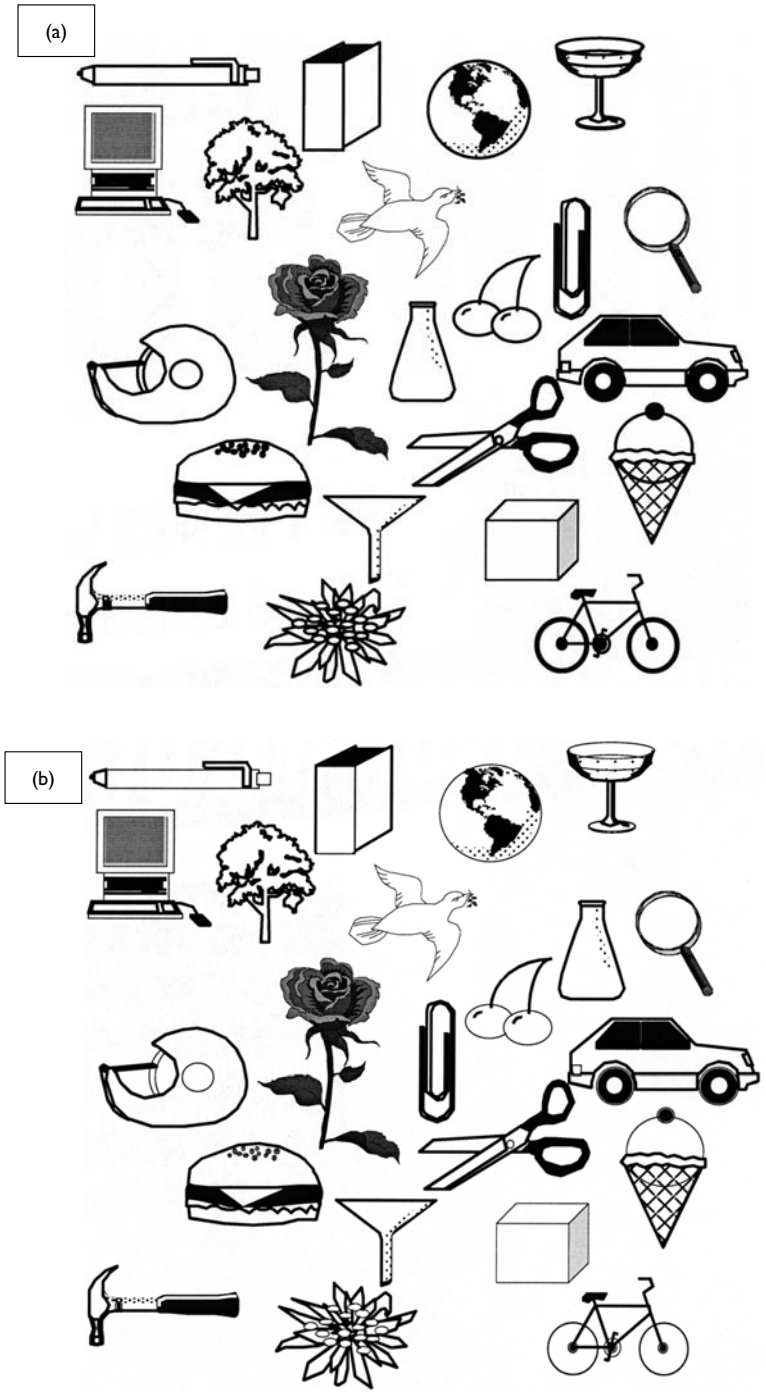

Figure 5.6 Moved objects. Subjects are required to study stimulus array (a). The task is to identify the two moved objects in the test array (b).

Forty-one females and 43 males participated in condition 1; 44 males and 46 females participated in condition 2. The protocol was the same for the two conditions. The subjects were asked to study an array of objects. After 1 minute, the original array was replaced with a new, test array. The subjects were asked to place an "X" on objects which had moved and to circle objects which had not moved. For the subjects responding to the computer array, an overhead transparency was placed over the screen and they marked their responses on this. When the results were analysed, there was no difference between paper presentations and computer presentations. In condition 1, location exchange, females performed more accurately than males. In condition 2, where objects had been moved rather than exchanged, female performance was similar to condition 1, and there was no difference between females and males. One of the major differences between the two conditions was in terms of filled and unfilled space. In condition 1, the pattern of filled and unfilled space remained the same. Two objects were exchanged but the occupied areas of the array remained constant. The critical feature was identification of the individual objects. In condition 2, the pattern of filled and unfilled space changed. An object was moved from its original location to a new place in the array, one gap was filled and another gap opened up. Identification of individual objects was de-emphasised. In terms of evolutionary advantage, James and Kimura suggest that for gatherers, correct object identification (edible vs non-edible) is the crucial discrimination. It is the individual objects that are remembered. For the wider ranging hunters, however, recognition of filled and unfilled space (a familiar or an unfamiliar horizon) may have literally made the difference between life and death. So, in condition 2 where the males had the additional cue of the pattern of filled space, their performance was equal to the performance of females.

The kinds of objects in a visual array, female-oriented or male-oriented, have been suggested to be important to visuo-spatial memory. McGivern *et al.* (1997) tested the effect of object type on people's ability to remember images. The subjects in the study were 39 female (mean age 21 years) and 23 male undergraduates (mean age 22 years). The subjects were asked to study a page containing an array of items for 60 seconds. The array could be female-oriented (e.g. doll, dancer, dress), male-oriented (e.g. football, lion, rocket) or random (e.g. umbrella, phone, guitar). After studying the array, subjects were then given a page containing the original stimulus array, with additional items added. The task of the subjects was to circle those items not included in the original array. The female subjects' recall was better than the male subjects' recall for the random and female items. Female and male recall was equal for the male items.

It has been suggested that females and males may differ in the way they process and, therefore, remember a visual array. A study of 24 females and 24 males, aged between 18–48 years, assessed the subjects on 4 different aspects of their visuo-spatial working memory formation processes including image generation, maintenance, scanning and transformation (Loring-Meier and Halpern, 1999). For the first task, image generation, the subjects were asked to study an image of a letter, draw that letter from memory and then decide whether an "X" on a computer screen would have been covered by the original (remembered) image. For the second task, image maintenance, the subjects were asked to memorise a shape on the computer screen, then decide if an "X" which appeared on the screen after the first image disappeared would have

covered that image. The third task, image scanning, required the subjects to study an arrangement of black and white boxes on a computer screen. When the boxes disappeared, an arrow was displayed and the subjects had to decide whether or not the arrow pointed to the position of a black box in the previous array. The fourth task was a standard mental rotation task. The results of the study were surprisingly uncomplicated: males performed the tasks faster than females, but the accuracy of the performance was equal for females and males.

It has been reported that females perform better than males on tests of episodic memory, the memory of specific events or items. One suggestion to explain this difference is that females' superior ability in verbal tasks may generalise to give better performance on tasks testing episodic memory, e.g. word recall tasks. Herlitz *et al.* (1999) addressed this question by assessing a group of 20 to 40 year olds (100 females, 100 males) on a series of 9 tasks which measured episodic memory on both verbal and spatial tasks (Table 5.1).

In analysing their data, the authors not only looked for male, female differences (male or female "advantage") on the different tasks, they also looked for relationships between verbal and spatial abilities and episodic memory. On the verbal tests, females performed better than males on the fluency and synonym tasks, but male and female performance was equal on the anagram task. As expected, males performed better on the mental rotation task, but there was no difference between females and males on the water level task. On the episodic memory tests, females were more accurate than males on free recall for abstract words and concrete pictures. Male and female performance did not differ significantly for the other tasks. After this initial analysis, Herlitz *et al.* used factor analysis to tease out the possible relationships between the different tasks. Factor analysis is a form of statistical analysis related to matrix algebra. The idea is that data from a number of different tests can be analysed, specifically looking for sets of variables whose individual variables initially correlate across subjects. Such sets of correlated variables are called factors. Three factors were found for the present study. The first factor grouped abstract word recognition (no advantage), abstract word recall (female advantage), concrete word recognition (no advantage) and concrete word recall (no advantage). The second factor contained synonyms (female advantage), fluency (female advantage) and concrete pictures free recall (also female advantage). This grouping strongly suggests that the female advantage for synonyms and fluency has contributed to the female advantage for the episodic memory task, concrete pictures free recall. The third factor contained mental rotations (male advantage), abstract picture recognition (no advantage) and concrete picture recognition (no advantage). It is particularly interesting to note that even though males scored much better than females on mental rotation, they did not have an advantage on the other factor 3 tasks, abstract and concrete picture recognition.

Female–male differences in event related potentials (ERPs) during verbal and abstract figure memory tasks have been reported. A study of 24 females and 24 males has demonstrated that ERP latencies were longer for males than for females for both tasks (Taylor *et al.*, 1990). The distributions of activity also differed between females and males, with females showing larger amplitude anterior P2 and N4 waves in response to abstract figures and larger amplitude posterior P2 and N4 waves in response to verbal stimuli. Auditory evoked potentials, hypothesised to be related to acoustic memory,

Table 5.1 Design of study by Herlitz *et al.* (1999)

Test	*Task and response required*	*Variable measured*
Verbal:		
Fluency	Generate and write words beginning with "F", "A", and "S"	Number of words written in 1 minute
Synonyms	Generate and write synonyms for "modern", "aspect", "caring", "important", "rich" and "dull"	Number of correct synonyms written in 5 minutes
Anagrams	Solve 5 letter anagrams	Number of correct solutions in 5 minutes
Visuospatial:		
Mental rotation	Match target figures to rotated test figure	Number of correct figures in 10 minutes
Water level	Determine horizontal water level from view of tipped bottles	Number of correct water level estimates Not timed
Episodic:		
Abstract words	View 30 abstract words (e.g. "statement", "feelings") for 3 sec; free recall, write remembered words on paper (3 mins); recognition test, indicate if viewed words were presented initially	Number of words recalled
Concrete words	View 30 concrete words (e.g. "window", "flower") for 3 sec; free recall, write remembered words on paper (3 mins); recognition test, indicate if viewed words were presented initially	Number of words recalled
Concrete pictures	View 30 concrete pictures (e.g. picture of window, picture of flower) for 3 sec; free recall, write remembered pictures on paper (3 mins); recognition test, indicate if viewed pictures were presented initially	Number of pictures recalled
Abstract pictures	View 30 abstract pictures for 3 sec; recognition test, indicate if viewed pictures were presented initially	Number of pictures recalled

have also been reported to differ between females and males. Rojas *et al.* (1999) have reported that the time constant (the amount of time required for the response to decay) of the 100 ms auditory evoked response is longer in females than in males. As the 100 ms response is suggested to underlie auditory sensory memory, this result may represent the biological basis of some of the observed behavioural differences.

Conclusions

> Precipitation reactions. When certain solutions of electrolytes are mixed, the cation of one solute may combine with the anion of the other to form an insoluble compound. This leads to the formation of a precipitate. A precipitate is an insoluble solid that settles from a solution.
>
> Watkins, K.W. (1994) *Study Guide to Accompany Chang: Chemistry. Fifth Edition*, McGraw-Hill, New York, p. 50.

In this chapter the results of quite a number of different studies have been presented. The problem, in trying to form the mass of divergent information into a coherent whole, is to decide what aspects of the studies are comparable and what aspects are not. The differences we are looking for may be small, on some tests half a standard deviation (Hampson, 1990), and easily obscured. Hampson (1990) tackled this problem of comparability head-on. She designed a study to administer a battery of cognitive and motor tests to the same group of females, once during the menstrual phase and once during the midluteal phase. The tests included female advantage and male advantage tasks. The crucial point is that the tests were all administered under the same conditions, using the same equipment and the same protocols. Hampson's hypothesis was that during the midluteal phase when oestrogen and progesterone are high, the performance on female advantage tasks should be at its best, while performance on male advantage tasks should be poor. Forty-five females, aged between 19 and 39 years (mean 24 years), were included in the study. The results of the study generally supported Hampson's hypothesis. During the menstrual phase, the subjects performed better on the male advantage tasks (e.g. spatial ability, deductive reasoning) than during the midluteal phase. During the midluteal phase, performance on female advantage tasks was better but the results were not as clear as the male advantage results (Hampson, 1990).

The following summarises the main points derived from this chapter. We will revisit some of these points in Chapter 7 in relation to psychiatric illness.

1. There are 3 categories of cognitive and perceptual tasks: female advantage tasks, male advantage tasks, and neutral tasks. The male advantage tasks are those requiring analysis and manipulation of spatial stimuli (e.g. Rod and Frame, Mental Rotation). The female advantage tasks are those requiring the analysis and manipulation of verbal and visual materials (e.g. Synonyms, Hidden Objects).
2. Performance on male advantage tasks improves during the menstrual phase, when female performance becomes more like male performance. Performance on female advantage tasks is better in the midluteal phase.
3. The female–male differences on spatial tasks are related primarily to reaction time, while accuracy is usually equal. Females can perform the tasks as accurately as male, but it may take more trials to acquire the skill initially.
4. There is a female advantage for recognising and remembering specific rather than global information.
5. There are differences in perceptual and sensory system sensitivity across the menstrual cycle. Prior to (or on) ovulation visual acuity is greatest, sensitivity to musk

is increased and tactile sensitivity is heightened. This makes good sense since the systems most useful for finding a mate are most sensitive when the female needs them most (Ivory, unpublished observation).

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6

Laterality

Tyger, tyger burning bright
In the forests of the night,
What immortal hand or eye
Could frame thy fearful symmetry?
William Blake, The Tyger.
In Keynes, G. (Ed.)
Blake: Complete Writings,
1972, p. 214.

A good indicator of the impact that a scientific discovery has made on the general population is to apply the "gossip test". Does the discovery feature in the popular press? Do talk show hosts allude to it? Can you buy books telling you how to: understand it, live with it, exploit it, enhance it or make money from it? Using these criteria, asymmetry of brain function, "laterality", passes the gossip test.

The idea of "two" brains with different skills has captured the public imagination. Not surprisingly, it is the "creative" right brain which has attracted the most interest. A quick browse through an internet bookstore will yield some interesting titles. Apparently, in addition to drawing with the right side of the brain, it is also extremely useful for cooking vegetarian food, riding horses and colouring Tibetan patterns. In addition, if you are a "right-brain person", you can learn how to use left-brain financial skills, manage your career and guide your right-brained children through the left-brained world.

Asymmetry in brain function has been recognised for over 100 years. Much of the early evidence on laterality came from studies of head injury patients. Similar lesions, but on opposite sides of the brain in different patients, produced remarkably different effects. Lesions in discrete regions of the frontal and temporal lobes were demonstrated to produce profound but region-specific language deficits. It was initially thought

that laterality was primarily important for language. Recently this view has changed. It is now understood that the two hemispheres play different but complementary roles in analysing, and responding, to a wide range of sensory stimuli.

Parallel processing and hemispheric advantage

> There are half a dozen basic techniques of analog-to-digital conversion, each with its peculiar advantages and limitations. Since you usually use a commercial A/D module or chip rather than build your own, we will describe the various conversion techniques somewhat briefly, mainly to serve as a guide for intelligent selection in a given application . . .
>
> Parallel encoder
>
> In this method the input signal voltage is fed simultaneously to one input of each of *n* comparators, the other inputs of which are connected to *n* equally spaced reference voltages. A priority encoder generates a digital output corresponding to the highest comparator activated by the input voltage.
>
> Parallel encoding (sometimes called "flash" encoding) is the fastest method of A/D conversion.
>
> Horowitz, P., Hill, W. (1987)
> *The Art of Electronics*, p. 415.

Asymmetry in brain function is not to be confused with the cross-over in motor pathways leading from the brain. Each side of the brain represents the opposite side of the body. A stroke which damages the left hemisphere will result in paralysis or other motor deficits on the right side of the body, as well as speech disruption.

The important feature of laterality is that the two sides of the brain process the same information for different attributes at the same time (parallel processing). This division of labour in processing is often referred to as "hemispheric advantage". Under normal circumstances, the results of the processing are communicated between the 2 hemispheres. Because the transfer of information is rapid, the result is a comprehensive analysis of information with the features extracted by the left and right hemispheres integrated into an "information package". This is an extremely efficient method of data analysis and undoubtedly confers an evolutionary advantage in terms of survival (Geschwind and Galaburda, 1985). The advantages for language processing are just one aspect of divided processing, which is particularly convenient for a language-using species.

It is difficult, in a person with an intact brain, to analyse the function of the two hemispheres independently. For a number of years, based primarily on the results of lesion studies, it was assumed that the left hemisphere was the dominant, more important hemisphere. This assumption is understandable in view of the behavioural effects observed following left and right hemisphere lesions. Lesions on the left tend to produce obvious, easily observed, disruptions to language. Lesions to the right hemisphere produce much more subtle deficits. In the absence of highly specialised neuropsychological testing, the effects of right hemisphere lesions may go undetected. Over the years, a list of attributes for the two hemispheres, in addition to "more important-less important" judgements has accumulated (see Table 6.1). The most com-

Table 6.1 Processing characteristics attributed to the left and right hemispheres

Left hemisphere	*Right hemisphere*
language	visual-spatial representation
analytic	holistic
verbal	spatial
amplifies small scale information	amplifies larger scale information
categorical representations	prosody
	topographical properties

monly suggested description is of a verbal left hemisphere and a spatial right hemisphere. In truth, the distinctions are far more subtle and interesting!

Much of what we understand about laterality comes from studies of patients with lesions to particular brain regions. Interpretation of lesion studies is always difficult. You look at behaviour following a lesion, try to determine how the behaviour has changed from the pre-lesion behaviour, then work backwards to try to determine what the area was doing in the first place. So, for example, a patient may be shown a figure containing a capital letter composed of a number of small letters (see Figure 6.1a). After the figure has been hidden the patient may be asked to draw the figure from memory. The result may be something like the drawing in Figure 6.1b. The challenge is to determine, from that drawing, the nature of the functional changes that have occurred.

The question of what the hemispheres do and how they do it needs to be explored before we can consider the case for sex differences in hemispheric function. The next section will discuss two recent theories of hemispheric function. The first, from Ivry and Robertson (1998), deals with what the respective hemispheres do. The second, from Miller (1996), deals with how they may do it.

Two theoretical perspectives on laterality

> The empirical basis of objective science has thus nothing "absolute" about it. Science does not rest upon solid bedrock. The bold structure of its theories rests, as it were, above a swamp. It is like a building erected on piles. The piles are

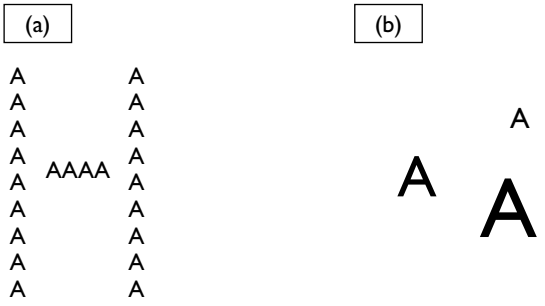

Figure 6.1 Global vs. local figure attributes. (a) The *global* letter, H, composed of the *local* letters, A. (b) Schematic representation of figure distortion following cerebral damage.

> driven down from above into the swamp, but not down to any natural or "given" base; and if we stop driving the piles deeper, it is not because we have reached firm ground. We simply stop when we are satisfied that the piles are firm enough to carry the structure, at least for the time being.
>
> K.R. Popper (1968)
> *The Logic of Scientific Discovery*, p. 106.

Much of what we know about hemispheric function comes from perceptual studies, particularly from the area of visual perception. In *The Two Sides of Perception*, Richard Ivry and Lynn Robertson use the vast literature on perception and laterality to support the "Double Filtering by Frequency Theory" of hemispheric specialisation which they propose.

In the areas of experimental psychology and visual perception, one of the most frequently asked questions is "What do we see first?" When we are presented with a figure, for example, a letter composed of smaller letters (Figure 6.1a), what do we recognise first? Do we perceive the large letter first (global analysis), then the small letters (local analysis), as we analyse for details? Or is it the reverse, do we first recognise the small letters which form the whole big letter? This question is extremely difficult to test directly in people with intact brains. Accordingly, a number of cognitive psychologists are at odds with each other. Some propose a "down-up" order of processing where the local details are analysed first, others propose "up-down" processing. In both cases serial processing is assumed. That is, one aspect of the figure is assumed to be analysed before the other.

Ivry and Robertson, by necessity, took an indirect approach to the problem of global vs. local features. "What", they asked, "happens to this type of cognitive processing in people who have suffered a brain lesion?" Ivry and Robertson analysed the results of a number of visual perception experiments in which people with left- or right-sided lesions were asked to draw from memory a picture shown to them by the experimenters. The results of their analysis were quite interesting. Individuals with lesions in the left hemisphere could draw the larger, global, aspects of the pictures they had been shown, but were unable to reproduce the finer (local) details. Individuals with lesions in the right hemisphere could reproduce the fine, local, features of the picture, but were unable to organise these local features into a coherent, global image (see Figure 6.2). In the terms of visual perceptionists, the left hemispheres of the experimental subjects were analysing the pictures for high frequency information and the right hemispheres were analysing for low frequency information.

Frequency analysis is an important tool for understanding the workings of the brain. Many parts of the CNS work in a frequency dependent manner. For most people, frequency analysis for auditory stimuli is commonplace. Judgements about the "pitch" of a particular tone are a form of frequency analysis. High frequency sounds, where the sound waves are close together, are perceived as high pitch. Low frequency sounds, where the sound waves are further apart, are perceived as low pitch. A healthy 20 year old is able to hear sounds in a range from 20,000 Hz right down to 20 Hz. As we age, the hearing in the upper frequency range decreases gradually. This age-related decrease is not important for everyday life since speech sounds are in the 600–2000 Hz range (Figure 6.3). Visual information is analysed in exactly the same

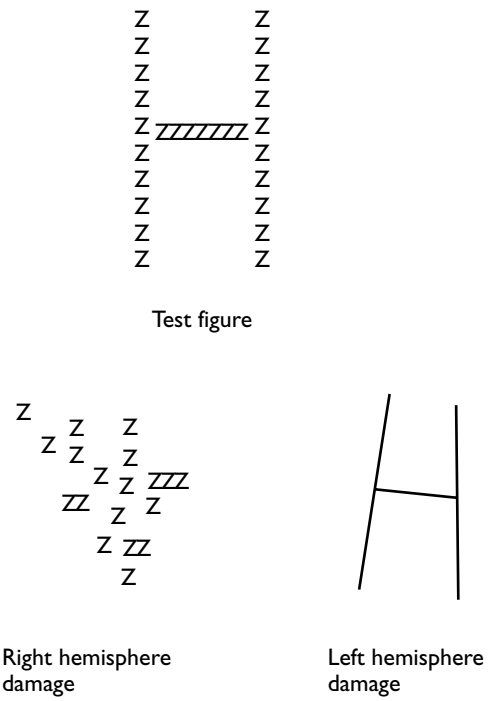

Figure 6.2 Schematic representation of visual processing deficits associated with left and right hemisphere damage. Adapted from Delis *et al.* (1986).

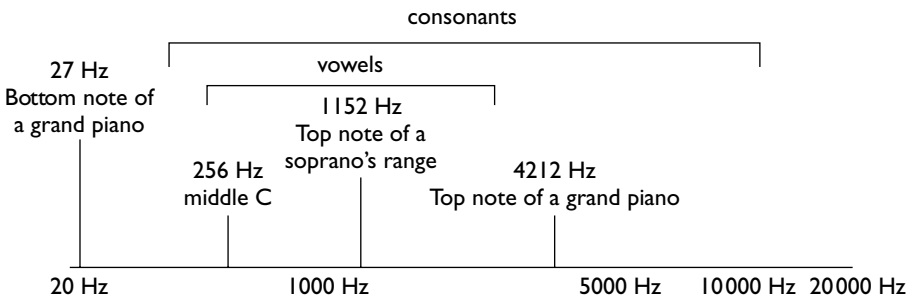

Figure 6.3 Frequency of selected sounds in the range of normal human hearing.

frequency-dependent manner. Large items in the visual field are low frequency stimuli, while the small details which make up the larger items are high frequency stimuli. In visual perception experiments, gratings of high and low frequency (Figure 6.4), without the distractions contained in a picture, are used to study the responses of the visual system.

Having determined that the left and right hemispheres seemed to be analysing visual information for high and low frequency components, respectively, Ivry and Robertson turned to the literature on auditory perception. If one of the main features of

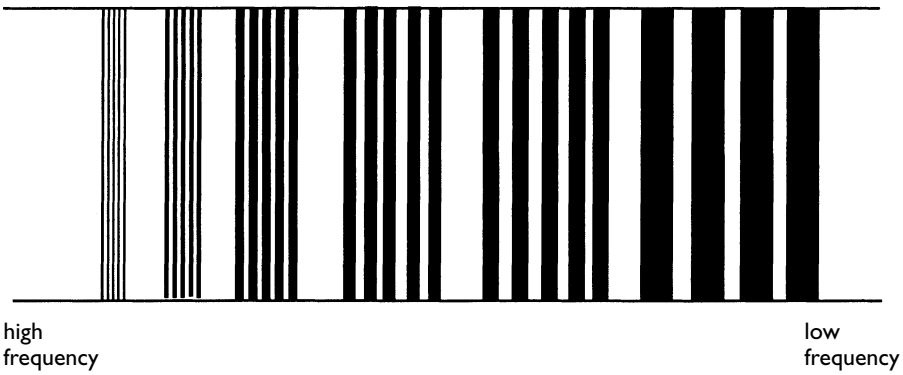

Figure 6.4 Examples of lines of relatively high and low spatial frequency.

hemispheric processing was a frequency bias, they reasoned that you might expect such a bias to be observed for other sensory systems. Indeed, from their analysis of the literature, evidence for such a bias in the auditory system emerged. One factor, which complicates frequency analysis by the auditory system, is the sequential nature of auditory stimuli. In the visual system, all of the parts of a picture are presented to the visual system at the same time. Complex auditory stimuli, on the other hand, are presented over time. For example, consider a spoken sentence. Single sounds, the vowels and consonants, are arranged into words, which are arranged to form the sentence. Frequency analysis of the sentence will include the frequencies of the individual sounds (local components) and the prosody or organisation of words (global components). Interestingly, it appears that prosody is analysed by the right hemisphere.

The examples above only touch upon the kind of evidence used by Ivry and Robertson to synthesise the "Double Filtering by Frequency (DFF) Theory". A "bare bones" description of the theory follows. For readers who would like more detail, *The Two Sides of Perception* (1998) is highly recommended.

There are three fundamental tenets of DFF:

1. Visual and auditory stimuli are analysed on the basis of frequency. As discussed above, there is a great deal of experimental evidence to support this.
2. Processing of material is divided between the two hemispheres. Both hemispheres are able to process the full stimulus array, but the results of that processing will be represented differently by each hemisphere. In addition, the two hemispheres will share their processing results via the corpus callosum, making it difficult to distinguish which side is doing which part of the analysis.
3. Selective attention is necessary for the frequency-based analysis to occur (and therefore, for hemispheric differences to become evident). There is evidence that the hemispheric differences do not occur if the individual is not attending to the properties of the particular stimulus.

In terms of describing processing attributes, the right hemisphere processes for and amplifies the topographical properties of the stimulus. In a visual display, this would

include judgements on the distance between two large objects. In auditory terms, the prosody of the sentence. The left hemisphere processes for and magnifies the information on the fine details of the stimulus. It attends to the single letters on a keyboard or the vowels and consonants in speech.

If DDF provides a description of "what" happens, Miller's "Conduction Delay Hypothesis of Cerebral Lateralisation" (CDH) tries to explain "how" it happens. It is clear that the two hemispheres process information differently and that they seem to be particularly adept at certain kinds of tasks. The question Miller tackles is, "What neurobiological processes underlie these observed differences?" For example, when a person listens to and comprehends spoken language, the information to be processed arrives not in a single presentation, as in a visual array, but as a series of sounds in a particular temporal sequence. The temporal nature of the speech requires a processing system with built-in delays, so that the first sound is related to the last sound in the sequence. The size of the necessary delays is tiny, in the range of 50 to 200 msec. However, in terms of synaptic transmission alone, that is a very long time to delay a signal. So the question is, how can this temporal analysis occur within the constraints of synaptic transmission? More specifically, what is different about the left and the right hemispheres that gives them their respective advantages in signal processing?

Drawing upon a wide range of experimental evidence from neuroanatomy, neurophysiology and experimental psychology, Miller proposes a functional/structural basis for hemispheric lateralisation. As in the case of the DDF, what follows is a "bare bones" summary and for the interested reader, *Axonal Conduction Time and Human Cerebral Laterality: A Psychobiological Theory* (1996) is recommended reading.

There are two ways that delays of 50 to 200 msec can be introduced into a neural pathway. First, by summing the delays produced by a large number of individual synapses. The incoming signal would have to be routed along multisynaptic pathways. At each synapse a degree of variability could be introduced which, when summed across a large number of synapses, would probably result in an inconsistent signal representation. Second, the delay could be introduced by slowing the conduction velocity along the axons themselves. If the signals were carried by small, unmyelinated axons, an appropriate delay could be introduced. In addition, the delay would be consistent across time. The conduction velocity of axons does not change under normal circumstances, and inconsistencies introduced by synaptic transmission would be minimised. Within their defined range, speech patterns should be consistent, as indeed they are. It is this second idea which underlies the CDH.

Stated simply, the CDH proposes that the differences in processing capabilities between the left and the right hemispheres are due to different proportions of "fast" and "slow" conducting axons. The nice thing about the CDH is that it generates a number of anatomical predictions that can be tested empirically.

Some of the major anatomical predictions are:

1. The volume ratio of white to grey matter should be lower on the left than on the right. *There is a limited amount of data and the results are inconclusive.*
2. Cortical cell density should be greater on the left than on the right. *An early 20th century post-mortem study offers some support.*

3. The overall volume of the right hemisphere should be greater than the overall volume of the left. *There is evidence to support this prediction.* Miller concludes that the weight of evidence suggests larger frontal and temporal lobes on the right, and larger occipital lobes on the left (at least for right-handed individuals).
4. The concentration of markers for myelin or myelin basic protein should be higher on the right than on the left. *There is no data at present on this.*

The support for these predictions is currently quite limited but, nevertheless, convincing in its consistency. In most cases, the number of studies is small. In addition, a variety of methods have been used, making interpretation difficult and comparison between the studies almost impossible. So, for example, for prediction 1 there are 10 studies, conducted between 1914 and 1991 (Miller, Table 3, p. 34). The methods used in the different studies include volume estimation from cortical surface area, CT density, clearance of Xenon, and histological sectioning of post-mortem tissue. In addition, an equal number of the studies report statistically significant and non-significant results, respectively.

