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REVIEW ARTICLE

Recent insights into the impairment of memory in epilepsy: transient epileptic amnesia, accelerated long-term forgetting and remote memory impairment

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Complaints of memory difficulties are common among patients with epilepsy, particularly with temporal lobe epilepsy where memory-related brain structures are directly involved by seizure activity. However, the reason for these complaints is often unclear and patients frequently perform normally on standard neuropsychological tests of memory. In this article, we review the literature on three recently described and interrelated forms of memory impairment associated with epilepsy: (i) transient epileptic amnesia, in which the sole or main manifestation of seizures is recurrent episodes of amnesia; (ii) accelerated long-term forgetting, in which newly acquired memories fade over days to weeks and (iii) remote memory impairment, in which there is loss of memories for personal or public facts or events from the distant past. Accelerated long-term forgetting and remote memory impairment are common amongst patients with transient epileptic amnesia, but have been reported in other forms of epilepsy. Their presence goes undetected by standard memory tests and yet they can have a profound impact on patients' lives. They pose challenges to current theoretical models of memory. We discuss the evidence for each of these phenomena, as well as their possible pathophysiological bases, methodological difficulties in their investigation and their theoretical implications.

Keywords: memory; epilepsy; transient epileptic amnesia; accelerated long-term forgetting; remote memory impairment

Abbreviations: TLE = temporal lobe epilepsy; TEA = transient epileptic amnesia; ALF = accelerated long-term forgetting; RMI = remote memory impairment

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> 'A proper understanding of the amnesia accompanying epileptic attacks would contribute much to an understanding of the neurophysiological mechanisms of formation of memory patterns and of recall.'
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> *Nisien JM. Memory and amnesia. Los Angeles: San Lucas Press, 1958.*

People with epilepsy frequently complain of memory difficulties. A community-based survey of over 1000 epilepsy patients in the United States revealed that cognitive difficulties ranked highest on a list of potential concerns (Fisher *et al.*, 2000). In another study, 54% of over 700 people with epilepsy regarded memory problems as a moderate to severe nuisance (Thompson and Corcoran, 1992). Many interacting factors may affect memory function in patients with epilepsy including the underlying neuropathology (Lencz *et al.*, 1992), seizure activity (Jokeit *et al.*, 2005), anticonvulsant medication (Motamedi and Meador, 2004), surgery (Téllez-Zenteno *et al.*, 2007), age (Lespinet *et al.*, 2002), genetic background (Busch *et al.*, 2007) and psychosocial factors (Elixhauser *et al.*, 1999).

Complaints of memory dysfunction are particularly widespread in temporal lobe epilepsy (TLE), the most common form of adult-onset epilepsy, in which memory-related brain structures including the hippocampus are directly involved by seizure activity. It is well recognized that TLE may cause deficits on neuropsychological tests of memory, which typically assess the ability to retain new information over a delay of about 30 min (Hermann *et al.*,

1997). The degree of impairment has been shown to correlate with pathological abnormalities (Oxbury and Oxbury, 1989; Rausch and Babb, 1993; Pauli *et al.*, 2006), hippocampal atrophy on brain MRI (Lencz *et al.*, 1992; Kilpatrick *et al.*, 1997; Reminger *et al.*, 2004) and a number of clinical variables such as the age of onset of epilepsy, seizure frequency and lifetime number of seizures (Dodrill, 1992; Giovagnoli and Avanzini, 1999; Lespinet *et al.*, 2002; Hendriks *et al.*, 2004; Oyegbile *et al.*, 2004). Furthermore, the laterality of the seizure focus has consistently been found to influence the type of material for which memory is most affected, with left TLE causing more pronounced deficits in verbal memory, and, less consistently, right TLE affecting non-verbal memory (Hermann *et al.*, 1997; Baxendale *et al.*, 1998; Gleissner *et al.*, 1998). However, the severity of memory difficulty reported by patients with epilepsy, as with other types of neurological disease, correlates poorly with objective measures, and many patients perform at average or above-average levels (Piazzini *et al.*, 2001).

Transient epileptic amnesia (TEA) is a form of TLE with a particularly intimate relation to memory (Kapur and Markowitsch, 1990; Zeman *et al.*, 1998; Butler *et al.*, 2007). In this syndrome, the principle manifestation of seizures is episodes of transient amnesia during which other cognitive functions remain intact. Patients also typically complain of prominent interictal memory difficulties (Gallassi, 2006). However, performance on standard tests of memory is usually normal. Recent work has revealed two relatively novel forms of memory impairment in TEA, which are not detected by standard tests (Manes *et al.*, 2005; Butler *et al.*, 2007). In accelerated long-term forgetting (ALF), individuals learn and initially retain information normally, but forget it at an unusually rapid rate over the following days or weeks. Secondly, there is often a patchy loss of autobiographical memories extending back over many years. It is possible that these phenomena also occur in other forms of epilepsy, and they may go some way towards explaining the common mismatch between subjective complaints and objective memory performance.

In this article, we review the available literature on these three 'unconventional' and interlinked forms of memory deficit associated with epilepsy: transient amnesic episodes, ALF and remote memory impairment (RMI). We discuss the evidence for their existence, their possible causes, their interrelations and the methodological difficulties surrounding their investigation.

Part I: Transient epileptic amnesia

Methods

We performed an exhaustive search of the medical and psychological literature for case reports and case series of transient amnesia associated with epilepsy. We looked for publications indexed in MEDLINE (from 1966), EMBASE (from 1980) and PSYCHINFO (from 1967) prior to the end of November 2007. The titles and available abstracts of pertinent papers were scrutinized and further hand searching of reference lists was used to identify un-indexed reports. For a case to be included, the following diagnostic criteria (Butler *et al.*, 2007) had to be met:

(1) a history of recurrent witnessed episodes of transient amnesia
(2) cognitive functions other than memory judged to be intact during typical episodes by a reliable witness
(3) evidence for a diagnosis of epilepsy based on one or more of the following:

   (a) epileptiform abnormalities on electroencephalography
   (b) the concurrent onset of other clinical features of epilepsy (e.g. lip-smacking, olfactory hallucinations)
   (c) a clear-cut response to anticonvulsant therapy

Using the same diagnostic criteria, 50 patients with TEA were recruited from around the United Kingdom between August 2003 and April 2005 as part of the TIME (The Impairment of Memory in Epilepsy) Project. A detailed clinical and neuropsychological evaluation was performed in each case. The methods used and results obtained have previously been reported (Butler *et al.*, 2007).

The cases were then studied for information about the following: (i) demographics, (ii) aetiology, (iii) clinical features of attacks, (iv) anatomical and physiological basis of the syndrome, (v) interictal memory deficits and the relation to other clinical features and (vi) prognosis.

Results and discussion

Our literature search resulted in 93 case reports in 45 papers. Of these we identified 54 cases in 28 papers meeting our diagnostic criteria. The remaining 39 cases were discarded due to incomplete description (21 cases), single episode (8 cases), no witness (5 cases), evidence of other cognitive impairment (3 cases), no evidence of epilepsy (1 case), pure anomia rather than typical amnesia (1 case). Of the 50 cases included in the TIME Study (Butler *et al.*, 2007), 10 had been previously described [8 in Zeman *et al.* (1998), 2 in Manes *et al.* (2005)]. The final analysis therefore included: 50 cases from the TIME study ('TIME cases') and 44 from elsewhere in the literature ('literature cases'). These cases are summarised in Table 1.

TIME cases were prospectively recruited and assessed. The available data on clinical features, past medical and psychiatric history and neuropsychological test performance are therefore comparatively consistent. In contrast, the relative inconsistency of the data available from literature cases is reflected by variability in the denominator used when proportions are calculated below. Importantly, certain literature case reports offer valuable insight from clinical and electrophysiological data obtained *during* the amnesic attack.

Demographics of TEA

The mean age of onset of amnesic attacks was 57.2 years (literature cases = 55.1 years; TIME cases = 62.1 years). The range was 11–82 years in the literature cases and 44–77 years in the TIME cases. Nine literature cases had an onset before 40 years of age. From the available data, no other clinical features clearly distinguish this subpopulation. TEA is therefore usually a syndrome of middle to old age. This is

Table 1 Summary of the clinical features of all reported cases of transient epileptic amnesia

Authors (year)	Age at onset	Sex	Duration of attacks	Total number	Waking attacks	Ictal AA	RQ	Olf aura	Automatisms	'blank spell'	EEG +ve	Imaging	Interictal memory	Response to AED
Lou (1968)	61	M	30–60 min	9	No	Yes	Yes	No	No	No	L			Complete
Lou (1968)	79	F	1–24 h	3		Partial	Yes				B			
Croft *et al.* (1973)	58	F	1–24 h	2	No	Yes	Yes				B			Complete
Morrell (1980)	27	M				Yes				Yes	B (ictal)			
Shuping *et al.* (1980)	60	M	30–60 min	3		Yes					N	L HC GBM		Died
Dugan *et al.* (1981)	82	M	1–24 h	3		Yes	Yes			No	B (ictal)	CT normal		Complete
Deisenhammer (1981)	11	F	1–15 min	3	Yes	Yes	Yes			No	R	CT normal		Complete
Meador *et al.* (1985)	47	F	1–15 min	2	No	Partial				No	B	R MTL meningioma		Complete
Pritchard *et al.* (1985)	65	M	1–15 min	10		Yes					B	CT normal	↓	Complete
Pritchard *et al.* (1985)	64	M	30–60 min	3		Yes					B		↓	Complete
Kapur *et al.* (1989)	74	M	15–30 min	20	Yes	Yes	No		Oral	Yes	B	MRI normal	↓	
Gallassi *et al.* (1986)	64	M	30–60 min	25	Yes	Yes	Yes	No	Oral	Yes	NS	Mod gen atrophy	↓	Partial
Miller *et al.* (1987)	22	M	1–15 min							Yes	L			Complete
Miller *et al.* (1987)	62	M	15–30 min	8	Yes		Yes	No	No	No	B			Complete
Gallassi *et al.* (1988*b*)	67	F	1–15 min	60	Yes	Yes	Yes		Oral	Yes	NS	CT normal	↓	Complete
Gallassi *et al.* (1988*b*)	65	M	15–30 min	9		Yes			Oral	Yes	NS	No	↓	Complete
Stracciari *et al.* (1990)	70	F	1–15 min	13		Yes	Yes		Oral	Yes	L	MRI normal	↓	Complete
Tassinari *et al.* (1991)	57	M	1–15 min			Yes	Yes	Yes	Oral	Yes	B (ictal)			Complete
Palmini *et al.* (1992)	30	F	<1 min			Yes	No	No	Manual	No	B (ictal)	L HS		Continued
Palmini *et al.* (1992)	36	F	<1 min			Yes		No			B (ictal)	Atrophy L HC/AG		Continued
Palmini *et al.* (1992)	44	F	<1 min			Yes		No		No	B	Normal		Continued
Kapur (1993*b*)	61	F	15–30 min	2	Yes	No		No	No		NS	L frontal infarct		Complete
Kapur (1993*b*)	63	F	1–24 h	35	Yes	Yes	No	No	Oral	No	NS	CT normal	↓	Partial
Kapur (1993*b*)	67	F	30–60 min	6	No	Partial	No	No	No		NS	CT normal	Normal	Complete
Kapur (1993*b*)	28	M	>24 h	20	Yes	Yes	Yes	No	Oral	No	B		↓	Complete
Kopelman *et al.* (1994)	54	M	30–60 min	9		Yes	Yes		Manual	No	B	MRI normal	↓	Complete
Meo *et al.* (1995)	69	F	1–24 h	3	Yes	Yes	No			Yes	L (ictal)			Complete
Cammalleri *et al.* (1996)	47	M	<1 min	4	No	No	No	No	No	No	N	Angioma R cing	↓	Complete
Vuilleumier *et al.* (1996)	Teens	F	1–24 h	40	Yes	Yes	No			No	B (ictal)	MRI normal	↓	Complete
Dasheiff (1997)	M/age	F			No	Y/N	No	No	No	No	B (ictal)			No
Hawley *et al.* (1997)	38	F				Yes				Yes	L			Complete
Zeman *et al.* (1998)	68	M	1–24 h	5	Yes	Partial	Yes	Yes		No	B	CT normal	↓	Complete
Zeman *et al.* (1998)	79	M	1–24 h	3	Yes		Yes				B	Post CC infarct	↓	
Corridan *et al.* (2001)	69	M		11	Yes	Yes	Yes	No	No	No	B			Complete
Mendes (2002)	45	M	30–60 min			Yes	No					CT normal		Partial
Mendes (2002)	71	F	30–60 min	4	No	Partial	Yes	No	No	No	N	MRI normal	↓	Complete
Mendes (2002)	74	M	30–60 min	4	No	Partial	Yes	No	No	No	NS	MRI normal	↓	Complete
Engmann and Reuter (2003)	48	M	>24 h	3	No	Yes		No	No	Yes	L	MRI mild atrophy		Complete
Maheu *et al.* (2004)	27	M	>24 h	10		Yes	No			No	R (ictal)	R MTL bleed	↓	
Manes *et al.* (2005)	48	M	30–60 min	4							B	CT normal		
Manes *et al.* (2005)	64	M	<1 min	7							B	CT normal		
Manes *et al.* (2005)	69	M	30–60 min	5								Normal		
Manes *et al.* (2005)	57	M	30–60 min	6								MRI CVD		
Manes *et al.* (2005)	46	M	30–60 min	4							R	MRI normal		
TIME (Butler *et al.*, 2007)	62.1 (44–77)	34 M	30–60 min	10	37/50	28/50 Partial	25/50	21/50	18/50	12/50	18/49	1 Meningioma	ALF 22/50 RMI 35/50 TA 18/50	46/48 Complete

AA = anterograde amnesia; AED = antiepileptic drug; AG = amygdala; ALF = accelerated long-term forgetting; B = bilateral; CC = corpus callosum; cing = cingulate gyrus; CVD = cerebrovascular disease; L = left; MTL = medial temporal lobe; GBM = glioblastoma multiforme; HC = hippocampus; olf aura = olfactory aura; R = right; RMI = remote memory impairment; RQ = repetitive questioning; TA = topographical amnesia; TIME = cases recruited in the TIME (The Impairment of Memory in Epilepsy) Project. M/age = middle age; a downwards arrow = decreased; Where entry is left blank, the information is not available.

similar to the age range of Transient Global Amnesia (TGA), a syndrome which also results in transient impairment of declarative memory and is attributed to neuronal dysfunction in the medial temporal lobes, although the precise mechanism remains to be established. It is not clear why advancing age should predispose to transient dysfunction of the medial temporal lobes. Given the sensitivity of this region to hypoxic damage and its situation at a 'watershed' between anterior and posterior circulation, it seems possible that cell damage secondary to vascular insufficiency may act as an epileptic focus. This is discussed later.

