

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

Running head: Memory impairment in epilepsy

Authors: Butler, C.R.¹. and Zeman, A.Z.²

¹Division of Clinical Neurosciences, University of Edinburgh, Edinburgh, UK;

²Department of Neurology, Peninsula Medical School, Exeter, UK

Corresponding author: Professor Adam Zeman, Professor of Cognitive and Behavioural Neurology, Peninsula Medical School, Barrack Road, Exeter, EX2 5DU, UK; tel: +44 (0) 1392 406754; fax: +44 (0) 1392 406767; email: adam.zeman@pms.ac.uk

Word count: Title: 172 chars Abstract: 197 Body: 13,023

Number of: References: 168 Tables: 3 Figures: 0

Abstract

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

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 (Télliez-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 recognised 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 minutes (Hermann et al., 1997). The degree of impairment has been shown to correlate with pathological abnormalities (Oxbury and Oxbury, 1989; Pauli et al., 2006; Rausch and Babb, 1993), hippocampal atrophy (Kilpatrick et al., 1997; Lencz et al., 1992; 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; Hendriks et al., 2004; Lespinet et al., 2002; 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 (Baxendale et al., 1998; Gleissner et al., 1998; Hermann et al., 1997). 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 (Butler et al., 2007; Kapur and Markowitsch, 1990; Zeman et al., 1998). 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 (Butler et al., 2007; Manes et al., 2005). 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 scrutinised 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) anatomico-physiological underpinnings of the syndrome, v) interictal memory deficits and the relation to other clinical features, 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').

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 to 82 years in the literature cases and 44 to 77 years in the TIME cases. 9 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 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 below.

The sex ratio of TEA cases was approximately 2 males to 1 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% to 74.6%). The reasons for this sex difference are not clear. A recent 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 amnesic attacks for each case was categorised as follows: <1min; 1-15min; 15-30min; 30-60min; 1-24hr and >24hr. 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 to 10 hours) 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, 1993b) 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 hours during which EEG revealed continuous generalised epileptic activity with phase reversal in bilateral fronto-temporal regions. However some prolonged TEA attacks may result from prolonged 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 recognised 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-recognised. Primary generalised 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 synchronised brain activity of non rapid eye movement sleep rather than the desynchronised 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 2am 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 report “being able to remember not having been 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 3 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. 5 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 3 TIME study patients volunteered that their TEA attacks permanently ‘erased’ memories of the preceding 24 hours.

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. 3 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 (Chen et al., 2003; Fried et al., 1995). 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 localised 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 (Andy et al., 1975; Bartolomei et al., 2004; Fergusson et al., 1969; Gloor et al., 1982; Jasper and Rasmussen, 1958). 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 5 (10%) TIME cases described experiencing frequent *déjà vu*, usually on occasions distinct from their amnesic 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 (Bancaud et al., 1994; Gloor et al., 1982; Halgren et al., 1985). 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 recognised, but that they go unnoticed or unreported. Generalised 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 localised 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 9 literature cases and 1 TIME case. All recordings showed seizure activity, which in 8/10 cases involved both temporal lobes and in the others remained unilateral (1 left- and one right-sided). Amnesia was observed as an ictal phenomenon in 6 cases and as post-ictal in 4 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 4 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 T2 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 (unpublished data). 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 hypothesised 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 (Gallassi, 2006; Gallassi et al., 1990; Gallassi et al., 1992; Gallassi et al., 1988a; Gallassi et al., 1988b; Gallassi et al., 1986) 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’ has been thought to render the memory trace progressively less vulnerable to disruption (Squire et al., 1984). This process, thought to involve a gradual reorganisation 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 minutes, 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 summarised in a recent review paper by Bell and Giovagnoli (2007). Although other authors have called this phenomenon long-term amnesia (LTA) (Kapur et al., 1997; Kapur et al., 1996; Mayes et al., 2003), we adopt the alternative accelerated long-term forgetting (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 one hour 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 hours 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 (Cronel-Ohayon et al., 2006; Kapur et al., 1997; Kapur et al., 1996; Lucchelli and Spinnler, 1998; Manning et al., 2006; Mayes et al., 2003; O'Connor et al., 1997). Three additional

cases were described as showing ALF but did not undergo formal testing (Kapur et al., 1996; Kapur et al., 1989) 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 summarised in Table 2. Four patients were male and 3 female. 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 2 cases (Kapur et al., 1996; Lucchelli and Spinnler, 1998) seizures resolved immediately with anticonvulsant medication. Structural brain imaging was abnormal in 6 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 4 cases (Cronel-Ohayon et al., 2006; Kapur et al., 1996; Manning et al., 2006; O'Connor et al., 1997), 2 of whom had undergone temporal lobectomy (Cronel-Ohayon et al., 2006; Manning et al., 2006). Only one patient had normal brain imaging (Lucchelli and Spinnler, 1998).

