Chapter 1

Introduction

This book is devoted to the many interactions between epilepsy and memory. As we hope that the book will attract readers from diverse backgrounds, including some readers with a primarily medical and others with a primarily psychological orientation, we thought it would be helpful, in the first and second sections of this chapter, to provide brief introductions to the science of epilepsy and the science of memory. These are intentionally basic, so that they will be useful to the relatively uninitiated reader. In the third section we will introduce the interactions between epilepsy and memory, which are discussed in detail in the various contributions that follow. The fourth section will outline the book’s structure, and sketch the content of the individual chapters.

A brief introduction to epilepsy

Epilepsy is characterized by recurrent episodes of neurological dysfunction—epileptic seizures—capable of affecting either or both behaviour and experience, due to the abnormally synchronized electrical discharges of large groups of neurons. These events are generally short-lived, measured in seconds to minutes. There are many different kinds of epilepsy: both the clinical features of seizures and their underlying causes are protean (Engel, 2001).

The most fundamental distinction in seizure classification lies between focal and generalized seizures (Table 1.1). Focal seizures result from epileptic activity occurring in a circumscribed region of brain tissue, usually, though not always, a region of the cerebral cortex (Fig. 1.1). The resulting clinical features involve alterations of behaviour, experience, cognition, or autonomic function. They are determined by the normal function of the affected brain region. Thus epileptic activity involving the motor cortex may give rise to jerking in the opposite limbs, typically spreading over the parts of the limb within seconds, a ‘Jacksonian seizure’. This sometimes leaves postictal (literally ‘after the seizure’) weakness in its wake for minutes or hours, a ‘Todd’s paresis’. Seizures arising in the occipital lobe give rise to paroxysmal visual experiences, ranging from coloured patterns to hallucinatory images. Parietal lobe seizures give rise to paroxysmal disturbance of bodily sensation, including out-of-the-body experiences. Temporal lobe seizures, the most common type of focal seizures, are often associated with a rising sensation spreading rapidly from the stomach to the head (the ‘epigastric aura’), olfactory hallucinations, and more complex alterations of experience and cognition, including *déjà vecu*, ‘dreamy states’, intense emotions, and transient amnesia. These phenomena provide particularly striking demonstrations of the dependence of behaviour and experience on the activity of the brain, and contributed to the evidence for localization of brain function in the early years of clinical neurology (Hughlings Jackson, 1888; Hughlings Jackson and Colman, 1898). Reflex epilepsies, in which a seizure can be triggered by a particular stimulus or activity, including mental acts such as recollection, illustrate the converse relationship: what we choose to do and think about can powerfully affect the activity of the brain (Martinez et al., 2001).
Table 1.1 Common seizure types (drawn from the International League Against Epilepsy (ILAE) classification)

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<tr>
<th>Self-limited seizure types</th>
<th>Continuous seizures types</th>
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<tr>
<td><strong>Generalized seizures</strong></td>
<td><strong>Generalized status epilepticus</strong></td>
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<tr>
<td>Tonic–clonic (grand mal)</td>
<td>Tonic–clonic status epilepticus</td>
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<td>Typical absence seizure (main feature is brief impairment of awareness)</td>
<td>Absence status epilepticus</td>
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<td>Myoclonic seizure (main manifestation is a sudden jerk)</td>
<td><strong>Focal status epilepticus</strong></td>
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<tr>
<td>Reflex seizures in a generalized epilepsy syndrome (e.g. provoked by flashing light)</td>
<td>Limbic status epilepticus ('psychomotor status')</td>
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**Focal seizures**
- Focal sensory seizures
  - with elementary sensory symptoms
  - with experiential sensory symptoms
- Focal motor seizures
- Secondarily generalized seizures (tonic–clonic seizures as the culmination of a focal seizure)

**Fig. 1.1** An electroencephalogram (EEG—brain-wave recording) showing a focal seizure recorded from the scalp. The prominent ‘spike and wave’ activity seen especially in ‘C4 P4’ and ‘P4 O2’ reflects epileptic activity originating over the right side of the brain.
In generalized seizures, by contrast, the epileptic activity invades the entire cerebral cortex, usually extinguishing awareness (Fig. 1.2). The public stereotype of epilepsy, the ‘grand mal’ or tonic–clonic seizure, involves loss of consciousness and tonic stiffening of the body followed by vigorous ‘clonic’ jerking of all four limbs, lasting a minute or so, often accompanied by tongue-biting and incontinence. Absence seizures, which cause transient loss of awareness with little else to see, and myoclonic seizures, involving sudden, short-lived muscle jerks, also reflect generalized epileptic activity in the brain.