The sex ratio of TEA cases was approximately two males to one female in both the literature cases (27 males, 17 females) and the TIME cases (34 males, 16 females). The overall percentage of males was 64.9% (95% CI = 55.3–74.6%). The reasons for this sex difference are not clear. A recent of review of 1333 published cases of TGA (Quinette *et al.*, 2006) found no significant sex difference. The proportion of males with TGA was 46.4%, significantly different from the proportion in TEA patients ($\chi^2 = 3.62$, $P < 0.001$).

Duration

The typical duration of amnestic attacks for each case was categorized as follows: <1; 1–15; 15–30; 30–60 min; 1–24 and >24 h. The median duration was 30–60 min for literature cases, TIME cases and the group as a whole. This is briefer than the typical duration of TGA (4–10 h) and confirms previous observations (Zeman *et al.*, 1998). Of note, however, 23 cases (24.5%) had attacks of similar duration to TGA, which could lead to diagnostic confusion. Very brief attacks (<1 min) are less likely to be noticed by the patient or observers. It remains to be explained why the majority of attacks are longer than would be expected for temporal lobe seizures and why some persist for several days. The possibility that these are due to persistent epileptic activity (non-convulsive status epilepticus) is supported by accounts of ongoing or intermittent automatisms (Kapur, 1993*b*) and the cases of Lee *et al.* (1992), Meo *et al.* (1995) and Vuilleumier *et al.* (1996). Lee *et al.* (1992) describe a 38-year-old woman who suffered a 12-day episode of pure amnesia accompanied by persistent epileptic activity isolated to the left temporal region. Meo *et al.* (1995) report a 69-year-old female with an amnesic episode lasting several hours during which ictal discharges originating from the right temporo-central region were recorded. In both these cases, the patient's behaviour during bursts of ictal discharges was indistinguishable from that observed during interictal activity. Vuilleumier *et al.* (1996) describe a 41-year-old woman with persistent failure of recollection for 10 h during which EEG revealed continuous generalized epileptic activity with phase reversal in bilateral fronto-temporal regions. However some prolonged TEA attacks may result from post-ictal amnesia or a 'Todd's paralysis of memory' (Morrell, 1980)—presumably following a brief or subclinical period of seizure activity—as in the cases described by Morrell (1980), Tassinari *et al.* (1991) and Maheu *et al.* (2004). It is recognized that both seizures and the post-ictal period can be prolonged in elderly patients (Rowan, 2000).

Frequency

Before treatment, the overall mean frequency of attacks was 14.8/year (literature cases = 19.7/year; TIME cases = 13.6/year). This is higher than previously reported (Zeman *et al.*, 1998) and distinguishes TEA from transient global amnesia in which the recurrence rate is low [around 3% per year (Hodges and Warlow, 1990)]. However, the range across individuals is wide (<1 to >60 attacks per year) and a low frequency of attacks does not preclude a diagnosis of epilepsy. There is, moreover, a likelihood that attacks will be underreported, particularly those that are not witnessed by another person.

Amnesia on awakening

An association between amnesic attacks and arousal from sleep was noted in 70.4% of TEA cases (13/21 literature cases and 37/50 TIME cases). In 11/50 TIME cases, amnesic attacks occurred exclusively upon waking. The close relationship between sleep and epilepsy is well-recognized. Primary generalized epilepsies are particularly associated with sleep, with purely nocturnal seizures occurring in 45% of cases (Janz, 1962), and seizures upon or shortly after waking being a characteristic feature of both juvenile myoclonic epilepsy (JME) and absence epilepsy. Among the focal epilepsies, nocturnal seizures are particularly common in frontal lobe epilepsy, whereas in temporal lobe epilepsy the percentage is much lower. In an electroencephalographic study of patients with medically intractable focal epilepsy, 61% of frontal seizures but only 10.9% of temporal lobe seizures were recorded during sleep (Crespel *et al.*, 1998). In general, both seizures and interictal epileptiform discharges are predominantly associated with the highly synchronized brain activity of non-rapid eye movement sleep rather than the desynchronized state of rapid eye movement sleep (Sammaritano *et al.*, 1991). The reason for the close relationship of TEA with sleep is unclear. It may be that the transition from sleep to waking acts as a trigger to a seizure focus in the medial temporal lobe. Alternatively, amnesia upon waking may reflect persistent post-ictal dysfunction of medial temporal lobe structures following a seizure during sleep. In one TIME case, for example, morning amnesia was always preceded by a brief arousal at around 2 a.m. when the patient sat up in bed, staring and said 'Oh, the smell, the smell' before going straight back to sleep (case 83).

Ictal amnesia

Anterograde amnesia is usually understood as a deficit in memory encoding or in storage mechanisms, whereas retrograde amnesia, as least insofar as it proves transient, can

be thought of as a memory retrieval problem. The relative impairment of anterograde and retrograde memory during TEA attacks, despite being difficult to ascertain from a retrospective patient or witness report, may therefore provide clues about the anatomy and degree of neuronal dysfunction. In transient global amnesia, anterograde amnesia is complete and the patient later has no recollection of events that occurred during the episode. In contrast, 44% of patients with TEA (10/36 literature cases; 28/50 TIME cases) describe at least partial preservation of anterograde memory during attacks and afterwards may remember not being able to remember. A small number of TEA patients (2/36 literature cases; 3/50 TIME cases) are able to remember their attacks in rich subjective detail, suggesting minimal impairment of encoding. This later recollection of ictal events does not necessarily correlate with the apparent anterograde amnesia during the attack. The three TIME cases referred to here displayed repetitive questioning of witnesses during their amnesic attacks. Vuilleumier *et al.* (1996) describe a patient who, during non-convulsive status epilepticus, could not perform anterograde memory tasks but who nevertheless encoded events into long-term memory. This presumably reflects temporary impairment of memory retrieval but preserved encoding and storage. In contrast, Dasheiff (1997) describes a patient who, during electrographic seizures recorded with both scalp and invasive EEG monitoring, performed normally on memory tests but was subsequently amnesic for these episodes.

The degree of retrograde amnesia experienced during an episode of TEA also varies across individuals. Of 22 classifiable cases in the TIME study, 12 were associated with extensive ictal retrograde amnesia, stretching years into the past, whereas 10 appeared to have an ictal retrograde amnesia that was limited to events of the most recent days or weeks. Five of 33 cases in the literature are described as having no apparent retrograde memory deficit during the attack, although none of them had formal retrograde memory testing during the ictus. Such cases of apparently pure anterograde amnesia may go unnoticed as the patient will remain orientated and behave normally during the attack unless very recent memory is probed. The possibility that attacks of TEA irreversibly disrupt retrograde memory is not mentioned in any of the literature case reports but three TIME study patients volunteered that their TEA attacks permanently 'erased' memories of the preceding 24 h.

Repetitive questioning

In transient global amnesia, the patient will repeatedly ask observers questions such as: 'Where am I?' 'What day is it?' or 'What is happening to me?' In TEA, however, this is a feature in just over 50% (17/30 literature cases; 25/50 TIME cases). Interestingly, the presence of repetitive questioning does not predict of the degree of later recollection of ictal events ($\chi^2 = 0.325$, $P = 0.569$).

Additional features

In 65.8% of cases (16/29 literature cases, 36/50 TIME cases), amnesic attacks were sometimes accompanied by additional features. However, 46/50 TIME cases had at least one attack with memory loss as the only feature.

Olfactory hallucinations. Amongst the TIME cases, olfactory/gustatory hallucinations were the most common additional feature and were reported by 42% (21/50) of patients upon direct questioning. Of these, 16 cases reported a purely olfactory sensation, 2 purely gustatory and 3 a mixed olfactory/gustatory sensation. The odour or taste was described as unpleasant in all but one case. In contrast, olfactory or gustatory hallucinations were described in only 2/16 literature cases. Three additional TIME cases complained of a greatly decreased sense of smell since the onset of their amnesic attacks. Olfactory and gustatory hallucinations are generally held to be a rare feature of epilepsy, and almost always associated with a temporal lobe focus. Estimations of frequency vary. Penfield and Perot (1963) found 7 cases (0.6%) in 520 temporal lobe seizure patients. Acharya *et al.* (1998) found only 13 patients (0.9%) with olfactory auras among 1423 evaluated at the Cleveland Clinic between 1991 and 1996. Higher prevalence rates have been reported by Chen *et al.* (2003) (5.5%), Ebner and Kerder (2000) (6.3%) and Manford *et al.* (1996) (7.1%). All studies except Manford *et al.* (1996) investigated only patients with medically intractable focal epilepsy. Several studies have reported a particularly high incidence of tumours among patients with olfactory auras, including Jackson and Beevor (1890), Penfield and Jasper (1954) and Acharya *et al.* (1998). The latter found a neoplastic lesion in 10 of the 13 patients in their study. Others, however, have disputed this and maintain that hippocampal sclerosis is the most commonly associated pathological finding (Fried *et al.*, 1995; Chen *et al.*, 2003). There is greater consensus about the approximate anatomical origin of epilepsy-associated olfactory hallucinations, with the majority of patients having a seizure focus in the anterior medial temporal lobe. Hughlings–Jackson localized olfactory and gustatory functions to the uncus. Olfactory hallucinations have also been provoked by direct cortical stimulation of the amygdala, rather than the hippocampus, in several studies (Jasper and Rasmussen, 1958; Fergusson *et al.*, 1969; Andy *et al.*, 1975; Gloor *et al.*, 1982; Bartolomei *et al.*, 2004). The hallucinations were, however, only rarely elicited, and it remains uncertain whether spontaneous events have the same precise anatomical origin.

Déjà vu. Déjà vu is a common experience amongst healthy individuals as well as being associated with a variety of neurological and psychiatric conditions, among them temporal lobe epilepsy (Warren-Gash and Zeman, 2003) in which prevalence estimates vary widely [from 6% to 80% (Brown, 2003)]. Given the probable involvement of medial temporal lobe structures in TEA, it is perhaps surprising that just five (10%) TIME cases described experiencing

frequent déjà vu, usually on occasions distinct from their amnestic attacks. This symptom was not reported in any of the literature cases. Ictal déjà vu may involve inappropriate activation of brain circuits underlying familiarity. Cortical stimulation studies have elicited déjà vu from stimulation in the anterior medial temporal lobes, more frequently on the right than the left in right-handed patients (Gloor *et al.*, 1982; Halgren *et al.*, 1985; Bancaud *et al.*, 1994). A recent study (Bartolomei *et al.*, 2004) found déjà vu to be more frequently produced by stimulation of the entorhinal cortex than the hippocampus or amygdala. The frequency of 'physiological' déjà vu declines with age, but it is otherwise unclear why TEA, which is likely to arise from structures in which epileptic activity can give rise to déjà vu, should so rarely be associated with it.

Automatisms. Automatisms (involuntary, semi-purposeful movements) were reported to accompany some amnesic attacks in 40.6% of patients (10/19 literature cases, 18/50 TIME cases). Oro-alimentary automatisms (chewing or lip smacking) were the most common (8/10 literature cases, 14/18 TIME cases) and the remainder were manual automatisms. Oral automatisms are significantly associated with a temporal rather than frontal seizure focus (Manford *et al.*, 1996) and with hippocampal rather than extra-hippocampal temporal lobe seizures (Gil-Nagel and Risinger, 1997).

Unresponsiveness. A brief period of unresponsiveness was sometimes associated with the amnesic episode in 28.2% of patients (10/28 literature cases, 12/50 TIME cases). Unresponsiveness, one of the hallmarks of 'altered consciousness' in complex partial seizures, is thought to represent bilateral spread of seizure activity. When this occurs at the beginning of the episode, it may indicate that the subsequent memory impairment is a post-ictal phenomenon (Morrell, 1980).

Other seizure types. Patients with TEA may also experience seizures in which amnesia is not a prominent feature. These occurred in 21.3% of cases (13/39 literature cases, 6/50 TIME cases) and were almost always complex partial seizures. This observation raises the possibility that transient episodes of amnesia are more widespread among TLE patients than is generally recognized, but that they go unnoticed or unreported. Generalized tonic–clonic seizures were only reported in 3/94 cases (3%).

Electroencephalography

Interictal EEG. Interictal epileptiform abnormalities on electroencephalography (EEG) were seen in 43.6% cases (23/44 literature cases, 18/49 TIME cases). Of these, 31.7% were left-sided, 12.2% were right-sided and 56.1% were bilateral. All were localized over the temporal or fronto-temporal region. The interictal EEG was entirely normal in 19.4% of cases (3/44 literature cases, 15/49 TIME cases). Surface EEG lacks sensitivity to discharges originating in the medial temporal lobes and the detection rate in TEA, given variable usage of routine or sleep EEG recording, is similar to that in other forms of temporal lobe epilepsy.

Ictal EEG. Surface EEG recording during an amnesic attack was performed in nine literature cases and one TIME case. All recordings showed seizure activity, which in 8/10 cases involved both temporal lobes and in the others remained unilateral (one left- and one right-sided). Amnesia was observed as an ictal phenomenon in six cases and as post-ictal in four cases.

Brain imaging

Brain imaging results were available for 29/44 literature cases (CT = 14, MRI = 15) and 49 TIME cases (CT = 2, MRI = 47). Focal lesions were detected in 7/78 cases of which four were likely to have played an aetiological role in the seizures (5.1%). These were: two right medial temporal lobe meningiomas [(Meador *et al.*, 1985) and TIME case 40], haemosiderin deposition in the right medial temporal lobe (Maheu *et al.*, 2004) and a glioblastoma multiforme in the left hippocampal region (Shuping *et al.*, 1980). We have recently observed medial temporal lobe high signal on T_2-weighted MRI sequences in two patients with particularly frequent episodes of TEA, with unilateral hippocampal hypermetabolism on a PET scan in one of these, resolving when the seizures subsided (Butler, in press). In general, therefore, TEA is not associated with clinically detectable, focal brain lesions, but where these are present they involve the medial temporal lobes.

Aetiology

Besides these rare structural abnormalities, the cause of TEA is usually obscure. Zeman *et al.* (1998) pointed out that a history of cardiac disease was common in their series, and hypothesized that cardiac-related hypoxic damage to medial temporal lobe structures might have caused the epilepsy. Amongst the TIME cases, however, Butler *et al.* (2007) failed to find an excess of overt cardiovascular or cerebrovascular disease.

Interictal memory disturbance

Complaints of interictal memory dysfunction are common in TEA and were noted in 80.6% patients (16/17 literature cases, 38/50 TIME cases). Inconsistency of neuropsychological assessment across the literature cases precludes useful analysis of data. Amongst TIME patients, the most common problems were (i) a patchy loss of memories for remote, personally experienced events (35/50 TIME cases), (ii) accelerated forgetting over days to weeks of newly acquired memories (22/50 TIME cases) and (iii) topographical memory deficits (18/50 TIME cases). Despite these complaints, the majority of patients performed normally on standard neuropsychological tests of memory, although the group as a whole showed a subtle but statistically significant impairment relative to matched control subjects (Butler *et al.*, 2007).