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 3 cases, standard memory tests revealed no abnormality (Kapur et al., 1997; Manning et al., 2006; O'Connor et al., 1997) whilst, in the remainder, subtle deficits were found in recognition memory (Kapur et al., 1996; Mayes et al., 2003) and recall (Cronel-Ohayon et al., 2006; Lucchelli and Spinnler, 1998).

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 minutes) 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 hours (Manning et al., 2006; O'Connor et al., 1997) to 6 weeks (Kapur et al., 1997; Kapur et al., 1996). 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., 1997; Kapur et al., 1996; Manning et al., 2006; Mayes et al., 2003), but never completely intact. More precise study of the forgetting rate is made in 4 papers. O'Connor et al (1997) described a rapid decline in memory over the first 24 hours, with subsequent decline to floor over 7 days. Lucchelli and Spinnler (1998) showed their patient to have good verbal recall at 24 hours 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 hours, 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 (Mayes et al., 2003; O'Connor et al., 1997). 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.

Accelerated long-term forgetting was accompanied in all cases by impairment in remote memory. In all but 2 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 ten studies addressing the issue of long-term anterograde memory in epilepsy (Bell, 2006; Bell et al., 2005; Bell and Giovagnoli, 2007; Blake et al., 2000; Butler et al., 2007; Davidson et al., 2007; Helmstaedter et al., 1998; Mameniskiene et al., 2006; Manes et al., 2005; Martin et al., 1991). These are summarised in Table 2. Nine examined patients with TLE, and one of these (Blake et al., 2000) also included a group of 7 patients with other focal epilepsies. Two studies (Butler et al., 2007; Manes et al., 2005) 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 generalised epilepsy (IGE) (Davidson et al., 2007), in whom

the mean age was 11.5 years (range 8 to 16). In total, 138 male and 172 female patients were studied.

In contrast to several of the case reports described above, 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. Post-operative patients were included in the studies by Martin et al (1988) (6 patients) and Bell (2006) (6 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 vascular disease. Davidson et al (2007) do not report imaging findings, but these are expected to be normal in IGE.

Memory retention over 30 minutes was found to be comparable in patients and controls in 5 studies (Blake et al., 2000; Butler et al., 2007; Davidson et al., 2007; Giovagnoli et al., 1995; Martin et al., 1991), and one (Manes et al., 2005) found normal verbal but impaired non-verbal memory. Four studies (Bell, 2006; Bell et al., 2005; Helmstaedter et al., 1998; Mameniskiene et al., 2006) identified impairment amongst patients even at this short delay. At extended intervals ranging from 24 hours (Bell et al., 2005; Martin et al., 1991) to 8 weeks (Blake et al., 2000), 7 studies (Blake et al., 2000; Butler et al., 2007; Davidson et al., 2007; Helmstaedter et al., 1998; Mameniskiene et al., 2006; Manes et al., 2005; Martin et al., 1991) found patients to show a disproportionate degree of forgetting compared with controls. In contrast, 3 studies (Bell, 2006; Bell et al., 2005; Giovagnoli et al., 1995) 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 minutes 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

1) 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, 3 studies report negative results. The reason for this discrepancy is not clear, but it may arise partly from methodological differences discussed below. ALF may also be more prominent in certain subtypes of TLE, such as TEA, in which 44% patients report symptoms consistent with ALF (Butler et al., 2007).

Patients were shown to learn at a normal rate in 3 studies (Blake et al., 2000; Butler et al., 2007; Martin et al., 1991), 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, 2 studies (Butler et al., 2007; Mameniskiene et al., 2006) 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 (Bell, 2006; Bell et al., 2005; Blake et al., 2000; Helmstaedter et al., 1998; Manes et al., 2005) 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 hours. 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 below.

2) Methodological issues in the assessment of accelerated long-term forgetting (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; Butler et al., 2007; Manes et al., 2005) performed more extensive testing and revealed no differences between patients and controls on measures of language, visuospatial 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, 1999a; Isaac and Mayes, 1999b).

iii) ALF is most convincingly demonstrated when patients exhibit normal initial learning and 30 minute recall, but clear impairment at longer delays (Blake et al., 2000; Butler et al., 2007; Manes et al., 2005; Martin et al., 1988). 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 4 studies (Blake et al., 2000; Butler et al., 2007; Davidson et al., 2007; Martin et al., 1991), 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 4 studies (Bell, 2006; Bell and Giovagnoli, 2007; Giovagnoli et al., 1995; Martin et al., 1991), 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 3 studies (Bell, 2006; Bell et al., 2005; 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 hours 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.