Some complexities relating to the distinction between focal and generalized seizures should be noted here. Focal epileptic activity can spread gradually through the brain, giving rise, for example, to a seizure that starts with an experience of déjà vu, progresses to loss of awareness as the sufferer looks blankly ahead and culminates in a ‘secondarily generalized’ tonic–clonic seizure. On the other hand true absence seizures, and some tonic–clonic seizures, reflect ‘primary generalized’ activity that appears simultaneously throughout the cortex (Fig. 1.2), although recent work suggests that cortical involvement may not be uniform.

The tendency for awareness to be impaired as focal seizures spread through the brain has given rise to a distinction between ‘simple’ and ‘complex’ focal seizures: consciousness is preserved in the former, impaired in the latter. Gloor drew attention to the difficulty of making this distinction in practice (Gloor, 1986). The impression of ‘impaired awareness’ may result from amnesia, pre-occupation with hallucinatory experiences, altered mood or language impairment, as well as from the complete extinction of consciousness. It is clinically and scientifically unhelpful to lump together these very different explanations for ‘unawareness’. The most recent ILAE (International League Against Epilepsy) classification of seizures has taken up Gloor’s suggestion that the simple/complex distinction should be abandoned.

There is, however, undoubtedly an important, if sometimes ambiguous, distinction between seizures that do and do not impair consciousness; i.e. between those that do and those that do not, partially or completely, extinguish mental activity. New techniques of functional imaging, in particular the combined, simultaneous, use of functional magnetic resonance imaging (fMRI) and the electroencephalogram (EEG) to identify the regional brain activity that correlates with epileptic discharges, are helping to elucidate the neurobiological explanation for the loss of...
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awareness during some seizures. Results to date suggest that the activation of deep structures, especially the thalamus, may be a common factor in seizures that impair awareness, with correlated hyper- or hypoactivation of frontal, parietal, and temporal association cortices (Blumenfeld and Taylor, 2003).

Identification of seizure type is the first step in classifying epilepsy, but it is often possible to provide a more informative classification into ‘epilepsy syndrome’ by taking into account additional information, such as age, family history, and the results of tests, including the EEG and brain imaging (Table 1.2).

Epilepsy is extremely common, and is presumably a price the brain pays for its massively interconnected organization. Around 10% of us will have an epileptic seizure at some time (5% of these are febrile seizures of childhood). At any one time, the prevalence of epilepsy in the developed world approaches 1%. It often starts in childhood and old age, less often in early/mid-adulthood. Its prognosis depends upon its cause, but about two-thirds of people who develop epilepsy stop having seizures either spontaneously or on treatment. Its causes include genetic predisposition (some single gene mutations with epilepsy as their chief manifestation have recently been defined), abnormalities of brain development, including subtle disturbances of cortical migration, brain infections (meningitis and encephalitis), head trauma, stroke, and dementia. In adult onset epilepsy, the cause remains undecided in around 50% of cases.

The detailed pathophysiology of epilepsy is understood only in part. Discharges seen in the EEG of patients with epilepsy between attacks are associated with abrupt ‘depolarization shifts’ in the majority of neurons in the seizure focus, causing them to fire rapid bursts of action potentials (a ‘depolarization shift’ is an increase in the electrical charge within the neuron that tends to increase its activity). The likelihood of these events is increased by factors that increase neuronal excitability and the strength of excitatory neurotransmission, reduce the strength of inhibitory neurotransmission, and allow the formation of tightly coupled networks of neurons. The physiological processes that allow subclinical events to develop into seizures are complex and controversial. Primary generalized epilepsies are thought to arise from abnormal interaction between cortex and thalamus, but the details here also remain a focus of current research.

