Section 1 Basic principles

Chapter 1

History of epilepsy

Edward H. Reynolds

Introduction

Throughout its recorded history of at least 3 to 4 millennia, epilepsy has usually been defined by its most visible and dramatic symptom, i.e. mysterious brief periodic attacks of one kind or another. Thus the ancient Sumerian term 'antasubba' and the later Babylonian and Assyrian word 'miqtu' both refer to 'the falling sickness' (Kinnier Wilson and Reynolds 1990), a term also adopted by the Greeks and Romans and employed by Temkin (1971) as the title of his classic history of epilepsy 'from the Greeks to the beginning of modern neurology', i.e. the late nineteenth century. Since the nineteenth century the paroxysms have been variously referred to as 'fits', 'convulsions', 'seizures' or 'epileptic attacks'. Currently the word 'seizure' is favoured by the International League Against Epilepsy (ILAE) in its classification of such paroxysmal episodes, but whatever word is chosen there are always similar or borderline non-epileptic attacks to confuse the physician in the differential diagnosis.

The word 'epilepsy' is of Greek origin and means to seize, to take hold of or to attack. The word 'seizure' is of Latin origin from 'sacire', i.e. to claim. These words reflect the ancient belief that the sufferer has been seized or claimed by a supernatural power, spirit or god.

Ancient descriptions and concepts

The oldest detailed description of epilepsy is in a Babylonian clay tablet in the British Museum from the second millennium BC (Kinnier Wilson and Reynolds, 1990). The tablet is one of 40 such tablets comprising a Babylonian 'textbook' of medicine and in number 26 the cuneiform text is wholly concerned with epilepsy. The Babylonians were remarkable observers of human illness and behaviour. They accurately described many of the seizure types we recognize today, which we call tonic clonic, absence, complex partial, Jacksonian or even gelastic seizures. They also documented status epilepticus, provocative and prognostic factors and inter-seizure events, including psychoses of epilepsy. However, they had no understanding of pathology or brain function and each seizure type was thought to be the result of an invasion of the body by a particular evil spirit or demon.

The first line of the text states:

> If epilepsy falls once upon a person or falls many times, it is the result of possession by a demon or a departed spirit.

The Babylonians apparently had no doubt about whether a single seizure is epilepsy. Every attack, whether single or multiple, was the result of possession. Here is a remarkable account, for example, of a left-sided focal motor attack in which the progression to loss of consciousness makes it harder to drive out the demon:

> If at the time of his possession, while he is sitting down, his left eye moves to the side, a lip puckers, saliva flows from his mouth, and his hand, leg and trunk on the left side jerk like a newly slaughtered sheep, it is miqtu. If at the time of the possession his mind is consciously aware, the demon can be driven out; if at the time of possession his mind is not so aware, the demon cannot be driven out.

By the time of the later Greco-Roman period, the responsible invading supernatural powers now included Gods. This is reflected in Hippocrates' famous fifth-century BC treatise on 'The sacred disease' in which he doubted whether the human body could be polluted by a God and for the first time suggests a natural causation mediated through disorder of brain

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function: 'The brain is the seat of this disease as it is of other very violent diseases'.

Epilepsy as a brain disorder

Unfortunately this Hippocratic insight had little influence on the prevailing supernatural view of epilepsy until the seventeenth and eighteenth centuries AD, when the concept of a brain disorder began to take root in Europe. By now the focus was on motor paroxysms and the problem was how to distinguish a particular form of motor convulsion, with or without loss of consciousness, from other periodic 'convulsive diseases', such as hysteria, tetanus, tremors, rigors and other paroxysmal movement disorders. The latter were gradually separated off from epilepsy in the nineteenth century especially in the Lumleian Lectures on 'convulsive diseases' by Todd in 1849 and Jackson in 1890.

Functional localization and unilateral seizures

Also the nineteenth century saw the development of the concept of functional localization in the brain (Ferrier, 1876) and the discovery, for example, of the motor cortex (Fritsch and Hitzig, 1870). The concept of 'epileptiform', focal, or partial seizures arose as models for the study of 'generalized' seizures (Jackson, 1870 and 1890). By meticulously studying the clinical features of unilateral motor seizures arising in the motor cortex, Jackson was able to conclude, as was later confirmed experimentally, that the motor cortex was concerned with movements rather than individual muscles.