Neuroscience is one of the most rapidly expanding areas in the biological sciences. Hopefully, within the next few years, experiments will be performed that will provide evidence to test Miller's predictions. Better yet, perhaps someone will set out to directly test the Conduction Delay Hypothesis. Either way, in the spirit of classic scientific theorising, the predictions are there to be tested.

Laterality and language processing

'Twas brillig, and the slithy toves
Did gyre and gimble in the wabe;
All mimsy were the borogoves
And the mome raths outgrabe.

"Beware the Jabberwock, my son!
The jaws that bite, the claws that catch!
Beware the Jubjub bird, and shun
The frumious Bandersnatch!"

He took his vorpal sword in hand:
Long time the manxome foe he sought-
So rested he by the Tumtum tree,
And stood awhile in thought.

And as in uffish thought he stood,
The Jabberwock, with eyes of flame,
Came whiffling through the tulgey wood,
And burbled as it came!

One, two! One, two! And through and through
The vorpal blade went snicker-snack!
He left it dead, and with its head
He went galumphing back.

"And hast thou slain the Jabberwock?
Come to my arms, my beamish boy!
O frabjous day! Callooh! Callay!"
He chortled in his joy.

'Twas brillig, and the slithy toves
Did gyre and gimble in the wabe;
All mimsy were the borogoves,
And the mome raths outgrabe.

Lewis Carroll, The Jabberwocky.
In Silver, K. (Ed.) *Selected Poems*,
(1995) pp. 27–28.

Understanding and appreciation of language requires a number of different kinds of analysis. The temporal analysis of the auditory stimulus is followed by analysis of word patterns and speech rhythms, and, of course, meaning. The evidence is overwhelming that the two hemispheres make different contributions to this process. It is also clear that the processing differs between females and males.

By far the greatest volume of recent research on laterality is devoted to language. Interestingly, some of the research involves people yet to complete the language acquisition process. One particularly interesting study involved recording auditory-evoked responses (AERs) from 16 month old infants as they listened to familiar and unfamiliar words (Molfese, 1990). Eighteen infants took part in the study, nine females and nine males. The hand preferences of the parents were matched between the two groups. AERs were recorded from the infants while they listened to a tape-recorded voice reading a list of words, a repetition of two words, one word familiar to the infant and one word unfamiliar. In order to make the words as consistent as possible, the spoken words (female voice) were recorded and then edited to a 474 msec duration. A different tape was constructed for each infant, based upon interviews with the parents when words known and not known to the child were identified. During the testing sessions the parents were asked to observe their child's reaction to the word to confirm its "known" status. In addition, 2 observers also rated the child's reaction to each word. Analysis of the AERs showed that the response to unknown words was a larger amplitude negative peak than the response to known words, occurring at about 180 msec after the onset of the word. In the female infants this differential response was recorded at the left temporal electrode. In the male infants, however, differences for known and unknown words were recorded at the left frontal, left temporal and right frontal electrodes. The meaning of the female–male response differences is not clear. The author suggests that the responses of the female infants may reflect either greater functional maturity or "a more lateralised system" (Molfese, 1990, p. 359). This is interesting in view of the adult evidence to follow.

In 1995, clear sex differences in language processing were first demonstrated by Shaywitz *et al.*, using MRI (Shaywitz *et al.*, 1995; Pugh *et al.*, 1996). Using echoplanar functional MRI, the brain activity of 19 females (mean age 24.0 years) and 19 males (28.5 years) was measured during four different language-related tasks. All of the participants were right-handed and all had reached the postgraduate level in

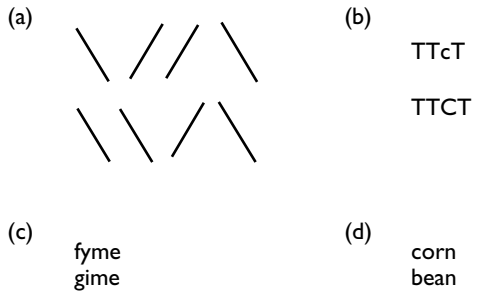

Figure 6.5 Schematic representation of the types of stimuli used in the "same–different" matching task by Shaywitz *et al.* (a) line recognition, (b) orthographic category, (c) phonological category, (d) semantic category.

education. The tasks all employed a visual display and the subjects were asked to make "same" or "different" judgements which were recorded by pressing a bulb to signal "same".

The first task required the subjects to view a display of 2 sets of 4 lines with different left-right tilts and to determine if the upper lines matched the lower lines in angle of tilt (Figure 6.5a). This task provided the control condition for the visual component of the following 3 tasks. The second test, the orthographic condition, required a same–different judgement for a series of consonants in upper- and lower-case letters (Figure 6.5b). In the third test, the phonological condition, the task was to decide whether two nonsense words rhymed (Figure 6.5c). In the final condition, the semantic category, subjects were asked to judge whether two real words came from the same semantic category (see Figure 6.5d). For analysis of the results, the first category, line orientation, was used to establish the baseline activity associated with the processing of the visual arrays.

Activity in 7 different regions of interest (abbreviated, not surprisingly, "ROI") in each hemisphere was analysed (see Figure 6.6). The accuracy in completing all 4 tasks was equal and high for both sexes, an average of 95% correct responses. An analysis of activity from all ROIs (total area analysis) showed that while overall activity increased significantly for males between the phonological condition and the semantic condition, a similar increase was not observed in the female subjects. In addition, left and right hemisphere activation was equal in females, but left hemisphere activity was greater than right hemisphere activity in males. Region-by-region analysis showed that in the occipital areas males showed increased activation for real words, compared to non-words; however, females did not exhibit this increase. In the frontal regions, activation was bilaterally distributed in females but was lateralised to the left in males. The sex differences were most apparent in the inferior frontal gyrus where greater than 50% of the females showed bilateral activation. No males showed bilateral activation in this region. A similar pattern of activation was also seen in the orbital gyrus; this region shows the greatest activation related to phonological processing. In the temporal regions there was a significant increase in activation associated with semantic processing relative to the rhyme task in males but not females. Based upon their results, the authors suggest that processing of reading may be divided into 4 anatomically dis-

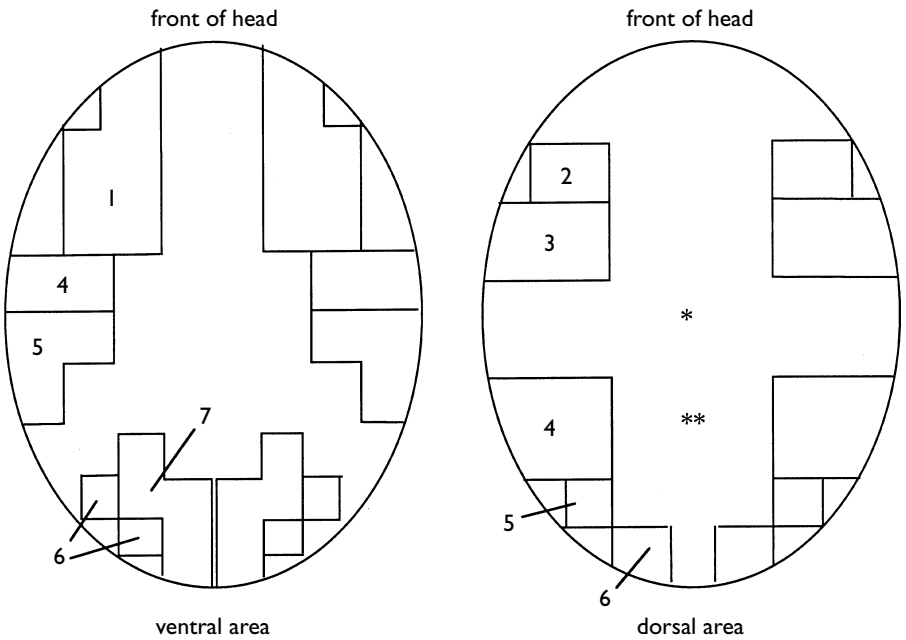

Figure 6.6 Schematic representation of the areas of interest of Shaywitz *et al.* (1995) and Pugh *et al.* (1996). 1. lateral orbital gyrus; 2. prefrontal dorsolateral area; 3. inferior frontal gyrus; 4. superior temporal gyrus; 5. middle temporal gyrus; 6. lateral extrastriate area; 7. medial striate area. Adapted from Pugh *et al.* (1996). For comparison with Frost *et al.* (1999), * represents thalamocapsular area, ** represents retrosplenial area.

tinct components: 1) visual processing, striate and extrastriate occipital areas; 2) orthographic representation, lateral and medial extrastriate areas; 3) phonological representations, inferior frontal gyrus and temporal lobe (left hemisphere in males, bilaterally in females); 4) lexical and semantic processing, middle and superior temporal gyri.

By contrast, a study published in 1999 by Frost *et al.* reported that language-related activity was clearly increased in the left hemisphere for both females and males during a language comprehension task. In this study, the subjects were 100 right handed, native English speakers (50 female, 50 male), who were matched for age and education. The mean ages of the subjects were 24 years (males) and 22 years (females). A "semantic monitoring" experimental task required the subjects to listen to words naming animals (e.g. rabbit) and to respond, by pressing a button, only to those animals which were "found in the United States" and "used by humans". A "tone-monitoring" task, used to establish baseline activity for auditory stimulation, required the subjects to listen to a series of tones. The series could contain 3 to 7 tones of high or low frequency. The subjects were instructed to respond only to a tone series which contained 2 high tones. The number of correct responses on both the tone-monitoring task and the semantic-monitoring task was the same for females and males. On the semantic task females scored a mean of 90.4% correct responses, while males scored

90.8%. On the tone task the female and male correct scores were 97.1% and 97.6%, respectively. Analysis of the activation patterns also showed little difference between females and males. The areas of greatest activation were in the left prefrontal, temporal, angular, retrosplenial and thalamocapsular areas (see Figure 5.6). The only region showing greater right-sided activity was the cerebellum. Frost *et al.* concluded that it is questionable whether large sex differences in processing patterns exist.

In comparing the two studies, one of the most obvious differences is the difficulty of the linguistic aspects of the task. Pugh *et al.* required their subjects to perform tasks of increasing linguistic difficulty. The third condition in their study required the subjects to imagine the pronunciation of the nonsense words in order to determine if the words would rhyme when spoken. The fourth condition, the semantic category, required word recognition, then word comparison for meaning. Finally, the word categories had to be determined and the two words compared. By contrast, in the Frost *et al.* study, many of the linguistic characteristics were by-passed. The subjects knew the words would be animal names. The analysis required complex processing for categories and knowledge including subjects such as geography and animal husbandry. A much more extensive memory processing was required for this task. Given the differences in the experimental designs of the two experiments, a direct comparison of the results is not possible.

Jaeger *et al.* (1998) have suggested that it is the degree of difficulty of linguistic tasks that determines whether or not sex differences appear. They suggest that at least some of the contradictions in the literature may be due to differences in the difficulty of the experimental tasks. In order to examine this possibility, they used PET to measure cerebral blood flow (CBF) while their subjects completed a series of language tasks. The subjects were 8 females and 9 males, all right-handed, native English speakers. In the baseline conditions, CBF was measured while the subjects fixated a visual target, "resting state". There were 5 tasks for the subjects to perform: 1) read aloud a series of verbs; 2) read aloud a series of nonsense verbs (e.g. jelt, brep); 3) view then speak the past tense of regular verbs (e.g. jump, dance); 4) view then speak the past tense of irregular verbs (e.g. fall, build); and 5) view then speak the past tense of nonsense verbs not previously viewed. When the results were analysed, it was clear that both reaction time and accuracy were equal for the males and females. However, differences in the pattern of CBF emerged which were dependent upon the task being performed. There was an overall increase in CBF in the bilateral occipital and motor areas, and the cerebellum. There was also an overall increase in the left frontal areas. These increases were the same in the females and the males. On tasks 1 and 2 (the easy tasks), there was a bilateral increase in the frontal and temporal areas which was equal in females and males. In the more difficult tasks (3, 4 and 5), the increased blood flow became lateralised to the left in males, but remained bilateral in females. When the CBF patterns of the two groups were compared to their respective baseline conditions, other differences became apparent. In all conditions, there was a greater increase in CBF in females bilaterally in the inferior occipital cortex and the cerebellum. On the tasks requiring past tense generation, females also showed a significantly greater increase in the right anterior temporal and right posterior frontal cortices. These areas overlap the areas where Shaywitz *et al.* found greater activation in females during the phonological tasks. These results support the authors' suggestion that it is

the difficulty of the linguistic task which distinguishes the female and male response patterns.

Anatomical differences have also been correlated with sex differences in cognitive performance. Gur *et al.* (1999) used MRI to study sex differences in the volume of grey and white matter of 80 right-handed people, 40 females and 40 males, aged between 18 and 45 years. The 2 groups were well matched on factors such as age, education and IQ. In addition to the measures of tissue volume, the subjects were also tested using 2 measures of language ability and two tests of spatial ability. The results of this study are complicated. Readers who are interested in the details of the analysis should really consult the original paper. Briefly, females showed a higher percentage of grey matter than males, while males showed a greater percentage of white matter and CSF. But while the distribution of grey and white matter was symmetrical in females, in males the percentage of grey matter was greater in the left hemisphere, white matter was symmetrical and CSF was greater on the right. The test of cognitive function showed that overall, females and males performed equally well (the Global Score). However, when the tasks were analysed by verbal and spatial subcategories, females performed better on the language tasks than the spatial tasks, while males performed better on the spatial tasks. In both females and males, the Global Score was correlated with brain volume. When analysed separately, verbal performance was correlated with cranial volume in females. Performance on the spatial tasks was correlated with cranial volume for both females and males.

This study is an interesting return to the old question of brain size differences between females and males. Although the total brain volume in this study was smaller for females, the authors point out that the larger proportion of grey matter accompanied by a smaller proportion of white matter probably equalises the differences. There is a larger percentage of tissue available for processing (greater percentage of grey matter) but shorter distances between brain regions (shorter axonal length, i.e. white matter, required).

A functional/anatomical study of magnetoencephalographic auditory evoked fields in response to an unattended auditory stimulus (pips) has reported female–male differences in the localisation of the source of the M100 wave. Seventeen females and males (1 left-hander in each group) were tested. The source of the M100 wave was in the superior temporal gyri, located along the gyri of the left hemisphere in the female and male subjects. In the right hemisphere, the M100 source was in the same location in females but was found to be significantly further forward in males (Reite *et al.*, 1995)

Because the hand preference of the subject is central to the question of laterality, many studies limit their experimental subjects to right-handed (or less frequently, left-handed) individuals. An interesting exception is a study by Okada *et al.* (1993), who used a measure of brain oxygenation to look for interactions between handedness and sex. Near-infrared (NIR) spectrophotometry was used to measure changes in blood oxygenation in the forebrains of 72 subjects while they performed a mirror drawing task. In this task, the subjects must trace a figure, in this case a star, which they can see only indirectly via the reflection in a mirror (see Figure 6.7). The task is to trace the star as fast and accurately as possible. The 72 experimental subjects were subdivided into 4 groups: right-handed males ($n = 22$); left-(mixed) handed males ($n = 20$); right-handed females ($n = 16$); and left-(mixed) handed females ($n = 14$). The left-(mixed)

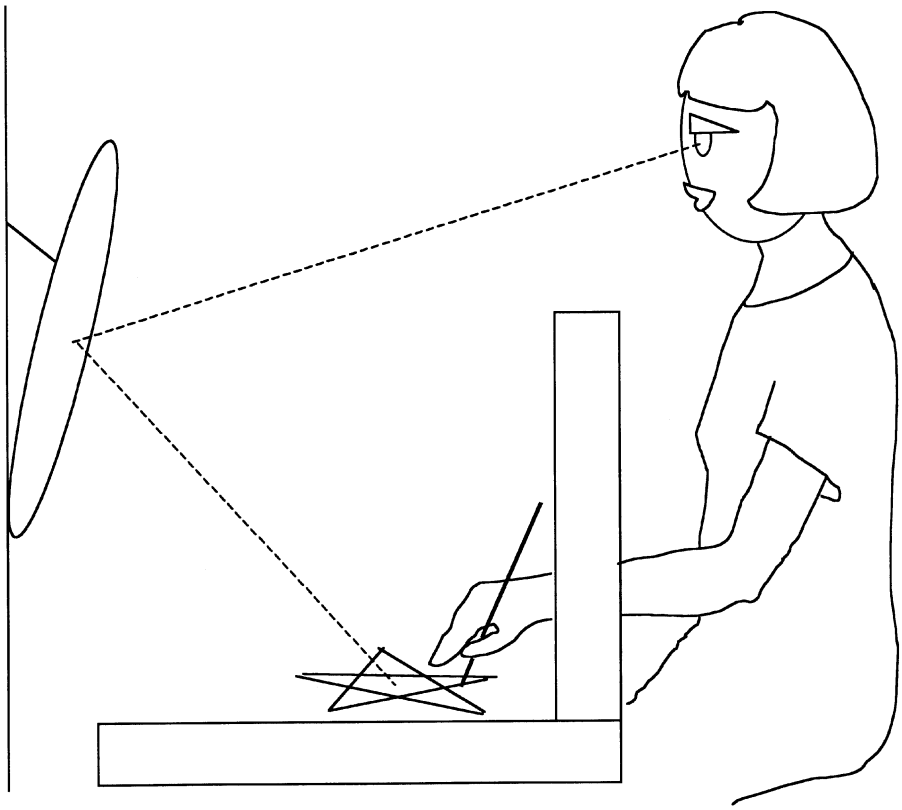

Figure 6.7 Schematic representation of the mirror drawing task.

classification is used because, as the authors point out, people in the age group of their subjects would have grown up during a time when left-handed children were trained to write and use chopsticks (this is a Japanese study) with their right hands. Three different patterns of blood oxygenation were observed. The "dominant hemisphere" response pattern was associated with an increase in blood volume in the dominant (as determined by handedness) hemisphere. For example, a right-handed subject showed an increase in the left hemisphere. A "bilateral" response pattern was associated with a symmetrical increase in the two hemispheres. Finally, in two subjects, one male and one female, no change in blood flow was observed during the task, a "no response" pattern. The results are summarised in Table 6.2. From the results table, a different response pattern between females and males is easy to see. The majority of males in both groups exhibited a dominant hemisphere response pattern while the majority of females exhibited a bilateral response pattern. In fact, no left-handed female exhibited a dominant hemisphere pattern. In this respect, the greatest sex differences were found in the left-handed group. The results of this study suggest that for the kind of visual and motor processing required for the mirror drawing task, females use bilateral processing while males process primarily with their dominant hemisphere.

Table 6.2 Results of the mirror drawing task**

Hand preference	*Dominant hemisphere response pattern*		*Bilateral response pattern*		*Total*
	n	%	*n*	%	
Right-handed:					
male	13	59	8	36	21
female	4	25	11	69	15
total	17	45	19	50	36*
Left-handed:					
male	15	75	5	25	20
female	0	0	14	100	14
total	15	44	19	56	34

* 1 female and 1 male showed no response pattern (not shown in table).
** Adapted from Okada *et al.* (1993).

Consider for a moment what these results would have looked like if this had been an experiment with only right-handed subjects. The results would have indicated left hemisphere processing in males (13/22 or 59%) and predominantly bilateral processing in females (11/16 or 69%). It is results such as these which illustrate the importance of experimental design.

Emotion and laterality

Light up your face with gladness
Hide every trace of sadness
Although a tear may be ever so near
That's the time you must keep tryin'
Smile, what's the use of cryin'?
You'll find that life is still worthwhile,
If you just smile.

C. Chaplin, J. Turner, G. Parsons,
Smile. Copyright: United Artists.

The laterality studies discussed so far have dealt with processing of well-defined stimuli such as lines, tones and words. Much more difficult to define are stimuli intended to carry an "emotional" component. The human face is often the stimulus selected to portray emotional content. In a study published in 1980, Ladavas *et al.* used photographs of actors' faces, expressing 6 different emotions, to measure the reaction time to discriminate different emotions.

This study was conducted at a time when computerised experiments were rare. The methods, by today's standards, seem primitive. The subjects were seated in front of a translucent screen and slides of the faces showing different expressions (happiness, sadness, surprise, fear, disgust, anger) were projected onto the back of the screen for a

period of 150 msec. The subjects were required to fixate a central point on the screen. The photograph was projected on either the left or right portion of the screen. The photo on the right side of the screen was assumed to stimulate the left hemisphere, the left image was assumed to stimulate the right hemisphere. In each trial a number of photos were presented 7 seconds apart and the subject was instructed to press a response key as quickly as possible only when the target emotion for the trial (e.g. disgust) appeared. The reaction time (RT), the amount of time taken to press the button after the picture appeared, and the number of correct responses, were recorded.

The responses of 24 right-handed subjects, 12 females and 12 males, were measured. Analysis of the results showed that, overall, RTs were faster for faces presented in the left visual field and that RTs in females were faster than RTs in males. The left–right difference in RTs was greater in females than in males. The accuracy in identification of the facial expression increased from trial 1 to trial 3, a good example of the practice effect. From this study, the authors concluded that the right hemisphere in females is superior to the left in discriminating emotional stimuli.

In 1983, a similar study was conducted using a larger number of subjects, 45 females and 45 males, divided into subgroups according to handedness (Natale *et al.*, 1983). There were two categories of left handers, those with an inverted writing posture (N = 15 F, 15 M) and non-inverted writing posture (n = 15 F, 15 M). A tachistoscope was used to view the individual stimulus cards. The duration of viewing time was adjusted according to individual thresholds for viewing, with a mean viewing time of 117.5 msec. The facial expressions portrayed were the same as the previous experiment. The response made by the subjects was different. In this case, the subjects were asked to adjust a lever to indicate how "sad" (1 = "very sad") or "happy" (10 = "very happy") the faces were. The female subjects gave a consistently "sadder" rating. When this result was analysed further, it was found that the difference was due to the tendency of the female subjects to give a lower rating to the pictures displaying sadness, anger, disgust and fear. There was no difference between females and males in their responses to the positive emotions. When the data were analysed for handedness, the ratings of the left inverters were higher than the left non-inverters' and right-handers' scores. Interestingly, there was also a visual-field effect with faces presented to the left visual field receiving overall lower ratings. The right-handers had the largest visual field effect, the left inverters had a smaller effect. There was no visual field effect for the left non-inverters. When the visual field effects were further analysed, they were found to apply only to the negative stimuli. From this result the authors concluded that the right hemisphere might be biased towards the emotionally negative aspects of a stimulus.

One hundred and four subjects took part in the second experiment. The groups consisted of right-handed males (n = 22), right-handed females (n = 16), left-handed inverter males (n = 19), left-handed inverter females (n = 8), left-handed non-inverter males (n = 19), and left-handed non-inverter females (n = 18). The stimuli were faces composed of two half-faces showing either happy or sad expressions. The two sides either matched, giving a whole "happy" or "sad" face, or mismatched, with one side "happy" and the other side "sad". The viewing time was much shorter than in the first experiment. The mean viewing time was 63 msec, just long enough to allow recognition that a face had been presented. As in experiment 1, females gave a lower overall

rating than males, but there was no effect of handedness. Females appeared to be better at differentiating between the 3 face types. The left visual field seemed to be better at discriminating "happy" from "sad". Other experimenters have reported similar results (Bibawi *et al.*, 1995).

Laterality, the menstrual cycle and hemispheric advantage

> In a number of modern cameras, a range-finder, or distance meter, is directly connected to the lens so that the lens is focused on the operation of determining the distance of the subject . . . The simplest form of reflecting finder consists essentially of a miniature box camera as shown in Figure 35 with a mirror placed at an angle of 45° behind the biconvex lens to reflect the image to the ground glass screen. The so-called "brilliant" finder is similar except that the ground glass screen is replaced by a second lens which results in a clearer and more brilliant image since the light is not scattered by the ground lens.
>
> In all reflecting finders, the image is erect, but reversed laterally, i.e., from right to left. This is true also of the image seen on the focusing screen of a reflex or twin-lens camera.
>
> Neblette, C.B. (1938)
> *Photography: Its Principles and Practice*, pp. 45–46.

A considerable deficiency in the studies discussed so far is the failure of the experimenters to consider the stage of the menstrual cycle of the female subjects. Weekes *et al.* (1999) directly addressed this problem, in the context of the "dual route" model of hemispheric specialisation. The dual route model suggests that there are two routes for the processing of language, a lexical route attributed to the right hemisphere, and both lexical and non-lexical routes operating in the left hemisphere. According to the model, the lexical route proceeds in stages from letter recognition through to semantic processing to phonological analysis and speech production. The non-lexical route (to which the ability to read and articulate nonsense words is attributed) proceeds from a letter to sound conversion stage through to phonetic construction to the same final speech production stage as the lexical route. To date, there is a body of experimental evidence both supporting and refuting the dual route model. The aim of this study was to try to dissect out individual differences which may have contributed to the contradictions in the experimental literature.

The study was composed of 3 experiments. In all 3 experiments, the subjects were presented with a letter string which was a real word or a nonsense word. The stimulus presentation was lateralised to the left or right hemisphere, or was bilateral. The subject was asked to decide whether or not the stimulus was a real word.

In the first experiment, the subjects were 12 females and 12 males, all right-handed, native English speakers. In the second experiment there was a total of 41 subjects: 14 female, 10 male right-handers; 9 female, 8 male left-handers, all native English speakers. In experiment 3, the subjects were 32 females, 16 midluteal phase and 16 menstrual phase. The subjects' responses were analysed for reaction time and number of correct responses, as well as the interactions of a number of variables including word length, frequency of presentation, word regularity and hemisphere.

The first variable to consider is the frequency of word presentation. Responses to high frequency words were more accurate than responses to low frequency words, with females being more accurate than males. Also, responses to right visual field (RVF) presentations were more accurate than responses to left visual field (LVF) presentations. In males, the RVF advantage was significantly greater than in females. When considering cycle phase and word frequency effects, the menstrual phase group showed a greater RVF advantage for low frequency words due to a significantly poorer performance for low frequency words presented to the LVF. The responses of the midluteal group RVF were equal for high and low frequency words. On word regularity, with bilateral presentations, females were significantly less accurate on irregular words. Males were significantly worse on accurately identifying regular words. Females showed an RVF advantage for regular but not irregular words. Males showed a similar RVF advantage for both categories. In discussing their results, Weekes *et al.* conclude that, at least in their study, the right hemisphere seems to be more sensitive to individual differences, including sex differences. In the present study, the RVF advantage for low frequency words (as a result of poor right hemisphere performance) during the menstrual phase, disappeared with the midluteal oestrogen peak (Figure 6.8). The authors suggest two possibilities to explain this effect: changes in callosal efficacy related to low oestrogen; or a reduction in the right hemisphere's processing ability related to low oestrogen. Based on the results of the present study, they favour the latter explanation.

Sanders and Wenmoth (1998) suggest that hemispheric advantage is the crucial factor in interpreting cyclic cognitive changes. Although many inconsistencies appear in the literature, the authors argue that when hemispheric advantage is considered, the inconsistencies are resolved. Specifically, the authors suggest that for tasks which generate a right hemisphere advantage (e.g. non-verbal tasks), the asymmetry is greatest when oestrogen is low. For left hemisphere (e.g. verbal) tasks, the asymmetry should be greatest when oestrogen is high.

Sanders and Wenmoth tested their hypothesis using a verbal task requiring consonant–vowel identification and a non-verbal, music chord-recognition task. Thirty two right-handed women participated in the study. The two tasks were administered during the menstrual phase and mid-luteal phase in a counter-balanced design. The stimuli were delivered to either the right or left ear and the number of correct responses was measured. For the vowel–consonant identification task, accuracy was greater for right ear presentation (left hemisphere) at mid-luteal phase than in the menstrual phase. For the music chord recognition task, accuracy was greatest for left ear presentations (right hemisphere), as would be expected for a non-verbal task, but accuracy was greater in the menstrual phase than during the mid-luteal phase. The changes between the menstrual and mid-luteal phase responses were due to a significant left ear (right hemisphere) performance decrement. There was only a small, non-significant improvement in left hemisphere performance at the same time. Other authors have reported similar results. In a study using a rhyming task and a face recognition task, the accuracy of identification of stimuli presented to the right hemisphere was greater during the menstrual phase for both kinds of stimuli (Mead and Hampson, 1995) (Figure 6.8). Rode *et al.* (1995) reported that there was a LH advantage for a lexical decision task and that it did not change across the menstrual cycle. On a figure

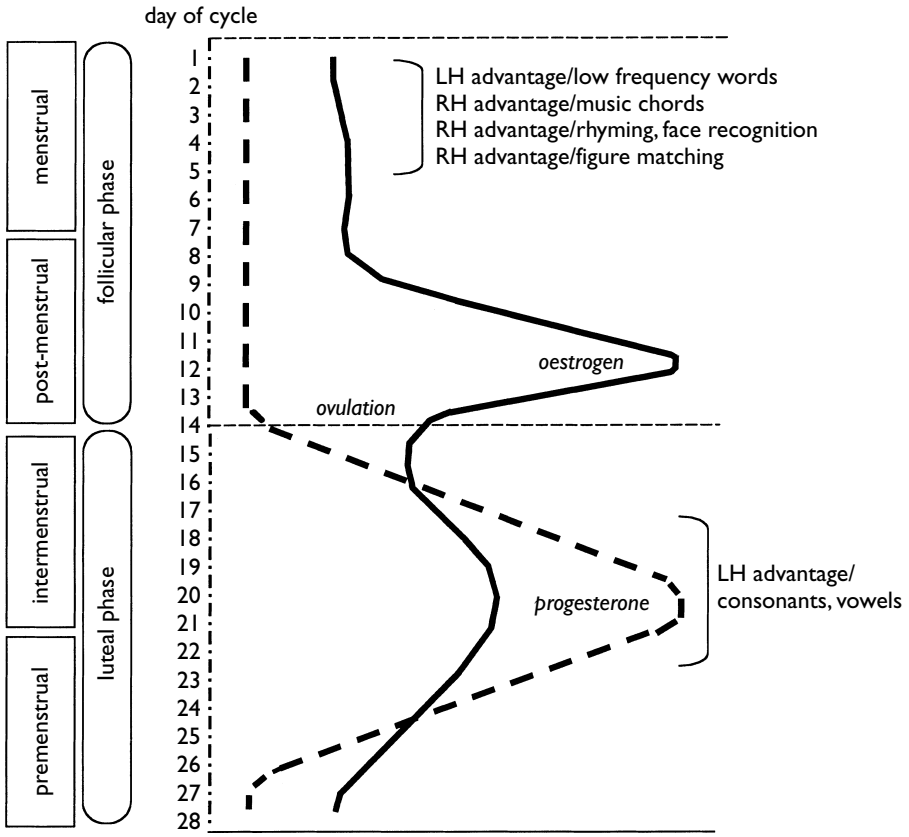

Figure 6.8 Hemispheric advantage and the menstrual cycle.

comparison task, reaction times were fastest and equal for LVF and RVF presentations during the luteal phase. However, during the menstrual phase, RT was greater for presentations to the RVF, indicating a right hemisphere advantage. This result is also generally consistent with the results of the Weekes *et al.* study previously discussed.