3) Aetiology and pathophysiology of ALF

Accepting that ALF occurs in some patients with epilepsy, we may hypothesise several contributory mechanisms: 1) clinical or subclinical seizure activity; 2) structural brain pathology; 3) an adverse effect of anticonvulsant medication or 4) 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 (Ellenbogen et al., 2006; Walker, 2005; Walker and Stickgold, 2006).

In a study directly addressing the question of whether incident seizures accelerate forgetting, Bergin et al (1995) tested immediate, 30 minute and 48 hour 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 hours 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 (Martin et al., 1998; Novelly, 1984). 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 minutes, 30 minutes and 30 hours in patients on two occasions: 2 hours 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 hours in head injury patients in PTA, compared with head injury patients who had recovered from PTA.

Structural lesions

Many of the case studies reviewed above 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, 1999a) 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, 1999a; Isaac and Mayes, 1999b) conclude that forgetting in the amnesic syndrome is accelerated over the first 10 minutes 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 minutes, 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 (Davis et al., 2003; Huppert and Kopelman, 1989), 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-minute 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 above 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 (Butler et al., 2007; Gallassi et al., 1988a; Gallassi, 2006; Zeman et al., 1998); 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 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 (Elixhauser et al., 1999; Giovagnoli et al., 1997). 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; Butler et al., 2007; Mameniskiene et al., 2006) assessed mood using the Hospital Anxiety and Depression Scale and found no correlation with very long-term memory performance. In addition, as mentioned above, 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 recognised 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, 2006; Gallassi et al., 1992). 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 organised.

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 one 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, 1993a; Kapur, 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, 2002a), 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 4 of the 7 cases of ALF described above, seizures resulted from extensive brain damage caused by trauma or encephalitis. We will restrict our considerations to seven cases (Chan et al., 2007; Kapur et al., 1997; Kapur et al., 1989; Lucchelli and Spinnler, 1998; Manes et al., 2001; Manning et al., 2005) in which structural imaging was either normal or revealed only very focal abnormalities, since it is well recognised that structural pathology in a variety of brain regions can cause retrograde amnesia in the absence of seizures (Kopelman, 2002b). There were 6 males and 1 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 (Chan et al., 2007; Manes et al., 2001). One (Manning et al., 2005) had undergone a recent left temporal lobectomy for hippocampal sclerosis. Two cases had nonparaneoplastic limbic encephalitis associated with antibodies against voltage-gated potassium channels

(VGKC-Ab) and bilateral medial temporal lobe damage seen on MRI. In the other 4 cases, seizures began in later life (range 58 to 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 2 cases (Kapur et al., 1989; Manes et al., 2001), and more general anterograde memory impairment in the 2 cases of VGKC-Ab encephalitis (Chan et al., 2007). Very long-term memory tests revealed ALF in 2 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 2 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 6 cases, the deficit was shown to affect memories from the previous 30 to 40 years (Chan et al., 2007; Kapur et al., 1989; Lucchelli and Spinnler, 1998; Manes et al., 2001; Manning et al., 2005). 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; Bergin et al., 2000; Butler et al., 2007; Lah et al., 2004; Lah et al., 2006; Manes et al., 2005; Noulhiane et al., 2007; O'Connor et al., 1999; Ratti et al., 1992; Upton et al., 1992; Viskontas et al., 2000; Voltzenlogel et al., 2007;

Voltzenlogel et al., 2006). The patient population varies across these studies. As discussed below, 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; Lah et al., 2004; Noulhiane et al., 2007; O'Connor et al., 1999; 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 (Butler et al., 2007; Manes et al., 2005) concentrated upon TEA, in which remote memory complaints are common. In total, over 262 patients were studied, and the mean age was approximately 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 2 studies (Lah et al., 2004; Lah et al., 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 5 studies (Barr et

al., 1990; Lah et al., 2004; Lah et al., 2006; Noulhiane et al., 2007; Viskontas et al., 2002).

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

1) 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 (Butler et al., 2007; Lah et al., 2004; Lah et al., 2006; Manes et al., 2005; Noulhiane et al., 2007; Upton et al., 1992; Viskontas et al., 2000; Voltzenlogel et al., 2007; Voltzenlogel et al., 2006). Of these, 2 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 7 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; Butler et al., 2007; Lah et al., 2004; Lah et al., 2006). 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; Lah et al., 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; Lah et al., 2006; Voltzenlogel et al., 2006), patients with left temporal epilepsy were more severely impaired than 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.