Idiopathic and symptomatic epilepsy

It was apparent to Jackson and to many others that unilateral or focal seizures were often associated with various local brain pathologies, e.g. vascular, tumour, tuberculosis, neuro-syphilis etc. There therefore began in the second half of the nineteenth century a very long-running debate, still with us today, concerning the distinction between primary idiopathic epilepsy in which the brain is macroscopically normal, and secondary symptomatic epilepsy with focal and generalized seizures, associated with various brain pathologies. Russell Reynolds (1861) and Gowers (1881) both viewed true epilepsy as the primary idiopathic variety, whereas Sieveking (1858) concluded that it was impossible to separate primary from secondary or idiopathic from symptomatic epilepsy. This debate continues in the twenty-first century and is at the heart of current controversies concerning modern ILAE classifications of seizures and epilepsy syndromes (Reynolds and Rodin, 2009).

Basic mechanisms: vascular and electromagnetic theories

As the neurological foundations of epilepsy became more firmly established, the dominant view in the nineteenth century was that it had a vascular origin, perhaps due to some temporary insufficiency of blood supply. Even the Babylonians understood that a sacrificed sheep displayed terminal convulsions associated with severe blood loss. The experimental studies by Brown-Sequard (1860), who influenced Jackson, supported this view and in his early writings in the 1860s Jackson favoured wholly vascular theories. Even when he later developed his famous hypothesis of neuronal instability and discharge in the 1870s he continued to invoke a vascular dimension.

Vascular theories were first challenged by Todd in 1849, who found them unsatisfactory. Todd was a scientific physician and Professor of Physiology and Morbid Anatomy at King's College in London, where he had a special interest in disorders of the nervous system before the discipline of neurology existed. He was greatly influenced by his contemporary in London, the famous Michael Faraday (1791–1867), at the Royal Institution, who at that time was laying the foundations of our modern understanding of electromagnetism. As a pioneering neuro-histologist Todd saw each nerve vesicle (cell) and its related fibres (neuron in later terminology) as a distinct apparatus for the development and transmission of 'nervous polarity' based on Faraday's concepts of the polar forces of electricity and magnetism. Todd applied these concepts to epilepsy in which he envisaged a periodic rise in electrical tension in grey matter, which could, at a certain threshold, result in a sudden change in polar state, leading to a seizure discharge, comparable to the spark from a battery or lightning. In his 1849 Lumleian Lectures Todd emphasized:

> These periodical evolutions of the nervous force may be compared to the electrical phenomena described by Faraday under the name of 'disruptive discharge'.

Todd supported his views by electrical experiments in the rabbit.

Although Jackson, who was more of a philosopher than a scientist, later in 1873 developed a theory of 'excessive discharge' in epilepsy, his concept was very different, based on chemistry, anabolism and catabolism. He had no understanding of physics or electromagnetism and he overlooked or ignored Todd's prior electrical theory of discharge. However, vascular theories continued to dominate late nineteenth century and early twentieth century thinking, reaching their peak with Turner in 1907.

Electromagnetic concepts of epilepsy were finally established in the middle of the twentieth century following the discovery of the human electroencephalogram (EEG) by Berger in 1929. Earlier Caton (1873) had reported electrical potentials from the cortex of various animal species, but relatively little notice was taken of this until Berger's human studies. Hans Berger was Head of the University Psychiatric Hospital in Jena, where he spent 27 years studying the electrical activity of cats, dogs and, later, human volunteers and patients. By 1933 he had described the interictal resting EEG, the EEG response to hyperventilation, the post-ictal EEG following a tonic-clonic seizure, and the ictal EEG of focal motor seizures. This led to a rapid growth in the discipline of electroencephalography in the middle of the twentieth century. Electromagnetic concepts of epilepsy were reinforced in the second half of the twentieth century by the development and application of video-telemetry.

In the meanwhile in 1906 Ramón y Cajal and Golgi received the Nobel Prize for their histological development of the 'neuron doctrine', already glimpsed more than 50 years earlier by Todd. It took another half century for the ionic basis of Todd's 'nervous polarity' or neurotransmission to be confirmed by the Nobel Prize-winning work of Hodgkin and Huxley (1953), who identified the role of sodium, potassium and chloride, elements that had first been discovered by Faraday's mentor at the Royal Institution, London, i.e. Sir Humphry Davy (1778–1829).