> How to weave a palm frond pole cover:
> Prop frond against pole. Starting a foot from the top, pull leaflets one by one around sides of pole and French braid them down. [1] Pull one leaflet from the left. Cross the top leaflet from the right over it. Then cross that with the next new leaflet from the left. Fold the right leaflet(s) to centre. [2] Cover the centre leaflet(s) with the next new leaflet from the right. [3] Fold the left leaflet(s) to centre. [4] Cover with the next new leaflet from the left.
>
> Repeat steps 1 through 4 as long as desired. The weight of the braid will grow with the addition of new leaflets. At the bottom keep braiding and end with an overhand knot.
>
> Arbeit, W. (1985) *What Are Fronds For?*,
> University of Hawaii Press, Honolulu, p. 40.

From the experimental evidence discussed in this chapter it appears that the sex differences reported in laterality studies are real. They are not, however, straightforward. The following points summarise the main points derived from this chapter.

1. The patterns of activity associated with some aspects of language processing are clearly different in females and males. In females the tendency is for bilateral activation with left-lateralised activation the prominent pattern in males.
2. Consideration of handedness is important for sex differences, at least for visuomotor tasks. Processing in males increases in the dominant hemisphere, but females show a bilateral increase, regardless of handedness.
3. The right hemisphere in both males and females appears to be biased towards negative emotional stimuli. The right hemisphere ability to discriminate emotional stimuli also appears to be better in females.
4. Hemispheric advantage is an important factor when considering changes associated with the menstrual cycle. For tasks with a right hemisphere advantage, the left–right asymmetry is greatest when oestrogen is low. For tasks with a left hemisphere advantage, asymmetry is greatest when oestrogen is high. Stated another way, right hemisphere ability is reduced when oestrogen is high (Figure 6.9).

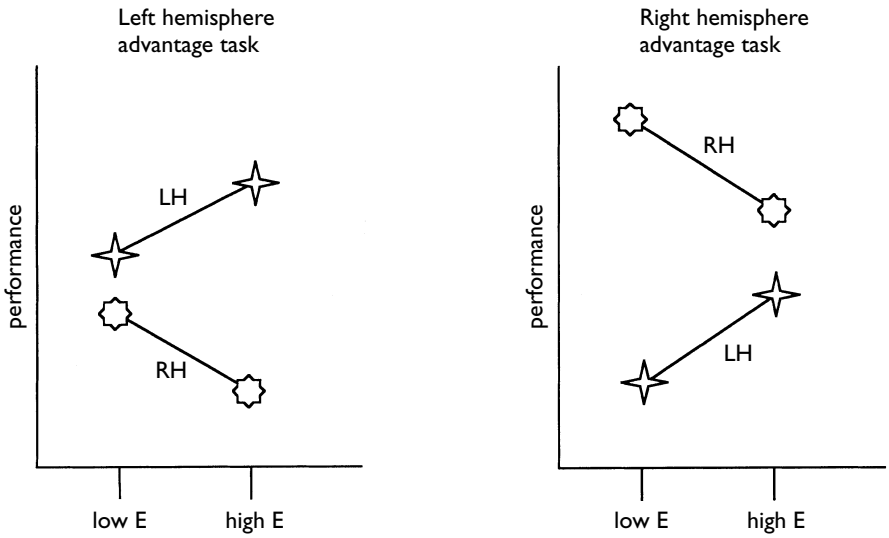

Figure 6.9 Schematic representation of the interaction between oestrogen levels and task-associated hemispheric advantage. ✦ represents left hemisphere task performance; ✹ represents right hemisphere task performance.

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7

Neurology, psychiatry and the female brain

> The idea that *what you are* is not simply a living body (or a living brain) but also a soul or spirit seems to many people to be unscientific, in spite of its ancient tradition. "Souls," they might want to say, "have no place in science and could never fit into the scientific world view. Science teaches us that there are no such things as souls. We don't believe in leprechauns and ghosts any more, thanks to science, and the suspect idea of a soul inhabiting a body – the 'ghost in the machine' – will itself soon give up the ghost." But not all versions of the idea that you are something distinct from your purely physical body are so vulnerable to ridicule and refutation. Some versions, as we shall see, actually flourish in the garden of science.
>
> Hofstadter, D.R., Dennet, D.C. (1981)
> *The Mind's I: Fantasies and Reflections on Self and Soul,*
> Harvester, Sussex, p. 6.

The problem of mind–body dualism is a wonderful playground for philosophers. Because the existence, or non-existence, of a soul cannot be "proven", the exercise becomes one of logical argument. In most circumstances, the problem can remain in the realm of the philosophers. Occasionally, however, the question of mind–body dualism intrudes upon the realm of real-life, sometimes with tragic consequences. A prime example of this intrusion is in the assumptions often made regarding the disciplines of neurology and psychiatry.

The domain of neurology is brain pathology, the study and treatment of brain diseases and injury. The perceived domain of psychiatry, on the other hand, is sometimes a bit unclear. It includes the study and treatment of disrupted or abnormal "mind" or "thought". Mind or thought . . . something removed from or beyond the physical substance of the brain? Here, the majority of biologically-oriented psychiatrists would say,

"Rubbish, it is brain pathology. Disorders with a biological basis, amenable to biologically-based treatments." Unfortunately, however, there are others (including health care professionals) who cling to the "disordered mind" perspective, apparently independently of biology, and once one removes the biology, then the ghosts and witches and prejudices are allowed to creep in. People who would never dream of saying to an insulin-dependent diabetic, "Get a grip, you're just using insulin as a crutch," will quite seriously make that remark to a depressed person who requires antidepressant drugs.

This chapter is divided into two main sections, neurological disorders and psychiatric disorders. The distinction is one of convenience and convention, not biology.

Neurology

> I like to compare the universe that modern science has unveiled to a *matryoshka*–one of those Russian dolls that opens up to reveal a smaller doll inside, which in turn contains a still smaller doll, and the process goes on until you get to the end, the smallest doll in the set.
>
> Trefil, J. (1999)
> *Other Worlds: Images of the Cosmos from Earth and Space*, National Geographic,
> Washington, D.C., p. 13.

It has been understood for a number of years that there are differences between females and males in the prevalence of some neurological disorders. For example, multiple sclerosis (MS) occurs more frequently in females than in males, as do migraine headaches. Amyotrophic lateral sclerosis (ALS) occurs more frequently in males than in pre-menopausal females (4:1), however, the rate of occurrence is equal for males and post-menopausal females (Bromberg, 1999). It has also been demonstrated that for some disorders the severity of the disease state changes with the menstrual cycle.

Multiple sclerosis

MS is often referred to as "the disease of young adults". It seldom occurs before puberty or after the age of 50. Across this 35 year age span the female–male ratio remains the same (approximately 2:1). There is a genetic component, possibly as a predisposing factor, to the development of MS. A study looking at concordance rates for parent–child pairs has reported that out of 75 pairs concordant for MS, the pairings were distributed as follows: mother–daughter ($n = 40$); father–daughter ($n = 21$); mother–son ($n = 13$); father–son ($n = 1$) (Sadovnick *et al.*, 1991). The cause of MS has not been determined. Even after controlling for the normal female/male disease rate, there is still a female bias to the inheritance (Figure 7.1).

MS is a demyelinating disease, generally held to be of autoimmune origin. Some yet to be determined factor causes the activation of T-lymphocytes sensitised to myelin basic protein. The activation of these T-cells (Th1 cells) results in a cascade of cytokines, the chemical messengers involved in immune/inflammatory responses. At the same time, another group of T-cells (Th2 cells) which produce anti-inflammatory

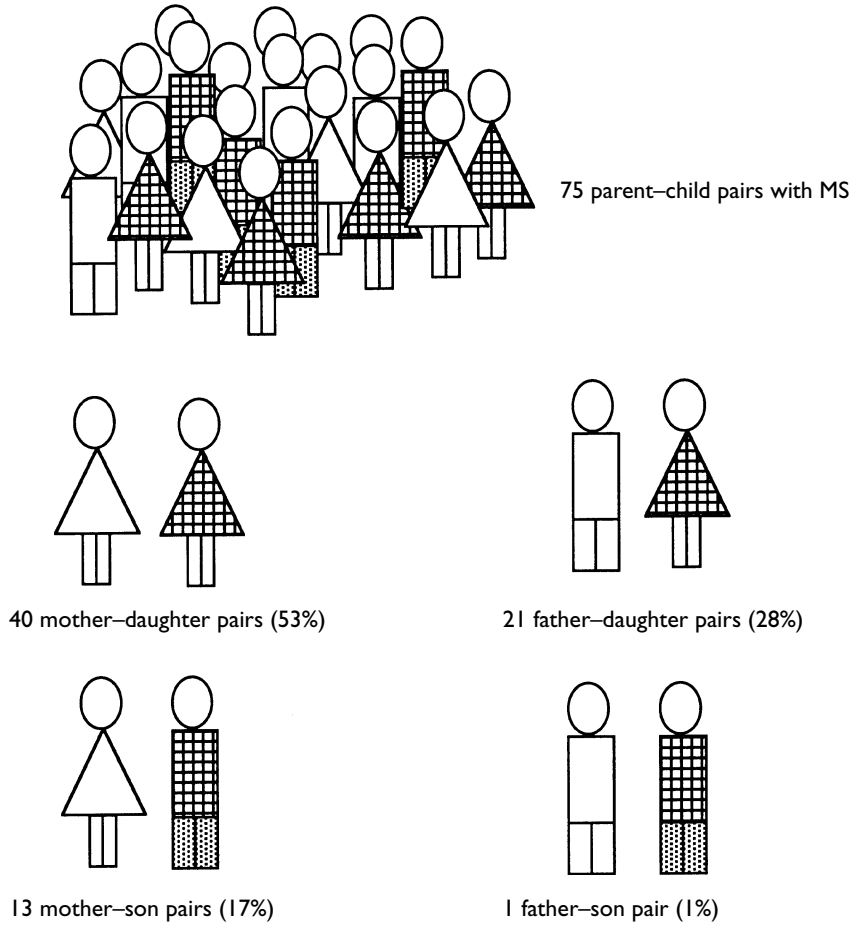

Figure 7.1 Concordance for multiple sclerosis in parent–child pairs. Data from Sadovnick *et al.* (1991).

cytokines, are also activated. Under normal conditions, the Th1 cells perform the necessary immune response, e.g. recognising and destroying bacterial invaders, then Th2 cells stop the inflammatory response and initiate the healing process. It is a finely tuned system of checks and balances with multiple feed-back mechanisms (Figure 7.2).

Once they have been activated, lymphocytes cross the blood brain barrier and ultimately attack the myelin sheaths surrounding the axons. In the CNS myelin is composed of the processes of a particular type of glial cell, oligodendrocytes. In the early stages of the disease, only the cell processes producing the myelin sheath are damaged. The cell body remains intact and able to repair the myelin. Later in the disease, however, the oligodendrocytes begin to die, and at that stage, the lesions become permanent. Demyelination results in a disruption of neural transmission and the conduction of action potentials along the axons is slowed. The symptoms

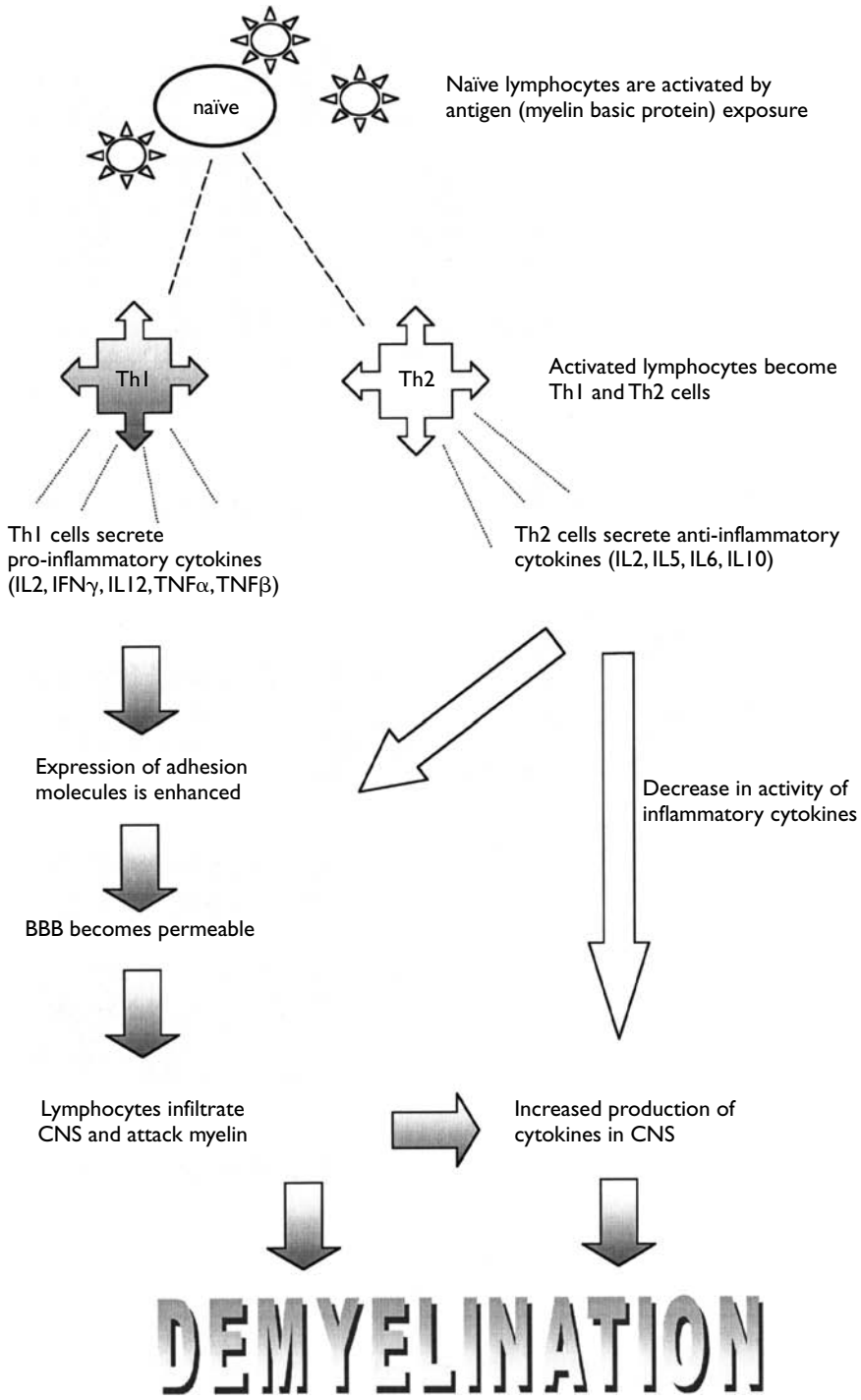

Figure 7.2 The cytokine cascade leading to demyelination.

produced by this slowing of action potentials will depend upon which axons are demyelinated at any particular time. It is this constant state of flux that characterises MS. Symptoms come and go. One symptom, e.g., tingling in the fingers of one hand, will disappear only to be replaced by another, e.g. weakness in one leg. A diagnosis of MS requires that the symptoms be "disseminated in time and space". There are 2 types of MS: relapsing-remitting (RR-MS) and progressive (P-MS). RR-MS is characterised by the appearing and disappearing symptoms as described above.

Experimental allergic encephalomyelitis (EAE) is an animal model of MS which resembles the human disease. It is produced in rats or mice by raising an immune response to myelin basic protein (MBP). An early study looked at the effects of hormones on EAE. Arnason and Richman (1969) administered oral contraceptives to EAE female rats. The authors found that although 8/10 of the control rats developed EAE within 3 weeks of inoculation, only 2/10 rats treated with the oral contraceptive Enovid (oestradiol), and 3/9 rats treated with the oral contraceptive Provest (oestradiol plus progesterone), developed EAE. When the oestradiol and progesterone constituents of Provest were administered separately to additional groups of rats, it was found that only the oestradiol inhibited the development of EAE. The precise form that EAE takes differs between the species used and so, depending upon the question being asked, the choice of species will be crucial. In addition, the effects of hormones show species differences. EAE in the SJL mouse closely resembles human MS, including greater disease susceptibility in females and a relapsing-remitting disease course. Voskuhl *et al.* (1996) used a preparation of myelin basic protein from guinea pig spinal cord to induce MBP activated T-cells in both female and male SJL mice (the donors). Following a 2 week incubation period, the lymph nodes were removed from the inoculated mice. The cells were removed from the lymph nodes, washed and incubated in a MBP culture for 4 days. Finally, the activated T-lymphocytes from the female donors were injected into one group of female and one group of male mice. T-lymphocytes from the male donors were injected into two other groups of female and male mice. The treated mice developed EAE. The female mice developed the disease faster and with greater severity than the male mice. A suspension containing 5×10^7 activated T-cells produced maximum disease severity in females, but did not produce the severe disease state in the male mice. The effect was the same whether the injected cells came from female or male donor mice. This result suggests that, at least in SJL mice with EAE, the females were more vulnerable to autoimmune attack than the males.

At the cellular level, it has been reported that when human helper-T cells are incubated in the presence of progesterone, the cells produce significantly greater amounts of Th2 (anti-inflammatory) cytokines, compared to the same cell line incubated under the same conditions, but without the addition of progesterone (Piccinni *et al.*, 1995). This suggests that the presence of progesterone should be beneficial in MS patients. Another study, this time comparing T-cells from people with MS with T-cells from control subjects, has reported that when the cells were incubated with oestradiol, the secretion of IFN-γ (inflammatory cytokine) was increased (Gilmore *et al.*, 1997). The secretion of TNF-$\alpha\beta$ (inflammatory cytokine) showed a concentration dependent modulation, an increase at low concentrations but a decrease at high concentrations. There was no effect on the secretion of IL-4 (anti-inflammatory cytokine) but, just to make things interesting, the secretion of IL-10 was increased. There was no difference

between the cells obtained from normal donors and from MS patients. From this study it appears that oestradiol can have both inflammatory and anti-inflammatory effects, making predictions very difficult.

At the clinical level, fluctuating hormone levels have been well demonstrated to play a role in MS. For example, a survey of 72 females with MS has reported that of the 60 patients with RR-MS, 23/45 (51%), normally menstruating patients reported the symptoms to be worse during the premenstrual or early menstrual phase; 22/45 (48%) reported no cycle-associated change (Zorgdrager and de Keyser, 1997). Of the patients taking oral contraceptives, 3/15 (20%) with RR-MS reported that their symptoms worsened premenstrually/menstrually, while 12/15 (80%) reported no change. Twelve patients in the study had P-MS and none of these patients reported cycle-associated changes in their disease state (Figure 7.3).

Two recent studies have used MRI to examine changes in MS lesions associated with different phases of the menstrual cycle. Interestingly, the 2 studies report apparently conflicting results. Pozzilli *et al.* (1999) used gadolinium-enhanced MRI to measure the disease activity in 8 female patients (mean age 34 years) with RR-MS (mean disease duration 7 years). A monthly MRI scan was performed on each patient

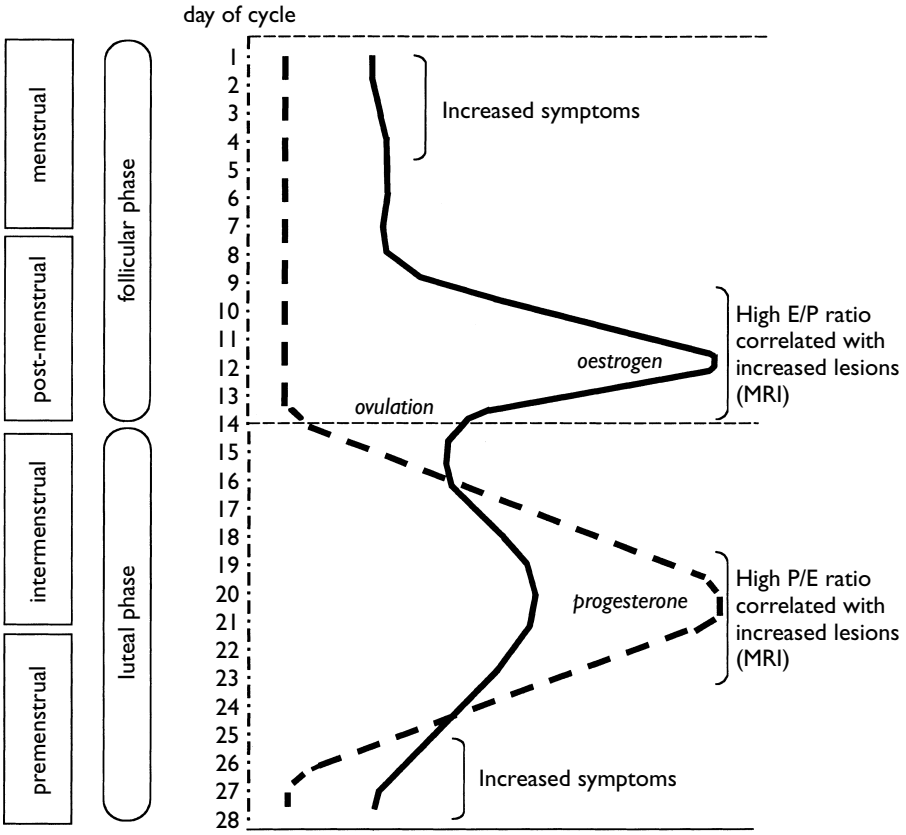

Figure 7.3 MS symptoms and the menstrual cycle.

for 4 consecutive menstrual cycles. For half of the patients the first scan was performed in the follicular phase (days 3–9), with the following scans performed in the luteal phase (days 21–28), follicular phase and luteal phase. For the remaining patients, the pattern of scans began with the first scan in the luteal phase then alternated for the remaining scans. This pattern of scanning resulted in 2 follicular phase scans approximately 2 months apart and 2 luteal phase scans also approximately 2 months apart. On the day of the first scan blood was collected and stored at −20° C; the blood samples were later analysed for follicle stimulating hormone, leutinising hormone, 17β-oestradiol and progesterone. On analysis, progesterone was detectable in the luteal phase only. MRI analysis showed that there was no difference in the frequency or volume of lesions between the follicular and luteal phase. There was, however, a significant positive correlation between the ratio of progesterone to oestradiol and both the number and volume of observed lesions in the luteal phase (Figure 7.3).

Bansil *et al.* (1999) also used gadolinium-enhanced MRI to study menstrual cycle-associated changes in MS patients. Thirty MS patients participated in the study (20 RR-MS, 10 P-MS). Each patient received 1 MRI scan and a blood sample was also taken on the day of the scan. The patients were divided into 3 groups based upon their serum hormone levels at the time of testing: Group 1, low oestradiol, low progesterone (early follicular, n = 14; RR-MS = 10, P-MS = 4); Group 2, high oestradiol, low progesterone (late follicular, n = 6; RR-MS = 2, P-MS = 4); Group 3, high progesterone but variable oestradiol (luteal, n = 10; RR-MS = 6, P-MS = 4). It is interesting that the patients were recruited for testing based on the day of the menstrual cycle, apparently to provide equal group sizes. Analysis of blood hormones, however, revealed that for some patients the hormone levels were not consistent with the reported cycle day. As a result, all of the subjects were grouped by hormone levels on day of testing. Analysis of the MRI scans revealed that there was a significantly higher number of lesions for Group 2, high oestrogen/low progesterone, compared to Group 1. In addition, there were significantly more lesions with a high oestrogen to progesterone ratio (Group 2) compared to a low oestrogen to progesterone ratio (Group 1 plus Group 3) (Figure 7.3). In considering how these results relate to the results of Pozzilli *et al.*, there is a potentially confounding factor which needs to be considered. The Pozzilli study included only patients with RR-MS, Bansil included patients with P-MS. In Group 2 (the smallest sample) there were only 2 RR-MS patients but 4 P-MS patients. No one knows if there are hormonal differences between people with RR-MS and P-MS, however, Zordrager and Keyser reported that P-MS was not associated with cycle-related changes. Because the profile of P-MS is substantially different from RR-MS, the possibility of an experimental confound must be considered.

It has been reported frequently that during pregnancy, when progesterone is continuously present, there are fewer relapses, and disability scores tend to be lower. Birk *et al.* (1990) followed the pregnancies of 8 patients with MS and continued their observations until 6 months postpartum. Six healthy pregnant females, who did not suffer from MS, were also observed for the same period. None of the patients experienced relapses during pregnancy. The number of CD8 suppressor T cells (a measure of immune system activity) was lower during pregnancy and the ratio of CD4 helper to CD8 suppressor T-cells was higher, indicating reduced disease activity. Within 7

weeks of delivery, 6/8 MS patients had experienced at least 1 relapse. This is a rate of relapse of 75% in the post-partum period. A similar result in a study of 269 MS pregnancies has been reported by Confavreux *et al.* (1998). For the patients in this study, the mean relapse rate in the year before pregnancy was 0.7 ± 0.9 relapses per patient. By the third trimester the rate of relapse had dropped to 0.2 ± 1.0 relapses per patient. In the first 3 months after delivery, the relapse rate rose significantly to 1.2 ± 2.0 before returning to the pre-pregnancy baseline. An MRI study of 2 MS patients, one scanned monthly and the other at 3 month intervals, demonstrated a reduction in active lesions, which correlated with the decreased clinical signs of the disease during the second half of the pregnancy (van Walderveen *et al.*, 1994). Finally, it has been reported in a survey of 19 post-menopausal MS patients, that 54% experienced a worsening of their symptoms after menopause while 8% reported that their symptoms had diminished (Smith and Studd, 1992). These same patients reported that their condition either improved (75%) or did not change (25%) with hormone replacement therapy. Also in this study, 9/11 pre-menopausal MS patients reported that their symptoms were worse pre-menstrually and 2/11 reported their symptoms improved at that time (Figure 7.4).

The results of the experiments discussed in this section are summarised in Table 7.1. Examination of the table reveals nothing but 2 columns of apparently contradictory results, at least in terms of the absolute values of oestrogen and progesterone. However, after close study of Figure 7.3, a possible pattern begins to emerge. Perhaps it is not only the absolute values of the 2 hormones that are important, but also the changes in hormone levels, particularly oestrogen levels. During the luteal phase and particularly pre-menstrually, the levels of both progesterone and oestrogen are fluctuating rapidly. During the menstrual phase there is a period of stability, then oestrogen begins to rise rapidly to its pre-ovulatory peak and then plummet a few days later. Pozzilli *et al.* tested their patients between days 3 to 9 (follicular) and days 21–28. If the patients were tested earlier in the follicular phase (the oestrogen level does not begin to rise until day 8), when there had been 5 or 6 days of relative hormonal stability, the symptoms might be expected to be less severe than on days 21 to 28 when both progesterone and oestrogen levels were falling. Bansil *et al.* tested their

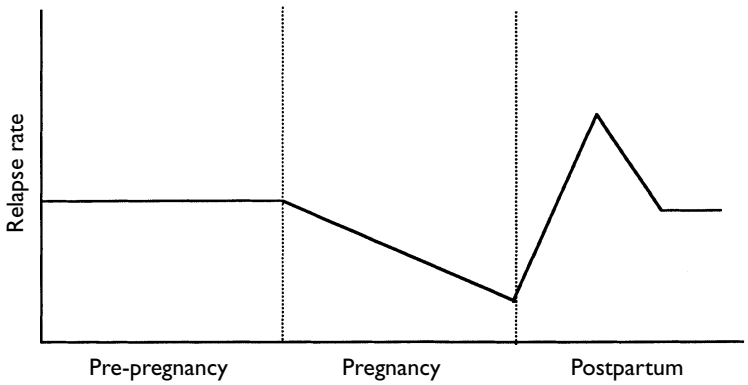

Figure 7.4 MS symptom relapse rate associated with pregnancy and childbirth.

Table 7.1 Summary of oestrogen and progesterone effects on MS

Variable	*Oestrogen*		*Progesterone*	
EAE in rats	beneficial		no effect	
T-cells *in vitro*	mixed		beneficial	
pregnancy			beneficial	
Menstrual cycle studies				
MRI/RR (8)			detrimental	
Pozzilli *et al.*				
MRI/RR (20) & P (10)	detrimental			
Bansil *et al.*				
	Day 1–5	*Day 6–14*	*Day 15–21*	*Day 22–28*
Self-report/RR (23/45)	worse at start			worse 26–28
Self-report/P (12/12)	no change	no change	no change	no change
Self-report (9/11)				worse
Self-report (2/11)				better

subjects on days 1–3 (Group 1), 14–16 (Group 2) and 21–23 (Group 3) and then adjusted their groups according to serum hormone levels. Between days 14 to 16, just after the oestrogen peak, when they reported the greatest number of lesions, oestrogen levels dropped rapidly. Between days 21 to 23, progesterone was dropping sharply and oestrogen was decreasing slowly. Relatively speaking, Group 2 were in the most unstable period.