In a series of papers, Gallassi (Gallasi *et al.*, 1986, 1988*a*, *b*, 1990, 1992; Gallassi, 2006) has described the 'epileptic amnesic syndrome', in which patients present with complaints of severe, persistent memory impairment in the context of usually subtle temporal lobe seizures. In some cases, these seizures are followed by a period of transient amnesia, which Gallassi, following Pritchard *et al.* (1985), has called 'epileptic amnesic attacks' (EAA). Clearly, the patients described by Gallassi have much in common with TEA patients and some of those for whom sufficient clinical data have been published have been included in the present review. The epileptic amnesic syndrome and TEA are not, however, coterminous as some patients with TEA do not have pronounced interictal memory disturbance and some patients with epilepsy and memory problems do not have transient amnesic attacks.

Treatment responsiveness

Complete cessation of transient amnesic episodes was achieved with anticonvulsant therapy in 88.5% patients (25/32 literature cases, 46/48 TIME cases). The remainder showed a substantial decrease in attack frequency. The reason for this excellent response rate is unknown but is generally reported in late-onset epilepsy (Stephen and Brodie, 2000).

Summary

This review reveals that the clinical features of TEA are consistent across numerous independent reports published over the past 40 years, strengthening the view that it should be regarded as a distinct syndrome of epilepsy. A number of clinically important questions relating to the aetiology, epidemiology and prognosis of TEA remain unanswered and should be addressed in future work.

Part II: Accelerated long-term forgetting

According to traditional models, information has been encoded into long-term memory if it can be accurately retrieved after an interval during which active rehearsal is prevented. Thereafter, a process of 'consolidation' renders the memory trace progressively less vulnerable to disruption (Squire *et al.*, 1984). This process, thought to involve a gradual reorganization of the memory trace at a neural-systems level (Squire and Alvarez, 1995), may continue for weeks, months or even years but it is often assumed that its efficacy can be assessed at relatively brief delays. Standard neuropsychological instruments, therefore, typically test memory retention at intervals of up to 30 min, and little is known about forgetting beyond that point. Over recent years, a number of case reports have described a novel form of forgetting, apparent only over extended periods of time, providing evidence for a prolonged multiple-stage consolidation process. These cases, together with group studies evaluating very long-term forgetting in epilepsy, are the focus of this section. Several of the studies included have been summarized in a recent review paper by Bell and Giovagnoli (2007). Although other authors have called this phenomenon long-term amnesia (LTA) (Kapur *et al.*, 1996, 1997; Mayes *et al.*, 2003), we adopt the alternative ALF to distinguish the disorder from the amnesic syndrome and to include cases in which long-term memory may be deficient but not completely absent.

Methods

Using the search methods described in Part I, we first identified case reports describing patients with epilepsy in whom learning and memory performance over delays of up to 1 h was considered to be in the normal range (by comparison with published norms or a matched control group) but in whom testing over longer delays revealed impairment. We then searched for studies comparing memory over delays of 24 h or longer in groups of patients with epilepsy and healthy control subjects.

Case reports

Seven case reports of ALF meeting our inclusion criteria were found (Kapur *et al.*, 1996, 1997; O'Connor *et al.*, 1997; Lucchelli and Spinnler, 1998; Mayes *et al.*, 2003; Cronel-Ohayon *et al.*, 2006; Manning *et al.*, 2006). Three additional cases were described as showing ALF but did not undergo formal testing (Kapur *et al.*, 1989, 1996) or were tested only at short delays (Maravita *et al.*, 1995). One report demonstrated abnormal long-term forgetting in a patient with no documented seizures (De Renzi and Lucchelli, 1993). The seven cases we consider are summarized in Table 2. Four patients were males and three females. Their ages ranged from 18 years to 65 years (mean = 48.1, SD = 15.6). In striking contrast with classically amnesic individuals, these patients maintained active, independent lives and several remained in employment.

The aetiology of the memory impairment included: closed head injuries (Kapur *et al.*, 1996; Mayes *et al.*, 2003), paraneoplastic limbic encephalitis (O'Connor *et al.*, 1997), neuronal dysplasia in the left amygdala and hippocampal sclerosis (Manning *et al.*, 2006). Two patients had late-onset temporal lobe epilepsy with no clear cause (Kapur *et al.*, 1997; Lucchelli and Spinnler, 1998). In two cases (Kapur *et al.*, 1996; Lucchelli and Spinnler, 1998) seizures resolved immediately with anticonvulsant medication. Structural brain imaging was abnormal in six patients. Damage was restricted to the temporal lobes in all cases except one (Mayes *et al.*, 2003), in whom the right orbitofrontal cortex was also affected. The hippocampus was the only abnormal region in one case (Kapur *et al.*, 1997), whereas this was spared in another (Mayes *et al.*, 2003). Both medial and lateral temporal cortices were damaged in the remaining four cases (Kapur *et al.*, 1996; O'Connor *et al.*, 1997; Cronel-Ohayon *et al.*, 2006; Manning *et al.*, 2006), two of whom had undergone temporal lobectomy (Cronel-Ohayon *et al.*, 2006; Manning *et al.*, 2006). Only one patient had normal structural brain imaging (Lucchelli and Spinnler, 1998).

Table 2 Investigations of accelerated long-term forgetting (ALF) in patients with epilepsy: series and individual case studies

Authors (year)	Initials/number of patients	Age mean (SD)	Sex	Seizures	Seizure lateralization	Structural pathology on brain imaging	Non-memory impairment	Memory impairment at 30 min?	First long delay (ALF found?)	Remote memory impairment
Cases										
Kapur *et al.* (1996)	SP	50	F	GTC	n/d	Bilat TL	Naming ↓	Recog mem ↓ (mild)	6 week (+)	Yes
O'Connor *et al.* (1997)	JT	42	M	CPS	Bilat	MTL bilat	No	No	24 h (+)	Yes
Kapur *et al.* (1997)	PA	62	F	CPS	L	L HC (subtle)	No	No	6 week (+)	Yes
Lucchelli and Spinnler (1998)	GB	65	M	CPS	L	No	No	Verbal ↓ (mild)	7 day (+)	Yes
Mayes *et al.* (2003)	JL	46	F	CHI → CPS	n/d	Bilat TL; HC normal	Fear perc ↓	Recog mem ↓ (mild)	3 week (+)	Yes
Manning *et al.* (2006)	JR	54	M	CPS → GTC	L	L HS (postop)	No	No	30 h (+)	Yes
Cronel-Ohayon *et al.* (2007)	JE	18	M	CPS	L	L AG (postop)	No	Yes (mild)	7 day (+)	Yes
Series										
Martin *et al.* (1991)	21	31 (7.5)	10 M	TLE	13 L; 8 R	6 postop	IQ ↓	No	24 h (+)	n/d
Giovagnoli *et al.* (1995)	24	38 (11.6)	14 M	TLE	12 L; 12 R	No	No	No	2 week (−)	n/d
Helmstaedter *et al.* (1998)	55	27	27 M	TLE	28 L; 27 R	45 TL lesion	IQ ↓	Yes	1 week	n/d
Blake *et al.* (2000)	21	34 (8.7)	7 M	14 TLE; 7 other	11 L; 10 R	HS 5/14	No	No	8 week (+)	n/d
Bell *et al.* (2005)	42	37 (11.4)	14 M	TLE	22 L; 20 R	No	IQ ↓	Yes	24 h (−)	n/d
Bell (2006)	25	39 (10.0)	10 M	TLE	11 L; 6 R; 2 B	6 postop	IQ ↓	Yes	2 week (−)	n/d
Manes *et al.* (2006)	7	57 (8.1)	6 M	TEA	n/d	No	No	No	6 week (+)	Yes
Mameniskiene *et al.* (2006)	70	33 (9.5)	29 M	TLE	n/d	11 TL lesion	n/d	Yes	4 week (+)	n/d
Butler *et al.* (2007)	24	68 (8.7)	14 M	TEA	n/d	No	No	No	1 week (+)	Yes
Davidson *et al.* (2007)	21	11.5	7 M	IGE	–	n/d	No	No	1 week (+)	n/d

AG = amygdala; n/d = not discussed; ALF = accelerated long-term forgetting; B = bilateral; CHI = closed head injury; CPS = complex partial seizures; GTC = generalised tonic-clonic seizure; HC = hippocampus; HS = hippocampal sclerosis; IGE = idiopathic generalised epilepsy; L = left; LE = limbic encephalitis; (M)TL = (medial) temporal lobe; R = right; TEA = transient epileptic amnesia; TLE = temporal lobe epilepsy.

Reporting of standard neuropsychological test results is variable. Five cases had no apparent deficits in non-memory domains, whilst others showed mild impairment at naming (Kapur *et al.*, 1996) and fear perception (Mayes *et al.*, 2003). In three cases, standard memory tests revealed no abnormality (Kapur *et al.*, 1997; O'Connor *et al.*, 1997; Manning *et al.*, 2006) whilst, in the remainder, subtle deficits were found in recognition memory (Kapur *et al.*, 1996; Mayes *et al.*, 2003) and recall (Lucchelli and Spinnler, 1998; Cronel-Ohayon *et al.*, 2006).

Very long-term memory was assessed using a variety of tests including a short story, word lists, verbal paired associates, the Rey complex figure and face recognition. Immediate and early (between 10 and 30 min) recall was within the range of control subjects in all patients for all types of material, except for story recall in two cases (Cronel-Ohayon *et al.*, 2006; Manning *et al.*, 2006). However, ALF was found at delays ranging from 24 h (O'Connor *et al.*, 1997; Manning *et al.*, 2006) to 6 weeks (Kapur *et al.*, 1996, 1997). Recall at the longest intervals was at floor in most cases, and several patients were unable even to remember the learning episode. Recognition memory was sometimes less impaired (Kapur *et al.*, 1996, 1997; Mayes *et al.*, 2003; Manning *et al.*, 2006), but never completely intact. More precise study of the forgetting rate is made in four papers. O'Connor *et al.* (1997) described a rapid decline in memory over the first 24 h, with subsequent decline to floor over 7 days. Lucchelli and Spinnler (1998) showed their patient to have good verbal recall at 24 h but to score at floor after 7 days. The patient of Manning *et al.* (2006) exhibited poor story recall and relatively preserved face recognition at 30 h, but was severely impaired on both tests after 7 days. Cronel-Ohayon *et al.* (2006) found accelerated forgetting after 7 days, and little subsequent change after 29 days.

Only two patients had documented seizures during the retention interval (O'Connor *et al.*, 1997; Mayes *et al.*, 2003). O'Connor *et al.* (1997) assessed forgetting before and during anticonvulsant therapy, and found an improvement in very-long term memory once seizures were controlled.

ALF was accompanied in all cases by impairment in remote memory. In all but two cases (Kapur *et al.*, 1997; Manning *et al.*, 2006), there was a profound loss of autobiographical memories from across the lifespan, not merely from the period since the apparent onset of their anterograde

memory problems. Memory for public events dating from the premorbid period was affected in every case.

Group studies

We identified 10 studies addressing the issue of long-term anterograde memory in epilepsy (Martin *et al.*, 1991; Helmstaedter *et al.*, 1998; Blake *et al.*, 2000; Bell *et al.*, 2005; Manes *et al.*, 2005; Mameniskiene *et al.*, 2006; Bell, 2006; Bell and Giovagnoli, 2007; Butler *et al.*, 2007; Davidson *et al.*, 2007). These are summarized in Table 2. Nine examined patients with TLE, and one of these (Blake *et al.*, 2000) also included a group of seven patients with other focal epilepsies. Two studies (Manes *et al.*, 2005; Butler *et al.*, 2007) exclusively investigated TEA. The mean patient age ranged from 27 to 39 years, except for TEA patients who were older. One study investigated children with idiopathic generalized epilepsy (IGE) (Davidson *et al.*, 2007), in whom the mean age was 11.5 years (range 8–16 years). In total, 138 male and 172 female patients were studied.

In contrast to several of the case reports described earlier, patients in these studies did not have epilepsy resulting from a specified brain injury. Neuroimaging revealed varying proportions of hippocampal sclerosis, neoplastic and other lesions among patients, but no study quantitatively assessed their relation to memory function. Postoperative patients were included in the studies by Martin *et al.* (1988) (six patients) and Bell (2006) (six patients). The TEA patients studied by Manes *et al.* (2005) and Butler *et al.* (2007) had no clinically apparent abnormalities on brain MRI besides, in some cases, evidence of small vessel disease. Davidson *et al.* (2007) do not report imaging findings, but these are expected to be normal in IGE.

Memory retention over 30 min was found to be comparable in patients and controls in five studies (Martin *et al.*, 1991; Giovagnoli *et al.*, 1995; Blake *et al.*, 2000; Butler *et al.*, 2007; Davidson *et al.*, 2007), and one (Manes *et al.*, 2005) found normal verbal but impaired non-verbal memory. Four studies (Helmstaedter *et al.*, 1998; Bell *et al.*, 2005; Bell, 2006; Mameniskiene *et al.*, 2006) identified impairment amongst patients even at this short delay. At extended intervals ranging from 24 h (Martin *et al.*, 1991; Bell *et al.*, 2005) to 8 weeks (Blake *et al.*, 2000), seven studies (Martin *et al.*, 1991; Helmstaedter *et al.*, 1998; Blake *et al.*, 2000; Manes *et al.*, 2005; Mameniskiene *et al.*, 2006; Butler *et al.*, 2007; Davidson *et al.*, 2007) found patients to show a disproportionate degree of forgetting compared with controls. In contrast, three studies (Giovagnoli *et al.*, 1995; Bell *et al.*, 2005; Bell, 2006) found no difference in long-term forgetting rate between patients and controls. Bell *et al.* (2005) and Bell (2006) also failed to identify a significant number of individual patients in whom memory performance was normal at 30 min but impaired at an extended delay.

These results raise questions about the existence, scope and prevalence of ALF amongst patients with epilepsy, the best means of assessing very long-term memory, the pathophysiology of ALF, and its relation to RMI.

Discussion

Does ALF occur in epilepsy? If so, for which types of material and is there a laterality effect?

The seven case reports suggest that ALF is an identifiable clinical phenomenon closely linked to epilepsy. Several of the group studies identified ALF in patients with TLE and one in patients with IGE. However, three studies report negative results. The reason for this discrepancy is not clear, but it may arise partly from methodological differences discussed later. ALF may also be more prominent in certain subtypes of TLE, such as TEA, in which 44% patients report symptoms of accelerated forgetting (Butler *et al.*, 2007).

Patients were shown to learn at a normal rate in three studies (Martin *et al.*, 1991; Blake *et al.*, 2000; Butler *et al.*, 2007), whereas learning was found to be impaired by Helmstaedter *et al.* (1998), Giovagnoli *et al.* (1995) and Davidson *et al.* (2007). In the latter study, the learning impairment showed by IGE patients accounted for most of the difference in very long-term forgetting, suggesting that an encoding problem underlies the ALF seen in IGE.