The psychiatry of epilepsy

Throughout most of its documented history, epilepsy has been viewed as a mental disorder, beginning with the supernatural concepts of the ancients. Despite the neurological progress in the late nineteenth and early twentieth centuries the concept of epilepsy as a psychiatric disorder prevailed in most parts of the world until the middle of the twentieth century, especially as epilepsy has always been noted to be associated with a high incidence of psychological, behavioural and personality disorders. Indeed in the nineteenth century it was widely believed in Europe by 'alienists' in charge of mental institutions, where much epilepsy was treated, that epilepsy, like much insanity, was a hereditary degenerative disorder leading to cognitive and moral decline. Some went so far as to diagnose 'epilepsy', 'epilepsy equivalent' or 'masked epilepsy' in patients with paroxysmal disorders of mood or behaviour in the absence of any clinical seizures. It was only in the middle of the twentieth century with the widespread acceptance of electromagnetic concepts and the rapid development of the discipline of neurology that the World Health Organization (WHO) in 1960 finally separated 'epilepsy per se' from 'epilepsy with deterioration or psychosis' in their International Classification of Diseases. At the same time epidemiological studies now revealed that most patients with epilepsy were leading relatively normal lives in the community, often well controlled by the relatively new antiepileptic drugs of phenobarbitone (1912) and phenytoin (1938). Only about a third of patients had significant psychological, behavioural or personality disorders, especially in the presence of underlying brain lesions or learning disabilities (Reynolds and Trimble, 1981).

By the middle of the twentieth century clinical neurophysiology, including cortical stimulation studies (Penfield and Jasper, 1954), had refined the concepts of temporal and frontal lobe epilepsy; and neuropsychology was clarifying their behavioural and cognitive associations. The stage was now set for increasingly precise distinction between pre-ictal, ictal, post-ictal and interictal psychiatric disorders, e.g. transient ictal mood change, hallucinations or automatisms; the rare brief interictal psychoses associated with cessation of seizures and 'forced normalization' of the EEG (Landolt, 1958); or the occasional chronic interictal psychoses associated with temporal lobe epilepsy (Slater, Beard and Glithero, 1963); all of which are much less common than interictal anxiety or depressive states.

At the turn of the nineteenth century neurology and psychiatry were diverging and epilepsy remained

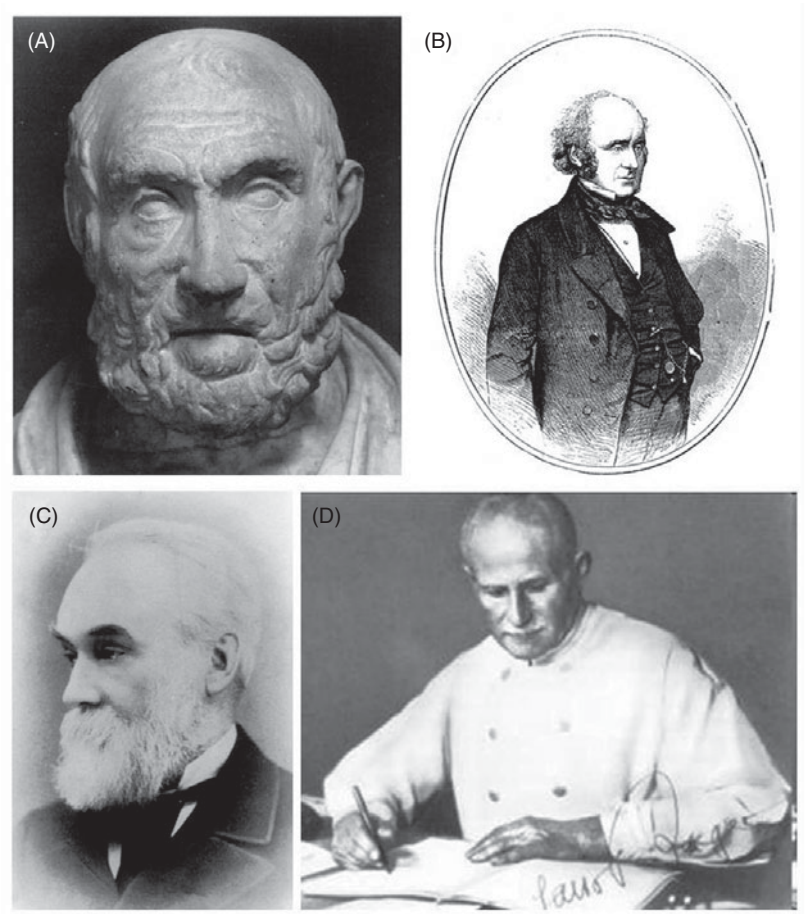

Figure 1.1. Four key people in the history of epilepsy. (A) Hippocrates (460?–377 or 359 BC); (B) Robert Bentley Todd (1809–1860); (C) John Hughlings Jackson (1835–1911); (D) Hans Berger (1873–1941).