Epilepsy

Epilepsy is not a single disorder but is, in fact, a cluster of disorders characterised by abnormal and excessive (epileptiform) activity in the brain, consisting of synchronised burst firing of populations of neurones. While the defining feature of epilepsy is this epileptiform activity, as diagnosed using EEG, the clinical signs of a seizure can range from the gentle twitching of a single finger (simple partial seizures) to full blown generalised seizures with loss of consciousness (generalised tonic-clonic seizures). The incidence of epilepsy is usually reported to be the same for females and males. However, sex differences in the expression of epilepsy have long been recognised and the hormonal basis of these differences is also understood. It is estimated that between 12% and 78% (depending upon the criteria applied) of females with epilepsy experience changes in the severity or frequency of seizures associated with the menstrual cycle. There is even a name for seizures which occur primarily or with increased frequency during a particular phase of the menstrual cycle: catamenial epilepsy (Zahn, 1999).

Although epileptiform activity can occur in any area of the brain, one of the regions most often affected is the hippocampus. Temporal lobe epilepsy (TLE, partial complex seizures) is a common form of the disease, and in TLE the locus of the epileptiform activity is often in the hippocampus. It has been demonstrated that a distinctive pattern

of cell loss in the hippocampus (mesiotemporal sclerosis) is associated with TLE (Woolley and Schwartzkroin, 1998). Oestradiol has been demonstrated to induce synaptic plasticity in the hippocampus by promoting the formation of new synapses. Significantly, the receptors in these newly induced synapses are primarily the NMDA subtype of the glutamate receptor, the receptor subtype whose overactivation is associated with hyper-excitability and cell death.

The kindling model of epilepsy uses electrical or chemical stimulation of an area of the limbic system, e.g. the amygdala, to produce epileptiform activity in an animal (e.g. rat). To deliver the stimulation, electrodes (or a cannula, in the case of chemicals) need to be positioned in the target brain region, on one or both sides of the brain, depending upon the experimental question. In addition to delivering the stimulus, electrodes are often used to record the brain activity resulting from the stimulation. In the early stages of the kindling, the stimulation will produce a short burst of neuronal activity (the after-discharge (AD)). With repeated stimulation the AD becomes prolonged and may spread to neighbouring brain regions. In the most extreme case, the epileptiform activity may spread to the limbic structures on the opposite side of the brain; hence the term "kindling" (Figure 7.5). Ultimately the rats exhibit generalised

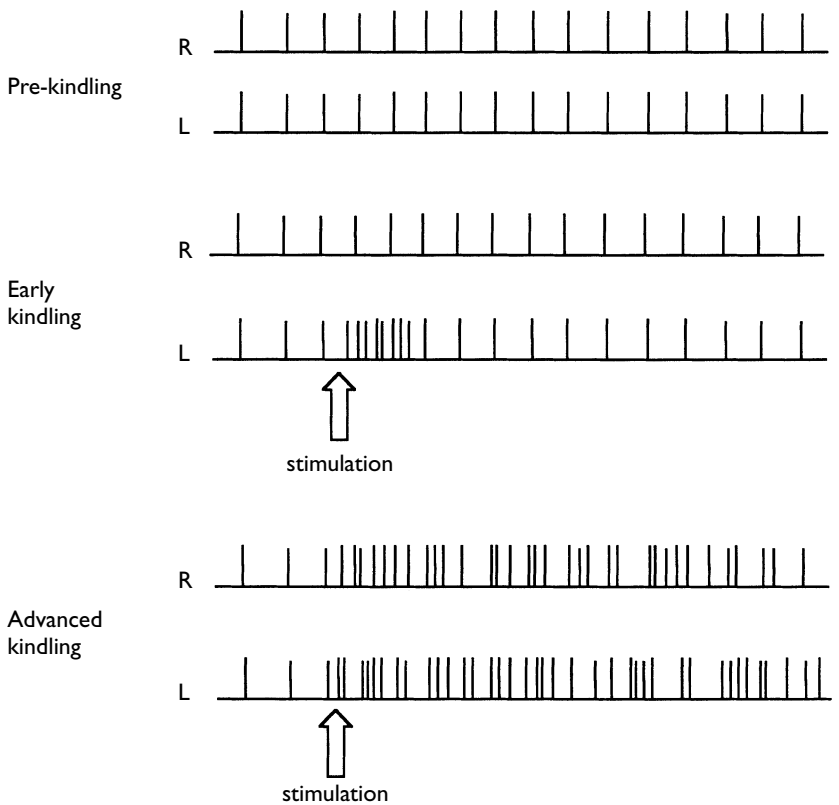

Figure 7.5 Schematic representation of kindling in the limbic system. Each vertical line represents an action potential of an amygdala neurone.

tonic-clonic seizures. Treatment of rats with oestradiol has been demonstrated to potentiate the kindling process by reducing the number of stimulations required to produce generalised seizures (Wooley and Schwartzkroin, 1998). In addition, it has been demonstrated that when oestradiol binds to the steroid binding site on the $GABA_A$ receptor, it reduces the chloride influx that normally occurs when GABA binds to the receptor, resulting in a decrease in the inhibitory effect of GABA. When progesterone binds to the steroid binding site on the $GABA_A$ receptor, there is an increase in the chloride influx associated with GABA binding and, therefore, an increase in the inhibitory actions of GABA (Morrell, 1999). There is substantial evidence supporting a seizure-promoting activity for oestrogen and a seizure-reducing activity for progesterone (Table 7.2)

Females with epilepsy consistently report that stress and the menstrual cycle, in that order, are the two most consistent precipitants of seizures (Spector *et al.*, 2000). There is a good deal of empirical evidence to support their reports. There are 3 patterns of seizure activity associated with catamenial epilepsy. Seizure activity may be worse in the 3 days before and the 3 days after the onset of the menstrual phase; at this time oestrogen is low but progesterone is virtually non-existent. Seizure activity may be worse at the time of ovulation, when oestrogen is high. In cycles where ovulation does not occur (anovulatory cycles) oestrogen remains relatively high but progesterone does not rise and seizures may occur apparently randomly in the luteal phase (Figure 7.6). In normal females and females with epilepsy who experience generalised seizures, less than 10% of cycles are anovulatory; however, in females with epilepsy who experience temporal lobe seizures, it has been reported that the rate of anovulatory cycles is around 33% (Zahn, 1999). Other sex-related differences in temporal lobe epilepsy have also been reported. A PET study of 48 people with epilepsy (21 males, 27 females) has reported that in females, between seizures, there was a decreased glucose utilisation (hypometabolism) within the temporal lobe contralateral to the area where the seizures begin (Savic and Engel, 1998). With seizure onset, the epileptiform activity rapidly spreads to this contralateral area where hypometabolism was observed. In males, on the other hand, the hypometabolism observed between seizures was primarily in the ipsilateral frontal areas and epileptiform activity spreads to this area with seizure onset.

Table 7.2 Actions of oestrogen and progesterone in animal models of epilepsy

Oestrogen	*Progesterone*
Lowers ECS threshold	raises ECS threshold
Prolongs duration of seizures	reduces seizure activity (including alcohol withdrawal)
Increased severity of seizures	raises seizure threshold
Creates epileptiform foci with direct application	causes sedation and anaesthesia (also in humans)

From Morrell (1999). ECS, electroconvulsive shock.

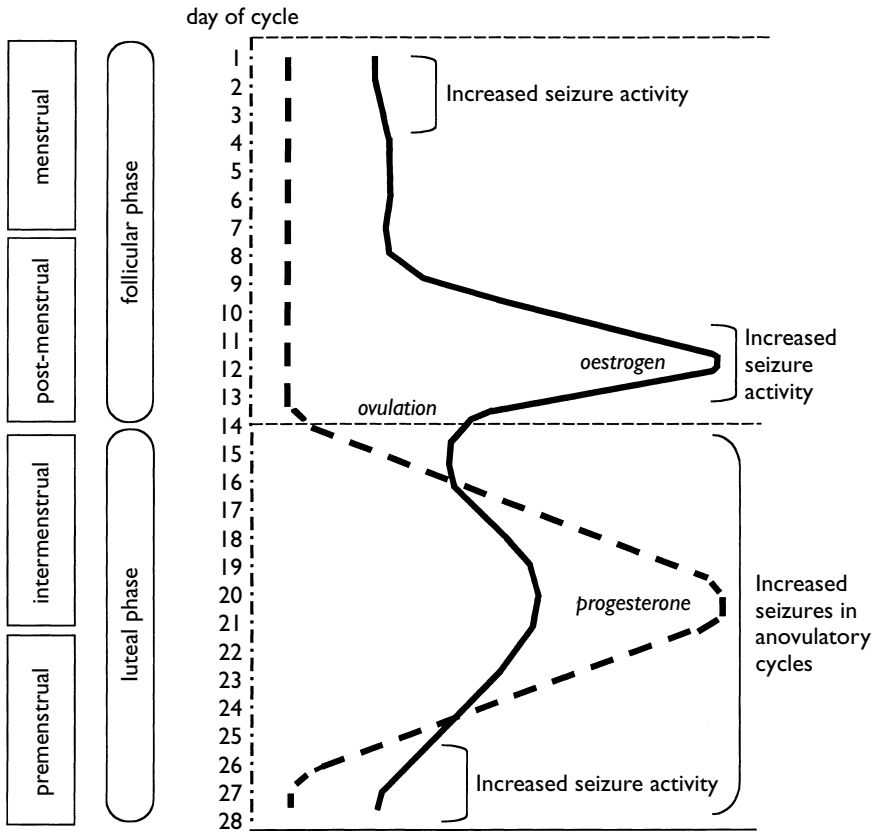

Figure 7.6 Changes in seizure activity and the menstrual cycle.

Parkinson's disease

Parkinson's disease (PD) was first described by James Parkinson in 1817 as the "shaking palsy". The "official" name given by the World Health Organisation is "paralysis agitans" (the Latin translation of "shaking palsy"). It is characterised by a resting tremor (4–6 Hz), bradykinesia (slowness of movement) and rigidity (the affected muscles appear to be constantly contracted). Cognitive deficits are also associated with PD in some patients. PD is associated with the loss of dopamine-containing neurones in the *pars compacta* region of the substantia nigra. The motor symptoms described above are a result of the loss of dopamine in the nigro-striatal pathway, which has profound effects on neural transmission in the basal ganglia (Figure 7.7).

The basal ganglia consist of 4 nuclei: the striatum, globus pallidus, substantia nigra and subthalamic nucleus. The striatum is the control centre for the basal ganglia (Parent *et al.*, 2000). It is the major target for inputs to the basal ganglia from other parts of the brain. It projects to the output nuclei of the basal ganglia and these projections are entirely GABAergic. The GABA-releasing neurones in the striatum have dopamine receptors. The neurones projecting to the internal segment of the globus pallidus (GPi) and the reticular section of the substantia nigra (SNr) have type I

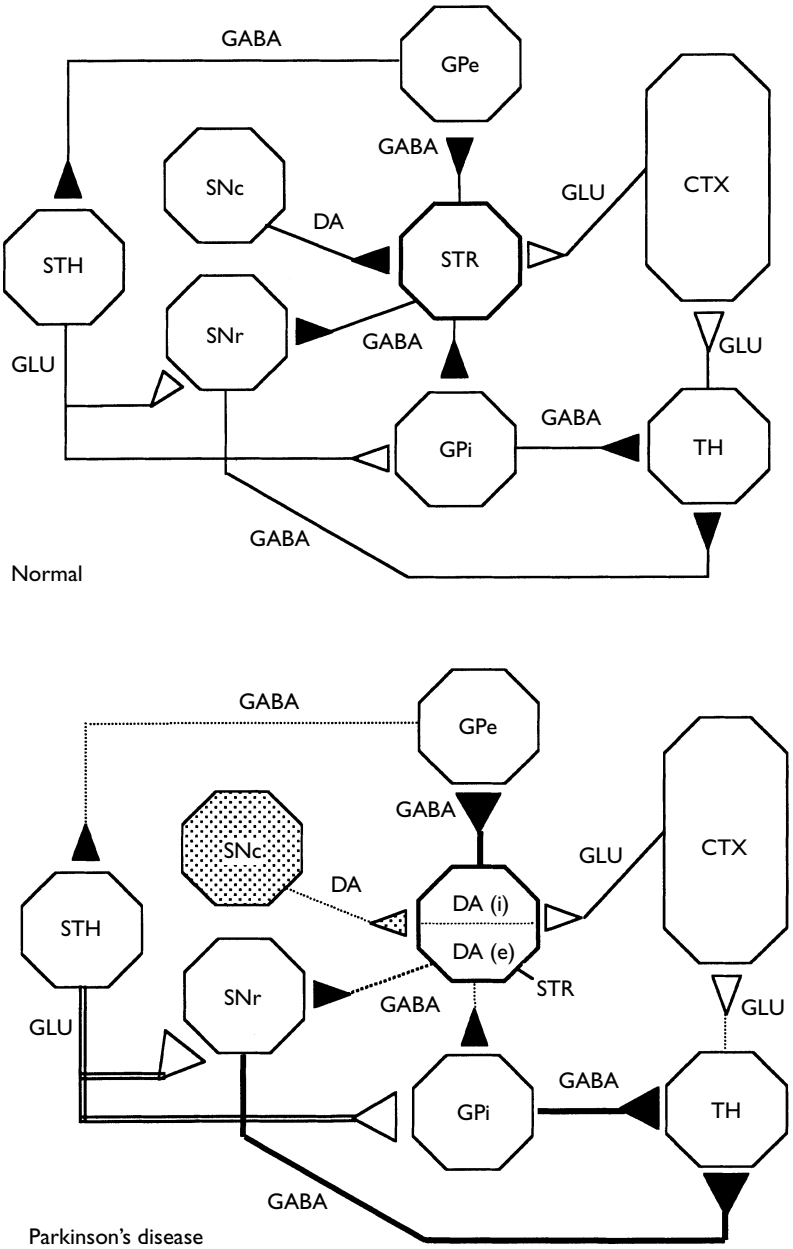

Figure 7.7 Schematic representation of changes in neurotransmitter activity in basal ganglia pathways associated with Parkinson's disease. Filled triangles represent inhibitory synapses, open triangles represent excitatory synapses. Broken lines indicate decreased activity in pathway. CTX, cortex; DA, dopamine; GLU, glutamate; GPe, Globus pallidus external segment; GPi, globus pallidus internal segment; SNc, substantia nigra *pars compacta*; SNr, substantia nigra *pars reticulata*; STH, subthalamic nuclei; STR, striatum; TH, thalamus. DA (i) indicates inhibitory effect of DA on GPe projection neurones. DA (e), excitatory effect of DA on GPi and SNr projection neurones. Adapted and modified from Parent *et al.*, 2000.

dopamine receptors (D_1) (which, according to Parent *et al.*, facilitate cell firing), while the neurones projecting to the external segment of the globus pallidus (GPe) contain type II dopamine receptors (D_2) (which, according to Parent *et al.*, inhibit cell firing). Under normal conditions, the GABAergic cells in the striatum receive DA projections from the *pars compacta* of the substantia nigra (SNc). In Parkinson's disease it is the dopamine-containing neurones in the SNc which degenerate, reducing the dopamine input to the striatum. When the striatal neurons projecting to the GPi lose their dopamine input, they decrease their release of GABA and therefore, their inhibition of the GPi neurones projecting to the thalamus. This thalamic inhibition is thought to account for the impaired movement and the other classical signs of Parkinson's disease.

The age of onset of PD is usually over 60; however, there is a rare early onset form of the disease which may begin as early as 30 years of age. The prevalence of PD is estimated to be 1% of the population over 50 years of age. PD occurs more frequently in males than in females. The age of onset of the disease, the severity and time course are the same in the two sexes. Interestingly, females with PD have the same life expectancy as males with PD. In other words, since females normally have a greater life expectancy than males, PD decreases the life expectancy of females disproportionately (Diamond *et al.*, 1990). Because PD is a disease normally associated with older age groups, the question of menstrual cycle effects on PD has seldom occurred. There are, however, a small number of reports that suggest that circulating hormones may affect disease severity. For example, in response to a questionnaire administered by mail to 352 females with PD, 75% of the patients not taking oral contraceptives reported a worsening of symptoms before and during menstruation; 48% of patients taking oral contraceptives reported the same menstrual phase-associated exacerbation in symptoms (Thulin *et al.*, 1996). A study of 138 post-menopausal PD patients has reported a beneficial effect from oestrogen replacement (Saunders-Pullman *et al.*, 1999). The patients in this study had a disease duration of less than 5 years and had never taken L-dopa. Thirty four patients had received oestrogen supplements (oestrogen alone = 11; oestrogen plus progesterone = 20, unknown formulation = 3). Analysis of the results indicated that there was a negative correlation between oestrogen replacement and the score on the Unified Parkinson's Disease Rating Scale. A subset of people with PD develop dementia. A retrospective study of 87 females with PD but without dementia and 80 females with PD and with dementia has reported a significantly greater incidence of dementia in patients not taking oestrogen replacement (Marder *et al.*, 1998), although the overall prevalence of PD was not affected by oestrogen replacement.

Alzheimer's disease and ageing

> Turning sixty sneaks up on you, like a difficult guest you know is coming – but since the guest's arrival is far in the future and you're not looking forward to it anyway, you postpone planning for the occasion. And suddenly Sixty knocks at the door.
>
> McConnell, M. (1990)
> *Still Dancing: Life Choice and Challenges for Women*, Harbinger, Tucson, p. xi.

The normal ageing process, which really begins about the time that development finishes, is accompanied by a mild, gradual decline in cognitive function very late in life. The changes include memory deficits, and a decline in abilities such as problem solving, visual-spatial orientation and verbal fluency. There is a change in sleep patterns with an increase in stage 1 slow wave sleep and a decrease in rapid eye movement sleep. There is a tendency to sleep less and to wake more frequently and many elderly people suffer from chronic sleep deprivation as a result of these changes. These behavioural changes are accompanied by a decrease in total brain weight, with some region-specific neuronal loss. There are decreases in the levels of dopamine, noradrenaline and acetylcholine. On histological examination of aged brains, small numbers of senile plaques and neurofibrillary tangles can also be observed. At some stage, in some individuals, the normal ageing process becomes a pathological process and dementia develops.

The most common form of dementia is Alzheimer's disease (AD). AD occurs more frequently in females than in males, with a ratio of approximately 2:1. It affects around 7% of the population over age 65, increasing to around 40% of the population over 80. There is a less common form of AD with early onset, between 30 and 50 years of age (see below). In the early stages of AD, it is difficult to distinguish the disease state from the normal ageing process. However, as the disease progresses, there is a rapid decline in cognitive function until the patient becomes unresponsive and bedridden.

The neuropathology of AD is characterised by a loss of neurones resulting in an apparent "shrinkage" of the brain and enlargement of the ventricles. Cell loss is particularly pronounced in the hippocampus, amygdala, entorhinal cortex, anterior thalamus, locus coeruleus, raphe nuclei and neocortex. On histological examination, the neuropathological changes which are the hallmarks of AD, namely cell loss, neurofibrillary tangles and senile plaques, may be observed. The first signs of AD are usually observed in the entorhinal cortex; however, as the disease progresses, plaques and neurofibrillary tangles spread to the other vulnerable areas listed above and may ultimately be seen throughout the brain. The intracellular components of AD, neurofibrillary tangles, are composed of chains of *tau* protein which collect in the cells' cytoplasm. Tau is normally a soluble protein associated with normal cellular structure. In AD, however, the tau protein is much less soluble and collects in the intracellular space, disrupting cellular function and ultimately leading to cell death. Senile plaques are the extracellular component of AD pathology. They are deposits of *amyloid* which occur in the extracellular space and in the walls of blood vessels in the CNS. The main constituent of amyloid is *β amyloid* and alterations in the expression of β amyloid have been demonstrated in both AD and Down's syndrome. As a result of the neuropathological changes, loss of acetylcholine-producing neurones in the nucleus basalis, the medial septum and the diagonal band of Broca results in a widespread loss of acetylcholine. Other neurotransmitters, including dopamine and noradrenaline, are also decreased.

In approximately 10% of AD cases, the disease onset is before the age of 50 (early onset). Early onset AD is considered to be familial (inherited). In addition, there are also genetic risk factors for late-onset AD. To date, 5 mutations have been identified which are associated with AD (Table 7.3). In approximately 30% of cases of early onset AD, there is a mutation of the gene encoding presenilin 1. Although the role of

Table 7.3 Genetic mutations associated with AD

Chromosome	*Element affected*	*AD type*
21	amyloid precursor protein	early onset/familial
14	presenilin 1	early onset/familial
1	presenilin 2	early onset/familial
19	apolipoprotein E	early onset/sporadic late onset/familial
12	alpha-2 macroglobulin	early onset/sporadic late onset/familial

presenilin in not understood, it has been demonstrated that mutations affecting amyloid precursor protein (the protein from which β amyloid is derived) and presenilin result in the production of the damaging forms of β amyloid. Another protein that has also been associated with AD is apolipoprotein E (ApoE). The ApoE locus on chromosome 19 can express 3 different forms of ApoE (alleles) and one of these alleles, E4, is expressed in 50% of AD patients with the late onset form of AD.

There is experimental evidence to support a protective role for oestrogen in AD. For example, it has been demonstrated *in vitro* using a mouse hippocampal cell line, that oestrogen can have antioxidant actions (Behl *et al.*, 1995). Batches of cells were incubated with 1 of 3 different neurotoxins: amyloid β protein, hydrogen peroxide, or glutamate. For each neurotoxin, subgroups were pre-incubated with either 17-β oestradiol, progesterone, aldosterone, corticosterone or cholesterol. The cells pre-incubated with 17-β oestradiol were protected against the neurotoxins; none of the other hormones showed this protective effect. The neuroprotective action of 17-β oestradiol was independent of oestrogen receptors. Oestrogen has also been reported to play a role in the metabolism of amyloid precursor protein, from which the material comprising senile plaques (β-amyloid protein) is derived (Jaffe *et al.*, 1994). β-amyloid protein is an essential constituent of all cells; it is the abnormal accumulation in AD that is associated with cell death. Samples of a human-derived cell line that expresses oestrogen receptors were incubated for 11 days in medium containing physiological levels of 17-β oestradiol or in control medium. Following the incubation period, the medium in which the different batches of cells had been incubated was analysed for the presence of a by-product of amyloid precursor protein metabolism. The levels of the by-product were significantly higher in the samples incubated with 17-β oestradiol, suggesting that in these cells the metabolism of the protein had been enhanced.

One of the most difficult aspects of ageing research is trying to obtain data in a retrospective study. No matter how co-operative the subjects and their caregivers may be, information becomes distorted (not to mention forgotten) with time. When the disease of interest is one characterised by cognitive deterioration and memory loss, as in AD, the problems become almost insurmountable. The Baltimore Longitudinal Study of Ageing (BLSA) is a multidisciplinary study of the normal ageing process which has followed 2000 individuals for almost 40 years. Every two years, participants in the BLSA undergo physical, neurological and psychological assessment, including collection of information on the use of oestrogen replacement (ER) or any other drugs or

supplements. In addition to providing invaluable data on the normal changes associated with the ageing process, BLSA also provides an excellent database for surveying the neuropathology of ageing. For example, the data from 472 post-menopausal women in the BLSA who had already been followed for 16 years were analysed for the incidence of AD (Kawas *et al.*, 1997). Over the 16 year period, approximately 45% of the subjects used ER. Also over that period, 34 subjects developed AD, including 9 subjects who had taken ER. The data were analysed to estimate the risk of developing AD when taking ER, including corrections for educational status and age. The calculated risk of developing AD was 0.457, which was a reduced risk compared to the subjects who did not take ER. Interestingly, it was also determined that there was a 0.45 risk associated with taking non-steroidal anti-inflammatory drugs. Another shorter-term study of 1124 post-menopausal women yielded similar results (Tang *et al.*, 1996). The subjects were recruited by mail and were asked to attend an initial interview and physical examination and at least one annual follow up examination (duration of follow up was 1 to 5 years). At the initial interview, information on ER status was collected. At the time the data were analysed, 12.5% of subjects had taken ER and 16% of the non-ER subjects developed AD compared to 6% of ER users. The calculated risk of AD for the subjects taking ER was 0.40. In addition, for the subjects taking ER who did develop AD, the onset of the disease was significantly later than in the non-ER subjects. It has also been reported from a study of 318 women with AD, that the subjects taking ER (14.5%) showed a significantly greater response to tacrine therapy than the non-ER subjects (Schneider *et al.*, 1996) (see Chapter 8).

Chronic pain

There is a good deal of evidence to suggest that the pain threshold is lower in females than in males, possibly by as much as 50%. There is also evidence to suggest that the pain threshold varies across the menstrual cycle, usually by about 5% to 10% (Rollman, 1993). Unfortunately, it is very difficult to compare results across pain studies because of methodological differences, including such factors as sex stereotypes ("males endure pain no matter what") and demand characteristics (if one knows it is a "pain" experiment, one has certain expectations). However, in addition to human studies, there is evidence from experimental animal studies to support the reported sex differences in pain perception. Two studies by Coyle *et al.* (1995, 1996) have used partial sciatic nerve ligation in rats to produce tactile allodynia, a pain syndrome in which innocuous stimuli (such as a light touch with a cotton bud) are experienced as painful. In these studies, the variable measured was paw withdrawal from the stimulus. The authors report that when the responses of female rats and male rats were compared, the procedure produced abnormal paw withdrawal in 64% of female rats, but in only 29% of male rats. In a further study, the responses of intact and OVX female rats were compared. The number of withdrawal responses of the intact rats was significantly greater than the withdrawal responses of the ovarectomised rats. Interestingly, this type of pain has also been reported to be more prevalent in human females than in human males.

A recent review of the literature on pain perception and the menstrual cycle analysed the results of 16 studies on experimental pain in healthy humans. Different

measures and methods were used in the studies, but the authors report remarkably consistent results. For all types of experimental pain, except pain produced by electrical stimulation, the threshold was highest in the follicular phase. For pain induced by electrical stimulation, the threshold was highest in the luteal phase (Riley *et al.*, 1999). There is evidence to suggest that the use of oral contraceptives may influence the perception of pain. Dao *et al.* (1998) have reported that in a study of females with myofascial pain, there was no difference in the pain experience across the menstrual cycle. However, the experience of pain was more severe and more constant in oral contraceptive users than in the normally cycling females.

Psychiatry

> Midway along the journey of our life I woke to find myself in a dark wood for I had wandered off from the straight path. How hard it is to tell what it was like, this wood of wilderness, savage and stubborn (the thought of it brings back all my old fears) a bitter place! Death could scarce be bitterer.
>
> Dante (1314) *Inferno*, 1–7.
> In *The Divine Comedy, Vol. 1: Inferno*,
> Translated by Musa, M., Penguin Classics,
> London, 1984, p. 67.

Depression and anxiety (particularly panic disorder, phobias and obsessive-compulsive disorder) occur more frequently in females. The responses to the drugs used to treat these disorders also differ between the sexes (see Chapter 8). Neither one of these statements should be surprising to people even marginally associated with the health care system. What is surprising is that so little effort has been expended to try to understand how and why these differences occur.

Depression

Depressive Disorder or "major depression" is defined in the DSM-IV as one or more episodes of depressed mood lasting 2 weeks or more involving feelings of depression, loss of interest and pleasure in all aspects of life. Such episodes are often accompanied by changes in body weight and sleep patterns, fatigue, loss of sexual drive, loss of self-esteem and sometimes, suicidal thoughts. Dysthymic Disorder is defined as ongoing feelings of depression (as opposed to depressive episodes) of at least 2 years duration, with feelings of depression occurring almost every day and no period greater than 2 months without feelings of depression. Both Depressive Disorder and Dysthymic Disorder occur approximately twice as frequently in females compared to males. There is evidence for a genetic component to depression, particularly in females.

A study of 2662 pairs of twins (1747 F pairs, 915 M pairs) followed the subjects over a 14 year period (Bierut *et al.*, 1999). The twin pairs were classified as follows: female-monozygotic, n = 928 pairs; female-dizygotic, n = 527 pairs; male-monozygotic, n = 395 pairs; male-dizygotic, n = 228 pairs, female/male-dizygotic, n = 584 pairs. The pairs of twins, who volunteered for the study between 1980–1982, completed an initial questionnaire at the time they entered the study. Eight years later

(1988–1990) they completed a second questionnaire. The second questionnaire was followed by a telephone survey approximately 4 years later (1992–1993). The results reported in the study were based on the telephone survey. The mean ages of the subjects at the time of the telephone survey were 44 years for the female subjects and 42 years for the male subjects. The survey used a modified form of the Semi-Structured Assessment for the Genetics of Alcoholism, which solicits data on psychiatric disorders as well as alcoholism. Analysis of the results showed that there was a greater concordance rate of depression in female monozygotic twins than in female dizygotic twins (Table 7.4). For male twins, the concordance rate for depression was similar for monozygotic and dizygotic twins.

A study of 1033 pairs of female twins also examined the question of genetic and environmental influences in the development of depression (Kendler *et al.*, 1992). Personal interviews with each subject were used to obtain the data (although the form of the interview was not specified). Analysis of the interview results revealed a life time prevalence of major depression of 31% and a 1 month prevalence of Generalised Anxiety Disorder (GAD) of 23.5%. The results of this study are particularly interesting because they suggest that a set of genetic factors are important in the aetiology of depressive disorder, and that these factors also figure in the aetiology of GAD. The authors suggest that the genetic factors predispose the individual to develop one of the two disorders and it is the non-familial environmental factors that determine which disorder will be expressed.