The available data are inconclusive on the issue of whether hemispheric differences cause material-specificity in ALF. Using a test of verbal memory, Blake *et al.* (2000) identified ALF in patients with left but not right TLE. On the other hand, Martin *et al.* (1991), again only using verbal material, found no hemispheric effect. Without identifying the seizure focus, two studies (Mameniskiene *et al.*, 2006; Butler *et al.*, 2007) found ALF for both verbal and non-verbal material. Amongst IGE patients, ALF was identified for verbal material and a trend towards ALF for non-verbal material.

The balance of evidence suggests that recognition memory is also affected by ALF, but the findings are inconsistent. Four studies (Helmstaedter *et al.*, 1998; Blake *et al.*, 2000; Bell *et al.*, 2005; Manes *et al.*, 2005; Bell, 2006) found patients to show impairment on recognition memory at extended delays. Martin *et al.* (1991), on the other hand, did not find recognition memory impairment, although their delay was just 24 h. Davidson *et al.* (2007) also found no recognition memory deficit amongst IGE patients, even after a 7-day delay, although patients and controls scored close to ceiling.

In summary, the data currently available suggest that, in some patients with epilepsy, anterograde memory performance is normal at standard test intervals but declines abnormally rapidly thereafter—the phenomenon of ALF. The negative results indicate that this does not always occur. Some possible explanations for these mixed results are considered later.

Methodological issues in the assessment of ALF

The assessment of long-term forgetting encounters a number of methodological problems:

(i) Patient and control groups should be matched as carefully as possible for demographic and non-memory cognitive variables to isolate the phenomenon

of interest. Thus it may be relevant that in the studies by Martin *et al.* (1991), Helmstaedter *et al.* (1998), Bell (2006) and Bell *et al.* (2005) patients had a significantly lower mean IQ than control subjects. Other groups (Blake *et al.*, 2000; Manes *et al.*, 2005; Butler *et al.*, 2007) performed more extensive testing and revealed no differences between patients and controls on measures of language, visuo-spatial perception and executive function.

(ii) The choice of study material is likely to be important. Relative impairments in verbal and non-verbal memory depend on the laterality of the seizure focus. Also, forgetting may be different for semantically related (e.g. a story) and unrelated (e.g. a word list) material (Isaac and Mayes, 1999*a*, *b*).

(iii) ALF is most convincingly demonstrated when patients exhibit normal initial learning and 30-min recall, but clear impairment at longer delays (Martin *et al.*, 1988; Blake *et al.*, 2000; Manes *et al.*, 2005; Butler *et al.*, 2007). In cases where patients are already impaired over short delays, a number of techniques may be used to assess long-term forgetting rates:

  (a) Using a variety of the technique introduced by Huppert and Piercy (1978), the experimenter can modulate exposure to the study material to ensure that patients and control subjects reach the same initial level of learning. In four studies (Martin *et al.*, 1991; Blake *et al.*, 2000; Butler *et al.*, 2007; Davidson *et al.*, 2007), all the material was repeatedly presented until the subject reached a learning criterion. As Bell has observed (Bell *et al.*, 2005), this 'over-learning' method may mask early forgetting with a ceiling effect. However, in the studies by Blake *et al.* (2000) and Butler *et al.* (2007), patients who showed ALF of 'over-learned' material nonetheless performed normally on standard memory tests. An alternative, employed by four studies (Martin *et al.*, 1991; Giovagnoli *et al.*, 1995; Bell, 2006; Bell and Giovagnoli, 2007), is to use a 'selective reminding' technique, in which only non-remembered items are represented at each learning trial.

  (b) Individual patients and controls may be matched for learning on a case-by-case basis. This method, however, risks producing non-representative results if 'upper range' patients are matched with 'lower range' control subjects.

  (c) Differing acquisition levels may be accepted and the overall shape of the forgetting curves compared. This method was employed by three studies (Bell *et al.*, 2005; Bell, 2006; Mameniskiene *et al.*, 2006), with mixed results. The problem which arises here is that there is no widely accepted model of how variations in initial learning level affect forgetting over time (Rubin and Wenzel, 1996).

(iv) Rehearsal of the material between test sessions may confound results. In some studies, subjects were forewarned about the delayed tests, whereas in others they were not. The material used will also influence this: a story is more likely to be rehearsed than a large number of meaningless visual designs.

(v) The length of the interval between testing sessions may determine whether or not ALF is found—the underlying mechanisms may operate over 24 h or several weeks. An interval should be chosen at which control subjects perform neither at ceiling nor floor.

(vi) The nature of the retrieval task—free recall, cued recall or recognition—may be important. Davidson *et al.* (2007) suggest that their failure to find a deficit in recognition memory at an extended delay implies that ALF in their patients was due to a problem with memory retrieval rather than storage.

Aetiology and pathophysiology of ALF

Accepting that ALF occurs in some patients with epilepsy, we may hypothesize several contributory mechanisms: (i) clinical or subclinical seizure activity; (ii) structural or other underlying brain pathology; (iii) an adverse effect of anticonvulsant medication or (iv) psychological mechanisms.

Seizures. Anecdotally, patients with TEA sometimes report that seizures seem to 'wipe out' memories of preceding events, and feel that their memory abilities improve once seizures are controlled with anticonvulsant therapy. O'Connor *et al.* (1997) document such an improvement in a single case of temporal lobe epilepsy. Mameniskiene *et al.* (2006) found a positive correlation between long-term forgetting and both (i) manifest seizures during the experimental period and (ii) subclinical epileptiform EEG activity. As in the study by Blake *et al.* (2000), however, long-term memory was not found to correlate with the average seizure frequency reported by patients. The close association between amnesic attacks and waking in TEA raises the intriguing question of whether sub-clinical, nocturnal epileptiform activity might disturb sleep-dependent memory consolidation processes (Walker, 2005; Ellenbogen *et al.*, 2006; Walker and Stickgold, 2006).

In a study directly addressing the question of whether incident seizures accelerate forgetting, Bergin *et al.* (1995) tested immediate, 30 min and 48 h memory for verbal and non-verbal material in 58 patients undergoing video telemetry for the investigation of medically refractory partial seizures. No difference was found in long-term forgetting between patients who did and did not have seizures during the study period. This important result does not, however, rule out a negative influence of seizures upon anterograde memory. Features such as the timing, duration and anatomical focus of seizures may play an important role. Jokeit *et al.* (2001) examined memory over 24 h for verbal material in a small group of patients ($n = 10$) undergoing

videotelemetry. They found a difference in long-term recall between days with and without seizures, but this was restricted to the group of patients with a left temporal lobe seizure focus. A further source of evidence comes from studies that document an improvement in verbal memory scores in patients following right temporal lobectomy (Novelly, 1984; Martin *et al.*, 1998). This suggests that a seizure focus in one hippocampus can negatively affect function in distant brain regions.

The question of whether transient impairment of neuronal function can disrupt very long-term memory has also been addressed in patients undergoing electroconvulsive therapy (ECT) for depression, a procedure known to induce anterograde and retrograde amnesia. Squire (1981) investigated recognition memory for pictures and sentences at intervals of 10, 30 min and 30 h in patients on two occasions: 2 h and 4 months after ECT. The subjects therefore acted as their own controls. Initial acquisition was matched by using longer stimulus presentation on the earlier occasion. Picture forgetting was significantly more rapid when the subjects had recently received ECT. On the other hand, patients with Korsakoff's syndrome (KS) (diencephalic amnesia) and a patient with chronic medial temporal lobe amnesia did not show accelerated forgetting when initial acquisition was matched to a group of healthy control subjects. These findings were replicated and extended by Lewis and Kopelman (1998) who included a group of depressed patients not undergoing ECT. Accelerated forgetting was again found solely in the post-ECT group and could therefore not be attributed to depression *per se*. Transient impairment of brain function also underlies post-traumatic amnesia (PTA). Levin *et al.* (1988), investigating recognition memory for photographs, found accelerated forgetting over 32 h in head injury patients in PTA, compared with head injury patients who had recovered from PTA.

Structural lesions. Many of the case studies reviewed earlier also had radiological evidence of structural brain pathology. ALF might, therefore, represent a mild form of the amnesic syndrome, caused by subtle damage to the medial temporal lobes.

If so, forgetting should be dramatically accelerated in amnesics. A number of studies have addressed this issue and results have been mixed [see Isaac and Mayes (1999*a*) for a review]. The problems of matching initial acquisition are of course much more acute here than in patients with normal or near-normal immediate memory. One early investigation suggested that accelerated forgetting was a feature of amnesia caused by medial temporal lobe lesions but not diencephalic lesions (Huppert and Piercy, 1979). However, this finding was later found not to be replicable (Freed *et al.*, 1987). Isaac and Mayes (Isaac and Mayes, 1999*a*, *b*) conclude that forgetting in the amnesic syndrome is accelerated over the first 10 min but only for certain types of material—particularly free recall of prose and semantically related words. They interpret this as reflecting impairment of early consolidation processes due to medial temporal lobe damage. Beyond 10 min, forgetting rates have been measured in patients with anoxic brain damage (McKee and Squire, 1992), Alzheimer's Disease (Kopelman, 1985) and head injury after recovery from post-traumatic amnesia (Levin *et al.*, 1988), and have been found to be normal. Accelerated forgetting over longer periods has been reported in healthy older subjects by some authors (Huppert and Kopelman, 1989; Davis *et al.*, 2003), but not others (Petersen *et al.*, 1992).

If ALF is essentially due to a mild form of hippocampal amnesia one might also predict some mild degree of impairment over standard testing intervals. The observation that some patients perform normally on standard tests yet exhibit ALF appears to argue against the existence of any defect in acquisition and initial retention of declarative memories. It could be, however, that standard tests are insufficiently sensitive to reveal a mild deficit in these stages of memory processing. Techniques such as recording event related EEG potentials at memory encoding could shed further light on this possibility.

Finally additional imaging techniques, including manual or automated volumetric measurement, MR spectroscopy and diffusion tensor imaging have the potential to reveal subtle regional pathology within or affecting the MTL that may elude less sophisticated studies.

Anticonvulsant medication. There is good evidence that antiepileptic drugs (AEDs) can have a negative impact upon cognition, although the field is fraught with methodological difficulties (Kwan and Brodie, 2001; Motamedi and Meador, 2004). The most commonly observed effects are slowed mental processing and reduced attention, and these are most marked with high doses and polytherapy. However, a specific impact on memory has been reported in several studies. Some newer drugs may have a better cognitive profile (Motamedi and Meador, 2003), although topiramate may be a significant exception (Thompson *et al.*, 2000). The specific question of whether anticonvulsants can accelerate shorter term forgetting has been addressed in a single, retrospective study (Jokeit *et al.*, 2005). Amongst 162 patients with medically refractory epilepsy, higher serum levels of AED were associated with greater forgetting of both verbal and visual material over a 30-min delay after controlling for potentially confounding variables such as IQ, age, duration of epilepsy and seizure frequency.

Whilst it remains possible that the ALF observed in some studies reviewed earlier is a direct result of treatment with anticonvulsants, it seems unlikely for a number of reasons: first, patients with TEA complain of ALF prior to initiation of therapy; second, patients with TEA usually report that their memory improves once treatment is started (Gallassi *et al.*, 1988a; Zeman *et al.*, 1998; Gallassi, 2006; Butler *et al.*, 2007); third, the forgetting observed by Blake *et al.* (2000) was specific to the group of patients with left temporal lobe epilepsy; and fourth, the doses of anticonvulsants used in

Table 3 Investigations of remote memory in patients with epilepsy: series and individual case studies

Authors (year)	No. of patients	Sex	Age mean	Age of onset	Type of epilepsy	Non-memory tests	Standard anterograde memory	ABM (episodic)	ABM (semantic)	Public knowledge	ALF
Cases											
Kapur *et al.* (1989)	ED	M	74	62	TEA	Normal	RMTF ↓	Normal	Normal	↓	n/d
Kapur *et al.* (1997)	PA	F	62	59	LTLE	Normal	Normal	n/d	n/d	↓	+
Lucchelli & Spinnler (1998)	GB	M	65	65	LTLE	Normal	Normal	↓	↓	Events ↓	+
Manes *et al.* (2001)	RG	M	68	68	TEA	Normal	RMTW ↓	↓	Normal	Normal	n/d
Manning *et al.* (2005)	JR	M	55	13	LTLE (postop)	Normal	Normal	Normal	Normal	↓	n/d
Chan *et al.* (2007)	KCI/KC3	M/M	52/57	52/57	TLE (VGKC-Ab)	Mild anomia/normal	↓/↓	n/d	n/d	↓	n/d
Series											
Barr *et al.* (1990)	12	4 M	38	21	Postop TLE	Naming: LTLE ↓	MSLE	n/d	LTLE ↓	LTLE ↓	n/d
Ratti *et al.* (1992)	15	n/d	n/d	n/d	TLE	n/d	n/d	n/d	n/d	↓	n/d
Upton *et al.* (1992)	27	n/d	n/d	n/d	TLE	n/d	n/d	Normal	Normal	n/d	n/d
O'Connor *et al.* (1999)	n/d	n/d	n/d	n/d	Postop TLE	n/d	n/d	LTLE=RTLE	n/d	LTLE<RTLE	n/d
Bergin *et al.* (2000)	33	11 M	32	9	TLE/ExTE/PGE	n/d	n/d	n/d	n/d	↓	n/d
Viskontas *et al.* (2000)	25	13 M	38	14	Pre/postop TLE	n/d	MSLE	↓	Normal	n/d	n/d
Lah *et al.* (2004)	30	12 M	34	12	Postop TLE	Naming/fluency: LTLE ↓	MSLE	Normal	↓	↓ (LTLE<RTLE)	n/d
Manes *et al.* (2005)	7	6 M	57	55	TEA	Normal	Normal	↓	n/d	n/d	+
Lah *et al.* (2006)	29	12 M	40	23	Preop TLE	Naming/fluency: LTLE ↓	MSLE	RTL ↓	↓	LTL ↓	n/d
Voltzenlogel *et al.* (2006)	38	12 M	36	16	Preop TLE	n/d	n/d	↓	Normal	↓ (LTLE<RTLE)	n/d
Butler *et al.* (2007)	24	14 M	68	63	TEA	Normal	Normal	↓	↓	n/d	+
Voltzenlogel *et al.* (2007)	22	8 M	38	12	Postop TLE	n/d	Verbal memory LTLE ↓	↓	n/d	n/d	n/d
Noulhiane *et al.* (2007)	22	12 M	34	13	Postop TLE	n/d	RAVLT ↓	↓	n/d	n/d	n/d

ABM = autobiographical memory; ALF = accelerated long-term forgetting; ExTE = extra-temporal epilepsy; L = left; MSLE = material-specific laterality effect; n/d = not discussed; PGE = primary generalised epilepsy; R = right; RMTF = recognition memory test (faces); RMTW = recognition memory test (words); RAVLT = Rey Auditory Verbal Learning Test TEA = transient epileptic amnesia; TLE = temporal lobe epilepsy; VGKC-Ab = voltage-gated potassium channel antibody associated limbic encephalitis.