to some extent in both camps. At the turn of the twentieth century the two disciplines have been converging again, led in many respects by epilepsy, which has provided several useful models of mental illness, a window on brain function, and a bridge between the two disciplines (Reynolds and Trimble, 1981 and 2009).

Epilepsy as a social disorder

No history of epilepsy would be complete without acknowledging the enormous social consequences of the disorder throughout the ages (Temkin, 1971). Seizures are such unusual, sudden, dramatic, frightening, potentially harmful and, until quite recently, mysterious events that they have always given rise to misunderstanding, fear, neglect, social penalties and stigma at all ages in all social classes, cultures and countries. Such misunderstanding and anxiety have profoundly affected family and other relationships, and the potential for marriage, employment and personal fulfilment. So deep is this legacy that notwithstanding greater knowledge of the disorder, negative public attitudes are still widespread, undermining fundraising, research, services and social integration. Against this background in 1997 the ILAE, IBE and WHO launched a global campaign to bring epilepsy 'out of the shadows' especially in developing countries (see Chapter 134: 'The International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE)').

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Learning objective

(1) To be aware of the main hallmarks in the historical development of Epileptology.

Section 1 **Basic principles**

Chapter 2

What is epilepsy?

Gonzalo Alarcón

Epilepsy is one of the most common neurological conditions. Epilepsy is usually defined as a tendency to suffer recurrent epileptic seizures. Epileptic seizures show a variety of clinical and electroencephalographic characteristics which are described in Chapter 17: 'Electroclinical classification of seizures and syndromes'. More pragmatically, epilepsy can be defined as suffering two or more unprovoked epileptic seizures occurring within a time frame of two years. This definition implies that epilepsy is essentially a chronic condition. The term 'unprovoked' refers to the absence of underlying acute conditions that can induce seizures in subjects who would not otherwise have seizures (hypoglycemia, alcohol withdrawal, hypercalcemia, encephalitis, electroconvulsive therapy, etc.; see Chapter 31: 'Acute symptomatic seizures').

In a small proportion of patients with epilepsy, seizures can be triggered by specific stimuli that do not trigger seizures in the general population (flashing lights, visual patterns, reading, music, intellectual activity, etc.). This type of epilepsy is called reflex epilepsy (see Chapters 91 to 94).

Besides the formal definition of epilepsy, there is the more practical problem of how to identify (diagnose) the condition. Epilepsy is often misdiagnosed (Leach *et al.*, 2005). The diagnosis of epilepsy is complicated by the fact that many key symptoms and signs of epilepsy are intermittent and brief (e.g. epileptic seizures, interictal epileptiform EEG discharges). This means that clinical and EEG examinations can appear normal, although they might have shown abnormalities had they been obtained earlier or later. This means that detailed medical history is of paramount importance for diagnosis (see Chapter 46: 'History-taking and physical examination in epilepsy'). To complicate matters further, epileptic seizures can show such a variety of clinical manifestations (see Chapter 17: 'Electroclinical classification of seizures and syndromes') that a reliable definition of epileptic seizures based on their clinical manifestations alone is impossible.

In practice, an epileptic seizure can be defined as a sensation, feeling, autonomic change, abnormal or automatic movement or alteration of consciousness associated with abnormal EEG changes. EEG changes can be detected on the scalp, unless seizures are very localized or restricted to deep brain regions (hippocampus, medial aspect of the hemispheres). In this case, EEG changes may only be detectable by intracranial electrodes.