When the symptoms of depression are restricted to the late luteal phase of the menstrual cycle, the term premenstrual dysphoric disorder (PMDD) is applied. PMDD is distinguished from premenstrual syndrome (PMS) on the basis of severity. PMS symptoms are usually described in terms such as "irritability", "tension", "depression" and do not fulfil the criteria for a major depressive episode (Yonkers, 1997). Interestingly, PMDD is associated in 30 to 50% of sufferers with depressive disorder. There have been mixed reports on the relationship of female suicide to the menstrual cycle. Some studies have reported a higher rate in the first week, others have reported the rate to be higher in the fourth week. A recent study of 113 females who attempted suicide has reported that 36% of the attempts were made during the first week of the cycle, 19% in the second week, 16% in the third week and 29% in the fourth week (Baca-Garcia

Table 7.4 Prevalence and concordance rate for DSM-IV Major Depressive Disorder in 2662 pairs of twins

Twin pair	*Prevalence*	*Concordance*
Monozygotic-female	21.0	0.38
Dizygotic-female	24.0	0.25
Monozygotic-male	15.3	0.20
Dizygotic-male	17.3	0.23
Dizygotic-mixed:		
Female twin	24.1	0.36
Male twin	14.9	0.22

From Bierut *et al.*, 1999.

et al., 1998). This result suggests that there may be increased vulnerability when oestrogen is low (Figure 7.8).

Bipolar Disorder, characterised by episodes of depression alternating with episodes of mania (hyperactivity, elevated mood or irritability, inflated self-esteem lasting at least a week) is represented equally in females and males. There is a subcategory of bipolar disorder, a rapid cycling type characterised by 4 or more cycles per year, which is more common in females than in males. A study of 186 females and 141 males with bipolar disorder found no female–male differences in age of onset (mean age 21 years) or in living conditions (Blehar *et al.*, 1998). However, the level of education attained was significantly higher for the males than the females. Of the female subjects, 75% reported having been pregnant, and of these subjects 45% reported experiencing severe emotional problems associated with pregnancy and birth. Thirty-one percent of the subjects reported that they had experienced menopause, 19% of whom reported that they had experienced severe emotional difficulties related to menopause. Finally, in relation to the menstrual cycle, 66% of subjects reported predictable changes in mood associated with the premenstrual or menstrual phase of the cycle (75% reported mood fluctuations and irritability, 25% reported depression)

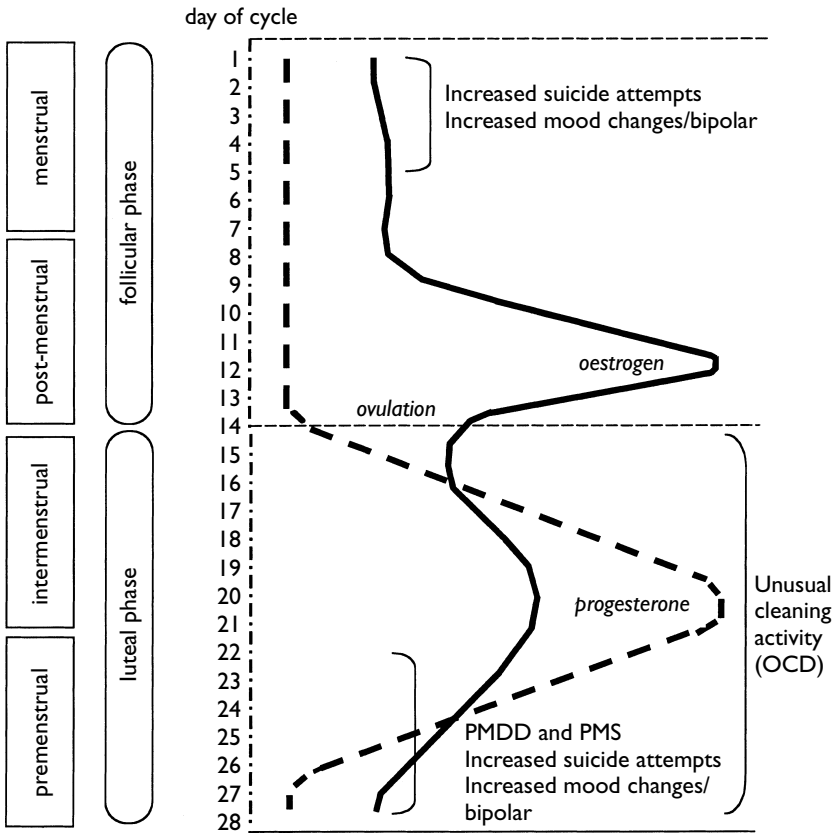

Figure 7.8 Depression, anxiety and the menstrual cycle.

(Figure 7.8). It was also reported in this study that significantly more females than males in the sample had a history of hyperthyroidism and migraine.

Postpartum mood disorders usually occur in the first 3 months following delivery. "Postpartum Blues" is an acute episode of dysphoria, tearfulness and anxiety that occurs in the first 3 to 7 days after delivery. It is considered by many health care providers to be a normal part of childbirth. Postpartum depression is estimated to occur in 10% to 20% of deliveries. Predisposing factors of postpartum depression are a history of depressive disorder or a previous episode of postpartum depression itself (Pariser, 1993).

Although, anecdotally, depressive disorder is associated with menopause, the relationship is not justified in the literature (Hunter, 1996). In fact, for both males and females, the number of episodes of affective disorders (which includes depression) is less in the 45 to 64 year old age group than in the 30 to 44 year old age group (Pariser, 1993). However, the menopause-depression association is pervasive and it has been suggested that while depression is not directly associated with menopause, there may be an increased rate of recurrence for women who have already suffered from depression (Pearlstein, 1995).

Anxiety

The DSM-IV classification for Generalised Anxiety Disorder (GAD) specifies that excessive anxiety and worry must have been experienced on an almost daily basis for a period of not less that 6 months. In addition to the anxiety, the person may experience restlessness, difficulty in concentrating, irritability, sleep disturbances (and fatigue). Anxiety disorders are generally more prevalent in females than males.

GAD develops twice as frequently in females as in males. Dysthymia is more likely to develop in female GAD sufferers than in male GAD sufferers and co-morbidity of GAD and dysthymia usually indicates a poor long-term outcome with fewer periods of remission (Pigott, 1999). There is evidence to suggest that genetic factors are important in the development of GAD and that the same (or similar) genetic factors may also predispose the individual to Major Depressive Disorder (see above) (Kendler *et al.*, 1992). GAD is also more frequent in PMS. A study of 41 GAD + PMS patients has reported that GAD symptoms were of greater severity than the symptoms of female GAD-only patients or control subjects. In the GAD + PMS patients, the GAD symptoms were also worse in the premenstrual phase (McLeod *et al.*, 1993). In addition to GAD, there are other categories of anxiety disorders that are more prevalent in females.

Panic Disorder (that is, recurrent, unexpected panic attacks) is experienced by 8% of females but only 3% of males. Panic disorder in females is also qualitatively different from the disorder in males, with females reporting more symptoms (e.g. palpitations, trembling, dizziness, etc.). There is also a greater risk in females with panic disorder for the development of agoraphobia, and for a recurrence of symptoms following remission (Yonkers *et al.*, 1998). Anxiety may be induced in people suffering from panic disorder by CO_2 (carbon dioxide) inhalation. A study of 10 panic disorder patients and 7 healthy control subjects has reported that anxiety induced by CO_2 inhalation was significantly worse in the early-follicular phase than in the midluteal

phase in panic disorder patients, while the control subjects experienced no anxiety reactions in either phase (Perna *et al.*, 1995). Somatisation disorder (previously referred to as hysteria), the experience of physical symptoms such as pain, gastrointestional distress and pseudoneurological signs which cannot be fully explained by a medical condition, occurs significantly more frequently in females with panic disorder than in females without psychiatric illness (Battaglia *et al.*, 1995).

Post-traumatic stress disorder (PTSD) is characterised by the re-experiencing of a fear-inducing, horrifying and/or life threatening experience. The person suffering PTSD will repeatedly relive the traumatic experience, for example, as nightmares, flashbacks or illusions. In addition to causing distress, PTSD usually also disrupts work, family and social life. The prevalence rate for PTSD in usually reported to be approximately the same for females and males. The cause of PTSD in females is most often assault (physical or sexual), a life-threatening experience or being witness to a life threatening experience (Foa, 1997). PTSD in males is most often combat-related.

A type of anxiety disorder that seems to have captured the imagination of stand-up comedians is Obsessive-Compulsive Disorder (OCD). Stories about room mates who repeatedly check power points or stir their tea 10 times in a clockwise direction, are usually good for a laugh. Lady Macbeth probably suffered from OCD. The disorder is characterised by obsessions, e.g. recurrent thoughts ("Have I turned off the water in the bathtub?") and compulsions, repeated behaviours (e.g. returning to the bathroom multiple times to check that the tap is off). Because most people indulge in checking or superstitious behaviours at some time, the behaviours must be distressing and disruptive to ongoing activities to be classified as a disorder. OCD is more frequent in females than in males, has a later onset in females and is usually less severe (Pigott, 1999). There is also evidence that in some cases, OCD may be linked to the menstrual cycle. Eighteen undergraduate females (mean age 19 years) took part in a 2 month study. Four of the subjects were taking an oral contraceptive. Each day, the subjects were asked to note on a questionnaire if they had completed any "usual" cleaning chores on that day. They were also asked to report if they had engaged in any "out of the ordinary cleaning activity", e.g. cleaning something they do not usually clean or spending a significantly greater amount of time in cleaning activities. Fourteen incidents of "unusual cleaning behaviour" were reported by 10 subjects, 11 of these 14 incidents took place during the luteal phase of the subjects' menstrual cycle (Figure 7.8). None of the subjects taking oral contraceptives reported unusual cleaning activities (Dillon and Brooks, 1992).

Social Phobia, also known as Social Anxiety Disorder, is a fear of public situations where the sufferer may be subject to embarrassment (e.g. proposing a toast at a dinner party). When placed in the potentially embarrassing situation, the person experiences severe anxiety or even a panic attack (DSM-IV). Social phobia is more common in females than in males, and there is evidence to suggest that genetic factors are involved in its development (Stein *et al.*, 1998).

Schizophrenia

Schizophrenia is defined by the presence of psychosis (hallucinations, delusions) that have lasted for at least 6 months. The expression of psychosis may take the form of

florid or bizarre behaviour (positive signs) or withdrawal and lack of emotional expression (negative signs). Within the diagnosis of schizophrenia there are many subcategories which further define the disease (DSM-IV). The diagnosis of schizophrenia is not straightforward. It is heavily dependent upon cultural factors. For example, in a culture where communication with one's ancestors is an accepted part of life, hearing voices may be a cultural norm rather than an auditory hallucination. Even in similar cultural settings, e.g. the United States and the United Kingdom, there are differences in the application of the diagnostic criteria. The incidence of schizophrenia is usually reported to be equal for females and males. However, analysis of different populations will give somewhat different results. Hospital-based studies, using in-patient samples, often report that the incidence is greater in males than in females. The prevalence is estimated to be 0.5% to 1% of the general population.

Schizophrenia is usually reported to be less severe in females, with a better prognosis, although whether this difference in disease severity is consistent throughout the life span has been questioned (Seeman, 1997). The age of onset is generally later in females (later 20s) than males (early 20s); however, in familial types of schizophrenia, the age of onset is the same for females and males (Seeman, 1997). Genetic factors are clearly important in schizophrenia, the incidence of the disease in first degree relatives of patients being 10 times the incidence in the general population. For late onset schizophrenia, over the age of 45 years, the incidence in females is greater than in males. This female disadvantage in the late onset group may be associated with oestrogen changes (Seeman, 1997). In animal models of psychosis, it has been demonstrated that oestrogen, but not testosterone, reduces the behavioural abnormality of the disorder (Hafner *et al.*, 1991).

The symptom profile in schizophrenia has often been reported to be different between females and males. Negative symptoms are generally reported to occur less frequently in females (e.g. Szymanski *et al.*, 1995; Goldstein *et al.*, 1990); however, some authors disagree that this is the case (Addington *et al.*, 1996; Seeman, 1996). Paranoia has been reported to occur more frequently in females (Andia *et al.*, 1995).

Divergencies from normal brain structure associated with schizophrenia are generally reported to be more pronounced in males than in females. The normal pattern of hemispheric asymmetry has often been reported (using CT and MRI) to be reversed in schizophrenia, although a number of studies have reported no differences between schizophrenia and control subjects (Bullmore *et al.*, 1995). In many cases, differences in methodology probably account for the conflicting results. Bullmore *et al.* (1995) have used MRI and "radius of gyration" analysis, which they suggest overcomes many of the previous analysis problems, to examine differences in structure between the brains of patients with schizophrenia and control subjects. Radius of gyration analysis measures the way that individual points in a structure are distributed about the centre of the structure. The outcome of the analysis is a value, the radius of gyration (R_g). A large R_g indicates that the points are widely dispersed about the centre of the object, a small R_g indicates that the points are concentrated centrally. Thirty-seven patients with schizophrenia (M = 29, F = 8) and 30 control subjects (M = 17, F = 13) were examined in this study. In the right-handed male control subjects, the R_g of the right hemispheres was significantly greater than the R_g of the left hemispheres and the pattern was reversed in the left-handed subjects. When the data were analysed by sex, there were

differences between the hemispheres for males but not for females. In right-handed males with schizophrenia (n = 26), the left–right pattern was reversed, with R_g reduced for the right hemisphere. There was no difference between the right-handed females with schizophrenia and the right-handed control females.

Bryant *et al.* (1999) examined 59 patients (F = 23, M = 36) with schizophrenia and 37 control subjects (F = 18, M = 19) using MRI. The mean duration of illness for the male and female patients was 12 years and 16 years, respectively. The areas measured in the study were the superior temporal gyrus, the amygdala/hippocampal complex, the prefrontal cortex and the caudate nucleus. The volumes of the superior temporal gyrus and the amygdala/hippocampal complex were significantly smaller in patients compared to controls. In male patients, the left temporal lobe volume was significantly smaller than in male controls. There was no difference in total temporal lobe volume between female patients and controls. Cowell *et al.* (1996) used MRI to correlate changes in frontal lobe volume with the clinical signs of schizophrenia. The study included 91 people with schizophrenia (F = 37, M = 54) and 114 control subjects (F = 52, M = 62). The average disease duration was 7 years for the females and 9 years for the males. The authors found a correlation between frontal lobe changes and symptoms and that there were sex differences in these correlations (Table 7.5).

Sex differences have also been reported in the inferior parietal lobe volume of people with schizophrenia. Frederikse *et al.* (2000) conducted an MRI study of 30 (15 F, 15 M) people with schizophrenia and 30 (15 F, 15 M) control subjects. The disease duration for the subjects in this study was not given. For the female patients, total brain volume was significantly less than for control females. For the male patients, there was no difference in overall brain volume between patients and controls. However, there was a significant decrease in the volume of the left inferior parietal lobe compared to controls and this left inferior parietal lobe decrease resulted in a reversal of the usual left–right asymmetry of this region. Two recent post-mortem anatomical studies have also reported differences between females and males. One study examined the anterior commissure of 17 brains of patients with schizophrenia (F = 8, M = 9) and 20 control brains from people without a neuropsychiatric disorder (F = 10, M = 10) (Highley *et al.*, 1999). The mean disease duration was approximately 40 years for the females and 34 years for the males. The anterior commissure was measured for cross-sectional area and fibre count. The cross-sectional area did not differ between patient and control brains; however, in the patient brains there was a

Table 7.5 Correlation between frontal lobe changes and clinical signs

Symptom classification	*Frontal volume: females*	*Frontal volume: males*
negative signs	no correlation	no correlation
disorganisation	increased volume	decreased volume
	increased symptoms	increased symptoms
hallucinations/delusions	no correlation	no correlation
suspicion/hostility	increased volume	no correlation
	increased symptoms	

From Cowell *et al.* (1996).

significant decrease in fibre count in the female brains only. The extent of gyrification (folding) of the cortices has been suggested to be an anatomical index of schizophrenia. A second post-mortem study measured the extent of gyrification of the prefrontal cortices from 24 patients with schizophrenia (f = 13, m = 11) and 24 control patients (F = 13, M = 11) (Vogeley *et al.*, 2000). The average disease duration for females and males was 19 years and 25 years, respectively. There was significantly greater gyrification on the right side of the brains of the male patients compared to the male controls. There was no difference between the female patients and the female control subjects. Because the formation of the gyri is stable soon after birth, the authors suggest that this result indicated a developmental component in schizophrenia (Table 7.6).

One confounding factor in many of the anatomical studies has been that the subjects have been long-term sufferers of schizophrenia, often hospitalised, and with a long history of treatment with anti-psychotic medications. In many cases, the drug history (and sometimes the disease duration) is either unknown or is not included in the study, making interpretation of the results difficult. It is impossible to determine if the observed changes are due to the disease or some other factor, e.g. drug treatments. Ideally, data should be collected before drug treatment has commenced. A CT study of people experiencing their first episode of schizophrenia has reported that the lateral

Table 7.6 Anatomical changes associated with schizophrenia

Anatomical measure	*Results*
hemispheres, volume (MRI)	RH m controls, right > left
	LH m controls, left > right
	RH m patients, left > right
	RH f controls, right = left
	RH f patients, right = left
superior temporal gyrus, amygdala/hippocampal complex, volume (MRI)	patients < controls
left temporal lobe, volume (MRI)	m patients < m controls
	f patients = f controls
lateral ventricles, volume (CT)	patients > controls
lateral ventricle to brain ratio	f patients > m patients
total brain volume (MRI)	f patients < f controls
	m patients = m controls
inferior parietal lobe, volume to brain ratio (MRI)	L, m patients < m controls
	f patients = f controls
anterior commissure, area and fibre count (post-mortem)	Area: patients = controls
	Count: f patients < f controls
gyrification of prefrontal cortices (post-mortem)	R, m patients > m controls
	f patients = f controls

RH, right handed; LH, left handed; m, male; f, female.

ventricles of the patients (n = 63) were larger than in controls (n = 21), resulting in a larger ventricle to brain ratio in the patients. This ratio was larger in the female patients (n = 30) than in the male patients (n = 33) (Vazquez-Barquero *et al.*, 1995). An MRI study of the hippocampus-amygdala and temporal horns in first episode schizophrenia (n = 34) compared to healthy control subjects (n = 25) has also yielded significant results (Bogerts *et al.*, 1990). This study reported that, in male (n = 22) and female patients (n = 12), there was an enlargement of the temporal horn on the left side compared to controls. There was also a significant decrease in the volume of the left hemisphere of male patients compared to control subjects.

A number of cognitive changes have been reported to occur in schizophrenia. The greatest cognitive impairments have generally been reported in males. It has also been suggested that impairment is greatest for left-hemisphere tasks and that disruptions in the patterns of laterality of brain function occur in schizophrenia. A 1997 study by Reite *et al.* has demonstrated that the auditory-evoked field component of magnetoencephalography (MEG) is disrupted in schizophrenia. The responses of a group of 20 patients with paranoid schizophrenia (F = 9, M = 11) and 20 control subjects (F = 10, M = 10) were compared using MRI and MEG. As discussed in Chapter 5, the M100 source in the male control subjects was more asymmetrical than in the female control subjects. In the male patients, the M100 source was significantly less asymmetrical than in the control subjects but in the female patients there was greater asymmetry than in the female control subjects. The superior temporal gyri (location of the M100 source) were also smaller in the male patients than in the male control subjects (Reite *et al.*, 1997).

Gruzelier *et al.* (1999) tested the responses of people with schizophrenia on a memory task for unfamiliar faces and words. There were 104 patients in the study (F = 38, M = 66) and 95 control subjects (F = 50, M = 45). The patients were categorised according to symptoms (delusional, positive symptoms, negative symptoms) and their disease state (active (M = 17, F = 7), withdrawn (M = 11, F = 5), mixed (M = 20, F = 12) and remitted (M = 18, F = 14)). Medication analysis by disease state was also given. The study was conducted in 2 stages. In the learning stage, 50 items were presented for 3 seconds each and the subjects were required to give an oral response (to ensure attention was focused on the task) indicating whether they "liked" or "disliked" the item presented. In the recognition stage, 50 pairs of items were presented, one item of each pair had been presented in the learning condition. The subjects were required to indicate the previously presented item. Overall, the control subjects demonstrated greater accuracy than the patients and males were more accurate than females. The female control subjects were more accurate for words than faces and the male controls were more accurate for faces. Within the patient groups, the males in the active category were more accurate for words than faces (a reversal of control performance). Both males and females in the withdrawn group were more accurate for faces than words (a reversal from controls for the females). For subjects in remission, females performed more accurately than males. These results are generally consistent with the commonly held view that left hemisphere function is more impaired than right hemisphere function in schizophrenia. These results are not consistent with the view that females fare better than males. However, the study was of hospitalised patients (except for some patients in the

remission group), so it may be that the female subjects represented a subset of more seriously affected females.

A study of 75 patients with schizophrenia (F = 30, M = 45) and 75 control subjects (F = 30, M = 45) used a battery of 18 tests to assess cognitive skills (Ragland *et al.*, 1999). The patients and controls were all right-handed and age-matched. The average disease duration for the patients was 10 years. The tests included measures of the following abilities: abstraction, attention, verbal memory, spatial memory, language ability, spatial (line orientation, block design), sensory (stereognosis, i.e. identification of objects by touch alone), and motor function (finger tapping). On the finger tapping test, both patients and controls tapped significantly faster with their right hands and in both groups males tapped faster than females. When asked to identify objects by touch alone, control subjects were faster than the patients. The control subjects were also faster with their left hands, but right and left hand times were equal for the patients. On language and spatial ability, the patients performed better on spatial tasks than language tasks, and males performed better on the spatial tasks. Female control subjects performed better on the verbal tasks than on the spatial tasks, but female patients performed equally well on both tasks. Comparing spatial and verbal memory, control subjects performed better than patients but there were no sex differences in performance. The authors note that while greater left hemisphere impairment may hold for some tasks, at least in the present study, it was not apparent for the motor and sensory tasks.

Variations in symptom severity across the menstrual cycle have been reported in schizophrenia. A group of 32 in-patient females with a mean age of 31 years were assessed on days 2, 7, 13, 14, 21 and 28 of their menstrual cycles (Riecher-Rössler *et al.*, 1994). The assessment on each of these days included psychiatric symptoms, self-assessed well-being, and analysis of serum levels of oestrogen and progesterone. In all of the patients there was a significant overall reduction in oestrogen levels as compared to population norms. This overall reduction in oestrogen resulted in a "flattening" of the oestrogen level changes across the cycle. However, there was still an effect of oestrogen on psychiatric state, and self-assessment, with the fewest symptoms and the greatest well-being reported when oestrogen levels were highest. Similar results were reported for a study of 39 female in-patients, mean age 35 years (Harris, 1997). The patients were assessed in the pre-menstrual phase (days 23–28) and the post-menstrual phase (days 5–10), using similar measures to the previous study. Analysis of the results revealed that fewer symptoms were reported when oestrogen was elevated. Interestingly, the increased symptoms reported when oestrogen was low were related to affective disorder (e.g. depression) rather than psychosis. A study of 5 outpatients with schizophrenia also reported a significant increase in symptoms associated with low oestrogen levels (Hallonquist *et al.*, 1993). Interestingly, the symptom that figured most prominently (and changed the most) was depression (Figure 7.9).

Finally, there is also evidence for changes in the symptoms associated with childbirth and the postpartum period, but the results are inconsistent.

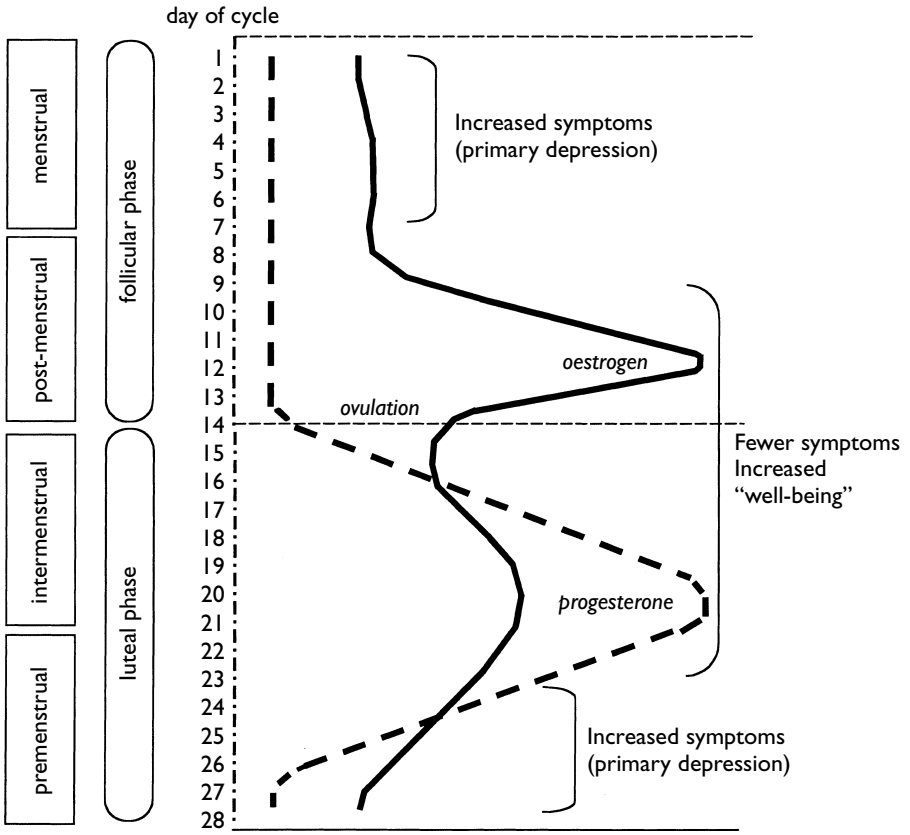

Figure 7.9 Symptoms of schizophrenia and the menstrual cycle.

Conclusions

> If a man does not keep pace with his companions, perhaps it is because he hears a different drummer. Let him step to the music which he hears, however measured or far away.
>
> Thoreau, H.D. (1854) *Walden.*
> In Atkinson, B. (Ed.) *Walden and Other Writings of Henry David Thoreau,*
> Modern Library, New York (1937) p. 290.

The disorders discussed in this chapter represent the most prominent neuropathologies facing the 21st century population. In some cases, e.g. Alzheimer's disease and Parkinson's disease, the increasing incidence is a by-product of our increasing life expectancy. In the case of disorders such as depression, anxiety and schizophrenia, it is our awareness and understanding that has increased. It is interesting that the majority of these disorders are more prevalent in females than in males (Table 7.7). The recognition of the vulnerability of females to some neurological and psychiatric disorders is slowly changing the perspective of health care providers and others con-

Table 7.7 Prevalence of neuropathologies in females and males

Disorder	*Prevalence*
Alzheimer's disease	F > M
amyotrophic lateral sclerosis	F < M
	F = M*
anxiety	F > M
bipolar disorder	F = M
depression	F > M
epilepsy	F = M
migraine	F > M
multiple sclerosis	F > M
obsessive compulsive disorder	F > M
panic disorder	F > M
Parkinson's disease	F < M
post-traumatic stress disorder	F = M
schizophrenia	F = M
social phobia	F > M
substance abuse	F < M

* Data for post-menopausal females with age of symptom onset over 60 yrs.

cerned with female health care issues. For the interested reader, *Folding Back the Shadows* (Romans, 1998) provides an interesting and challenging perspective on these issues.

The following summarises the main points to be drawn from Chapter 7.

1. Overall, females appear to be more vulnerable to the development of the most common neurological and psychological disorders.
2. In the majority of cases, an important hormone seems to be oestrogen. We will return to this subject in Chapter 8 in the discussion of drugs and their actions in females. The exception may be MS and epilepsy, for which there is some evidence to support a beneficial role for progesterone.
3. For a number of the disorders, menstrual cycle changes have also been demonstrated. Again, the majority of symptoms seem to worsen during the low oestrogen phases of the cycle. The exception is MS . . . unless one looks at changes in oestrogen as opposed to absolute values.

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8

Drugs, sex and . . .

Rt. Hon. James Hacker: "Humphrey, what is it that I don't know?"
Sir Humphrey Appleby: "What precisely do you mean, Minister?"
Rt. Hon. James Hacker: "I don't know. That's just it. I don't know. And I don't know because I can't find what questions to ask you. And I don't know what to ask you because I don't know. What is it that I don't know?"
Sir Humphrey Appleby: "Minister, I don't know what you don't know. It could be almost anything."

Jay, A., Lynn, J. (1980)
"The Right To Know". *Yes, Minister*, BBC Television.

In many ways this chapter, which is about pharmacology, is a continuation of the last chapter. In Chapter 7 we discussed neurological and psychiatric disorders. In Chapter 8 we will look at drug treatments for those disorders and how the drugs' actions may differ in females and males. We will also look at drugs used for non-therapeutic purposes.

Although this chapter is primarily concerned with drug actions in the brain (neuropharmacology and psychophamacology), only in very rare instances are drugs delivered directly into the brain. Instead, drugs are usually administered orally or by injection and are carried to the brain by the blood. Along the way a number of processes take place which may alter not only the amount of drug reaching the brain, but also the form of the drug itself. These processes are part of the subject of *pharmacokinetics*, "what the body does to the drug".