2) 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 longstanding

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 (O'Connor et al., 1999; Upton et al., 1992; Viskontas et al., 2000; Voltzenlogel et al., 2006). Of these, none found a difference in personal semantic memory and just 2 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; Lah et al., 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 (Butler et al., 2007; Manes et al., 2005; Noulhiane et al., 2007; Voltzenlogel et al., 2007; Voltzenlogel et al., 2006). 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 (Bernasconi et al., 2004; Diehl et al., 2003; Liu, 2003; Vermathen et al., 2002).

3) 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. Summarising 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; Butler et al., 2007; Lah et al., 2004; Lah et al., 2006; Manes et al., 2005; Noulhiane et al., 2007; Viskontas et al., 2000). 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 (Butler et al., 2007; Manes et al., 2005; Viskontas et al., 2000), 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 (Butler et al., 2007; Manes et al., 2005; Zeman et al., 1998). 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 3 studies (Barr et al., 1990; Lah et al., 2004; Lah et al., 2006). The only significant group by time interaction was found for patients who had undergone a right temporal lobectomy, who were worse at recognising 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.

4) Aetiology and pathophysiology of RMI in epilepsy

Six studies examined the possible causes of RMI in epilepsy (Bergin et al., 2000; Lah et al., 2004; Lah et al., 2006; Noulhiane et al., 2007; Viskontas et al., 2000; Voltzenlogel et al., 2006). Data were variously gathered on demographics, seizure variables (lifetime number of all or only generalised 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 generalised 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 generalised tonic-clonic seizures (Lah et al., 2004; Lah et al., 2006), age of epilepsy onset (Lah et al., 2004; Noulhiane et al., 2007; Voltzenlogel et al., 2006), 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 3 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 postoperative 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 (Butler et al., 2007; Manes et al., 2005; Manes et al., 2001) and in the 5 case reports discussed above, extensive retrograde amnesia occurs with minimal or no clinically apparent structural brain damage. Kapur (2000) has suggested that, in such cases, intermittent clinical or subclinical 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 subcortical 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; Lah et al., 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 difference in scores on the Hospital Anxiety and Depression Scale between patients and controls. 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) (Moscovitch and Nadel, 1998; Nadel and Moscovitch, 1997). 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 above, 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 summarised 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: accelerated long-term forgetting (ALF) is the unusually rapid decay of memories that were initially accessible at a testing interval of 30 minutes 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.

Acknowledgements: this work was supported by grants from the Patrick Berthoud Charitable Trust (C.R.B.) and The Health Foundation (A.Z.).

The authors have no conflicts of interest

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 déjà 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 déjà vu and reminiscence of memories. *Neurology* 2004; 63: 858-864.
- 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: 158-166.
- 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. *Psychological Assessment* 2005; 17: 103-109.
- Bell BD, Giovagnoli AR. Recent Innovative Studies of Memory in Temporal Lobe Epilepsy. *Neuropsychol Rev* 2007; 17: 455-476.

- Bergin PS, Thompson PJ, Baxendale SA, Fish DR, Shorvon SD. Remote memory in epilepsy. *Epilepsia* 2000; 41: 231-239.
- Bergin PS, Thompson PJ, Fish DR, Shorvon SD. The effect of seizures on memory for recently learned material. *Neurology* 1995; 45: 236-240.
- 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: 717-723.
- Blake RV, Wroe SJ, Breen EK, McCarthy RA. Accelerated forgetting in patients with epilepsy: evidence for an impairment in memory consolidation. *Brain* 2000; 123: 472-483.
- Bortz JJ. Neuropsychiatric and Memory Issues in Epilepsy. *Mayo Clin Proc* 2003; 78: 781-7.
- Brown AS. A review of the déjà vu experience. *Psychological Bulletin* 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: 409-414.
- Butler CR, Graham KS, Hodges JR, Kapur N, Wardlaw JM, Zeman AZ. The syndrome of transient epileptic amnesia. *Ann Neurol* 2007; 61: 587-598.
- 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: 321-326.
- Chan D, Henley SM, Rossor MN, Warrington EK. Extensive and temporally ungraded retrograde amnesia in encephalitis associated with antibodies to voltage-gated potassium channels. *Archives of Neurology* 2007; 64: 404-410.