There is a widespread misconception that the diagnosis of epilepsy is purely clinical (i.e. that it relies solely on history and clinical examination). This is not necessarily the case. Indeed, it may be more realistic to say that, in general, the diagnosis of epilepsy is electro-clinical. As in any medical condition, a good history will raise the suspicion of epilepsy as part of a differential diagnosis (a differential diagnosis is a list of conditions that can explain the symptoms). In many patients, a detailed history with a reliable witness will be sufficiently convincing to diagnose epilepsy, but in others epilepsy needs to be confirmed with the identification of EEG abnormalities consistent with the suspected epilepsy syndrome. The EEG is also instrumental in the classification of epilepsy, which can be seen as a refined diagnosis. Indeed, the diagnosis of some epilepsy syndromes cannot be made without specific EEG abnormalities (e.g. West syndrome, epilepsy with continuous spike and waves during sleep, childhood absence epilepsy, Lennox-Gastaut syndrome). What appears to be clear is that the diagnosis of epilepsy is not only electrical, i.e. finding EEG abnormalities without a compatible

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history of epilepsy should not trigger the diagnosis of epilepsy.

Of course, in some patients it may not be possible to obtain sufficient clinical or EEG information to confirm the diagnosis of epilepsy, either because there are not reliable witnesses to the seizures or because EEG abnormalities are repeatedly absent, or both. In such cases, it may not be possible to confirm the diagnosis of epilepsy.

A further difficulty arises because in some syndromes, particularly in adults, a normal interictal EEG cannot rule out the diagnosis of epilepsy, as abnormalities can be intermittent. Nevertheless a repeatedly normal interictal EEG should cast a doubt on the diagnosis of epilepsy. In such cases, ictal EEG recordings or videos of seizures may be necessary (see Chapter 47: 'Role of video-EEG monitoring in epilepsy').

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Learning objectives

(1) To be aware of the main issues and difficulties met in defining epilepsy.
(2) To understand the present definition(s) of epilepsy.
(3) To understand the principles and difficulties involved in the diagnosis of epilepsy.

Section 1 Basic principles

Chapter 3

Functional anatomy of the central nervous system

Gonzalo Alarcón

Cerebral hemispheres

The upper brain contains two symmetrical round structures called the cerebral hemispheres (or simply the hemispheres). A section of the hemispheres will reveal grey areas (grey matter) and white areas (white matter). Grey matter contains dendrites, neuronal bodies and axons, whereas white matter contains largely axons. There is a strip of grey matter surrounding each hemisphere, immediately under its surface, called the cerebral cortex (in plural, cortices). Each hemisphere also contains multiple internal islands of grey matter (nuclei in plural and nucleus in singular) such as the thalamus, basal ganglia and hypothalamus. The cerebral cortex surrounds both cerebral hemispheres and folds in a complicated fashion, defining depressions of the surface of the brain (the sulci, or sulcus in singular) and bulging regions (the gyri, or gyrus in singular) (Figure 3.1). In addition, there are two deep depressions called fissures: the rolandic or central fissure between frontal and parietal lobes, and the sylvian fissure between frontal and temporal lobes. We will hereafter use the term cortex to refer to the cerebral cortex since the other brain cortex, the cerebellar cortex, is not directly involved in the generation of epileptic seizures.

The sylvian fissure is particularly deep and ends in a virtual space surrounded by cortex, called the insula. The cortical regions around the sylvian fissure which cover the insula are called the operculum.

Both hemispheres communicate with each other though several structures: mainly the corpus callosum, but also the anterior and posterior commissures and the fornix (trigon). The beginning of the fornix is called fimbria, runs medial to the hippocampus on the floor of the temporal horn and contains the main output from the hippocampus.

A line defined by the imaginary plane that runs between both hemispheres is called the midline. Structures near the midline are called medial (or mesial) whereas structures furthest away from the midline are called lateral.

The hemispheres contain cavities filled with cerebrospinal liquid, called ventricles. There are two lateral ventricles, one within each hemisphere, and one medial ventricle (between both hemispheres), called the third ventricle. Each lateral ventricle has portions that extend within the frontal, temporal and occipital lobes, often referred to as horns (the frontal or anterior horn, the temporal or inferior horn and the occipital or posterior horn). Each lateral ventricle communicates with the third ventricle through the interventricular foramen or foramen of Monro (foramen is a medical term for hole, the plural is foramina). Ventricles will enlarge if there is loss of brain tissue or if there is an obstacle to the normal circulation of cerebrospinal liquid. There is a thin wall existing between both lateral ventricles outside the interventricular foramen. This wall is called the septum pellucidum. The anterior and superior region of the septum pellucidum contains islands of grey matter called the septum nuclei.