Pharmacokinetic processes operate from the moment the drug enters the body to the time that it (or its by-products) leaves (Figure 8.1). The drug must be absorbed into the bloodstream from the site of administration, e.g. the gastrointestinal tract after oral administration, and distributed throughout the body. Drugs absorbed from the

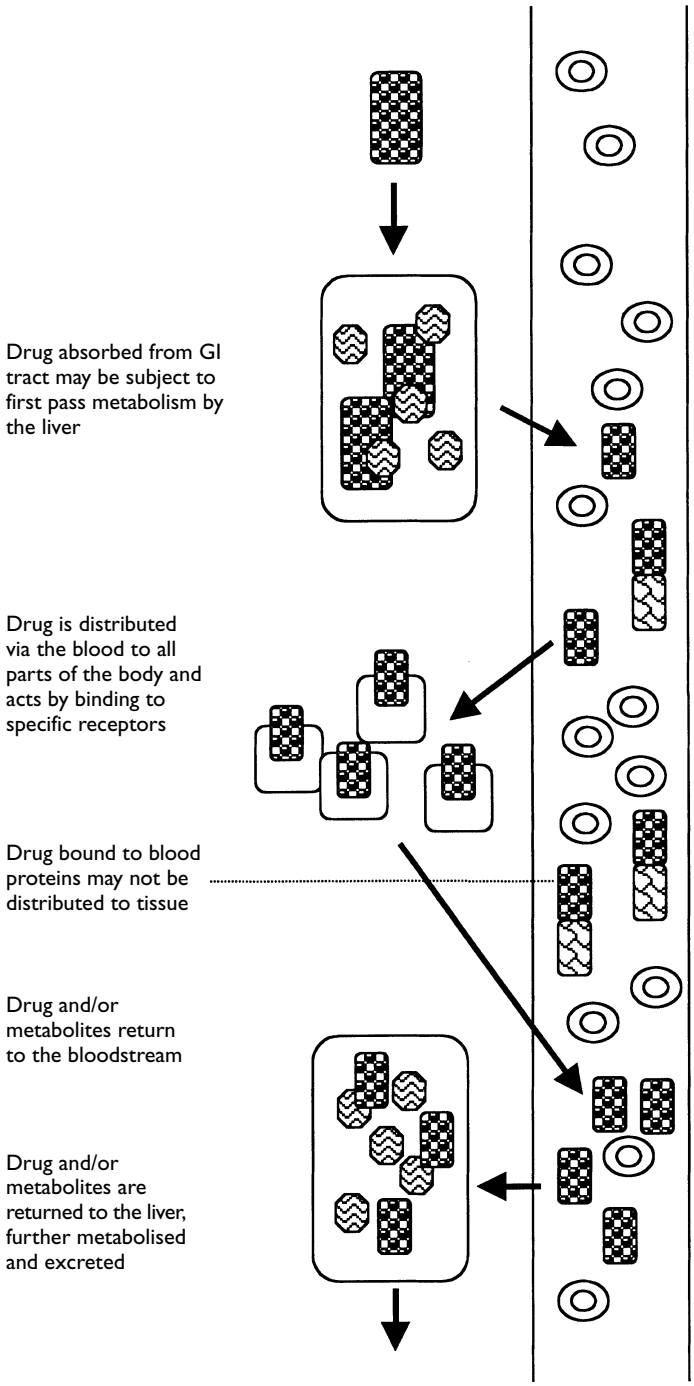

Figure 8.1 The steps in drug absorption, distribution and elimination (pharmacokinetics) following oral administration.

gastrointestinal tract travel via the portal vein directly to the liver where they may undergo preliminary processing, known as *first pass metabolism*. Some preliminary processing may also occur in the intestinal epithelial cells. Some drugs undergo such extensive first pass metabolism that only a small proportion of the initial dose remains. An example of this occurs with the analgesic drug, morphine. Approximately 75% of orally administered morphine is lost due to first pass metabolism. From the liver, the remaining drug is distributed throughout the body by the blood. The phrase "throughout the body" is particularly important. Drugs destined for a particular target are not distributed to that area alone. Once a drug enters the bloodstream it is distributed to every place that the blood goes, and if receptors for the drug are available in a particular place, then the drug will have an effect, whether such action is desirable or not. This is an important issue for drugs targeted at the CNS; many of them have unwanted side effects due to actions on receptors in other parts of the body. L-dopa, for example, the mainstay of treatment for Parkinson's disease, is metabolised to dopamine in the brain and binds to dopamine receptors. There are also dopamine receptors in the *area postrema*, the body's "emetic centre" which is outside the blood-brain barrier. If L-dopa is metabolised outside the blood-brain barrier, it binds to the dopamine receptors in the area postrema producing severe nausea and vomiting. To overcome this problem, L-dopa is administered with an agent (a decarboxylase inhibitor) which prevents its metabolism outside the blood-brain barrier.

Following their distribution and (hopefully) therapeutic action, drugs or their metabolites are transported to the liver and/or the kidneys for elimination. The metabolites of some drugs also have drug actions (active metabolites) which may prolong the action of the parent drug. Diazepam, for example, is metabolised to nordiazepam (active metabolite), which is in turn metabolised to oxazepam (active metabolite) before finally being inactivated. Various factors including age, state of health, genetics and the sex of the person taking the drug, can all affect pharmacokinetics.

Pharmacodynamics is the area of pharmacology devoted to the action of drugs on receptors ("what the drug does to the body"), and can also be altered by a number of factors. The effect that the drug has on a particular person, at a particular time, will depend upon the age and health of the person, genetic factors, previous drug exposure, environmental factors and the sex of the person taking the drug.

There is a limited amount of data to suggest that there are differences in the pharmacokinetics and pharmacodynamics of some drugs administered to human females and males. The reason that there is a limited amount of data is that females have been excluded from participation in drug trials. The data have simply not been collected. There is, however, a great deal of evidence from the literature using experimental animals, around 60 years worth. By necessity much of the discussion in this chapter, on CNS drug effects, as well as pharmacokinetics and pharmacodynamics, will centre on experimental data from animal studies.

Pharmacokinetics and pharmacodynamics

Pharmacokinetics can be divided into its component processes: absorption, distribution, metabolism and excretion. Each component process may be modified by a number of factors. There are a number of physiological variables which differ between

females and males. Some of these variables are likely to have a direct influence on the different pharmacokinetic processes. One very important factor to be considered in the case of distribution is the difference in the proportion of body fat between females and males. In young adult females, the proportion of body fat is approximately 33%. This percentage rises to around 48% in elderly females. The proportion in males is approximately 18%, rising to 36% (Pollock, 1997). The volume of distribution is a measure of the amount of drug distributed into body tissue, particularly fat. Taken on its own, how the drug is distributed into body tissue may not seem particularly interesting. However, a particularly important variable, plasma half-life (a measure of how long a drug remains in the body), is directly proportional to the volume of distribution. So, bodies with a higher proportion of fat will retain certain drugs for a longer period of time than bodies with a lower proportion of fat. Enter sex differences in pharmacokinetics. It has been reported that the volume of distribution of alcohol is smaller in females than in males, while the volume of distribution of diazepam is larger in females than in males (Harris *et al.*, 1995). It has also been reported that both the volume of distribution and the plasma half-life of the antidepressant drug, buproprion, are significantly increased in elderly females when compared to young males (Sweet *et al.*, 1995). In the gastrointestinal tract, the rate of gastric emptying is decreased in females compared to males. The decreased rate may be observed during menopause in females not taking hormone supplements, suggesting that the slowing is not due to direct effects of oestrogen or progesterone (Pollock, 1997). Differences in drug metabolism may be due in part to different amounts of available liver enzymes. It has been reported, for example, that alcohol dehydrogenase activity is lower in females, while CYP3A4 activity (see below) is increased in young adult females compared to males and postmenopausal females (Pollock, 1997).

The next question, of course, is do these variables change across the menstrual cycle? Kashuba and Nafziger (1998) have reviewed the data on changes in a number of physiological variables associated with the menstrual cycle (which may have the potential to influence pharmacokinetics and pharmacodynamics) (Table 8.1) and the data on pharmacokinetics across the menstrual cycle. The opening paragraph of the review gives an accurate summary of the current state of this area of pharmacological research, "There is an increasing awareness that the exclusion of women from clinical trials may lead to inaccurate application of drug therapy in women. Gender and oestrous cycle differences in pharmacokinetics and pharmacodynamics of drugs in animals have been appreciated for over 60 years, but investigation into these differences in humans has only recently occurred." (1998, p. 203).

From the data on physiological variables summarised in Table 8.1, it is clear that there are functional differences between males and females that have the potential to change pharmacokinetic and pharmacodynamic parameters. One factor not included in this table is the menstrual cycle-related fluid retention that occurs in a subset of females, and has the potential to lower plasma concentrations of drugs (Yonkers *et al.*, 1992).

The only area of pharmacokinetics where there is evidence for differences associated with the menstrual cycle is in drug metabolism by the liver, sometimes referred to as biotransformation. Interestingly, the metabolism of a number of drugs is influenced by administration of oral contraceptives. The liver enzyme system involved in the

Table 8.1 Physiological variables and the menstrual cycle

	Cycle/hormone-related changes
Kidney function	
creatinine clearance	no clear evidence
glomerular filtration	no effect of oestrogen
vasopressin	higher in luteal phase
sodium excretion	decreases with increasing oestrogen
GI system	
colonic transit time	f > m, no cycle differences
Cardiovascular system	
heart rate	higher in luteal phase
diastolic BP	lower in luteal phase
systolic BP	higher in luteal phase
stroke volume	increased in luteal phase
cardiac output	increased in luteal phase
lipids/lipoproteins	no change across cycle
Metabolism	
temperature*	increased in early luteal phase
energy expenditure	increased in luteal phase
Blood	
platelet aggregation	increased in luteal phase
immune responses	decreased with high oestrogen/progesterone

From Kashuba and Nafziger (1998).
* Both core and skin temperature; BP, blood pressure; GI, gastrointestinal.

metabolism of many drugs is the cytochrome P450 (CYP) system and within this system there are different isoforms of CYP with specificity for different drugs. One of the primary pathways for drug metabolism is via the CYP3A4 isoform. In humans, this pathway accounts for the metabolism of approximately 50% of all therapeutic drugs (Kharasch *et al.*, 1999). Whether or not there are female/male differences in the activity of CYP3A4 is debatable. An *in vitro* study comparing the activity of CYP3A4 in human liver microsomes from females and males has reported that CYP3A4 activity is higher in the microsomes from females. There is *in vivo* evidence to suggest that systemic clearance of some drugs metabolised by CYP3A4 is faster in females than in males; however, there is also evidence suggesting that there is no difference (Kharasch *et al.*, 1999). There are data to suggest that oral contraceptives may alter the actions of CYP3A4 and that the rate of CYP3A4-related drug clearance may differ between premenopausal and post-menopausal females (Kharasch *et al.*, 1999). One reason for the inconsistency in CYP3A4 results may be the methods used. For example, a number of different drugs including alfentanil, diazepam, erythomycin, methylprednisolone, midazolam, prednisolone and verapamil have been used as CYP3A4 probes. These

Table 8.2 Data on pharmacokinetics and the menstrual cycle

	Available data
Absorption	no clear evidence for cyclic changes
Distribution	few studies, no clear evidence for changes
Metabolism	evidence for differences in metabolism of some drugs
Excretion	conflicting data, no clear evidence for changes

From Kashuba and Nafziger (1998).

drugs vary in their specificity for CYP3A4 and, not surprisingly, have yielded variable results. The benzodiazepine, midazolam, is reported to be one of the most reliable CYP3A4 probes currently available (Kharasch *et al.*, 1999).

Kharasch *et al.* (1999) measured midazolam clearance on days 2, 13 and 21 of the same menstrual cycle of 11 healthy, female volunteers. The subjects ranged in age from 18 to 32 years (mean 26 years) and were within 20% of ideal body weight. Blood hormone levels were not measured, which is somewhat surprising as venous blood was taken for drug clearance analysis. On each experimental day, for each subject, an intravenous catheter for drug administration was positioned in a hand or arm vein, while an intravenous catheter for blood sampling was placed in a vein in the other hand or arm. The drug probe was an intravenous injection of 1 mg midazolam. Blood samples were obtained over the following 8 hours and analysed using gas chromatography-mass spectrometry. The mean plasma concentrations of midazolam (approx. 40 ng/ml immediately following injection, decreasing to approximately 1 ng/ml after 8 hours) were not significantly different for the 3 test days. The volume of distribution was also unchanged. These results suggest that, for drugs metabolised primarily by CYP3A4, metabolism may be consistent across the menstrual cycle. For drugs which use other metabolic pathways, either alone or in addition to CYP3A4, menstrual cycle-related differences have been observed (Kashuba *et al.*, 1998). For example, the antiepileptic drug, phenytoin, which is metabolised by CYP2C, has been reported to be metabolised more slowly at ovulation compared to metabolism during the menstrual phase (Shavit *et al.*, 1984). Caffeine and the related compound, theophylline (used to relieve severe acute asthma), are metabolised by CYP1A2. Metabolism of both drugs has been reported to be prolonged during the luteal phase compared to the early follicular phase (Kashuba and Nafziger, 1998).

Drug entry into the CNS

The transport of drugs to the brain requires that the drug be carried by the blood circulation into the brain's blood vessels, first in the arteries and finally in the capillaries. From the capillaries, the drugs must cross the capillary wall (the blood-brain barrier) to enter the brain tissue. The quantity of drug available to cross the blood-brain barrier will depend in part on the amount of blood protein and the binding of the drug molecules to protein. There is very little, if any, difference between males and females in the binding of drugs to various plasma proteins. Blood constituents that may bind drugs include hormone binding globulins and lipoproteins and, although some sex dif-

ferences have been reported, the physiological effects for most drugs would be negligible (Harris *et al.*, 1995).

Although the blood-brain barrier has traditionally been assumed to be the same in females and males, there is some evidence to suggest that there may be sex-related differences in permeability for some drugs. Nordin (1993) reported that the CSF to plasma ratio for a metabolite of the antidepressant drug, nortriptyline, but not for nortriptyline itself, differs between human females and males. The subjects in the study were 17 females (mean age 46 years) and 8 males (mean age 45 years) who were inpatients suffering from depression. CSF was collected by lumbar puncture and blood samples were taken weekly from the second week of antidepressant treatment. When the CSF/plasma ratios of the drug were compared across subjects, the ratios were significantly higher in females compared to males. In males, but not females, the ratio was correlated with body height (which affects the clearance rate of some drugs). If both males and females had shown the same height/ratio correlation, the results could have been explained in terms of clearance alone. However, as the height to ratio correlation did not occur for females, other possible explanations, including differences in blood-brain barrier permeability, can be considered.

A study of blood-brain barrier permeability in rats using a labelled amino acid marker, revealed no female/male differences in permeability in intact animals (Saija *et al.*, 1990). However, when overiectomised (OVX) female rats were compared with rats in oestrous and proestrous, the OVX rats showed significantly higher blood-brain barrier permeability. Finally, it has also been demonstrated in rats, using a fluorescent marker, that some drugs which enter the brain via the circumventricular organs (Chapter 1), rather than across the blood-brain barrier, may enter in greater quantities in females than in males (Martinez and Koda, 1988).

Drug treatment of neurological disorders

> Quilting, for example, holds together the layers of the traditional futon which the Japanese use as both mattress and bed cover. Futons of the past were beautifully decorative and made either of silk (for the rich) or indigo-dyed and patterned cotton. Centuries ago the Chinese were among many Eastern peoples who wore quilted armor as a protection against arrows and swords and quilted clothing as protection against the cold. It is believed that the Crusaders in the eleventh century brought the idea of quilted garments to Europe and that these eventually led to quilted bed covers.
>
> Sudo, K. (1998)
> *East Quilts West II*,
> Quilt Digest Press, Chicago, p. 9.

Neurodegeneration

In the majority of neurological disorders there is a neurodegenerative process which underlies, or occurs as a result of, the pathological condition. In Parkinson's disease, it is the loss of dopaminergic neurons in the substantia nigra, in Alzheimer's disease it is the loss of cortical neurones. There is evidence to suggest that oestrogen may act as a

neuroprotectant and since some neurological disorders are more prevalent in older people, it is logical to ask if hormone replacement therapy (HRT) may be a useful adjunct to some drug therapies.

Because of the prevalence of neurodegenerative disorders, and the increasing average age of the world's population, increasing amounts of resources have been dedicated to studying the processes associated with neurodegeneration. There are animal models that attempt to reproduce the neurodegenerative process observed in humans. For example there are animal models of Parkinson's disease, Alzheimer's disease and stroke (both ischemic and haemorrhagic) which are used to study the disease process and to test possible therapeutic agents.

There are two types of degenerative process that produce neuronal loss, apoptosis and necrosis (Figure 8.2). Apoptosis, sometimes referred to as programmed cell death, occurs in neural development when an excess of neurones is initially produced. Once developmental patterns are established, the extra neurones die off in the process of apoptosis. This process is not restricted to development, however, and occurs throughout the life span in response to a number of physiological triggers, including disease. During apoptosis the cell and its nucleus shrink and condense; when examined under a microscope, apoptotic cells are often characterised by dark patches of condensed cellular material called "blebbing" and fragmentation. As fragmentation occurs, the cellular debris is rapidly removed by macrophages before an inflammatory response can occur. Necrosis, on the other hand, is the "accidental" form of cell death, often resulting from injury. When necrosis occurs, the cells swell and burst, spilling their intracellular material into the extracellular space, which triggers an inflammatory response.

The excitatory neurotransmitter, glutamate, has been associated with cell death following stroke and other forms of neural damage. It is thought that the axon terminals of damaged neurones release excessive amounts of glutamate, which in turn causes damage (secondary damage) to the neurones receiving their synaptic input (Figure 8.3). When a stroke occurs, damage is initially restricted to the area directly around the lesion (the core). After a period of time, however, secondary damage begins to occur in secondary regions (the penumbra), often quite a distance away from the area of primary damage. It is often the penumbral damage that is fatal to the stroke victim.

The AMPA subtype of glutamate receptor (GluR1 and GluR2/3) and oestrogen receptors have been reported to be co-localised (that is both types of receptors are expressed on the cell surface) on neurones in several brain regions (Diano *et al.*, 1997). Using immunohistochemical methods, neurones containing receptors for oestrogen and GluR1 or GluR2/3 receptors have been identified in the amygdala and hypothalamus (Diano *et al.*, 1997). There is also evidence to suggest that the NMDA subtype of glutamate receptor is co-localised with oestrogen receptors. It has been demonstrated that mRNA for the 2D subunit of the NMDA receptor is co-localised with oestrogen receptors in the hypothalamus, diencephalon and brainstem of female rats and that the 2D subunit mRNA is up-regulated by oestrogen (Watanabe *et al.*, 1999). The effect that this co-localisation of receptors may have is not well understood. However, it provides a possible mechanism for modulation of glutamatergic activity by oestrogen, or oestrogenergic activity by glutamate, which could be important in the development of some

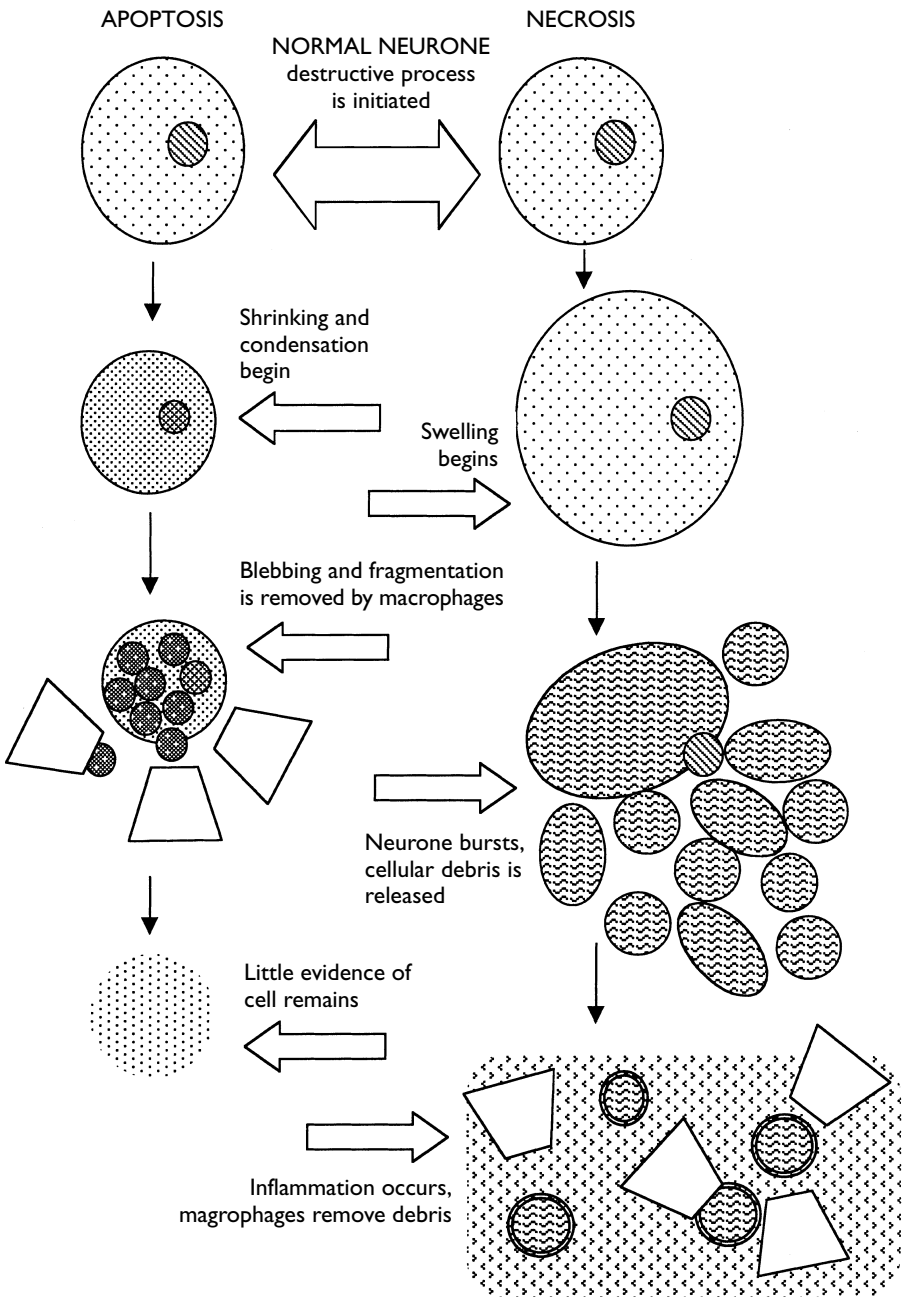

Figure 8.2 Schematic representation of apoptosis and necrosis.

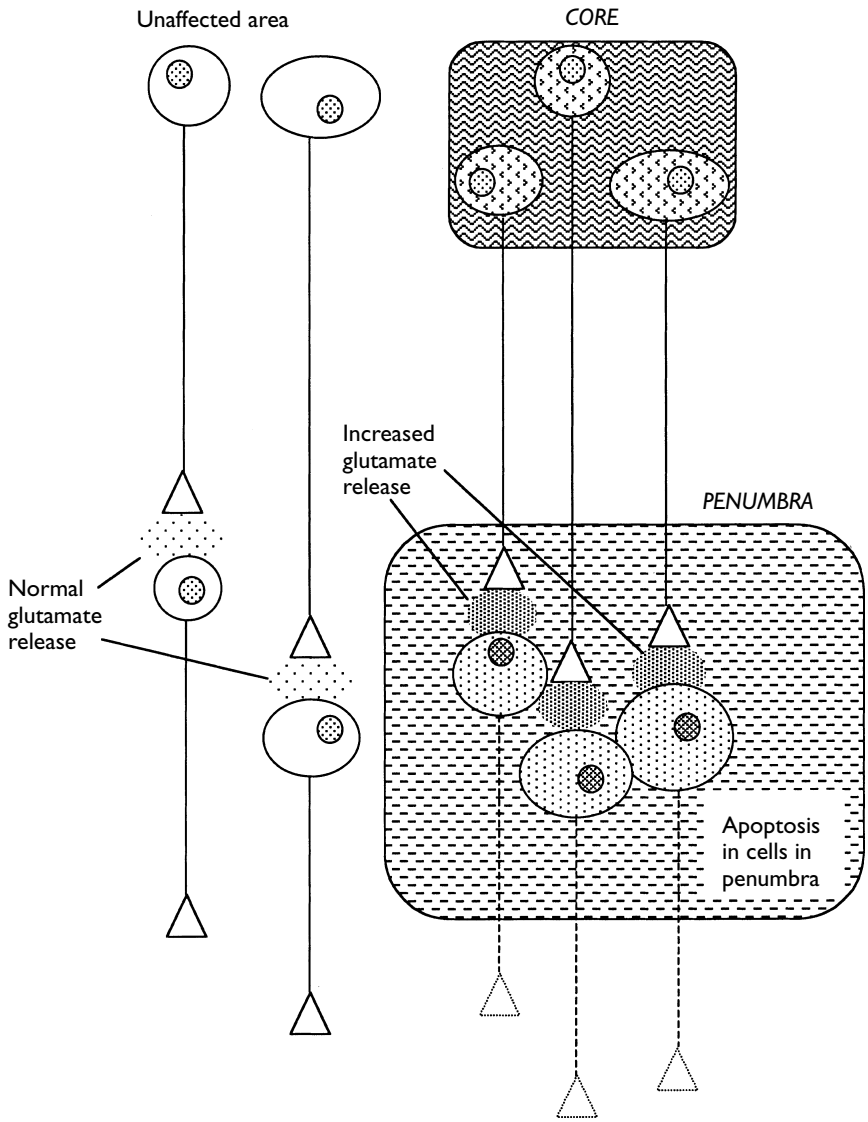

Figure 8.3 Neurones in the core region of the stroke release increased amounts of glutamate. Neurones in the penumbral region are damaged by glutamate excitotoxicity.

drug treatments. Some NMDA receptor antagonists have been demonstrated to be useful in limiting the neural damage following a stroke. Recently, however, it has been demonstrated that the NMDA receptor antagonist, dizocilpine maleate, which at high doses produces cell death in selected neuronal populations, produces more severe damage in female rats than in male rats (Colbourne *et al.*, 1999). This is particularly interesting, because dizocilpine maleate is one of the NMDA receptor antagonists that has been demonstrated to act as a neuroprotectant under some conditions.

In a number of experimental studies, administration of oestrogen has been demonstrated to reduce the damage caused by experimentally induced stroke in rats (Dubal *et al.*, 1998; Simkins *et al.*, 1997; Alkayed *et al.*, 1998). Although the protective effect has been well demonstrated, its mechanism has not been clear. Recently, it has been reported that the activity of *bcl-2*, a proto-oncogene which has been demonstrated to block both apoptosis and necrosis, is enhanced by oestrogen treatment (Dubal *et al.*, 1999). In this study, 2 groups of ovariectomised female rats were subjected to cerebral ischemia. One group received continuous oestrogen treatment, the other group was treated with the oil vehicle only. Twenty-four hours after the ischemia was induced, the animals' brains were removed for analysis. In situ hybridisation was used to look for changes in the expression of oestrogen receptor mRNA, and RT-PCR was used to analyse the tissue for *bcl-2* gene expression. Analysis of the results revealed that expression of *bcl-2* was down-regulated following ischemia, but the down-regulation was prevented by administration of oestrogen. In addition, expression of oestrogen receptors was changed after injury.

Parkinson's disease

In animal models of Parkinson's disease, administration of oestrogen has been demonstrated to protect neurones in the substantia nigra against the damaging effects of neurotoxins (Dluzen, 1997; Disshon and Dluzen, 1997). The question is whether or not this protective effect seen in the laboratory will translate to a useful clinical application. A study of post-menopausal female patients with Parkinson's disease of less than 5 years' duration suggests that there may be a clinical benefit from oestrogen as indicated by lower disability scores. The study included 138 subjects, of whom 34 subjects (mean age 61 years) had taken HRT at some stage, 104 subjects (mean age 66 years) had never taken HRT. However, the average age of disease onset was significantly lower (5.6 years) in the group who had taken HRT, and the average symptom duration was significantly longer (0.5 years) in the HRT group (Saunders-Pullman *et al.*, 1999). Another study of post-menopausal females with Parkinson's disease ($n = 167$) has reported that although HRT protected against the development of dementia associated with Parkinson's disease, it did not reduce the risk of developing the disease itself (Marder *et al.*, 1998). The mainstay of treatment for Parkinson's disease is L-dopa, a precursor of dopamine, which crosses the blood-brain barrier and is metabolised to dopamine in the brain. There is little evidence on interactions between L-dopa and either oestrogen or progesterone; however, it has been reported that, in rats, administration of progesterone increases L-dopa-stimulated release of dopamine from neurones in the caudate nucleus (Dluzen and Ramirez, 1989).

Alzheimer's disease

The possible role of oestrogen in the enhancement of memory and cognition has received a great deal of media attention recently. It has been suggested that there is an "oestrogen setpoint", possibly different in each person, and that when oestrogen levels drop below that setpoint, cognitive function is disrupted (Arpels, 1996). Not only has HRT been suggested as a way of slowing the cognitive changes associated with

normal ageing, it has also been suggested as a possible treatment strategy for Alzheimer's disease.

Wolf *et al.* (1999) tested the effects of transdermal administration of HRT on cognitive performance in a double blind study of 38 healthy, elderly female subjects. Twenty-one subjects (mean age 70 years) received oestrogen via transdermal patches placed on the back, 17 subjects (mean age 68 years) received placebo patches. Before placement of the patches and again, after 2 weeks of treatment, the subjects completed a range of cognitive tasks. At the same time, blood samples were taken to assess blood oestrogen levels. Analysis of the results of the cognitive tests showed no differences in performance that could be attributed to oestrogen treatment. However, analysis of blood oestrogen levels revealed large variations in plasma oestrogen in the treated group. When the data for the treated group were reanalysed with plasma oestrogen levels as one of the independent variables, differences in cognitive performance became apparent. The performance on the verbal memory task with delayed recall was positively correlated with plasma oestrogen; the higher the oestrogen, the better the performance. This study is particularly interesting because the memory improvement was seen after only 2 weeks of treatment and the subjects, who were, on average, 17 years post-menopause, still benefited from oestrogen.

Results from the Baltimore Longitudinal Study of Ageing indicate that HRT significantly decreases the risk of developing Alzheimer's disease, as does the use of non-steroidal anti-inflammatory drugs (Kawas *et al.*, 1997). Of 472 peri- and post-menopausal female subjects followed for up to 16 years, 45% reported using HRT. There were 34 cases of Alzheimer's disease out of the 472 subjects and only 9 of the cases were HRT users. A longitudinal study of 1124 elderly females living in New York City has also reported that HRT significantly reduces the occurrence of Alzheimer's disease (Tang *et al.*, 1996). Of the 1124 subjects in the study, 167 (14.9%) developed Alzheimer's disease. Of the subjects developing the disease, 158 (95%) had never taken HRT, 5 (3%) had taken HRT for a year or less, and 1 subject (0.5%) had taken HRT for more than 1 year (Figure 8.4).

Tacrine, an acetylcholinesterase inhibitor, is used in the treatment of Alzheimer's disease. Although tacrine does not ultimately alter the course of the disease, it can, in the earlier stages, improve cognitive function and enhance the quality of the patient's life. A double-blind, randomised, placebo controlled study ($n = 318$) on the effect of combining tacrine with HRT has reported that subjects taking the combination of drugs showed more improvement over the 30 week study than subjects taking tacrine alone (Schneider *et al.*, 1996).