TEA patients, those who complain most profoundly of ALF, are generally low.

Psychosocial factors. The disparity between subjective reports of memory difficulty amongst patients with epilepsy and their performance on neuropsychological tests (Corcoran and Thompson, 1992) has been attributed to disturbances of mood and poor self-esteem (Giovagnoli *et al.*, 1997; Elixhauser *et al.*, 1999). It is undoubtedly important to take such factors into account when investigating cognitive function in epilepsy. However, they are unlikely to play a major causal role in ALF. Three studies (Blake *et al.*, 2000; Mameniskiene *et al.*, 2006; Butler *et al.*, 2007) assessed mood using the Hospital Anxiety and Depression Scale and found no correlation with very long-term memory performance. In addition, as mentioned earlier, Lewis and Kopelman (1998) did not find accelerated forgetting in a group of depressed patients after equating initial levels of learning.

Part III: Remote memory in epilepsy

Although anterograde memory deficits, at least over brief retention intervals, are well-recognized in TLE, comparatively little is known about the integrity or otherwise of remote memory. However, RMI can have profound effects on an individual's life and may, on occasions, be the presenting complaint of patients with TLE (Gallassi *et al.*, 1992; Gallassi, 2006). It is important, therefore, to ascertain the extent, aetiology and anatomical basis of any RMI as well as to explore potential therapeutic measures. From a theoretical perspective, investigation of the neuropsychological features of RMI will shed light on the way in which long-term memories are organized (Table 3).

Remote memory is multifaceted. Broadly, the term encompasses memories that were encoded in the distant past. The temporal boundary at which recent memories become remote is vague but remote memories are usually thought of as being at least 1-year old. Research has

concentrated on the declarative components of remote memory, which fall into several categories. Episodic memories relate to personally experienced events and are part of an individual's broader autobiographical memory, which also includes knowledge about 'personal semantics' such as where they went to school and what their first job was. Autobiographical memory can be distinguished from general knowledge—memory for public events, famous people, words and so forth. Deficits in remote memory may be due in part to a long-standing anterograde amnesia whereby neurological damage has impaired memory accumulation. However, there is evidence that retrograde amnesia, with loss of, or loss of access to, previously well-established memories can also occur, albeit rarely, in the absence of any anterograde impairment. Reports of neurological disease causing such 'focal retrograde amnesia' have generated considerable debate (Kapur, 1993*a*, 2000; Kopelman, 2000). If brain regions involved in the storage or retrieval of old memories are damaged, it is difficult—though not necessarily impossible (Evans *et al*., 2003)—to explain how newly acquired information could be successfully remembered over the long term. Moreover, a disproportionate affliction of retrograde memory is characteristic of psychogenic amnesia (Kopelman, 2002*a*), making a careful neuropsychiatric assessment mandatory in such cases. Examples of apparently focal retrograde amnesia have been associated with a range of aetiologies including traumatic brain injury (Levine *et al*., 1998), herpes simplex encephalitis (Tanaka *et al*., 1999), cerebral vasculitis (Evans *et al*., 2003), stroke (Miller *et al*., 2001) and TLE (Manes *et al*., 2001).

In this section, we review the evidence that TLE may be associated with remote memory deficits by examining individual case reports and larger series.

Methods

Using the methods described in Part I, we searched the literature for studies of remote memory in patients with epilepsy. In addition, we examined all reported cases of focal or disproportionate retrograde amnesia in which seizures were also a feature. As in Part II, we first discuss the case studies demonstrating that RMI can be associated with epilepsy, and then review group studies to investigate whether it occurs more generally.

Case studies

Eighteen case reports were found describing pronounced RMI in the context of epilepsy. In several, including four of the seven cases of ALF described earlier, seizures resulted from extensive brain damage caused by trauma or encephalitis. We will restrict our considerations to seven cases (Kapur *et al*., 1989, 1997; Lucchelli and Spinnler, 1998; Manes *et al*., 2001; Manning *et al*., 2005; Chan *et al*., 2007) in which structural imaging was either normal or revealed only very focal abnormalities, since it is well-recognized that structural pathology in a variety of brain regions can cause retrograde amnesia in the absence of seizures (Kopelman, 2002*b*). There were six males and one female patient. The ages ranged from 52 to 74 years.

All seven patients had mesial temporal lobe epilepsy. This arose clearly from the left hemisphere in four cases, and was probably bilateral in three cases (Manes *et al*., 2001; Chan *et al*., 2007). One (Manning *et al*., 2005) had undergone a recent left temporal lobectomy for hippocampal sclerosis. Two cases had non-paraneoplastic limbic encephalitis associated with antibodies against voltage-gated potassium channels (VGKC-Ab) and bilateral medial temporal lobe damage seen on MRI. In the other four cases, seizures began in later life (range 58–69 years), there was no clear cause and neuroimaging was unremarkable except for a subtle left hippocampal lesion seen in one patient (Kapur *et al*., 1997). Two patients had TEA. Seizures were well-controlled on medication in all cases.

General neuropsychological assessment was normal in most patients except for subtle recognition memory impairment in two cases (Kapur *et al*., 1989; Manes *et al*., 2001), and more general anterograde memory impairment in the two cases of VGKC-Ab encephalitis (Chan *et al*., 2007). Very long-term memory tests revealed ALF in two patients (Kapur *et al*., 1997; Lucchelli and Spinnler, 1998). The relative disturbance of autobiographical and public memory varies between cases. Public semantic memory appears disproportionately impaired in two cases (Kapur *et al*., 1989; Manning *et al*., 2005), whereas detailed testing revealed disturbance only in the autobiographical domain in one case (Manes *et al*., 2001). In six cases, the deficit was shown to affect memories from the previous 30 to 40 years (Kapur *et al*., 1989; Lucchelli and Spinnler, 1998; Manes *et al*., 2001; Manning *et al*., 2005; Chan *et al*., 2007). In the other, it extended back just 5 years, and is interpreted by the authors as an anterograde memory problem caused by accelerated forgetting (Kapur *et al*., 1997).

Group studies

We found 13 studies that investigated remote memory in groups of patients with epilepsy (Barr *et al*., 1990; Ratti *et al*., 1992; Upton *et al*., 1992; O'Connor *et al*., 1999; Bergin *et al*., 2000; Viskontas *et al*., 2000; Lah *et al*., 2004, 2006; Manes *et al*., 2005; Voltzenlogel *et al*., 2006; Noulhiane *et al*., 2007; Butler *et al*., 2007; Voltzenlogel *et al*., 2007). The patient population varies across these studies. As discussed later, these differences have major implications for the interpretation of the resulting data. The only study to include patients with extratemporal or primary generalised epilepsy is that by Bergin *et al*. (2000), and these patients were found not to differ from controls on memory for remote public events. Five studies examined only patients who had undergone unilateral temporal lobectomy (Barr *et al*., 1990; O'Connor *et al*., 1999; Lah *et al*., 2004; Noulhiane *et al*., 2007; Voltzenlogel *et al*., 2007), whilst Viskontas *et al*. (2000) had a patient group

consisting of both pre- and post-operative patients. In two further studies (Lah *et al.*, 2006; Voltzenlogel *et al.*, 2006), the patients investigated were candidates for surgery. There is therefore an emphasis towards the study of patients with medically intractable seizures. Interestingly, in one study no significant differences in remote autobiographical memory were found between the pre- and post-operative patients (Viskontas *et al.*, 2000) and, in another, surgery was found to improve memory for recent events (Voltzenlogel *et al.*, 2007). Of the remaining five studies, two (Manes *et al.*, 2005; Butler *et al.*, 2007) concentrated upon TEA, in which remote memory complaints are common. In total, over 262 patients were studied, and the mean age was ~42 years.

The detail in which the performance of patients and their age- and sex-matched control subjects on standard neuropsychological tests is reported varies considerably across the studies. Non-memory deficits are reported in two studies (Lah *et al.*, 2004, 2006), in which patients with left TLE were impaired on verbal fluency and naming. With regard to anterograde memory, material-specific impairments were found amongst patients depending upon the side of their seizure focus in five studies (Barr *et al.*, 1990; Viskontas *et al.*, 2002; Lah *et al.*, 2004, 2006; Noulhiane *et al.*, 2007).

Twelve of the 13 studies found deficits in some form of remote memory, episodic memory, personal semantics or public knowledge, amongst TLE patients. The results raise several questions about RMI in epilepsy including its prevalence and extent, the best methods for studying it, its aetiology and its relation with anterograde amnesia.

Discussion

Is remote memory impaired in temporal lobe epilepsy? If so, for which types of material and is there a laterality effect?

Nine studies compared autobiographical episodic memory in TLE patients and healthy controls (Upton *et al.*, 1992; Viskontas *et al.*, 2000; Lah *et al.*, 2004, 2006; Manes *et al.*, 2005; Voltzenlogel *et al.*, 2006, 2007; Butler *et al.*, 2007; Noulhiane *et al.*, 2007). Of these, two found no evidence of impairment in the epilepsy group. The abstract published by Upton *et al.* (1992) reports no autobiographical memory impairment in a group of 29 TLE patients with subjective memory complaints. Lah *et al.* (2004) failed to find a deficit in the number of autobiographical events recalled by post-temporal lobectomy patients. This result is at odds with that reported in their subsequent study of pre-operative epilepsy patients (Lah *et al.*, 2006) in which impairment was found. The remaining seven studies report significant impairment amongst TLE patients. One group (Voltzenlogel *et al.*, 2006) found left TLE patients to be more impaired than right TLE patients on memory for autobiographic episodes, whereas two (Lah *et al.*, 2006; Noulhiane *et al.*, 2007) found greater impairment in the right TLE group.

Seven studies examined memory for personal semantics. Subtle differences were found in four (Barr *et al.*, 1990; Lah *et al.*, 2004, 2006; Butler *et al.*, 2007). These were generally less marked than the differences in episodic memory. In the remaining three studies (Upton *et al.*, 1992; Viskontas *et al.*, 2000; Voltzenlogel *et al.*, 2006), non-significant differences could be explained by a ceiling effect.

Five studies examined memory for public events (Barr *et al.*, 1990; Bergin *et al.*, 2000; Lah *et al.*, 2004, 2006; Voltzenlogel *et al.*, 2006). All found significant impairment amongst epilepsy patients compared with healthy controls. Deficits were also found for other non-personal, semantic memories including famous faces, famous names, television programmes and famous scenes. In four of these studies (Barr *et al.*, 1990; Lah *et al.*, 2004, 2006; Voltzenlogel *et al.*, 2006), patients with left temporal epilepsy were more severely impaired that those with right temporal lobe epilepsy, a result also described in the abstract by O'Connor *et al.* (1999), who did not include a healthy control group.

Methodological issues in the assessment of remote memory

The study of remote memory poses several methodological challenges:

(i) The original acquisition of the memories in question is beyond the control of the investigator. Thus it is difficult to be certain whether apparently 'missing' memories were ever actually acquired or retained for any length of time. Several factors may be in play here. First, it is important to consider the possibility that a long-standing anterograde memory deficit might explain an individual's RMI, through defective initial acquisition. In some patients, for example some of those with TEA, it is possible to be confident that remote memories had been successfully acquired as they were captured in family photographs that were reviewed regularly or had been repeatedly discussed. Second, even individuals with normal anterograde memory function differ markedly in their exposure to and interest in current events (Kapur *et al.*, 1999). This is rarely taken into account in research studies. Third, the persistence of autobiographical event memories is closely linked to contextual factors such as emotional arousal ('flashbulb' memories), current goals (Conway and Pleydell-Pearce, 2000) and life period (Rubin and Schulkind, 1997): these must be considered in interpreting variations in autobiographical recollection.

(ii) The 'age' of a memory—often important in theorising about consolidation processes—cannot be straightforwardly equated with the time since its initial acquisition: re-exposure and rehearsal are important confounding factors.

(iii) There is no universally accepted method for eliciting and probing remote memories. For autobiographical memories, cuing may be minimal, for example: 'tell me

about something that happened to you in your 30's'; moderate: 'tell me about an incident involving a boat' (Crovitz, 1973); or highly specific and derived from information obtained from a close friend or relative. Cues may be verbal or non-verbal (e.g. photographs). Similarly, the third-party validation of reported memories can be difficult, although frank confabulation is thought to be rare (Tranel and Jones, 2006).

(iv) There is a range of possible methods for scoring the subject's report ranging from simple true/false discrimination, to detailed textual analysis of transcribed responses (Levine *et al.*, 2002). The third and fourth considerations are reflected in the variety of tools available for the study of autobiographical memory, several of which are mentioned in the following paragraph.

Four studies used the Autobiographical Memory Interview (AMI) (Kopelman *et al.*, 1989) to investigate episodic and semantic autobiographical memory (Upton *et al.*, 1992; O'Connor *et al.*, 1999; Viskontas *et al.*, 2000; Voltzenlogel *et al.*, 2006). Of these, none found a difference in personal semantic memory and just two found a deficit in episodic memory, amongst TLE patients. However, the AMI has been criticised as being relatively insensitive to milder or patchy retrograde memory deficiencies (Fujii *et al.*, 2000; Manes *et al.*, 2001). Two studies used an autobiographical fluency test, whereby subjects are given a fixed amount of time to generate as many names of acquaintances or personally experienced events as possible from a particular life period (Lah *et al.*, 2004, 2006). Notably, this test does not examine detailed episodic memories, but awards points even for vague memories of recurrent events and depends heavily on intact executive control mechanisms. Finally, five studies used quite specific probes to prompt recall for events from different life periods and scored memories according to the degree of experiential richness conveyed by the subject (Manes *et al.*, 2005; Voltzenlogel *et al.*, 2006, 2007; Noulhiane *et al.*, 2007; Butler *et al.*, 2007). These all found impairment amongst TLE patients.

Particular challenges arise when investigating remote memory in epilepsy. First, the clinical onset of seizures, especially in TLE, often dates back many years to childhood or adolescence, and the underlying pathological processes perhaps even to infancy. It can therefore be particularly difficult to distinguish between the anterograde and retrograde components of memory impairment. Second, the presence of an active seizure focus in a young brain induces remodelling of the neural pathways involved in memory so that the cognitive and neural processes occurring in patients and controls may differ. Third, a diagnosis of epilepsy often has further consequences that may influence the formation and retrieval of memories, including the use of medication, interrupted schooling and restricted employment opportunities. Fourth, the interpretation of the effects of the site and laterality of pathology upon remote memory is not straightforward: even when structural imaging reveals pathology only in one temporal lobe, there may be impairment of function remotely in both ipsilateral and contralateral hemispheres (Vermathen *et al.*, 2002; Diehl *et al.*, 2003; Liu, 2003; Bernasconi *et al.*, 2004).