Cerebral cortex

Seizure manifestations result from dysfunction of the cerebral cortex and its interaction with subcortical structures. The cortex is the structure responsible for complex brain functions (the so-called 'higher brain functions'): perception, voluntary movement, memory, motivation, production and understanding of language. During seizures, the cortex functions abnormally. This has two consequences:

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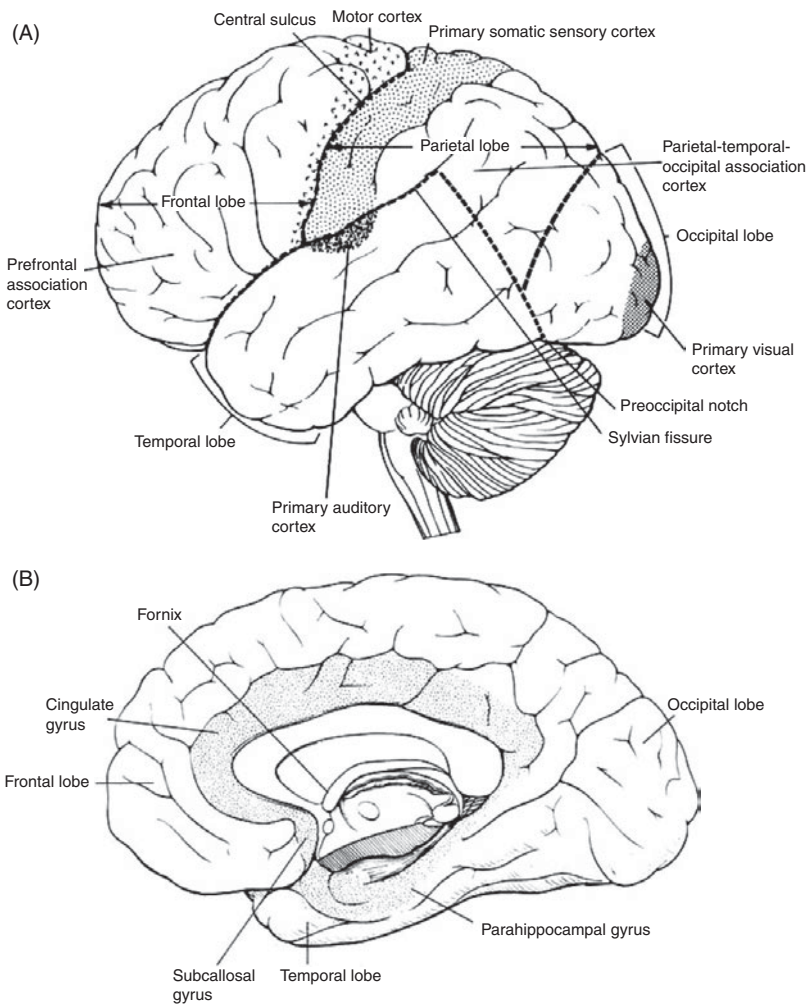

Figure 3.1. The major divisions of the human cerebral cortex. (A) Lateral view of the hemisphere. (B) Medial view of the brain showing the limbic lobe as dotted areas (reproduced with permission, *Principles of Neural Science*, second edition, edited by ER Kandel and JH Schwartz, Elsevier, New York, 1985, Figures 19–3A of page 214 and 46–1A of page 613).

- Normal functions of the cortex can be suppressed during seizures: lack of memory for the event, unresponsiveness, aphasia, behavioural arrest, etc.
- Additional abnormal behaviour and perceptions can occur during seizures: hallucinations, illusions, automatic unconscious movements, convulsions.

To a large degree, the nervous system's function is hierarchical. The cortex appears to be the most dominant structure, responsible for higher functions. The remaining brain structures (such as the thalamus, brainstem and cerebellum) are sometimes termed subcortical structures.

Regions of cortex

The cortex is divided into lobes (frontal, temporal, parietal, occipital, limbic), which are shown in Figure 3.1.

Some regions of the cortex are specialized in processing certain tasks:

- The primary motor cortex (in the posterior portion of the frontal lobes, immediately anterior to the rolandic fissure) commands voluntary movements to muscles. The primary motor cortex is sometimes called the motor strip.
- The supplementary motor cortex (in the medial aspect of the frontal lobes, anterior to the primary motor cortex) is crucial for planning movements.
- The somatosensory cortex (in the anterior region of the parietal lobes, immediately posterior to the rolandic fissure) processes information from the body (somatosensory information), i.e. information from skin, joints, muscles, tendons. It is necessary to feel sensations from skin and to be aware of our body posture in the absence of visual information.