Multiple sclerosis

There is very little evidence, for or against, the use of HRT in MS. A study of experimental allergic encephalomyelitis in female rats has demonstrated that administration of oestradiol, but not medroxyprogesterone, inhibits the development of this experimental form of MS (Arnason and Richman, 1969). The results of a questionnaire survey of 19 peri- or post-menopausal females with MS suggest that HRT may be beneficial in alleviating symptoms. The subjects responding to the questionnaire had a mean age of 56 years and a mean disease duration of 17 years. Seventy-five percent of

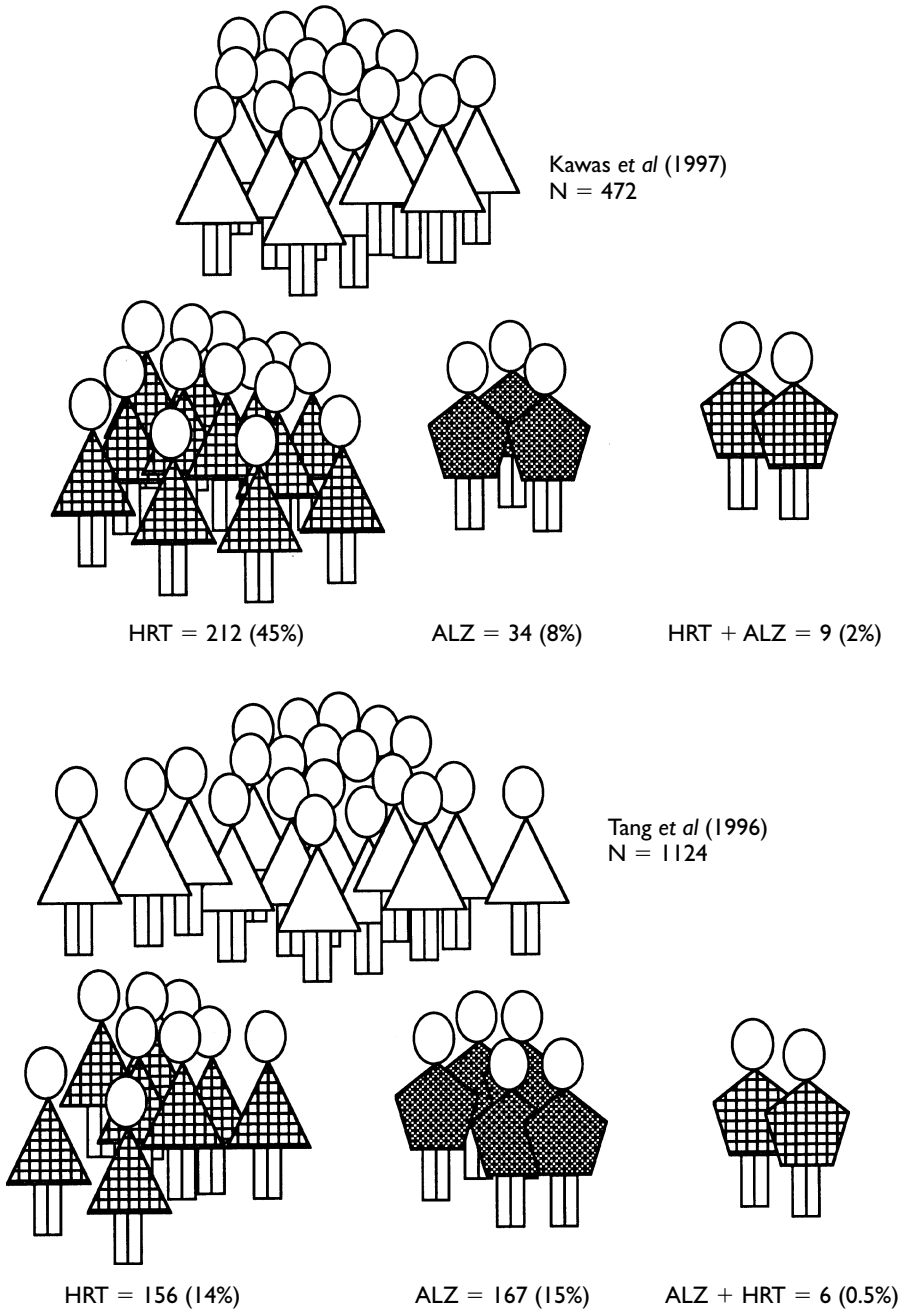

Figure 8.4 Effects of HRT on the development of Alzheimer's disease. Data from Kawas *et al.* (1997) and Tang *et al.* (1996).

the subjects reported an improvement in their MS symptoms with HRT (Smith and Studd, 1992).

Epilepsy

The treatment of epilepsy in females requires the consideration of a number of different factors. If changes in the frequency or intensity of seizures appear to be associated with the menstrual cycle, then it may be possible to introduce hormone therapy to alter seizure susceptibility. However, altering hormone levels may lead to unwanted side effects, such as changes in cognitive function associated with low oestrogen levels. It has been suggested that the dose of antiepileptic drugs could be increased during the phases of the cycle when seizures are most likely to occur, or that other drugs, such as benzodiazepines, could be added during phases of increased seizure activity (Morrell, 1999; Zahn, 1999). Although all of these strategies have been reported to be useful in individual patients, none of them has been systematically tested. Two forms of hormone supplementation which may have fewer, or at least more tolerable, side effects, are the low-oestrogen/high-progesterone oral contraceptive or progesterone supplements. Progesterone supplements may be particularly useful in cases where there are frequent anovulatory cycles or where the luteal phase is consistently irregular. However, progesterone supplementation is associated with cognitive side effects such as depression or sedation as well as breast tenderness and breakthrough bleeding (Zahn, 1999).

There is very little evidence on the effects of menopause on epilepsy (Table 8.3). A

Table 8.3 Effects of menopause and HRT on seizure activity

	Number of patients
Peri-menopausal patients	39
pre-peri-menopausal catamenial epilepsy	28 (72%)
effect of peri-menopause:	
decreased seizure activity	5 (13%)
increased seizure activity	25 (64%)
no change in seizure activity	9 (23%)
patients taking HRT	8 (15%)
HRT	no significant effect
Post-menopausal patients	42
pre-menopausal catamenial epilepsy	16 (38%)
effect of menopause:	
decreased seizure activity	17 (40%)
increased seizure activity	13 (31%)
no change in seizure activity	12 (29%)
patients taking HRT	16 (38%)
effect of HRT	increased seizure activity during peri-menopause

From Harden *et al*. (1999).

recent questionnaire study of 42 post-menopausal patients (aged between 41 and 86 years) and 39 peri-menopausal patients (aged between 38–55) with epilepsy asked the participants about the pattern of their seizure activity and their treatment both before and after menopause. Sixteen (38%) of the subjects reported a pre-menopausal pattern consistent with catamenial epilepsy. In both groups, the patients with catamenial epilepsy reported that post-menopause was significantly associated with a decrease in seizure activity, however, seizure activity was reported to increase during the peri-menopause (Harden *et al.*, 1999)

Pain and analgesia

Analgesics, drugs that reduce pain, are often divided, for descriptive purposes, into prescription and non-prescription (over-the-counter) drugs. A survey of analgesic use in Sweden for 1988 and 1989 showed that females purchased more prescription and non-prescription analgesics than males. Prescription analgesics were most often purchased by people aged 45 or older, while the greatest use of non-prescription analgesics was in people aged 18 to 44. When analgesics were purchased for headache pain, both females and males purchased more non-prescription drugs. When the cause of pain was musculoskeletal, however, females were more inclined to use non-prescription analgesics than males (Antonov and Isacson, 1998).

Sex differences have been reported in the effectiveness of different analgesics. Interestingly, the effect is not the same across drugs, suggesting very specific interactions between hormones and analgesics. In rats it has been reported that males are more sensitive than females to morphine-induced analgesia (which acts on the μ opioid receptor) (Cicero *et al.*, 1996). In humans, nalbuphine (which acts on the κ opioid receptor) has been reported to produce better analgesia in females than in males following dental surgery (Gear *et al.*, 1999). The non-steroidal anti-inflammatory drug, ibuprofen, has been reported to be more effective in reducing experimentally-produced pain (electrical stimulation of the earlobe) in males than in females (Walker and Carmody, 1998).

Drug treatment of psychiatric disorders

Anxiety

Until fairly recently, the treatment of anxiety has relied heavily on drugs categorised as CNS depressants (Table 8.4). Many of the drugs in this category act by potentiating the action of the inhibitory neurotransmitter GABA, and exert their effects by generally suppressing the activity of many CNS neurones. It is a characteristic of drugs in the CNS depressant category that at low doses they produce a mild sedative effect. At higher doses they cause drowsiness and sleep, until at the highest doses they can produce coma and death. Drugs in this category also have a high dependence liability (see section on drug abuse).

> High in the picturesque Swiss Alps, the fourth generation of the Elsener family continues the tradition of quality cutlery started by Charles and Victoria Elsener in 1884. In 1891 they obtained the first contract to supply the Swiss Army with a

Table 8.4 Examples of anxiolytic drugs

Drug	*Site of action*
CNS depressant:	
benzodiazepines:	$GABA_A$ receptor
diazepam	
chlordiazepoxide	
barbiturates*:	$GABA_A$ receptor
pentobarbital	
alcohol	$GABA_A$ receptor
atypical anxiolytic:	
buspirone	$5HT\text{-}1_A$ receptor

* Because of their serious side effects, barbiturates are no longer considered the drug of choice in the treatment of anxiety.

> sturdy ≪Soldier's Knife≫. Shortly afterwards, Charles Elsener developed the elegant ≪Officer's Knife≫. This revolutionary knife, design officially registered on June 12th 1897, became popular throughout the world because of its high quality, versatility and excellence in design.
>
> Victorinox **GUARANTEES** all knives to be of first class stainless steel and also guarantees a life time against any defects in material and workmanship. Damages caused by misuse or abuse are not covered by this guarantee.
>
> Victorinox Sales Brochure, 9.60 18.1.

CNS depressants act on the $GABA_A$ receptor, which is widely distributed on neurones throughout the brain. The $GABA_A$ receptor is particularly interesting because, in addition to a binding site for GABA, it has additional specific binding sites (allosteric binding sites) for anxiolytic drugs and hormones (Figure 8.5). Binding of ligands to the allosteric binding sites modulates the activity of the $GABA_A$ receptor produced by the binding of GABA to its binding site. In humans, using PET and radioactively-labelled flumazenil, it has been demonstrated that benzodiazepine binding to the $GABA_A$ receptor is reduced throughout the brains of patients with panic disorder compared to normal control subjects. The decreases were greatest in the brain regions thought to be associated with anxiety, the right orbitofrontal cortex and the right insular cortex (Malizia *et al.*, 1998).

Steroids that act as agonists at the $GABA_A$ receptor have the effect of sedatives, inducing sleep and acting as anaesthetics as well as reducing anxiety (Majewska, 1992). Steroids that act as antagonists, on the other hand, may cause insomnia and anxiety, and have also been reported to improve memory (Majewska, 1992).

It has been demonstrated that tetrahydroprogesterone, tetrahydrodeoxycorticosterone and androsterone activate the $GABA_A$ receptor and that the effect of these steroids is to prolong the opening of the receptor-associated chloride ion channel (Majewska, 1992) (Table 8.5) (Figure 8.5). Wilson and Biscardi (1997) have reported that the magnitude of the effects on chloride influx of tetrahydrodeoxycorticosterone,

Table 8.5 Effects of 3 steroids on $GABA_A$ receptor activity

Steroid	*Effect*
tetrahydroprogesterone	prolongs chloride channel opening: hippocampus > cortex, amygdala > hypothalamus, cerebellum
tetrahydrodeoxycorticosterone	prolongs chloride channel opening: hippocampus > cortex, amygdala (m > f) > hypothalamus (m > f), cerebellum
androsterone	prolongs chloride channel opening: amygdala, hippocampus > cortex, hypothalamus > cerebellum

From Wilson and Biscardi (1997), Majewska (1992).

tetrahydroprogesterone and androsterone differs between brain regions. For tetrahydrodeoxycorticosterone and tetrahydroprogesterone the greatest effect was found in the hippocampus, with less effect in the cortex and amygdala and the least effect in the hypothalamus/preoptic area and cerebellum. For androsterone, the effect was greatest in the amygdala and hippocampus, with less effect in the cortex and hypothalamus/preoptic area and the least effect in the cerebellum. In addition, there were differences between female and male rats for tetrahydrodeoxycorticosterone in the amygdala and hypothalamus/preoptic area, where chloride influx increase was largest in males.

Two other steroids, stanozolol and 17α-methyltestosterone (synthetic anabolic-androgenic steroids), act on the $GABA_A$ receptor by inhibiting the binding of GABA agonists. Masonis and McCarthy (1995) used radioactively labelled flunitrazepam (a drug that acts as an agonist for the benzodiazepine binding site, one of the allosteric binding sites known to modulate $GABA_A$ receptor activity) to measure the binding of the steroids in rat brain. The authors report that although both drugs did inhibit the binding of flunitrazepam, stanozolol demonstrated much greater affinity, requiring a much lower concentration than 17α-methyltestosterone to inhibit binding. More interestingly, however, were the reported differences in binding between female and male brain tissue. By measuring the amount of radioactivity in the brain tissue and comparing changes in radioactivity across different drug concentrations, it is possible to determine some of the characteristics of the drug binding site, especially the number of different kinds of sites to which the drug is binding. In the brain tissue from male rats, the drug appeared to bind only to a single kind of binding site. In the brain tissue from female rats, however, there were two different kinds of binding sites, one with a high affinity for the drug and one with a lower affinity.

The results of binding studies of the $GABA_A$ receptor suggest a mechanism for sex differences in behaviours related to GABA function. In rats subjected to restraint stress, the pattern of binding of labelled flunitrazepam in the frontal cortex and amygdala differed between female and male rats (Farabollini *et al.*, 1996). In the frontal cortex from female animals, there was lower affinity binding but there were more receptors, while

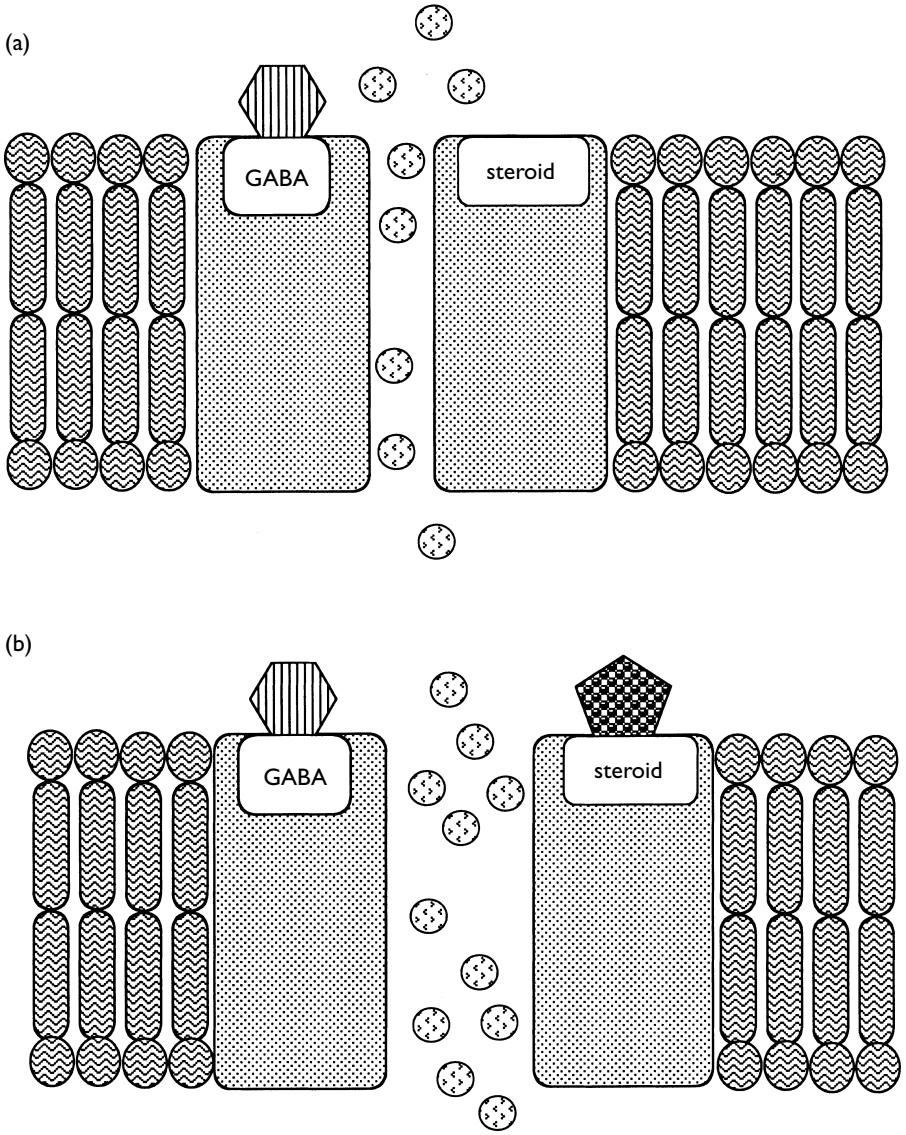

Figure 8.5 Binding of GABA to the $GABA_A$ receptor produces an influx of chloride ions (A). Binding of GABA when the steroid binding site is occupied produces an increased chloride influx (B).

males showed an increased affinity but no change in receptor numbers after restraint. There were no restraint-associated changes in the binding of flunitrazepam in the amygdala of either females or males. In addition, the threshold for producing seizures in rats using the GABA antagonist, bicuculline, was lower in adult male rats than in adult female rats (Bujas *et al.*, 1997).

Because anxiety disorders are more prevalent in females than in males (Chapter 7),

females also receive more prescriptions of anxiolytic drugs. As there are differences in the actions of the $GABA_A$ receptor between females and males, the possibility that anxiolytic drugs may act differently in females and males is very real. In addition, changes in drug actions across the menstrual cycle and the possibility for interactions between oral contraceptives and drugs, has to be considered.

A randomised, double-blind study of the effects of triazolam at different phases of the menstrual cycle has yielded interesting results (de Wit and Rukstalis, 1997). The participants in the study were 20 healthy, non-depressed females aged between 18 and 35 years. There were six 24 hour test sessions for each subject, 2 sessions in the follicular phase, 2 sessions at ovulation and 2 sessions in the luteal phase. A test session commenced at 8 pm when the subject entered the research facility. Urine specimens were taken at that time, and the subject then stayed overnight in the facility. At 8 am the next day, an i.v. catheter was placed in an arm vein and a baseline blood sample was taken to establish baseline levels for progesterone, oestradiol and allopregnanolone. The subject then completed a series of tests to assess mood, arousal and cognitive performance. At 8.30 am a capsule containing either 0.25 mg triazolam or placebo was administered. Over the following 12 hours blood samples were taken, and mood, arousal and cognitive performance were assessed. When mood and cognitive performance were compared across the 3 test days, there was no clear correlation between hormone levels and test results. However, when the different phases of the menstrual cycle were analysed independently, before drug administration in the luteal phase, there was a clear relationship between self-reported levels of arousal and the amount of allopregnanolone in the plasma. Higher levels of the hormone were associated with lower levels of arousal. However, in the luteal phase following triazolam administration, higher levels of allopregnanolone were associated with a self-reported increase in arousal. The presence of the drug reversed the relationship between the hormone and level of arousal.

An interaction between triazolam and progesterone has been reported in postmenopausal females. Kroboth and McAuley (1997) administered progesterone to subjects, followed 2.5 hours later by triazolam. In the group receiving pretreatment with progesterone, the psychomotor and sedative effects of the triazolam were significantly increased, and were independent of pharmacokinetic changes.

Although benzodiazepines as a drug class have very similar effects, there are two different metabolic pathways for benzodiazepines. Whether or not there is an interaction between benzodiazepines and another drug will depend, in part, upon whether they share the same metabolic pathway. These two processes are known as oxidation and conjugation, and oral contraceptives have been demonstrated to increase the conjugation process but inhibit oxidation. Therefore, benzodiazepines (such as alprazolam, triazolam, and diazepam) which are oxidised by liver enzymes, may have their metabolism inhibited in the presence of oral contraceptives (i.e. they may remain in the system much longer). On the other hand, the benzodiazepines metabolised via the conjugation pathway (such as lorazepam, oxazepam and temazepam) may be metabolised much more quickly with oral contraceptives. Kroboth *et al.* (1997) have studied the effects of oral contraceptives on responses to lorazepam, temazepam, alprazolam and triazolam. Clearance of alprazolam was significantly decreased in the subjects taking oral contraceptives compared to the control subjects. Clearance of

temazepam was increased in the contraceptive users and clearance of lorazepam was the same as controls.

An interaction between diazepam and oral contraceptives has also been reported. An early study by Ellinwood *et al.* (1984) reported that females taking oral contraceptives showed significant impairment in a motor task on an "off" day compared to an "on" day. Eight female subjects aged between 21 and 26 years, and taking oral contraceptives, participated in the study. A number of tasks were used to assess cognitive and motor performance but only 2 tasks were discussed (Figure 8.6). The cognitive task required the subjects to learn a set of symbols, each of which corresponded to a digit between 1 and 9. During testing, the symbols were presented individually on a computer screen and the subject was required to press the keypad number corresponding to the symbol. In the motor task, a moving vertical line was presented on a computer screen. A short segment of the vertical line moved independently of the rest of the line. The task of the subjects was, using a "steering wheel" joystick, to keep the small line aligned with the large line. Subjects were tested before and after administration of 0.28 mg/kg diazepam, on cycle day 10 ("on" the oral contraceptive) and day 28 ("off" the oral contraceptive). There were no differences between day 10 and day 28 in pre-drug performance on either task. Following drug administration, performance was significantly impaired on both tasks, however, the impairment on the tracking task was significantly greater on day 28 compared to day 10. Performance on the digit matching task was equal on the two days. The peak impairment was also reached earlier on day 28 (20 mins) than on day 10 (60 minutes) (Ellinwood *et al.*, 1984).

To date, there is no evidence to suggest that the anxiolytic drug buspirone, which acts on the 5HT-1_A receptor, has sex-specific effects.

> In interview after interview, Sellers explained his strangeness by claiming: "I have no personality of my own, you see. I could never be a star because of this. I'm a character actor. I couldn't play Peter Sellers the way Cary Grant plays Cary Grant, say – because I have no concrete image of myself. I look in the mirror and what I see is someone who has never grown up – a crashing sentimentalist who alternates between great heights and black depths. You know, it's a funny thing, but when I'm doing a rôle I feel it's the rôle doing the rôle, if you know what I mean. When someone tells me, 'You were so great as so-and-so', I feel they should be telling this to so-and-so, and when I finish a picture I feel a horrible sudden loss of identity".
>
> Lewis, R. (1994)
> *The Life and Death of Peter Sellers*,
> Random House, London, p. xvii.

Depression

There are four main categories of drugs primarily used to treat unipolar depression: tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors and atypical agents (e.g. bupropion) (Table 8.6). The first three categories of drugs act by modulating the serotonergic and noradrenergic neurotransmitter systems. While tricyclics were the first antidepressants and are still an important

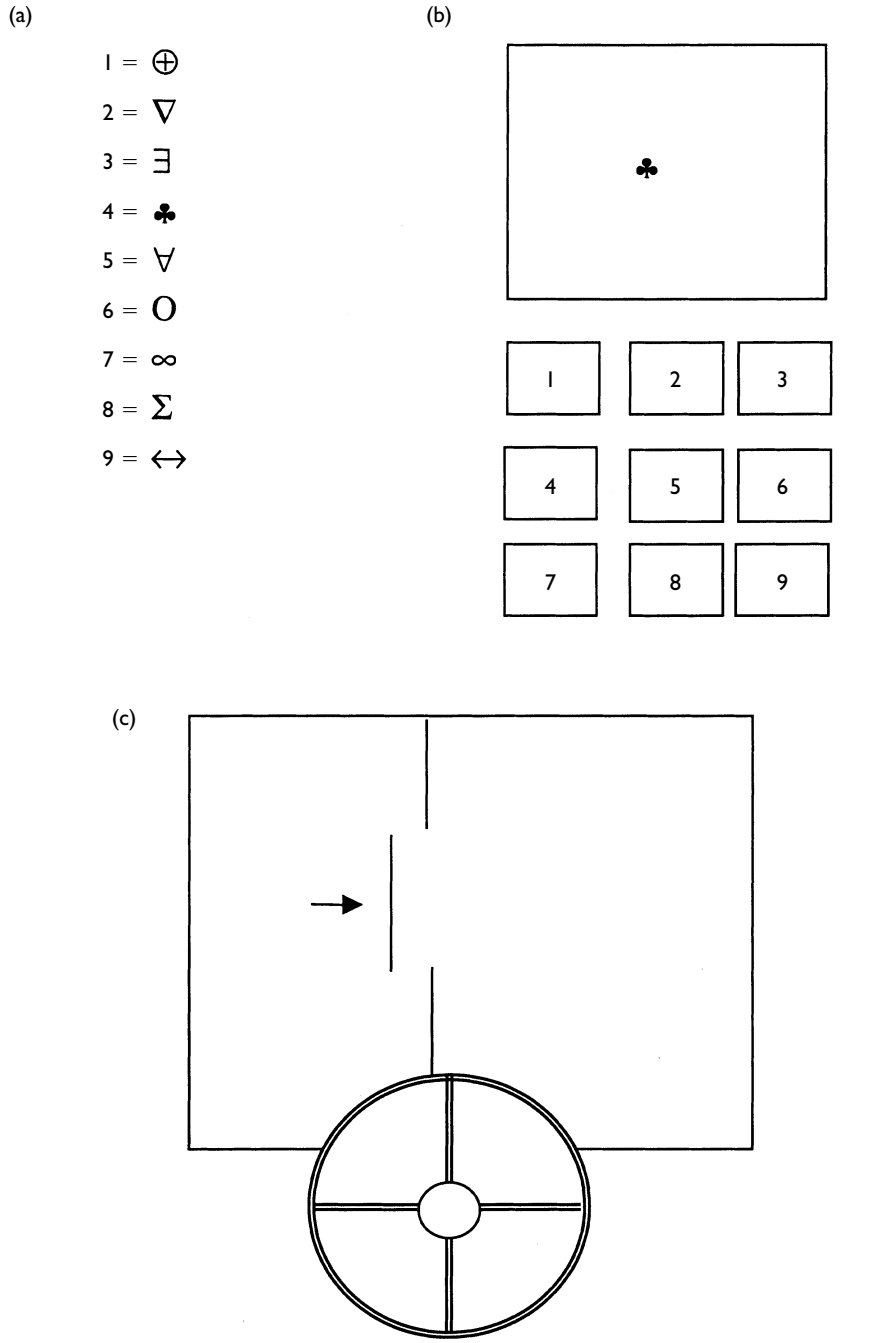

Figure 8.6 Schematic representation of tasks used by Ellinwood *et al.* (1984). Digit-Symbol Substitution Task, memorise list of digits and symbols (A), when symbol is displayed, press button to select corresponding digit. Motor task, use "steering wheel" to keep moving centre line aligned with fixed vertical line.

Table 8.6 Examples of antidepressant drugs

Drug	*Site of action*
Unipolar depression:	
Tricyclic antidepressants	
imiprimine	noradrenaline and 5-HT reuptake
desipramine	
amitryptiline	
Selective serotonin reuptake inhibitors	
paroxetine (Aropax)	noradrenaline and 5-HT reuptake*
fluoxetine (Prozac)	
Monoamine oxidase inhibitors	
moclobemide	inhibits monoamine oxidase type A
Atypical antidepressants	
bupropion	unknown
Bipolar Disorder:	
carbamazepine, valproate	inhibition of voltage-dependent sodium conductances
lithium	intracellular calcium pathways

* These drugs are not nearly as selective for the 5-HT transporter protein as was originally claimed (Rang *et al.*, 1999).

part of the treatment for depression, it is the SSRIs that have captured the attention of the media and the public imagination. The best known SSRI, Prozac, has been dubbed the "happy pill" and the "personality pill" by the popular press. Drugs in the third category, the monoamine oxidase inhibitors, have regained popularity. Forms of the drug which are not specific for a single type of monoamine oxidase (type "A") interact with tyramine-containing foods with sometimes fatal consequences. The dietary restrictions required to take these drugs safely mean that they are only suitable for people who will carefully follow the prescriber's advice. Monoamine oxidase inhibitors which are specific for monoamine oxidase A do not have the severe tyramine interactions and are a very effective treatment option for some people with depression.

There is evidence demonstrating that females and males respond differently to antidepressant drugs. Given the demonstrated differences in the serotonergic system between females and males (Chapter 4), differences in responses to drug treatments would certainly be expected. However, because females were excluded from many antidepressant drug trials, there is much less evidence than might be expected given that females receive the majority of antidepressant prescriptions. In 2000, Frackiewicz *et al.* conducted an extensive literature review to try and determine the extent of the data on female/male differences in antidepressant drug responses. The authors reviewed 124 published references. They found only one study which specifically evaluated female/male differences in response to antidepressants, but many studies which suggested that differences do occur (Frackiewicz *et al.*, 2000).

A number of studies have reported pharmacokinetic differences between females and males for antidepressant drugs, particularly for tricyclics, where higher plasma levels in females have been reported. Unfortunately, many of the studies are retrospective, have very small sample sizes and have not controlled for factors such as smoking and concurrent medication usage, which can significantly alter plasma levels of a number of drugs. Overall, the evidence for sex differences in antidepressant pharmacokinetics is limited. One consistent result, however, is that pregnancy and the use of oral contraceptives may change the metabolism of some antidepressants (Yonkers *et al.*, 1992; Frackiewicz *et al.*, 2000).

There is evidence of female/male differences in the side effects produced by SSRIs. Sexual dysfunction is a major side effect associated with the use of SSRIs: loss of libido and delayed or failed orgasm have been reported by both males and females. In individuals suffering from chronic depression, sexual dysfunction is generally greater in females than in males. SSRI treatment in females has been reported to be associated with significantly improved sexual function, while in males it is associated with significantly worse sexual function (Piazza *et al.*, 1997). Breast enlargement in females has been reported to occur with chronic SSRI treatment (Amsterdam *et al.*, 1997).