The diagnosis of epilepsy can be difficult. It rests above all on a clear description of the events occurring in seizures, both from the sufferer’s perspective and by an eye witness. Competing possibilities often include ‘syncopy’, due to temporary loss of the blood supply to the brain, as in a faint, and ‘nonepileptic attack disorder’, an umbrella term for a variety of ‘psychological’ causes of paroxysmal symptoms, e.g. panic attacks. Several tests can be helpful in making a diagnosis, but it may remain unclear despite these. Standard investigations include the EEG (see Figs 1.1 and Table 1.2 Examples of common or well-known epilepsy syndromes (drawn from the International League Against Epilepsy (ILAE) classification)

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<td>Landau–Kleffner syndrome</td>
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<td>Childhood absence epilepsy</td>
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<tr>
<td>Juvenile myoclonic epilepsy</td>
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<tr>
<td>Familial temporal lobe and familial frontal lobe epilepsies</td>
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Symptomatic focal epilepsies:
- limbic epilepsies, e.g. mesial temporal lobe epilepsy with hippocampal sclerosis
- Neocortical epilepsies defined by location and aetiology
1.2); brain imaging, ideally with Magnetic Resonance Imaging (Fig. 1.3); an electrocardiogram (ECG—to help exclude cardiac causes); blood tests (e.g. blood glucose and calcium concentrations). A single EEG will detect clear epileptiform abnormalities in about one-third of people with epilepsy; repeated recordings, particularly after sleep deprivation, can raise this figure to around three-quarters.

Although epilepsy remains a worrying and sometimes stigmatizing disorder, effective treatments are available. Anticonvulsant drugs are the mainstay of treatment. These work principally by reducing the tendency of neurons to fire spontaneously and/or by increasing inhibition through an action on synaptic receptors. Modern anticonvulsants often control seizures with little sedation or other side-effects, though these sometimes occur. In highly selected cases, surgical removal of the brain tissue that is responsible for generating seizures, most often in the temporal lobes, can be curative. Other, broadly ‘psychological’, approaches to treatment are being explored.

**A brief introduction to memory**

Evidence from cognitive science, clinical neurology, and imaging neuroscience all suggests human memory is best viewed as comprising a number of distinct but separable memory systems (Baddeley et al., 2009; Squire and Kandel, 2009), even though at the biological level and at the cognitive level some commonalities may be present across such systems (Fig. 1.4).
Information that reaches the brain from the external environment is first processed by a network of sensory systems that form part of the perceptual apparatus of the human brain. Such perceptual systems may be important for later 'implicit' identification of stimuli, and thus can be seen as representing a form of memory system.

In chronological terms, the post-perceptual memory system that is then engaged is one relating to 'working memory', which includes components of what previously had been subsumed under the term 'short-term memory'. Working memory can be fractionated into four subsystems: the central executive, which is an attentionally-limited control system; two modality-specific storage systems—one for auditory-verbal information, called the phonological loop, and the other for visuospatial information, called the visuospatial scratchpad; a fourth component of working memory has also been postulated, called the 'episodic buffer', which takes on the role of a multimodal temporary store that helps to link the three other components to perception and to long-term memory (Fig. 1.5).

Long-term memory itself is generally acknowledged to be best viewed as two memory systems: an episodic memory system that deals with personally experienced events that are specific to time
and place, e.g. the ability to ‘mentally time-travel’ and remember what you were doing and where you were when a major event happened, such as learning that someone famous or someone personally familiar had died; and a semantic memory system that deals with our general knowledge about the world and also personal factual knowledge, such as our name.

A final memory system is that which covers domains such as motor skills, perceptual priming, classical conditioning, and habit learning. This system is generally considered to be accessed implicitly/unconsciously by individuals, and is sometimes called ‘nondeclarative memory’, whereas, by contrast, episodic and semantic memory systems are usually accessed explicitly/consciously, and are sometimes called ‘declarative memory’. Nondeclarative memory is important in clinical settings since it may often be relatively preserved in the amnesic syndrome. It is important to note that everyday memory lapses may reflect the operation of more than one memory symptom, e.g. prospective memory lapses, forgetting to do things some time in the future, may involve both episodic memory and working memory.