- 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: 257-260.
- 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: 150-157.
- Croft PB, Heathfield KWG, Swash M. Differential diagnosis of transient amnesia. *British Medical Journal* 1973: 593-596.
- 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: 317-324.
- Crovitz HF. Frequency of episodic memories as a function of their age. *Bulletin of the Psychonomic Society* 1973.
- Dasheiff RM. Pure transient amnesia during nonconvulsive status epilepticus. *Neurology* 1997; 48: 1736-1737.
- Davidson M, Dorris L, O'Regan M, Zuberi SM. Memory consolidation and accelerated forgetting in children with idiopathic generalized epilepsy. *Epilepsy & Behavior* 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: 449-466.
- Deisenhammer E. Transient global amnesia as an epileptic manifestation. *Journal of Neurology* 1981; 225: 289-292.
- 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: 559-564.
- 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: 633-637.
- Ebner A, Kerder MS. Electrical stimulation of the olfactory and gustatory cortex. In: Luders HO and Noachtar S, editors. *Epileptic seizures: pathophysiology and clinical semiology*. Vol Churchill Livingstone. New York, 2000: 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 Research* 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. *Current Biology* 2006; 16: 1290-1294.

- Engmann B, Reuter M. A case history of sudden memory dysfunction - Caused by transient epileptic amnesia. *Aktuelle Neurologie* 2003; . 30.
- 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: 767-790.
- 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: 479-498.
- 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: 60-66.
- Fujii T, Moscovitch M, Nadel L. Memory consolidation, retrograde amnesia, and the temporal lobe. In: Boller F and Grafman J, editors. *Handbook of neuropsychology*. Amsterdam: Elsevier, 2000: 223-250.
- 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-S25.
- Gallassi R, Morreale A, Lorusso S, Pazzaglia P, Lugaresi E. Epilepsy presenting as memory disturbances. *Epilepsia* 1988a; 29: 624-629.
- Gallassi R, Morreale A, Lorusso S, Pazzaglia P, Lugaresi E. Epileptic transient amnesia. *Italian Journal of Neurological Sciences* 1988b; Suppl 9: 37-39.
- Gallassi R, Pazzaglia P, Lorusso S, Morreale A. Neuropsychological findings in epileptic amnesic attacks. *European Neurology* 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: 904-911.
- 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: 665-669.
- Gloor P, Olivier A, Quesney LF, Andermann F, Horowitz S. The role of the limbic system in experiential phenomena of temporal lobe epilepsy. *Annals of Neurology* 1982; 12: 129-144.

- Halgren E, Wilson CL, Stapleton JM. Human medial temporal-lobe stimulation disrupts both formation and retrieval of recent memories. *Brain & Cognition* 1985; 4: 287-295.
- Hawley RJ, Cuenco N, Lastinger L. Pure transient amnesia during nonconvulsive status epilepticus. *Neurology* 1997; 48: 1736-1737.
- 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. *Journal of Clinical and Experimental Neuropsychology* 1998; 20: 365-375.
- Hendriks MPH, Aldenkamp AP, Alpherts WCJ, Ellis J, Vermeulen J, van der Vlugt H. Relationships between epilepsy-related factors and memory impairment. *Acta Neurologica Scandinavica* 2004; 110: 291-300.
- Hermann BP, Seidenberg M, Schoenfeld J, Davies K. Neuropsychological characteristics of the syndrome of mesial temporal lobe epilepsy. *Archives of Neurology* 1997; 54: 369-376.
- Hodges JR, Warlow CP. Syndromes of transient amnesia: towards a classification. A study of 153 cases. *Journal of Neurology, Neurosurgery & Psychiatry* 1990; 53: 834-843.
- 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. *Journal of Experimental Psychology: Learning, Memory, & Cognition* 1999a; 25: 942-962.
- Isaac CL, Mayes AR. Rate of forgetting in amnesia: II. Recall and recognition of word lists at different levels of organization. *Journal of Experimental Psychology: Learning, Memory, & Cognition* 1999b; 25: 963-977.
- 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: 316-334.
- Jokeit H, Daamen M, Zang H, Janszky J, Ebner A. Seizures accelerate forgetting in patients with left-sided temporal lobe epilepsy. *Neurology* 2001; 57: 125-126.
- Jokeit H, Kramer G, Ebner A. Do antiepileptic drugs accelerate forgetting? *Epilepsy Behav.* 2005; 6: 430-432.
- Kapur N. Focal retrograde amnesia in neurological disease: a critical review. *Cortex* 1993a; 29: 217-234.
- Kapur N. Transient epileptic amnesia--a clinical update and a reformulation. *Journal of Neurology, Neurosurgery & Psychiatry* 1993b; 56: 1184-1190.
- Kapur N. Focal retrograde amnesia and the attribution of causality: An exceptionally benign commentary. *Cognitive Neuropsychology* 2000; 17: 623-637.