The nature of the deficit: the relationship between anterograde and retrograde memory loss and the temporal gradient of retrograde amnesia

RMI can, in principle, reflect a deficit at any stage of memory processing: acquisition, consolidation, storage or retrieval. Strong correlations between measures of anterograde and retrograde memory would raise the possibility that an impairment of remote memory is due to failure of acquisition. On the other hand, a lack of correlation between measures of anterograde and retrograde memory, or apparent loss of memories that were previously accessible, point to failure of storage or retrieval. However, as Kopelman (2000) has pointed out, it is important to remember that, in assessments of anterograde and retrograde memory impairment, 'like' is not always being compared with 'like'. Tests of retrograde memory may, for example, require greater effort or be more dependent on visual imagery than tests of anterograde memory. Scoring methods for remote memories [e.g. that described by Levine *et al.* (2002)] may be more exacting than those usually applied in anterograde tests.

Whilst the majority of single cases reviewed here show profound retrograde loss of remote memories for events and facts learned decades before the onset of epilepsy but relatively preserved new learning, the evidence bearing on these matters in the group studies is mixed. Barr *et al.* (1990), examining post-surgical TLE patients, found significant correlations between two measures of remotely acquired semantic memory—famous face naming and recognition of television programs—and verbal anterograde memory, but only amongst left temporal lobectomy patients. Lah and colleagues, in studying both pre-surgical (Lah *et al.*, 2006) and post-surgical (Lah *et al.*, 2004) patients, found numerous correlations between remote memory measures and both anterograde memory and language tasks. Only autobiographical event memory failed to correlate with any anterograde memory task. In contrast, Butler *et al.* (2007) describe a group of 22 patients with TEA who performed normally on standard tests of anterograde memory but showed substantial impairment on a test of autobiographical memory across many decades. Finally, Voltzenlogel *et al.* (2007) found that patients who underwent right temporal lobectomy showed improvement in their ability to remember recent events after surgery, and that this change correlated with their improvement on delayed recall of a short story. Summarizing these results, it appears that performance on standard anterograde memory tests can account for at least some of the impairment seen in remote memory amongst patients with TLE, both before

and after surgery. Nevertheless, there remain cases, particularly in the TEA literature, where other factors must play a role. ALF may be part of the explanation, but this cannot be responsible for the loss of remote memories that had previously been accessible for many years, a phenomenon commonly reported by patients with TEA. Thus the impairment of remote memory that occurs in patients with epilepsy is likely to have a number of distinct causes, each with its own underlying pathophysiology.

Several studies have examined the distribution of RMI across the life span—its 'temporal gradient' (Barr *et al.*, 1990; Viskontas *et al.*, 2000; Lah *et al.*, 2004, 2006; Manes *et al.*, 2005; Butler *et al.*, 2007; Noulhiane *et al.*, 2007). Of the six studies that investigated autobiographical episodic memory, all except Lah *et al.* (2004) found a significant group effect: patients scored lower than controls across the lifetime. However, only Manes *et al.* (2005) found a group by time interaction and, here, the patients were *better* at recalling more recent memories: there was a reversed temporal gradient. In three studies (Viskontas *et al.*, 2000; Manes *et al.*, 2005; Butler *et al.*, 2007), memory was shown to be impaired for events that occurred prior to the clinical onset of seizures. A notable feature of the RMI described by patients with TEA is that it appears to be patchy, with 'islands' of preserved memory (Zeman *et al.*, 1998; Manes *et al.*, 2005; Butler *et al.*, 2007). This symptom remains to be explored using appropriate objective measures, but may provide important clues with regard to the underlying mechanism.

No study found a significant group by time interaction for personal semantic memory. Memory for public events from different life periods was investigated in three studies (Barr *et al.*, 1990; Lah *et al.*, 2004, 2006). The only significant group by time interaction was found for patients who had undergone a right temporal lobectomy, who were worse at recognizing more recent public events (Lah *et al.*, 2006). Since this difference was not found for pre-operative patients with right-sided TLE, the authors suggest that it may be a direct result of the surgery rather than the epilepsy itself.

Aetiology and pathophysiology of RMI in epilepsy

Six studies examined the possible causes of RMI in epilepsy (Bergin *et al.*, 2000; Viskontas *et al.*, 2000; Lah *et al.*, 2004, 2006; Voltzenlogel *et al.*, 2006; Noulhiane *et al.*, 2007). Data were variously gathered on demographics, seizure variables (lifetime number of all or only generalized tonic–clonic seizures, age of onset, current seizure frequency, duration of epilepsy), structural variables (underlying pathology, extent of any temporal lobe excision) and anticonvulsant therapy.

Seizures. No study identified correlations between seizure-related variables and autobiographical memory performance. However, several factors were found to correlate negatively with remote memory for public events and general knowledge including: a greater lifetime number of generalized tonic–clonic seizures (Bergin *et al.*, 2000), earlier age of epilepsy onset (Lah *et al.*, 2006) and continuing post-operative seizures (Lah *et al.*, 2004). However, contradictory findings are reported by other studies that found no effect of generalized tonic–clonic seizures (Lah *et al.*, 2004, 2006), age of epilepsy onset (Lah *et al.*, 2004; Voltzenlogel *et al.*, 2006; Noulhiane *et al.*, 2007), duration of epilepsy (Lah *et al.*, 2004; Voltzenlogel *et al.*, 2006) or seizure frequency (Voltzenlogel *et al.*, 2006). Several factors may account for these inconsistencies, including the difficulty of accurately estimating seizure frequency, the emphasis on patients with medically intractable seizures and the possible contribution of other factors such as mood and general intelligence.

Structural lesions. The lack of firm evidence for a correlation between seizure variables and remote memory performance led three groups (Bergin *et al.*, 2000; Lah *et al.*, 2004; Voltzenlogel *et al.*, 2006) to conclude that temporal lobe pathology, rather than the resulting seizures, was responsible for patients' difficulty in remembering the past. Recently, Noulhiane *et al.* (2007), investigating a small group ($n = 22$) of post-operative TLE patients, found correlations between autobiographical memory scores and the volumes of residual medial temporal lobe structures, particularly in the right hemisphere, as measured on MRI scans. In other studies, remote semantic memory impairment was found to vary with aetiology (Viskontas *et al.*, 2000; Voltzenlogel *et al.*, 2006), pre- or post-operative status (Viskontas *et al.*, 2000) and the extent of operative excision (Lah *et al.*, 2004). Two studies found an additional correlation with age (Bergin *et al.*, 2000; Viskontas *et al.*, 2000). On the other hand, in the syndrome of TEA (Manes *et al.*, 2001, 2005; Butler *et al.*, 2007) and in the five case reports discussed earlier, extensive retrograde amnesia occurs with minimal or no clinically apparent structural brain damage. Kapur (2000) has suggested that, in such cases, intermittent clinical or sub-clinical seizure activity beginning in the medial temporal lobes may disrupt neocortical networks that act as storage or retrieval sites for remote memory.

Functional brain imaging studies of activation patterns during autobiographical memory recall [see Maguire (2001); Svoboda *et al.* (2006) for reviews] implicate the involvement of a wide network of brain regions, including frontal, temporal and posterior cortices, as well as cerebellum and sub-cortical structures. The relative importance of these areas is likely to vary with factors such as the age of the memory, the emotional and perceptual content and the degree of personal significance (Svoboda *et al.*, 2006). Future studies of patients with disproportionate impairments of autobiographical memory, such as those considered here, using both structural and functional imaging in life, together with post-mortem examination, will help to clarify which brain regions and processes contribute to this deficit.

Anticonvulsant medication. Two studies found a positive correlation between remote semantic memory loss and the number of anticonvulsants taken (Lah *et al*., 2004, 2006). Interpretation of this result is confounded by the close relation between medication dose and the severity of epilepsy. It would be possible to investigate the relation between remote memory and anticonvulsants more directly by studying patients taking these drugs for conditions other than epilepsy. However, it seems unlikely that this is the principle cause of the problem since, for example, TEA patients complain of profound autobiographical memory loss prior to starting treatment and are usually maintained on low dose monotherapy (Butler *et al*., 2007).

Psychosocial factors. Mood disturbance is associated with 'overgeneral' memory for public and autobiographical events (Warren and Haslam, 2007). It is therefore important to consider the possibility that mood disturbance associated with epilepsy may be playing a part in producing RMI. Only one of the studies reports data pertaining to this: Butler *et al*. (2007) found no evidence of a difference in past or present diagnoses of major depression or generalized anxiety, and no correlation between scores on the Hospital Anxiety and Depression Scale and RMI or ALF in patients with TEA. In future explorations of the mechanisms underlying RMI, detailed data on possible mood disturbance will be essential.

Part IV: Theoretical aspects and future directions

We have reviewed three linked forms of memory impairment related to epilepsy which, collectively, may help to explain the high prevalence of memory complaints in people with epilepsy who score normally on standard neuropsychological tests. The three phenomena co-occur regularly in the syndrome of TEA, but ALF and RMI are also seen in other forms of epilepsy, and RMI can result from a variety of neuropathologies.

In this final section we will (i) place these phenomena in the context of current theories of memory consolidation; (ii) review the possible roles of seizures and structural pathology in ALF and RMI occurring in epilepsy; (iii) briefly explore the association between amnesia on awakening and persistent memory disruption evident in the syndrome of TEA.

(i) *Theories of consolidation*

According to the 'standard theory' of consolidation (STC) (Squire, 1997), the medial temporal lobes facilitate the gradual formation of direct connections between neocortical elements of declarative memory traces. Thus, over time, these traces become independent of the medial temporal lobes. The theory proposes that this process consolidates both semantic and episodic memory traces. The STC has been challenged by a rival view, 'multiple trace theory' (MTT) (Nadel and Moscovitch, 1997; Moscovitch and Nadel, 1998). This suggests that certain types of declarative memories, true 'episodic' memories, remain dependent on the hippocampus regardless of their age, and that their rehearsal and reactivation lead to the creation of multiple memory traces within the medial temporal lobe.

Which of these theories better accommodates the linked phenomena of TEA, ALF and RMI in epilepsy? At first sight, MTT appears a more promising model. It allows for the possibility that pathology restricted to the medial temporal lobes may impair both anterograde and remote episodic memory. Whether it would predict the particular combination of features observed in TEA—subtle hippocampal pathology, normal or near normal anterograde memory on standard tests, marked accelerated forgetting and remote episodic memory loss—is less clear: computational modelling of medial temporal lobe function, and its pathologies, may help to clarify whether this cluster of phenomena is compatible with the predictions of MTT. The STC, on the other hand, can readily explain the occurrence of ALF in the context of hippocampal pathology. But it cannot so readily explain the occurrence of RMI, assuming (in keeping with evidence cited earlier) that this is not the result of impaired initial acquisition. To explain this, the STC must invoke some other factor, perhaps disruption of distributed neocortical memory traces by epileptiform activity, as suggested by Kapur (2000).

(ii) *The roles of seizures and structural pathology in the genesis of ALF and RMI in epilepsy*

The case series and group studies discussed in sections II and III indicate that ALF and RMI occur in some patients with epilepsy, particularly TLE. It is tempting to infer that seizures or subclinical seizure activity can disrupt memory consolidation, giving rise to ALF, and degrade the neural representations of remote memories, causing autobiographical amnesia and other varieties of RMI. However, ALF and RMI often persist after successful treatment of the associated seizures, and as indicated earlier, there are plausible alternative explanations for ALF and RMI, in particular the structural pathology that is responsible for the epilepsy in the first place. The evidence summarized in sections II and III suggests that both epileptiform activity and structural pathology are likely to play a part. Teasing apart their contributions is an important task for future research, as it will have implications for the prevention and treatment of these forms of memory loss, as well as for their theoretical interpretation.

(iii) *The association between amnesia on awakening and memory disruption in the syndrome of TEA*

The occurrence of amnesia on awakening is a useful clinical clue to a diagnosis of TEA. As discussed earlier it

is unclear whether this reflects the occurrence of epileptiform activity on awakening or a post-ictal state. In either case, it suggests that the epileptiform activity responsible for TEA occurs commonly during the hours of sleep. As several recent studies have drawn attention to a possible role for sleep in memory consolidation [see for e.g. (Walker and Stickgold, 2006)], subclinical epileptiform activity during sleep provides one possible explanation for the persistent interictal memory disturbances—ALF and RMI—that commonly occur in patients with TEA specifically and TLE more generally. This possibility merits further study using a combination of polysomnography and memory measures in patients with TEA.

Part V: Conclusion

We have reviewed the existing evidence relating to three relatively novel, linked, forms of memory impairment occurring among patients with epilepsy. Patients with transient epileptic amnesia (TEA), who are usually middle-aged or elderly, experience brief, recurrent episodes of anterograde and/or retrograde amnesia, that often occur on awakening, and reflect either ictal or post-ictal disturbance of medial temporal lobe function. Patients with TEA, and those with TLE more generally, often also describe two persistent disorders of interictal memory: ALF is the unusually rapid decay of memories that were initially accessible at a testing interval of 30 min over the following days and weeks; remote memory impairment (RMI) is the impairment of memory for autobiographical and public events, often from life periods predating the onset of epilepsy by many years. It is likely that both seizure activity and underlying structural pathology play a part in producing ALF and RMI but further work is required to define their respective contributions. The relationship between sleep and attacks of TEA raises the possibility that disruption of sleep-related processes of memory consolidation may be involved. Further data from patients with these forms of memory impairment occurring in epilepsy will both help to guide the prevention and treatment of these disorders and test and inform theoretical models of memory.

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References

Acharya V, Acharya J, Luders H. Olfactory epileptic auras. Neurology 1998; 51: 56–61.

Andy OJ, Jurko MF, Hughes JR. The amygdala in relation to olfaction. Confin Neurol 1975; 37: 215–22.

Bancaud J, Brunet-Bourgin F, Chauvel P, Halgren E. This paper is dedicated to the memory of Jean B. Anatomical origin of deja vu and vivid 'memories' in human temporal lobe epilepsy. Brain 1994; 117: 71–90.

Barr WB, Goldberg E, Wasserstein J, Novelly RA. Retrograde amnesia following unilateral temporal lobectomy. Neuropsychologia 1990; 28: 243–55.

Bartolomei F, Barbeau E, Gavaret M, Guye M, McGonigal A, Regis J, et al. Cortical stimulation study of the role of rhinal cortex in deja vu and reminiscence of memories. Neurology 2004; 63: 858–64.

Baxendale SA, Paesschen W, Thompson PJ, Connelly A, Duncan JS, Harkness WF, et al. The Relationship between quantitative MRI and neuropsychological functioning in temporal lobe epilepsy. Epilepsia 1998; 39: 158–66.

Bell BD. WMS-III logical memory performance after a two-week delay in temporal lobe epilepsy and control groups. J Clin Exp Neuropsychol 2006; 28: 1435–43.