Traditionally, stages of memory processing have been divided into those relating to acquisition, storage, and retrieval. The acquisition stage is generally considered to involve mainly primary and secondary sensory areas that are located in visual and auditory neocortex, but to the extent that language and complex perceptual processes are involved, then associative areas of neocortex may also be implicated. Where attentional mechanisms are actively involved in the acquisition of information, regions in the frontal cortex will usually also be brought into play. Some researchers argue that limbic diencephalic memory structures, such as the hippocampus and the thalamus, are in an active (‘default’) mode at the memory-acquisition stage, so this potentially adds further to the anatomical network active at acquisition. Such deeper structures have, however, been more closely implicated in the storage of new information, and are considered to form part of a network that includes other structures such as the fornix, the mammillary bodies, the basal forebrain, and retrosplenial cortex (Fig. 1.6). Retrieval and recognition of information at the time of

**Fig. 1.6** Anatomical structures crucial to episodic memory.
retention testing is considered to involve some of those areas that were initially involved in acquisition, but also to specifically involve areas within prefrontal cortex. The terms ‘anterograde’ and ‘retrograde’ are often used in relation to memory and memory impairment: ‘anterograde’ memory refers to memory for ongoing events; ‘retrograde’ memory refers to memory for events occurring prior to the time point of interest, usually the onset of an illness or injury.

Memory is, therefore, a complex process. Its malfunction is one of the most common symptoms presented by neurological patients because of the large network of areas involved: dysfunction in just one part of the network will cause a disruptive effect on memory functioning generally.

A range of factors will play a part in information that is lost or retained in long-term memory. Some of these factors will be intrinsic to the individual (e.g. age, fatigue, stress), but others relate to particular psychological ‘encoding’ variables, such as those illustrated in Fig. 1.7.

Memory disorders are traditionally divided into those that are transient and those that are chronic. They are also often classified in terms of severity of memory impairment, the term ‘amnesia’ being retained for marked impairment that is clinically obvious, falls well outside normal everyday memory difficulties, and has a major disabling effect on the individual.

Transient amnesias take many forms—perhaps the most common form of transient amnesia is in the early stages of recovery from a major brain insult, such as a traumatic brain injury. During the acute phase of a severe closed-head injury, after recovery from coma, the patient may often be ‘confused’—this confusion will generally take the form of both impaired memory and impaired attention. Often, the patient may show evidence of ‘confabulation’—the unintentional fabrication of apparent memories that have only partial or no foundation in reality. The subsequent memory loss that the patient will have for this early phase of recovery is termed ‘post-traumatic amnesia’.

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**Fig. 1.7** Encoding factors relevant to long-term memory consolidation. Reactivation pattern refers to the enhancing effects of retrieval of information, and features such as the spacing of such retrieval attempts may be critical.
It is important to note that such confusion and memory loss may also be present in non-traumatic conditions, such as encephalitis or stroke. Transient amnesia may also occur as a ‘stand-alone’ condition, and the most common form of this memory loss is transient global amnesia. Transient global amnesia is a condition that is thought to be caused by sudden and transient dysfunction of the medial temporal lobes of, so far, uncertain cause. It usually lasts around five hours, with the patient suffering from severe loss of the ability to take in new information. This is evident in symptoms such as repetitive questioning, and also in a variable degree of memory loss for events prior to the onset. Other cognitive and physical functions are generally intact. The patient will make a complete recovery, the episode will seldom recur, and the patient is simply left with a memory ‘gap’ for the period when he/she was amnesic. The other common type of transient memory loss, transient epileptic amnesia, is a form of temporal lobe epilepsy where, most commonly, transient hippocampal dysfunction results in acute memory loss that at first seems similar to transient global amnesia, but where the attack of memory loss is usually of much shorter duration and less severe than that in transient global amnesia.

Severe chronic memory disorders fall into the category of an ‘amnesic syndrome’. The absence of major deficits in other cognitive domains distinguishes the amnesic syndrome from conditions such as Alzheimer’s disease, where memory loss may also be severe, but where there are usually additional deficits in areas such as executive, language, and visuospatial function. The amnesic syndrome is associated with a diverse range of aetiologies, including alcoholic Wernicke–Korsakoff’s syndrome, bilateral infarction of the thalamus, herpes simplex encephalitis, and hypoxia. The profile of memory loss may vary across these conditions, both in the extent of additional cognitive impairment, such as executive or language dysfunction, and in the extent to which major retrograde amnesia accompanies the anterograde amnesia.