- 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: 140-151.
- 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 & Cognition* 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. *Journal of Cognitive Neuroscience* 1996; 8 416-434.
- 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. *Cognitive Neuropsychology* 2000; 17: 585-621.
- Kopelman MD. Disorders of memory. *Brain* 2002; 125: 2152-90.
- Kopelman MD. Retrograde amnesia. In: Baddeley AD, Kopelman MD and Wilson BA, editors. *The handbook of memory disorders*. Chichester: John Wiley & Sons Ltd, 2002: 189-207.

- Kopelman MD, Panayiotopoulos CP, Lewis P. Transient epileptic amnesia differentiated from psychogenic "fugue": neuropsychological, EEG, and PET findings. *Journal of Neurology, Neurosurgery & Psychiatry* 1994; 57: 1002-1004.
- Kwan P, Brodie MJ. Neuropsychological effects of epilepsy and antiepileptic drugs. *Lancet* 2001; 357: 216-222.
- 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: 615-625.
- 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: 1042-1046.
- 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: 1591-1600.
- 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: 1951-1973.
- 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. *Journal of Neurology, Neurosurgery & Psychiatry* 1998; 65: 890-898.
- Liu R.S.N. Progressive neocortical damage in epilepsy. *Annals of Neurology* 2003; 53: 312-324.
- Lou H. Repeated episodes of transient global amnesia. *Acta Neurologica Scandinavica* 1968; 44: 612-618.
- Lucchelli F, Spinnler H. Ephemeral new traces and evaporated remote engrams: a form of neocortical temporal lobe amnesia? A preliminary case report. *Neurocase* 1998; 447-459.
- 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: 1459-1460.
- 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: 278-288.
- 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 Research* 2005; 64: 45-47.
- 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: 222-228.
- Maravita A, Spadoni M, Mazzucchi A, Parma M. A new case of retrograde amnesia with abnormal forgetting rate. *Cortex* 1995; 31: 653-667.
- 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: 1075-1082.

- 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: 769-771.
- Mendes MH. Transient epileptic amnesia: an under-diagnosed phenomenon? Three more cases. *Seizure* 2002; 11: 238-242.
- Meo R, Bilo L, Striano S, Ruosi P, Estraneo A, Nocerino C. Transient global amnesia of epileptic origin accompanied by fever. *Seizure* 1995; 4: 311-317.
- Miller JW, Yanagihara T, Petersen RC, Klass DW. Transient global amnesia and epilepsy. Electroencephalographic distinction. *Archives of Neurology* 1987; 44: 629-633.
- Miller LA, Caine D, Harding A, Thompson EJ, Large M, Watson JD. Right medial thalamic lesion causes isolated retrograde amnesia. *Neuropsychologia* 2001; 39: 1037-1046.
- 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 & Behavior* 2003; 4: 25-38.
- Motamedi GK, Meador KJ. Antiepileptic drugs and memory. *Epilepsy & Behavior* 2004; 5: 435-439.

- 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: 3184-3199.
- Novelly R.A. Selective memory improvement and impairment in temporal lobectomy for epilepsy. *Annals of Neurology* 1984; 15: 64-67.
- O'Connor M, Sieggreen MA, Ahern G, Schomer D, Mesulam M. Accelerated forgetting in association with temporal lobe epilepsy and paraneoplastic encephalitis. *Brain & Cognition* 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 and 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: 1736-1742.
- Palmini AL, Gloor P, Jones-Gotman M. Pure amnesic seizures in temporal lobe epilepsy. Definition, clinical symptomatology and functional anatomical considerations. *Brain* 1992; 115: 749-769.
- 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: 1383-1389.