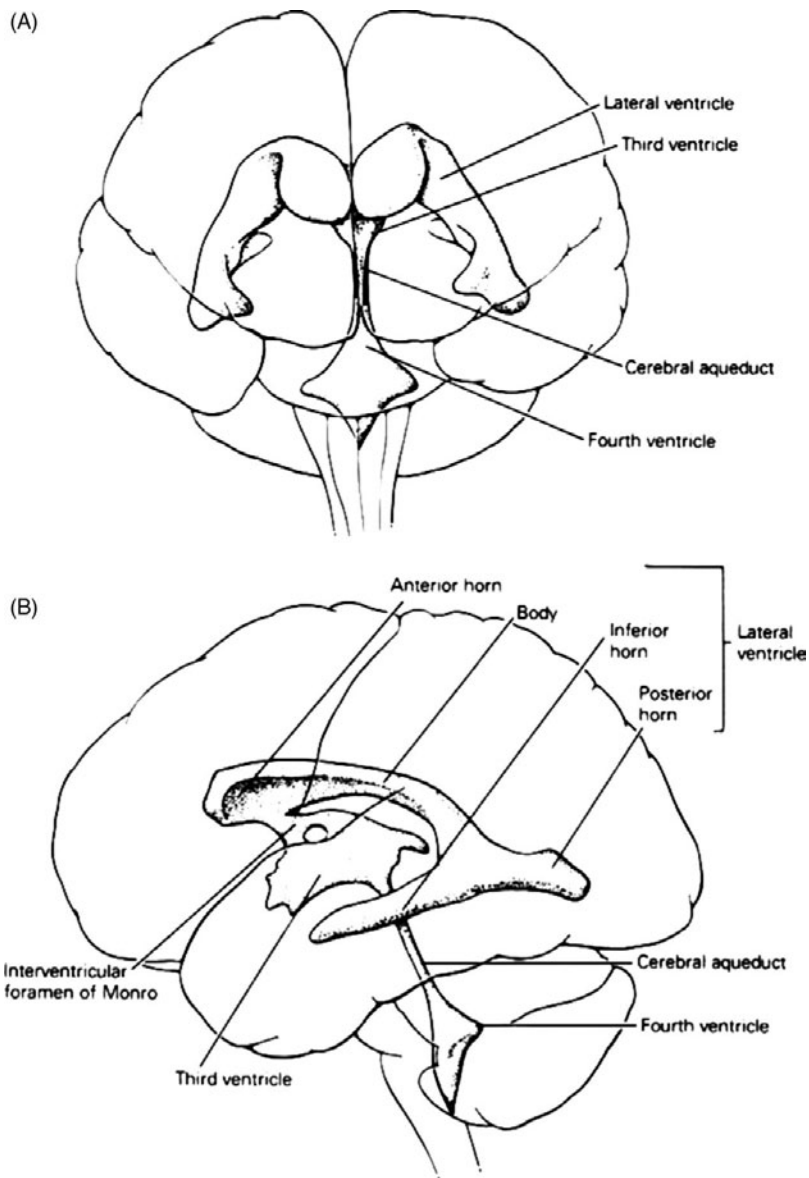

Figure 3.2. The ventricular system of the human brain. (A) Frontal view; (B) lateral view (reproduced with permission, *Principles of Neural Science*, second edition, edited by ER Kandel and JH Schwartz, Elsevier, New York, 1985, Figure 1.19–4, page 216; adapted from Noback and Demarest, 1981).

- The auditory cortex (in the lateral cortex of the temporal lobes) is involved in processing sound.
- The visual cortex (in the occipital lobes) is involved in processing visual information.
- The sensory speech area (usually in the left temporal lobe), also called Wernicke's area, is responsible for interpreting language (both spoken and written) (Figure 3.5).
- The motor speech area (also called Broca's area, located in the lateral inferior and posterior regions of the frontal lobe, usually on the left) is responsible for generating speech (Figure 3.5).
- The hippocampus is involved in processing memories and emotions.
- The limbic system is involved in processing emotions (see below).

Topographic and contralateral organization of motor and sensory cortices

Motor, somatosensory and visual cortices have a topographic organization (somatotopic representation). This means that each area of these cortices processes information from (or for) specific areas of