Chronic memory loss may also affect the semantic memory system—that is, general knowledge about the world—and this will often be manifest either in the form of a language disturbance, where the person has difficulty in finding or understanding certain words, or in a failure to know the meaning of objects or to recognize familiar faces. Such semantic memory loss can occur in conditions such as frontotemporal dementia and in the aftermath of herpes simplex encephalitis.

In clinical practice, the distinction between memory loss with a neurological origin and that with a psychological origin poses a common diagnostic difficulty. This is most often encountered in the context of chronic memory difficulties, but acute psychogenic memory loss may sometimes present to a clinician: in such situations the patient will often have loss of ‘personal semantic’ information, such as personal identity, and also a dense memory loss for most events of his/her life, going back to childhood, typically with relatively well-preserved anterograde memory function. Acute psychogenic memory loss usually follows a particularly stressful event, such as a marital or financial crisis. The more common chronic presentation of psychologically-based memory loss is generally related to the presence of anxiety or depression, and attention-based memory lapses will often be a feature of the presenting memory complaints, e.g. going into a room and forgetting what one went in for.

**A brief introduction to memory in the context of epilepsy**

As we have seen at the beginning of this introduction, among the effects wrought by epilepsy on the individuals suffering from it are cognitive changes. Most prominent among the cognitive changes occurring in people with epilepsy are troubles with memory. This is not surprising, as epilepsy arises most commonly from brain regions that are important for memory. In particular, the temporal lobes are the most frequent site of seizure origin in focal epilepsy, and they are also the site of brain structures that are critical in learning and memory. Interestingly, there is often a
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mismatch between patients’ appraisal of their own memory and objective measurements of it. In some instances, patients do not complain despite serious memory deficits, while in other instances patients may complain of memory problems that are not significant on objective tests. Still, a basic truism in neuropsychological evaluations of patients with epilepsy, especially those with temporal lobe epilepsy (TLE), is that memory is affected.

As discussed above, memory is not a unitary entity. Deficient memory may reflect a breakdown in the system at one or more of the many steps leading from initial perception and encoding to eventual retrieval. In epilepsy, the weak point or points in the system can help locate the site where seizures originate, and in any case examining the different steps to determine the greatest source of difficulty gives a better understanding of a patient’s difficulty and can allow some help or advice to be offered.

In the mid-1950s a groundbreaking discovery was made that led to mountains of research on where in the brain memories are laid down, where they are stored, and from where they are retrieved. There were three factors that culminated in this discovery, all of them involving surgical treatment of intractable epileptic seizures. First, in 1952 Wilder Penfield performed a unilateral resection from the left temporal lobe to alleviate or cure the seizures of a patient with TLE. Cognitive testing was carried out before and after surgery by Brenda Milner, a neuropsychologist working with Penfield; she provided objective evidence of a severe postoperative memory loss in the context of preservation of other cognitive functions (Milner and Penfield, 1955). The second instance began in 1946, when, in another patient, Penfield had performed a modest anterior resection (4 cm) from the left temporal lobe, again to alleviate temporal-lobe seizures, without extraordinary sequelae but also without sufficient seizure relief. He therefore extended the resection five years later in further removal from the same side, encroaching this time upon the uncus, hippocampus, and parahippocampal gyrus, and this time the patient showed a postoperative global amnesia (Milner and Penfield, 1955). In attempting to understand the unexpected outcome in these two patients, Penfield and Milner hypothesized that, although the surgical excisions were unilateral, the patients must have had additional damage in the unoperated temporal lobe, a hypothesis that was supported by bilateral abnormalities on the EEG of these patients, and that was later confirmed at autopsy for the first patient after he died of causes unrelated to his epilepsy and surgery. There had been isolated earlier reports suggesting the importance of the hippocampus in memory; e.g., Bekhterev, based on autopsy results, reported a bilateral hippocampal lesion in a patient who had shown a severe impairment of memory (Bekhterev, 1900), and in 1947 and 1952, two other publications had reported memory loss associated with hippocampal damage (Grunthal, 1947; Glees and Griffith, 1952), but Penfield’s surgical cases, with Milner’s pre- and post-surgical objective memory tests showing a clear and lasting memory loss related to resection from the hippocampal region, brought ‘the hippocampal hypothesis’ sharply to the attention of the scientific community, and especially to neurosurgeons.