Bell BD, Fine J, Dow C, Seidenberg M, Hermann BP. Temporal lobe epilepsy and the selective reminding test: the conventional 30-minute delay suffices. Psychol Assess 2005; 17: 103–9.

Bell BD, Giovagnoli AR. Recent tnnovative studies of memory in temporal lobe epilepsy. Neuropsychol Rev 2007; 17: 455–76.

Bergin PS, Thompson PJ, Baxendale SA, Fish DR, Shorvon SD. Remote memory in epilepsy. Epilepsia 2000; 41: 231–9.

Bergin PS, Thompson PJ, Fish DR, Shorvon SD. The effect of seizures on memory for recently learned material. Neurology 1995; 45: 236–40.

Bernasconi N, Duchesne S, Janke A, Lerch J, Collins DL, Bernasconi A. Whole-brain voxel-based statistical analysis of gray matter and white matter in temporal lobe epilepsy. NeuroImage 2004; 23: 717–23.

Blake RV, Wroe SJ, Breen EK, McCarthy RA. Accelerated forgetting in patients with epilepsy: evidence for an impairment in memory consolidation. Brain 2000; 123: 472–83.

Brown AS. A review of the déjà vu experience. Psychol Bull 2003; 129: 394–413.

Busch RM, Lineweaver TT, Naugle RI, Kim KH, Gong Y, Tilelli CQ, et al. ApoE-4 is associated with reduced memory in long-standing intractable temporal lobe epilepsy. Neurology 2007; 68: 409–14.

Butler CR, Graham KS, Hodges JR, Kapur N, Wardlaw JM, Zeman AZ. The syndrome of transient epileptic amnesia. Ann Neurol 2007; 61: 587–98.

Butler CR, Zeman AZ. A case of transient epileptic amnesia with radiological localization. Nat Clin Prac Neurol 2007 (in press).

Cammalleri R, Gangitano M, D'Amelio M, Raieli V, Raimondo D, Camarda R. Transient topographical amnesia and cingulate cortex damage: a case report. Neuropsychologia 1996; 34: 321–6.

Chan D, Henley SM, Rossor MN, Warrington EK. Extensive and temporally ungraded retrograde amnesia in encephalitis associated with antibodies to voltage-gated potassium channels. Arch Neurol 2007; 64: 404–10.

Chen C, Shih Y-H, Yen D-J, Lirng J-F, Guo Y-C, Yu H-Y, et al. Olfactory auras in patients with temporal lobe epilepsy. Epilepsia 2003; 44: 257–60.

Conway MA, Pleydell-Pearce CW. The construction of autobiographical memories in the self-memory system. Psychol Rev 2000; 107: 261–88.

Corcoran R, Thompson P. Memory failure in epilepsy: retrospective reports and prospective recordings. Seizure 1992; 1: 37–42.

Corridan BJ, Leung SN, Jenkins IH. A case of sleeping and forgetting. Lancet 2001; 357: 524.

Crespel A, Baldy-Moulinier M, Coubes P. The relationship between sleep and epilepsy in frontal and temporal lobe epilepsies: practical and physiopathologic considerations. Epilepsia 1998; 39: 150–7.

Croft PB, Heathfield KWG, Swash M. Differential diagnosis of transient amnesia. Br Med J 1973; 593–6.

Cronel-Ohayon S, Zesiger P, Davidoff V, Boni A, Roulet E, Deonna T. Deficit in memory consolidation (abnormal forgetting rate) in childhood temporal lobe epilepsy. Pre and postoperative long-term observation. Neuropediatrics 2006; 37: 317–24.

Crovitz HF. Frequency of episodic memories as a function of their age. Bull Psychon Soc 1974; 4: 517–8.

Dasheiff RM. Pure transient amnesia during nonconvulsive status epilepticus. Neurology 1997; 48: 1736–7.

Davidson M, Dorris L, O'Regan M, Zuberi SM. Memory consolidation and accelerated forgetting in children with idiopathic generalized epilepsy. Epilepsy Behav 2007; 11: 394–400.

Davis HP, Small SA, Stern Y, Mayeux R, Feldstein SN, Keller FR. Acquisition, recall, and forgetting of verbal information in long-term memory by young, middle-aged, and elderly individuals. Cortex 2003; 39: 1063–91.

De Renzi E, Lucchelli F. Dense retrograde amnesia, intact learning capability and abnormal forgetting rate: a consolidation deficit? Cortex 1993; 29: 449–66.

Deisenhammer E. Transient global amnesia as an epileptic manifestation. J Neurol 1981; 225: 289–92.

Diehl B, LaPresto E, Najm I, Raja S, Rona S, Babb T, et al. Neocortical temporal FDG-PET hypometabolism correlates with temporal lobe atrophy in hippocampal sclerosis associated with microscopic cortical dysplasia. Epilepsia 2003; 44: 559–64.

Dodrill CB. The relationship of neuropsychological abilities to seizure factors and to surgery for epilepsy. Acta Neurol Scand Suppl 1992; 140: 106–10.

Dugan TM, Nordgren RE, O'Leary P. Transient global amnesia associated with bradycardia and temporal lobe spikes. Cortex 1981; 17: 633–7.

Ebner A, Kerder MS. Electrical stimulation of the olfactory and gustatory cortex. In: Luders HO, Noachtar S, editors. Epileptic seizures: pathophysiology and clinical semiology. New York: Churchill Livingston; 2000. p. 237–42.

Elixhauser A, Leidy NK, Meador K, Means E, Willian MK. The relationship between memory performance, perceived cognitive function, and mood in patients with epilepsy. Epilepsy Res 1999; 37: 13–24.

Ellenbogen JM, Hulbert JC, Stickgold R, Dinges DF, Thompson-Schill SL. Interfering with theories of sleep and memory: sleep, declarative memory, and associative interference. Curr Biol 2006; 16: 1290–4.

Engmann B, Reuter M. A case history of sudden memory dysfunction – caused by transient epileptic amnesia. Aktuelle Neurologie 2003; 30: 350–353.

Evans JJ, Graham KS, Pratt KH, Hodges JR. The impact of disrupted cortico-cortico connectivity: a long-term follow-up of a case of focal retrograde amnesia. Cortex 2003; 39: 767–90.

Fergusson SM, Rayport M, Gardner E, Kass W, Weiner H, Reiser MF. Similarities in mental content of psychotic states, spontaneous seizures, dreams, and responses to electrical brain stimulation in patients with temporal lobe epilepsy. Psychosom Med 1969; 31: 479–98.

Fisher RS, Vickrey BG, Gibson P, Hermann B, Penovich P, Scherer A, et al. The impact of epilepsy from the patient's perspective I. Descriptions and subjective perceptions. Epilepsy Res 2000; 41: 39–51.

Freed DM, Corkin S, Cohen NJ. Forgetting in H.M.: a second look. Neuropsychologia 1987; 25: 461–71.

Fried I, Spencer DD, Spencer SS. The anatomy of epileptic auras: focal pathology and surgical outcome. J Neurosurg 1995; 83: 60–6.

Fujii T, Moscovitch M, Nadel L. Memory consolidation, retrograde amnesia, and the temporal lobe. In: Boller F, Grafman J, editors. Handbook of neuropsychology. Amsterdam: Elsevier; 2000. p. 223–50.

Gallassi R. Epileptic amnesic syndrome: an update and further considerations. Epilepsia 2006; 47 (Suppl 2): 103–5.

Gallassi R, Morreale A, Di Sarro R. Epileptic amnesic syndrome: further observations and considerations. Bollettino – Lega Italiana Contro L'Epilessia 1990; Issue 70–71.

Gallassi R, Morreale A, Di Sarro R, Lugaresi E. Epileptic amnesic syndrome. Epilepsia 1992; 33 (Suppl 6): S21–5.

Gallassi R, Morreale A, Lorusso S, Pazzaglia P, Lugaresi E. Epilepsy presenting as memory disturbances. Epilepsia 1988a; 29: 624–9.

Gallassi R, Morreale A, Lorusso S, Pazzaglia P, Lugaresi E. Epileptic transient amnesia. Ital J Neurol Sci 1988b; Suppl 9: 37–9.

Gallassi R, Pazzaglia P, Lorusso S, Morreale A. Neuropsychological findings in epileptic amnesic attacks. Eur Neurol 1986; 25: 299–303.

Gil-Nagel A, Risinger MW. Ictal semiology in hippocampal versus extrahippocampal temporal lobe epilepsy. Brain 1997; 120: 183–92.

Giovagnoli AR, Avanzini G. Learning and memory impairment in patients with temporal lobe epilepsy: relation to the presence, type, and location of brain lesion. Epilepsia 1999; 40: 904–11.

Giovagnoli AR, Casazza M, Avanzini G. Visual learning on a selective reminding procedure and delayed recall in patients with temporal lobe epilepsy. Epilepsia 1995; 36: 704–11.

Giovagnoli AR, Mascheroni S, Avanzini G. Self-reporting of everyday memory in patients with epilepsy: relation to neuropsychological, clinical, pathological and treatment factors. Epilepsy Res 1997; 28: 119–28.

Gleissner U, Helmstaedter C, Elger CE. Right hippocampal contribution to visual memory: a presurgical and postsurgical study in patients with temporal lobe epilepsy. J Neurol Neurosurg Psychiatry 1998; 65: 665–9.

Gloor P, Olivier A, Quesney LF, Andermann F, Horowitz S. The role of the limbic system in experiential phenomena of temporal lobe epilepsy. Ann Neurol 1982; 12: 129–44.

Halgren E, Wilson CL, Stapleton JM. Human medial temporal-lobe stimulation disrupts both formation and retrieval of recent memories. Brain Cogn 1985; 4: 287–95.

Hawley RJ, Cuenco N, Lastinger L. Pure transient amnesia during nonconvulsive status epilepticus. Neurology 1997; 48: 1736–7.

Helmstaedter C, Hauff M, Elger CE. Ecological validity of list-learning tests and self-reported memory in healthy individuals and those with temporal lobe epilepsy. J Clin Exp Neuropsychol 1998; 20: 365–75.

Hendriks MPH, Aldenkamp AP, Alpherts WCJ, Ellis J, Vermeulen J, van der Vlugt H. Relationships between epilepsy-related factors and memory impairment. Acta Neurol Scand 2004; 110: 291–300.

Hermann BP, Seidenberg M, Schoenfeld J, Davies K. Neuropsychological characteristics of the syndrome of mesial temporal lobe epilepsy. Arch Neurol 1997; 54: 369–76.

Hodges JR, Warlow CP. Syndromes of transient amnesia: towards a classification. A study of 153 cases. J Neurol Neurosurg Psychiatry 1990; 53: 834–43.

Huppert FA, Kopelman MD. Rates of forgetting in normal ageing: a comparison with dementia. Neuropsychologia 1989; 27: 849–60.

Huppert FA, Piercy M. Dissociation between learning and remembering in organic amnesia. Nature 1978; 275: 317–8.

Huppert FA, Piercy M. Normal and abnormal forgetting in organic amnesia: effect of locus of lesion. Cortex 1979; 15: 385–90.

Isaac CL, Mayes AR. Rate of forgetting in amnesia: I. Recall and recognition of prose. J Exp Psychol Learn Mem Cogn 1999a; 25: 942–62.

Isaac CL, Mayes AR. Rate of forgetting in amnesia: II. Recall and recognition of word lists at different levels of organization. J Exp Psychol Learn Mem Cogn 1999b; 25: 963–77.

Jackson JH, Beevor CE. Case of tumour of the right temporo-sphenoidal lobe bearing on the localization of the sense of smell and on the interpretation of a particular variety of epilepsy. Brain 1890; 12: 346–57.

Janz D. The grand mal epilepsies and the sleeping-waking cycle. Epilepsia 1962; 3: 69–109.

Jasper H, Rasmussen H. Studies of clinical and electrical responses to deep temporal stimulation in man with some consideration of functional anatomy. Res Publ Assoc Re Nerv Ment Dis 1958; 36: 316–34.

Jokeit H, Daamen M, Zang H, Janszky J, Ebner A. Seizures accelerate forgetting in patients with left-sided temporal lobe epilepsy. Neurology 2001; 57: 125–6.

Jokeit H, Kramer G, Ebner A. Do antiepileptic drugs accelerate forgetting? Epilepsy Behav 2005; 6: 430–2.

Kapur N. Focal retrograde amnesia in neurological disease: a critical review. Cortex 1993a; 29: 217–34.

Kapur N. Transient epileptic amnesia–a clinical update and a reformulation. J Neurol Neurosurg Psychiatry 1993b; 56: 1184–90.

Kapur N. Focal retrograde amnesia and the attribution of causality: an exceptionally benign commentary. Cogn Neuropsychol 2000; 17: 623–37.

Kapur N, Markowitsch HJ. Transient epileptic amnesia: a clinically distinct form of neurological memory disorder. Transient global amnesia and related disorders. New York: Hogrefe and Huber; 1990. p. 140–51.

Kapur N, Millar J, Colbourn C, Abbott P, Kennedy P, Docherty T. Very long-term amnesia in association with temporal lobe epilepsy: evidence for multiple-stage consolidation processes. Brain Cogn 1997; 35: 58–70.

Kapur N, Scholey K, Moore E, Barker S, Brice J, Thompson S. Long-term retention deficits in two cases of disproportionate retrograde amnesia. J Cogn Neurosci 1996; 8: 416–34.

Kapur N, Thompson P, Kartsounis LD, Abbott P. Retrograde amnesia: clinical and methodological caveats. Neuropsychologia 1999; 37: 27–30.

Kapur N, Young A, Bateman D, Kennedy P. Focal retrograde amnesia: a long term clinical and neuropsychological follow-up. Cortex 1989; 25: 387–402.

Kilpatrick C, Murrie V, Cook M, Andrewes D, Desmond P, Hopper J. Degree of left hippocampal atrophy correlates with severity of neuropsychological deficits. Seizure 1997; 6: 213–8.

Kopelman MD. Rates of forgetting in Alzheimer-type dementia and Korsakoff's syndrome. Neuropsychologia 1985; 23: 623–38.

Kopelman MD. Focal retrograde amnesia and the attribution of causality: an exceptionally critical review. Cogn Neuropsychol 2000; 17: 585–621.

Kopelman MD. Disorders of memory. Brain 2002a; 125: 2152–90.

Kopelman MD. Retrograde amnesia. In: Baddeley AD, Kopelman MD, Wilson BA, editors. The handbook of memory disorders. Chichester: John Wiley & Sons Ltd; 2002b. p. 189–207.

Kopelman MD, Panayiotopoulos CP, Lewis P. Transient epileptic amnesia differentiated from psychogenic "fugue": neuropsychological, EEG, and PET findings. J Neurol Neurosurg Psychiatry 1994; 57: 1002–4.

Kwan P, Brodie MJ. Neuropsychological effects of epilepsy and antiepileptic drugs. Lancet 2001; 357: 216–22.