- Penfield W, Jasper HH. *Epilepsy and the Functional Anatomy of the Human Brain*: Little, Brown, 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-.
- Piazzini A, Canevini MP, Maggiori G, Canger R. The perception of memory failures in patients with epilepsy. *European Journal of Neurology* 2001; 8: 613-620.
- Pritchard PB, III, Holmstrom VL, Roitzsch JC, Giacinto J. Epileptic amnesic attacks: benefit from antiepileptic drugs. *Neurology* 1985; 35: 1188-1189.
- 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. *Archives of Neurology* 1993; 50: 812-817.
- 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 & Behavior* 2004; 5: 687-695.
- Rowan AJ. *Epilepsy and the Elderly*. *Epilepsy Behav.* 2000; 1: S12-S14.
- 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. *Psychological review* 1996; 103: 734-760.
- 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-.
- 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. *Journal of Neuroscience* 1981; 1: 635-640.
- Squire LR. Amnesia, memory and brain systems. *Philosophical Transactions of the Royal Society B: Biological Sciences* 1997; 352: 1663-1673.
- Squire LR, Cohen N, Nadel L. The medial temporal lobe and memory consolidation: a new hypothesis. In: Eingertner E and Parker E, editors. *Memory consolidation: psychobiology of cognition*. Hillsdale, NJ: Lawrence Erlbaum, 1984: 185-210.
- Squire LR, Alvarez P. Retrograde amnesia and memory consolidation: a neurobiological perspective. *Current Opinion in Neurobiology* 1995; 5: 169-177.
- Stephen LJ, Brodie MJ. Epilepsy in elderly people. *Lancet* 2000; 355: 1441-1446.
- Stracciari A, Ciucci G, Bianchedi G, Rebucci GG. Epileptic transient amnesia. *European Neurology* 1990; 30: 176-179.
- 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: 344-350.
- 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: 882-885.
- 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: 334-345.
- Thompson PJ, Corcoran R. Everyday memory failures in people with epilepsy. *Epilepsia* 1992; 33 Suppl 6: S18-S20.
- Thompson PJ, Baxendale SA, Duncan JS, Sander JWAS. Effects of topiramate on cognitive function. *J Neurol Neurosurg Psychiatry* 2000; 69: 636-641.
- Tranel D, Jones R. Knowing What and Knowing When. *Journal of Clinical and Experimental Psychology* 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. *Journal of Neuroscience* 2000; 20: 5853-5857.

- 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: 605-608.
- 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: 1036-1039.
- Walker MP. A refined model of sleep and the time course of memory formation. *Behavioral and Brain Sciences* 2005; 28: 51-64.
- Walker MP, Stickgold R. Sleep, memory, and plasticity. *Annu Rev Psychol* 2006; 57: 139-166.
- Warren Z, Haslam C. Overgeneral memory for public and autobiographical events in depression and schizophrenia. *Cognit Neuropsychiatry* 2007; 12: 301-21.
- Warren-Gash C, Zeman A. Deja vu. *Practical Neurology* 2003; 3: 106-109.
- 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. *Journal of Neurology, Neurosurgery & Psychiatry* 1998; 64: 435-443.

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	30-60min	9	no	yes	yes	no	no	no	L			complete
Lou (1968)	79	F	1-24hr	3		partial	yes				B			
Croft et al (1973)	58	F	1-24hr	2	no	yes	yes				B			complete
Morrell (1980)	27	M				yes				yes	B (ictal)			
Shuping et al (1980)	60	M	30-60min	3		yes					N	L HC GBM		died
Dugan et al (1981)	82	M	1-24hr	3		yes	yes			no	B (ictal)	CT normal		complete
Deisenhammer (1981)	11	F	1-15min	3	yes	yes	yes			no	R	CT normal		complete
Meador et al (1985)	47	F	1-15min	2	no	partial				no	B	R MTL meningioma		complete
Pritchard et al (1985)	65	M	1-15min	10		yes					B	CT normal		complete
Pritchard et al (1985)	64	M	30-60min	3		yes					B			complete
Kapur et al (1989)	74	M	15-30min	20	yes	yes	no		oral	yes	B	MRI normal		
Gallassi et al (1986)	64	M	30-60min	25	yes	yes	yes	no	oral	yes	NS	mod gen atrophy		partial
Miller et al (1987)	22	M	1-15min							yes	L			complete
Miller et al (1987)	62	M	15-30min	8	yes		yes	no	no	no	B			complete
Gallassi et al (1988b)	67	F	1-15min	60	yes	yes	yes		oral	yes	NS	CT normal		complete
Gallassi et al (1988b)	65	M	15-30min	9		yes			oral	yes	NS	no		complete
Stracciari et al (1990)	70	F	1-15min	13		yes	yes		oral	yes	L	MRI normal		complete
Tassinari et al (1991)	57	M	1-15min			yes	yes	yes	oral	yes	B (ictal)			complete
Palmini et al (1992)	30	F	<1min			yes	no	no	manual	no	B (ictal)	L HS		continued
Palmini et al (1992)	36	F	<1min			yes	N (?)	no			B (ictal)	atrophy L HC/AG		continued
Palmini et al (1992)	44	F	<1min			yes	N (?)	no		no	B	normal		continued
Kapur (1993b)	61	F	15-30min	2	yes	no		no	no		NS	L frontal infarct		complete
Kapur (1993b)	63	F	1-24hr	35	yes	yes	no	no	oral	no	NS	CT normal		partial