In particular, the neurosurgeon William Scoville took note. He had been performing bilateral surgical resections from ‘various portions of the rhinencephalon’ in schizophrenic patients and in some epileptic patients, and had reported that the more anterior resections did not produce marked physiological or behavioral changes, except in one patient who showed a ‘very grave recent memory loss’ (Scoville, 1954). Upon learning of Penfield’s patients and Milner’s memory findings on them, Scoville invited Milner to study his patients. Most of them were psychotic and could not give reliable results on cognitive tests, but some testing was possible on ten patients. Two of them had extensive resections from the hippocampus, reported at the time by the surgeon to be 8 cm, and one of those two patients had been operated in an effort to control intractable epileptic seizures. Milner’s tests showed that he had average intelligence and preserved abilities in most cognitive spheres, but his memory was profoundly impaired (Scoville and Milner, 1957).
This patient was H.M., who is probably the most famous and perhaps the most studied patient in medicine. His bilateral resections from the temporal lobes included the amygdala, uncus, hippocampus, and parahippocampal gyrus but spared the temporal neocortex. Almost countless studies of learning and memory in patients with epilepsy have attempted to examine the respective roles of these temporal-lobe structures and how the different components of memory relate to them; those studies started with H.M. (Figs 1.8 and 1.9), a modest man who tended to apologize to researchers during memory tests, explaining ‘I have a problem with my memory’.

Before the existence of sophisticated brain-imaging methodologies, studying memory in patients with epilepsy—especially those who underwent elective focal resective surgery—was an important means of relating specific brain regions to different memory functions in humans. Because such patients were studied thoroughly before and after operation, allowing one to measure postoperative changes, and because neurosurgeons reported as precisely as they could what structures they had resected and how extensively, it was possible to study the effects of removal of well-defined areas of brain; thus, those patients were important research subjects. On the other hand, knowledge gained from those studies fuelled improvements in the clinical treatment of patients with epilepsy through clearer understanding of their cognitive deficits, leading to better memory tests and more directed counselling.

High-resolution neuroimaging has taken these advantages to the next level; scanning patients while they perform memory tests allows us to observe in vivo the brain structures that are active during different memory functions. While this capability has expanded greatly the access to research in this field and the level of anatomical detail possible, it does not replace lesion studies in providing an understanding of the role of particular brain structures. Functional neuroimaging data show structures involved in a given function but they do not show which ones are critically involved, whereas lesion studies show which structures, when damaged, result in a loss or

Fig. 1.8 Portrait of Henry Molaison (H.M.), the man whose bilateral surgical excisions from the medial temporal lobes resulted in a profound and lasting amnesia. H.M. died in 2008 when he was just short of 83 years old, leaving his brain for research and thus continuing to contribute to science as he had done for most of his life. © Suzanne Corkin, 1997.
reduction of function. Both approaches are valuable and continue to contribute to knowledge about brain function and about specifics of memory impairments associated with epilepsy.

The study of memory in patients with epilepsy has focused primarily on the temporal lobes, although the frontal lobes are also implicated in memory. As detailed above, memory is far from being a unitary function, and in the years since discovering the importance of the hippocampal region in memory, researchers have been teasing apart the components of memory and the brain regions participating in them. Important distinctions exist between the initial encoding-and-learning, and the subsequent retention of what has been learned; within retention there are important distinctions between recall and recognition. A first step in learning and memory is perception: patients have to be able to perceive that which they are to learn; if they cannot, a later memory test is meaningless. Next, they have to be able to maintain attention in the presence of that which they are to learn; if they have not attended to it, it will not be encoded. Sensory systems are involved in the former, and frontal lobes in the latter. With perception and attention intact, the hippocampus comes into play during encoding of that which is to be learned. There are several factors involved in the success of encoding, such as depth of encoding (e.g. meaningfulness enhances encoding), pre-existing knowledge forming a context into which the new material fits, and the type of material to be learned. When testing retention in clinical evaluation of patients with epilepsy, we want to know that the material has indeed been learned. Therefore it is best to have several learning trials, or to require learning to a specific criterion, during the learning phase so that one can be confident that forgotten material was in fact forgotten and not that there was limited learning in the first place. However, outside the formal testing environment, patients will most often have to acquire memories with a single exposure. We know that patients with TLE have deficits both for learning and for retention; we know also that patients with left (dominant)
TLE are impaired primarily for verbal material, whereas the impairments of those with right, nondominant TLE are primarily for nonverbal material. We know further that the deficits of patients with nondominant TLE are primarily for learning nonverbal material (e.g. faces, designs, routes), with retention for whatever has been learned being relatively spared (Jones-Gotman et al., 1997).