Lah S, Grayson S, Lee T, Miller L. Memory for the past after temporal lobectomy: impact of epilepsy and cognitive variables. Neuropsychologia 2004; 42: 1666–79.

Lah S, Lee T, Grayson S, Miller L. Effects of temporal lobe epilepsy on retrograde memory. Epilepsia 2006; 47: 615–25.

Lee BI, Lee BC, Hwang YM, Sohn YH, Jung JW, Park SC, et al. Prolonged ictal amnesia with transient focal abnormalities on magnetic resonance imaging. Epilepsia 1992; 33: 1042–6.

Lencz T, McCarthy G, Bronen RA, Scott TM, Inserni JA, Sass KJ, et al. Quantitative magnetic resonance imaging in temporal lobe epilepsy: relationship to neuropathology and neuropsychological function. Ann Neurol 1992; 31: 629–37.

Lespinet V, Bresson C, N'Kaoua B, Rougier A, Claverie B. Effect of age of onset of temporal lobe epilepsy on the severity and the nature of preoperative memory deficits. Neuropsychologia 2002; 40: 1591–600.

Levin HS, High WM Jr, Eisenberg HM. Learning and forgetting during posttraumatic amnesia in head injured patients. J Neurol Neurosurg Psychiatry 1988; 51: 14–20.

Levine B, Black SE, Cabeza R, Sinden M, McIntosh AR, Toth JP, et al. Episodic memory and the self in a case of isolated retrograde amnesia. Brain 1998; 121: 1951–73.

Levine B, Svoboda E, Hay JF, Winocur G, Moscovitch M. Aging and autobiographical memory: dissociating episodic from semantic retrieval. Psychol Aging 2002; 17: 677–89.

Lewis P, Kopelman MD. Forgetting rates in neuropsychiatric disorders. J Neurol Neurosurg Psychiatry 1998; 65: 890–8.

Liu RSN. Progressive neocortical damage in epilepsy. Ann Neurol 2003; 53: 312–24.

Lou H. Repeated episodes of transient global amnesia. Acta Neurol Scand 1968; 44: 612–8.

Lucchelli F, Spinnler H. Ephemeral new traces and evaporated remote engrams: a form of neocortical temporal lobe amnesia? A preliminary case report. Neurocase 1998; 4: 447–59.

Maguire EA. Neuroimaging studies of autobiographical event memory. Philos Trans R Soc Lond B Biol Sci 2001; 356: 1441–51.

Maheu G, Adam C, Hazemann P, Baulac M, Samson S. A case of postictal transient anterograde and retrograde amnesia. Epilepsia 2004; 45: 1459–60.

Mameniskiene R, Jatuzis D, Kaubrys G, Budrys V. The decay of memory between delayed and long-term recall in patients with temporal lobe epilepsy. Epilepsy Behav 2006; 8: 278–88.

Manes F, Graham KS, Zeman A, de Lujan Calcagno M, Hodges JR. Autobiographical amnesia and accelerated forgetting in transient epileptic amnesia. J Neurol Neurosurg Psychiatry 2005; 76: 1387–91.

Manes F, Hodges JR, Graham KS, Zeman A. Focal autobiographical amnesia in association with transient epileptic amnesia. Brain 2001; 124: 499–509.

Manford M, Fish DR, Shorvon SD. An analysis of clinical seizure patterns and their localizing value in frontal and temporal lobe epilepsies. Brain 1996; 119: 17–40.

Manning L, Chassagnon S, Hirsch E, Kehrli P, Maitrot D. Selective memory impairment for public events in a patient with left temporal lobe epilepsy. Epilepsy Res 2005; 64: 45–7.

Manning L, Voltzenlogel V, Chassagnon S, Hirsch E, Kehrli P, Maitrot D. Selective memory impairment for public events associated with accelerated forgetting in a patient with left temporal lobe epilepsy. Revue Neurologique 2006; 162: 222–8.

Maravita A, Spadoni M, Mazzucchi A, Parma M. A new case of retrograde amnesia with abnormal forgetting rate. Cortex 1995; 31: 653–67.

Martin RC, Loring DW, Meador KJ, Lee GP. Differential forgetting in patients with temporal lobe dysfunction. Arch Clin Neuropsychol 1988; 3: 351–8.

Martin RC, Loring DW, Meador KJ, Lee GP, Thrash N, Arena JG. Impaired long-term retention despite normal verbal learning in patients with temporal lobe dysfunction. Neuropsychology 1991; 5: 3–12.

Martin RC, Sawrie SM, Roth DL, Gilliam FG, Faught E, Morawetz RB, et al. Individual memory change after anterior temporal lobectomy: a base rate analysis using regression-based outcome methodology. Epilepsia 1998; 39: 1075–82.

Mayes AR, Isaac CL, Holdstock JS, Cariga P, Gummer A, Roberts N. Long-term amnesia: a review and detailed illustrative case study. Cortex 2003; 39: 567–603.

McKee RD, Squire LR. Equivalent forgetting rates in long-term memory for diencephalic and medial temporal lobe amnesia. J Neurosci 1992; 12: 3765–72.

Meador KJ, Adams RJ, Flanigin HF. Transient global amnesia and meningioma. Neurology 1985; 35: 769–71.

Mendes MH. Transient epileptic amnesia: an under-diagnosed phenomenon? Three more cases. Seizure 2002; 11: 238–42.

Meo R, Bilo L, Striano S, Ruosi P, Estraneo A, Nocerino C. Transient global amnesia of epileptic origin accompanied by fever. Seizure 1995; 4: 311–7.

Miller JW, Yanagihara T, Petersen RC, Klass DW. Transient global amnesia and epilepsy. Electroencephalographic distinction. Arch Neurol 1987; 44: 629–33.

Miller LA, Caine D, Harding A, Thompson EJ, Large M, Watson JD. Right medial thalamic lesion causes isolated retrograde amnesia. Neuropsychologia 2001; 39: 1037–46.

Morrell F. Memory loss as a Todd's paralysis. Epilepsia 1980; 21: 185.

Moscovitch M, Nadel L. Consolidation and the hippocampal complex revisited: in defense of the multiple-trace model. Curr Opin Neurobiol 1998; 8: 297–300.

Motamedi G, Meador K. Epilepsy and cognition. Epilepsy Behav 2003; 4: 25–38.

Motamedi GK, Meador KJ. Antiepileptic drugs and memory. Epilepsy Behav 2004; 5: 435–9.

Nadel L, Moscovitch M. Memory consolidation, retrograde amnesia and the hippocampal complex. Curr Opin Neurobiol 1997; 7: 217–27.

Noulhiane M, Piolino P, Hasboun D, Clemenceau S, Baulac M, Samson S. Autobiographical memory after temporal lobe resection: neuropsychological and MRI volumetric findings. Brain 2007; 130: 3184–99.

Novelly RA. Selective memory improvement and impairment in temporal lobectomy for epilepsy. Ann Neurol 1984; 15: 64–7.
O'Connor M, Sieggreen MA, Ahern G, Schomer D, Mesulam M. Accelerated forgetting in association with temporal lobe epilepsy and paraneoplastic encephalitis. Brain Cogn 1997; 35: 71–84.
O'Connor M, Morin M, Verfaellie M, Greenblatt D, Doherty R, Cahn G, et al. Performance of temporal lobectomy patients on tests of remote memory. J Int Neuropsychol Soc 1999; 5: 117.
Oxbury JM, Oxbury SM. Neuropsychology, memory and hippocampal pathology. In: Reynolds EH, Trimble MR, editors. The bridge between neurology and psychiatry. New York: Churchill Livingstone Inc.; 1989.
Oyegbile TO, Dow C, Jones J, Bell B, Rutecki P, Sheth R, et al. The nature and course of neuropsychological morbidity in chronic temporal lobe epilepsy. Neurology 2004; 62: 1736–42.
Palmini AL, Gloor P, Jones-Gotman M. Pure amnestic seizures in temporal lobe epilepsy. Definition, clinical symptomatology and functional anatomical considerations. Brain 1992; 115: 749–69.
Pauli E, Hildebrandt M, Romstock J, Stefan H, Blumcke I. Deficient memory acquisition in temporal lobe epilepsy is predicted by hippocampal granule cell loss. Neurology 2006; 67: 1383–9.
Penfield W, Jasper HH. Epilepsy and the functional anatomy of the human brain. Boston, MA: Little, Brown and Company; 1954.
Penfield W, Perot P. The brain's record of auditory and visual experience: a final summary and discussion. Brain 1963; 86: 595–696.
Petersen RC, Smith G, Kokmen E, Ivnik RJ, Tangalos EG. Memory function in normal aging. Neurology 1992; 42: 396–401.
Piazzini A, Canevini MP, Maggiori G, Canger R. The perception of memory failures in patients with epilepsy. Eur J Neurol 2001; 8: 613–20.
Pritchard PB III, Holmstrom VL, Roitzsch JC, Giacinto J. Epileptic amnesic attacks: benefit from antiepileptic drugs. Neurology 1985; 35: 1188–9.
Quinette P, Guillery-Girard B, Dayan J, de la Sayette V, Marquis S, Viader F, et al. What does transient global amnesia really mean? Review of the literature and thorough study of 142 cases. Brain 2006; 129: 1640–58.
Ratti M, Galimberti C, Manni R, Tantara A. Remote memory impairment in temporal-lobe epilepsy. Seizure 1992; 1: 11.
Rausch R, Babb TL. Hippocampal neuron loss and memory scores before and after temporal lobe surgery for epilepsy. Arch Neurol 1993; 50: 812–7.
Reminger SL, Kaszniak AW, Labiner DM, Littrell LD, David BT, Ryan L, et al. Bilateral hippocampal volume predicts verbal memory function in temporal lobe epilepsy. Epilepsy Behav 2004; 5: 687–95.
Rowan AJ. Epilepsy and the elderly. Epilepsy Behav 2000; 1: S12–4.
Rubin DC, Schulkind MD. Distribution of important and word-cued autobiographical memories in 20-, 35-, and 70-year-old adults. Psychol Aging 1997; 12: 524–35.
Rubin DC, Wenzel AE. One hundred years of forgetting: a quantitative description of retention. Psychol Rev 1996; 103: 734–60.
Sammaritano M, Gigli GL, Gotman J. Interictal spiking during wakefulness and sleep and the localization of foci in temporal lobe epilepsy. Neurology 1991; 41: 290–7.
Shuping JR, Toole JF, Alexander E Jr. Transient global amnesia due to glioma in the dominant hemisphere. Neurology 1980; 30: 88–90.
Squire LR. Two forms of human amnesia: an analysis of forgetting. J Neurosci 1981; 1: 635–40.
Squire LR. Amnesia, memory and brain systems. Phil Trans Roy Soc B: Biol Sci 1997; 352: 1663–73.
Squire LR, Cohen N, Nadel L. The medial temporal lobe and memory consolidation: a new hypothesis. In: Eingertner E, Parker E, editors. Memory consolidation: psychobiology of cognition. Hillsdale, NJ: Lawrence Erlbaum; 1984. p. 185–210.
Squire LR, Alvarez P. Retrograde amnesia and memory consolidation: a neurobiological perspective. Curr Opin Neurobiol 1995; 5: 169–77.
Stephen LJ, Brodie MJ. Epilepsy in elderly people. Lancet 2000; 355: 1441–6.
Stracciari A, Ciucci G, Bianchedi G, Rebucci GG. Epileptic transient amnesia. Eur Neurol 1990; 30: 176–9.
Svoboda E, McKinnon MC, Levine B. The functional neuroanatomy of autobiographical memory: a meta-analysis. Neuropsychologia 2006; 44: 2189–208.
Tanaka Y, Miyazawa Y, Hashimoto R, Nakano I, Obayashi T. Postencephalitic focal retrograde amnesia after bilateral anterior temporal lobe damage. Neurology 1999; 53: 344–50.
Tassinari CA, Ciarmatori C, Alesi C, Cardinaletti L, Salvi F, Rubboli G, et al. Transient global amnesia as a postictal state from recurrent partial seizures. Epilepsia 1991; 32: 882–5.
Tellez-Zenteno JF, Dhar R, Hernandez-Ronquillo L, Wiebe S. Long-term outcomes in epilepsy surgery: antiepileptic drugs, mortality, cognitive and psychosocial aspects. Brain 2007; 130: 334–45.
Thompson PJ, Corcoran R. Everyday memory failures in people with epilepsy. Epilepsia 1992; 33 (Suppl 6): S18–20.
Thompson PJ, Baxendale SA, Duncan JS, Sander JWAS. Effects of topiramate on cognitive function. J Neurol Neurosurg Psychiatry 2000; 69: 636–41.
Tranel D, Jones R. Knowing what and knowing when. J Clin Exp Psychol 2006; 28: 43–66.
Upton D, Corcoran R, Fowler A, Thompson P. Autobiographical memory in epilepsy. Seizure 1992; 1: 14.
Vermathen P, Laxer KD, Schuff N, Matson GB, Weiner MW. Evidence of neuronal injury outside the medial temporal lobe in temporal lobe epilepsy: N-acetylaspartate concentration reductions detected with multisection proton mr spectroscopic imaging – initial experience. Radiology 2002; 2226: 195–203.
Viskontas IV, McAndrews MP, Moscovitch M. Remote episodic memory deficits in patients with unilateral temporal lobe epilepsy and excisions. J Neurosci 2000; 20: 5853–7.
Viskontas IV, McAndrews MP, Moscovitch M. Memory for famous people in patients with unilateral temporal lobe epilepsy and excisions. Neuropsychology 2002; 16: 472–80.
Voltzenlogel V, Despres O, Vignal J-P, Kehrli P, Manning L. One-year postoperative autobiographical memory following unilateral temporal lobectomy for control of intractable epilepsy. Epilepsia 2007; 48: 605–8.
Voltzenlogel V, Despres O, Vignal JP, Steinhoff BJ, Kehrli P, Manning L. Remote memory in temporal lobe epilepsy. Epilepsia 2006; 47: 1329–36.
Vuilleumier P, Despland PA, Regli F. Failure to recall (but not to remember): pure transient amnesia during nonconvulsive status epilepticus. Neurology 1996; 46: 1036–9.
Walker MP. A refined model of sleep and the time course of memory formation. Behav Brain Sci 2005; 28: 51–64.
Walker MP, Stickgold R. Sleep, memory, and plasticity. Annu Rev Psychol 2006; 57: 139–66.
Warren Z, Haslam C. Overgeneral memory for public and autobiographical events in depression and schizophrenia. Cogn Neuropsychiatry 2007; 12: 301–21.
Warren-Gash C, Zeman A. Deja vu. Practical Neurol 2003; 3: 106–9.
Zeman AZJ, Boniface SJ, Hodges JR. Transient epileptic amnesia: a description of the clinical and neuropsychological features in 10 cases and a review of the literature. J Neurol Neurosurg Psychiatry 1998; 64: 435–43.