Kapur (1993b)	67	F	30-60min	6	no	partial	no	no	no		NS	CT normal	normal	complete
Kapur (1993b)	28	M	>24hr	20	yes	yes	yes	no	oral	no	B			complete
Kopelman et al (1994)	54	M	30-60min	9		yes	yes		manual	no	B	MRI normal		complete
Meo et al (1995)	69	F	1-24hr	3	yes	yes	no			yes	L (ictal)			complete
Cammalleri et al (1996)	47	M	<1min	4	no	no	no	no	no	no	N	angioma R cing		complete
Vuilleumier et al (1996)	teens	F	1-24hr	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	1-24hr	5	yes	partial	yes	yes		no	B	CT normal		complete
Zeman et al (1998)	79	M	1-24hr	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	30-60min			yes	no					CT normal		partial
Mendes (2002)	71	F	30-60min	4	no	partial	yes	no	no	no	N	MRI normal		complete
Mendes (2002)	74	M	30-60min	4	no	partial	yes	no	no	no	NS	MRI normal		complete
Engmann and Reuter (2003)	48	M	>24hr	3	no	yes		no	no	yes	L	MRI mild atrophy	↓	complete
Maheu et al (2004)	27	M	>24hr	10		yes	no			no	R (ictal)	R MTL bleed		
Manes et al (2005)	48	M	30-60min	4							B	CT normal		
Manes et al (2005)	64	M	<1min	7							B	CT normal		
Manes et al (2005)	69	M	30-60min	5								normal		
Manes et al (2005)	57	M	30-60min	6								MRI CVD		
Manes et al (2005)	46	M	30-60min	4							R	MRI normal		
TIME (Butler et al., 2007)	62.1	34	30-60min	10	37/50	28/50	25/50	21/50	18/50	12/50	18/49	1 meningioma	ALF 22/50	46/48
	(44-77)	M				partial							RMI 35/50	complete
													TA 18/50	

Key: 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

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

Authors (year)	Number of patients	Age mean (SD)	Sex	Seizures	Seizure lateralisation	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	CHI → 1*GTC	?	bilat TL	naming ↓	recog mem ↓ (mild)	6 wk (+)	yes
O'Connor et al (1997)	JT	42	M	LE → CPS	bilat	MTL bilat	no	no	24 hr (+)	yes
Kapur et al (1997)	PA	62	F	CPS	L	L HC (subtle)	no	no	6 wk (+)	yes
Lucchelli and Spinnler (1998)	GB	65	M	CPS	L	no	no	verbal ↓ (mild)	7 d (+)	yes
Mayes et al (2003)	JL	46	F	CHI → CPS	?	bilat TL; HC normal	fear perc ↓	recog mem ↓ (mild)	3 wk (+)	yes
Manning et al (2006)	JR	54	M	CPS → GTC	L	L HS (postop)	no	no	30 hr (+)	yes
Cronel-Ohayon et al (2007)	JE	18	M	CPS	L	L AG (postop)	no	yes (mild)	7 d (+)	yes
Series										
Martin et al (1991)	21	31 (7.5)	10 M	TLE	13 L; 8 R	6 postop	IQ ↓	no	24 hr (+)	n/d
Giovagnoli et al (1995)	24	38 (11.6)	14 M	TLE	12 L; 12 R	no	no	no	2 wk (-)	n/d
Helmstaedter et al (1998)	55	27	27 M	TLE	28 L; 27 R	45 TL lesion	IQ ↓	yes	1 wk	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 wk (+)	n/d
Bell et al (2005)	42	37 (11.4)	14 M	TLE	22 L; 20 R	no	IQ ↓	yes	24 hr (-)	n/d
Bell (2006)	25	39 (10.0)	10 M	TLE	11 L; 6 R; 2 B	6 postop	IQ ↓	yes	2 wk (-)	n/d
Mameniskiene et al (2006)	7	57 (8.1)	6 M	TEA	n/d	no	no	no	6 wk (+)	yes
Manes et al (2006)	70	33 (9.5)	29 M	TLE	n/d	11 TL lesion	n/d	yes	4 wk (+)	n/d
Butler et al (2007)	24	68 (8.7)	14 M	TEA	n/d	no	no	no	1 wk (+)	yes
Davidson et al (2007)	21	11.5	7 M	IGE	-	n/d	no	no	1 wk (+)	n/d

Key: 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

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)	KC1/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	

Key: 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;