Our understanding of these subdivisions of memory and their relationship to areas of brain dysfunction in epilepsy has progressed considerably in the past 50-plus years, and our ability to offer advice to patients has increased accordingly. The chapters in this volume reflect the diversity of current knowledge concerning memory in the context of epilepsy.

**Epilepsy and memory: the state of the art**

This book originated in a meeting held at Dartington Hall on 3–6 May 2009 to review the broad topic of memory and epilepsy. Everyone who spoke at the meeting—and three additional authors—has contributed a chapter to this volume. We hope that it will provide a comprehensive, and—within the limitations of the publishing process—up-to-date survey of the field. In this final section of the Introduction we briefly outline the book’s structure and each chapter’s scope.

In the opening historical section of the book, Morris Moscovitch and German Berrios provide contrasting views of the history of the interwoven sciences of epilepsy and memory. Moscovitch focuses on twentieth-century developments, placing the discoveries of Scoville, Milner, and Penfield from the 1950s in the context of thinking about memory earlier in the century, with an extensive review of their subsequent impact. Berrios examines the study of epilepsy and memory in the nineteenth century, emphasizing the difficulties created for medical history by changing systems of thought that complicate comparisons of scientific observations across time.

In ‘Overviews of memory and epilepsy’, three sets of contributors provide a broad perspective on the main topic of this volume, introducing several themes that will recur throughout the book. Jokeit, Bosshardt, and Reed compare the varieties of memory impairment seen among patients with epilepsy, with those occurring in a range of other neurological disorders and in the course of normal ageing. Their chapter highlights the importance of considering the—often high—‘base rates’ of memory complaints in the community generally, and the possibility that memory difficulties—which might easily be attributed to epilepsy—in fact reflect its comorbidity with other disorders. Engman and Malmgren complement Jokeit, Bosshardt, and Reed’s cross-sectional approach with a review of longitudinal studies of memory in epilepsy. This reveals suggestive but equivocal evidence for memory decline in patients with chronic epilepsy, while underlining the common occurrence of memory impairment at the time of first assessment. This last observation is echoed in Smith and Direnfeld’s chapter on memory impairment in children with epilepsy, which, similarly, shows that memory impairment is a common finding among children with epilepsy at large. These chapters make it clear that memory assessment is valuable in people with epilepsy, though, in the context of research, the small numbers of patients studied and variations in approaches to assessment often qualify the interpretation of results.

Part 3 focuses on ictal and interictal memory phenomena. Illman, Moulin, O’Connor, and Chauvel review the topic of *déjà vu* in epilepsy, integrating this with current understanding of familiarity and recollection in dual-process theories of memory. They argue for an intriguing distinction between ‘*déjà vu*’, which they regard as a pathology of familiarity, and ‘*deja vecu*’ (‘already lived’), a pathology of recollection. *Déjà vu* is an ‘ictal excess’ of memory: Zeman, Butler, Hodges, and Kapur consider the complementary phenomenon of ictal amnesia in a chapter reviewing the recently described, and still debated, syndrome of Transient Epileptic Amnesia.
Finally, Aldenkamp considers another controversial topic, ‘transient cognitive impairments’ (TCIs)—disturbances of cognition caused by otherwise clinically silent discharges. He concludes that ‘subtle seizures’ often underlie the deficits sometimes attributed to TCIs, but looks forward to further research that will establish whether, in some instances, ‘epileptiform discharges that are not part of a seizure need to be treated’.

Part 4 examines approaches to the assessment of memory in epilepsy. Djordjevic and Jones-Gotman review the more widely used tests of episodic memory used around the world in patients with epilepsy, and offer a series of recommendations for memory testing based on the protocol developed at the Montreal Neurological Institute. Risse surveys the interesting past, present, and somewhat uncertain future of the intracarotid anaesthetic (previously amobarbital or Amytal) procedure, which, she argues, retains an important role in the selection of patients for epilepsy surgery. Bohbot and Dahmani outline the use of virtual reality in the assessment of spatial memory in patients with epilepsy: the technique is proving helpful in identifying the relative contributions of the left and right medial temporal lobes to navigation and the range of alternative strategies available to the brain in spatial tasks.