A large body of anecdotal evidence, including case studies, suggests that oestrogen may have antidepressant properties, particularly for menopause-associated depression. The majority of evidence to date suggests that for mild depression, oestrogen may be effective; however, evidence for oestrogen's effectiveness in clinical depression is lacking (Pearlstein, 1995). An exception is in the case of postnatal depression, where oestrogen treatment has been reported to be effective (Gregoire *et al.*, 1996). An interesting question regarding the efficacy of HRT in the treatment of depression concerns the formulation of the HRT administered. In females with an intact uterus, oestrogen needs to be supplemented by progesterone to allow the sloughing of the uterine lining and prevent the development of endometrial cancer. Progesterone acts on the $GABA_A$ receptor to increase the inhibitory influx of chloride. It has been reported to produce dysphoria in females and it has also been reported to increase monoamine oxidase activity, which could be expected to increase depression rather than alleviate it (Pigott, 1999).

For the treatment of bipolar disorder, in the past, lithium was the drug of choice and there do not appear to be sex differences in the efficacy of lithium treatment. Recently, the strategies for treating bipolar disorder have changed, and now antiepileptic drugs, such as carbamazepine and valproate, are widely used as the first choice of treatment. Lithium treatment is sometimes augmented by other drugs, such as antipsychotic drugs. When other drugs are used in the treatment of bipolar disorder, then sex differences associated with those specific drugs will also apply to the bipolar patient.

Psychosis

The most compelling evidence for sex differences in response to psychoactive drugs is for antipsychotic medications. Many antipsychotic drugs act on dopamine or 5-HT receptors, and interactions between dopamine or 5-HT and oestrogen are well documented (Chapter 4).

Antipsychotic drugs are classified as classical antipsychotics and atypical antipsychotics. All antipsychotic drugs act, to some extent, on the D_2 subtype of the

Table 8.7 Examples of receptor actions of some antipsychotic drugs

Drug	*Site of action*
Classical antipsychotics:	
chlorpromazine	D_2, α-adr > D_1, H_1, mACh > 5-HT_2
flupenthixol	5-HT_2, D_2 > D_1, α-adr
haloperidol	D_2 > D_1, 5-HT_2, H_1 > mACh, α-adr
thioridazine	α-adr > D_2, mACh, 5-HT_2 > D_1
Atypical antipsychotics:	
clozapine	5-HT_2 > D_1, D_2, α-adr, H_1, mACh
risperidone	D_2, 5-HT_2 > α-adr
seroquel	α-adr > mACh > 5-HT_2, D_2
sulpiride	D_2

Adapted from Rang *et al.* (1999) p. 543. α-adr, alpha subtype, adrenergic receptor; D, dopamine; H, histamine; mACh, muscarinic subtype, acetylcholine receptor; 5-HT, serotonin.

dopamine receptor; some drugs act on other subtypes of dopamine receptors and/or other subtypes of other neurotransmitter receptors. In other words, there is no single mechanism of action guaranteed to have antipsychotic effects. Rather, it is the pattern of action on a number of different receptor subtypes that distinguishes the different antipsychotic drugs (Table 8.7).

Trying to establish an animal model of a complex human condition, such as psychosis, is fraught with difficulties, empirical and logical. How can one possibly tell if an animal is experiencing psychosis? One way of approaching the problem is to administer drugs known to produce psychosis in humans to experimental animals and observe the behaviour. Then, in a leap of faith, to use those same behaviours, when produced by another drug, as an indicator of the psychosis-producing potential of the new drug. Using this approach, stereotyped behaviour in rodents (excessive grooming, rearing, sniffing, etc.) has come to be considered as an "animal model" of psychosis. One drug which produces the symptoms of psychosis in humans and stereotyped behaviour in rats is the NMDA receptor antagonist, dizocilpine maleate.

Administration of dizocilpine maleate (in mg/kg matched doses) to female and male rats has been demonstrated to produce significantly greater stereotyped behaviour, and significantly greater serum and brain levels of dizocilpine maleate, in females compared to males (Andiné *et al.*, 1999). Administration of apomorphine will also induce stereotyped behaviour in rats, and haloperidol can be used to induce catalepsy. Both effects can be reduced by the administration of oestradiol (Häfner *et al.*, 1991). The escape-avoidance response is used to assess drug effects in experimental animals. In this kind of experiment, the animals are placed in an apparatus, usually a 2-way shuttle box, which has distinct areas for the animals to move between. The animal is placed in one side of the apparatus and a signal (often a light) comes on followed a few seconds later by an aversive stimulus, often an electric shock. Initially, the animal leaves the chamber when the shock comes on (escape) but after training, it learns to leave when the light comes on (avoidance). Administration of antipsychotic

drugs impairs the escape-avoidance response in mice, and the impairment is greater in males than in females (Monleón *et al.*, 1998; Parra *et al.*, 1999).

If sweeping generalisations can be made, then one sweeping generalisation that it is fairly safe to make is that females are more sensitive to antipsychotic drugs than males. Females respond "better" to the drugs, but unfortunately they also experience more severe side effects, especially tardive dyskinesia (Pollock, 1997; Jeste *et al.*, 1996; Yonkers *et al.*, 1992). Tardive dyskinesia is a syndrome of motor symptoms, especially grimacing and lip-smacking, which develops as a result of antipsychotic administration. Initially, if treatment is discontinued, the tardive dyskinesia will abate. If, however, treatment is continued, the tardive dyskinesia becomes a permanent, and severe, disability. It appears from the majority of the evidence that oestrogen increases female sensitivity to antipsychotic drugs. However, it has been observed that tardive dyskinesia develops more frequently in postmenopausal females (Yonkers *et al.*, 1992).

A study of hospital admissions of 65 females with schizophrenia to an acute psychiatric ward has reported that 62% of the patients were admitted during the late luteal phase or menstrual phase, when oestrogen levels were lowest. This difference in admission rate between the low- and high-oestrogen phases was interesting, but not statistically significant. However, there was a significant difference between the two groups in the amount of antipsychotic medication required to control the symptoms. The low oestrogen group needed significantly less medication than the high oestrogen group (Gattaz *et al.*, 1994).

Drug abuse

> To such a deep delight 'twould win me,
> That with music loud and long,
> I would build that dome in air,
> That sunny dome! Those caves of ice!
> And all who heard should see them there,
> And all should cry, Beware! Beware!
> His flashing eyes, his floating hair!
>
> Weave a circle round him thrice,
> And close your eyes with holy dread,
> For he on honey-dew hath fed,
> And drunk the milk of Paradise.
>
> Coleridge, S.T. Kubla Khan.
> In *Oxford Book of English Verse: 1250–1918*, Oxford University Press, London (1940).

Drugs that act on the $GABA_A$ receptor, for example, benzodiazepines and alcohol, have a high dependence liability. Abrupt discontinuation of the drugs can result in a withdrawal syndrome which can include restlessness, anxiety, depression and in extreme cases, seizures. Benzodiazepines are particularly liable to produce dependence, even after only a short period of administration, and current prescribing

guidelines usually suggest limiting benzodiazepine prescriptions to 10 days. Although sex differences in liability to benzodiazepine tolerance have not been reported, worldwide the majority of benzodiazepine prescriptions are for females.

The use and abuse of alcohol raises a number of issues for females. Alcohol metabolism is via the liver enzyme alcohol dehydrogenase. The amount of alcohol dehydrogenase available is limited by its rate of synthesis. If the amount of alcohol consumed exceeds the metabolic capacity of available enzyme, the enzyme stores will be depleted and the left-over alcohol will simply stay in the bloodstream until more enzyme is synthesised. This type of elimination, zero order kinetics, is in contrast to the first order kinetics which applies to most drugs. With first order kinetics, the rate of elimination is proportional to the plasma level of the drug (Figure 8.7). In practical terms, excessive alcohol consumption the night before can lead to blood alcohol levels in the morning that are higher than the legal limit for driving a car. On a drink per drink basis, females reach higher blood alcohol concentrations, and eliminate alcohol faster. The higher blood alcohol concentrations may be due to smaller body size and/or differences in alcohol dehydrogenase activity between females and males (Mumenthaler *et al.*, 1999). The basis for the sex differences in the rate of elimination is unclear. It has been reported that neither peak plasma concentration nor elimination of alcohol changes across the menstrual cycle, either in macaque monkeys (Green *et al.*, 1999) or in humans (Mumenthaler *et al.*, 1999). Excessive and prolonged alcohol

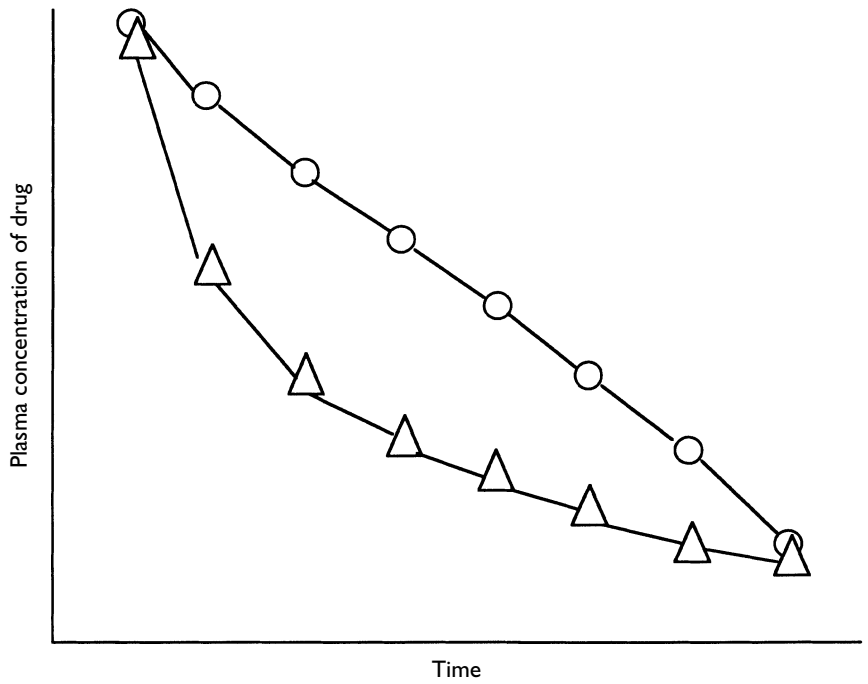

Figure 8.7 Illustration of zero-order and first-order kinetics. Open circles represent zero-order, rate of clearance of drug is independent of plasma drug concentration. Open triangles represent first-order kinetics, rate of elimination is proportional to plasma drug concentration.

consumption causes a number of health problems. In the United States it is estimated that 24% of males and 5% of females suffer from alcohol-related disorders (Seeman, 1997). Although the prevalence of the disorders is significantly lower in females (due to the lower rate of alcoholism in females), the time course of alcohol-related pathology is accelerated (Seeman, 1997). Females generally start drinking later but develop the problems earlier. In addition to the alcohol-related health problems common to males and females, there is an increased risk of breast cancer associated with heavy alcohol consumption and the adverse effects on the foetus caused by alcohol consumption during pregnancy are well publicised and well documented. Recent evidence suggests that foetal alcohol exposure may increase the risk of drug use as an adult (Yates *et al.*, 1998).

Nicotine is the most addictive of all of the drugs of abuse. Smoking and its health-related problems were once more prevalent in males than females. Now, however, female smokers are rapidly closing the gap. In fact, according to a 1997 report, the dependence rates in the United States for alcohol and marijuana are higher in adult males, but the dependence rates for nicotine are higher in adult females (Kandel *et al.*, 1997). The action of nicotine in the brain is as an agonist of the nicotinic subtype of the acetylcholine receptor. One interesting characteristic of the acetylcholine receptor is that it desensitises very quickly. Repeated administration and larger doses of nicotine are required to sustain the initial response. In rats, binding studies have demonstrated that in untreated rats, or in rats withdrawn from nicotine, receptor binding is higher in females than in males. However, chronic nicotine administration results in higher receptor density in male rats, when the measurements are taken before the drug is withdrawn (Koylu *et al.*, 1997). It has also been reported that dopamine release in the striatum of rats evoked by nicotine is greater in females than in males (Dluzen and Anderson, 1997). In human smokers, nicotine has been reported to enhance cognitive performance relative to performance following a period of nicotine abstinence. A group of 13 female smokers were tested, following 12 hours of abstinence and following smoking, on a series of computerised tests of reaction time, motor coordination and the Stroop test. A significant improvement in performance was seen only for the Stroop test and there was no effect of menstrual cycle phase on performance (Pomerleau *et al.*, 1994).

Cannabis (marijuana and hashish) is one of the most widely used drugs in the western world. Cannabis is obtained from the leaves and flowers of the plant, *cannabis sativa*. The psychoactive component of cannabis is Δ^9-tetrahydrocannabinol. Two to twenty-two mg are required to produce psychological effects from smoked cannabis (Ambrosio, 1999). In the past 15 years, the actions of the active constituent of cannabis, Δ^9-tetrahydrocannabinol, have been extensively researched. Cannabinoid receptors in the brain, both of rats and humans, have been identified, and binding studies have established the patterns of receptor distribution in different brain regions. In addition, an endogenous cannabinoid, anandamide, has been identified.

The literature to date suggests that cognitive impairment is associated with a high level of cannabis use. It has also been demonstrated that cannabis is passed almost unchanged into breast milk and that if mother smokes then so does baby (Riordan and Riordan, 1984). Prenatal cannabis smoking has been associated with neonatal distress and sleep disturbances, which can last up to 3 years (Dahl *et al.*, 1995).

Cocaine use in males is estimated to be 3 times more prevalent than in females, possibly because females may experience less effect than males. Sex differences in peak plasma levels for inhaled cocaine have been reported. A study of 14 subjects (F = 7, M = 7) demonstrated that plasma levels in response to 0.9 mg/kg cocaine hydrochloride, reached a significantly higher peak, and the effects were felt significantly faster, in males than in females. In females peak plasma levels were significantly higher during the follicular phase, although the subjects reported no subjective differences in euphoria between the phases (Lukas *et al.*, 1996). A study of male and female responses to smoked cocaine has reported lower subjective ratings of euphoria in females than in males and lower subjective ratings for females in the luteal phase compared to the follicular phase (Sofuoglu *et al.*, 1999) (Figure 8.8).

Menstrual cycle-related changes have also been reported for the subjective effects of amphetamine. In a double-blind, placebo controlled study of 16 female volunteers, aged 18–35, responses to oral administration of 15 mg amphetamine or a placebo, were recorded for 4 hours following administration. Each subject was tested 4 times, twice in the follicular phase (amphetamine and placebo) and twice in the luteal phase

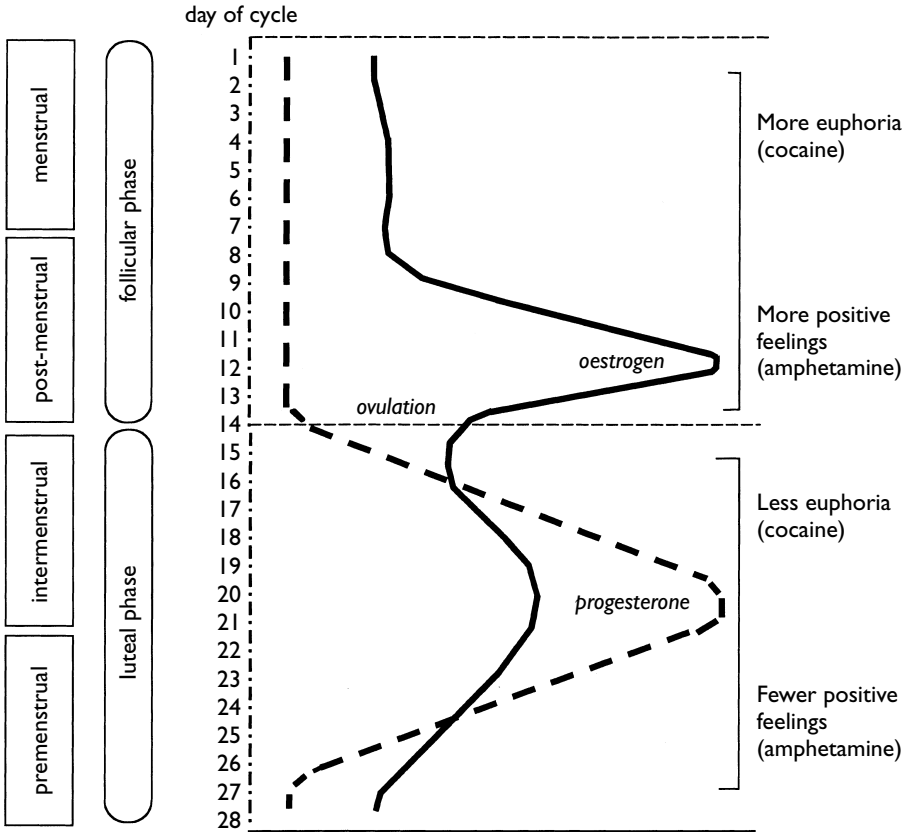

Figure 8.8 Ratings of subjective experiences of cocaine and amphetamine in two phases of the menstrual cycle. From Sofuoglu *et al.* (1999) Justice and de Wit (1999).

(amphetamine and placebo). Blood was drawn at the beginning of each session for analysis of hormone levels. There were no baseline differences in mood between the two cycle phases. Positive feelings following amphetamine administration were reported to be significantly greater in the follicular phase and the magnitude of the experience was related to the levels of oestrogen. Interestingly, in the luteal phase, when progesterone was also present, there was less reported effect of amphetamine and the magnitude of reported response was not related to the level of oestrogen (Justice and de Wit, 1999). An interesting paradoxical response to amphetamine has been reported in post-menopausal females, with the response to i.v. administration of amphetamine being dysphoria rather than euphoria (Halbreich *et al.*, 1981).

Conclusions

> ice′ berg (is bûrg′), n. [of Scand. origin, perh. through D.; cf. Sw. *isberg*, Dan. *isbjerg*, D. *ijsberg*, G. *eisberg*; prop., a mountain of ice. See ICE; BARROW hill. CF. BERG.].
>
> 1. A glacier. *Obs.*
> 2. A floating mass of ice, detached from a glacier when it reaches the sea. Icebergs occur as huge blocks or in peaked forms of great variety and beauty. About one ninth of the bulk projects above sea level.
> 3. A person of cold temperament.
>
> *Websters New International Dictionary*, Second Edition. Unabridged. Merriam, Springfield (1934).

The following summarises the main points to be drawn from Chapter 8.

1. Oestrogen may have neuroprotective properties in conditions such as stroke and Alzheimer's disease, and to a lesser extent in Parkinson's disease.
2. There is limited, but sufficient, evidence to suggest that there are differences between females and males in the effects of anxiolytic, antidepressant and antipsychotic drugs due to differences in drug actions in the CNS.
3. There is a female vulnerability/disadvantage for the long-term effects of antipsychotic drugs. Antipsychotic medications are generally more effective in females than in males, but females are also more likely to develop tardive dyskinesia.
4. There may be a place for oestrogen supplementation of some drug therapies, for example, in Alzheimer's disease and depression.
5. Hormonal status should be a consideration in the prescription of psychoactive drugs to female patients.

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9

Where do we go from here?

> How to solve LOGIC PROBLEMS
> Welcome to the world of Logic Problems! They may *look* complicated, but you don't need any specialist knowledge to solve them. You'll soon find that common-sense and a cool head are all that are required to meet the challenge.
>
> With each standard problem we provide a chart that takes into account every possibility to be considered in the solution. First, you carefully read the statement of the problem in the introduction, and then consider the clues. Next, you enter in the chart all the information immediately apparent from the clues, using an "X" to show a definite "no" and a "/" to show a definite "yes". You'll find that this narrows down the possibilities and might even reveal some new definite information. So now you re-read the clues with these new facts in mind to discover further positive/negative relationships. Be sure to enter information in all the relevant places in the chart, and to transfer newly-discovered information from one part of the chart to all the other relevant parts. The smaller grid at the end of each problem is simply a quick-reference chart for all your findings.
>
> Duncum *et al.* (2000) *Logic Problems*, **89**, 4.

In the last six chapters, evidence has been presented which (although lean in places) clearly supports the premise that there are differences between females and males in both brain structure and brain function. The question, "What does it mean?", however, has not been addressed. In any kind of science, the development of the discipline progresses in stages. Initial interesting observations lead to experimentation. If the observed event occurs naturally, can it also be replicated under experimental conditions? If it can be replicated, then what are the rules governing the replication? What is required for the event to take place and, just as importantly, what is *not* required. What are the *necessary* and *sufficient* conditions to produce the event? Once the

conditions required for the event are established, then predictions about the event can be generated and tested. Take, for example, the development of the understanding of the N-methyl-D-aspartate (NMDA) subtype of glutamate receptor.

Researchers working on the actions of glutamate observed that the activity of glutamate receptors was not consistent in their experiments, suggesting that they were dealing with more than one kind of receptor. One type of receptor seemed to follow the usual activity pattern of a receptor that was activated by neurotransmitter alone. The other (suspected) subtype of receptor, however, seemed to follow a different set of rules. Further research demonstrated that the second receptor subtype, which could be selectively activated by a synthetic substance, NMDA, had an additional requirement for activation: the receptor would only operate when the cell membrane was already partially depolarised by excitatory inputs from other types of receptors. The binding of glutamate or aspartate (or NMDA in experimental conditions) to the NMDA receptor was necessary for the receptor activation but not sufficient. The *necessary and sufficient conditions* were glutamate or aspartate binding and membrane depolarisation. Once the requirements for NMDA receptor activation had been established, then hypotheses about its activity could be generated and tested. Now, a great deal is understood about the NMDA receptor. It is known to be associated with learning and memory processes. It is also associated with glutamate-induced neuronal damage in conditions such as stroke. Drugs which act as antagonists at the NMDA receptor have been used as neuroprotectants in experimental models of stroke, but have also (paradoxically) been shown to induce neural damage at high concentrations. The NMDA receptor has been modelled (model building is the final stage in understanding an area of science) and the model is now used to further test hypotheses. In terms of scientific method, the NMDA receptor has been quite a success story.

In terms of scientific development, the investigation of the female brain is at only the very beginning of the process (probably equivalent to the stage when the researchers discovered that there seemed to be more than one type of glutamate receptor). There are a lot of disparate pieces of information to be analysed. Some of the information is consistent and seems to form a pattern; other information seems contradictory or makes no sense at all. The first step in the development of a science (and ultimately, a model) of the female brain has to be a sorting process. The oestrogen table (Table 9.1) includes subheadings for the type of oestrogen effect (anatomical, physiological, psychological), the nature of the effect, and just for convenience, in which chapter the information can be found. Table 9.2 provides the same "sorted" information for progesterone.

When the actions of oestrogen and progesterone are organised in this way, a pattern begins to emerge. Progesterone seems to be more straightforward, so we will discuss it first. When you read down the table, the entries consistently suggest an inhibitory, CNS depressant activity for progesterone. Most obviously, progesterone increases the inhibitory effects of GABA. This alone could account for the reported sedative effects and dysphoria produced by progesterone. It also could account for the raised seizure threshold. This is also reflected in the increased sedative effects of triazolam and the decreased effects on the CNS of the stimulants, cocaine and amphetamine. Decreased alpha frequency is consistent with decreased arousal, which in turn is consistent with poorer performance on mental rotation tasks. Increases in

Table 9.1 Effects of oestrogen on brain function

	Nature of oestrogen effect	*Chapter*
Neurotransmitters:		
GABA	increases extracellular concentrations in some brain areas	4
serotonin	high levels may desensitise 5-HT_1 receptor	4
	decreases 5-HT_1 binding in cortical regions	
	increases 5-HT_2 binding in cortical regions	
dopamine	increases receptor binding in striatum	4
	decreases amphetamine-stimulated release	
glutamate	upregulates NMDA receptor expression	8
EEG:	increases alpha frequency	4
Laterality:	R hemisphere advantage when low	6
Psychophysics:	mental rotation best when low	5
	increased sensitivity to musk, rose, sucrose, tactile sensations when high	5
Neurology:	MS lesions worst when changing, symptoms worst when low, HRT may reduce symptoms	7
	lowers seizure threshold, increases seizure activity	
	reduces rate of dementia in Parkinson's disease	
	reduces development of Alzheimer's disease	8
	increases perception of pain (?)	
	reduces neural damage	
Psychiatry:	increased suicide attempts when low	7
	increased mood changes when low	
	decreases symptoms of schizophrenia	
Drugs:	mild antidepressant	8
	decreases monoamine oxidase activity	
	less antipsychotic medication needed when levels are rising	
	greater positive feelings from cocaine and amphetamine	

monoamine oxidase activity could also account for feelings of dysphoria (as a result of increased metabolism of noradrenalin and serotonin). The increased suicide attempts and unstable mood when progesterone is low suggest that the loss of inhibition may have a destabilising effect in susceptible individuals.

Oestrogen is more complicated; however, the majority of the evidence points to a general action as a CNS stimulant. Interpretation of the increases in extracellular

Table 9.2 Effects of progesterone on brain function

	Nature of progesterone effect	*Chapter*
Neurotransmitters:		
GABA	increases inhibition	
dopamine	increases L-dopa-stimulated release	8
EEG:	decreased alpha frequency	
Laterality:	L hemisphere advantage when high	6
Psychophysics:	mental rotation worst when high	5
Neurology:	MS symptoms worst when low	7
	raises seizure threshold	
	causes sedation	
Psychiatry:	decreases susceptibility to panic disorder	7
	increased suicide attempts when low	
	increased mood changes when low	
	decreases symptoms of schizophrenia	
Drug interactions:	increases sedative effects of triazolam (post-menopause)	8
	increases monoamine oxidase activity	
	produces dysphoria	
	reduces positive feelings from cocaine and amphetamine	

concentrations of GABA is a difficult issue. GABA is an inhibitory neurotransmitter, however, the effect of increased amounts of GABA will depend upon what kind of cells and receptors it is acting upon. Increased binding of serotonin to 5-HT_2 receptors produces excitatory effects, and interestingly this is in cortical regions. Increased expression of NMDA receptors might also be expected to have an excitatory effect. Consistent with the excitatory effect is the effective lowering of the seizure threshold in experimental models of epilepsy. However, oestrogen cannot be the full story because in catamenial epilepsy, greatest seizure activity is associated with the time when the concentrations of both oestrogen and progesterone are lowest. It is not surprising that oestrogen increases EEG alpha frequency, but it is a little surprising that it does not improve mental rotation. The oestrogen effect in schizophrenia is interesting. If, as has been suggested, one of the problems in psychosis is failure to attend to appropriate stimuli, then perhaps the slight arousing effect of oestrogen assists attention. The effect of decreasing monoamine oxidase activity is consistent with a mild antidepressant effect, which may also explain the increased suicide attempts and mood instability when oestrogen is low.

The neuroprotective effects of oestrogen probably account for the effects in Parkinson's disease and Alzheimer's disease. The odd one out is multiple sclerosis. Increased lesion activity seems to be associated with changes in oestrogen, independent of the direction of the change. However, the well documented decrease in symptoms associated with pregnancy strongly suggests that oestrogen and progesterone are important

considerations. Probably one of the first questions to ask is, "Do oligodendrocytes have oestrogen receptors?"

Oestrogen and progesterone are only two of the areas of information to be sifted through and sorted, but already the evidence for clear and important differences in brain function between females and males is overwhelming. What is important is that the evidence for difference is sound. It is available in the experimental literature to anyone who wants to read it. One of the problems in the past has been an intellectual "shrugging of the shoulders" and dismissal of evidence that should have been recognised and acted upon. So, if as a reader, you are still doubtful about the importance of this area, do not take my word for it, go to the nearest medical library and start reading.

Having established that there is an empirical basis to work from, the next step is to decide how to proceed. In this matter, the NIH Women's Health Initiatives discussed in Chapter 2 serve as an excellent guide. For a start, just the requirement that males and females are equally represented in, *and advantaged by*, medical research should mean that the gaps in the experimental literature start to be filled. In addition, the requirement for representation of females, as researchers, will ensure that, at least in the long term, attention is paid to questions of particular female importance. Another very helpful exercise would be the reanalysis of some of the existing experimental data. Often in the literature, it is clear from the description of the methods that both female and male animals were used but they were then grouped together for analysis. It is conceivable that, stored in labs around the world, are some very important data sets on male and female differences. For future research, experimental design will be a crucial issue. In order to extract the maximum amount of information from a project, the data has to be collected at the appropriate times. Ideally, every study of differences across the menstrual cycle would use blood analysis for hormone levels to establish the exact phase of the cycle. Practically, many researchers will not have the facilities or the financial support to allow blood testing. However, by designing experiments around (at the very least) a 4 phase cycle, a fair degree of experimental control can be introduced. In experiments comparing female and male responses, the importance of menstrual cycle phase for the female subjects is obvious.

It is probably too early to begin making predictions from the data, except possibly in the area of drug development. From the available evidence on the actions of oestrogen and progesterone, there are logical questions to pursue, particularly in areas such as neuroprotection. One of the big problems will be to capitalise on the positive aspects of oestrogen and progesterone use, while minimising the adverse aspects.

Another important direction for development is education, understanding and awareness. The functional differences, which have already been demonstrated, should not be ignored until there is "more evidence". Drug prescribing practice could be modified immediately. Enormous changes are not required. Simply taking into account the phase of the menstrual cycle when prescribing medication would be a good place to start. It is possible to imagine that in a few years' time, prescriptions would actually be modified according to the cycle. So, for example, antidepressant medication might be altered to take advantage of the natural antidepressant properties of high oestrogen levels, then adjusted when oestrogen drops (one can imagine antidepressants coming in little round dispensers with a numbered compartment for each day of the cycle).

Such a strategy just might reduce some of the fluctuations observed in antidepressant therapy. In terms of education, the starting place is for female patients to have the confidence to ask, "Should that prescription be adjusted for my menstrual cycle?"

An Afterthought

After all the chapters were finished, and the figures were in place, someone who had just read the manuscript said to me, "This is really good, but you haven't even mentioned the greatest challenge which the female brain has to overcome."

My heart sank as I envisaged an extensive rewrite. "What's that?", I asked.

"Ah," he replied, "the male brain."

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