The artificiality of the distinction between neurological and psychiatric disorders is becoming ever more evident. In Part 5 we consider some areas of intersection between psychiatry, neurology, and epilepsy. Focal retrograde amnesia is often ‘functional’ or psychogenic, but there is growing evidence that a marked and sometimes disproportionate retrograde amnesia can occur as a feature of temporal lobe epilepsy. McAndrews reviews this topic, in relation, particularly, to medial temporal lobe function. ECT has been a controversial but effective treatment for refractory depression for many decades: Soderlund, Percy, and Levine review evidence that ECT may have a particularly deleterious effect on autobiographical memory for both recent and remote events. Goldstein and Kapur consider memory complaints in epilepsy in relation to comorbid psychiatric disorder: this provides a partial explanation for discrepancies between self-reported cognitive complaints and performance on objective tests.

The investigation of patients with epilepsy has been, and continues to be, transformed by advances in structural and functional brain-imaging. Richardson reviews structural imaging and neuropathological studies in which quantitative variables were correlated with memory test scores. A rigorous analysis of these studies allows important but unsurprising and limited conclusions—that the hippocampus is involved in long-term episodic memory processes, and the left hippocampus may be specialized for verbal memory processes. Richardson anticipates that methodological refinements will soon allow this field to advance. Frings and Wagner review promising recent work on the functional imaging of memory in epilepsy. While this line of work is shedding valuable light on the organization of memory processes in the brain, at the time of writing the technique does not yet have well-proven validity in the prediction of the effects of temporal lobe surgery in individual cases. Grunwald and Vanucci review evidence from studies using event-related potentials, which indicates that an important subcomponent of memory processing in the hippocampus, novelty detection, is dependent on N-methyl D-aspartate NMDA receptors. Their contribution is impaired or lost in hippocampal sclerosis.

Epilepsy provides a ‘natural laboratory for the study of memory’ in part because of the rare opportunity provided by the electrodes that are sometimes implanted, for clinical indications, to study intracranial physiology in humans. Such electrodes can be used both to record neural activity, at rest or during natural stimulation, and for electrical stimulation of the brain. In Part 7, Lenck-Santini and Holmes set the scene by reviewing neurophysiological studies of the effects of seizures on cognition in nonhuman animals. These reveal a range of possible neurobiological models for memory disturbances caused by epilepsy in humans. Morris, Coleshill, Lacruz, Valentin, and Alarcon survey the effects of stimulation of the human brain via intracranial
electrodes, demonstrating, for example, that low-intensity stimulation at the point of encoding, below the threshold required to excite any epileptic after-discharge, has a hemisphere-specific effect on subsequent memory performance. In separate chapters, Axmacher and Viskontas then examine two contrasting, and exciting, applications of intracranial recording in humans. Axmacher describes forms of oscillatory activity in the medial temporal lobes that have recently been linked to memory encoding and consolidation, including theta and gamma oscillations and sharp wave-ripple complexes. Viskontas presents fascinating findings from single-cell recordings in the medial temporal lobes that became famous when the ‘Jennifer Aniston’ cell was described in the human brain (or, at least, in the great number of human brains sufficiently exposed to Friends, the celebrated television programme in which Jennifer Aniston performed). Viskontas describes the rich source of evidence for students of human memory provided by these innovative studies.

We consider aspects of treatment and outcome in the book’s final Part. The treatment of epilepsy is predominantly medical, with a rapidly growing armamentarium of drugs. Taylor and Baker appraise the effects of anticonvulsant medication on memory. They highlight the methodological limitations of most existing studies, but convey broadly reassuring news about the cognitive side-effects of contemporary anticonvulsants. The news about the cognitive effects of exposure to these drugs in utero is more disquieting. Banks and Jones-Gotman compare the effects of different surgical approaches to temporal lobe resection, and examine the reasons for the complex pattern of results that they discover. Finally, Thompson and Kapur discuss the current options for memory rehabilitation in patients with epilepsy, acknowledging the limitations of the current evidence for their efficacy, while pointing to future refinements that have potential to enhance their value.

References


